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Modelling the drying behaviour of wet granules in the context of fully continuous pharmaceutical tablet manufacturing
Dutch translation of the title:
Modellering van het droogproces van natte granulaten binnen de context van continue farmaceutische productie van tabletten

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Het starten van een project, het verrichten van onderzoek en het uiteindelijk afronden van het project. Het was een lange trip waarvan de eindbestemming is bereikt dankzij de steun van vele mensen.

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Séverine
Ghent, March 2014
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Acronyms

**AIC**  Akaike’s Information criterion.
**AICc**  corrected Akaike’s Information criterion.
**API**  Active Pharmaceutical Ingredient.
**AREM**  Advanced Rate Elimination Method.
**BIC**  Bayesian Information Criterion.
**CARPT**  Computer-Aided Radioactive Particle Tracking.
**CDF**  Cumulative Distribution Function.
**CDRC**  Characteristic Drying Rate Curve.
**CFD**  Computational Fluid Dynamics.
**CSM**  Contribution to Sample Mean.
**CSV**  Contribution to Sample Variance.
**DEM**  Discrete Element Method.
**DIAT**  Digital Image Analysis Technique.
**DPM**  Discrete Particle Model.
**DQMOM**  Discrete Quadrature Method of Moments.
**DWS**  Diffusing Wave Spectroscopy.
**ECT**  Electrical Capacitance Tomography.
**EE**  Elementary Effect.
**EVT**  Eulerian Velocimetry Technique.
**FDA**  Food and Drug Administration.
**FIM**  Fisher Information Matrix.
**FPE**  Final Prediction Error.
**GLUE**  Generalised Likelihood Uncertainty Estimation.
**GMP**  Good Modelling Practice.
**GMP**  Good Manufacturing Practices.
**GSA**  Global Sensitivity Analysis.
**HRFV**  High Resolution Finite Volume.
HSY  Hornberger-Spear-Young.

ISAT  In Situ Adaptive Tabulation.

KTGF  Kinetic Theory of Granular Flow.

LDA  Laser Doppler Anemometry.

LES  Large Eddy Simulation.

LHS  Latin Hypercube Sampling.

LILC  Khinchin’s law of Iterated Logarithm Criterion.

LOD  Loss On Drying.

LSA  Local Sensitivity Analysis.

LVT  Lagrangian Velocimetry Technique.

MBE  Mean Bias Error.

MOC  Method of Characteristics.

MOM  Method of Moments.

MRT  Microwave Resonance Technology.

NIRS  Near Infra-red Spectroscopy.

NMR  Nuclear Magnetic Resonance.

OAT  One Factor at a Time.

ODE  Ordinary Differential Equation.

OED  Optimal Experimental Design.

PAT  Process Analytical Technology.

PBE  Population Balance Equation.

PBM  Population Balance Model(ling).

PCA  Principal Component Analysis.

PCC  Partial Correlation Coefficient.

PCM  Particle Cloud Model.

PD  Product-Difference.

PDE  Partial Differential Equation.

PDF  Probability Density Function.

PIV  Particle Image Velocimetry.

PLS  Partial Least Squares.

POD  Proper Orthogonal Decomposition.

PRCC  Partial Rank Correlation Coefficient.

PRESSp  Prediction Sum of Squares.

PSD  Particle Size Distribution.

PTV  Particle Tracking Velocimetry.
Acronyms

**PVP** polyvinylpyrrolidone.

**QbD** Quality By Design.

**QMOM** Quadrature Method of Moments.

**RANS** Reynolds-averaged Navier-Stokes Equations.

**Re** Reynolds number.

**REA** Reaction Engineering Approach.

**REV** Representative Elementary Volume.

**RMSE** Root Mean Squared Error.

**RPT** Radioactive Particle Tracking.

**RSA** Regional Sensitivity Analysis.

**RSM** Reynolds Stress Model.

**RTP** Rapid Thermal Processing.

**SAE** Sum of Absolute Errors.

**SLS** sodiumlaurylsulfate.

**SMOM** Standard Method of Moments.

**SRC** Standardized Regression Coefficient.

**SRE** Sum of Relative Errors.

**SRRC** Standardized Rank Regression Coefficient.

**SSE** Sum of Squared Errors.

**SVD** Singular Value Decomposition.

**TFM** Two-Fluid Model.

**TIC** Theil’s Inequality Coefficient.

**UDF** User Define Function.

**VSM** Variable Simplification Method.

**wSSE** Weighted Sum of Squared Errors.
PART I

Introduction, literature review, objectives and system under study

Black box

White box
The first part of this PhD dissertation starts with a short introduction to situate the research in the industrial context and the modelling context (Chapter 1 section 1.1), which is then followed by the thesis outline (Chapter 1 section 1.2). Subsequently, a literature overview is given providing the reader a general background on the subject and the state-of-the-art (Chapter 2). At the end of this chapter, the objectives of this thesis are listed (Section 2.10). The last chapter of this part (Chapter 3) gives a detailed description of the system under study, i.e. the ConsiGma™.
CHAPTER 1

Introduction

1.1 Background and thesis outline

Traditionally, the pharmaceutical industry has mainly relied on batch processing. However, currently the intention and opportunity exist to take a step forward and move towards continuous production processes [Leuenberger, 2001b]. Continuous production processes are already well established in other industries, such as the bulk chemical industry and the food industry. This trend in the pharmaceutical industry obviously has implications regarding regulation, quality assurance, etc. The quality regulation for pharmaceuticals is for good reasons very strict, and in the past it was nearly impossible to change something in the way of processing once a process had been approved for production. However, the publication of the Process Analytical Technology (PAT) guidance has facilitated innovation and efficiency, and as such, the possibility exists to take the step towards continuous production processes. To meet the PAT regulations, a thorough understanding of the process, and its subprocesses, is important to guarantee the production of high quality end products that meet these high quality standards.

Process knowledge can be gathered in two ways; experimentally and model-based (Fig. 1.1). The collection of experimental data is costly and time-consuming, for instance due to the need of a large amount of raw material and/or energy to run the experiments. Validated models can be used to run a large number of scenarios very fast in order to gain process knowledge. Mechanistic models are based on physical laws, and the included parameters have a physical meaning. As such, the development of these models facilitates the process understanding. However, before mechanistic models can be used an extensive validation is necessary, which requires the availability of experimental data. Therefore, the development of reliable robust mechanistic models is
time-consuming and not straightforward. However, in the area of pharmaceutical applications limited work has been performed thus far in order to improve the model-based description of multi-phase systems i.e. the development of mechanistic models. Nevertheless, more research on multi-phase systems would be desirable, since several phases typically interact with each other during the production of pharmaceutical tablets: gas, liquid and solid phases. A development of a mechanistic description of the behaviour of multi-phase systems would be an advantage for the pharmaceutical industry in general, as it would form a good starting point for the development of improved process understanding and, as a consequence, better control of such processes. Another advantage would be the reduced amount of experiments that would need to be performed. The mechanistic description of processes is already well established in some other industries, for example in the chemical industry. A design improvement of the modelled process can also be the consequence of the development and use of a detailed mechanistic model. For example the model can predict the evolution of the process when changing process parameters, lying outside the boundary conditions of the available equipment.

1.2 Thesis Outline

The PhD dissertation is structured in six parts, which are visualised in figure 1.2. Part I of the thesis contains the introductory material which forms the background for the other parts of the thesis. Chapter 2 gives a general literature
1.2. Thesis Outline

Overview. First, the incentives for the development of mechanistic models for pharmaceutical production processes are discussed in more detail, as well as the production routine for tablets and the quality regulation in the pharmaceutical industry. Subsequent sections focus on the mechanistic modelling of the drying behaviour in a fluidized bed, several possibilities to model the drying behaviour of single porous particles, Population Balance Model(ing) (PBM) for the extension towards a population of particles and Computational Fluid Dynamics (CFD) to describe the fluidization behaviour in the drying unit that was the object of study of this PhD dissertation.

Chapter 3 gives a detailed description of the ConsiGma™, a full continuous tableting device, and more specifically about the six-segmented drying unit. Part II presents a model to describe the drying behaviour of single pharmaceutical granules, which is calibrated and validated using self collected experimental data (Chapter 4). The model is analysed using a Global Sensitivity Analysis (GSA) (Chapter 5) and an uncertainty analysis (Chapter 6). Furthermore, the performed model reduction (Chapter 7), which is necessary to later extend the model towards a model describing the drying behaviour of a population of granules (Part III), is discussed in detail.

Part III develops a model that allows to model the behaviour of a population of drying granules. Several solution strategies for this type of model are discussed in detail and compared (Chapter 8). In chapter 9 a GSA is performed on the one-dimensional PBM model. Furthermore, the reconstruction of moments towards a Particle Size Distribution (PSD) is investigated (Chapter 10), which is recommended when using a moment-based solution method for the PBM. Based on the moments it can be difficult to draw conclusions about the system behaviour, but moment-based solution methods are fast to compute and easier to couple with a CFD model. In a last section of this part the extension towards a two-dimensional PBM is established (Chapter 11). This model includes both drying as well as breakage of the granules.

In part IV preliminary results from CFD-simulations are presented investigating the fluidization pattern of the granules in the six-segmented dryer.

Part V shows the real-time on-line experimental data that is collected during operation of the ConsiGma™ and the performed analysis on this data. This includes the use of a mass and energy balance which can be used for monitoring the moisture content of the granules leaving the unit.

Part VI provides the major conclusions of this PhD dissertation as well as the perspectives for further research.
Figure 1.2: Outline of the thesis: continuously logged data' instead of 'continuous logged data'
CHAPTER 2

Literature review & Objectives


2.1 Introduction

This PhD dissertation focuses on the mechanistic modelling of fluidized bed drying processes of wet granules. The main incentive to undertake the research work described in this thesis is the current general trend towards development of mechanistic models of unit operations in pharmaceutical production, often as part of ongoing efforts in defining the Design Space of a process. Fluidized bed drying is an important unit operation in the production process of solid dosage forms. Whereas modelling of reactive systems with homogeneous catalysis can be relatively straightforward, the development of a mechanistic model of multi-phase systems such as a fluidized bed drying process is still a scientific challenge. In a first part of this chapter, the focus is given to the pharmaceutical industry and the importance of mechanistic modelling for traditionally applied and new (continuous) pharmaceutical production processes. The incentives to model pharmaceutical production processes are listed, hereby considering regulatory aspects and challenges.

In a second part of this chapter, the different steps during the production of pharmaceutical tablets are briefly discussed, including the available equipment for the continuous production of tablets.

A third part focuses on fluidized bed drying systems. Information is given about fluidization, the fluidized bed drying system and the current difficulties to optimise the operation of these dryers. The basic concepts and advantages
of mechanistic modelling of a process are discussed. The section ends by presenting the conceptual structure of a model of a fluidized bed drying process. In a next part, the different steps in the modelling approach are discussed. The available models describing the drying of porous materials are reviewed: the continuum approach, pore network modelling and variants of these models using a crust formation approach. A subsequent section deals with the modelling of processes for a population of particulate entities, namely Population Balance Model(ling) (PBM).

The use of either a one or a higher dimensional PBM-model is discussed. As fluidization is important for the local ambient conditions, a tool to describe the flow of fluid, namely Computational Fluid Dynamics (CFD), is introduced. Here a section about turbulence modelling is included as well as two approaches to calculate the flow: the Eulerian-Lagrangian and the Eulerian-Eulerian approach. Obviously, the focus is on the flow of particles in gas. Furthermore, the coupling of PBM and CFD-models is highlighted. Where relevant, a short overview about validation methods is included in the different sections.

Since the pharmaceutical industry is currently investigating how to shift from traditional batch processing towards continuous production processes, the advantages and opportunities of this new approach (w.r.t. the shift from batch to continuous and hence the necessity for modelling) to pharmaceutical production are provided as well.

### 2.2 Incentives for developing mechanistic models for pharmaceutical production processes

#### 2.2.1 Advantages of mechanistic process modelling

Mechanistic process models can be used in two ways: (1) to increase the fundamental scientific understanding about a process and (2) to optimise a process that is understood up to a certain level of detail, for example by model-based design of improved control strategies. The process knowledge about the most important input-output relations is coded in equations, and can then later on be helpful in detecting input variables which have a significant influence on the process. Most important, indeed, is that such a mechanistic model is actively used for in-silico testing of a set of potential process operating strategies, e.g. by comparing different control strategies in a series of dynamic simulations, without the need of disturbing the actual full-scale process operation \cite{Gernaey2012}. When using this information to establish control loops with sufficient control authority, the process can subsequently be controlled based on in-process measurements and real-time adjustment of input variables in order to stay inside the Design Space (Section 2.2.2).
A clear advantage of using models is their solution speed, allowing to compute many different scenarios as opposed to performing many expensive experiments (i.e. scenario analysis). This usually allows process development and optimization with a significantly reduced number of experiments to be performed (i.e. Optimal Experimental Design (OED)). Indeed, a range of values can be selected for different input variables and adopted in the model. Of course, it should be clear that a limited number of experiments will always be required for checking the model performance with respect to the real process (i.e. model validation). The usefulness of the model will depend on the reliability of the model, i.e. reliable mathematical models are necessary to allow for trustworthy conclusions or decisions based on them.

An important aspect in this respect, often overlooked in practice, is the thorough validation of the model, i.e. an evaluation of the performance of the model to ensure that the model is a sufficiently accurate representation of the real process. Without validation it is impossible and dangerous to use the model for improving, understanding and explaining a process and its performance. A model should include all process elements that are considered to be important for the purpose of the model (model objective) (Section 2.4.2). Furthermore, it needs to be able to describe experimental data of the real system. Lack of these characteristics provides a lack of confidence in the model [Curtis et al., 1992].

2.2.2 Quality regulation and its impact on the pharmaceutical industry

The pharmaceutical industry is strictly regulated. [Good Manufacturing Practices (GMP)] are defined to ensure that pharmaceutical products are consistently produced according to the quality standards appropriate to their intended use. The main purpose of the GMP rules is to ensure that each product is produced consistently, safely, reliably and with high quality [Gui, 2002]. Before pharmaceuticals can be released on the market, a product license from the relevant regulatory body is obligatory. The latter is time consuming and expensive to obtain, but is required for distribution of the product [Plumb, 2005].

Traditionally, regulations had a serious impact on the way pharmaceuticals are produced. Indeed, once a process was licensed, it was considered to be nearly impossible to change something in the way of processing [Plumb, 2005]. The intention of the Food and Drug Administration (FDA) with its publication of the PAT guidance is to overcome this situation of unchangeable, unflexible traditional 'frozen' production processes. Indeed, despite the fact that it is known that many processes could operate in a better way (e.g. more cost-effective), changes to the production process have not been implemented due
to the considerable amount of work that was related to obtaining an updated manufacturing license. The scope of PAT is to support innovation and efficiency in pharmaceutical development, manufacturing and quality assurance. As mentioned in the PAT guidance - A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance: *Quality cannot be tested into products; it should be built-in or should be by design* [FDA 2010].

A risk and science-based approach has to be applied to pharmaceuticals in a quality system. The ICH guidelines on Pharmaceutical Development (Q8), Quality Risk Management (Q9) and Pharmaceutical Quality System (Q10) were drafted. The ICH Quality vision statement is 'Develop a harmonised pharmaceutical quality system applicable across the life cycle of the product emphasizing an integrated approach to quality risk management and science'. *Quality By Design (QbD)* is an important concept and has been defined as 'a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management' [ICH 2010].

A central PAT concept is the Design Space. The process Design Space is defined as: 'The multidimensional combination and interaction of input variables i.e. material attributes and process parameters that have been demonstrated to provide assurance of quality. Working within the Design Space is not considered as a change. Movement out of the Design Space is considered to be a change and would normally initiate a regulatory post approval change process. The Design Space is proposed by the applicant and is subject to regulatory assessment and approval (ICH Q8).’ The pharmaceutical industry now has to demonstrate that the product is safe within the Design Space. Once such a Design Space has been approved, it is allowed to further optimise the process as long as one guarantees that the production process stays within the Design Space. However, process and product knowledge form the basis for the definition of the Design Space. Advanced mechanistic models are by far the most powerful means to gain this missing process knowledge, and to actively optimise processes. Therefore, a thorough overview of models and how they can assist in achieving the above is crucial and is part of the purpose of this thesis.

A final aim of the PAT and QbD concept is Real-Time Release Testing, meaning 'the ability to evaluate and ensure the quality of in-process and/or final product specifications based on process data, which typically includes a valid combination of measured material attributes and process controls' [ICH 2010 Vervaet and Remon 2005].

Also here, models can be used to support the development of a Design Space for the process. In other words, process model development is completely in line with the PAT guidance. The model summarizes available process knowledge.
2.2. Incentives for developing mechanistic models

which would help to understand the influence of input variables on the process and hence on the quality of the product.

2.2.3 Towards continuous production in pharmaceutical industry

Batch versus continuous production

In several industries (e.g. bulk chemical industry and food industry) continuous manufacturing is already well-established. In contrast, the pharmaceutical industry still heavily relies on batch processing.

Batch processes have certain advantages [Leuenberger, 2001b]:

- In terms of **quality assurance**, i.e. a batch is well-defined and can simply be accepted or rejected based on a quality assessment. In the continuous approach the quality of the product can be monitored during the process. Hence, once process knowledge is developed, the continuous approach will be equally able to guarantee product quality and on the long run be more effective due to its higher flexibility and, hence, reduced losses.

- The **flexibility** in the equipment. Indeed, in batch processing a set of different operations can be performed in almost any sequence of the available equipment in order to produce the pharmaceutical product. For instance, after the drying of wet granules, a milling or a post-blending step can be performed (Fig. 2.1). Establishing a suitable sequence of unit process operations is considerably more complicated in a continuous process. However, improved process knowledge and process control of continuous processes will help to overcome such drawbacks and, hence, eliminate this advantage of batch processing.

- The **expertise** that has been compiled, as batch processes have been optimised for decades. A similar learning curve is needed for continuous operation. It is expected that the batch expertise will be of value for this and, hence, will most likely result in a much shorter learning curve.

Some of the disadvantages of batch production processes can be tackled by switching to continuous production processes. Advantages of continuous processing are [Plumb, 2005] [Leuenberger, 2001b]:

- **Easier to understand.** The problems are three-dimensional instead of four-dimensional, at least at steady state, because the time-variable can be eliminated.

- **Increasing the production rate** can be achieved by **numbering up** (scaling out) instead of scaling up, which would reduce the time-to-market. During the development of a pharmaceutical product, the amount
of product needed for clinical trials is relatively low. Afterwards scale-up is of major importance in order to design production-scale equipment with larger volume, and will affect the operational conditions to achieve a similar system behaviour and performance. This step is strictly speaking no longer required when operating in continuous mode.

- **Connection with naturally (semi-)continuous processes** such as spray drying or tableting is more straightforward. To date, these process steps need to be started up when a batch of for instance dried granules arrives and shut down when awaiting the next product batch, making this very inefficient and introducing additional variability in the product properties.

- **Improving the quality.** In a batch the transfer of mass, heat and momentum is not homogeneous, which leads to a lower product quality [Leuenberger 2001a]. A lot of process properties will be locally varying, leading to a wide distribution in the properties of the output. Continuous processes can minimize these effects (i.e. less variance), because mass and heat transfer is more efficient as the surface to volume ratio is higher as a consequence of reduced equipment size. Last but not least, continuous processes are typically easier to control compared to batch processes, as a consequence of the smaller scale.

- **Reduced problems due to increased market share.** A need for a higher capacity in batch processes gives rise to a large capital investment, whereas in a continuous operation this is only necessary if no spare capacity is available. If spare capacity exists, the output can simply be expanded by means of a longer production time. The ability to vary production rates reduces startup and shutdown of process chains.

- **Reduced generation of waste** through in-line measurements.

- **Increased safety** due to the fact that a continuous process will operate at a much smaller scale compared to a batch process (less material is processed at the same time in the continuous process) and less start-up and shut down time is needed.

Evaluating the advantages and the disadvantages of both ways of operating pharmaceutical processes, and given the fact that continuous processes still have a large marginal improvement potential, it can be concluded that the continuous way of operation is the way to go for the industry. However, as stated before the shift towards continuous processes largely depends on improved process knowledge. This emphasises the necessity for the development
2.2. Incentives for developing mechanistic models

of mechanistic models. A validated model will be essential to develop a trustworthy system to control quality based on on-line measurements and real-time adjustment of process parameters. A model can help to better understand the process and can be used to develop and test algorithms to control the process. Next to the fact that a model is necessary to take full advantage of a continuous process, the development of a model can be easier for a continuous process. As mentioned earlier, a batch process is four-dimensional. Also, the ambient conditions are often more homogeneous for a continuous process compared to batch processes, often allowing reduction of the full model to a model without spatial heterogeneity.

State of the art and required needs for the pharmaceutical industry

Conventional pharmaceutical manufacturing is generally accomplished using batch processing with off-line time-consuming and less efficient laboratory testing conducted on randomly collected samples to evaluate quality. Hence, limited relevant information is mainly obtained after the batch process has been finished, making process control difficult and provoking unnecessary batch losses. Furthermore, the batch processes themselves are often poorly understood inefficient black-boxes. In this respect, availability of a mechanistic model would increase the understanding of the fundamental scientific phenomena and processes. The advantages of continuous production increase when a model is available to support the development of real-time process control. The pharmaceutical industry has a continuous focus on research and development of new drugs. It is in the interest of the pharmaceutical industry to reduce the development time for new drug products as much as possible. In this way the product can be brought quickly to the market and the profit is maximized. Indeed, patent-life is finite and rather short, and the market share in most cases decreases significantly when a patent expires due to competition from generic drug product manufacturers [Plumb, 2005]. This is a strong driver for investigating new systems. However, the belief that continuous production systems are only feasible for large volume productions and production sites that systematically produce the same product hamper the development of continuous production processes. Further reasons for not moving towards continuous operation are the difficulties to meet the high product quality standards (Section 2.2.2). Finally, also regulatory authorities have delayed the introduction through their conservatism and negativism towards continuous processes [Vervaet and Remon, 2005]. The 'Real-Time Release' concept is an important driver for the increased interest of the pharmaceutical industry in continuous production processes, since the benefits of 'real-time release' are highest when applied to a continuous process. However, to my opinion such continuous production methods need to be implemented already in the development phase of
the drug production process [ICH, 2010] [Vervaat and Remon, 2005]. From the above it is clear that improved process understanding is really the key to launch continuous production in the pharmaceutical industry and convince those who are still hesitant. The switch to continuous production processes with on-line control requires, next to a validated model, reliable sensors and adapted equipment. The eventual goal should be to build a set of validated models for the whole continuous line.

2.3 Production of pharmaceutical tablets

Industrial-scale pharmaceutical production can be subdivided in a number of stages. A pharmaceutical product typically consists of both Active Pharmaceutical Ingredients (APIs) and excipients. An API is either produced through chemical synthesis, through biological processing, or a combination of both. The excipients are produced separately, often at a different production site or by a different company. Examples of excipients are water, lactose, starch, sugar, coloring agents, etc. Excipients have no therapeutic effect, but are necessary for the manufacturing of the drug product.

Subsequently, the API and the excipients are formulated into drug products, which are in many cases tablets, but could also be capsules, aerosols, injectables, etc. The last step in the production sequence is the packaging, which can be bottles, blister packs, etc. [Plumb, 2005].

The focus of this thesis will be on tablets as pharmaceutical solid dosage end-product form. Their classical manufacturing process consists of several consecutive steps (Fig. 2.1). The starting point is the blending of the individual components, i.e. the APIs and the excipients. After blending, granulation is performed to agglomerate particles into granules. The purpose of this step is to improve the powder flow properties, to reduce demixing, to reduce dust formation and to promote the compressibility of the powder mix. Several granulation procedures exist (e.g. wet granulation, dry granulation) [Muzzio et al., 2002]. The choice of the technique for drying wet granules might influence the properties of the granules and, hence, the further downstream processing. Convection, conduction or vacuum drying are the means to supply thermal energy needed for the drying process. Fluidized bed drying, an example of a convective drying method, is the most commonly used method in production-scale pharmaceutical manufacturing [Hegedus and Pintye-Hódi, 2007]. Fluidized bed drying has been compared with microwave-vacuum drying processes. Using a vacuum chamber the resulting dried granules had a lower level of porosity, and higher bulk and tapped densities. Another aspect is the spherical form that is more retained when using a vacuum chamber. Furthermore, the mean particle size was larger for granules dried in the vacuum chamber. The powder frac-
2.3. Production of pharmaceutical tablets

tion after drying was comparable for both vacuum and fluidized bed drying. An advantage of fluidized bed drying is the shorter drying time [Hegedus and Pintye-Hódi, 2007].

This PhD dissertation focuses on a first isolated unit process during continuous

Figure 2.1: Scheme of typical processing of pharmaceutical products during the formulation of tablets

tableting, i.e. the fluidized bed dryer, and more specifically on the development

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of a detailed mechanistic model.

To date, the equipment to produce tablets in continuous mode is limited. The ConsiGma\textsuperscript{TM} continuous from-powder-to-tablet manufacturing line of Collette\textsuperscript{TM} (GEA Pharma Systems) enables the production of tablets from powders in 20 minutes. It consists of the ConsiGma\textsuperscript{TM} high shear granulator and fluidized bed dryer, combined with the GEA Courtoy MODUL P rotary tablet press \cite{GEA, 2010}. The CWG line (Lödige Process Technology) is a continuous wet granulation line and is also a complete system from raw material dosing till tableting \cite{lod, 2010}.

### 2.4 Fluidized bed drying process

#### 2.4.1 Introduction and related problems

Fluidized bed dryers are widely used in industrial applications for the drying of wet solid particles. Products such as maize \cite{Mourad et al., 1995}, coconut \cite{Niammay and Devahastin, 2005}, baker’s yeast \cite{Türker et al., 2006}, beans \cite{Nitz and Taranlo, 2007}, black tea \cite{Temple and van Boxtel, 1999} are successfully dried in a fluidized bed. In industrial processes a high drying rate is desirable, in other words a high rate of heat and mass transfer. Fluidized beds have the advantage of achieving a large contact area between the solids and the gas, a high mixing degree of the solids and high transfer coefficients of heat and moisture between solids and gas. All these factors shorten the drying time without the disadvantage of damaging the materials (e.g. heat sensitive products). However, the process also has some downsides: scale-up problems, poor fluidization, non-uniform product quality. These are in fact mainly caused by poor understanding of the process. Due to the lack of reliable mathematical models for fluidized bed drying processes, process optimization and scale-up is typically performed empirically based on pilot-plant data. Prediction of the performance of industrial fluidized bed dryers is impossible without such data \cite{Daud, 2008}.

Several materials are nowadays mostly produced in batch mode. However drying is a very energy and time consuming process. Significant benefits could be achieved by improving the drying process, for example through the implementation of a continuous drying process \cite{Plumb, 2005}.

The fluidization process, the process whereby the granular material behaves in a fluid-like state, in itself is not so trivial. Solid particles can be divided into several fluidization classes, the so-called Geldart classes \cite{Geldart, 1973}. Particles are classified based on (1) the density difference with the gas phase and (2) their mean particle size (Fig. 2.2). Each group has distinguishable characteristics, and displays a certain fluidization pattern (Fig. 2.3) \cite{Kunii and}.
Levenspiel [1991] Geldart, 1973. Powders, belonging to group A will display a dense phase expansion after minimum fluidization, before bubbling starts, whereas particles of group B start bubbling at minimum fluidization. Group C particles are even more difficult to fluidize. Finally, particles in group D, characterized by large size and/or density, can show a spouted bed behaviour. A spouted bed is a fluidized bed where the air forms a single channel through which some particles flow, whereas particles fall down again once they are outside of this channel. In practice, it is more difficult to distinguish between these different groups. Next to the criteria of Geldart, additional criteria exist to classify fluidized beds. Some are based on interparticle forces in the vicinity of bubbles, leading to a dimensionless Froude number, or combinations of this number with the Reynolds number. Others consider the stability or growth of disturbances, the maximum size of the bubble to be stable or the occurrence of shock waves for defining criteria [Geldart, 1973].

Drying of particles makes it even more difficult to characterize the fluidization behaviour of powders since the drying itself will influence the fluidization behaviour. During drying the moisture content drops, which improves the fluidization. Using the classification of Geldart, it is known that particles can shift from a Geldart C type of powder to Geldart B powders during drying. The high moisture content at the start is responsible for the larger forces between the particles, therefore the Hausner ratio is higher. During drying the forces between the particles decreases (the packing becomes looser) and the fluidization is improved. Parameters such as the full support velocity, full support bed voidage and Hausner ratio have been used to determine the powder behaviour [Wormsbecker and Pugsley, 2008].

Granulation is the process whereby smaller particles are converted into larger
agglomerates. This size enlargement process occurs often in the pharmaceutical industry to agglomerate powders to granules. During this process, granules of different sizes are produced. A certain PSD of the granules is desired for the subsequent tableting step. The influence of the PSD on the fluidization pattern is discussed in the literature, and it is concluded that granules with a wider PSD are more inclined to show a spouted bed behaviour [Tanfara et al., 2002].

### 2.4.2 Modelling of fluidized bed drying processes

**Objective of mechanistic models**

Every model development exercise should start with formulating the goal or objective of the model (upper part of fig. 2.4). One should list the requirements and questions one wants to answer. In the case of the drying process under study, the model will typically help to understand the process in more detail. Changing input variables and parameters, e.g. in the frame of a sensitivity analysis, helps to gain information about the dynamics of the process. Moreover, such simulations can also be helpful to find out which input variables are important to control in order to produce granules with the required quality. Furthermore, a model can also be helpful to develop and tune control systems. Using the knowledge about the process incorporated in the model will indeed be important for the selection of input variables that can be used to adapt the process in real-time, resulting in enhanced product quality and/or an optimised
2.4. Fluidized bed drying process

energy consumption.
The development of a mechanistic model is typically an iterative process, where several consecutive steps need to be repeated in an iterative way until the proposed mechanistic model satisfies the requirements of the model developer (upper part of fig. 2.4). Experimental data are important to recognize physical mechanisms of the process, which are translated into mathematical equations (step 1 in fig. 2.4). Following a number of experiments, the modeler can use the available experimental data in order to estimate model parameters (step 2 in fig. 2.4). Empirical parameters can show a dependency on one or more input variables and a submodel can be developed. Several relations between the parameter and the input variables can be investigated. The goodness-of-fit of such a relation can be investigated in more detail by making use of model selection criteria. Subsequently a model validation is performed where model predictions and experimental data are compared [Sargent, 2005] [Kleijnen, 1995]. Several options exist for validation: approaches with an independent dataset and approaches which are not based on an independent dataset can be distinguished. The simulated data and real data can be compared using simple tests as Graphical, Schruben-Turing and t-tests. The residuals can be analysed: an appropriate model and successful calibration would generate residuals, which behave in the same manner as measurement errors. Possible residual analysis are autocorrelation assessment methods [Fielding and Bell, 1997] or run tests [Dochain and Vanrolleghem, 2001]. A good coincidence between simulated and experimental data in the validation step allows to conclude that one can use the model for predictive simulations. In the other case, one can either decide to change the model structure and re-use the available data to check how the updated model fits to the data, or one can opt for collecting additional experimental data, and then repeat the parameter estimation for the original model structure in order to get a better idea on whether or not this model can be fitted to the data.

Once a model is validated and judged as sufficient for the process under study the model can be used to obtain knowledge about the process by performing a scenario analysis, a GSA an uncertainty analysis, etc. Moreover, the model can be helpful for the development of control systems.

Structure of fluidized bed drying models

When modelling the fluidized bed drying process of wet granules, two distinct processes need to be accounted for. First, granules are dried, a process which is significantly influenced by the local conditions of the gas (velocity, vapour pressure). Secondly, the granules are fluidized in the dryer, thereby exhibiting a certain fluidization pattern which depends on the gas flow rate and the particle density. Depending on the fluidization pattern, particles will follow a
certain trajectory in the dryer. The gas that is flowing through the body of the dryer will exhibit dynamic varying properties when moving from inlet to outlet. This is caused by water evaporating from the granules inducing the temperature of the gas to drop and the moisture content to increase. Hence, the drying behaviour of particles in different locations of the dryer will be different. Both processes, the drying process and the fluidization, are obviously
2.5 Modelling the drying of porous material

strongly interrelated.

A thermodynamic model for a fluidized bed drying process has been developed in order to optimise the input and output conditions. For this study energy and exergy models were used [Syahrul et al., 2003]. Operating conditions, such as gas velocity, inlet gas temperature, outlet gas temperature, feed temperature influence the quality of the dried product. Drying processes require significant amounts of energy, and optimizing process operation, for example on the basis of model simulations, can reduce the process operating costs significantly. An exergy and energy analysis can help to determine the influence of thermodynamic and hydrodynamic parameters on process effectiveness in order to improve the drying process [Syahrul et al., 2003].

A batch fluidized bed dryer for fine powders has been modelled in order to predict the bed temperature, the humidity of the outlet gas, the moisture content of the solid particles, and heat and mass transfer in an inert medium fluidized bed. Model predictions agreed well with the experimental data [Lee and Kim, 1999].

2.5 Modelling the drying of porous material

The drying behaviour of porous material can be described with a model. In this section an overview of such models is given.

2.5.1 Introduction

The development of models for the description of drying kinetics of porous material has received a lot of attention in the literature. Drying of porous media is commonly used in several industries, for example the food industry [Zhang et al., 2006], the pharmaceutical industry [Chaplin et al., 2004], the paper industry [Kudra et al., 2002], and the chemical industry [Gawrzynski et al., 1999]. The process is studied at different scales, ranging from the pore scale to the dryer scale. Modelling at the scale of the pore can be the starting point for a detailed model. Performing a sensitivity analysis on a detailed model can give insight in the most influential parameters. This information can then be used in a subsequent model reduction step, where the behaviour is approximated by a simpler model, leading to a model that can be implemented to describe the process on a larger scale with an acceptable computational cost.

Hence, the development of a model at the dryer scale could be seen as a scale-up problem, meaning that the application field of the model is extended [Prat, 2002]. In this case, the interesting scale is the product scale, being one single granule. When the dried product is an intermediate, the ultimate goal is optimizing the quality of the end-product.
Several aspects have been taken into account when describing drying processes at the pore scale. There is a difference in the way water is fixed in the product, in the porosity of the product, in the size of the pore, etc. [Datta, 2007]. Hygroscopic materials will fix a large amount of water by adsorption, whereas non-hygroscopic porous media will fix water only by capillarity. Next to capillarity, gravity and viscous forces are also responsible for liquid transport, whereas diffusion is the important mechanism in the gas phase [Prat, 2002]. During drying, both heat and mass transfer have to be taken into account. Some studies do not account for temperature gradients, which is a valid assumption in the case of slow drying. However, a more detailed model, which incorporates the transport of energy, and thus also temperature gradients, will be more accurate [Surasani et al., 2008]. Distinct approaches for the modelling of the drying of porous media can be found in literature: the continuum approach, pore network models and variants of crust formation. These will be briefly discussed in the next sections.

2.5.2 The continuum approach

This first approach was proposed by Whitaker and considers the porous medium as a fictitious macroscopic continuum [Whitaker, 1977]. The effects of the different physical phenomena (e.g. capillary effects) are lumped into phenomenological coefficients, implying that the detailed effects of the pore micro-structure are ignored. The state variables (pressure, volume, temperature of the solid media) are spatially averaged and are dynamic with respect to time and position. Gradients in quantities and effective parameters are responsible for transport. These effective parameters have to be determined by experiments [Whitaker, 1977] [Quintard and Whitaker, 1993] [Prat, 2002]. By means of volume averaging techniques or homogenization methods, the continuum model is derived from the drying process at the pore level. This means that the macroscopic properties are predicted based on the microscopic description of the porous, heterogeneous medium. Since the medium is taken as a continuum, the system should be large compared to the pores. In many situations (due to the lack of length-scale separation, i.e. the difference in length between the pores and the medium) this is not the case, and it is assumed that the approach is valid. However, in these situations the discrete approach should in fact give better results [Laurindo and Prat, 1998]. The homogenization method is frequently described in the literature [Sanchez-Palencia et al., 1987] [Hornung, 1997] [Sanchez-Palencia, 1980]. Most work has been done in the area of volume averaging. In each individual macroscopic averaging volume a solid, free liquid and gas exists. In this averaging volume model parameters are measurable [Ferguson and Turner, 1996]. Variables (e.g. temperature) are averaged over the volume, the Representative
2.5. Modelling the drying of porous material

**Elementary Volume (REV).** This REV should be large enough to define averaged quantities. On the other hand, variations of the averaged quantities should be avoided by limiting the size due to macroscopic gradients and non-equilibrium equations at the microscopic level [Perré and Turner, 1996]. Equations for the conservation of liquid, air and energy are supplemented with boundary and initial conditions [Perré and Turner, 1999]. The resulting non-linear Partial Differential Equations (PDEs) have no analytical solutions and require a numerical solution technique. The equations can be solved using the control volume finite element technique (Fig. 2.5), otherwise known as the vertex centered control volume method, which is a combination of the finite element method and the cell-centered control volume method [Ferguson and Turner, 1996].

The volume averaging method has been developed in two and three dimensions. Several models are available for the study of the drying process, and have been applied to materials such as wood [Perré and Turner, 1996] [Couture et al., 1995] and brick [Boukadda and Nasrallah, 1995]. The two-dimensional models provide a good understanding of the drying process, but certain physical phenomena (e.g. drying stresses) have to be investigated in three dimensions. The TransPore code is extended to a three-dimensional version [Perré and Turner, 1999]. The development of a three-dimensional version is motivated by two reasons. First, drying stresses that develop in wood during drying depend strongly on the board width, while the longitudinal direction is important to represent transport phenomena. Second, the three-dimensional model is necessary to simulate comprehensive radio frequency or microwave drying behaviour. When moving from two to three dimensions, the computational burden to solve the equations increases significantly [Perré and Turner, 1999]. The continuum approach can be solved by efficient numerical techniques at a large scale in comparison with the pore scale, which is a great advantage.

![Figure 2.5: Construction of a control volume from the triangular finite element mesh after Ferguson and Turner 1996](image-url)
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When the micro and macro scale cannot be separated, this is a problem where a discrete approach can provide a solution [Perré and Turner 1996]. Another difficulty is the determination of the effective parameters, such as vapour diffusivity, permeability, thermal conductivity and capillary pressure. These need to be obtained through dedicated, time-consuming experiments. The continuum approach is not able to easily take structural features of the medium into account. To study the influence of the size of pores, pore network modelling will give more satisfactory results [Perré and Turner 1996] [Metzger et al. 2008].

2.5.3 Pore network modelling

Pore network models represent the porous structure as a network of pores and throats. The different pores are connected by the throats, forming an irregular network, in which each pore receives a coordination, i.e. the number of neighbouring connected pores (Fig. 2.6). In most cases the irregular network is substituted by a regular one with a mean coordination in order to simplify the model. In the network, the width of the throats is not taken uniformly, but varies according to a distribution function. A bottleneck is the strong assumption about the geometry of the pores [Prat, 1993]. These models can be used to simulate the drying process at the pore level. The continuum approach fails when the pores are large compared to the system. Moreover, an appealing approach for the computation of the effective properties at the scale of a REV is necessary in the continuum approach. Furthermore it is useful to investigate the influence of the micro-structure on these effective transport parameters [Metzger et al., 2007]. Pore network models can offer the advantage of taking the features of the micro-structure into account [Prat, 2002]. Drying of porous material takes place at pore scale: motion of the gas-liquid menisci in the pores, diffusion, viscous flow, capillarity, liquid flow. The role of large pores and their distribution can be examined.

The development of these models in drying processes is fairly recent [Daian and Saliba 1991] [Nowicki et al., 1992]. A pore network model was used to study the patterns that are formed during drying and their influence on the drying rate [Prat, 2002].

Pore network models have been described in two [Yiotis et al., 2001] and three dimensions [Le Bray and Prat, 1999]. Gravity can be included by defining an appropriate invasion throat potential, which depends on the width of the throat, the relative position in the gravity field and the Bond number (the ratio between gravity and capillary forces) [Prat, 1993]. The pore network model needs to be coupled with mass transfer at the open surfaces. Traditionally, isothermal conditions are assumed when doing this, but one might want to include thermal effects. Indeed, temperature has an effect on several aspects of
2.5. Modelling the drying of porous material

Figure 2.6: Pore network with boundary layer and control volume after Surasani et al. [2009]

the liquid, e.g. viscosity, surface tension, and vapour diffusion coefficient, among others. Moreover, the temperature gradient influences the drying process and distribution of water during drying. The combination of heat and mass flow has been examined [Plourde and Prat 2003] [Huinink et al., 2002].

This approach is very detailed and provides more rigour and accuracy. However, the downside is the CPU time required to solve the drying problem. It is therefore only used if this level of accuracy is needed to meet the objective of the modelling exercise. It is also useful for verifying a continuum approach model. The parameters of the continuum model can be assessed for a certain pore structure using a pore network model.

2.5.4 Modelling of drying processes for single particles

In this approach, the internal structure of the particle is ignored and the porous medium is treated as a whole. The continuum approach and pore network modelling (Section 2.5.2 and 2.5.3) are described in the literature for the drying of structures with a large volume compared to pharmaceutical granules (e.g. pieces
Chapter 2. Literature review & Objectives

of 1 m x 3 cm x 3 cm [Perré and Turner, 1999] versus particles of 0.272 µm as diameter for a pharmaceutical product [Mezhericher et al., 2008b]). During drying the evaporation of liquid occurs and a diffusion equation can be used to describe the diffusion of water from the entire particle. In literature the description of theoretical models for the drying of single droplets is subdivided in droplets containing dissolved and/or insoluble solids. Both approaches are of interest for pharmaceutical applications since pharmaceutical granules can both contain soluble and insoluble solids.

Models for soluble solids

A drying model for a single droplet with dissolved solids was developed by several researchers [Dolinsky, 2001][Kuts et al., 1996][Sano and Keey, 1982][Chen and Lin, 2005]. The temperature gradients in the wet particle were either ignored or only taken into account for the crust (the region of the particle that is already dry). In the latter case, a linear temperature distribution in the crust is mostly assumed. The drying rate of the particles was calculated assuming a constant change of total particle mass [Dolinsky, 2001]. In contrast, an energy conservation equation was used to describe the temperature variations. For the boundary condition of the PDE, the assumption was made that the temperature of the wet core-crust interface equals the wet-bulb temperature of the drying air. In this model the change of the moisture content was either linear or exponential in time [Kuts et al., 1996]. Equations for the evaporation from a single spherical droplet that contains colloidal material were also derived. The authors assumed a uniform droplet temperature, and that water is diffusing through the solid and evaporates at the surface. A diffusion equation with an effective diffusivity was used to describe the water diffusion. The latter is different from the molecular diffusivity and is difficult to measure. The effective and the molecular diffusivity are related through the tortuosity and the particle porosity [Eaton et al., 1995]. In this model, no explicit crust formation is considered. Due to crust formation, a resistance for mass transport builds up, reducing the effective diffusion. Experimental data of droplets containing skimmed milk were compared with the computed results. A good agreement was found. However, comparisons between their model predictions and experimental data, provided by other scientists, showed a distinct discrepancy [Mezhericher et al., 2007][Sano and Keey, 1982]. The drying behaviour was described by two different models. They first modelled the drying behaviour as a competition between evaporation and condensation [Reaction Engineering Approach (REA)-model]. In the other approach, the Characteristic Drying Rate Curve (CDRC) model, the process was divided in different drying stages. Both models displayed a good agreement with the experimental data, but the REA model performed globally better [Chen and Lin, 2005].
Models for insoluble solids

The kinetics of models for particles with insoluble solids are in several cases based on average moisture content and the temperature distribution in the wet core is ignored. The temperature distribution in the crust region was assumed to be linear [Cheong et al., 1986]. In this model the core temperature is not linked to the wet-bulb air temperature. Ignoring the sensible heating of the crust significantly simplified the model. Simulations compared well with experimental data. These data were collected using single drops of slurry, which were suspended on the tip of a flexible glass cantilever inserted in a vertical wind tunnel. A thermocouple was formed with a nickel wire to measure the temperature at the core of the drop, where the deflection of the beam gave the loss in weight during drying [Cheong et al., 1986]. The evaporation rate was determined by multiplying the vapour diffusion mass flow rate through one crust pore with the void fraction of the crust [Abuaf and Staub, 1986]. This evaporation rate is also used by Elperin and Krasovitov [Elperin and Krasovitov, 1995]. A more simple equation of the evaporation rate of Abuaf and Staub was derived, that can be used for relatively low temperatures of the drying air under atmospheric pressure [Borde and Zlotniksky, 1991].

Models for insoluble and soluble solids

Models were developed for droplets containing dissolved and insoluble solids [Nešić, 1989] [Nešić and Vodnik, 1991]. Nesić’s approach is based on the formation of a crust. The distribution of the temperature for the whole droplet is neglected in both models. A diffusion equation was used to describe the diffusion of water vapour through the crust, using a diffusivity which depends on the water concentration. Several experiments were executed with droplets of water, colloidal silica, sodium sulphate and skimmed milk. The weight and temperature of the individual droplets was measured during the evaporation. Comparison with simulations showed good agreement for droplets containing colloidal silica and sodium sulphate. However, for skimmed milk a great discrepancy was found [Nešić, 1989] [Nešić and Vodnik, 1991].

A model based on average moisture content was developed [Farid, 2003]. A PDE of energy conservation for the crust and the wet core region was solved (Fig. 2.7). It was assumed that the temperature over the wet core-crust interface is constant and equal to that of the wet bulb, similar to Kuts et al. [1996]. The model neglected, however, the resistance of mass transfer through the crust. The porosity of the crust has to be accounted for in order to obtain accurate calculation of the particle drying rate. A model was developed taking into account the permeability of the crust. The evaporation of liquid from the wet core is due to heat transfer from the drying air. The vapour then moves
through the pores towards the particle surface \cite{Mezhericher2007}. The vapour mass transfer rate is calculated with the equation of \cite{Abuaf1986}. Simulations showed good agreement with experimental data. Under different conditions the temperature and the mass were evaluated for the drying of colloidal silica. In the case of skimmed milk droplets the discrepancy did not exceed 5% for temperature prediction. The mass predictions had a relative difference below 4% \cite{Mezhericher2007}. A modified equation was utilized for the calculation of the vapour mass transfer rate \cite{Mezhericher2008a} for experiments exhibiting a pressure difference between the crust and the ambient environment. In this case, the mass transfer rate through the pores is the sum of the diffusion and the forced flow rate due to the pressure gradient. In a further development of the drying model, full unsteady heat and mass transfer were considered. The pores were considered as cylindrical bodies, where conservation laws for mass, energy and momentum were applied \cite{Mezhericher2008b}.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{drying_model.png}
\caption{Drying of a wet particle - crust formation after \cite{Mezhericher2007}}
\end{figure}

### 2.5.5 Validation of the drying model

The developed drying model for one single particle has to be validated by experimental data. In other words, key variables (moisture content, gas temperature, temperature of particles, etc.) need to be measured and compared with model predictions. If the model does a good job (using e.g. evaluation of the Mean Bias Error (MBE) or Root Mean Squared Error (RMSE)), it can be regarded as validated. If not, one has to re-iterate the model structure and figure out why the predictions are poor. Dependent on the model structure it can be necessary to measure the temperature or the moisture content of
2.6. Population Balance Modelling (PBM)

the particles and/or the gas flow at different locations. In this section some methods to measure these key variables during drying are summarized. The drying behaviour of single apricots, hanging in the flow direction of hot air in a drying chamber was described. Drying data were collected through measuring the mass and inner temperature of the apricots. Apricots were hanging in an air stream. With an Fe-constantan thermocouple of 1.2 mm diameter, inserted in the apricot, the inner temperature was continuously monitored. The mass of the apricots was measured using a balance with an accuracy of $\pm 0.001 \text{g}$. The initial and final moisture content were determined with a Mettler infrared moisture analyser at $80^\circ \text{C}$ [Toğrul and Pehlivân, 2003].

A steam drying process of a single porous ceramic sphere (10 mm diameter) was modelled. The drying process was investigated with a thermo balance in order to accurately register the sample weight and the surrounding temperature. The temperature of the inlet steam and the weight of the sample were monitored every 10 s. A gravimetric method was used to determine the final moisture content. In some experiments the temperature at the center of the sample was measured using a thermocouple. In these cases it was impossible to register the weight of the samples [Hager et al., 1997].

The glass-filament method (Fig. 2.8) is described as an accurate measurement of drying kinetics of liquid droplets. It is a cost-effective system that generates high quality results. With the help of a TV monitor and video camera the droplet diameter and the glass filament deflections were monitored, which allows to determine the droplet weight loss, droplet size and droplet morphology at any time. The droplet diameter, the feret diameter, is measured from the perpendicular direction of the flow of the drying air. In drying modelling the drying surface area is an important parameter, and an estimated accuracy of 10% is mentioned for the drying area. Using the deflection of the glass filament, the change of weight of the particle/droplet can be determined. Several experiments were executed, considering all uncertainties, an accuracy of 0.05 mg can be mentioned for the weight measurement. The droplet temperature was measured separately with two thermocouple wires [Lin and Chen, 2002].

Comparing the different possibilities, the glass-filament method seems to be a good compromise between accuracy and cost. Using this system several variables of the drying process can be measured simultaneously.

2.6 Population Balance Modelling (PBM)

2.6.1 Introduction

The sections above focused on the drying behaviour of individual particles. As a multitude of particles are dried together, the interest can also be focused on
the drying behaviour of a batch of particles. A modelling framework to describe this behaviour is PBM. It is indeed often assumed that the system behaviour can be described by the ‘averaged’ behaviour of single particles. However, in a real system, this is a coarse assumption as both spatial and population heterogeneity occur and will impact the system behaviour. Indeed, particles can both interact with the continuous phase and with each other. Hence, the behaviour
2.6. Population Balance Modelling (PBM)

of individual particles in a population depends on different (distributed) properties of the individuals and the local environment. For thorough analysis of this type of systems, PBM can be applied. In the PBM framework a distinction is made between external and internal coordinates, which represent respectively the physical position and the distributed properties of the particles. A basic Population Balance Equation (PBE) which describes the change of the number density distribution \( n(x,r,t) \) in time is given by:

\[
\frac{\partial}{\partial t} n(x,r,t) + \nabla \cdot \dot{X}(x,r,Y,t) n(x,r,t) + \nabla \cdot \dot{R}(x,r,Y,t) n(x,r,t) = h(x,r,Y,t)
\]  

(2.1)

where \( x, r, t, Y \) and \( h \) are the internal coordinate, the external (spatial) coordinate, the time, the continuous phase vector and the net birth rate. \( \dot{X} \) and \( \dot{R} \) are the partial derivatives of the internal and external coordinates respectively. The continuous phase vector should cover all continuous phase quantities that affect the behaviour of single particles. The two divergence terms represent the convective transport, one along the internal coordinate and one along the external coordinate. These terms are continuous in time, and describe the evolution of \( x \) and \( r \). The net birth rate term is responsible for the change in number of particles due to discrete birth and death processes, and can include different phenomena such as aggregation, nucleation, agglomeration, breakage, etc. This last term is discontinuous, as particles appear and disappear at discrete time steps. This equation has to be supplemented by initial and boundary conditions to be solved [Ramkrishna, 2000].

A PBM model for simultaneous agglomeration and drying in fluidized beds has been described [Peglow et al., 2007]. The interesting internal properties were the particle size, the moisture content and the temperature of the particles. In terms of PBM the agglomeration gives rise to a discrete term or the birth term, whereas the drying process is a continuous process, leading to a growth term. When considering a fluidized bed with drying particles, each particle has a drying rate dependent on the local ambient conditions. During drying, the moisture content of particles drops. In terms of a PBM this could be described by an internal coordinate. In this case the interesting output is the temporal change of the number distribution with respect to the moisture content [Peglow et al., 2007].

Evaporation of water from a granule means that the total mass of the granules is not conserved, and in this sense it becomes a variable [Khosid, 2002]. The granules have an input size distribution, and thus a second internal coordinate could be defined. The disadvantage of increasing the number of internal coordinates of the Population Balance Equation (PBE) is the increasing mathematical complexity and computational power required to solve the resulting
set of equations for a specific problem. An interesting approach could be reducing the resulting two-dimensional PBE to a set of one-dimensional PBEs. The resulting two-dimensional PBM would have \( n(t, c, d) \) as general form, where \( t \) represents time and \( c \) and \( d \) are two other properties, in this case particle size and moisture content. The particle size can either be the entire volume, i.e. including the water content, or a representation of the volume, such as the diameter. Another approach is using a one-dimensional PBE for a selection of size classes. In this case only the moisture content is truly adopted as internal coordinate.

### 2.6.2 Studies using a PBM with a growth term for drying

Limited work is done in the area of drying of a population of granules using PBM. However, in a PBM context, other processes like spray-drying [Birchall et al., 2006] or wet granulation in combination with drying [Immanuel and Doyle, 2005] are discussed more frequently in literature. In these cases, less attention is paid to the drying kinetics. In spray-drying the crystallisation receives most attention, whereas for the wet granulation process aggregation of solids is regarded as most important.

Studies about the modelling of the drying of one single particle using a PBM approach are more frequently reported. In these studies the particles are described as a number of discrete solid particles. These models are interesting for simulating the dried particle morphology. Droplets containing dissolved or suspended solids will develop different morphologies during drying [Handscomb et al., 2009]. Depending on the temperature, droplet size and temperature of the micro-structure that is formed will vary [Ranz and Marshall, 1952]. Specifically for a pharmaceutical production line, the morphology of the dried granule is important for the subsequent tableting step. However, including this detail into drying models would result in a significant increase of the computational burden. This is not desired when the goal is to describe the dynamic behaviour of the moisture content of the entire batch of granules using a PBM. In this case, a PBM with only a growth term seems sufficient.

Population balances with a growth term are most often found for crystallisation processes, where the size of the crystals is the internal coordinate of interest. In this case the growth term is a positive term. In industrial applications, the crystallizer is often assumed as being well mixed, meaning that the number density does not depend on the spatial coordinates, and the PBM can be simplified to a PBM without spatial coordinates. In the secondary step of the crystallisation nucleation can also be neglected, as the secondary nucleation most likely only produces infinitesimally small crystals, further simplifying the PBM [Mesbah et al., 2009].

Fluidized bed coating and agglomeration of solid particles has been studied.
2.6. Population Balance Modelling (PBM)

The developed model assumed also independency of spatial coordinates for the batch fluidized bed. With this model the PSD could be simulated, and the duration of the stable operation could also be predicted successfully [Saleh et al., 2003].

2.6.3 Two-dimensional PBMs to model drying processes

Two-dimensional PBMs were investigated [Hounslow et al., 2001]. As internal coordinates the particle size and the particle tracer mass was chosen. The two-dimensional PBE was reduced to a set of two one-dimensional PBE using the marginal distribution approach, which is based on the assumption that particles of the same size contain the same amount of tracer.

A two-dimensional PBM was used for the simultaneous agglomeration and drying in fluidized beds [Peglow et al., 2007]. The energy and mass balances for the solid and the gas phase were derived by means of a heterogeneous fluidized bed with an active bypass. The solid phase was described with a set of one-dimensional PBEs using the reduction proposed by Hounslow et al. [2001]. A PBM with only the particle size as internal coordinate is not sufficient, as the kinetics for heat and mass transfer require the temperature and moisture content of the particles. As a consequence, a vector of internal coordinates is used. The PBE cannot be applied to the temperature and the moisture content of the solid phase. These properties are therefore related to the corresponding extensive properties. The resulting set of equations was solved using a new discrete formulation of the PBE and simple backward differences.

2.6.4 Validation of stand-alone PBM-models

Focusing on the validation of a stand-alone PBM-model, it will be necessary to register variables for an entire bed of granules. On the other hand, methods to determine the moisture content or the temperature can be the same as for the drying model described in section 2.5.5.

Experiments for the validation of the mathematical model describing the fluidized bed spray agglomeration and drying were conducted. Microcrystalline cellulose was used as material. For each sample (with a time interval of 2 minutes) the moisture content and the PSD were measured several times during the experiment using a Halogen Moisture Content Analyzer and a camera. In addition, the inlet gas temperature, the inlet flow rate and the humidity of the gas were measured [Peglow et al., 2007].

For the validation of a steam drying process of a bed of porous spheres it was necessary to register the weight of the entire bed, the inlet and outlet steam temperature and the steam mass flux accurately. At the inlet the steam was kept at a constant temperature with a temperature controller, which assured a
maximum temperature deviation of $+/- 0.3^\circ$C. The mass flux was controlled with a flow-regulating valve. A high resolution load cell continuously monitored the weight of the entire bed. The steam inlet and outlet and the temperature of a varying number of spheres were measured [Hager et al., 2000].

2.7 Computational Fluid Dynamics (CFD)

2.7.1 Introduction

In order to capture detailed spatial behaviour of the system, the flow of the particles can be analysed using CFD. As mentioned in section 2.4.1 several fluidization patterns can be distinguished, i.e. particles can be classified in several Geldart classes [Geldart, 1973]. Considering the configuration of the gas inlet, the fluidized bed dryer used in our case produces a normal fluidized bed, and not a spouted bed behaviour.

CFD consists of mathematical expressions that describe the conservation laws for momentum, mass and energy (contains thermal energy, contributions from radiation or other heat sources). The resulting PDEs are simplified using a discretisation technique, which translates the continuous equations into discrete ones. The result is a set of algebraic equations. Numerical solution techniques yield the flow field at discrete points in the domain. CFD models are thoroughly explored for single phase flow, however multi-phase flow - i.e. more than one phase is considered in the model - or complex geometries are more difficult to handle. In multi-phase flow CFD applications each phase is described in terms of a separate set of conservation equations, while appropriate interaction terms are necessary to describe the coupling between the phases [Chiesa et al., 2005].

In industry, gas/particle flow and fluidization applications are widespread and, hence, as a consequence, there is a need for fundamentally based and realistic simulations, accurate and detailed experiments, and also a proper set of design tools for these systems. Recently, significant progress has been achieved in the area of gas/particle flows [Arastoopour, 2001]. Several multi-fluid models can be found in the literature describing the dynamics in fluidized beds. Basically two approaches can be distinguished: the Eulerian-Eulerian and the Eulerian-Lagrangian approach. Both will be discussed in detail (Section 2.7.3 and 2.7.4 respectively).

In a fluidized bed several regions are apparent: (1) dense regions where particles are in long term contact with each other and the solid volume fraction is high and frictional stresses dominate and (2) dilute regions where particles are in collisional contact and the kinetic stresses are most important. In the intermediate region both kinetic and frictional stresses are important [Reuge et al., 2008].
2.7. Computational Fluid Dynamics (CFD)

2.7.2 Turbulence modelling

Introduction

An important aspect in CFD is turbulence modelling which is necessary when the Reynolds number (Re) exceeds the value of 3,000. The mathematical modelling of turbulence is very complex due to the three-dimensional behaviour and the time dependence. Different models have been developed to describe turbulence [Wilcox, 1998]. Traditionally, the time-averaged Navier-Stokes equations (Reynolds-averaged Navier-Stokes Equations (RANS)) have received most attention. In the latter, several options exist to describe turbulent stresses, including zero-equation models (or algebraic models), one-equation models, two-equation models and the second-order closure models (or Reynolds Stress Model (RSM) models). In general the \(k-\epsilon\)-model, a two-equation model, is most frequently used. Alternative to the RANS approach, turbulence can also be modelled using Large Eddy Simulation (LES). Here, the time-dependent flow equations for the mean flow and for the largest eddies are solved, and the effect of the smaller eddies are modelled using representative equations. Models based on LES have recently received more attention, despite their large computational power requirement. Finally, direct numerical simulation takes all scales relevant to turbulent motion into account, further increasing the computational burden [Wilcox, 1998] [Tabib et al., 2008] [Lije et al., 2010].

Turbulence modelling in fluidized beds

A \(k-\epsilon\) turbulence model on two-dimensional and three-dimensional grids was used for the simulation of a bubble plume in a rectangular, flat bubble column. A low Reynolds \(k-\epsilon\)-model has also been tested, and no significant changes were observed from the standard \(k-\epsilon\)-model [Mudde and Simonin, 1999]. The influence of the turbulence modelling was investigated in a rectangular bubble column with different types of spargers. Experimental results were obtained using Laser Doppler Anemometry (LDA) and Particle Image Velocimetry (PIV). PIV is an optical method for the visualisation of fluid motion. The particle concentration is limited in order to identify individual particles in an image. Three-dimensional simulations are necessary to show the periodic bubble hose movement. Simulations were performed using a laminar and a standard \(k-\epsilon\) turbulence model with and without dispersion. The laminar model was insufficient to describe the turbulence in the continuous fluid. The turbulence model without dispersion gave good agreement with the experimental results, while the model with dispersion did not seem to be necessary for the test cast [Pfleger et al., 1999]. The concept of LES turbulence modelling was applied to describe turbulence for vertical bubble-driven flows. According to these authors, this gives the best physical representation of the actual flow. If the
detailed bubble flow has to be described, the unaveraged equations should be used, and in practice the LES model is a suitable alternative [Jakobsen et al., 1997]. The performance of LES and $k$-$\epsilon$ turbulence models for gas-liquid flow were compared for a bubble column reactor. The equations of the motion of the gas-liquid flow were studied by the Eulerian-Eulerian approach. It was found that the LES results were in better quantitative agreement with the experiments compared to the $k$-$\epsilon$-model [Deen et al., 2001].

Three different turbulence models were compared, i.e. two RANS-based models, the $k$-$\epsilon$-model and the RSM, and the LES-model [Tabib et al., 2008]. Simulation results were compared with experimental data of Bhole et al. [2006]. The experiments were conducted with laboratory scale cylindrical bubble columns with three different spargers [Bhole et al., 2006]. The Reynolds stress model was expected to perform better than the $k$-$\epsilon$-model in predicting average axial velocity profiles. However, results were found to be comparable. For the prediction of the turbulent kinetic energy the Reynolds stress model performed better than the $k$-$\epsilon$-model. The LES-model was able to predict the average flow behaviour. However, the required computational resources are much higher for the LES-model compared to the Reynolds stress model and the $k$-$\epsilon$-model (Table 2.1). Moreover, the gain in information is limited (comparing results of the radial profile of axial velocity, the radial profile of gas hold-up, the radial profile of turbulent kinetic energy and the radial profile of Reynolds stress), which leads to the conclusion that the $k$-$\epsilon$-model is sufficient for the simulation of a three-dimensional bubble column [Tabib et al., 2008].

<table>
<thead>
<tr>
<th>Geometry details</th>
<th># of nodes used for simulations and time step</th>
</tr>
</thead>
<tbody>
<tr>
<td>$D = 0.15 \text{ m}$</td>
<td>$k$-$\epsilon$</td>
</tr>
<tr>
<td>$H = 1 \text{ m}$</td>
<td>36000</td>
</tr>
<tr>
<td></td>
<td>0.05 s</td>
</tr>
</tbody>
</table>

### 2.7.3 Eulerian-Lagrangian approach

**Introduction**

In the Eulerian-Lagrangian approach, or the discrete approach, the behaviour of each single particle is calculated, taking into account interactions with other particles and with the continuous phase. The limitation is, however, the number of particles which can be tracked, as the computational effort increases significantly with the number of particles. The numerical simulation performed with the Eulerian-Lagrangian approach needed a CPU time which is four orders
of magnitude higher than the time required to perform an Eulerian-Eulerian simulation [Chiesa et al., 2005]. The insight gained in the fluid dynamics and the straightforward inclusion of PSDs are on the other hand great advantages of the Euler-Lagrangian approach [Chiesa et al., 2005]. For complex physics the Eulerian-Lagrangian approach is the easiest way to describe the motion of the particles. Two methods prevail depending on the size of the particles compared to the grid points: when particles are much smaller, particle methods are used; when particles are larger, the immersed boundary method is used. The particles in a gas-fluidized bed are relatively small, so a point particle method needs to be used. In the Discrete Particle Model (DPM), a grid point particle method, one numerical particle represents one physical particle and in this case the interparticle forces can be modelled directly. This means that only a limited number of particles can be tracked in order not to blow up the computational load. Using the Particle Cloud Model (PCM) another grid point particle method, one numerical particle represents many real physical particles with the same physical properties [Melheim, 2007]. In fluidized bed drying, the DPM method is mostly applied.

**DPM and fluidized bed modelling**

In [DPMs] a hard or a soft sphere approach for the collision model can be used. In a hard sphere collision model the trajectory of particles is determined by momentum-conserving binary collisions. Collisions are assumed to be additive and instantaneous. This collision model was used [Hoomans et al., 1996] [Hoomans et al., 2000] to study gas-solid two-phase flows in gas-fluidized beds. Bubble formation due to particle-particle interaction and the particle segregation due to differences in particle size and density were investigated [Hoomans et al., 1996] [Hoomans et al., 2000].

In the soft sphere collision model, trajectories are determined by integrating the Newtonian equations of motion. Particles can overlap slightly [Deen et al., 2007]. Tsuji et al. [1993] were the first who used the soft sphere model for gas-fluidized beds. The contact forces were modelled by Cundall’s Distinct Element Method. The flow of the gas was solved simultaneously with the motion of the particles, taking into account the interaction between both. Experimental results and calculated pressure fluctuations compared well [Tsuji et al., 1993].

In studies about spouted bed systems the hard sphere [DPM] is mostly used, whereas the soft sphere approach is most suited for cases in which defluidized zones can prevail [Link et al., 2005].

The equations for the gas phase and the solids are coupled using the porosity and the inter-phase momentum exchange. Quantities should be averaged over a relevant volume, which has to be large compared to the particles. The method of [Hoomans et al., 1996] can be used for the calculation of the porosity.
It gives good results for small particles in large grid cells. However, detailed information of the gas flow is achieved using smaller grid cells [Hoomans et al., 1996]. The porosity was calculated in a grid-independent manner and a similar method was used for the calculation of the drag force acting on the particle [Link et al., 2005]. The flow of particles in bubbling fluidized beds was studied using LES and DPM. The gas phase model was based on locally averaged two-dimensional Navier-Stokes equations for two-phase flow whereby the turbulence is calculated by LES. The latter accounted for particle effects on subgrid-scale gas flow. Particles were assumed to interact through binary, instantaneous and non-elastic collisions [Zhou et al., 2004].

2.7.4 Eulerian-Eulerian approach

Introduction

The Eulerian-Eulerian approach, also referred to as the continuum approach, is used most frequently for studying the behaviour of gas-particle flows in fluidized beds [Ding and Gidaspow, 1990] [Samuelsberg and Hjertager, 1996]. In this approach both phases, i.e. the gas phase and the solids phase, are considered as being continuous and fully interpenetrating. For both phases the conservation equations are solved, which have to be supplemented by interaction terms for the coupling between both phases. The disadvantage of this approach is the difficulty with the incorporation of complex particle physics. Indeed, the continuum balances contain terms which require a constitutive relation. Eulerian-Eulerian models which include the effects of cohesion are very limited, and in this case the Eulerian-Lagrangian approach can offer a way out. The averaging technique used to derive the continuum balances gives rise to terms which require a constitutive relation. The incorporation of cohesion into constitutive quantities is less straightforward than its incorporation into an Eulerian-Lagrangian model [Weber and Hrenya, 2006].

The Eulerian-Eulerian approach requires closure laws for particle interactions. Several options for the stress terms in the particulate momentum equations can be found in literature. The theory for frictional stresses is derived from soil mechanics. The frictional contribution of the momentum transfer is predicted using empirical correlations [Reuge et al., 2008] [Boemer et al., 1998]. Also, several semi-empirical models can be found in the literature, described by among others [Srivastava and Sundaresan, 2003] [Ocone et al., 1993] [Johnson et al., 1990]. In the past, the constant viscosity model was used whereby the solid phase pressure was assumed to be only a function of the local solid porosity, and the solid phase viscosity was assumed to be constant [Gidaspow and Ettehadieh, 1983]. More recently, the Kinetic Theory of Granular Flow...
2.7. Computational Fluid Dynamics (CFD)

(KTGF) was accepted for modelling of kinetic stresses. Here, the solid phase properties are described in more detail, which yields a better insight in the particle-particle interactions \cite{Johansson2006}. The influence of frictional stresses on bubble dynamics was studied. Solid frictional stresses have a significant influence on the bubble size distribution, bubble rise velocity and visible bubble flow rate and the predictions are significantly improved by the incorporation of these stresses in the KTGF model \cite{Patil2005a, Patil2005b}. Different frictional stress models were compared for the simulation of dense gas-particle flows in bubbling fluidized beds. Experimental data were collected with a bubbling fluidized bed with central jet and a freely bubbling fluidized bed in order to investigate the effects of the frictional stress models on the numerical predictions. The general conclusion was that the sensitivity of the frictional stress models to the values of their parameters makes them inadequate. A more fundamental research effort is necessary to understand the dynamics of particles in ensuring contact in order to develop general expressions for the particulate phase stresses that are more reliable \cite{Passalacqua2009}.

Eulerian-Eulerian approach and fluidized bed

A Two-Fluid Model (TFM) was used for gas-fluidized beds. The mass, momentum and thermal energy conservation equations, and the constitutive equations were solved by a finite difference method \cite{Kuipers1992}. The disadvantage of this approach is the continuous character of the solid phase: physical characteristics such as shape and size are included through empirical relations for the interfacial friction, but the discreteness of the solids is not fully recognized \cite{Chiesa2005}. The TFM was further extended to a multi-fluid model, i.e. instead of one solid phase a higher number of solid phases were considered, yielding a more realistic description of the PSD in gas-solids flow systems. The different solid phases were given respective diameters, densities and restitution coefficients. The presence of each phase was described by a volume fraction, varying from zero to unity. For each phase individually the conservation laws for momentum, mass and energy are satisfied. The volume fraction and the momentum equations were solved for each phase. The gas phase turbulence was modelled by a LES model \cite{Mathiesen2000a}.

2.7.5 Validation of CFD-models

The bubbles in a fluidized bed can be monitored using several methods: X-ray imaging techniques \cite{Rowe1997}, laser \cite{Sung1987}, optical fibre probes \cite{Glicksman1987} coupled to spectrometers (e.g.,
Near Infra-red Spectroscopy (NIRS) and Raman), pressure probes [Atkinson and Clark, 1988], high-speed three-dimensional capacitance imaging technique [Halow et al., 1993]. Bokkers et al. [2004] took images of the fluidized bed by means of a high-speed digital camera. The PIV technique was used to determine the particle velocity fields [Bokkers et al., 2004]. The PIV technique was also used by Cheng et al. [2005] to investigate the bubble velocity field in a bi-dimensional gas-liquid column at high bubble density. A CCD camera was used to record the bubble images, whereas the post-processing was done using several PIV and Particle Tracking Velocimetry (PTV) cross-correlation methods. It was found that the PIV algorithm based on recursive cross-correlation gave a fine structure of the bubble flow in a relatively short computational time [Cheng et al., 2005].

A high-speed video camera was used to observe the motion of the bubbles. The bubble velocity was determined with an image analysis technique. First a binarisation processing was applied to distinguish a bubble from the background. Subsequently the position of the center of gravity of the binarised bubble image in a cylindrical coordinate system was determined for each bubble individually. Based on the displacement of the center of gravity over time the instantaneous radial and angular bubble velocities were calculated [Nakamura et al., 2009].

A Digital Image Analysis Technique (DIAT) was developed to study the hydrodynamics of a lab-scale two-dimensional bubbling fluidized bed. With the help of an in-house developed software simultaneous measurements of the most significant bubble properties (position, shape and dimension) was possible. In order to self-validate velocity measurements two kinds of velocimetry techniques were developed: (1) an Eulerian Velocimetry Technique (EVT) and (2) a Lagrangian Velocimetry Technique (LVT) [Busciglio et al., 2008].

Electrical Capacitance Tomography (ECT) systems can give both quantitative and qualitative data for solid-gas flow. Several numerical methods are used to solve the inverse problem to render permittivity images from raw voltage data. The use of a back-projection algorithm was described [Dyakowski et al., 1997]. The ECT method was used to investigate the influence of pressure on the average bed voidage and bubble size [Cao et al., 2008].

The multiple light scattering technique or Diffusing Wave Spectroscopy (DWS) was applied for a variety of dense fluidized bed systems. With DWS the motion of particles and the mean of the square of the particle velocity fluctuations about the mean flow velocity can be studied [Zivkovic et al., 2009].

Radioactive Particle Tracking (RPT) is based on the continuous detection of the positions of the tracer particles using high sampling rates. Therefore, it can be used to assess information about turbulent solid flows. The drawback is the limited number of tracer particles that can be monitored [Duarte et al., 2009]. Particle velocities in a three-dimensional spouted bed reactor has been
measured using a $\gamma$-ray-emitting particle tracking technique [Roy et al., 1994]. Limtrakul et al. [2005] described the use of Computer-Aided Radioactive Particle Tracking (CARPT) to measure solid motion in a fluidized bed. It is a non-invasive technique which is shown to be one of the best techniques to measure velocities in systems with large volume fraction of the dispersed phase. It is possible to monitor the motion in the whole bed and provides true Lagrangian data [Limtrakul et al., 2005]. CARPT has been used to measure the local liquid velocities in a bubble column [Degaleesan et al., 1996]. The model for liquid mixing compared well with the tracer data.

A technique based on tracking a phosphorescent tracer particle by means of video recording followed by digital image analysis has been developed by Pallarès and Johnsson [2006]. The data included concentration, velocity and dispersion fields of the tracer particle and could be obtained with high accuracy. The technique has shown to be an efficient tool for the characterization of the particle mixing process of fuel particles in a fluidized bed [Pallarès and Johnsson, 2006].

2.8 The combination of CFD and PBM for fluidized bed drying of granules

2.8.1 Introduction

As mentioned in previous sections of this review the fluidized particles in a fluidized bed dryer are subjected to a drying process. Hence, depending on the local ambient conditions the drying process will be faster or slower, leading to a distribution of the granules’ moisture content, and, hence, also their behaviour in the fluidized bed. For an even more accurate description of the dynamic system behaviour, a combined PBM-CFD model can be used.

Recently, the integration of PBM and CFD frameworks has received considerable attention. Examples can be found in distinct areas: oxygen transfer in bioreactors [Dhanasekharan et al., 2005], production of solar grade silicon in fluidized beds [Balaji et al., 2010], emulsification processes for food products [Agterof et al., 2003], production of cellulase [Bamnari et al., 2010], turbulent gas-liquid systems [Buffo et al., 2010], soot prediction models [Chittipotula et al., 2010], aerosol modelling [Chittipotula et al., 2010], etc.

2.8.2 Added value of the combination PBM-CFD

Traditionally the PBE was solved in a spatially homogeneous system, where the fluid was assumed to be well mixed or to behave in sequences of well-mixed flows. In reality, however, poly-dispersed particles, in this context indicating
particles, with one or more distributed characteristics, which move in a flow field, will lead to an inhomogeneous spatial distribution of the particles in the gas flow. This is particularly true when the influence of the flow field on the process under study cannot be neglected, and vice versa, i.e. the presence of particles influences the flow field. A detailed review of the potential and limits of the PBE approach to flow problems, the link with Lagrangian and multi-fluid approaches and numerical solution methods was recently given. The described applications are reactive precipitation, soot formation and nanoparticle synthesis and sprays and bubbles. The turbulent flows receive the most attention, whereas the extension with PBE is still considered to be a great challenge [Rigopoulos 2010].

2.8.3 PBM-CFD with growth term

Similar problems/systems can be found in other application domains. For the development of detailed models for a fluidized bed drying process these other domains can offer knowledge, in particular the models for crystallisation are quite similar to the drying case. Batch crystallisation processes are difficult to understand well. Indeed, due to the combination of fluid mixing, particle aggregation and particle breakage the process becomes highly complex. The heterogeneity in the ambient conditions will lead to different local crystallisation rates. For a correct prediction of the PSD a coupling has to be made of a PBM with turbulent CFD. The Standard Method of Moments (SMOM) and the Quadrature Method of Moments (QMOM) are both methods able to solve the PSD for industrial problems, such as batch crystallisation and batch precipitation. SMOM and QMOM were compared for a batch crystallisation process [Wan and Ring 2006]. Comparing the simulation results showed that the QMOM method was able to predict the analytical solution of a PBE more accurately [Wan and Ring 2006].

The problem of the computational expense of coupling a standard discretized population balance with a CFD model was addressed. This involves the solution of enormous amounts of transport equations. Indeed, instead of having one transport equation for a solid phase, now a transport equation for every size class of this solid phase is required in every bin of the CFD model. A higher number of discrete classes results in a more accurate prediction of the population balance dynamics, but also in a high number of scalars, making it computationally expensive to couple with CFD. The QMOM was tested for size-dependent growth and aggregation, and validated by comparison with Monte Carlo simulations and analytical solutions. For the size independent and dependent growth rate the QMOM showed a good agreement with the analytical solution. [Marchisio et al. 2003] concluded that the QMOM offers a great potential for the coupling of a PBE with CFD. The advantage over
2.8. The combination of CFD and PBM

direct methods are the low number of scalars, the lower computational burden and the fact that there is no lower and upper limit on the number of involved classes.

The QMOM approach was also applied for the simulation of nano-particle formation by reactive precipitation. A new algorithm, namely In Situ Adaptive Tabulation (ISAT) was implemented for the simulation of micromixing, mostly applied together with CFD [Wang and Fox, 2003]. The ISAT algorithm was proposed by Pope [1997] to incorporate detailed chemistry in reactive flow calculations. In this algorithm results are stored in a table as these are computed. Combined with information concerning the accuracy of local linear interpolation, this linear interpolation replaces the direct integration. Combined with CFD it has been demonstrated that a detailed kinetic mechanism can be used in calculations of turbulent combustion [Pope, 1997]. The PBE for turbulent aggregation of the growing particles was solved by the QMOM. The combined model with ISAT predicted the results accurately, and needed considerably less computational time compared to direct integration [Wang and Fox, 2003].

Starting from a three-dimensional PBM several reductions were done to a simplified PBM which was implemented in the CFD code. The reduced model has been validated using available experimental results for the homogeneous situation. A qualitatively good agreement was observed for stoichiometric conditions, whereas in the case of higher concentration excess of one reactant larger deviations were found. With the implementation in the CFD code several three-dimensional inhomogeneous hydrodynamic conditions could be investigated with acceptable computational time [Öncül et al., 2008].

CFD and PBM were combined for the modelling of ice crystallisation. For the solution of the four-dimensional PBM, the internal coordinate and the three external coordinates, the PBE was discretized into several ice crystal size ranges. The resulting diffusion-like PDEs could be implemented into conventional CFD models. Experimental data were compared with the predicted ice crystal distribution. In general, a good agreement was found, although an over-estimation of small and an under-estimation of large ice-crystals was predicted. This deviation could be the consequence of undetected small ice crystals or the over-simplified fluid flow and crystallisation kinetics models. Through the combination, a generic tool was developed for testing of various hypotheses and kinetic models of ice crystallisation under relatively simple experimental conditions [Lian et al., 2006].

The growth term in CFD-PBM models is not able to represent particle-particle interactions, since this term is merely convective. Incorporating particle-particle interactions in a CFD-PBM framework necessitates the use of agglomeration/aggregation kernels. In these kernels the interaction can be modelled as a source term, and in this way multiple properties can be introduced in the models, such
as impact velocity, wetting, roughness of particles, etc.

2.8.4 Validation of coupled CFD-PBM models

In-line NIRS can be applied to obtain the granule moisture content and particle size change during fluidized bed granulation [Frake et al., 1997]. NIRS is described as a fast non-destructive and low-cost technique, which is frequently used in the pharmaceutical industry for quality and process control [Sarraguça et al., 2010]. Real-time monitoring allows modifying the process conditions, if required, during granulation and can be used as well to identify the end-point of the granulation. This can lead to increased process reliability [Frake et al., 1997].

Continuous on-line measurement of solid moisture content during fluidization is possible using triboelectric probes. The latter were validated with a Karl Fischer titration in gas-solid fluidized beds. The obtained sensitivity ranged from 0.01 to 0.2 wt%. These inexpensive probes make it possible to perform real-time measurements of the moisture content at low cost [Portoghese et al., 2008].

The ECT-method, earlier discussed in the section about the validation of CFD models, was used in a fluidized bed drying process of pharmaceutical granules. With the help of the S-statistic, it was possible to analyze both the reconstructed and the non-reconstructed ECT-images to determine radial variations in hydrodynamic behaviour [Chaplin and Pugsley, 2005].

2.9 Towards mechanistic models for fluidized bed drying of porous granules in pharmaceutical production processes

The use of a mathematical model is strongly influenced by the modelling objective (Section 2.4.2). Before developing a model, the scope and the intended use of the model have to be clear indeed. Specifically for a fluidized bed dryer, to allow a detailed description of the drying kinetics and the distributed properties of the outgoing granules, both the fluidized bed behaviour as well as local drying behaviour need to be described (Fig. 2.9). This can be established using a PBM model integrated in a CFD code as described in section 2.8. The evaporation is the process that couples both modelling frameworks together. However, the coupled PBM-CFD model is challenging to formulate, solve and validate.

In the case of a dryer which is to be integrated and used within a continuous process, the model objective is to obtain a good prediction of several quality
2.9. Mechanistic models for fluidized bed drying processes

aspects (e.g. the compressibility or the moisture content) of the granules (that are required to be in specified ranges). The fluidized bed dryer embedded in the continuous process, implies that a continuous supply of dried product to the tableting machine is required. On the other hand, the continuous input of the dryer, originating from the granulator (Fig. 2.1), has distributed properties over the population of granules. Hence, the model needs to be able to predict process states depending on the input state properties. Moreover, the drying process model should be able to predict the impact of changing operating conditions on the output states. Hence, the model structure should include those parameters and state variables that influence the properties of the granules leaving the system if one wants to optimise or control the system.

Table 2.2 provides a concise overview of the different types of models.

![Figure 2.9: Structure of fluidized bed drying process model](image)

In section 2.5 an overview of existing drying models for porous material was given (see also figure 2.10). The first two approaches, namely the continuum and the pore network approach, are computationally expensive in order to calculate the detailed moisture content of the particles. These models calculate how the moisture content is evolving in the porous material. The question that has to be asked is whether it is necessary to describe the local moisture content in each particle in detail, considering that the global moisture content of the whole particle can give enough information. In this sense the choice of one of these models will depend on the scope of the research that forms the basis for supporting a modelling project.

The choice of the drying model is also influenced by the global scope of the fluidized bed drying. Bearing in mind that the goal is to implement a drying model in a PBM and coupled PBM-CFD model limits the required computational demand for the drying model. The drying model has to be applied to a population of particles with different sizes, which are fluidized and will exhibit a distribution in the moisture content. However, the computational demand of the drying model needs to be limited in a first modelling attempt of the system. More complex models are useful to highlight possible major shortcomings of the simplified models.
<table>
<thead>
<tr>
<th>Section</th>
<th>Type</th>
<th>Goal</th>
<th>Implementation</th>
<th>Limitation</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5</td>
<td>Drying of porous material</td>
<td>Allows describing the dynamic moisture content</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>2.6</td>
<td>Spatial coordinate not accounted for</td>
<td>Allows describing the behavior of a population from an initial distribution</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>2.7</td>
<td>CFD</td>
<td>Does not include the drying process</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>2.8</td>
<td>PBM-CFD</td>
<td>For spatially heterogeneous systems, the distributions influence of internal coordinates, the dyes, etc. can be calculated</td>
<td>-</td>
<td>Through the use of a coupled CFD-PBM model, the distribution of internal properties will be influenced by the environmental conditions</td>
<td></td>
</tr>
<tr>
<td>2.9</td>
<td>PBM</td>
<td>Does not include the drying process</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>2.10</td>
<td>CFD</td>
<td>Allows describing the fluid dynamics, the flow of particles, humidity, gas, etc. can be calculated</td>
<td>-</td>
<td>Through the use of a coupled CFD-PBM model, the distribution of internal properties will be influenced by the environmental conditions</td>
<td></td>
</tr>
</tbody>
</table>

Table 2.2: Overview of the different model concepts discussed.
2.9. Mechanistic models for fluidized bed drying processes

Drying of porous material

Continuum approach
Pore network modelling
Single particle drying

Large bodies

Figure 2.10: Different options for the modelling of the drying behaviour of porous material

An extension of the drying model for one single particle towards a population of particles is made through the adoption of the PBM-concept (Table 2.2). PBM is a tool to describe the behaviour of a population of particles. In a PBE the amount of internal coordinates can vary. The one-dimensional PBM with one internal coordinate, is mostly used. However, in some cases the results from a one-dimensional PBM are insufficient to describe the experimental data. An extension to a two-dimensional PBM can be done, however, the necessary computational power will increase. Moreover, when a coupling to a spatial CFD-model is pursued, the computational burden will become even larger. Hence, the choice for a specific modelling approach strongly depends on the objective. It is our belief that a step-wise approach in tackling such a complex problem is the best one. Once a one-dimensional PBM has been formulated, solved and validated, more complexity can be added, e.g. based on a sensitivity analysis that can point towards the weak parts of the model.

A CFD-model is used to describe the flow of the particles during fluidization (Table 2.2). Two options are available, the Eulerian-Lagrangian and the Eulerian-Eulerian approach. The first approach is very time consuming, as the force balance for every particle in the system needs to be solved. For systems of industrial size, the Eulerian-Eulerian approach is computationally more efficient. As a rule of thumb, the Eulerian-Lagrangian approach is currently limited to systems containing less than 100,000 particles. When the modelling objective requires taking into account some instantaneous interactions, this approach is however preferable [Weber and Hrenya, 2006]. Moreover, general numerical diffusion errors are less apparent with this approach, and another advantage is the greater stability for flows with large particle velocity gradients. The application to poly-dispersed systems can be easily achieved. Disadvantages disappear in concentrated systems with plenty of interactions between particles and between fluid and particles. In these cases, computational limitations like storage capacity and calculation time surface. Moreover, these models are characterized by a lack of fundamental understanding of the interactions. For high particle concentrations the Eulerian-Eulerian approach is preferred. Using well designed averaging methods it can account for direct and indirect
particle interactions and fluid turbulence. However, the constitutive equations for stresses are not yet fully understood and developed. Chiesa et al. (2005) compared the Eulerian-Lagrangian and the Eulerian-Eulerian approach qualitatively by performing numerical simulations of the flow behaviour of a laboratory scale fluidized bed and also comparing simulation output with experimental results. The multi-fluid model of Mathiesen et al. (2000b) was used as Eulerian-Eulerian model. The DPM - an Eulerian-Lagrangian model - results were in better agreement with the experimental data, but the computational time was four orders of magnitude higher (Chiesa et al., 2005).

The combination of a CFD- and PBM-model can be necessary to include the heterogeneity of the ambient conditions in the PBM. When the local ambient conditions vary along the reactor, this can have an influence on the distribution of the internal coordinates of the PBM. In literature the coupling of CFD with PBM including a growth term is rarely found. Mostly the QMOM approach is described as solution method, and seems to offer a great potential for coupling with CFD. The acceptable computational effort of this method is a great advantage, while the validation of the QMOM method gives good results. However, the integrated CFD-PBM has to our knowledge never been used to describe a pharmaceutical drying process. Hence, this opens perspectives, especially since it has been applied successfully in many other applications.

Currently, Discrete Element Method (DEM)PBM models gain popularity in cases where knowledge on the particle level is needed. Such models are indeed useful to study phenomena on the particle level because an explicit calculation of the particle contact mechanics in the particle-scale reference frame is done by means of a Lagrangian approach. The computational time needed for these type of calculations is however a major drawback. Limiting the number of particles, the needed computational time can be reduced, and in this way it can be possible to study agglomerate growth and kinetics.

Although much effort is done in the area of fluidized beds and drying, a complete descriptive model of a fluidized bed drying process is still lacking. Mostly both processes, i.e. the fluidized bed and the drying process, are studied separately. However, a coupled model is essential to better understand the process, and in a later instance to optimise and control the process. Without a more complete description of the process it is indeed impossible to predict the future process behaviour, given a set of inputs.

Model validation is crucially important in order to give credibility to a model. The complexity of the model is not only influenced by the process itself, but depends also on the data that can be obtained by experiments. As such, before the development of a model, one has to think about the capability to measure the variables that are modelled. A detailed mathematical model does not
provide conclusive information about a process without validation using experimental data. The gathering of experimental data is an important step, as the data contain the most important dynamics of the process. Data collection for this type of models is often not straightforward.

As a general conclusion, it is suggested to use a step-wise approach to model the drying behaviour of wet pharmaceutical granules in a fluidized bed, which is reflected in the different parts of this PhD dissertation (Fig. 1.2).

2.10 Objectives

The objectives of this thesis are multiple. The general one pursues the development of a mechanistic model for a fluidized bed drying process used in a continuous tablet manufacturing process. To meet this general objective, a step-wise approach is followed (reflected in the different chapters of this PhD dissertation). The different subprocesses occurring during drying and fluidization are analysed using a model-based approach. The submodels have been developed using experimental data used for calibration and validation, moreover, several model selection criteria have been used in the decision step of the model building procedure. Submodels, validated or not, are investigated using different tools; scenario analysis, GSA, and uncertainty analysis, to gain detailed process knowledge and to investigate the relation between the input and output variables. A GSA is interesting to compare the sensitivity of the different input factors of the model, whereas an uncertainty analysis gives information about the uncertainty of the output of interest. This information is important for the development of control strategies to interfere directly in the process during continuous operation (out of the scope of this PhD dissertation).

In order to enable controlling a continuous production process a real-time reliable monitoring of the interested output should be possible to guarantee the quality of the end-product. Therefore, the on-line real-time data collected during the operation of the fluidized bed dryer is analysed using a mass and energy balance. These balances should allow a real-time monitoring of the moisture content of the granules leaving the dryer unit, which is the key performance parameter of the dryer.

The combination of the real-time monitoring of the process and the relation between the input and the output variables is a first step towards on-line control strategies.
Chapter 2. Literature review & Objectives
CHAPTER 3

The ConsiGma\textsuperscript{TM} full continuous from-powder-to-tablet manufacturing line: System description

Give the fact that this PhD dissertation focuses on a specific system, a thorough description of this system is in place. The system used in this PhD dissertation is a full continuous tableting line, i.e. the ConsiGma\textsuperscript{TM} full continuous from-powder-to-tablet manufacturing line from GEA Pharma Systems (Collette\textsuperscript{TM}, Wommelgem, Belgium) (Fig. 3.1). The continuous line consists of three major parts: a continuous twin screw granulator (high shear) (2 in fig. 3.1), followed by a six-segmented fluidized bed dryer system (3 in fig. 3.1) and a discharge system (4 in fig. 3.1). After discharging, a lubricant can be added and blended into the dried granules, after which this mixture can be compressed using an in-line tableting device. Figure 3.2 provides a more schematic overview of the ConsiGma\textsuperscript{TM} line.

The feeder (1 in fig. 3.1 and 3.2) operates in a loss-in-weight-controlled manner, and feeds the powder continuously into the granulator (2 in fig. 3.1 and 3.2). A pre-blended mixture, which consists of excipients and APIs, is used in this dosing unit. The granulation unit has a barrel with two segments, i.e. a feed segment and a work segment. In the work segment the powder is mixed, wetted and granulated. With the help of a loss-in-weight peristaltic pump the granulation liquid is pumped into two injection nozzles, mounted in the work segment of the granulator. The wet granules, produced by the granulator, leave the unit through the discharge element of the barrel and are pneumatically transported to the six-segmented fluidized bed dryer (3 in fig. 3.1 and 3.2). Dry granules are extracted from the fluidized bed dryer through a rotational outlet valve and are transported to a product control hopper (4 in fig. 3.1 and 3.2), which collects the granules. Gravitationally the granules are
subsequently transferred to the milling device, which is fed at a constant flow rate by a metering valve. Finally, the granules can be blended with a lubricant.
and tabletted.

This PhD dissertation focuses on the drying step using the fluidized bed dryer (Fig. 3.3) which consists of six different segments and operates in a semi-continuous way. The gas entering the drying unit is heated till a certain preset temperature. It is possible to dehumidify the gas at the inlet of the dryer by using an additional unit, however, this is not provided at the Laboratory of Pharmaceutical Process Analytical Technology (Ghent University, Ghent, Belgium). The properties of the inlet gas (i.e. the gas temperature, the gas velocity) are identical for all six segments. The working of the dryer is visualised in figure 3.4. Each segment is sequentially filled during a certain preset filling period \( t_{\text{fill}} \), which equals 1/6 of the total drying cycle. After the filling period the wet granules in the segment are further dried. When referring in this thesis to the 'total drying time' \( t_{\text{dry}} \), this also includes the filling time. This means that some granules are dried longer compared to others, i.e. the drying time varies between the total drying time minus the filling time and total drying time. After the drying of the wet granules, the granules are discharged, which takes only a few seconds. Between the discharge and the filling of the segment the segment is inactive.

The fluidized bed dryer is conical in shape, which is clearly visible in figure 3.3. As such, each of the six segments is wider at the top compared to the bottom. The holes in the distributor plate (Fig. 3.5) are oriented in such a way that the fluidization pattern is optimized (i.e. the orientation of the holes is dependent on the location). The flow of the gas should prevent that granules stick to the wall of the dryer and enables a good fluidization of the wet and the dry granules.

In part II the fluidized bed dryer is used to collect experimental data, which is used for the calibration and validation of the single particle drying model (Section 4.3.1). This dataset is further used in chapter 6 for the Generalised Likelihood Uncertainty Estimation (GLUE) uncertainty analysis. Furthermore, the working of the drying unit is taken into account when performing the GSA analysis on the single particle drying model (Part II chapter 5) and the PBM model (Part III chapter 9).

In part V the automatically in-line logged data is used to monitor the drying process by using a mass and energy balance.
Chapter 3. ConsiGma™: System description

Figure 3.3: Six-segmented fluidized bed dryer

Figure 3.4: Operation of the six-segmented fluidized bed dryer
Figure 3.5: Top view of one segment of the fluidized bed dryer (Upper left) - Schematic overview of the distributor plate (Lower left) - The distributor plate (Right)
PART II

Modelling the drying behaviour of single pharmaceutical granules
Part II of this thesis describes the mechanistic modelling of the drying behaviour of single porous pharmaceutical granules. It starts with the development of the drying model (Chapter 4). The gathered experimental data is used for calibration and validation of the model. Moreover, different model selection criteria are evaluated and compared. Chapter 5 and 6 describe two tools in which the model is used to gain process knowledge. In chapter 5 different GSA techniques are investigated and compared for the single particle drying model. A GLUE uncertainty analysis is performed on the model, which is discussed in chapter 6. In the last chapter of this part (Chapter 7) a preparatory step is taken for part III. The single particle drying model is reduced to end up with an empirical model, which is fast to compute and can be used in a model describing the drying behaviour of a population of particles (using PBM).
Development of a single particle drying model & evaluation of different model selection criteria


Abstract:
This chapter focuses on the drying behaviour of a single wet granule before tableting, using a six-segmented fluidized bed drying system. The drying model is based on a model described by Mezhericher et al. [2007] and consists of two submodels. In the first drying phase (submodel 1) the surface water evaporates, while in the second drying phase (submodel 2) the water inside the granule evaporates. The second submodel contains an empirical power coefficient, $\beta$. A [Local Sensitivity Analysis (LSA)] was performed to study the influence of model parameters on the moisture content of single pharmaceutical granules, which clearly points towards the importance of $\beta$ on the drying behaviour. Experimental data with the six-segmented fluidized bed dryer were collected to calibrate $\beta$. A dependency between $\beta$ and the gas temperature was found, and three candidate model structures were analysed by using different model selection criteria (linear, quadratic and exponential). Model selection is an important step in any model development. When computing different model selection criteria, different conclusions could be drawn with regard to...
the selected model structure. Moreover, when criteria were corrected for small sample size, again other conclusions were obtained. In order to test this further, cross-validation was performed, hereby also changing the subsets of experiments used for calibration and validation as well as the number of datasets used for respectively calibration and validation. Overall, it was found that the exponential relation performed best for most criteria. However, it is clearly illustrated that model selection is a tedious task, where proper conclusions can often not be made by trusting only a single criterion. There is clearly a need for a more comprehensive model selection criterion. Finally, independent experiments were done for the validation of the drying model.

4.1 Introduction

4.1.1 Single particle drying model

This chapter deals with the development and calibration of a mechanistic model of the drying process of a continuously produced pharmaceutical granule in a six-segmented fluidized bed drying system and its validation using independent experiments. The development of this model should be considered as an attempt to build up process knowledge in the frame of a [PAT] project, which then later on can be used for the definition of a Design Space and for the development of suitable control strategies to optimally guarantee the end-product quality of the drying process under study. The development of a mechanistic model is innovative for pharmaceutical applications, as most studies are based on black box models, i.e. empirical data-driven models containing parameters with no physical meaning. However, recently more and more mechanistic models became available. Examples are work on blending [Ketterhagen et al., 2009], granulation [Boukouvala et al., 2011], film coating [Ketterhagen et al., 2009], etc.

Several methods have been reported in the literature to model the drying behaviour of granules. An extensive review can be found in chapter 2. This chapter focuses on the drying behaviour of a single wet granule using a six-segmented fluidized bed drying system, which is part of a fully continuous from-powder-to-tablet manufacturing line (ConsigMata, Colletetm, GEA Pharma Systems) (see chapter 3). Taking into account the size of pharmaceutical granules (0.1-2 mm), produced continuously using the continuous twin-screw granulator, models for drying processes of single particles were chosen for the work described here. The continuum approach [Perré and Turner, 1996] [Perré and Turner, 1999] [Couture et al., 1995] [Boukadida and Nasrallah, 1993] and the pore network models [Prat, 2002] [Plourde and Prat, 2003] [Huimink et al., 2002] [Yiotis et al., 2001] describe how water is evolving in the porous material, while
such detailed information is really not necessary for the drying of the particles studied here. Hence, the focus of the work presented here lies in describing the dynamics of the moisture content of a certain mass (20-1,000 g) of continuously produced granules (i.e. one segment of the six-segmented fluidized bed dryer filled with granules).

A mechanistic model for the description of drying processes of single granules was found in the literature [Mezhericher et al., 2007] [Mezhericher et al., 2008a]. This model describes the drying of a motionless single porous droplet in a flow of atmospheric air and consists of two drying phases. A droplet consists of a wet porous particle surrounded by a water layer at the surface. The model takes the time-dependent character of the heat transfer during the drying process into account. The temperature profile within the wet particle is calculated during drying. The crust region, formed during the second drying period (i.e. when the surrounding water is removed), is responsible for the resistance to diffusion mass transfer, dependent on the crust porosity, and heat absorption. The temperature dependence of physical properties (such as the specific heat, the coefficient of vapour diffusion, the specific heat of evaporation) is taken into account during drying, using the temperature profile of the granule.

In the first drying phase, the water from the droplet surface evaporates (Fig. 4.1 left). The second drying phase begins when the radius of the droplet equals the radius of the dry particle (Fig. 4.1 middle). In the second phase two regions are formed: a wet core and a dry crust (Fig. 4.1 right). The vapour, evaporated at the interface between the wet core and the dry crust, diffuses through the crust pores until it exits the pores, and forms a thin boundary layer over the particle surface. This vapour is removed through advection by the air flow.

In the first drying phase a uniform droplet temperature profile is assumed, which is based on the fact that the Biot number is smaller than 0.1. The evaporation rate in the first drying phase is calculated by:

$$\dot{m}_v = h_D(\rho_{v,s} - \rho_{v,\infty})A_d$$

Figure 4.1: Evolution of the moisture content for one single granule
where \( \dot{m}_v \) is the mass transfer rate, \( h_D \) the mass transfer coefficient, \( \rho_{v,s} \) the partial vapour density over the droplet surface, \( \rho_{v,\infty} \) the partial vapour density in the ambient air and \( A_d \) the surface area of the droplet [Mezhericher et al., 2008a]. The heat and mass transfer coefficients are calculated based on respectively the Nusselt and the Sherwood number, which are determined using the modified Ranz-Marshall correlations for evaporating spherical droplets. Therefore, the Stefan flow in the droplet boundary layer is taken into account. The equation for the diffusion coefficient of water vapour in the air is the one proposed by Grigoriev and Zorin [1988].

In the second drying phase the evaporation rate is given by [Abuaf and Staub, 1986]:

\[
\dot{m}_v = -\frac{8\pi \epsilon \beta D_{v,cr} M_w p_g}{R(T_{cr,s} + T_{wc,s})} \ln \left[ \frac{\rho_g - \rho_{v,i}}{\rho_g - \left( \frac{R}{4\pi M_w h_D R_p^2} \dot{m}_v + \frac{\rho_{v,\infty}}{T_g} T_{p,s} \right)} \right] \tag{4.2}
\]

with \( \epsilon \) the crust porosity, \( \beta \) an empirical power coefficient, \( D_{v,cr} \) the vapour diffusion coefficient (crust pores), \( M_w \) the molecular weight of the liquid, \( p_g \) the pressure of the drying agent, \( T_{cr,s} \) and \( T_{wc,s} \) respectively the temperature of the crust outer surface and of the crust-wet core interface, \( \rho_{v,i} \) and \( \rho_{v,\infty} \) respectively the partial vapour pressure at the crust-wet core interface and in the ambient air, \( h_D \) the mass transfer coefficient, \( R_p \) the particle radius and \( T_g \) the temperature of the drying agent. It is assumed that the crust pores are much greater than vapour molecular mean free path, i.e. the Knudsen number is much smaller than 1 and Knudsen diffusivity is not taken into account. Therefore, a single crust pore is considered as a semi-open Stefan’s system. The equation for the vapour diffusion coefficient is analog as for the first drying phase.

These equations have to be solved simultaneously with an Ordinary Differential Equation (ODE) for the decrease in droplet radius, an ODE for the temperature of the droplet, an ODE for the decrease in wet core radius, a PDE for the temperature profile in the dry crust and a PDE for the temperature profile in the wet core [Mezhericher et al., 2007]. The equations are reproduced for the reader’s convenience (Eqs. 4.3-4.7).

\[
\frac{dR_d}{dt} = -\frac{1}{\rho_w 4\pi R_d^2} \dot{m}_v \tag{4.3}
\]

\[
h_f g \dot{m}_v + c_{p,w} m_d \frac{dT_d}{dt} = h (T_g - T_d) 4\pi R_d^2 \tag{4.4}
\]

\[
\frac{dR_i}{dt} = -\frac{1}{\epsilon \rho_w 4\pi R_i^2} \dot{m}_v \tag{4.5}
\]
4.1. Introduction

\[
\rho_{wc} c_{p,wc} \frac{\partial T_{wc}}{\partial t} = \frac{1}{r^2} \frac{\partial}{\partial r} \left( k_{wc} r^2 \frac{\partial T_{wc}}{\partial r} \right), \quad 0 \leq r \leq R_i(t) \quad (4.6)
\]

\[
\frac{\partial T_{cr}}{\partial t} = \frac{\alpha_{cr}}{r^2} \frac{\partial}{\partial r} \left( r^2 \frac{\partial T_{cr}}{\partial r} \right), \quad R_i(t) \leq r \leq R_p \quad (4.7)
\]

with \( R_d \) and \( R_i \) the droplet and crust-wet core interface radius, \( \rho_w \) the density of the liquid, \( h_{fg} \) the specific heat of evaporation, \( c_{p,wc} \) the specific heat of the liquid, \( m_d \) the mass of the droplet, \( T_d, T_{wc} \) and \( T_{cr} \) respectively the temperatures of the droplet, the wet core and the crust region, \( \rho_{wc} \) the density of the wet core, \( c_{p,wc} \) the specific heat of the wet core, \( k_{wc} \) the thermal conductivity of the wet core and \( \alpha_{cr} \) the thermal diffusivity of the crust. The exact calculation of the parameters is described by Mezhericher et al. [2007, 2008a].

4.1.2 Model selection criteria

In the literature several model selection criteria are available. In table 4.1 some of those criteria are listed. The use of these criteria is usually based on an optimisation of their value. For most of the criteria this means that the value of the criterion should be minimised. The \( R^2 \) has to be maximised, with a maximum value of 1. The paired t-test is a statistical test, where the p-value has to be compared with a tabulated value at a chosen significance level.

The RMSE, the \( R^2 \), the Theil’s Inequality Coefficient (TIC) and the p-value of the paired t-test are all criteria which do not take into account the model structure. However, other model selection criteria such as the Akaike’s Information criterion (AIC), the Bayesian Information Criterion (BIC), the Final Prediction Error (FPE) and the Khinchin’s law of Iterated Logarithm Criterion (LILC) do penalise overly complex models. The equations for the calculation of the above mentioned criteria are:

\[
RMSE = \sqrt{\frac{\sum_i (y_i - \hat{y}_i)^2}{N}} \quad (4.8)
\]

\[
R^2 = 1 - \frac{\sum_i (y_i - \hat{y}_i)^2}{(N - 1) \text{var}(y_i)} \quad (4.9)
\]

\[
TIC = \frac{\sqrt{\sum_i (y_i - \hat{y}_i)^2}}{\sqrt{\sum_i y_i^2} \sqrt{\sum_i \hat{y}_i^2}} \quad (4.10)
\]

where \( y_i \) is an observed data point, \( \hat{y}_i \) the model prediction for this data point and \( N \) the number of data points. Subscript \( i \) refers to the number of each data point. A TIC value lower than 0.3 is considered to indicate a good agreement between the observed value and the model prediction [Audenaert et al., 2010].
<table>
<thead>
<tr>
<th>Criterion</th>
<th>Requirement</th>
<th>Incorporation model</th>
<th># of models</th>
<th>Reference</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>R²</td>
<td>Yes</td>
<td>Minimization</td>
<td>1</td>
<td>[Buckland et al., 1997]</td>
<td></td>
</tr>
<tr>
<td>P-value (F-test)</td>
<td>Yes</td>
<td>Minimization</td>
<td>1</td>
<td>[Ljung, 1999]</td>
<td></td>
</tr>
<tr>
<td>LILC</td>
<td>Yes</td>
<td>Minimization</td>
<td>1</td>
<td>[Dochain and Vanrolleghem, 2001]</td>
<td></td>
</tr>
<tr>
<td>FPE</td>
<td>Yes</td>
<td>Minimization</td>
<td>1</td>
<td>[Dochain and Vanrolleghem, 2001]</td>
<td></td>
</tr>
<tr>
<td>BIC</td>
<td>Yes</td>
<td>Minimization</td>
<td>1</td>
<td>[Dochain and Vanrolleghem, 2001]</td>
<td></td>
</tr>
<tr>
<td>AIC</td>
<td>Yes</td>
<td>Minimization</td>
<td>1</td>
<td>[Dochain and Vanrolleghem, 2001]</td>
<td></td>
</tr>
<tr>
<td>FPE</td>
<td>Yes</td>
<td>Minimization</td>
<td>1</td>
<td>[Korbicz et al., 2004]</td>
<td></td>
</tr>
<tr>
<td>LILC</td>
<td>Yes</td>
<td>Minimization</td>
<td>1</td>
<td>[Hannan, 1980]</td>
<td></td>
</tr>
<tr>
<td>P-value (F-test)</td>
<td>No</td>
<td>Minimization</td>
<td>&lt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RMSE</td>
<td>No</td>
<td>Minimization</td>
<td>&lt;</td>
<td>[Audenaert et al., 2010]</td>
<td></td>
</tr>
</tbody>
</table>

Table 4.1: Overview of the different model selection criteria available in the literature.

Chapter 4. Development of a single particle drying model
4.1. Introduction

The following set of criteria are based on the Sum of Squared Errors (SSE):

\[
AIC = N \log(\text{SSE}/N) + 2K \tag{4.11}
\]

\[
FPE = \text{SSE}/N \left(1 + \frac{2K}{(N - K)}\right) \tag{4.12}
\]

\[
BIC = N \log(\text{SSE}/N) + K \log(N) \tag{4.13}
\]

\[
LILC = N \log(\text{SSE}/N) + K \log(\log(N)) \tag{4.14}
\]

with \( K \) the number of parameters introduced due to the fit and \( N \) the number of data points used in the fit. The SSE is calculated as follows:

\[
\text{SSE} = \sum_{i} (y_i - \hat{y}_i)^2 \tag{4.15}
\]

However, it should be emphasized that \( K \) is the number of parameters involved in the model under consideration. AIC and FPE are not consistent, while BIC and LILC are consistent. This means that if the true model is among the candidates, the probability of selecting the true model approaches one if the number of data points equals infinity.

However, for the AIC criterion a correction for small sample size (i.e. small value of \( N \)) exists as well [Hurvich and Tsai, 1989] [Burnham and Anderson, 2004]:

\[
AIC_c = N \log(\text{SSE}/N) + 2K + \frac{2K(K+1)}{N-K-1} \tag{4.16}
\]

This correction is recommended when the value of \( K \) is large relative to \( N \), and should be used unless \( N/K > 40 \) for the model with the largest value of \( K \) [Burnham and Anderson, 2004].

Another possibility to evaluate the goodness of fit of a model is a statistical hypothesis test [Dochain and Vanrolleghem, 2001] to decide whether or not a more complex model performs significantly better than another yet simpler model (complexity is based on the number of parameters used for the fit, or the number of degrees of freedom). The most frequently applied test is probably the F-test. The statistical test is given by:

\[
\frac{\text{SSE}_j - \text{SSE}_i}{K_j - K_i} \frac{SSE_i}{n - K_i} \tag{4.17}
\]

with the subscript \( j \) referring to the more complex model and the subscript \( i \) referring to the less complex model [Söderström, 2002]. This statistical test is compared with

\[
F(K_j - K_i, N - K_j) \tag{4.18}
\]
which is a tabulated F-value at a certain level of significance $\alpha$ (typically 95 or 99%). If the value of the statistic is higher than the tabulated F-value, model $j$ is significantly better than model $i$ [Söderström, 2002]. The conclusions drawn based on the above mentioned model selection criteria might be subjective since the experiments used for the calibration and the validation are subjectively selected upfront. The question arises whether the results will be different when splitting the dataset differently. In order to check this, cross-validation can be performed. A first approach is the leave-one-out cross-validation. The Prediction Sum of Squares ($\text{PRESS}_p$) is a commonly used criterion for model selection in this case. $\text{PRESS}_p$ is calculated for the whole dataset as:

$$\text{PRESS}_p = \sum_{i} (Y_i - \hat{Y}_i)^2$$

(4.19)

where $Y_i$ is a vector with experimental data points and $\hat{Y}_i$ is a vector with the model predictions (estimator of $Y$), in which for both the $i^{th}$ observation is excluded.

### 4.2 Objectives

The objective of this chapter is the calibration and validation of a model to describe the drying behaviour of single pharmaceutical particles. The drying model is based on the work described by Mezhericher et al. [2007]. The added value of this work is the LSAs, the calibration, the introduction of a submodel to describe the gas temperature dependence of $\beta$ and the model validation. Moreover, different model selection criteria are investigated. The objectives for this part can be summarised as follow:

- Data collection to calibrate and validate the single particle drying model
- Investigation of different relations between the gas temperature and $\beta$ (Eq. 4.2): linear and quadratic
- Investigation of the consistency of the selected relation when using different model selection criteria
- Determination of the influence of splitting the dataset differently on the selected relation
4.3 Materials & methods

4.3.1 Experimental data

As data collection set-up, the ConsiGma™ continuous from-powder-to-tablet production line was used (Chapter 3). The formulation of the dry premix consisted of theophylline anhydrate (Farmaq Quimica sur SL, Malaga, Spain) (30%, w/w), lactose monohydrate 200 M (DMV fonterra) (67.5%, w/w) and polyvinylpyrrolidone (PVP) (Kollidon 30, BASF, Burgbernheim, Germany) (2.5%, w/w). This premix was granulated with a 0.5% (w/v) sodiumlaurylsulfate (SLS) solution (Fagron, Waregem, Belgium) in distilled water at a barrel temperature of 25°C. SLS was added to improve the wettability of the dry premix. The screw speed was held constant at 950 rpm, the powder mass flow at 10 kg/h and the liquid mass flow at 18 g/min. The ConsiGma™ standard screw configuration was used. Wet granules were collected in closed vessels.

Experimental drying data were collected in order to perform a calibration of $\beta$ followed by a validation of the drying model. To achieve this, continuously produced granules were dried at different drying air temperatures: 35°C, 40°C, 50°C, 60°C and 70°C. The gas flow rate was kept constant at 200 m³/h. In each drying experiment a limited amount of equally sized granules were used in order to measure the behaviour of one single granule. This was achieved by using a sieve-fraction of the granulated wet granules (1,000-1,400 µm). During each drying experiment, samples were collected at several drying time instants. In order to achieve this sampling in practice, the drying process was stopped, and the granules were captured and stored in closed vessels.

The moisture content was determined with Karl Fischer titration using a V30 volumetric KF titrator (Mettler Toledo, USA). Before the titration of the granules, these granules were stirred and dissolved (methanol (Hydranal, Sigma Aldrich, Germany)) during 5 minutes.

During the collection of the experimental data the humidity of the drying agent (air) and the pressure in the dryer were continuously monitored. During one experiment the humidity and the pressure can be assumed constant, but between the different experiments especially the humidity can vary in a broad range.

The measured moisture content corresponding to the early time steps is less reliable and more noisy compared to later time steps. The reason for this is twofold. First, it takes some time to introduce the granules in the dryer body. Secondly, after stopping the drying process there is a certain delay till the granules can be collected. Water at the surface of the granules can evaporate easily during this delay. At later time instants the water is less available, because
surface water is no longer present.

For each experiment $\beta$ was determined using the data points of the second drying phase. This was done by minimizing the $\text{SSE}$ (Eq. 4.15) between the experimental data and the model prediction. In this case $y_i$ and $\hat{y}_i$ represent respectively an experimental data point and the model prediction at time $t_i$. With the help of three independent experiments at a gas temperature of 50°C, 60°C and 70°C the validation was performed. The experimental set-up for these experiments was similar as for the calibration experiments. The measured moisture content was compared with the predicted result using the calibrated drying model.

### 4.3.2 Numerical solution

The first drying phase consists of an ODE for the temperature (Eq. 4.4), an ODE for the droplet radius (Eq. 4.3) and several algebraic equations, which have been solved simultaneously [Mezhericher et al., 2008a]. The ODE for the temperature is solved using a forward Euler scheme, while the ODE for the droplet radius can easily be solved analytically.

The equations of the second drying phase consist of a PDE for the temperature in the dry crust and one for the temperature in the wet core (Eq. 4.6 and 4.7) with accompanying boundary conditions. An ODE for the decrease in wet core radius (Eq. 4.5) is responsible for the moving boundary [Mezhericher et al., 2007]. The combination of the PDEs and the ODEs is solved using the numerical methods described by Illingworth and Golosnoy [2005]. The positional variable of the PDEs is first transformed by a Landau transformation. The resulting PDEs are discretized using a fully implicit, conservative finite difference technique, which are solved using a Crank-Nicolson scheme.

### 4.3.3 Local Sensitivity Analysis (LSA)

A LSA was performed to detect the most sensitive parameters in the model. This information can be used to understand how the input of the model (e.g. a parameter or initial condition) will influence the variation in the output. For this analysis the central difference scheme was used:

\[
\frac{\partial y(t)}{\partial \theta_j} = \frac{y(t, \theta_j + \xi \theta_j) - y(t, \theta_j - \xi \theta_j)}{2\xi \theta_j}
\]

with $y$ the output variable, $\theta_j$ the value of the perturbed parameter and $\xi$ the perturbation factor. In this application, the output variable is the moisture content.

The choice of the perturbation factor was based on the sum of the absolute
4.3. Materials & methods

Two sensitivity functions are calculated:

\[
\frac{\partial y(t)}{\partial \theta_{j,+}} = \frac{y(t, \theta_j + \xi \theta_j) - y(t, \theta_j)}{\xi \theta_j} \quad (4.21)
\]

\[
\frac{\partial y(t)}{\partial \theta_{j,-}} = \frac{y(t, \theta_j) - y(t, \theta_j - \xi \theta_j)}{\xi \theta_j} \quad (4.22)
\]

The difference between both sensitivity functions should be minimal to ensure that the numerical error and the error introduced by the nonlinearity of the model are as small as possible. This can be used to determine the optimal perturbation factor. Several criteria to quantify this difference exist, the Sum of Absolute Errors (SAE) and the Sum of Relative Errors (SRE) were used and compared:

\[
SAE = \frac{\sum \left| \frac{\partial y(t)}{\partial \theta_{j,+}} - \frac{\partial y(t)}{\partial \theta_{j,-}} \right|}{N} \quad (4.23)
\]

\[
SRE = \frac{\sum \left| 1 - \frac{\frac{\partial y(t)}{\partial \theta_{j,+}}}{\frac{\partial y(t)}{\partial \theta_{j,-}}} \right|}{N} \quad (4.24)
\]

with \( N \) the number of data points where the sensitivity is evaluated [De Pauw and Vanrolleghem 2006].

To evaluate the information about the sensitivity analysis the total relative sensitivity is calculated (Eq. 4.25). This enables to compare and rank the sensitivity of the parameters. This ranking can be used to decide on parameters to be used for model calibration (most sensitive parameters) or parameters to be removed from the model (in case the model is not at all sensitive to a parameter).

\[
\frac{\partial y(t)}{\partial \theta_j} \frac{\theta_j}{y(t)} \quad (4.25)
\]

The nominal values of the parameters as used in the LSA are given in table 4.2. Parameters which are not included in the LSA are calculated (e.g. the mass transfer coefficient, the heat transfer coefficient, etc.).

### 4.3.4 Confidence interval on parameters of the implemented relation

A way to express the accuracy of the coefficients of a model is by calculating the confidence interval of these coefficients. The confidence interval is given by:

\[
[c_i - w_i \quad c_i + w_i] \quad (4.26)
\]
Chapter 4. Development of a single particle drying model

Table 4.2: Parameters used for the LSA of the single particle drying model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Numerical value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_g$</td>
<td>50°C</td>
</tr>
<tr>
<td>$V_g$</td>
<td>200 m$^3$/h</td>
</tr>
<tr>
<td>$p_g$</td>
<td>101,300 Pa</td>
</tr>
<tr>
<td>$R_p$</td>
<td>0.6 mm</td>
</tr>
<tr>
<td>$RH_g$</td>
<td>9%</td>
</tr>
<tr>
<td>$\epsilon$</td>
<td>0.05</td>
</tr>
<tr>
<td>$\mu_g$</td>
<td>0.00002 kg/m/s</td>
</tr>
<tr>
<td>$\rho_g$</td>
<td>1.2 kg/m$^3$</td>
</tr>
<tr>
<td>$k_g$</td>
<td>0.0285 W/m/K</td>
</tr>
<tr>
<td>$cp_g$</td>
<td>1,009 kg/m$^3$</td>
</tr>
<tr>
<td>$cp_s$</td>
<td>1,252 kg/m$^3$</td>
</tr>
<tr>
<td>$\rho_l$</td>
<td>1,000 kg/m$^3$</td>
</tr>
<tr>
<td>$\rho_s$</td>
<td>1,525 kg/m$^3$</td>
</tr>
<tr>
<td>$k_d$</td>
<td>0.07 W/m/K</td>
</tr>
<tr>
<td>$k_l$</td>
<td>0.63 W/m/K</td>
</tr>
<tr>
<td>$k_s$</td>
<td>0.75 W/m/K</td>
</tr>
<tr>
<td>$\epsilon_{rs}$</td>
<td>0.8</td>
</tr>
<tr>
<td>$\beta$</td>
<td>1.84</td>
</tr>
</tbody>
</table>

where $c_i$ is a coefficient of the model and $w_i$ is the half-width of a 2-sided confidence interval based on a specified level of significance, $\alpha$. $w_i$ is calculated according to:

$$ w_i = t_{\alpha, df}^2 se_i $$

with $t_{\alpha, df}^2$ the t-value of the student’s t distribution with $df$ the degrees of freedom for error and $se_i$ is the standard error for the $i^{th}$-coefficient.

4.4 Results & discussion

4.4.1 Experimental data

The collected experimental data are summarised in table 4.3. The unit of moisture content is % (kg water/kg total mass).

This data involves the first and the second drying phase. Only the data points of the second drying period were used for the calibration of $\beta$. One data point was eliminated, i.e. 0.67% at 15 s for the experiment at 60°C, as it was identified as an outlier. The reason for this unreliable measurement was due to some problems which occurred during the collection of this sample.
### Table 4.3: Experimental data for the calibration and validation of the single particle drying model

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>Time (s)</th>
<th>X (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>35°C</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t(s)</td>
<td>0 1 4 9 13 14 31 84 348 567</td>
<td></td>
</tr>
<tr>
<td>X (%)</td>
<td>8.46 4.72 3.85 3.58 3.91 3.91 3.55 2.96 3.00 3.01</td>
<td></td>
</tr>
<tr>
<td><strong>40°C</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t(s)</td>
<td>0 5 10 20 40 80 200 400 1,000</td>
<td></td>
</tr>
<tr>
<td>X (%)</td>
<td>8.51 3.88 3.40 3.34 2.84 2.68 2.24 2.06 1.60</td>
<td></td>
</tr>
<tr>
<td><strong>45°C</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t(s)</td>
<td>0 2 8 20 50 200 360 720</td>
<td></td>
</tr>
<tr>
<td>X (%)</td>
<td>8.17 3.33 3.44 2.96 2.50 1.73 1.84 1.21</td>
<td></td>
</tr>
<tr>
<td><strong>50°C</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t(s)</td>
<td>0 1 5 10 15 40 80 200 720</td>
<td></td>
</tr>
<tr>
<td>X (%)</td>
<td>8.12 3.86 3.56 3.04 2.33 2.37 1.75 1.35 0.22</td>
<td></td>
</tr>
<tr>
<td><strong>55°C</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t(s)</td>
<td>0 1 2 5 10 15 40 80 200 300 420</td>
<td></td>
</tr>
<tr>
<td>X (%)</td>
<td>8.19 3.57 2.46 2.94 2.84 2.69 1.90 1.28 1.36 0.72 0.14</td>
<td></td>
</tr>
<tr>
<td><strong>60°C</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t(s)</td>
<td>0 1 2 5 7 10 15 20 40 80 200 240 360</td>
<td></td>
</tr>
<tr>
<td>X (%)</td>
<td>7.75 2.94 2.69 1.77 1.92 2.16 0.67 1.89 1.03 0.56 0.40 0.12 0.05</td>
<td></td>
</tr>
<tr>
<td><strong>65°C</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t(s)</td>
<td>0 1 5 7 10 15 20 40 80 100</td>
<td></td>
</tr>
<tr>
<td>X (%)</td>
<td>7.98 2.46 3.77 1.92 2.05 1.72 1.80 0.62 0.05 0.04</td>
<td></td>
</tr>
<tr>
<td><strong>70°C</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t(s)</td>
<td>0 1 5 7 10 15 20 40 80</td>
<td></td>
</tr>
<tr>
<td>X (%)</td>
<td>8.12 4.20 3.66 2.98 2.01 1.62 1.09 0.27 0.01</td>
<td></td>
</tr>
</tbody>
</table>
4.4.2 Local Sensitivity Analysis (LSA)

Equation 4.2 contains an empirical power coefficient: $\beta$. Information about this parameter is not present in the literature. However, the influence of this parameter on the evaporation rate is significant. An increase in $\beta$ causes a decrease in the evaporation rate and, hence, a slower drying process. A sensitivity analysis was performed to determine the contribution of $\beta$.

To determine the optimal perturbation factor $\xi$ the summation of the SAEs and the SREs for all parameters is made. The result is presented in figure 4.2. According to the SAE criterion the optimal perturbation factor is $10^{-6}$, whereas according to the SRE criterion $10^{-5}$ would be chosen. De Pauw and Vanrolleghem [2006] concluded that the SRE criterion was useful to assess the quality of sensitivity function calculations. Therefore, it was decided to use $10^{-5}$ as perturbation factor.

The results of the LSA performed on the parameters, are presented in figure 4.2:

![Figure 4.2: Criteria values for the SAE (Left) and the SRE (Right) for different values of the perturbation factor $\xi$](image)

The simulation was stopped when the particle was dry (after 270 s). In this time range the mean of the absolute value of the total relative sensitivity was calculated and presented.

It can be concluded that the gas temperature is the most sensitive parameter, followed by $\beta$. It can be noted that the gas temperature determines the drying behaviour for the whole time range of the drying process, whereas the $\beta$-parameter only has an influence in the second drying phase (Eq. 4.1 and 4.2). The major influence of $\beta$ is important, and is in fact rather critical, as there is no information available about this parameter.
4.4 Results & discussion

Figure 4.3: Mean of the absolute value of the total relative sensitivity for the different parameters included in the LSA of the single particle drying model

4.4.3 Model calibration

In figure 4.4 the resulting model prediction at each evaluated drying temperature is presented, together with the experimental data.

The goodness-of-fit was determined by calculation of the RMSE (Eq. 4.8) and the TIC (Eq. 4.10). The calculated values (Table 4.4) show that the values of the RMSE and the TIC are in the same range for the five experiments. Both criteria resulted in a similar conclusion with regard to the goodness-of-fit; the model prediction experiment at 70 °C was the best according to the RMSE and TIC while the worst model prediction was either the experiment at 50 °C (RMSE), or at 60 °C (TIC). Furthermore, it can be observed that optimal β-values exhibited a decreasing trend with increasing gas temperature. This means that the model with a fixed β-value cannot be used to predict drying behaviour at different gas temperatures. This proves the importance of model validation.

In figure 4.5 the calibrated β-values along with their 95% confidence interval (Eq. 4.28) are shown. The calculation of the covariance for the confidence interval is based on the Fisher Information Matrix (FIM). The inverse of the FIM is the lower limit of the parameter estimation error covariance matrix [Dochain and Vanrolleghem 2001], which means that the real confidence interval will be
Chapter 4. Development of a single particle drying model

Figure 4.4: Calibration of $\beta$ for the different experiments of the single particle drying model

Table 4.4: TIC and RMSE for the calibration experiments of the single particle drying model

<table>
<thead>
<tr>
<th>Experiment</th>
<th>35°C</th>
<th>40°C</th>
<th>50°C</th>
<th>60°C</th>
<th>70°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta$</td>
<td>3.088</td>
<td>2.275</td>
<td>1.840</td>
<td>1.389</td>
<td>1.289</td>
</tr>
<tr>
<td>RMSE</td>
<td>0.1852</td>
<td>0.1455</td>
<td>0.2998</td>
<td>0.2543</td>
<td>0.09552</td>
</tr>
<tr>
<td>TIC</td>
<td>0.02961</td>
<td>0.02864</td>
<td>0.06943</td>
<td>0.1024</td>
<td>0.02882</td>
</tr>
</tbody>
</table>

a bit larger.

$$CI = \beta \pm t_{N-p}^{\alpha} \sqrt{C_{ii}}$$

(4.28)

Here, $\sqrt{C_{ii}}$ is the covariance and $t_{N-p}^{\alpha}$ the t-value of the student’s t distribution with $N - p$ degrees of freedom and $\alpha$ the significance level. $N$ is the total number of data points for each experiment, while $p$ is the number of estimated parameters (i.e. 1).

It can be observed that the confidence interval for the experiment at 35°C was larger than for the other experiments. As mentioned in section 4.3.1 the collected experimental data contain some unreliabilities, which can form an explanation for the difference in size of the confidence interval. It was therefore decided to investigate the relation between $\beta$ and $T_g$ with (Case A) and without (Case B) considering this experiment in order to eliminate the more noisy data.
4.4. Results & discussion

4.4.4 Relation between $\beta$ and the gas temperature based on the 5 experiments used for calibration

Three different model structures for the submodel were investigated as relations between $\beta$ and $T_g$: linear (Eq. 4.29), quadratic (Eq. 4.30) and exponential (Eq. 4.31).

\begin{align*}
\beta &= a T_g + b \\
\beta &= a T_g^2 - b T_g + c \\
\beta &= b e^{a T_g} 
\end{align*}

The exponential relation was investigated using two different approaches. The first approach fits a linear model to the logarithmic transform of the $\beta$-value data (logarithmic approach). The other approach consists of directly estimating the parameters of the exponential relation by minimizing the SSE between the calibrated $\beta$-values and the calculated $\beta$-value using the exponential relation (direct parameter estimation). The resulting calibrated equations are presented in Table 4.5, again for case A as well as for case B.

For the parameters of the resulting submodels the corresponding 95% confidence interval is calculated (Table 4.6). The size of the confidence interval of the coefficients gives an idea about the quality of the coefficient estimation of the submodel. A confidence interval of 95% means that the real value of the coefficient will be in this interval with a certainty of 95%. A large confidence interval, which is true for this case, is typical for parameter estimations of low
quality. In other words, the size of the confidence interval provides an indication on whether or not the model structure is compatible with the data. Comparing the difference between the model with and without including the experiment at 35 °C there are some obvious differences between the relations. For the linear relation the size of the confidence intervals are larger when including the experiment at 35 °C, while for the quadratic relation the result is opposite. For the exponential relation the result is dependent on the coefficient. Focusing on the quadratic relation it can be seen that the size of the confidence interval of coefficient \(c\) is large. Or, in other words, there is not much confidence in this value. The addition of a third parameter, although improving the fit (i.e. lower RMSE in table 4.7), introduces a significant uncertainty in the parameter estimates.

For the exponential relation, a clear difference between the logarithmic approach and the direct parameter estimation can be observed. For the case including the experiment at 35 °C the interval for coefficient \(a\) is larger for the direct parameter estimation approach, however, the opposite is true for the case excluding 35 °C. For coefficient \(b\) the lower boundary gets a negative value for the direct parameter estimation and the confidence intervals are very large. Hence, from a parameter estimation point of view, the logarithmic approach is clearly superior. The direct parameter estimation method was therefore not further considered.

The criteria, presented in table 4.1, are calculated for the calibrated linear, quadratic and exponential relations.

\[ \text{BIC (Eq. 4.13)}, \ \text{FPE (Eq. 4.12)} \text{ and } \text{LILC (Eq. 4.14)} \text{ do not contain a correction for small sample size. However, the structure of the mathematical expression of these criteria is the same as for the AIC-criterion (Eq. 4.11). Hence, a similar correction term as for the AIC-criterion (i.e. corrected Akaike’s Information criterion (AIC\(_c\))) was included and these criteria were termed with suffix ‘c’}. \]
### Table 4.6: Confidence intervals for the different coefficients in the relations between $\beta$ and $T_g$

<table>
<thead>
<tr>
<th>Coefficient</th>
<th>Linear</th>
<th>Quadratic</th>
<th>Case A</th>
<th>Exponential</th>
<th>Case B</th>
<th>Exponential</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$a$</td>
<td>[-0.0818, -0.0140]</td>
<td>[-0.0011, 0.0045]</td>
<td>-0.0360, -0.0125</td>
<td>[-0.04196, -0.01281]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>+/- 70.8%</td>
<td>+/- 166.9%</td>
<td>+/- 48.4%</td>
<td>+/- 53.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>+/- 62.8%</td>
<td>+/- 159.9%</td>
<td>+/- 97.8%</td>
<td>+/- 461.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$c$</td>
<td>[-100.8486, 489.3124]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>+/- 151.9%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$a$</td>
<td>[-0.0594, -0.0088]</td>
<td>[-0.0043, 0.0060]</td>
<td>-0.0324, -0.0073</td>
<td>[-0.03157, -0.009972]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>+/- 74.3%</td>
<td>+/- 618.4%</td>
<td>+/- 63.0%</td>
<td>+/- 52.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>+/- 64.6%</td>
<td>+/- 582.3%</td>
<td>+/- 98.4%</td>
<td>+/- 349.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$c$</td>
<td>[-454.0845, 659.9377]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>+/- 541.2%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Although no evidence was found in the literature of applying this AIC correction to other criteria, we do not see any reason why it would not be allowed. The results of the model selection criteria are presented in Table 4.7. It can be observed that the uncorrected versions of the criteria select the quadratic relation, whereas the corrected version selects the exponential relation. The parameter estimation without including the experiment at 35 °C is again better based on the calculated criteria values (higher when maximisation is needed, lower when minimisation is needed). Note that this is not only due to the lower sum of squared errors (which is expected to be lower for less data points), but also due to ‘N’ as this is accounted for in the different criteria as well. Based on the p-value, the linear model is selected. Note that this is the only criterion favouring the linear model.

Comparing the results for case A and B, it can be concluded that for most criteria case B is favoured over case A. However, the difference between case A and B is not significant.

Based on the F-test (Table 4.8) the quadratic model is not significantly better than the linear and the exponential model (with a confidence level of 95%).

### Table 4.7: Calculated values of the criteria for the determination of the goodness-of-fit of the relations between $\beta$ and $T_g$

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Case A</th>
<th>Case B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Linear</td>
<td>Quad.</td>
</tr>
<tr>
<td>RMSE</td>
<td>0.2363</td>
<td>0.1137</td>
</tr>
<tr>
<td>R²</td>
<td>0.8708</td>
<td>0.9701</td>
</tr>
<tr>
<td>TIC</td>
<td>0.0569</td>
<td>0.0273</td>
</tr>
<tr>
<td>AICc</td>
<td>3.7354</td>
<td>20.5564</td>
</tr>
<tr>
<td>BIC</td>
<td>-3.0457</td>
<td>-4.6152</td>
</tr>
<tr>
<td>BICc</td>
<td>2.9543</td>
<td>19.3848</td>
</tr>
<tr>
<td>FPE</td>
<td>0.1303</td>
<td>0.0517</td>
</tr>
<tr>
<td>FPEc</td>
<td>6.1303</td>
<td>24.0517</td>
</tr>
<tr>
<td>LILC</td>
<td>-5.3128</td>
<td>-8.0159</td>
</tr>
<tr>
<td>LILCc</td>
<td>0.6872</td>
<td>15.9841</td>
</tr>
<tr>
<td>p-value</td>
<td>0.9999</td>
<td>0.9997</td>
</tr>
</tbody>
</table>

### Table 4.8: Results of the F-test for the relations between $\beta$ and $T_g$

<table>
<thead>
<tr>
<th>Models</th>
<th>Case A</th>
<th>Case B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linear vs. quad.</td>
<td>1.6616</td>
<td>18.5128</td>
</tr>
<tr>
<td>Exp. vs. quad.</td>
<td>0.7889</td>
<td>18.5128</td>
</tr>
</tbody>
</table>
4.4.5 Model validation

Model validation was performed using independent datasets collected at gas temperatures of 45 °C, 55 °C and 65 °C. The equations for the submodel were implemented in equation 4.2 which changed the model structure. The resulting model was used for the validation. The validation was done for the three different relations, either based on five data points (Eq. 4.32-4.35, fig. 4.6) or excluding the experiment at 35 °C (Eq. 4.36-4.39, fig. 4.7).

For case A, it can be observed that all models give a reasonable prediction of the validation experiments. Differences between model predictions are largest at low gas temperature (45 °C and 55 °C), whereas at a gas temperature of 65 °C all models give the same prediction. The linear function consistently yields a slower drying curve (higher X-values), whereas the quadratic relation consistently yields the fastest drying curve. The exponential relation yields an intermediate prediction.

Table 4.9 summarises the results of the calculated goodness-of-fit criteria. The values of the RMSE and the TIC are almost equal for the experiment at 65 °C. Comparing the results for case A and B it can be seen that the performance of the submodel, including the experiment at 35 °C, was in general
better than the performance obtained when excluding this experiment. This is in contradiction with the results of Table 4.7, as it was expected that the sub-model excluding the experiment at 35°C would describe the gas temperature dependency better. As the elimination of the experiment at 35°C means a loss of information, and considering also that in pharmaceutical applications drying at 35°C is sometimes necessary in cases with temperature sensitive drugs, it was decided to include this experiment in the analysis.

Based on these results, it can be concluded that no single model is superior.

### 4.4.6 Cross-validation

The conclusions drawn until now are based on a subjective splitting of the dataset into a part for calibration and a part for validation. The question now arises whether the results would have been different when splitting the dataset differently. The $\text{PRESS}_p$ (Eq. 4.19) was calculated for several model structures, where the sum was made for all 8 experiments (i.e. $N$ equals 8). It was concluded that the performance of the exponential model is the best (Table 4.10).

Note that the dataset of 8 data points can be split into two parts in several
4.4. Results & discussion

Table 4.9: Results of the goodness-of-fit criteria for the validation datasets

<table>
<thead>
<tr>
<th></th>
<th>Case A</th>
<th>Case B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Linear</td>
<td>Quad.</td>
</tr>
<tr>
<td></td>
<td>RMSE</td>
<td>TIC</td>
</tr>
<tr>
<td>Validation experiment 1: 45°C</td>
<td>0.3209</td>
<td>0.0707</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Validation experiment 2: 55°C</td>
<td>0.3121</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Validation experiment 3: 65°C</td>
<td>0.5153</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Overall validation</td>
<td>0.4054</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4.10: Results of cross validation using PRESS_p

<table>
<thead>
<tr>
<th></th>
<th>Linear</th>
<th>Quadratic</th>
<th>Exponential</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRESS_p</td>
<td>0.7352</td>
<td>0.4692</td>
<td>0.4254</td>
</tr>
</tbody>
</table>

ways. First, the number of data points in each subset can be changed, and secondly the choice of which data points belong to which subset can be varied. In a first case five experiments were taken for calibration, and hence three experiments for validation. The performance of the submodel was again tested on all criteria introduced above. For each criterion the set of experiments that lead to the best and the worst performance can be seen in Table 4.11. Results can be summarised as follows:

- For all different relations, all different criteria select the same set of experiments for calibration to find the optimal relation between $\beta$ and the gas temperature. This set is the same for the linear and exponential model, but different for the quadratic model. This illustrates that the different experimental datasets contain a different amount of information for the different model structures.

- Based on the criteria not corrected for small 'N' (RMSE, $R^2$, TIC, AIC, BIC, FPE, and LILC) the quadratic relation is selected.

- Based on the AICc, BIC, FPE, and LILC the exponential relation is selected.
Table 4.11: Results of the cross-validation using 5 experiments for calibration

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Linear relation</th>
<th>Quadratic relation</th>
<th>Exponential relation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Best</td>
<td>Worst</td>
<td>Best</td>
</tr>
<tr>
<td></td>
<td>Value</td>
<td>Exp. (°C)</td>
<td>Value</td>
</tr>
<tr>
<td>RMSE</td>
<td>0.0446</td>
<td>40, 45, 50, 60, 65</td>
<td>0.2363</td>
</tr>
<tr>
<td>$R^2$</td>
<td>0.9866</td>
<td>40, 45, 50, 60, 65</td>
<td>0.8265</td>
</tr>
<tr>
<td>TIC</td>
<td>0.0122</td>
<td>40, 45, 50, 60, 65</td>
<td>0.0569</td>
</tr>
<tr>
<td>AIC$_c$</td>
<td>-3.5112</td>
<td>40, 45, 50, 60, 65</td>
<td>3.7354</td>
</tr>
<tr>
<td>BIC</td>
<td>-10.2923</td>
<td>40, 45, 50, 60, 65</td>
<td>-3.0457</td>
</tr>
<tr>
<td>BIC$_c$</td>
<td>-4.2923</td>
<td>40, 45, 50, 60, 65</td>
<td>2.9543</td>
</tr>
<tr>
<td>FPE</td>
<td>0.0046</td>
<td>40, 45, 50, 60, 65</td>
<td>0.1303</td>
</tr>
<tr>
<td>LILC$_c$</td>
<td>-6.5594</td>
<td>40, 45, 50, 60, 65</td>
<td>0.6872</td>
</tr>
</tbody>
</table>

Criteria:
- RMSE: Root Mean Square Error
- $R^2$: Coefficient of Determination
- TIC: Tucker's Index
- AIC: Akaike Information Criterion
- AIC$_c$: Corrected AIC
- BIC: Bayesian Information Criterion
- BIC$_c$: Corrected BIC
- FPE: Final Prediction Error
- FPE$_c$: Corrected FPE
- LILC: Least Informative Linear Criterion
- LILC$_c$: Corrected LILC

Note: All values are rounded to the nearest decimal.
4.4. Results & discussion

**Table 4.11:** Results of the cross-validation using 5 experiments for calibration

<table>
<thead>
<tr>
<th></th>
<th>LILC</th>
<th>LILC_c</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-12.9034</td>
<td>40, 45, 50, 60, 65</td>
</tr>
<tr>
<td></td>
<td>-6.9034</td>
<td>40, 45, 50, 60, 65</td>
</tr>
</tbody>
</table>

Table 4.11 shows the results of the criteria for the linear and exponential model when calibrating on the best experimental set for the quadratic model.

Comparing these results with the values of the best and worst calculated criteria mentioned in Table 4.11, it can be seen that the chosen experiments to optimize the value of the criteria for the quadratic relation are not sufficient when fitting a linear relation to the data points. The values in Table 4.12 for the linear case are closer to the worst scenario. For the exponential relation, the values of the calculated criteria mentioned in Table 4.12 are more in the middle between the best and the worst scenario compared to the linear case. Finally, the number of data points in each subset (resp. calibration and validation) can be varied. The influence of choosing six experiments for calibration instead of five on the performance of the submodel was investigated (Table 4.13). Similar conclusions can be drawn as in the case where 5 experiments were used for calibration: (1) the linear and exponential model lead to optimal criteria values for the same set of experiments, whereas the quadratic model points towards a different set of experiments; (2) the quadratic model yields best values for the uncorrected criteria, whereas the exponential model is superior for the corrected criteria.

**Table 4.12:** Results for the linear and exponential relation using the experiments that gives the best performance for the quadratic relation based on 5 experiments for calibration

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Linear</th>
<th>Exponential</th>
</tr>
</thead>
<tbody>
<tr>
<td>RMSE</td>
<td>0.1998</td>
<td>0.1273</td>
</tr>
<tr>
<td>R²</td>
<td>0.9145</td>
<td>0.9653</td>
</tr>
<tr>
<td>TIC</td>
<td>0.0525</td>
<td>0.0336</td>
</tr>
<tr>
<td>AIC</td>
<td>-2.9947</td>
<td>-4.9504</td>
</tr>
<tr>
<td>AIC_c</td>
<td>3.0053</td>
<td>1.0496</td>
</tr>
<tr>
<td>BIC</td>
<td>-3.7758</td>
<td>-5.7316</td>
</tr>
<tr>
<td>BIC_c</td>
<td>2.2242</td>
<td>-0.2684</td>
</tr>
<tr>
<td>FPE</td>
<td>0.0931</td>
<td>0.0378</td>
</tr>
<tr>
<td>FPE_c</td>
<td>6.0931</td>
<td>6.0378</td>
</tr>
<tr>
<td>LILC</td>
<td>-6.0429</td>
<td>-7.9987</td>
</tr>
<tr>
<td>LILC_c</td>
<td>-0.0429</td>
<td>-1.9987</td>
</tr>
</tbody>
</table>
Table 4.13: Results of the cross-validation using 6 experiments for calibration

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Linear relation</th>
<th>Quadratic relation</th>
<th>Exponential relation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Best Value</td>
<td>Exp. (°C)</td>
<td>Worst Value</td>
</tr>
<tr>
<td>RMSE</td>
<td>0.0637</td>
<td>40, 45, 50, 55, 65, 70</td>
<td>0.2226</td>
</tr>
<tr>
<td>R²</td>
<td>0.9706</td>
<td>40, 45, 50, 55, 65, 70</td>
<td>0.8508</td>
</tr>
<tr>
<td>TIC</td>
<td>0.0176</td>
<td>40, 45, 50, 55, 65, 70</td>
<td>0.0548</td>
</tr>
<tr>
<td>AIC</td>
<td>-10.3484</td>
<td>40, 45, 50, 55, 65, 70</td>
<td>-3.8308</td>
</tr>
<tr>
<td>AICc</td>
<td>-6.3485</td>
<td>40, 45, 50, 55, 65, 70</td>
<td>0.1692</td>
</tr>
<tr>
<td>BIC</td>
<td>-10.7650</td>
<td>40, 45, 50, 55, 65, 70</td>
<td>-4.2473</td>
</tr>
<tr>
<td>BICc</td>
<td>-6.7650</td>
<td>35, 45, 50, 55, 65, 70</td>
<td>-2.473</td>
</tr>
<tr>
<td>FPE</td>
<td>0.0081</td>
<td>40, 45, 50, 55, 65, 70</td>
<td>0.0991</td>
</tr>
<tr>
<td>FPEc</td>
<td>4.0081</td>
<td>40, 45, 50, 55, 65, 70</td>
<td>4.0991</td>
</tr>
<tr>
<td>LILC</td>
<td>-13.1821</td>
<td>40, 45, 50, 55, 65, 70</td>
<td>-6.644</td>
</tr>
<tr>
<td>LILCc</td>
<td>-9.1821</td>
<td>40, 45, 50, 55, 65, 70</td>
<td>-2.644</td>
</tr>
<tr>
<td></td>
<td>Best Value</td>
<td>Exp. (°C)</td>
<td>Worst Value</td>
</tr>
<tr>
<td>RMSE</td>
<td>0.0193</td>
<td>35, 45, 50, 60, 65, 70</td>
<td>0.1431</td>
</tr>
<tr>
<td>R²</td>
<td>0.9991</td>
<td>35, 45, 50, 60, 65, 70</td>
<td>0.9306</td>
</tr>
<tr>
<td>TIC</td>
<td>0.0050</td>
<td>35, 45, 50, 60, 65, 70</td>
<td>0.0362</td>
</tr>
<tr>
<td>AIC</td>
<td>-14.5763</td>
<td>35, 45, 50, 60, 65, 70</td>
<td>-4.1311</td>
</tr>
<tr>
<td>AICc</td>
<td>-2.5763</td>
<td>35, 45, 50, 60, 65, 70</td>
<td>7.8689</td>
</tr>
<tr>
<td>BIC</td>
<td>-15.2010</td>
<td>35, 45, 50, 60, 65, 70</td>
<td>-4.7558</td>
</tr>
<tr>
<td>BICc</td>
<td>-3.2010</td>
<td>35, 45, 50, 60, 65, 70</td>
<td>7.2442</td>
</tr>
<tr>
<td>FPE</td>
<td>0.0011</td>
<td>35, 45, 50, 60, 65, 70</td>
<td>0.0615</td>
</tr>
<tr>
<td>FPEc</td>
<td>12.0011</td>
<td>35, 45, 50, 60, 65, 70</td>
<td>12.0615</td>
</tr>
<tr>
<td>LILC</td>
<td>-18.8267</td>
<td>35, 45, 50, 60, 65, 70</td>
<td>-8.3812</td>
</tr>
<tr>
<td>LILCc</td>
<td>-6.8267</td>
<td>35, 45, 50, 60, 65, 70</td>
<td>3.6185</td>
</tr>
<tr>
<td></td>
<td>Best Value</td>
<td>Exp. (°C)</td>
<td>Worst Value</td>
</tr>
<tr>
<td>RMSE</td>
<td>0.0620</td>
<td>40, 45, 50, 60, 65, 70</td>
<td>0.1759</td>
</tr>
<tr>
<td>R²</td>
<td>0.9756</td>
<td>40, 45, 50, 60, 65, 70</td>
<td>0.9038</td>
</tr>
<tr>
<td>TIC</td>
<td>0.0177</td>
<td>40, 45, 50, 60, 65, 70</td>
<td>0.0422</td>
</tr>
<tr>
<td>AIC</td>
<td>-10.4928</td>
<td>40, 45, 50, 60, 65, 70</td>
<td>-5.1973</td>
</tr>
<tr>
<td>AICc</td>
<td>-6.4928</td>
<td>40, 45, 50, 60, 65, 70</td>
<td>-1.1973</td>
</tr>
<tr>
<td>BIC</td>
<td>-10.9093</td>
<td>40, 45, 50, 60, 65, 70</td>
<td>-5.6138</td>
</tr>
<tr>
<td>BICc</td>
<td>-6.9093</td>
<td>40, 45, 50, 60, 65, 70</td>
<td>-1.6138</td>
</tr>
<tr>
<td>FPE</td>
<td>0.0077</td>
<td>40, 45, 50, 60, 65, 70</td>
<td>0.0586</td>
</tr>
<tr>
<td>FPEc</td>
<td>4.0077</td>
<td>40, 45, 50, 60, 65, 70</td>
<td>4.0586</td>
</tr>
</tbody>
</table>
4.5 Conclusion

Table 4.13: Results of the cross-validation using 6 experiments for calibration

<table>
<thead>
<tr>
<th></th>
<th>40, 45, 50, 60, 65, 70</th>
<th>35, 40, 50, 55, 60, 70</th>
</tr>
</thead>
<tbody>
<tr>
<td>LILC</td>
<td>-13.3264</td>
<td>-8.0309</td>
</tr>
<tr>
<td>LILC&lt;sub&gt;c&lt;/sub&gt;</td>
<td>-9.3264</td>
<td>-4.0309</td>
</tr>
</tbody>
</table>

Comparing the results of table 4.11 and table 4.13 shows that the linear relation and exponential models add the experiment at 70 °C as extra, whereas the quadratic relation adds the experiment at 45 °C.

However, the relative calculated values of the criterion are different based on five or six experiments for calibration:

- Linear relation: using 6 experiments for calibration: RMSE, R<sup>2</sup>, TIC and FPE are worse, the opposite is valid for the other criteria
- Quadratic relation: using 6 experiments for calibration: RMSE, R<sup>2</sup>, TIC, AIC, BIC, FPE, FPE<sub>c</sub> and LILC are worse, the opposite is valid for the other criteria
- Exponential relation: using 6 experiments for calibration: RMSE, R<sup>2</sup>, TIC and FPE are worse, the opposite is valid for the other criteria

All the above illustrates that model selection is a very tedious task and that no clear solution is provided when applying different model selection criteria. The picture gets even more blurred when considering different subsets for calibration and validation. It can be concluded that deciding on a model structure based on a single criterion is dangerous. At this stage we recommend that at least different criteria need to be investigated. In the case investigated here most checks point in the direction of the exponential model as the superior one. However, this choice remains subjective and clearly there is a need for a more comprehensive model selection criterion. Finding such a criterion is, however, beyond the scope of this work.

4.5 Conclusion

The drying behaviour of pharmaceutical granules can be modelled with the drying model as presented by [Mezhericher et al., 2007]. The drying behaviour elapses in two phases, which gives rise to two submodels in the mechanistic drying model (Table 4.14). In the first drying phase the surface water evaporates, while in the second drying phase the water inside the granule evaporates. The submodel of the second drying phase consists of an empirical power coefficient, β, however, no information about this parameter was found in the literature. Based on a sensitivity analysis it can be concluded that β has a significant influence on the moisture content of the granule.
In this work the aim was to calibrate the $\beta$-parameter by means of drying experiments with a continuous fluidized bed dryer. The extension of a drying model with a relation for an empirical parameter as function of the gas temperature was investigated in detail with respect to the choice of model structure. Different criteria, either accounting for the model complexity or not, and either corrected for small sample size or not, were tested for three different model candidates: linear, quadratic, exponential. The following conclusions can be drawn:

- Dependent on the model selection criterion different submodels are selected:
  - The uncorrected criteria select the quadratic relation
  - The corrected criteria, the F-test and the $\text{PRESS}_p$ select the exponential relation

- Different model structures have a different 'ideal' experimental subset for their calibration meaning that the information content of each dataset is different for different relations

- When using 6 datasets for calibration, again different subsets are optimal for different relations; the uncorrected criteria values get worse though when using more datasets for calibration

- Taking all aspects into account the exponential relation based on the logarithmic approach has been chosen as final model structure (Eq. 4.34)

- More work is needed to develop a comprehensive model selection criterion

The resulting model was validated using experimental data of independent experiments at different gas temperatures. The resulting validated drying model is able to predict the evolution of the moisture content for one single granule (Table 4.14).

The validated drying model can now be used in further research. The model can be extended towards a certain amount of granules, meaning the implementation in a PBE (Chapter 8), to investigate the distribution in moisture content of granules.
Table 4.14: Summary of the drying model

<table>
<thead>
<tr>
<th>Assumptions</th>
<th>Possible input variables</th>
<th>Critical end characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spherical granules</td>
<td>Gas temperature</td>
<td>Moisture content of the granule X (kg water/kg total mass)</td>
</tr>
<tr>
<td></td>
<td>Gas flow rate</td>
<td>Temperature distribution in the granule</td>
</tr>
<tr>
<td>Spherical wet core</td>
<td>Gas humidity</td>
<td>Mass of the granule (kg)</td>
</tr>
<tr>
<td></td>
<td>Pressure in the dryer</td>
<td></td>
</tr>
<tr>
<td>Constant particle radius</td>
<td>Granule radius</td>
<td>Density of the granule (kg granule/m³ granule)</td>
</tr>
<tr>
<td></td>
<td>Porosity of the granule (Volume gas of a dried granule per total volume of the granule)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Initial moisture content of the particle</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Density of the solid phase</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Thermal conductivity of the solid phase</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Specific heat of the solid</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dynamic viscosity of the gas</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Density of the gas</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Thermal conductivity of the gas</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Specific heat of the gas</td>
<td></td>
</tr>
</tbody>
</table>
Chapter 4. Development of a single particle drying model
CHAPTER 5

Global Sensitivity Analysis applied to a single particle drying model


**Abstract:**
The development of mechanistic models for pharmaceutical processes is of increasing importance due to a noticeable shift towards continuous production in the industry. Sensitivity analysis is a powerful tool during the model building process which is the ultimate objective of this thesis. A GSA, exploring sensitivity in a broad parameter space, is performed to detect the most sensitive factors in the single particle drying model. \( \beta_2 \) is found to be the most important factor which is useful information when performing model calibration and/or model reduction. In addition, several GSA techniques are analysed and compared with respect to the correct conclusion and computational load.

5.1 Introduction

5.1.1 Pharmaceutical fluidized bed drying process

The ongoing transition from batch to continuous production systems in the pharmaceutical industry [Leuenberger 2001b] requires a confident control strategy of the process to safeguard the product quality at all times. In this respect, batch processes mostly rely on off-line time-consuming measurements, whereas continuous systems could make use of on-line measurement tools and real-time
adaptation of sensitive input variables. The latter requires thorough process
knowledge and insight. Mechanistic models are a useful tool to obtain detailed
information about the process and, hence, to support development of control
strategies.
In the next part of the introduction the focus is on the use of a sensitivity anal-
ysis during model building. A section is added to introduce the symbols and
the notation used in this chapter for the reader’s sake. Furthermore, several
sampling techniques that are used during a GSA are discussed. In the last part
of the introduction, the GSA techniques used in this contribution are described
in more detail.

5.1.2 Sensitivity analysis and its added value to mathematical modelling

Models are becoming increasingly important to gather knowledge about pro-
cesses, but also to support decision-making processes. Good practice in model
development and application is needed to obtain credible results, valuable
information and insight in the process. Ten basic steps of good, disciplined model
practice are described by Jakeman et al. [2006]. During model building, uncertain-
ty and sensitivity analysis are important steps. In an uncertainty analysis
the uncertainties in input variables are propagated through the model in order
to compute the uncertainty on the output. A sensitivity analysis is the study
of how the uncertainty in the output of a model (numerical or otherwise) can
be apportioned to different sources of uncertainty in the model input (or model
structure, parameters) [Saltelli et al., 2004]. This provides useful information
if one is to reduce the model output uncertainty.
In figure 5.1 a schematic representation of a model is presented. A model $H$
computes one or more outputs $y$ with a number of input variables $u$ and par-
parameters $P$. The vector $z$ represents the variables calculated during the simulation
of the model. Performing a sensitivity analysis means that different values for
the inputs and parameters are investigated, respectively indicated with the sub-
scripts $R$ and $S$ in figure 5.1 In the following, inputs and parameters used in
the analysis are referred to as factors. Depending on the way a factor appears
in the model, the output can decrease or increase in a more or less significant
way.

A first differentiation in available techniques can be made between the local,
One Factor at a Time (OAT) and the global methods for sensitivity analy-
sis (Fig. 5.2). The local methods (i.e. LSA) focus on the sensitivity around
one point in the factor space. An example in a certain two-dimensional fac-
tor space is presented in figure 5.2 To calculate the sensitivity in a LSA the
5.1. Introduction

The central difference scheme is most often used:

\[
\frac{\partial y(t)}{\partial x_i} = \frac{y(t, x_i + \xi x_i) - y(t, x_i - \xi x_i)}{2\xi x_i}
\] (5.1)

with \(y(t, x_i)\) the output variable, \(x_i\) the nominal value of the perturbed factor and \(\xi\) the perturbation factor. The perturbation factor should be chosen adequately, as a too low value can lead to numerical issues and whereas too high values lead to potentially inaccurate sensitivities due to model non-linearity (given the factor is non-linear in the model). The drawback of this local method is that sensitivity can be very different at different locations in the factor space which limits the conclusions to the chosen point only. The OAT technique simply varies one factor at a time, and is a pseudo-global technique. The difference between the values for the factor is much larger compared to a LSA, but as only one factor is varied, the technique is not able to detect interactions among the factors. GSA can potentially also cope with the interactions as it explores the whole factor space, and as such much more information can be obtained. Downside is that these methods are computationally more expensive.

Several methodologies to test the sensitivity are available in the literature

\[\text{Saltelli et al., 2004} \quad \text{Saltelli et al., 2005} \quad \text{Cacuci and Ionesco-Bujor, 2004}.\]

The GSA techniques can be roughly divided into the following types: quantitative approaches (regression-based, rank-based regression, variance-based, moment-independent techniques, meta-modeling, techniques based on Monte Carlo sampling, etc.), qualitative techniques (Saltelli et al. 2008, or methods...
with regional properties [Pappenberger et al., 2006]. On the other hand screening techniques exist, e.g. the OAT screening techniques. An estimate of partial derivatives is used to detect the effect of one uncertain factor on the output while the other factors are fixed. In this sense there are also the so-called local sensitivity measures [Campolongo et al., 2011]. These methods require a lower number of model evaluations, which is interesting when a high number of factors is present in the model [Campolongo et al., 2007]. However, interactions between factors cannot be assessed since no more than one input is simultaneously changed [Campolongo et al., 2011]. Morris [Morris, 1991] proposed a screening method for models with a high number of uncertain factors and/or an expensive computation of the model output [Morris, 1991]. The Morris Screening is an interesting tool to use as a first step when dealing with complex models.

There are several incentives to perform a sensitivity analysis:

- Increased understanding of the model behaviour: What is the quantitative impact of decreasing or increasing a factor $F$ on the output $y$: $F \uparrow \Rightarrow y \uparrow$ or $\downarrow$ (or a non-sensitive output).

- Model calibration: Based on the sensitivity of the factors it can be decided which factor should preferably be estimated using the experimental data. If a factor is more sensitive, the factor should be changed less to achieve a better description of the experimental data. In contrast, if a factor is not sensitive then it is impossible to estimate that factor based on the available data.

- Model reduction: The presence of non-sensitive parameters in the model can be questioned. Such parameters can be eliminated eventually when building a reduced model.

- Prediction uncertainty: If the model has an uncertain sensitive parameter, the output will also be uncertain. When one aims to reduce output uncertainty, focus should be on these parameters

Symbols and notation

The model of interest computes several scalar outputs $y$, which is required for most sensitivity analysis methods, based on $k$ factors ($x_1, x_2 \ldots x_k$) ($y = H(x)$), where these factors can be input variables ($u$) and/or parameters ($P$) (Fig. 5.1). A computational experiment consists of $N$ runs, meaning that $N$ output values are generated. Given an experimental design, the $j$th row of the design matrix $X$ ($N \times k$-matrix) is the set of factor values ($x$) for the $j$th run. $X_i$ denotes a vector with values for factor $i$, and $X_{-i}$ the $N \times (k - 1)$-matrix with all factors except $X_i$. $Y$ is the vector ($N \times 1$) containing all scalar outputs.
5.1. Introduction

Sampling techniques

Performing a sensitivity analysis requires a set of factor values for each of the input factors that is considered in the sensitivity analysis. For this purpose, different sampling techniques are available, which sample values for the input factors with an interval. The interval used in the analysis can be chosen based on expert knowledge; e.g. the experimental and/or physical limitations of the input variables. For parameters the range can also be fixed by performing a literature study or by choosing realistic values. Random numbers or standard random numbers is the most basic form of probability sampling. It means that independent values of the random factor are uniformly distributed over the entire interval that is to be sampled. Pseudo-random numbers are numbers computed using a specific algorithm, but satisfying an accepted set of tests to mimic a truly random natural process [Sobol’, 1998] [Giunta et al., 2003].

In Monte Carlo computations the values for the factors are replaced by various pseudo-random numbers, pseudo-random sampling is also known as pseudo-Monte Carlo sampling [Giunta et al., 2003]. An advantage of pseudo-random sampling is the ease of implementation, however, the disadvantage is that large regions of the design space are not explored [Giunta et al., 2003]. Stratified Monte Carlo sampling generates a more uniform sampling of the design space, because each interval is subdivided into bins [Koehler and Owen, 1996]. The bins have an equal size if all variables have a uniform probability distribution. A better coverage of the design space and the flexibility to choose the number of subintervals are advantages of this approach. In some methods the option exists to use a different number of bins for each interval [Giunta et al., 2003]. For stratified samples it is recommended that there are two bins for each variable, and as such there are at least $2^k$ samples generated. For expensive models or models with large $k$ this is a serious drawback.

Latin Hypercube Sampling (LHS) is a type of stratified sampling [Diwekar and Kalagnanam, 2004] [McKay et al., 2000]. LHS is based on the idea of a Latin square meaning that there is only one sample in each row and each column [Minasny and Bratnay, 2006]. In each interval one value is selected at random with respect to the probability density in the interval. The $N$-values for the different factors are then paired with each other in a random manner based on a pseudo-random number generator. The drawback is that the method is one-dimensional and does not provide good uniformity over the whole volume of a $k$-dimensional unit hypercube [Diwekar and Kalagnanam, 2004]. The possible correlation between the variables is another deficiency, which can be compensated by using the correlation control method proposed by Iman and Conover (1982). When quasi-random sequences are used, also called low-discrepancy sequences, it is called a quasi-Monte Carlo simulation. The term ‘low discrepancy’ means that the discrepancy between the distribution of generated points and a distribution
with equal proportions of each sub-cube of a uniform partition of the hypercube is minimised. Several quasi-random sequences have been described in the literature; Sobol’ [1979], Halton [1960], Faure [1982], Hammersley [1960], etc. The objective of these quasi-Monte Carlo methods is that they ensure even coverage and normally have a faster speed of convergence. Quasi-random sequences are deterministic sequences; the position of previously sampled points is known and the construction of the samples is done in such a way to avoid the presence of gaps and clusters [Sobol’ and Kucherenko, 2005] [Tarantola and Becker, 2012]. There are three characteristics of the commonly used Sobol’ quasi-random sequences; (1) best uniformity of the generated distribution if $N \to \infty$, (2) good distribution for small initial sets and (3) a very fast algorithm [Sobol’, 1976] [Tarantola and Becker, 2012].

Morris Screening

Morris Screening, also known as the original Elementary Effect (EE)-method, is used to determine the factors which are (1) negligible, (2) linear and additive, or (3) nonlinear or (4) involved in interactions with other inputs. Two sensitivity measures are computed for each input; $\mu$ and $\sigma$. $\mu$, an (absolute) measure of central tendency, determines the ‘overall’ influence of the factor, while $\sigma$, a measure of spread, is important to detect the higher order effects of the factor, i.e. non-linear and/or interactions with other parameters [Morris, 1991].

Several individually randomized OAT experiments form the experimental design. It is assumed that $x_i$ is scaled (values in the interval $[0, 1]$, uniformly distributed), which is a commonly used approach within sensitivity analysis. The method computes for each factor a number of incremental ratios, which are called the $EE$s. The method is restricted to a region of experimentation $\omega$, which is a regular $k$-dimensional $p$-level grid, as each factor is assumed to vary across $p$ selected levels in the input factor space [Morris, 1991]. The $EE$ of the $i^{th}$ factor is defined as:

$$EE_i(x) = \frac{[y(x_1, x_2, \ldots, x_i-1, x_i + \Delta, x_{i+1}, \ldots, x_k) - y(x)]}{\Delta}$$ (5.2)

with $\Delta$ a predetermined multiple of $1/(p - 1)$. The finite distributions $F_i$ of the calculated $EE$s for factor $i$ are obtained by randomly sampling different factors from $\omega$, i.e. $d_i(x) \sim F_i$. The number of $EE$s for each $F_i$ is $p^{k-1}[p - \Delta(p - 1)]$. To ensure at least a certain symmetric treatment of inputs, although the design strategy does not guarantee equal-probability sampling from each $F_i$, $p$ is chosen even and $\Delta$ as $p/[2(p - 1)]$. Morris proposed an efficient design that constructs $r$ trajectories of $(k + 1)$-points in the factor space, each providing $k$
5.1. Introduction

The sensitivity measures are estimated with these $r$ EEs from each $F_i$. The total number of runs is thus $r(k + 1)$ [Morris, 1991]. $x$ produces a simple random sample, and with this design matrix the output $y$ is computed which is used for the calculation of the sample mean ($\bar{d}_i$) and variance ($S_i^2$) of the observed EEs for input $i$. These two measures are unbiased estimators of the mean and variance of $F_i$, and the standard error of the mean can be estimated as $SEM_i = S_i/\sqrt{r}$ [Morris, 1991]. Campolongo et al. [2007] described the use of $\mu^*$, which is the estimate of the mean of the distribution of the absolute values of the EEs, because for a complex model with several inputs and outputs the simultaneous use of the two sensitivity measures may be inefficient. $\mu^*$ is enough for a reliable ranking of the factors. When the model is non-monotonic, $\mu^*$ solves the problem of the effects of opposite signs, however, there is a loss of information on the sign of the effect. A high value for $\mu$ and $\mu^*$ indicates that the sign of the effect is always identical; suggesting a monotonic output function. A low value for $\mu$ in conjunction with a high value for $\mu^*$ occurs when the other factors lead to a variation in sign of the output deviations [Campolongo et al., 2007].

Contribution to Sample Mean/Variance (CSM/CSV) plot

Graphical sensitivity tools, being qualitative techniques, are interesting to detect the relationship between uncertain model factors and model outputs [Tarantola et al., 2012]. The Contribution to Sample Mean (CSM) plot was developed by Sinclair [1993], and further developments were made by Bolado-Lavin et al. [2009]. In this tool a random sample of the factors is used for the analysis. An extension of the CSM plot was made by Tarantola et al. [2012] by introducing the Contribution to Sample Variance (CSV) plots. A lot more information can be obtained by the CSV compared to the standard sensitivity indices (Section 5.1.2) when investigating input-output relationships. The standard indices are helpful to detect the most important input factor, however, no information is obtained about how to reduce the range of uncertainty of the important input factor for a given target reduction of the output variance [Tarantola et al., 2012]. An advantage of the graphical tools is the low number of simulations which are required to draw conclusions compared to e.g. Monte Carlo based methods.

The CSM for an input $X_i$ is defined by:

$$CSM_{X_i}(q) = \frac{1}{E(Y)} \int_{-\infty}^{\infty} \cdots \int_{-\infty}^{\infty} \int_{-\infty}^{F_i^{-1}(q)} \prod_{i=1}^{k} p_i(X_i)H(X_1, X_2, ..., X_k) dX_i dX_1 ... dX_{i-1} dX_{i+1} ... dX_k$$

(5.3)

99
\[ E(Y) = \int_{-\infty}^{\infty} \cdots \int_{-\infty}^{\infty} \prod_{i=1}^{k} p_i(X_i) H(X_1, X_2, \ldots, X_k) \, dX_1 \cdots dX_k \quad (5.4) \]

with \( q \in [0, 1] \), \( E(Y) \) the mean value of the model output, \( F_i^{-1}(q) \) the inverse cumulative distribution of \( X_i \) at quantile \( q \) and \( p_i \) the probability density function. The \( CSM_{X_i}(q) \) is plotted as function of \( q \), representing a fraction of the distribution range \( X_i \). \( CSM_{X_i}(q) \) is the fraction of the output mean which corresponds to the values of \( X_i \) smaller or equal than its \( q \)-quantile. By definition \( CSM_{X_i}(0) = 0 \) and \( CSM_{X_i}(1) = 1 \) \cite{Bolado-Lavin2009, Tarantola2012}. The CSV for factor \( i \) is defined as:

\[
CSV_{X_i}(q) = \frac{1}{V(Y)} \int_{-\infty}^{\infty} \cdots \int_{-\infty}^{\infty} \prod_{i=1}^{k} p_i(X_i) (H(X_1, X_2, \ldots, X_k) - E(Y))^2 \, dX_1 \cdots dX_i \cdots dX_{i-1} \cdots dX_{i+1} \cdots dX_k \quad (5.5)
\]

\[
V(Y) = \int_{-\infty}^{\infty} \cdots \int_{-\infty}^{\infty} \prod_{i=1}^{k} p_i(X_i) (H(X_1, X_2, \ldots, X_k) - E(Y))^2 \, dX_1 \cdots dX_k \quad (5.6)
\]

with \( V(Y) \) the variance of the model output. The CSV is calculated using a constant mean \( E(Y) \) over the full range of all factors. CSV is plotted in a similar way as CSM. When the curve of the CSM and the CSV is near the diagonal, it means that the contribution to the mean or the variance is equal throughout the full range of the factor.

**Regression-based and rank-based regression**

For the performance of a sensitivity analysis several Monte Carlo-based techniques are available \cite{Helton1993}. The space of the input factors is sampled and the relationship between the model output and input factors is analysed via Standardized Regression Coefficients (SRCs) correlation coefficients, Partial Correlation Coefficient (PCC) or correlation ratios. However, the assumptions of linearity or monotonic relationship are serious limitations, especially for complex models \cite{Urbonas2010}. Most popular in this group are the SRCs and these measures are based on a linear regression model and not on the original output. For this method, it is assumed that no correlation is apparent between the different input factors. If one assumes that the model
5.1. Introduction

has an error-free linear form, the following is valid \cite{Saltelli2008}:

\[ Y = \sum_{i=1}^{k} \Omega_i X_i \]  \hspace{1cm} (5.7)

with \( \Omega_i \) the fixed coefficients and \( X_i \) the independent factors which are normally distributed \( (X_i \sim N(\bar{x}_i, \sigma_{X_i}) \) with \( \bar{x}_i = 0 \) for \( i = 1, 2, ..., k \) (where \( \bar{x}_i \) and \( \sigma_{X_i} \) are respectively the mean and the standard deviation of the factor)). Additional assumptions are:

\[ \sigma_{X_1} < \sigma_{X_2} < ... < \sigma_{X_k} \]  \hspace{1cm} (5.8)

\[ \Omega_1 > \Omega_2 > ... > \Omega_k \]  \hspace{1cm} (5.9)

The assumption mentioned in equation 5.9 is because of equation 5.8. Because the independent variables are normally distributed, the output variable \( Y \) is also normally distributed, and the standard deviation of the output \( \sigma_Y \) becomes

\[ \sigma_Y = \sqrt{\sum_{i=1}^{k} \Omega_i^2 \sigma_{X_i}^2} \]  \hspace{1cm} (5.10)

If the relative importance of \( X_i \) on the output variable \( Y \) is of interest, the partial derivative of \( Y \) to \( X_i \) is most often taken:

\[ S_{\sigma_{X_i}} = \frac{\sigma_X \partial Y}{\partial X_i} \]  \hspace{1cm} (5.11)

which yields for the linear model \( S_{\sigma_{X_i}} = \Omega_i \). However, this is not really reasonable, because this means that the ordering of the factors by importance would be

\[ X_1 > X_2 > ... > X_k \]  \hspace{1cm} (5.12)

Equation 5.11 can be improved by normalizing the derivative using the input-output standard deviations:

\[ S_{\sigma_{X_i}} = \frac{\sigma_{X_i} \partial Y}{\sigma_X \sigma_Y} = \Omega_i \frac{\sigma_{X_i}}{\sigma_Y} \]  \hspace{1cm} (5.13)

If equation 5.13 is combined with equation 5.10 then it can be concluded that

\[ \sum_{i=1}^{k} (S_{\sigma_{X_i}})^2 = 1 \]  \hspace{1cm} (5.14)

The use of the normalized equation is a good way to rank the different input factors based on sensitivity. It depends both on \( \sigma \) and \( \Omega \), just as it should, and
secondly the sensitivity measures are normalized to one. This is the reason why after performing a Monte Carlo simulation, the output \((Y)\) at a specific point in time of the simulation is processed using a linear regression [Saltelli, 2006]. This linear regression is performed on the scaled output and scaled degrees of freedom (autoscaling: scaling by first subtracting the mean followed by division by the standard deviation).

\[
Y_{(j)} = b_0 + \sum_{i=1}^{k} b_{X_i} X_{i}^{(j)}
\] (5.15)

with \(Y_{(j)}\) the output for one simulation, \(X_{i}^{(j)}\) are the degrees of freedom used in this simulation and \(b_0, b_{X_i}\) are respectively the intercept and linear coefficients of the linear model that is constructed. The coefficients \(b_0\) and \(b_{X_i}\) are determined by solving a straightforward least squares problem, based on the squared differences between the output values produced by the regression model and the actual model output produced by Monte Carlo simulation. Asymptotically \(\hat{b}_0 \approx 0\) and \(\hat{b}_{X_i} \approx \Omega_i\) for \(i = 1, 2...k\). Besides these coefficients, their standardized equivalents \(\hat{\beta}_{X_i}\) (the SRC) are determined as

\[
\hat{\beta}_{X_i} = \hat{b}_{X_i} \sigma_{X_i} / \sigma_Y \approx \Omega_i \sigma_{X_i} / \sigma_Y
\] (5.16)

Comparing equation 5.16 with equation 5.13 it can be proven that \(\hat{\beta}_{X_i}\) coincides with \(S_{X_i}^{\sigma}\) for linear models. Therefore for linear models:

\[
\sum_{i=1}^{k} (S_{X_i}^{\sigma})^2 = \sum_{i=1}^{k} (\hat{\beta}_{X_i})^2 = 1
\] (5.17)

If the model is non-linear, both measures (\(\hat{\beta}_{X_i}\) and \(S_{X_i}^{\sigma}\)) will be different, but the \(\beta\)'s will be a more robust and reliable measure of sensitivity, even for non-linear models. \(\beta\)’s take the entire space of input factors into account, which is advantageous over \(S_{X_i}^{\sigma}\). To ensure a reliable value for \(\beta\), \(N\) should be large compared to \(k\). The \(\sum_{i=1}^{k} (\hat{\beta}_{X_i})^2\) equals the fraction of linearity of the model, more precisely known as the coefficient of determination, \(R_Y^2\), which is equal to the fraction of variance of the original data (Monte Carlo simulation results), explained by the regression model (Eq. 5.15) [Saltelli, 2006]. This value should at least be 0.7 for SRC to be a valid technique. In fact, for all regression-based methods the ranking is good as long as \(R_Y^2\) is close to 1, as a low value means that a large part of the model output variance is left unaccounted in the sensitivity ranking [Urbonas et al., 2010] [Homma and Saltelli, 1996]. A low value for \(R_Y^2\) can be tackled by applying a rank transformation of the output, and the ranked output is then used for computing the corresponding
5.1. Introduction

rank sensitivity measures (Standardized Rank Regression Coefficient (SRRC), Spearman rank coefficient of correlation, Partial Rank Correlation Coefficient (PRCC)). However, this rank transformation is only valid for monotonic data [Urbonas et al., 2010].

The disadvantage of these methods is that they are computationally expensive, because a lot of samples are required, however, after simulation of the model the analysis is fast, and all measures can be calculated using the same sample and model. The obtained coefficients can only be used to assess the importance of a given parameter, whereas the $S_i$ and $S_{Ti}$ can be considered as clues of parameter influence (more details about these indices can be found in the next section). This information is much more precise and more informative with respect to the model behaviour. Homma et al. indicated the latter as being superior compared to the information obtained from other GSA methods, and as such also compared to the information obtained by the regression-based techniques [Homma and Saltelli 1996].

Variance-based sensitivity analysis

Variance-based methods are very popular nowadays, and the obtained indices are much more informative compared to the SRCS which are discussed in the previous section. They are defined from the decomposition of the total output variance into the contribution of the input factors. Advantages are [Tarantola and Becker 2012] [Saltelli et al. 2004] [Urbonas et al. 2010]:

- The analysis is independent of the model structure, no prior assumptions about the model output are taken
- The full range of variation/uncertainty of the input variables can be incorporated in the analysis
- The use of total sensitivity indices enables to quantify the overall interaction effects between factors
- The analysis can be performed on groups of inputs

The decomposition of the model output variance $V(Y)$ for independent input factors is:

$$V(Y) = \sum_i V_i + \sum_i \sum_{j > i} V_{ij} + ... + V_{12...k} \quad (5.18)$$

where

$$V_i = V_{X_i}(E_{X_{\sim i}}(Y | X_i)) \quad (5.19)$$

$$V_{ij} = V_{X_iX_j}(E_{X_{\sim ij}}(Y | X_i, X_j)) - V_{X_i}(E_{X_{\sim i}}(Y | X_i)) - V_{X_j}(E_{X_{\sim j}}(Y | X_j)) \quad (5.20)$$
Division of both sides of equation 5.18 by $V(Y)$ yields:

$$1 = \sum_i S_i + \sum_i \sum_{j>i} S_{ij} + ... + S_{12...k}$$

(5.21)

with $S_i$, $S_{ij}$ the sensitivity indices for first and higher order effects. $S_i$ is normalised, because:

$$V(Y) = V(X_i(E_{X\sim i}(Y | X_i))) + E_{X_i}(V_{X\sim i}(Y | X_i))$$

(5.22)

and $V(X_i(E_{X\sim i}(Y | X_i)))$ varies between 0 and $V(Y)$. This variance decomposition has $(2k - 1)$-terms, but in general only the $k$ first order effects ($S_i$) and the $k$ total effects ($S_{Ti}$) are calculated.

$$S_{Ti} = \frac{E_{X\sim i}(V_{X\sim i}(Y | X_i))}{V(Y)} = 1 - \frac{V_{X\sim i}(E_{X\sim i}(Y | X_i))}{V(Y)}$$

(5.23)

$S_i$ indicates the actual fraction of variance accounted for by each factor [Homma and Saltelli, 1996]. $S_{Ti}$ represents the total effect of factor $i$, i.e. the sum of the first order effects and all interactions with other factors. Another interpretation of the indices is in terms of the expectation of the reduction of the variance, but this is only valid when the factors are not independent [Saltelli and Tarantola, 2002]. $V(X_i(E_{X\sim i}(Y | X_i)))$ is the expected reduction in variance when $X_i$ would be fixed and $E_{X\sim i}(V_{X\sim i}(Y | X_i))$ is the expected residual variance if all factors are fixed except $X_i$, since $V_{X\sim i}(E_{X\sim i}(Y | X_i))$ is the expected value of the variance reduction if all factors except $X_i$ could be fixed [Saltelli et al., 2010].

Different designs are known to calculate these sensitivity indices [McKay et al., 2000] [Campolongo et al., 2011]. Saltelli et al. [Saltelli et al., 2010] proposed to approximate the estimator of $V_i$ as

$$V(X_i(E_{X\sim i}(Y | X_i))) \approx \frac{1}{N} \sum_{j=1}^{N} f(B_j) \left( f(A_B^{(i)})_j - f(A)_j \right)$$

(5.24)

where $A$ and $B$ are $N \times k$-matrices of input factors and $A_B^{(i)}$ is a $N \times k$-matrix where column $i$ is taken from matrix $B$ and the other columns are those of matrix $A$. This is an improvement of the estimator related to the use of quasi-Monte Carlo samples. For the estimate of $S_{Ti}$ the equation of Jansen [Jansen, 1999] is used as proposed by [Saltelli et al., 2010]. To obtain the best estimator for $S_{Ti}$ quasi-random number generation in the $A$, $A_B^{(i)}$ configuration and radial sampling are proposed [Saltelli et al., 2010].

Also here a rank transformation can be performed. However, the use of the rank is conceptually different compared to the rank transformation used in the regression-based techniques. Whereas the rank is essential for these analyses...
5.2. Objectives

to tackle the problem of non-linearity, for the sensitivity indices it is a matter of robustness. To obtain the same results with a different set of input factors, the rank-transformed version of the sensitivity indices is more suitable. But due to the forced linearization, the fraction of the total variance accounted for by the first order indices increases [Homma and Saltelli 1996].

5.2 Objectives

A GSA is performed on the model which describes the drying behaviour of a single pharmaceutical granule as developed in chapter 4. Several GSA techniques are compared to investigate their performance. The GSA is performed for all factors included in the model in order to investigate the influence of the factors on the drying time. The outcome of the GSA on the drying model can be used to perform a better model calibration and/or model reduction (Chapter 7).

5.3 Materials & methods

The single particle drying model consists of two submodels each describing a distinct drying phase (more details can be found in chapter 4). The equation for the evaporation rate of the first drying phase is given by:

\[ \dot{m}_v = h_D (\rho_v, s - \rho_v, \infty) A_d \] (5.25)

where \( \dot{m}_v \) is the mass transfer rate, \( h_D \) the mass transfer coefficient, \( \rho_v, s \) the partial vapour density near the droplet surface, \( \rho_v, \infty \) the partial vapour density in the ambient air and \( A_d \) the surface area of the droplet. The evaporation rate of the second drying phase is given by:

\[
\dot{m}_v = - \frac{8 \pi \varepsilon \beta_1 e^{\beta_2 T_g} D_{v,cr} M_w p_g}{\Re (T_{cr,s} + T_{wc,s})} \ln \left[ \frac{p_g - p_v,i}{p_g - (\frac{\Re}{4 \pi M_w h_D R_p^2} \dot{m}_v + \frac{p_v,\infty}{T_g}) T_p,s} \right] \] (5.26)

with \( \varepsilon \) the crust porosity, \( D_{v,cr} \) the vapour diffusion coefficient (crust pores), \( M_w \) the molecular weight of the liquid, \( p_g \) the pressure of the drying agent, \( T_{cr,s} \) and \( T_{wc,s} \) respectively the temperature of the crust outer surface and of the crust-wet core interface, \( p_v,i \) and \( p_v,\infty \) respectively the partial vapour pressure at the crust-wet core interface and in the ambient air, \( h_D \) the mass transfer coefficient, \( \beta_1 \) and \( \beta_2 \) two calibrated coefficients, \( R_p \) the particle radius and \( T_g \) the temperature of the drying agent. \( R_{w,0, fac} \) refers to the initial moisture content, as a fraction of the dry particle radius \( R_p \).

The nominal values of the factors used in the model are given in table 5.1.
The molecular weight of water has been taken into account because the liquid, evaporating during drying, contains some dissolved solids, and is not purely water. Most GSA techniques require a single value for the output $y$; for this purpose it was opted to choose the time to reach a moisture content of 1.4% as single output value ($t_{\text{proc}}$). A value of 1.4% is a reasonable moisture content to end the drying process and perform the next step in the production of pharmaceutical tablets. The drying model contains 23 factors of interest. In a first step a Morris Screening was performed for all 23 factors, subsequently the 10 most sensitive factors were used for further analysis. Two different sampling techniques were used; LHS, proposed by McKay et al. [2000], and the Sobol sampling technique [Sobol', 1979].

**Table 5.1:** Factors used in the GSA for the single particle drying model. Factors indicated in bold are used for all GSA techniques, whereas the others are only used for the Morris screening.

<table>
<thead>
<tr>
<th>Nr.</th>
<th>Factor</th>
<th>Nominal value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$T_g$</td>
<td>55°C</td>
</tr>
<tr>
<td>2</td>
<td>$V_g$</td>
<td>200 m$^3$/h</td>
</tr>
<tr>
<td>3</td>
<td>$p_g$</td>
<td>101,000 Pa</td>
</tr>
<tr>
<td>4</td>
<td>$R_p$</td>
<td>0.6 mm</td>
</tr>
<tr>
<td>5</td>
<td>Humidity</td>
<td>9%</td>
</tr>
<tr>
<td>6</td>
<td>$T_p,0$</td>
<td>25°C</td>
</tr>
<tr>
<td>7</td>
<td>$\epsilon$</td>
<td>0.05</td>
</tr>
<tr>
<td>8</td>
<td>$\mu_{\text{gas}}$</td>
<td>0.00002 kg/m/s</td>
</tr>
<tr>
<td>9</td>
<td>$\rho_{\text{gas}}$</td>
<td>1.2 kg/m$^3$</td>
</tr>
<tr>
<td>10</td>
<td>$k_{\text{gas}}$</td>
<td>0.0285 W/m/K</td>
</tr>
<tr>
<td>11</td>
<td>$c_{p,\text{gas}}$</td>
<td>1,009 kg/m$^3$</td>
</tr>
<tr>
<td>12</td>
<td>Mw</td>
<td>18.015e-3 kg/mol</td>
</tr>
<tr>
<td>13</td>
<td>$\rho_{\text{liquid}}$</td>
<td>1,000 kg/m$^3$</td>
</tr>
<tr>
<td>14</td>
<td>$\rho_{\text{solid}}$</td>
<td>1,525 kg/m$^3$</td>
</tr>
<tr>
<td>15</td>
<td>$k_{\text{droplet}}$</td>
<td>0.07 W/m/K</td>
</tr>
<tr>
<td>16</td>
<td>$k_{\text{liquid}}$</td>
<td>0.63 W/m/K</td>
</tr>
<tr>
<td>17</td>
<td>$k_{\text{solid}}$</td>
<td>0.75 W/m/K</td>
</tr>
<tr>
<td>18</td>
<td>$c_{p,s}$</td>
<td>1,252 kg/m$^3$</td>
</tr>
<tr>
<td>19</td>
<td>TWC</td>
<td>647.13 K</td>
</tr>
<tr>
<td>20</td>
<td>$\epsilon_{rs}$</td>
<td>0.8</td>
</tr>
<tr>
<td>21</td>
<td>$\beta_1$</td>
<td>4,912.4</td>
</tr>
<tr>
<td>22</td>
<td>$\beta_2$</td>
<td>-0.024282</td>
</tr>
<tr>
<td>23</td>
<td>$R_{w,0,\text{fac}}$</td>
<td>1.025</td>
</tr>
</tbody>
</table>
5.4. Results

5.4.1 Morris Screening

The 23 factors of the drying model are used for the Morris Screening to differentiate in a first approach between the more and less sensitive factors. Subsequently, the less sensitive parameters are not taken into account in applying the other GSA methods. The range for the factors is chosen as 95 - 105% of the nominal value of the factors (Table 5.1). $r$ is chosen as 10, so in total 240 simulations are performed. In figure 5.3 and 5.4 the result is presented for respectively $d_i$ and $d_i^*$. Using $d_i$ to detect the most important factors it is obvious that factor 22 ($\beta_2$) and 1 ($T_g$) are the most important factors, followed by factor 21 ($\beta_1$) and 23 ($R_{w,0, fac}$) where the factor numbers correspond to the numbers mentioned in table 5.1. In fact there are 8 inputs which are clearly separated from the other inputs, which have a mean and standard deviation clearly different from zero. For these 8 inputs with a mean significantly different from 0, the standard deviation is also clearly different from 0. These inputs appear to have effects that involve either curvature (nonlinear) or interactions. The result for $d_i^*$ is comparable, i.e. also in this case the factors with the highest value for $d_i^*$ are the factors 22 and 1. In fact the ranking of the factors is identical for both techniques. As both cases gave the same result, this also means that the sign of the effect is always identical.

The low number of simulations required for this method is very attractive as

![Figure 5.3: $d_i$ and $S_i$ for the Morris Screening of the single particle drying model with 23 factors (Left) and a zoom of the area around the origin (Right) (a first screening method, however it provides only qualitative sensitivity measures. The method ranks the input factors in order of importance, and there is no quantification possible to indicate how much a certain factor is more important than another [Crosetto and Tarantola 2001]. Therefore, further analysis
using other techniques is performed with the aim of obtaining more information about the 10 most sensitive factors resulting from this first screening.

### 5.4.2 Dotty plots

Further analysis is done using the 10 most sensitive factors determined by the Morris screening. Dotty plots were created to gain insight in input-output relations. The scatter plots of the modeled output ($t_{\text{proc}}$), generated by the LHS sampling technique, are presented in figure 5.5. Note that only the dotty plots where the influence is dependent on the value of the factor are presented. It is obvious that the drying time is higher for lower gas temperatures (Fig. 5.5). The single particle drying model was calibrated earlier for $\beta$ and an exponential relationship was introduced as a function of $T_g$, where 2 parameters were introduced ($\beta_1$ and $\beta_2$) (Chapter 4). When $\beta$ decreases, the evaporation rate increases and the drying time will decrease. Based on figure 5.5 it can be concluded that the drying time increases for increasing values of $\beta_1$, as a consequence of the decreasing evaporation rate. The clearest trend was found for $\beta_2$. A high value for $\beta_2$ decreased the drying time enormously independent of the values of the other parameters. However, a low value for $\beta_2$ leads to more variation in drying time. This factor $\beta_2$ was included in the drying model during the calibration step, but no physical explanation can be given for this particular dependence of $\beta$ on the gas temperature. When $R_{w,0,fac}$ increases, it can be expected that the drying time will also increase.
5.4. Results

Figure 5.5: The scatter plots for the single particle drying model with $N = 1000$ using LHS sampling

5.4.3 Contribution to Sample Mean/Variance (CSM/CSV) plot

The analysis was done for 1000 simulations ($N$) using the LHS and the Sobol sampling technique. In figure 5.6, the two-dimensional scatter plots of the $p_g$ and $T_g$ are presented for the LHS and Sobol sampling methodology. The difference between both methods is obvious, whereas the pattern for the LHS design looks random, the design matrix using the Sobol generator is quite regular.

In figure 5.7, the CSM and the CSV plot are presented. $\beta_2$ deviates obviously the most from the bisector, and as such it can be concluded that this is the most important factor. $T_g$, $\beta_1$ and $R_{w,0,frac}$ are subsequently the most sensitive factors. Some curves cross the bisector multiple times. Bolado-Lavin et al. [2009] suggested to calculate the sum of the absolute maximum distances from the diagonal and use this value to rank the factors. The concavity of the CSM plot indicates the relation between the input and the output when this relation is monotonic. A positive monotonic relation leads to a curve below the bisector and a negative monotonic relation to a curve above. This means that
for increasing values of $\beta_2$ the drying time decreases, which was also clear from figure 5.5. In the CSV plot $\beta_2$ deviates the most from the diagonal, indicating that the output variance is the most unevenly distributed for this parameter. This is confirmed by looking at the scatter plots (Fig. 5.5). For most factors the width of the output is equal over the whole range, whereas for $\beta_2$ the width is much smaller for high values compared to lower values. Also for $T_g$, $\beta_1$ and to a lesser extent $R_{w,0,fac}$ the width is dependent on the value of the factor, whereas for the other 6 factors the variance is more evenly distributed over the range of the input.

The scatter plots using the Sobol design matrix are similar to the scatter plots using the LHS sampling method, and are not shown. In figure 5.8, the...
5.4. Results

The CSM and the CSV plot are visualized for the Sobol sampling method. In general the same conclusions can be drawn as for the LHS sampling, but some small deviations can be detected. The curve of $R_{w,0, fac}$ deviates less from the diagonal compared to the LHS sampling method. The same is valid for the CSV plot, and here, $\rho_{liquid}$ and $R_p$ have an even larger influence on the variance.

![Figure 5.8: The CSM (Left) and CSV (Right) plot for the single particle drying model with $N = 1000$ using Sobol sampling. The factors which have less influence are indicated in gray](image)

5.4.4 Regression-based sensitivity analysis

This method is based on 1000 samples, again generated by LHS and Sobol sampling. Using the raw output data, simulated using LHS sampling, the $R_y^2$ is only 0.62, however, the rank transformation increases the coefficient of determination (0.95) significantly (Table 5.2). The rank transformation is performed by ranking the output and use the rank number instead of the actual output value. In fact, this means that the SRCs are not able to provide a reliable ranking of the input factors. The linear regression for both methods is presented in figure 5.9. The difference between both methods is obvious, whereas the data points of the raw values show a more exponential behaviour, the data points resulting from rank transformation are clearly more linear. The linear model outputs of the rank transformed data points follow the linear trend of the simulated model outputs. The linear regression without performing an a priori rank transformation is not able to describe the simulated output of the drying model. The difference between both $R_y^2$ values is a useful indicator for the non-linearity of the model. The SRRCs have no quantitative value compared to the SRCs, but can only be used to rank the input factors.

Both the SRC and the SRRC are the largest for $\beta_2$, but for further ranking the results between the coefficients based on raw values and rank transformation are
Chapter 5. GSA applied to a single particle drying model

Figure 5.9: The linear regression of the output together with the simulated output (raw output (Left) and rank transformed output (Right)), where the input is generated using LHS sampling for the single particle drying model.

different (Table 5.2). The order of significance is switched for $T_g$ and $R_{w,0,fac}$. It is remarkable that the ranking is different compared to the ranking obtained by the CSM plot.

The result, using Sobol to generate the input factors, is presented in figure 5.10.

Table 5.2: Results of the regression-based method for the single particle drying model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SRC</th>
<th>SRRC</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_g$</td>
<td>0.2329</td>
<td>0.2121</td>
</tr>
<tr>
<td>$p_g$</td>
<td>0.0370</td>
<td>0.0727</td>
</tr>
<tr>
<td>$R_p$</td>
<td>0.0119</td>
<td>0.0230</td>
</tr>
<tr>
<td>$\epsilon$</td>
<td>0.0262</td>
<td>0.0187</td>
</tr>
<tr>
<td>Mw</td>
<td>0.0341</td>
<td>0.0753</td>
</tr>
<tr>
<td>$\rho_{liquid}$</td>
<td>0.0351</td>
<td>0.0424</td>
</tr>
<tr>
<td>$\rho_{solid}$</td>
<td>0.0089</td>
<td>0.0057</td>
</tr>
<tr>
<td>$\beta_1$</td>
<td>0.1185</td>
<td>0.1108</td>
</tr>
<tr>
<td>$\beta_2$</td>
<td>0.7293</td>
<td>0.9015</td>
</tr>
<tr>
<td>$R_{w,0,fac}$</td>
<td>0.1242</td>
<td>0.2438</td>
</tr>
<tr>
<td>$R^2_Y$</td>
<td>0.62</td>
<td>0.95</td>
</tr>
</tbody>
</table>

5.10 together with the result of the LHS sampling scheme. The $R^2_Y$ is nearly unchanged when performing the linear regression on the data generated using Sobol sampling compared to LHS. For the most sensitive parameters, i.e. those with the highest values, both sampling schemes give approximately the same result. On less significant factors, e.g. $R_p$ or Mw, the difference between both sampling schemes is more pronounced.
5.4. Results

Figure 5.10: Results of the regression-based GSA for LHS and Sobol as sampling techniques for the single particle drying model

5.4.5 Variance-based sensitivity analysis

The sensitivity indices are computed based on the method proposed by Saltelli et al. [2010]. In table 5.3 the values for the $S_i$ and $S_{Ti}$ are presented. It is important to mention that negative values for the sensitivity indices are theoretically impossible, since the indices are a ratio of variances. But the relative importance of the factors is not affected by this phenomenon [Archer et al., 1997]. The sum of the first order indices is 0.8, meaning that 20% of the variance in the model output is due to interactions between the input factors. The difference between $S_i$ and $S_{Ti}$ and a different ranking for both indices forms a measure for non-linearity. For $S_i$ the highest value corresponds to parameter $\beta_2$, followed by $T_g$ and $\beta_1$, and here, the same conclusions are drawn as for the CSM plot, which was not the case for the SRCs or the SRRCs. Based on $S_i$ it can be concluded that $R_{w,0,fac}$ has almost no impact on the model output. As such, it can be concluded that due to the rank transformation the impact of $R_{w,0,fac}$ is erroneously increased. However, based on $S_{Ti}$ the impact of $R_{w,0,fac}$ is not as low as indicated by the $S_i$, meaning that $R_{w,0,fac}$ is involved in interactions with other factors. As $S_i$ equals 0.73 for $\beta_2$, this means that a reduction of 73% in the variance can be obtained if the value for $\beta_2$ can be fixed. $S_{Ti}$ is 0.85 for $\beta_2$, indicating the variance of $\beta_2$ alone and the
Chapter 5. GSA applied to a single particle drying model

fraction of variance explained by any combination of $\beta_2$ and the other factors. As $S_{Ti}$ for the factors $p_g$ and $\epsilon$ equals almost zero, it means that both factors

<table>
<thead>
<tr>
<th>Parameter</th>
<th>$S_i$</th>
<th>$S_{Ti}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_g$</td>
<td>0.0518</td>
<td>0.1553</td>
</tr>
<tr>
<td>$p_g$</td>
<td>-7.1411e-5</td>
<td>8.9759e-6</td>
</tr>
<tr>
<td>$R_p$</td>
<td>0.0021</td>
<td>0.0055</td>
</tr>
<tr>
<td>$\epsilon$</td>
<td>2.6870e-7</td>
<td>2.4060e-4</td>
</tr>
<tr>
<td>Mw</td>
<td>0.0036</td>
<td>0.0013</td>
</tr>
<tr>
<td>$\rho_{\text{liquid}}$</td>
<td>1.2346e-4</td>
<td>0.0118</td>
</tr>
<tr>
<td>$\rho_{\text{solid}}$</td>
<td>0.0014</td>
<td>0.0033</td>
</tr>
<tr>
<td>$\beta_1$</td>
<td>0.0191</td>
<td>0.0593</td>
</tr>
<tr>
<td>$\beta_2$</td>
<td>0.7279</td>
<td>0.8543</td>
</tr>
<tr>
<td>$R_{w,0,\text{fac}}$</td>
<td>-3.7338e-4</td>
<td>0.0059</td>
</tr>
<tr>
<td>Sum</td>
<td>0.8</td>
<td></td>
</tr>
</tbody>
</table>

can be fixed anywhere in their range of variability without affecting the output. The fact that the porosity ($\epsilon$) has almost no influence on the drying time is quite unexpected.

5.4.6 Comparison of different GSA techniques

In table 5.4 the results of the different methods are summarized. It is clear that the computational effort is low for the Morris screening compared to the other techniques, for which the number of investigated factors is even decreased from 23 to 10. The ranking of the factors is also somewhat different; the ranking of the regression-based technique is obviously different compared to the other techniques. The rank transformation of the output ensures that the original output values are not used to calculate the sensitivity. As such, information is lost during this transformation, which can form an explanation for the different ranking. The difference between $S_i$ and $S_{Ti}$ is limited when looking at the ranking, but is more obvious when looking at the absolute values. This information is important to unravel which factors are responsible for non-linearity.

When a GSA is used to perform a reduction of the full model, the suggestion is to choose the factors included in the analysis based on the goal of the reduced model. The reduction of the single particle drying model has been performed (Chapter 7), where the developed reduction scheme also includes a GSA. The objective was to use the PBM model for simulating the evolution of the moisture content distribution in a fluidized bed drying unit, part of the Consigma™. Therefore the factors are chosen based on the ability to adapt or control these factors during the operation of the dryer. In this chapter, how-
Table 5.4: Comparison of different GSA techniques for the single particle drying model

<table>
<thead>
<tr>
<th>Technique</th>
<th>$k$</th>
<th>$N$</th>
<th>Most sensitive factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morris screening</td>
<td>23</td>
<td>240</td>
<td>$\beta_2-T_g-\beta_1-R_{w,0, fac}$</td>
</tr>
<tr>
<td>CSM plot</td>
<td>10</td>
<td>400</td>
<td>$\beta_2-T_g-...$</td>
</tr>
<tr>
<td>SRC</td>
<td>10</td>
<td>1000</td>
<td></td>
</tr>
<tr>
<td>SRRC</td>
<td>10</td>
<td>1000</td>
<td>$\beta_2-R_{w,0, fac}-T_g-\rho_{solid}$</td>
</tr>
<tr>
<td>$S_i$</td>
<td>10</td>
<td>1000</td>
<td>$\beta_2-T_g-\beta_1-Mw$</td>
</tr>
<tr>
<td>$S_{Ti}$</td>
<td>10</td>
<td>1000</td>
<td>$\beta_2-T_g-\rho_{liquid}$</td>
</tr>
</tbody>
</table>

ever, a more extensive GSA is performed including all factors in the model and the objective was to investigate the influence on the drying time, as well as to compare the different techniques in terms of performance and computational effort. For this reason the outcome of the GSA has to be interpreted in another way. $\beta_2$ is the most sensitive factor, however, it has no physical interpretation. It is a coefficient, introduced in the model during calibration. Due to its sensitivity, this factor is important during calibration, and when the model will be extended or recalibrated for other formulations, this information is important.

### 5.5 Discussion

The different GSA techniques obviously have advantages and disadvantages. A strong limitation of the methods is the requirement to choose one single output value of interest. The result will in any case be dependent on the selection of this output value. When one is only interested in the end quality of the product, one can choose an end point as output value. However, when one wants to monitor and control a process based on the information obtained by a GSA, the mean of a simulated time series or another point during transient conditions can be chosen.

The Morris screening is an interesting technique to start with when a lot of factors are involved in the analysis. A differentiation between less and more important factors can be made without the need for a lot of samples, which limits the analysis time. Graphical tools are useful to detect input-output relations, and dotty plots give basic information about trends (i.e. positive or negative correlations) and the standard deviation of the output. The CSM/CSV plots give the same information, but are also useful to rank factors.

The regression-based sensitivity analysis is an often used technique, however the assumption of linearity is a serious drawback. Performing a rank transformation on the simulated output can be a solution, where the difference between the $R^2$ of the linear regression is an indicator for the non-linearity of the model. Also this method requires significantly more simulations compared...
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to the graphical tools.
The variance-based sensitivity analysis have the same computational effort compared to regression-based sensitivity analysis, but more information is obtained. By calculating the sum of the sensitivity indices the variance explained by the factors, included in the analysis, is known. The difference between the first order effect ($S_i$) and the total effect ($S_{Ti}$) forms an indication for non-linearity.

To conclude for a model with a lot of factors, it is recommended to start with the Morris screening to eliminate part of the factors in further analyses which require more computational effort. The variance-based sensitivity technique is the best option to obtain as much information as possible about the model.

The results shows that $\beta_2$ is the most influential factor. This is an important aspect when performing a model calibration, and the same is valid for $\beta_1$. However, both factors have no physical meaning and were introduced during calibration of the single particle drying model. The significant influence of the gas temperature $T_g$ is of interest when performing experiments or using the equipment during the production of pharmaceutical tablets. If for instance the set point of the gas temperature does not match with the real gas temperature, the drying time will be inaccurately predicted by the model. The fact that the gas velocity has no influence on the drying time gives the operator the possibility to use this input factor to control the fluidization of the particles without disturbing the drying behaviour. However, the real effect of the gas velocity will have to be further investigated. Here, the ambient conditions are constant, whereas in the case of a population of particles the ambient conditions will be different due to drying. The local gas temperature and humidity will therefore also be affected by the local gas velocity. This effect will be further analysed using Population Balance Model(ing) (PBM) (Part III) and Computational Fluid Dynamics (CFD) (Part IV).

5.6 Conclusion

Different GSA techniques are compared for the single particle drying model for pharmaceutical granules using one output, i.e. the time to reach a moisture content of 1.4%.

An important remark is that the used methods can be computationally expensive (depending on the model complexity), but are easy to automate towards other cases. Based on the results, it is suggested to start with a Morris screening when the model consists of a lot of factors. Afterwards, a variance-based sensitivity technique can be performed, which provides a lot of information about the model and the underlying process.

The most sensitive factor for the single particle drying model is $\beta_2$, and thus
5.6. Conclusion

this factor is important for model calibration to reduce output uncertainty.
Chapter 5. GSA applied to a single particle drying model
A GLUE uncertainty analysis of a single particle drying model of pharmaceutical granules


Abstract:
The transition from batch to continuous production processes requires detailed knowledge and process understanding of all consecutive unit operations in a continuous manufacturing line to design adequate control strategies. This can be facilitated by developing mechanistic models of the multi-phase systems in the process. Since modelling efforts only started recently in this field, uncertainties about the model predictions are generally neglected. However, model predictions have an inherent uncertainty (i.e. prediction uncertainty) originating from uncertainty in input data, model parameters, model structure, boundary conditions and software. In this chapter, the model prediction uncertainty is evaluated for a model describing the continuous drying of single pharmaceutical wet granules in a six-segmented fluidized bed drying unit. A validated model describing the drying behaviour of a single pharmaceutical granule in two consecutive phases is used. First of all, the effect of the assumptions at the particle level on the prediction uncertainty is assessed. Secondly, this chapter focuses on the influence of the most sensitive parameters in the model. Finally, a combined analysis (particle level plus most sensitive parameters) is performed and discussed. To propagate the uncertainty originating from the parameter uncertainty to the model output, the Generalised Likelihood Uncertainty Estimation (GLUE) method is used. This method enables a modeller to incorporate...
Chapter 6. A GLUE uncertainty analysis of a drying model

the information obtained from the experimental data in the assessment of the uncertain model predictions and to find a balance between model performance and data precision. A detailed evaluation of the obtained uncertainty analysis results is made with respect to the model structure, interactions between parameters and uncertainty boundaries.

6.1 Introduction to uncertainty analysis

A model is a conceptualisation of reality and inherently includes assumptions and simplifications of the system under study. The latter gives rise to uncertainty of the model predictions [McKay et al., 1999] and evaluating the effect of these uncertainties on the model output is helpful to find out where potential model improvements might be needed. Uncertainty and sensitivity analysis are considered a necessity when composing and evaluating models and are an essential part of Good Modelling Practice (GMP) [Sin et al., 2009].

Prediction uncertainty (= model output uncertainty) results from uncertainties in the model input (data and initial conditions), model structure and model parameters. Furthermore, uncertainty induced by the implementation of the model code in the software package (bugs, numerical integration, etc.) is addressed as an additional source of uncertainty [Belia et al., 2009] [Claeys et al., 2010].

Input uncertainty is mainly due to errors in the measurements or inaccurate sampling techniques or simply in the case the input is unknown (in case of future predictions). Model structure uncertainty arises from the mathematical formulation of the system, which is always an incomplete description of reality as the 'perfect' model does not exist. Model parameter uncertainty originates from an incomplete knowledge of the parameter values used in the model. This lack of knowledge can be caused by the absence of measurements of the parameters or even because the parameters are not directly related to measurable data. The unknown parameter values need to be estimated by calibration based on available data, also referred to as inverse modelling [Refsgaard et al., 2007] [Vrugt, 2002]. Overparameterization (models with too many degrees of freedom) and parameter interactions (i.e. correlations) result in hardly identifiable parameters, i.e. when different parameter combinations give rise to equally good predictions and, hence, no 'unique' optimal parameter set can be determined based on the available data. This leads to increased parameter uncertainty and thus to larger prediction uncertainty as uncertainty propagates through the model to the output.

Different methods for uncertainty analysis have been described in the literature, mostly focusing on the propagation of parameter uncertainty to the model output [Helton et al., 2006] [Matott et al., 2009] [Omlin and Reichert, 2010].
6.1. Introduction to uncertainty analysis

Several frameworks exist to describe parameter uncertainty, including probability theory and possibility theory [Helton and Oberkampf, 2004]. Probability distribution functions are useful to represent uncertainty originating from randomness or variability. However, they are not able to represent ignorance or lack of information, i.e. when the modeller has no (complete) knowledge about the distribution of the uncertain parameter or variable. Still, ignorance is commonly represented in the applied fields by defining uniform distributions over an interval containing all possible values of the variable or parameter [Dubois et al., 2004]. Nevertheless, stating that all possible values are all equally likely (or probable) a priori is a very precise statement about their distribution. On the other hand, possibility distributions are good at representing ignorance but are very conservative. However, Vernieuwe et al. [2011] showed that the inclusion of parameter interactions could lead to more specific possibility distributions of the model output without decreasing the quality of the distribution. Integration methods for uncertainty frameworks exist and a promising, quantitative integration framework is the 'Transferable Belief Model' [Parsons, 2001] [Smets, 1990]. However, practical applications are limited and restricted to very simple, static models (e.g. Demotier et al. [2006]). Probabilistic approaches remain dominant for the representation of uncertainty at large [Dubois et al., 2004]. Pros and cons of alternative uncertainty representations are extensively discussed in the literature [Helton and Oberkampf, 2004].

Probabilistic uncertainty analysis is often performed using a Monte Carlo-based sampling procedure propagating the specified parameter uncertainty (mostly a uniform probability distribution between a minimum and maximum value is assumed) to determine the prediction uncertainty [Sin et al., 2009] [Gernaey et al., 2010]. When these techniques are applied, parameter interactions are mostly not taken into account resulting in unrepresentative prediction bounds [Cierkens et al., 2012]. Therefore, more elaborated methodologies have been developed, combining the parameter estimation and model prediction uncertainty process into a unified strategy, by improving the estimation of the parameter uncertainty distribution [Beven, 2007] [Beven, 2008] [Vrugt and Robinson, 2007]. These methods are mainly based on Bayesian approaches, where an a priori estimated parameter distribution is conditioned to a posterior distribution based on the evaluation of a likelihood function relating modelled and measured values. These methods can be roughly classified into (1) formal Bayesian methods using an explicit statistical error (residual) model and using mostly a Markov Chain Monte Carlo sampling procedure [Krzysztofowicz, 1999] [Schoups and Vrugt, 2010] [Thieman et al., 2001] and (2) informal Bayesian approaches, based on the GLUE method [Beven, 2006] [Freer et al., 1996] [Smith et al., 2008]. Both types of methods have advantages and disad-
vantages which have been discussed extensively in the literature [Beven et al., 2008] [Beven, 2009] [Mantovan and Todini, 2006] [Vrugt et al., 2008] [Vrugt et al., 2009].

The GLUE methodology is selected in this work as it enables us to incorporate the information obtained from the experimental data in the assessment of the uncertain model predictions [Beven, 2006]. Additional benefits are its conceptual simplicity, ease of implementation and flexibility with different sources of information and different criteria [Stedinger et al., 2008]. The methodology is further explained and applied to the single particle drying model (Chapter 4).

6.2 Objectives

In chapter 4 a model describing the drying behaviour of one single wet granule was calibrated and validated and a LSA was performed to study the most influential parameters on the model output of interest, which is the moisture content of the granule. However, some uncertainties remained present, i.e. the collected data were not entirely reliable and some clear deviations between the experimental data and the model predictions persisted. Also, it was of interest to gain more insight in the model structure (w.r.t. correlations between parameters) and the prediction uncertainty. Moreover, GMP for pharmaceutical applications strongly advises the performance of a sensitivity analysis and an uncertainty analysis and more applied studies are needed in this field to show the potential of these methods for the industry [Sin et al., 2009]. All this led to the performance of an uncertainty analysis of the drying model. From the different methods to quantify prediction uncertainty reported in the literature, the GLUE method was selected and the following questions were sought to be answered:

- How should the method be applied? (Choices made w.r.t. experimental data, objective function, etc.)
- What information can be extracted from the uncertainty analysis?
- Is the GLUE method applicable for this pharmaceutical case?

This work thus reports on:

1. The prediction uncertainty induced by the main assumptions at the particle level, i.e. the particle radius \( R_p \), the particle porosity \( \epsilon \) and the gas flow rate at the particle’s surface \( V_g \).

2. The effect of including the most sensitive parameters in the uncertainty analysis on the overall model prediction uncertainty \( \beta_1 \) and \( \beta_2 \).
The added value of this work is the application of an uncertainty analysis (GLUE) to a mechanistic model of a unit operation that is essential in many pharmaceutical production processes. The detailed evaluation and interpretation of the results of the uncertainty analysis form a significant contribution to future research in development and application of mechanistic models to pharmaceutical production processes.

6.3 Materials & methods

The basic principle of the GLUE approach is the recognition that, when using potentially overparameterized models, different parameter sets can lead to similar behaviour in terms of model performance [Beven, 2008]. So, rather than one single global optimal parameter set, there may be many different parameter sets that produce acceptable simulations, especially if the errors in both model input and observations are taken into account. Indeed, when large errors in the observations are not solely resulting from noise in the measurements and parameters are fitted by minimizing the error between the model output and observations, the risk of accepting non-realistic parameter sets arises. Moreover, appropriate parameter combinations can potentially be missed, comparable with a statistical type II error, where a 'hit' is disregarded and seen as a 'miss'. The GLUE approach accounts for this by accepting all model simulations (and corresponding parameter sets) with sufficient performance relative to the measurement errors, instead of looking to the overall best fit.

The GLUE approach was initially proposed by Beven and Binley [1992] and is developed out of the Hornberger-Spear-Young (HSY) method of sensitivity analysis, which is also called the Regional Sensitivity Analysis (RSA) technique as introduced by Hornberger and Spear [1981]. These types of sensitivity analyses are based on Monte Carlo filtering. In Monte Carlo filtering, a large set of model simulations is performed after sampling the a priori (estimated) parameter space with Monte Carlo sampling. Subsequently, all model simulations are evaluated and split into behavioural simulations, representing the 'good' or 'acceptable' simulations, and non-behavioural simulations. Finally, parameter distributions of the two subsets are determined and parameters are considered more influential if the parameter distribution of the behavioural simulations is highly dissimilar to the parameter distribution of the non-behavioural ones [Saltelli et al., 2008]. The GLUE approach extends this concept by translating the outcomes of the behavioural simulations into prediction uncertainty bounds.

The major steps of the GLUE method are:

1. Decision about the informal (or formal) likelihood function to be used in the evaluation of the different model simulations in combination with
a rejection criterion (threshold) to identify non-behavioural model outputs. The likelihood function can be both informal like common objective functions such as $\text{SSE}$ measures or formal measures using an explicit representation of model and measurement error, although the latter is mostly hard to identify due to the unknown combinations of uncertainties and errors involved. However, when more specific information is available about the measurement and input errors, this could be included in the expression of the likelihood function. As such, the likelihood function can be described as a formal likelihood function incorporating the error characteristics (e.g. non-normal, heteroscedastic or autocorrelated model errors) [Stedinger et al., 2008]. Ideally, the rejection criterion should be chosen before starting the simulations based on the possible observation errors [Pappenberger and Beven, 2006], but in practice the definition of this criterion is mainly a learning process during the analysis itself.

2. Selection of model parameters and input variables (or boundary conditions) to consider uncertain inputs and defining the prior distributions of these uncertain inputs. The Monte Carlo runs will be sampled randomly from these distributions and, as such, these must reflect the prior knowledge about the parameters. When only little prior information is available, a non-informative uniform distribution is typically selected \textit{a priori}. The range of the distribution is based on expert knowledge or reported values in the literature.

3. Running a sufficient set of model simulations using a Monte Carlo-based technique, sampling from the prior distributions. [LHS] can be used in order to ensure a representative sampling of the parameter space at a lower number of samples than achieved using random sampling. The outcomes of the different runs are compared to the measured values and for each parameter set the corresponding likelihood function value (defined in step 1) is calculated.

4. The parameter sets with insufficient behaviour (objective function values below the agreed threshold) are considered non-behavioural and excluded from the subsequent analysis by attributing them a zero likelihood. Applying this threshold is a crucial step in the analysis, since it is directly related to the prediction uncertainty. In the ideal situation of exactly one single global optimal parameter set, a threshold would be sought resulting in a likelihood value of the optimal set of one and zero for all the other parameter sets [Beven and Binley, 1992].

5. The obtained likelihood values of the behavioural model outputs are normalised. To determine model prediction uncertainty, the model outputs
are ranked at every time step and the normalised likelihood values are used to construct the cumulative distribution for the output variable. Prediction uncertainty is subsequently determined by selecting the appropriate percentiles (e.g., 5% and 95%) from the Cumulative Distribution Function (CDF) at that time step.

The presented stepwise approach of the GLUE method will be used to structure the consecutive sections of 'Materials & Methods' (Section 6.3) and 'Results' (Section 6.4). The choices in setting the threshold value, the prior parameter space, the sampling method and the number of simulations are described in section 6.3. Indeed, these are not an outcome of the uncertainty analysis, but rather an input (steps 1-3). The outcome of the GLUE method (steps 4-5) is considered to be the main topic of this analysis and is consequently discussed in section 6.4.

6.3.1 Likelihood function

The likelihood function used in this case is a variation on the weighted SSE (Weighted Sum of Squared Errors (wSSE)). Weighting factors for the measurements at different time steps were set using the knowledge about the collection of the experimental data (Table 6.1).

Since the granules did not enter the fluidized bed dryer yet, the measurement of the initial moisture content is considered to be highly reliable and a weighting factor of 1 was chosen. The initial moisture content does not coincide with the moisture content calculated based on the amount of liquid and solid added to the granulator, because the wet granules has undergone a sieving. During the manipulation of the wet granules already a part of the liquid has been evaporated. The time between stopping the drying process and collecting the granules has an impact on the measurement error. At early time steps with quickly changing moisture content this influence is largest. This results in more noisy data and thus a weighting factor of 1/10 was selected. Measurements at later time steps are considered reliable, so a factor of 1 was chosen. Finally, two adaptations were made. First, the weighting of the measurement at 15 s was reduced based on the low degree of confidence in this measurement by the experimenters. Second, for the interphase between the fast and slow drying phase, the weighting factor was increased to 1/2.

Likelihood values associated with each parameter set (1) should be positive, (2) should increase monotonically with improved performance and (3) should be zero for non-behavioural simulations. These conditions are important to weigh the behavioural simulations and to calculate the CDFs. Therefore, the selected
Chapter 6. A GLUE uncertainty analysis of a drying model

The likelihood function is:

$$\ln |L| = - \sum_i (y_i - y_{m,i}) W(i))^2$$

(6.1)

where $y_i$ is an experimental data point, $y_{m,i}$ is the model output and $W(i)$ is the weighting factor for the data point at time $i$.

A threshold value of 0.25 was selected to distinguish between the behavioural and non-behavioural runs. This particular threshold was chosen because it balances the data fit and measurement errors. The runs with a lower likelihood value were given a zero-value and the remaining weights were rescaled to add up to '1' to fulfill the requirements.

6.3.2 Selection of parameters

A commonly used expert knowledge based method to set the uncertainty boundaries of parameters is the division of the selected parameters into three groups according to their uncertainty (i.e. low, intermediate and high), each corresponding with a predefined variability of a uniform distribution around the calibrated value (e.g. 5%, 20% and 50% around the calibrated value) [Reichert and Vanrolleghem, 2001]. The uncertainty analysis is performed on three cases (Table 6.2).

In the first case, the influence of the 'particle assumptions' on the model output is investigated. The particle is modelled as a perfect spherical particle with radius $R_p$, a certain porosity $\epsilon$ and a constant, known gas flow rate at the surface of the particle $V_g$. The particles used in the experiment originate from a continuous from-powder-to-tablet production line and it was visually observed that the particles are not spherical, but rather irregular or cylindrical. Furthermore, a number of particles that were retained by a sieve of 1,000-1,400 µm were fed to the dryer. The effective particle radius of the used particles is consequently not known. Next, the porosity of the particles, which equals the particle volume filled with fluid (air and water, excluding the solid fraction) divided by the total volume of the particle, is a result of the preceding granulating step and cannot be accurately determined or preset. Finally, the gas flow rate passing at the particle’s surface might differ locally due to hydrodynamic effects in the
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fluidized bed. The location in the fluidized bed dryer and the movement of the particle both influence the absolute flow rate at the surface.

Summarizing, parameter uncertainty boundaries were put on the radius of the particle \( (R_p) \), porosity of the particles \( (\epsilon) \) and the gas flow rate \( (V_g) \). Since all these parameters are assumed to be very uncertain, a uniform distribution between the default parameter value plus or minus 50% was used as prior distribution.

The second case consists of the parameters that have the highest influence on the model output according to an earlier study addressing model sensitivity to changes in the parameter values (Chapter 4 and 5). The gas temperature \( (T_g) \) and the empirical parameter \( \beta \) have most influence on the model output. Since later experiments showed that \( \beta \) is temperature dependent, an exponential relation with two new empirical parameters \( (\beta_1 \text{ and } \beta_2) \) was developed to describe the relation between the gas temperature and \( \beta \) (Eq. 4.34) (Section 4.4). The latter, in combination with the option to accurately set the temperature of the incoming gas flow of the fluidized bed dryer and the assumption that the amount of particles is too small to significantly influence the gas temperature by the endothermic evaporation of water, justifies the assumption of excluding the gas temperature from the uncertainty analysis. \( \beta_1 \) and \( \beta_2 \) were classified into the second uncertainty class (i.e. 20% variation) because they were calibrated on the indirectly measured variable \( \beta \) at different temperatures, and as such there is more confidence in these parameters compared to case 1.

The third case that is investigated consists of the combined cases 1 and 2. Initially, uniform distributions with the previously defined prior uncertainty boundaries were used. However, it turned out to be practically impossible to sample the entire parameter space and obtain a large enough sample of behavioural parameter combinations. Therefore, the parameter boundaries were adjusted (Table 6.2) by excluding areas yielding no potentially behavioural simulations based on the initially performed simulations (results from cases 1 and 2). While investigating one case, all other parameters are set to their calibrated value.

6.3.3 Monte Carlo simulations

The previously described parameter distributions were sampled with LHS and convergence of the resulting Probability Density Functions (PDFs) was checked by comparing the PDFs of different sample sizes. 10,000 runs revealed to be sufficient for the cases with two or three uncertain parameters (Fig. 6.1).

Subsequently, the likelihood between the model outputs and the data was calculated and all parameter combinations resulting in a fit with a likelihood larger than the threshold were considered as behavioural.
Table 6.2: Parameters used for the uncertainty analysis (based on assumptions, calibration and experimental setup)

<table>
<thead>
<tr>
<th>Case</th>
<th>Parameter</th>
<th>Calibrated value</th>
<th>Range in uncertainty</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$\epsilon$</td>
<td>$0.05$</td>
<td>$50%$</td>
</tr>
<tr>
<td>1</td>
<td>$V_g$</td>
<td>$200 \text{ m}^3/\text{h}$</td>
<td>$50%$</td>
</tr>
<tr>
<td>1</td>
<td>$R_p$</td>
<td>$0.6 \times 10^{-3} \text{ m}$</td>
<td>$50%$</td>
</tr>
<tr>
<td>2</td>
<td>$\beta_1$</td>
<td>$4.91 \times 10^4$</td>
<td>$20%$</td>
</tr>
<tr>
<td>2</td>
<td>$\beta_2$</td>
<td>$2.43 \times 10^{-2}$</td>
<td>$20%$</td>
</tr>
<tr>
<td>3</td>
<td>$\epsilon$</td>
<td>$0.05$</td>
<td>$[0.03, 0.06]$</td>
</tr>
<tr>
<td>3</td>
<td>$V_g$</td>
<td>$200 \text{ m}^3/\text{h}$</td>
<td>$20%$</td>
</tr>
<tr>
<td>3</td>
<td>$R_p$</td>
<td>$0.6 \times 10^{-3} \text{ m}$</td>
<td>$[0.3 \times 10^{-3}, 0.65 \times 10^{-3}]$</td>
</tr>
<tr>
<td>3</td>
<td>$\beta_1$</td>
<td>$4.91 \times 10^3$</td>
<td>$20%$</td>
</tr>
<tr>
<td>3</td>
<td>$\beta_2$</td>
<td>$2.43 \times 10^{-2}$</td>
<td>$[0.022, 0.026]$</td>
</tr>
</tbody>
</table>

Figure 6.1: Output uncertainty boundaries (the 5th and 95th percentile) for case 1 using Monte Carlo simulation without performing a GLUE analysis. Sample size varies between 100 and 1,000 sampled parameter sets.

6.4 Results

6.4.1 Uncertainty analysis for case 1

The results for this case will be extensively explained and graphically illustrated to show the potential of the applied uncertainty analysis method.
6.4. Results

**Likelihood versus parameter values (Dotty plots)**

Dotty plots are constructed by plotting the value of an evaluation criterion, in this case the likelihood, against the value of one of the uncertain parameters for every Monte Carlo simulation. Thus, every single Monte Carlo simulation is represented by one dot in the plot. Dotty plots can be made for all uncertain parameters and are projections of the Monte Carlo simulations on a single parameter axis. They are a first and easily understandable source of information about the model parameters. By giving different colours to 'behavioural' and 'non-behavioural' parameter values (which are separated by the selected threshold for the likelihood), the following analysis can be performed. Under the experimental conditions of this experiment, it can be seen that the porosity and radius (not shown) of the particle are quite well defined because a clear region of behavioural values can be observed (between roughly 0.037 and 0.061 for the porosity), whereas the gas flow rate can give equally good fits with any flow rate in the range used in the analysis (Fig. 6.2).

The latter can be due to two reasons. Insensitive parameters do not have a significant influence on the model output and will most probably not be discriminated in the evaluation of the fitting criterion. On the other hand, correlated parameters, i.e. parameters for which changes have a similar or opposite influence on the model outputs, may result in scattered dotty plots. Indeed when two parameters are correlated, the effect of changing one parameter value on the output, can be balanced by a similar or opposite change of the other parameter. To discriminate between these two scenarios, two-dimensional plots can be made (if working on a low-dimensional problem) or (linear) correlation coefficients of behavioural runs could be determined. As such, two-dimensional dotty plots can conceal some of the information related to the model structure.

![Figure 6.2: Dotty plots of the likelihood evaluation criterion against parameter $\epsilon$ (Left) and $V_g$ (Right) for case 1. Model outputs with an L-value higher than 0.25 are considered as behavioural](image-url)
Objective function value versus parameter combinations and parameter histograms

Looking at the posterior parameter combinations is a major information source of the GLUE approach. For low-dimensional problems, two-dimensional dotty plots can be constructed between all one-by-one parameter combinations and at the top and side of the dotty plots, separate histograms can be shown for the respective parameter range that contain information on the behavioural points only.

By doing this, potential correlations between parameters can be detected, i.e. when the behavioural parameter combinations show a clear relation between two parameters. For $V_g$, it was obvious that any value was sufficient given the experimental condition and data, and this was potentially due to correlations with other parameters. However, no clear correlations between $V_g$ and the other parameters is observed (Fig. 6.3). This means that it can be concluded that the model output is not sensitive to the parameter $V_g$, which was also an outcome of the sensitivity analysis (Section 4.4 and chapter 5). For $R_p$ and $\epsilon$ a slightly negative correlation is observed (Fig. 6.4).

For the parameters $\epsilon$ and $R_p$, it can be seen that a distinct region within both prior distributions is obtained as posterior parameter space. The prior parameter distributions were consequently wide enough to include all possible parameter combinations and the local optimum seems to be the global one (if it is assumed that the parameter values could not vary more than what was included as range in the prior distribution). For $V_g$ no convergence can be observed, nevertheless based on the physics of the experimental setup it is very unlikely that the gas flow rate would vary more than the range that was taken into account (Fig. 6.4 and 6.3). The two-dimensional dotty plot for $V_g$ and $R_p$ is not shown.

Construction of output uncertainty boundaries

Finally, CDFs were constructed at all simulated time points by ranking the output of the behavioural simulations and weighing them according to their normalised likelihood value (Fig. 6.5). The cumulative distribution shows a gradually increasing CDF at early time points (Fig. 6.5), whereas at later time points, the cumulative distribution shows a discontinuity at ambient moisture content, indicating that in 60% of the behavioural simulations the particle was entirely dried after 720 s (Fig. 6.5). Based on the CDF, selected percentiles (e.g. 5th and 95th) can be used to show the prediction uncertainty in time (Fig. 6.6).
6.4. Results

Figure 6.3: Two-dimensional dotty plot of the likelihood evaluation criterion for the different one-by-one parameter combinations of parameters $V_g$ and $\epsilon$ for case 1. Parameter combinations with a corresponding L-value higher than 0.25 are considered behavioural.

It can be seen that the first data points are not included in the confidence intervals. This mismatch is not caused by the lower weighting factor for the first data points. Indeed, when running all Monte Carlo simulations from the prior parameter space, and plotting the 0th and the 100th percentiles, the data points are not contained in the interval either. It should be remembered that these data points are considered unreliable.

Fig. 6.6 shows the output uncertainty graph for case 1. The graph needs to be read as follows: with a 90% confidence, the moisture content will drop to 1% after 120 to 270 s from the start of the experiment. Or with a 90% confidence, the moisture content will drop from the initial content to a value between 1.2% and 1.8% after 100 s. In very favourable conditions, the particle will be completely dried in 400 s, whereas in unfortunate conditions, it might take up to 1,000 s.
Figure 6.4: Two-dimensional dotty plot of the likelihood evaluation criterion for the different one-by-one parameter combinations of parameters $R_p$ and $\epsilon$ for case 1. Parameter combinations with a corresponding L-value higher than 0.25 are considered behavioural.

Figure 6.5: CDF of the moisture content of all behavioural simulations for case 1 at time step 80 s and 720 s (L-value of 0.25)
6.4. Results

Figure 6.6: Model output uncertainty boundaries of the moisture content of a particle for case 1. The resulting percentiles are obtained with GLUE analysis and an L-value of 0.25

6.4.2 Uncertainty analysis for case 2

In figure 6.7 the dotty plots for the second case ($\beta_1$ and $\beta_2$) are presented. The previously set threshold (L of 0.25) is never reached, leading to the classification of all parameter combinations as non-behavioural. This can be explained by looking at the results of case 1, where all behavioural parameter combinations have a value of $R_p$ smaller than the previously assumed calibrated value of 0.6 mm. In the first drying period, $\beta$ is not included in the evaporation rate equation, but $R_p$ is. Wrongly setting $R_p$ might result in both an offset of the real moisture content at the beginning of the second drying period and a too low L-value in the first drying period. This results in an overall likelihood that is lower than in case 1. Therefore, determining the prediction uncertainty originating from case 2 will not make sense and it was decided to perform an uncertainty analysis on the combination of cases 1 and 2 (= case 3). However, still some important insights can be obtained from the uncertainty analysis of case 2 after increasing the original threshold value to an illustrative less stringent value (= 0.05 instead of 0.25) (Fig. 6.7). Indeed, the shape of the clouds can be explained by the drying process itself. As said, $\beta$ is a function of $\beta_1$, $\beta_2$ and gas temperature and it has a large influence on the evaporation rate in the second drying period. The lower $\beta$, the larger the evaporation rate and the faster the moisture content of the particle drops to almost zero, whereas a low $\beta$ results in almost no drying in the second drying period. A seminstant drying (Scenario A) and an almost no drying simulation (Scenario B), i.e. a simulation where the moisture content stays almost equal to the moisture content at the end of the first drying period results in a very low L-value. The
former occurs when $\beta$ is low, the latter when $\beta$ is high and intermediate $\beta$’s give rise to a gradual decrease to the maximum likelihood. Since $\beta$ is mainly determined by $\beta_2$ (a low value for $\beta_2$ results in a high value for $\beta$), this pattern can be observed in the dotty plot of $\beta_2$ and the width of the two branches in figure 6.7 shows the influence of $\beta_1$.

Looking at the combined dotty plot of both parameters (Fig. 6.8), a higher value for $\beta_2$ is compensated by a higher value for $\beta_1$. This is logical since these two parameters only have an impact on the $\beta$-parameter (Eq. 4.31).

### 6.4.3 Uncertainty analysis for case 3

As the number of parameters is increased from 2 (Section 6.4.2) or 3 (Section 6.4.1) to 5, the number of Monte Carlo samples is increased to 50,000, compared to 10,000 in the other cases, to make sure the posterior distribution of the behavioural cases is extensive enough for interpretation. Again the threshold is set to 0.25, accepting cases giving reasonable results taking into account the measurement errors. The resulting posterior parameter sets are shown in figure 6.9 as combined dotty plots with on the diagonal the histograms of the prior and posterior distribution of the individual parameters. Three out of the five parameters under study ($R_p$, $\epsilon$ and $\beta_2$) are converging to a distinct region in the combined parameter space, whereas the other two are not identifiable within the selected limits of acceptability.

When comparing the scatterplot of $R_p$ and $\epsilon$ in figures 6.4 and 6.3 and figure 6.9, a different convergence is achieved, due to parameter interactions between parameters investigated for case 1 and parameters investigated for case 2. The incorporation of $\beta_2$ leads to an expansion of the behavioural parameter region.
6.5 Discussion

Figure 6.8: Two-dimensional dotty plot of the likelihood evaluation criterion for different one-by-one parameter combinations of parameters $\beta_1$ and $\beta_2$ for case 2. Parameter combinations with a corresponding L-value higher than 0.05 are retained.

In figure 6.10, the output uncertainty boundaries are presented. The output uncertainty boundaries for the third case show that the data points of the first drying period are again not included in the confidence intervals.

6.5 Discussion

An in-depth analysis of the model prediction uncertainty was performed using the GLUE methodology, focusing on (1) assumptions at the particle level such as porosity, (2) the most influential parameters on the model output of the particle moisture content and (3) the combination of both cases.

The GLUE method reveals information about the model structure, which can be very useful (especially) when the mathematical models become too complex for the modeller, and focuses not only on the output uncertainty boundaries as such. In the case study presented, the following conclusions could be drawn from the uncertainty analysis:

- By performing the GLUE analysis, the hypothesis of the unrealistic assumption of a particle radius of on average 0.6 mm (equal to half of the mean sieve pore size 1,000-1,400 $\mu$m) was rejected, which seems reasonable because of the irregular shapes of the particles (Fig. 6.11). Moreover, the experimental data to calibrate the drying model has been collected.
Chapter 6. A GLUE uncertainty analysis of a drying model

Figure 6.9: Two-dimensional dotty plots of the likelihood evaluation criterion for all parameters included in case 3. Parameter combinations with an L-value higher than 0.25 are considered as behavioural. At the diagonal the histograms of both the prior uniform distribution (grey) and the retained parameter values (black) are shown using a sieve fraction. The mean of this sieve fraction has been used to determine the particle radius, whereas in reality a range of particles with different sizes has been used in the drying experiments.

- An example of how model structure is included in the uncertainty analysis can be found in the results of case 1. Parameter $V_g$ is clearly not identifiable and has almost no influence on the particle drying, which is confirmed by the sensitivity analysis (Section 4.4 and chapter 5). When looking at the shape of the area of behavioural runs for $\epsilon$ and $R_p$ in figure 6.4 it can be seen that smaller particles with a high porosity
6.5. Discussion

Figure 6.10: Output uncertainty boundaries on the prediction of the moisture content of a particle using case 3 for the uncertainty analysis. The resulting percentiles are obtained with GLUE analysis and a threshold for the L-value of 0.25

Figure 6.11: Irregular shape of the wet pharmaceutical granules

and larger particles with a low porosity can yield a similar quality of fit (both behavioural runs). This means that the amount of water in the particle determines if a fit is qualified as behavioural or non-behavioural. However, common sense would predict that a large particle with a low porosity will dry less efficiently than a small particle with a large porosity because in case of the large particle both the distance the water needs to travel in the particle is larger and the water needs to travel through smaller channels or holes in the crust region. This can be seen from the uncertainty analysis results when indicating the parameter combinations of the runs lying near the upper output uncertainty boundary, i.e. the particles that dry the slowest, and those at the lower boundary (Fig.
Chapter 6. A GLUE uncertainty analysis of a drying model

6.12). Figure 6.12: Two-dimensional dotty plot for $R_p$ and $\epsilon$ (Case 1). The parameter combinations leading to simulations at the 95th percentile prediction uncertainty boundary are indicated with X (up) and the predictions at the 5th percentile uncertainty boundary with + (low). An L-value of 0.25 is used as threshold

- The difference between the a posteriori distributions of cases 1 and 2 separately and case 3 indicates the influence of the parameters of the two drying phases on each other. When fixing one of the two cases by experimental determination of the parameters, the remaining uncertain parameters delineate towards a more distinct region (as mentioned in section 6.4.3). Moreover, the model prediction uncertainty will reduce.

- Based on the almost linear interaction between $\beta_1$ and $\beta_2$ in figure 6.8, it can be questioned what the benefit is of introducing two parameters ($\beta_1$ and $\beta_2$) in the model as opposed to retaining only one parameter ($\beta$). However, the former makes it possible to simulate at different temperatures. Previously, $\beta$ needed to be determined experimentally for every temperature. To get more insight in this phenomenon an additional evaluation could be made by performing a combined GLUE analysis at 2 different values of $T_g$. 

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6.5. Discussion

The performed analysis is important when the model is used for design and testing of process control strategies. Mechanistic models are important to understand processes in detail and build control strategies based on on-line measurements and real-time adjustment of input variables (Chapter 2). Knowing the relation between parameters and the uncertainty of the model is helpful to direct the process in a specific direction.

However, some subjective decisions needed to be taken when applying the GLUE uncertainty analysis. The a priori parameter ranges and distributions, the objective function used (i.e. likelihood) and the selection of the threshold value (i.e. 0.25) can be subject to discussion [Li et al., 2010] [Mantovan and Todini 2006]:

- Different sampling techniques and initial distributions are possible. In the analysis presented in this study, an LHS sampling technique with uniform distributions was used. However, a random sampling with triangular distribution was also investigated for case 1. The two-dimensional dotted plots and histograms are presented in figure 6.13. For $\epsilon$ the a priori assumption of a triangular distribution is justifiable, since the median value of the prior and posterior distribution do agree, whereas for $R_p$, the posterior distribution is situated on the left hand side of the a priori distribution. The latter means that relatively more samples would be needed as compared to sampling from a uniform distribution. With little prior knowledge, uniform distributions are in principle preferable to perform the uncertainty analysis. Because the GLUE analysis retains only the behavioural runs and a sufficient number of runs was performed, the posterior distributions are to some extent similar for both sampling techniques. Consequently, the uncertainty boundaries, presented in figure 6.14 are very similar for both sampling schemes.

- The objective function needs to represent the ability of the model to fit the data by characterising the desirable features in the relationship between the model output and corresponding observed data [Smith et al. 2008]. The use of the likelihood is justified since it gives the opportunity to incorporate the knowledge of the measurement accuracy obtained during the experimental study. Moreover, the weights (1, 1/2 and 1/10) are used to put more emphasis on the second drying phase, as the first drying phase is independent of $\beta$.

- Furthermore, the selection of the threshold value has a direct influence on the resulting prediction uncertainty. Since error measurements are not only caused by noise, the rejection criterion should not be too severe, but representing the balance between measurement uncertainty and model performance. This highlights the issue about the possibility of
making Type II errors in rejecting good (behavioural) models because of input uncertainties [Liu et al., 2009]. Furthermore, the selection of the threshold must be strict enough to allow the modeler to identify the parameters [Freni et al., 2008]. Li et al. [2010] also found that when using strict enough selection criteria, the GLUE approach is more comparable to other Bayesian methods. In this study, the value of 0.25 for the likelihood was selected and rejecting simulations with lower values enabled to distinguish the interesting regions in the parameter space taking into account that the measurements contain significant errors.

The prediction uncertainty, which is the direct outcome of an uncertainty analysis, is determined by the choice of the methodology, but in a further step also determined by choices about the objective function, threshold, etc. The output uncertainty bands are strongly dependent on these choices, but when taking into account knowledge about the measurements, model, method and literature a well-founded choice can be made. All choices should be made explicitly in any uncertainty analysis method.
6.6 Conclusion

An uncertainty analysis gives additional insight in the drying model behaviour of single pharmaceutical granules. Performing a sensitivity analysis (global and/or local) is helpful to detect the most sensitive parameters, but additional information can be obtained by investigating the influence of assumptions and simplifications of the system on the prediction uncertainty.

- The parameter space was assessed by evaluating simulations according to the objective function, which is based on experimental data. This is done for two different cases; one to detect the prediction uncertainty from the main assumptions at the particle level and another one for the most sensitive parameters. At the end both cases are combined.

- Additional insight in the model structure can be obtained by performing a GLUE analysis (correlations between parameters), which can help to understand relations between parameters, and as such it can give insight in the drying process. This can be interesting for controlling the process in a later stage of the project.

Direct outcomes of the analysis are:

- The rejection of the unrealistic assumption of a particle radius of on average 0.6 mm (equal to half of the mean sieve pore size 1,000-1,400 µm).
• It was shown that when experimentally determining the parameters related to one drying phase, the knowledge about the parameters of the other drying phase also increases.
Reduction of a single particle drying model: An essential step in preparation of a PBM with a continuous growth term


Abstract: The development of a Population Balance Model(s) (PBM) for a pharmaceutical granule drying process requires a continuous growth term; the latter actually represents the drying process as the moisture content is the internal coordinate of the PBM. To establish such a PBM, a complex drying model for a single granule needs reduction in complexity. The starting point is a detailed model that describes the drying behaviour of single pharmaceutical granules. A Global Sensitivity Analysis (GSA) was performed to detect the most sensitive degrees of freedom in the model as these need to be retained in the reduced model. Simulations of the complex drying model were, in a next phase, used to develop the reduced model, which describes the decrease of the moisture content in function of the gas temperature and the gas velocity, the main manipulated variables in the dryer.

7.1 Introduction

The development of a complete mechanistic model for the fluidized bed drying process is a step-wise approach, as mentioned earlier. The single particle drying model to describe the evolution of the moisture content of one single pharmaceutical granule is used as the starting point for the extension towards a
model for a population of granules. The latter will be done using [PBM] which requires a kernel to describe the decrease of the moisture content. The general [Population Balance Equation (PBE)] is given by:

$$\frac{\partial}{\partial t} n(x, r, t) + \nabla \dot{X}(x, r, Y, t) n(x, r, t) + \nabla \dot{R}(x, r, Y, t) n(x, r, t) = h(x, r, Y, t)$$

(7.1)

where $n(x, r, t)$, $x$, $r$, $t$, $Y$ and $h$ are the number density distribution, the internal coordinate, the external (spatial) coordinate, the time, the continuous phase vector and the net birth rate. Further details about [PBM] models can be found in chapter 2 section 2.6 and chapter 8.

In the case the kernel, referred to as the 'growth'-term ($G_r$) is dependent on the current moisture content, this is called a size dependent growth term. As the structure of the growth term for a continuous drying process, i.e. the two-stage drying model, is quite complex, it cannot as such be implemented in the [PBE] and needs to be reduced by means of a model reduction step. An overview of techniques for that model reduction is given first.

### 7.2 Model reduction techniques

Model reduction techniques are usually described in the literature for very complex models, e.g. semiconductor devices, weather forecast models, molecular systems, etc. [Antoulas, 2005]. Such detailed complicated physically based mathematical models are time consuming to solve and require the use of sophisticated hardware and software resources [Banerjee et al., 1998].

A first group of model reduction techniques are heuristic model reduction methods. However, these require a lot of user input. A detailed analysis of the model behaviour w.r.t. the selected set of parameters is needed. The interaction and feedback between model components to identify key processes of the system should be assessed. The changes in model structure must be decided upon by domain experts [Van Nes and Scheffer, 2005].

Another group of model reduction techniques are those based on mathematical concepts. Several methods are projection based, i.e. where the systems are projected onto a lower-dimensional subspace and the model equations are solved for the substituted projected states [Bernhardt, 2008]. A class in this area is based on [Singular Value Decomposition (SVD)] which cannot be applied to highly complex systems. For non-linear systems the [Proper Orthogonal Decomposition (POD)] method (also known as [Principal Component Analysis (PCA)]) is one of the possibilities [Antoulas, 2005]. This method was for example applied for a [Rapid Thermal Processing (RTP)] system [Banerjee et al., 1998]. The eigenfunctions from the [POD] method are subsequently used as ba-
sis functions in spectral Galerkin expansions of the governing PDEs solved by the finite element method to generate the reduced models. A good agreement between the reduced model and the original model was obtained, and a reduction in execution time was found.

Krylov-based approximation methods form another class of methods within the projection based methods, and can be implemented iteratively. As such, this method can be applied to systems of high complexity [Antoulas, 2005]. Antoulas combined the SVD-based and Krylov-based methods which is appropriate for application to large-scale circuits arising in VLSI chip performance verification [Antoulas, 2005].

The most simple non-linear model reduction methods are based on linearizaton or reduced-order series expansion of the system’s non-linearities using Taylor or Volterra series. However, these methods are only applicable for weakly non-linear systems [Phillips, 2000].

Bernhardt [2008] described a data adaptive model reduction scheme, which can be applied to the transformation and reduction of systems of ODEs. It is a multistep approach using a low dimensional projection of the model data followed by a Genetic Programming/Genetic Algorithm hybrid method to evolve the new model systems [Bernhardt, 2008]. POD and parameter tuning importance are two techniques that were used and compared by Degenring et al. [2004]. The PCA can be used as a self-controlled routine, which means that the procedure can be repeated automatically until a predefined upper limit of the error-functionals is achieved, which is advantageous over the parameter tuning importance technique. The latter should be used step-by-step, and each model reduction step should be studied critically.

Reduction methods based on evaluating the sensitivity of the performance indicators to a parameter vector are also known. The Advanced Rate Elimination Method (AREM) belongs to this category, and focuses on the importance of individual rates, leading to a reduction of the number of rates. The Variable Simplification Method (VSM) looks at the importance of variation of each state variable to indicate which variable can be set to a constant value. No prior detailed understanding about the model is required. Both methods have been used to reduce ecosystem models, which helped to understand the mechanisms that influence ecosystem health indicators [Lawrie and Hearne, 2007].

In this work the model reduction is performed on the full drying model of a single granule. A custom model reduction procedure is introduced and the reduced model is implemented in the PBM-model for description of the drying of a population of granules (Chapter 8).
7.3 Materials & methods

A GSA was performed to detect the most sensitive degrees of freedom in the drying model. More details about the GSA can be found in chapter 5. The GSA in this study was performed using five degrees of freedom (r): the gas temperature \((T_g)\), the gas velocity \((V_g)\), humidity of the gas \((RH_g)\), the pressure of the gas \((p_g)\) and the initial temperature of the particle \((T_{p,0})\). These five degrees of freedom were specifically chosen on the basis of their sensitivity and the ability to adapt or control these degrees of freedom during the operation of the dryer. Indeed, the gas velocity can be set in the fluidized bed dryer (ConsiGma\textsuperscript{TM}). The humidity of the inlet air can be measured and controlled using specialised equipment. The initial temperature depends on the temperature set point of the granulator. The pressure at the inlet is also measured. All other degrees of freedom in the drying model are fixed and cannot be controlled. For each degree of freedom an uncertainty range was determined based on physical limitations and physical reality. Since no prior knowledge on values for the degrees of freedom is available, the degrees of freedom are sampled from a uniform distribution between chosen minimum and maximum values (the uncertainty range). The range of the degrees of freedom was based on the physical boundaries of the fluidized bed dryer for which the mechanistic model is developed in chapter 4 and is given in Table 7.1.

The regression-based sensitivity analysis is used for the analysis (details can be found in section 5.1.2), for which 2,000 samples were generated using the LHS method. The evaluation of the sensitivity analysis is performed for both drying phases separately. As such, the sensitivity of the model to the degrees of freedom could be evaluated for both periods separately, and can be different. The output variable used in the GSA is the evolution of the granule’s water content, which for the drying model corresponds respectively to the decrease of the radius of the particle (first drying phase) and the decrease of the wet core radius (second drying phase) as a function of time. The time step used in the simulation is respectively 0.02 and 0.2 s for the first and the second drying phase.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>(T_g)</td>
<td>20 - 80 °C</td>
</tr>
<tr>
<td>(V_g)</td>
<td>150 - 500 m(^3)/h</td>
</tr>
<tr>
<td>(RH_g)</td>
<td>1 - 15%</td>
</tr>
<tr>
<td>(p_g)</td>
<td>100,500 - 101,700 Pa</td>
</tr>
<tr>
<td>(T_{p,0})</td>
<td>25 - 50 °C</td>
</tr>
</tbody>
</table>
7.4 Results

7.4.1 General procedure of the model reduction

Evaluating the different available methods for model reduction, described in the introduction, it was concluded that none of the techniques based on mathematical concepts were feasible for our specific case. Antoulas [2005] used the model reduction techniques on a set of \( n \) coupled first order ODEs to replace them with \( k \) coupled first order ODEs where \( k \ll n \) [Antoulas, 2005]. The reduction of second-order systems remained an open problem. Chahlaoui et al. [2005] used a second-order balanced truncation to reduce a second-order linear time-invariant system. Stability, error bounds, choice of Gramians (set of vectors) remained a problem [Chahlaoui et al., 2005]. In fact, for all projection based methods non-linear model reduction is difficult [Bernhardt, 2008]. The ability to use the reduction method described by Bernhardt [2008] depends on the system dynamics being confined to a low-dimensional subspace. The method is applied for simple models with oscillatory dynamics. Several reduction methods are quite complex to use. Van Nes and Scheffer [2005] formulated this as follows: 'The most drastic way to simplify the model is to make an independent minimal model that describes the dominant mechanisms of the full model'. This approach is very powerful, if both models produce qualitatively similar results [Van Nes et al., 2002].

A new strategy was developed here. Basically it involves a GSA step and a model reduction step (Fig. 7.1). A GSA is performed on the full model \( f \) in order to detect the most sensitive degrees of freedom. The full model is function of variables \( x \) and parameters \( P \). Second, the outcome of the sensitivity analysis is used to develop an empirical model \( g \), which is function of variables, the selected degrees of freedom \( D \) and the determined coefficients \( C \).

7.4.2 Global Sensitivity Analysis (GSA)

The distribution of the degrees of freedom, generated by a uniform LHS technique, is presented in figure 7.2. The degrees of freedom are distributed uniformly in the parameter space, which can be seen clearly in the scatter plots. On the diagonal, histograms of the different degrees of freedom used in the GSA are presented. The off-diagonal plots are normal scatter plots, and it is clear that the whole parameter space is explored by the LHS technique.

Each set of degrees of freedom was evaluated and the growth term for the first and the second drying phase were calculated. Figure 7.3 shows the decrease in \( R_{w} \) as a function of time (top), as well as the resulting growth term (bottom). The first drying period is characterised by a growth term that shows an in-
Chapter 7. Model reduction in preparation of a PBM

Figure 7.1: Problem statement. The full model is too complex to be incorporated in the PBM directly, and therefore GSA is applied in the frame of achieving a reduced model that can be incorporated in the PBM.

Figure 7.2: Distribution of the degrees of freedom resulting from applying LHS

crease in negative rate at the start (i.e. increased drying rate), but levels off to a constant value near the end of the phase (Fig. 7.3). The absolute value of the growth term for the second drying period decreased strongly (becoming less negative, meaning drying at a slower rate) in the beginning, but after reaching a minimum rate, it increased again (Fig. 7.3). It can be concluded that the
7.4. Results

dynamics of both drying phases are clearly different.
In figure 7.4 the growth term is plotted as a function of time for all different sets of degrees of freedom in the Monte Carlo analysis. It is obvious that the chosen combination of degrees of freedom for the sensitivity analysis has an influence on the drying time and behaviour.

The black vertical line crossing the different simulations in figure 7.4 marks the time point that is used for the linear regression. Results of simulations at this point are scaled and used in a least squares linear regression. As the drying model does not reach steady state, the alternative is that the output of the model has to be compared after a certain time step. Another choice would have been to take the average of all outputs for one simulation, and to perform the linear regression with those averaged output values. The disadvantage of this approach is that the $R^2$ can become too low, so no conclusion can be made about the sensitivity of the degrees of freedom. In the first drying phase the linear regression was performed after 3 s, where an $R^2$ of 0.97 was obtained. The second drying phase is longer, and therefore two time steps were chosen for the linear regression, namely 1 s and 11 s, showing a clear difference in $R^2$ (Table 7.2). An $R^2$ of 0.57 is too low to draw conclusions, since normally a minimum of 0.7 is assumed to be required for $R^2$.

The SR Cs for the linear regression were calculated (Table 7.2). The ranking can be used to detect the most sensitive degrees of freedom. In both drying periods, the gas temperature clearly comes out as being the most sensitive degree of freedom. For the first drying phase the gas velocity is also a quite sensitive degree of freedom, followed by the humidity. For the second drying phase a different ranking can be observed when comparing evaluation after 1 s or 11 s. Because the gas temperature is clearly the most sensitive degree of freedom in both drying phases, first the drying model was reduced using this degree of
Chapter 7. Model reduction in preparation of a PBM

Figure 7.4: The growth term $G_r$ for different parameter sets for the first (Left) and the second (Right) drying phase

freedom. Subsequently, an extension for the first drying phase was made by including the gas velocity as second input.

<table>
<thead>
<tr>
<th>Degree of freedom</th>
<th>Drying Phase</th>
<th>First</th>
<th>Second</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>3 s</td>
<td>1 s</td>
</tr>
<tr>
<td>$T_g$</td>
<td>0.93</td>
<td>0.87</td>
<td>0.73</td>
</tr>
<tr>
<td>$V_g$</td>
<td>0.29</td>
<td>0.02</td>
<td>0.03</td>
</tr>
<tr>
<td>$RH_g$</td>
<td>0.13</td>
<td>0.02</td>
<td>0.05</td>
</tr>
<tr>
<td>$p_g$</td>
<td>0.00</td>
<td>0.00</td>
<td>0.01</td>
</tr>
<tr>
<td>$T_{p,0}$</td>
<td>0.02</td>
<td>0.03</td>
<td>0.03</td>
</tr>
<tr>
<td>$R^2$</td>
<td>0.97</td>
<td>0.75</td>
<td>0.57</td>
</tr>
</tbody>
</table>

7.4.3 Model reduction

The reduced model should be able to describe the decrease of the moisture content for a population of drying particles when incorporated in a PBE model. Analysis of figure 7.3 revealed that the growth term is strongly dependent on the radius of the particle (first drying phase) and the radius of the wet core (second drying phase). It was therefore decided to develop a reduced model in function of this radius, which means a size dependent growth term will be used in the PBM model (Eq. 8.31). Based on the GSA the gas temperature and the gas velocity were chosen as the most sensitive degrees of freedom. The reduced model, function of the most sensitive degrees of freedom only, implemented in
7.4. Results

The PBE should be able to compute the evolution of the moisture content of a population of particles that are drying, all subjected to the same ambient conditions.

The general procedure followed during the model reduction is presented in figure 7.5. More details about the elaboration of the method are described in the appendix A and B, where the procedure is demonstrated in detail for our specific case study.

As mentioned in previous sections, a GSA was performed to detect the most

![Diagram](image_url)

**Figure 7.5:** Scheme of the steps taken during the model reduction procedure
Chapter 7. Model reduction in preparation of a PBM

sensitive degrees of freedom. Simulations are performed while varying the selected degrees of freedom \(D\) in a range between a minimum and a maximum value. \(M\) is the number of simulations that are performed, which can be chosen by the user. The range is based on the physical limitations of the dryer and the physical reality as for the GSA. The most obvious simulation, which is situated in the middle of the range or is physically most frequently used, is chosen as basic scenario to develop a model structure \(g\) with \(n\) coefficients. The model structure is verified for the other simulations, and afterwards the coefficients \(P'\) are optimised by minimizing the RMSE between the simulated data and the predictions of the developed model structure for each value of the selected degrees of freedom in the range. This results in a matrix with \(n\) rows and \(M\) columns:

\[
P' = \begin{pmatrix}
p'_{1,1} & p'_{1,2} & \cdots & p'_{1,M-1} & p'_{1,M} \\p'_{n,1} & p'_{n,2} & \cdots & p'_{n,M-1} & p'_{n,M}\end{pmatrix}
\]

with \(p'_{i,j}\) the parameter value corresponding to the \(i^{th}\) coefficient and \(j^{th}\) simulation. \(p'_{i}\) is a vector with the values for coefficient \(i\) for all simulations, whereas \(p'_{j}\) is a vector with all coefficients for one simulation. The optimised values of the coefficients are then plotted in function of the degree of freedom. One or more coefficients are selected and a relation \(h_i\) is determined between \(p'_{i}\) and \(D\) introducing coefficients \(c_i\). The sensitivity of the coefficients \(p'_{i}\) or the absence of noise can help to select these first coefficients. The relation can be a polynomial for which the order is dependent on the desired accuracy. Afterwards the relation \(h_i\) is implemented as fixed in the developed model structure and the other coefficients \(P'_A\) are optimised again. As such a deviation in the relation with respect to the fitted coefficient can be caught. At certain steps in the procedure the global model structure is verified again. These last steps are repeated till all relations \((h_1\text{ till } h_n)\) between the coefficients \(P'\) and the selected degrees of freedom \(D\) are determined. At the end a global optimization can be performed to optimize the values of all coefficients \(C\) of the reduced model simultaneously.

**Reduced model with the gas temperature as input**

The drying model was simulated for gas temperatures ranging from 20 till 80 °C with a particle radius of 0.6 mm. For both drying phases the growth term, i.e. the derivative of \(R_w\) (Eq. 7.2), was calculated numerically with a resolution \((\Delta t)\) of 0.2 s and plotted against the wet radius \(R_w\) (Fig. 7.6 and 7.7).

\[
\dot{R}_w = G_{r,1}(R_{w,nor}, T_g) \approx \frac{R_w(t_{i+1}) - R_w(t_i)}{\Delta t} \quad (7.2)
\]
7.4. Results

It is obvious that a different model structure will be required for both drying phases. The objective is the development of a simpler model able to describe the behaviour visualised in figure 7.6 and 7.7.

The developed model structure for the first drying phase is:

\[ G_{r,1}(R_{w,\text{nor}}, T_g) = A + B R_{w,\text{nor}} + C e^{D R_{w,\text{nor}}} \] (7.3)
Chapter 7. Model reduction in preparation of a PBM

\[ R_{w,nor} = \frac{R_w - R_p}{R_{w,0} - R_p} \quad (7.4) \]

with \( A, B, C \) and \( D \) empirical coefficients, \( R_p \) the radius of the dry particle and \( R_{w,0} \) the initial (wet) radius. The equations for the different coefficients of the first drying phase are provided in table 7.3. More details about the used procedure are mentioned in appendix A.

The global empirical equation for the first drying phase exhibits a mean weighted relative error of 0.53\% between the simulated detailed drying model prediction and the empirical model.

For the second drying phase the resulting equation is:

\[ G_{r,2}(R_{w,nor}', T_g) = A'(R_{w,nor}')^{B'} + C' \left( 1 + D' R_{w,nor}' \right)^{E'} + R_f'(A' 0.5^{B'} + C' (1 + D' 0.5)^{E'}) \quad (7.9) \]

\[ R_{w,nor}' = \frac{R_w}{R_p} \quad (7.10) \]

with \( A', B', C', D' \) and \( E' \) empirical coefficients and \( R_f' \) a factor to reduce the offset. In table 7.4 the equations for the different coefficients are mentioned for the second drying phase. Details about the procedure can be found in appendix B.

The global equation for the second drying period has a mean weighted relative error of 1.97\% between the full model result and the empirical fit.

The resulting optimised values for the parameters of the reduced model for both drying phases are tabulated in table 7.5 and 7.6 respectively.

The developed reduced drying model was intended for use in a PBE. The developed reduced model, a quite straightforward combination of algebraic equations, can be easily implemented in different solution methods for PBM which was not possible for the original drying model.

### Table 7.3: Resulting equations for the different coefficients of the first drying phase

<table>
<thead>
<tr>
<th>Coefficient</th>
<th>Polynomial function</th>
</tr>
</thead>
<tbody>
<tr>
<td>( A )</td>
<td>( a_1 T_g^4 + a_2 T_g^3 + a_3 T_g^2 + a_4 T_g + a_5 ) (7.5)</td>
</tr>
<tr>
<td>( B )</td>
<td>( b_1 T_g^3 + b_2 T_g^2 + b_3 T_g + b_4 ) (7.6)</td>
</tr>
<tr>
<td>( C )</td>
<td>( c_1 e^{-(T_g+c_2)/c_3} + c_4 e^{-(T_g+c_5)/c_6} ) (7.7)</td>
</tr>
<tr>
<td>( D )</td>
<td>( d_1 T_g^2 + d_2 T_g + d_3 ) (7.8)</td>
</tr>
</tbody>
</table>

The developed reduced drying model was intended for use in a PBE. The developed reduced model, a quite straightforward combination of algebraic equations, can be easily implemented in different solution methods for PBM which was not possible for the original drying model.
7.4. Results

Table 7.4: Resulting equations for the different coefficients for the second drying phase

<table>
<thead>
<tr>
<th>Coefficient</th>
<th>Describing function</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A'$</td>
<td>$-e^{a_1'} T_g^{b_2} \ (7.11)$</td>
</tr>
<tr>
<td>$B'$</td>
<td>$b_1' e^{b_2'(T_g-20)} - 1 \ (7.12)$</td>
</tr>
<tr>
<td>$C'$</td>
<td>$-e^{c_1'} T_g^{c_2} \ (7.13)$</td>
</tr>
<tr>
<td>$D'$</td>
<td>$e^{d_1'} e^{d_2'} T_g - 1 \ (7.14)$</td>
</tr>
<tr>
<td>$E'$</td>
<td>$e_1' e^{e_2'}(T_g-20) - 1 \ (7.15)$</td>
</tr>
<tr>
<td>$R_f'$</td>
<td>$R_{f,1} T_g R_{f,2}^2 + R_{f,3} \ (7.16)$</td>
</tr>
</tbody>
</table>

Table 7.5: Parameter values for the first drying phase

<table>
<thead>
<tr>
<th>Coefficient</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$a_1$</td>
<td>$-6.4310^{-15}$</td>
</tr>
<tr>
<td>$b_1$</td>
<td>$1.4510^{-12}$</td>
</tr>
<tr>
<td>$c_1$</td>
<td>$4.9710^{-12}$</td>
</tr>
<tr>
<td>$d_1$</td>
<td>$0.0037$</td>
</tr>
<tr>
<td>$a_2$</td>
<td>$-2.7410^{-12}$</td>
</tr>
<tr>
<td>$b_2$</td>
<td>$-1.3010^{-10}$</td>
</tr>
<tr>
<td>$c_2$</td>
<td>$62.4$</td>
</tr>
<tr>
<td>$d_2$</td>
<td>$-0.408$</td>
</tr>
<tr>
<td>$a_3$</td>
<td>$-5.2810^{-10}$</td>
</tr>
<tr>
<td>$b_3$</td>
<td>$-3.9910^{-9}$</td>
</tr>
<tr>
<td>$c_3$</td>
<td>$202.82$</td>
</tr>
<tr>
<td>$d_3$</td>
<td>$23.5$</td>
</tr>
<tr>
<td>$a_4$</td>
<td>$-7.2410^{-9}$</td>
</tr>
<tr>
<td>$b_4$</td>
<td>$-2.5710^{-8}$</td>
</tr>
<tr>
<td>$c_4$</td>
<td>$-3.0510^{-13}$</td>
</tr>
<tr>
<td>$a_5$</td>
<td>$-2.3510^{-7}$</td>
</tr>
<tr>
<td>$c_5$</td>
<td>$36.43$</td>
</tr>
<tr>
<td>$c_6$</td>
<td>$96.14$</td>
</tr>
</tbody>
</table>

Table 7.6: Parameter values for the second drying phase

<table>
<thead>
<tr>
<th>Coefficient</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$a_1'$</td>
<td>$9.93$</td>
</tr>
<tr>
<td>$b_1'$</td>
<td>$-0.130$</td>
</tr>
<tr>
<td>$c_1'$</td>
<td>$10.3$</td>
</tr>
<tr>
<td>$d_1'$</td>
<td>$0.0995$</td>
</tr>
<tr>
<td>$e_1'$</td>
<td>$-0.0998$</td>
</tr>
<tr>
<td>$R_{f,1}'$</td>
<td>$7.2410^4$</td>
</tr>
<tr>
<td>$a_2'$</td>
<td>$-55.1$</td>
</tr>
<tr>
<td>$b_2'$</td>
<td>$-0.381$</td>
</tr>
<tr>
<td>$c_2'$</td>
<td>$-56.7$</td>
</tr>
<tr>
<td>$d_2'$</td>
<td>$-10.0$</td>
</tr>
<tr>
<td>$e_2'$</td>
<td>$-0.486$</td>
</tr>
<tr>
<td>$R_{f,2}'$</td>
<td>$-3.51$</td>
</tr>
<tr>
<td>$R_{f,3}'$</td>
<td>$-0.113$</td>
</tr>
</tbody>
</table>

Extension with the gas velocity as second input for the reduced model

The gas velocity is identified as the second input to be included in the reduced model. As the gas velocity has only an influence on the first drying phase, only the reduced model for this phase has been extended. The relative effect on the growth rate is rather limited when considering the effect of $R_w$ and $T_g$. Therefore, a straightforward strategy is developed to incorporate $V_g$, i.e. find a supplementary function which is only dependent on $V_g$, but is able to predict the growth rate with high accuracy. A polynomial function of second order was implemented. The resulting empirical equation for the first drying phase is determined to be:

$$G_{r,1}^*(R_{w,nor}, T_g, V_g) = (v_1 V_g^2 + v_2 V_g + v_3) G_{r,1}(R_{w,nor}, T_g) \quad \quad (7.17)$$
where $v_1$, $v_2$ and $v_3$ are the extra empirical coefficients. The coefficients for the first drying phase $G^*_r(R_{w,nor}, T_g, V_g)$ were optimised simultaneously with the coefficients of the original empirical function $G_r(R_{w,nor}, T_g)$ in order to reduce the error. The resulting coefficients are given in Table 7.7.

Table 7.7: Parameter values for the extended first drying phase (coefficients which are changed compared to the reduced model without $V_g$ as input and the extra coefficients are indicated in bold)

<p>| | | | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>$a_1$</td>
<td>-6.43e-15</td>
<td>$b_1$</td>
<td>1.45e-12</td>
<td>$c_1$</td>
<td>4.97e-12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$a_2$</td>
<td>-2.74e-12</td>
<td>$b_2$</td>
<td>-1.35e-10</td>
<td>$c_2$</td>
<td>62.67</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$a_3$</td>
<td>-5.28e-10</td>
<td>$b_3$</td>
<td>-3.99e-09</td>
<td>$c_3$</td>
<td>202.82</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$a_4$</td>
<td>-7.24e-09</td>
<td>$b_4$</td>
<td>-2.57e-08</td>
<td>$c_4$</td>
<td>-3.05e-13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$a_5$</td>
<td>-2.35e-07</td>
<td></td>
<td></td>
<td>$c_5$</td>
<td>36.43</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$d_1$</td>
<td>0.0037</td>
<td>$v_1$</td>
<td>-1.28e-6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$d_2$</td>
<td>-0.408</td>
<td>$v_2$</td>
<td>0.00238</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>$d_3$</td>
<td>23.5</td>
<td>$v_3$</td>
<td>-0.427</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

7.5 Discussion

The procedure developed and illustrated in this study clearly has advantages and disadvantages. It is a heuristic reduction technique, but as stated by Van Nes et al. [2002] it is very powerful, if the complex and the reduced model produce similar results [Van Nes et al., 2002]. In order to start the model reduction procedure, knowledge about the process is required. Here, the difference in drying behaviour of the first and second drying phase was known a priori, and this knowledge was used to decide to make a separate reduced model for both phases. A GSA was used to detect the most influential input variables, but also insight into the process and the model was helpful to understand why these variables were important. If two input variables were equally influential, a choice was made based on the expected range in the dryer and experience with the process under consideration. The pitfall of model reduction techniques described in the literature can be that the result is a reduced model that is too complex for the purpose. The described approach has the advantage of allowing full control over the reduction process in the sense that the complexity of the empirical model to be obtained can be chosen. This is always a trade-off against the loss of accuracy (i.e. the relative error between the physical model and the reduced empirical model). In the derived model here, the complexity of the model was not penalised as it was no restriction for the subsequent step. The resulting reduced model contains the input variable that is the most sensitive variable, but is also a variable that is important in the
7.6. Conclusion

subsequent research. The reduced model will be used in a PBM model, and at a later stage the PBM model can be extended with the information of a CFD model of the dryer. The disadvantage of choosing the equations of the reduced model arbitrarily lies in the fact that these equations are not necessarily the best equations to describe the drying behaviour. There is always a chance that more simple equations are sufficient. On the other hand the choice of the equations can be made in function of the purpose, in this case the implementation into a PBM model, and maybe later in a coupled PBM-CFD model.

7.6 Conclusion

Starting from a complex model describing the drying behaviour of individual granules it was possible to develop a reduced model that can now be used as submodel in other models, for example a PBM model. A new strategy to perform a model reduction was introduced and demonstrated. The development of the reduced model started with a GSA to detect the most sensitive degrees of freedom in the model. The full drying model was simulated for a range of values of the most sensitive degree of freedom in order to generate data to use for the development of the reduced model. Based on the data a proposal for an empirical model is made, which can be reviewed in a later stage of the model reduction procedure. The coefficients of the proposed reduced model are described in function of the most sensitive degree of freedom. The reduced model is an empirical model able to calculate the decrease in $R_w$ for different gas temperatures and gas velocities regardless the granule radius. Using the developed procedure, one is able to construct a reduced model with a low mean weighted relative error.

The empirical model can now be used to further analyse the drying behaviour of pharmaceutical granules in a fluidized bed dryer. The objective is to study the properties of a population of particles and the evolution of the moisture content in the dryer. This analysis, which is done using PBM, is extensively discussed in part III of the thesis. To fully understand the behaviour of wet granules the developed PBM model should be combined with a CFD model to take into account local variations of temperature and humidity in the dryer and their effect on the drying process.
Chapter 7. Model reduction in preparation of a PBM
PART III

Population Balance Modelling for the drying of pharmaceutical granules
Part III of this thesis deals with modelling of a population of drying granules which can be accomplished by a PBM. In chapter 8 of part III a one-dimensional PBM model describing the drying behaviour of wet particles is developed. Moreover, several solution techniques to solve the PBE are implemented. These techniques are compared w.r.t. the obtained accuracy and the calculation time. In chapter 9 the GSA techniques, introduced in chapter 5 of part II are investigated and compared for the PBM model. The use of a moment-based solution technique for the PBE implies the need to reconstruct the number density distribution, which is the subject of chapter 10. Parameter fitting methods are compared with the method of splines, which is further analysed w.r.t. the incorporated parameters, the number of splines and the number of moments. In the last chapter of part III chapter 11 the one-dimensional PBM model is extended to a two-dimensional PBM model in order to include breakage during the drying of pharmaceutical granules. This is a preliminary simulation study to indicate the potential of this approach.
CHAPTER 8

Introduction to Population Balance Modelling & model development


Abstract:
Drying is frequently used during the production of pharmaceutical tablets. Simulation-based control strategy development for such a drying process requires a detailed model. First, the drying of wet granules is modelled using a Population Balance Modelling (PBM). A growth term based on a reduced model was used, which describes the decrease of the moisture content, to follow the moisture content distribution for a batch of granules. Secondly, different solution methods for solving the PBM are compared. The effect of grid size (discretisation methods) is analysed in terms of accuracy and calculation time. All tested methods are compared based on their ability to predict moment dynamics and the distribution, and their computational burden. The Method of Characteristics (MOC), a fast method, is able to calculate the distribution accurately with a coarse grid. The Quadrature Method of Moments (QMOM) requires even less calculation time, but results in a set of moments.

8.1 Introduction

The development of a complete mechanistic model for the fluidized bed process that allows predicting the spatial changes in the distribution of the moisture content in a population of granules and eventually the moisture content distri-
bution in the outlet product of the dryer is approached in a step-wise manner. The drying model for single pharmaceutical granules should first be extended towards a population of granules using the well-known (in several engineering branches, but not in pharmaceutical sciences) framework of PBM. A stand-alone PBM model is a first step towards a potentially coupled CFD-PBM model, should this be required. The behaviour of many systems, including a pharmaceutical drying system is often described by the 'averaged' behaviour of single particles. However, in a real system this could turn out to be an overly rough approximation. Spatial and population heterogeneity occur in a real system, implying that the 'state' of the particles can be different and also the environment they 'observe' is not the same throughout the system. This can potentially have an impact on the system behaviour which can be quite different from the 'average' behaviour. It really depends on the goal of the modelling study whether this level of detail is required or not. Since the goal of this work is to develop detailed process knowledge, it is important to explore the impact of these heterogeneities. For a thorough analysis of particles that are interacting with each other and the continuous phase, PBMs can be applied. If the ambient condition is identical for all granules, a stand-alone PBM model gives no added value for understanding the drying process, because the heterogeneity in e.g. the gas temperature, will influence the drying rate and the final moisture content distribution. However, after gaining knowledge about the flow pattern of granules in a fluidized bed, this information can be coupled with the PBM. In this case individual granules are not subjected to the same ambient condition, and a distinct drying behaviour for the granules can be simulated. Moreover, the dryer is fed over a longer period of time implying that not all granules are at the same stage in the drying process. This effect can also be accounted for using a PBM.

### 8.1.1 Introduction towards the general Population Balance Equation (PBE)

The change of the number density $n(x,r,t)$ can be described by the general PBE:

$$\frac{\partial}{\partial t} n(x,r,t) + \nabla \cdot (\dot{X}(x,r,Y,t)n(x,r,t)) + \nabla \cdot (\dot{R}(x,r,Y,t)n(x,r,t)) = h(x,r,Y,t) \quad (8.1)$$

where $x$, $r$, $t$, $Y$ and $h$ are respectively the internal coordinate (i.e. the internal property of the particles that is considered to be distributed), the external (spatial) coordinate, the time, the continuous phase vector and the net birth rate due to discrete processes. The net birth rate can include different phenomena.
8.1. Introduction

such as nucleation, aggregation, agglomeration, breakage, etc. \cite{Ramkrishna2000}. \( \nabla \), the nabla operator, represents the vector differential operator. In a three-dimensional Cartesian coordinate system, \( \nabla \) is defined in terms of partial derivative operators as

\[
\nabla = \hat{x} \frac{\partial}{\partial x} + \hat{y} \frac{\partial}{\partial y} + \hat{z} \frac{\partial}{\partial z}
\]  

(8.2)

where \( \hat{x} \), \( \hat{y} \) and \( \hat{z} \) represent the unit vectors in each direction. \( \hat{X} \) and \( \hat{R} \) are the partial derivatives of the internal and external coordinates respectively. \cite{Ramkrishna2000}.

8.1.2 Solution techniques for solving PBEs with a growth term

PBEs which have to take growth into account are more difficult to solve. At first sight it seems simpler to include growth compared to breakage or aggregation. However, the difficulty of including growth terms is that they lead to hyperbolicity in the resulting equations. The population density function can span over several orders of magnitudes and the distribution can show very steep changes. Both factors complicate achieving an accurate numerical simulation of the PBM within an acceptable computational time \cite{Qamar2006}. For solving of PBEs several numerical methods exist such as Method of Moments (MOM), Monte Carlo simulation, discretisation methods such as finite difference method, finite volume method, finite element method, method of lines, methods of weighted residuals/orthogonal collocation, etc. \cite{Gunawan2004}.

The main requirement for the model is the accurate prediction of the desired properties. Sectional methods are the best choice for this type of problem \cite{Kumar2008}. Dividing the entire domain in a number of bins leads to a set of ODEs which have to be solved simultaneously in order to calculate the number of particles in each bin. The number of bins, or in other words the coarseness of the grid, influences the accuracy of the method. Certain sectional methods utilize a linear grid, and several examples can be found in literature \cite{Gelbard1980}. The disadvantage of linear grid discretisation is the necessary computational power as a lot of size classes are required to cover large ranges. In this respect, geometric grids can offer a solution. A geometric grid with a factor of two in progression in size was proposed \cite{Hounslow1988}, and in this way the total number and total volume of particles could be predicted correctly. An extended discretisation technique for aggregation to size-dependent particle growth was proposed by Hounslow \cite{Hounslow1988}. Coefficients are estimated using expressions conserving three moments. The method can lead however to a negative value for the number of particles,
which is corrected by replacing the negative value by zero [Hounslow et al., 1988].

The method of lines is used for a PBE with only growth and nucleation in order to transform a PDE into a set of ODEs. In a first paper the growth term was rewritten using central differences, leading to negative density function values [Muhr et al., 1995]. In a second paper this was solved by adopting a first order upwind differentiation [Muhr et al., 1996]. Another problem in the homogeneous model of the first paper is the sensitivity to size spacing, which was solved by adopting a small fixed size spacing of 1 nm [Muhr et al., 1995, Muhr et al., 1996].

The method of Hounslow was adjusted for adjustable geometric discretisations with a factor of $2^{1/q}$ [Litster and Hounslow, 1995], and a further development was done [Wynn, 1996]. The fixed pivot technique is consistent with the first two moments [Kumar and Ramkrishna, 1996]. The formulation generalizes the method proposed by Hounslow. It calculates some selected moments accurately, but becomes less accurate for the calculation of the whole particle property distribution, i.e. the distribution of the size of all particles. However this method can only be applied for aggregation and breakage problems [Kumar and Ramkrishna, 1996]. An alternative scheme is proposed for combined processes of aggregation or breakage with growth and nucleation. It is a combination of the discretisation technique and the Method of Characteristics (MOC). The technique can be used for pure growth problems or combinations.

Particle growth and nucleation have the feature of being continuous, and in this way they are more difficult to implement in the discrete version of the PBEs [Kumar and Ramkrishna, 1997]. A general scheme was developed to solve all processes simultaneously [Kumar et al., 2008]. It is an extension of the cell average technique [Kumar et al., 2006], but could only be used for aggregation problems. The idea is that growth of a particle can be seen as the adherence of small nuclei on the particle surface. In such a way the model concept is similar to aggregation, namely the aggregation of particles with imaginary particles. These models can be solved with the extended cell average technique. The numerical discretisation is consistent with the first two moments.

Other solution methods used for growth problems are variants of the MOM [Madras and McCoy, 2002], where the PBE is simplified into a series of a few discrete moment equations, typically only six moments are calculated. In this case it is necessary to convert the growth term via a moment transformation. The reduction in dimensionality is an advantage with respect to computational requirements. Under certain conditions the moment equations are closed, and the differential equations for the lower order moments do not depend on values for the higher-order moments, resulting in a set of ODEs which can be solved efficiently and accurately. However, for complex problems the moment
8.2. Objectives

closure conditions are violated \cite{HulbertKatz1964}. A solution for this problem is the use of the QMOM \cite{McGraw1997} or the Discrete Quadrature Method of Moments (DQ MOM) \cite{Marchisioetal2003}. The QMOM method requires a relatively small amount of scalar equations to compute the moments of populations with small errors. The QMOM method is preferred in the case of size dependent growth. A quadrature approximation is the basis of the technique and calculates a number of weights and abscissas, which is achieved using e.g. the Product-Difference (PD) algorithm. The moment-based population balance results in a number of transport equations for the first moments. The growth of crystals without aggregation is described by \cite{MadrasMcCoy2002}. The PBEs are solved with the moments method in order to have detailed information about the crystal size distribution \cite{MadrasMcCoy2002}.

High Resolution Finite Volume (HRFV) algorithms were proposed for solving highly nonlinear multidimensional PBEs as the growth of crystals is associated with the change of multiple internal coordinates. These algorithms are developed for solving hyperbolic PDEs and are state-of-the-art methods in engineering areas such as aerodynamics, astrophysics, detonation waves, etc. The HRFV methods for compressible gas dynamics were adapted for PBEs. This method provides an accurate solution without large computational effort \cite{Maetal2002}. The growth problem was compared with the advection problem, which has been thoroughly studied in fluid dynamics. One-dimensional and multidimensional PBEs were simulated using HRFV methods. The simulated results were consistent and accurate for batch and continuous PBEs using several initial conditions \cite{Gunawanetal2004}.

Several population balance solution methods were compared for a crystallisation process, namely the MOC, the finite volume methods and the finite element methods, in terms of the performance requirements essential for on-line control applications. The MOC gave the most accurate predictions, but the needed computational effort is, however, a disadvantage. HRFV methods in combination with flux limiting functions gave satisfactory results with a reduced computational demand, whereas finite element methods failed due to the complex implementation and high computational demand \cite{Mesbahetal2009}.

8.2 Objectives

The objective of this study is to develop a PBM for the drying of a batch of pharmaceutical granules. Furthermore, different solution methods are tested. The influence of the grid size, which is important for discretisation methods, is investigated. Different solution methods are compared in terms of accuracy
and calculation time: the HRFV scheme, the MOC and the QMOM.

8.3 Numerical solution methods

8.3.1 High Resolution Finite Volume (HRFV) scheme

High resolution schemes have already been used for the numerical solution of hyperbolic systems (astrophysical flows, gas dynamics, detonation, etc.) to obtain high accuracy on coarse grids and to resolve sharp discontinuities [Qamar et al., 2006]. Qamar et al. [2006] started from the high resolution semi-discrete scheme of Koren based on a uniform grid [Koren, 1993]. The scheme is discrete in the internal coordinate for the space but continuous in time. A finite volume scheme is applied to the resulting homogeneous PBE (Eq. 8.30, which is presented in section 8.4.1), and in order to achieve this, the domain of interest of the internal coordinate is subdivided into $N$ subdomains. $R_{w,i}$ refers to the cell center of cell $i$ and $\Delta R_{w,i}$ represents the cell width. In this context, the application of the cell centered finite-volume discretisation to the PBM generates the following expression [Qamar et al., 2006]:

$$\int_{R_{w,i}^-}^{R_{w,i}^+} \frac{\partial n}{\partial t} dR_w + \left( (G_r n)_{R_{w,i}^+} - (G_r n)_{R_{w,i}^-} \right) = 0 \quad (8.3)$$

In this semi-discrete equation $R_{w,i}^+$ and $R_{w,i}^-$ are the cell faces and $G_r n$ are the fluxes. One can now define $n_i(t)$ as the average value of the number density in each cell, i.e.

$$n_i(t) = \frac{1}{\Delta R_{w,i}} \int_{R_{w,i}^-}^{R_{w,i}^+} n(R_w, t) dR_w \quad (8.4)$$

Using this information equation 8.3 can be rewritten as

$$\frac{\partial n_i}{\partial t} + \frac{1}{\Delta R_{w,i}} \left( (G_r n)_{R_{w,i}^+} - (G_r n)_{R_{w,i}^-} \right) = 0, \forall i = 1, 2...N \quad (8.5)$$

The computation of the fluxes at the cell-faces determines the accuracy of the scheme. Using an upwind scheme, the cell fluxes can be calculated, and a high order accuracy can be obtained by piecewise polynomial interpolation:

$$(G_r n)_{R_{w,i}^+} = G_{r,R_{w,i}^+} \left( n_{i+1} + \frac{1 + \kappa}{4} (n_i - n_{i+1}) + \frac{1 - \kappa}{4} (n_{i+1} - n_{i+2}) \right), \quad (8.6)$$

$\kappa \in [-1,1]$.

When $\kappa = -1$, the result is a second-order accurate fully one-sided upwind scheme. For $\kappa = 1$ the standard second-order accurate central scheme is ob-
8.3. Numerical solution methods

tained. This piecewise polynomial interpolation is described by \textcite{van Leer 1985}. \textcite{Qamar et al. 2006} have chosen a value of 1/3 for $\kappa$:

$$ (G_r n)_{R_{w,i}}^+ = G_{r,R_{w,i}}^+ \left( n_{i+1} + \frac{1}{2} \left( \frac{1}{3} + \frac{2}{3} r_i^+ \right) (n_{i+1} - n_{i+2}) \right) $$

(8.7)

with $r_i^+$ the upwind ratio of two consecutive solution gradients:

$$ r_i^+ = \frac{n_i - n_{i+1} + \epsilon}{n_{i+1} - n_{i+2} + \epsilon} $$

(8.8)

where $\epsilon$ is a parameter with a small value to avoid division by zero. To suppress and avoid wiggles and negative solution values the Sweby’s monotonicity theory is used \textcite{Sweby 1984}, which leads to the following:

$$ (G_r n)_{R_{w,i}}^+ = G_{r,R_{w,i}}^+ \left( n_{i+1} + \frac{1}{2} \Phi(r_i^+) (n_{i+1} - n_{i+2}) \right) $$

(8.9)

with $\Phi$ a flux limiting function \textcite{Koren 1993}. Several possibilities for the flux limiting function exist, and a commonly applied one is defined as:

$$ \Phi_{KO}(r) = \max(0, \min(2r, \min(\frac{1}{3} + \frac{2}{3} r, 2))) $$

(8.10)

A series of flux limiting functions $\Phi$ are available \textcite{Sweby 1984, LeVeque 1996}: van Leer \textcite{van Leer 1974} (Eq. 8.11), minmod (Eq. 8.12), Roe \textcite{Roe 1983}, superbee (Eq. 8.13), Chakravarthy and Osher \textcite{Chakravarthy and Osher 1983}, monotized central \textcite{van Leer 1977}, UMIST \textcite{Lien and Leschzines 1994}, etc. These flux limiting functions should avoid the occurrence of negative number density values and spurious oscillations (due to discontinuities, sharp changes in the solution domain, etc.). The various limiters have different switching characteristics and have to be chosen according to the particular problem and the used solution scheme.

$$ \Phi_{VL}(r) = \frac{|r| + r}{|r| + 1} $$

(8.11)

$$ \Phi_{R,m}(r) = \max(0, \min(r, 1)) $$

(8.12)

$$ \Phi_{R,s}(r) = \max(0, \min(1, 2r), \min(2, r)) $$

(8.13)

Discontinuous solutions have second-order accuracy in smooth regions, while first-order accuracy is used in the district of shock discontinuities. The boundary conditions are not straightforward. At the outflow boundary $i = 0$ (i.e. completely dried granules) the fully one sided upwind scheme is used ($\kappa = -1$). At the inflow boundary central interpolation is used ($\kappa = 1$) for $i = N-1$. The
resulting boundary conditions are:

\[(G_r n)_{1 \frac{1}{2}} = G_{r, 2 \frac{1}{2}} (n_1 + \frac{1}{2} (n_1 - n_2)), \quad i = 0,\]
\[(G_r n)_{N-1 \frac{1}{2}} = G_{r, N-2 \frac{1}{2}} (n_N + n_{N-1}), \quad i = N - 1,\]
\[(G_r n)_N = G_{in n_in}, \quad i = N,\]
\[(G_r n)_{R_w, i} = G_{r, R_w, i} (n_{i+1} + \frac{1}{2} \Phi (r_i^+(n_{i+1} - n_{i+2})), \quad i = 1, 2...N - 2 \quad (8.14)\]

The high resolution scheme with \(\kappa\) equal to -1 is also used to investigate the differences of both schemes. For both schemes different flux limiting functions are tested.

### 8.3.2 Method of Characteristics (MOC)

The MOC starts with the discretisation of the domain. In this work a regular grid is used, but also irregular or geometric grids can be applied [Qamar and Warnecke 2007]. \(N\) is the number of subdivisions in the domain \([R_{w, min}, R_{w, max}]\).

\[x_{1 \frac{1}{2}} = x_{min}, \quad x_{N+1 \frac{1}{2}} = x_{max} \quad \text{and} \quad x_{i+1 \frac{1}{2}} = x_{min} + i \Delta x_i \quad (8.15)\]

with

\[x_i = \frac{x_{i-\frac{1}{2}} + x_{i+\frac{1}{2}}}{2} \quad \text{and} \quad \Delta x_i = x_{i+\frac{1}{2}} - x_{i-\frac{1}{2}} \quad (8.16)\]

The simplified PBE (Eq. 8.30 developed in section 8.4.1) is multiplied by \(R_w\):

\[R_w \frac{\partial}{\partial t} n(R_w, t) + R_w \frac{\partial}{\partial R_w} \dot{R}_w (R_w, Y) n(R_w, t) = 0 \quad (8.17)\]

A new variable is defined:

\[\tilde{n}(t, R_w) := R_w n(t, R_w) \quad (8.18)\]

The combination of this definition with the product rule implies:

\[\frac{\partial}{\partial t} \tilde{n}(R_w, t) + \frac{\partial}{\partial R_w} G_r(t, R_w) \tilde{n}(R_w, t) - \frac{G_r(t, R_w)}{R_w} \tilde{n}(R_w, t) = 0 \quad (8.19)\]

Equation 8.19 is integrated over the control volume \(\Omega_i(t) = [x_{i-\frac{1}{2}}(t), x_{i+\frac{1}{2}}(t)]\) and the growth term \(G_r(t, R_w)\) is substituted by:

\[G_r(t, R_w) = \frac{dR_w}{dt} \quad (8.20)\]
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\[
\int_{\Omega_i(t)} \frac{\partial}{\partial t} \tilde{n}(R_w, t) dR_w + \left( \frac{dR_w}{dt} \tilde{n}(R_w, t) \right) \bigg|_{R_w,i-\frac{1}{2}(t)}^{R_w,i+\frac{1}{2}(t)} = \int_{\Omega_i(t)} \frac{G_r(t, R_w)}{R_w} \tilde{n}(R_w, t) dR_w \tag{8.21}
\]

The Leibniz formula is now applied to equation 8.21 and combined with equation 8.22:

\[
\tilde{n}_i := \frac{1}{\Delta R_{w,i}(t)} \int_{\Omega_i(t)} \tilde{n}(R_w, t) dR_w \tag{8.22}
\]

\[
\frac{d}{dt} \left[ (R_{w,i+\frac{1}{2}}(t) - R_{w,i-\frac{1}{2}}(t)) \tilde{n}_i \right] = \frac{G_{r,i+\frac{1}{2}} \tilde{n}_i}{R_{w,i}(t)} - \frac{G_{r,i-\frac{1}{2}} - G_{r,i}(t)}{\Delta R_{w,i}(t)} \tag{8.23}
\]

On the left-hand side of equation 8.23 the product rule is applied, and as a result:

\[
\frac{d\tilde{n}_i}{dt} = \frac{G_{r,i+\frac{1}{2}} \tilde{n}_i}{R_{w,i}(t)} - \frac{G_{r,i+\frac{1}{2}} - G_{r,i-\frac{1}{2}}}{\Delta R_{w,i}(t)} \tag{8.24}
\]

The resulting set of ODEs consists of equation 8.24 combined with:

\[
\frac{dR_{w,i+\frac{1}{2}}}{dt} = G_{r,i+\frac{1}{2}}, \forall i = 1, 2, ... N \tag{8.25}
\]

Note that this implies the MOC uses a moving grid. The resulting ODEs can be solved using a standard ODE solver.

8.3.3 Quadrature Method of Moments (QMOM)

The MOM is a solution method where the distribution is approximated by its moments. The \( k \)th moment is defined as:

\[
m_k(t) = \int_0^\infty R_w^k n(R_w, t) dR_w \tag{8.26}
\]

The first integral moments are interesting because of their relation to important physical properties. \( m_0 \) is a representation for the total particle number density (\( m_0 = N_t \)), \( m_1 \) is a kind of average wet diameter (\( m_1 \sim d_t \)), \( m_2 \) represents the total particle wet area (\( m_2 \sim A_t \)), and \( m_3 \) the total wet volume (\( m_3 \sim V_t \)). The PBE can be rewritten in terms of moments as:

\[
\frac{dm_k(t)}{dt} = \int_0^\infty kR_w^{k-1} G_r(R_w)n(R_w, t) dR_w \tag{8.27}
\]

The moment equations are only closed under certain conditions, which means that the differential equations for the lower order moments do not depend on values of higher order moments [Hulbert and Katz, 1964]. The QMOM is
a variation where the closure problem is solved using a Gaussian quadrature approximation [McGraw, 1997] [Marchisio et al., 2003]:

\[ n(R_w, t) \approx \sum_{i=1}^{N_q} w_i(t) \epsilon [R_w - R_{w,i}(t)] \]  \hspace{1cm} (8.28)

Using this quadrature approximation the moments become:

\[ m_k(t) \approx \sum_{i=1}^{N_q} w_i(t) R_{w,i}^k(t) \]  \hspace{1cm} (8.29)

where \( R_{w,i}(t) \) are the abscissas and \( w_i(t) \) are the weights, which can be specified from the lower order moments. The weights and abscissas can be determined by different algorithms; the PD-algorithm, the Chebyshev algorithm, etc. A sequence of moments is used by the PD-algorithm for the computation of the coefficients of the 'three-term-recurrence relationship' that is satisfied by orthogonal polynomials. With the help of these coefficients the quadrature points and weights are calculated, which are then used to approximate the integrals over the unknown number density function. The Chebyshev algorithm had been used previously for the computation of the coefficients of the recurrence relations of orthogonal polynomials with known density function. Upadhyay adapted the algorithm to work with a sequence of moments with the underlying density function being unknown. The algorithm directly uses the 'three-term-recurrence relationship' among the orthogonal polynomials to establish recursive formulas for the coefficients [Upadhyay, 2012]. According to Upadhyay the Chebyshev algorithm is more general and more robust, and it can also be applied to symmetric distributions, where the PD-algorithm would struggle with odd moments which have a value of zero. High order moments can be calculated to obtain accurate high order quadratures [Upadhyay, 2012].

8.4 Results

8.4.1 Development of a one-dimensional PBM for the evaluation of the moisture content distribution

In the system at hand the internal coordinate of interest is a representation of the moisture content of the granule, which corresponds to the wet radius of the particle. It is assumed that the particles do not break up during drying. When breakage would be taken into account, the one-dimensional PBM should be extended towards a two-dimensional form in order to also consider particle size as an additional dimension in the vector \( x \) (see chapter 11). Increasing the
number of internal coordinates has the disadvantage that it leads to an increase in mathematical complexity and required computational power. Moreover, it also results in difficulties in case one later on would like to combine the PBM with a CFD code. Since drying of wet granules is a continuous process, i.e. no discrete processes occur, $h$ equals zero. When the ambient air phase is assumed to be constant, meaning there is no spatial variation, the third term of the general PBE (Eq. 8.1) vanishes. The resulting reduced, homogeneous PBE is a linear hyperbolic differential equation in $(R_w, t)$.

$$\frac{\partial}{\partial t} n(R_w, t) + \frac{\partial}{\partial R_w} \dot{R}_w(R_w, Y)n(R_w, t) = 0$$  (8.30)

where $R_w$ is the wet radius of the particle. In this equation the growth term $G_r$ is defined as

$$G_r = \dot{R}_w(R_w, Y)$$  (8.31)

The growth term is based on the single particle drying model (Part II), that underwent a reduction step (Chapter 7 section 7.4.3). In this chapter the reduced model which is only function of the gas temperature was used. In the literature, population balances are typically found with a positive growth term. However, in this study a negative growth term occurs, similar to a PBM that models dissolution. The difficulty of the incorporation of a growth term in a PBE is that they lead to hyperbolicity in the resulting equations. Since no analytical solution for the developed PBM exists, a numerical method to solve the PBE is required.

### 8.4.2 Model analysis and simulation parameters

In table 8.1 the variable types are listed for the reduced drying model, in which a division is made between the variables which should be specified (the known variables) and the variables predicted with the model equations (unknown variables). For the reduced model the growth term of the first and second drying phase are the unknowns, and are calculated using algebraic equations (Section 7.4.3). The reduced drying model consists of respectively 18 and 13 coefficients for the first and second drying phase. The gas temperature, particle radius and initial moisture content are fixed in the problem to be solved.

Simulations for testing the PBM were performed at a specific gas temperature and for particles with a certain size (Table 8.2). A normal probability density function was used as initial distribution of the internal coordinate $R_w$:

$$n_0 = \frac{1}{\sigma \sqrt{2\pi}} e^{-\frac{(R_w - \mu)^2}{2\sigma^2}}$$  (8.32)
Table 8.1: Variable types in the reduced drying model and the PBE

<table>
<thead>
<tr>
<th>Number</th>
<th>Status</th>
<th>Symbol</th>
<th>Model</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Differential</td>
<td>Unknown</td>
<td>174</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Known</td>
<td>Fixed by problem</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Unknown</td>
<td>Fixed by problem</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Unknown</td>
<td>Fixed by problem</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Phase 1:</th>
<th>Phase 2:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Part 1:</td>
<td>Part 2:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable Types</th>
<th>Reduced model</th>
<th>PBE</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R$, $T$, $p$, $\rho$, $\gamma$</td>
<td>Fixed by problem</td>
<td>Known</td>
</tr>
<tr>
<td>$G_r$, $G_r$</td>
<td>Fixed by problem</td>
<td>Unknown</td>
</tr>
<tr>
<td>$u$, $\mu$, $\sigma$</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>$R$, $T$, $p$, $\rho$, $\gamma$</td>
<td>Fixed by problem</td>
<td>Known</td>
</tr>
<tr>
<td>$G_r$, $G_r$</td>
<td>Fixed by problem</td>
<td>Unknown</td>
</tr>
<tr>
<td>$u$, $\mu$, $\sigma$</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable Types</th>
<th>Reduced model</th>
<th>PBE</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R$, $T$, $p$, $\rho$, $\gamma$</td>
<td>Fixed by problem</td>
<td>Known</td>
</tr>
<tr>
<td>$G_r$, $G_r$</td>
<td>Fixed by problem</td>
<td>Unknown</td>
</tr>
<tr>
<td>$u$, $\mu$, $\sigma$</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>$R$, $T$, $p$, $\rho$, $\gamma$</td>
<td>Fixed by problem</td>
<td>Known</td>
</tr>
<tr>
<td>$G_r$, $G_r$</td>
<td>Fixed by problem</td>
<td>Unknown</td>
</tr>
<tr>
<td>$u$, $\mu$, $\sigma$</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
</tbody>
</table>
with \( n_0 \) the initial distribution, \( \sigma \) the standard deviation and \( \mu \) the mean. The known and unknown variables of the used PBE are listed in table 8.1. As the reduced model is used to calculate the growth term of the PBE, the number of coefficients is the same for both models. Using the PBE, two variables are calculated \( R_w \) and \( n \).

For the HRFV scheme the discretisation domain ranged from 0 till 1.032 times \( R_p \). The MOC uses a moving domain, so the minimum initial value of the domain should not be 0, but was set to \( R_p \). The maximum value for the initial discretisation domain was also set at 1.032 times \( R_p \).

All calculations were performed using Matlab®, and a built-in ODE-solver was used (ode23, which uses a variable step size for the time).

### 8.4.3 Solution methods based on discretisation of the domain

The two methods based on discretisation are first evaluated for a very small grid size, which is assumed to represent the pseudo-analytical solution. For the HRFV scheme this is done for a \( \kappa \)-value equal to 1/3 and -1. The influence of coarsening the grid is investigated for the HRFV scheme with a \( \kappa \)-value of 1/3 and the MOC. Furthermore the effect of different flux limiting functions is analyzed for the HRFV scheme. Finally, the different methods based on discretisation are compared and conclusions are drawn.

#### PBM solution using the HRFV scheme with highest accuracy for a \( \kappa \)-value of 1/3

The HRFV scheme was in a first approach used with the largest accuracy (i.e. \( N = 2,000 \)). This is assumed to be the most accurate solution that can be obtained within a reasonable calculation time. A too large grid size (e.g. 5,000) leads to a significantly larger computational burden (calculation time of several weeks). Moreover, further increasing \( N \) (\( > 2,000 \)) did not result in an improvement of the accuracy.

In figures 8.1 and 8.2 the model predictions are presented for \( N \) equal to 2,000 and the flux limiting function of Koren (\( \Phi_{KO} \)). The normalised moments are calculated using the discrete version of equation 8.26 (normalisation based on...
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moment value at $t = 0$). At the beginning the curve of $m_0$ displays a dynamic behaviour, but after less than 5 s, the curve becomes horizontal (Fig. 8.1). As the total number of particles does not change in time, $m_0$ should ideally not change in time and stay at 1. This is established apart from a numerical error of 0.13%. The first moment, a representation of the average wet diameter, should logically decrease from the start which is indeed observed (Fig. 8.1). In figure 8.2 the number density is presented at different points in time. It is clear that the wet radius decreases. Because some particles complete the first drying phase sooner compared to other particles, the width of the number density distribution increases a bit as time evolves. However, this effect is limited as all particles are subjected to the same ambient conditions. In figure 8.2 the transient between drying phase 1 and 2 is illustrated in more detail for a population of particles. It can be seen that this effect explains the transient observed in the inset of figure 8.1 and only acts during the first few seconds of the simulation (depending on $T_g$).

In figure 8.3 the standard deviation of the moisture distribution is plotted as a function of time. A clear increase in the beginning can be seen, which represents the occurrence of a bimodal distribution (due to the presence of two drying phases). This is followed by a decrease (bimodal distribution again becomes a monomodal distribution), reaching a minimum value. Later on, an increase can again be observed which means that the variance of the distribution increases again due to the difference in growth rate of particles with different moisture content (cfr. size dependent growth term). At the end of the drying process the wet radius is very small, and for a certain decrease in wet radius only a limited amount of water should evaporate. This is why at the end of the simulation the evaporation rate increases again, but as some particles still have a larger wet radius, with a lower evaporation rate, the width of the distribution

---

**Figure 8.1:** $m_0(t)$ (Left) and $m_1(t)$ (Right) for the HRFV-scheme with $\kappa = 1/3$ and $N = 2,000$
8.4. Results

Figure 8.2: $n(R_w)$ at different time instants for the HRFV-scheme with $\kappa = 1/3$ and $N = 2,000$ (the value for $R_w$ decreases in time) with a detail of the bimodal distribution (Right) increases at the end.

Figure 8.3: The standard deviation of the distribution as a function of time for the HRFV-scheme with $\kappa = 1/3$ and $N = 2,000$

Investigation of grid coarseness for the HRFV-scheme for a $\kappa$-value of 1/3

To investigate the effect of the grid size $N$, as well as to determine the 'optimal' grid size, $N$ was decreased and varied between 50-500. The scenario with an $N$-value of 2,000 was used as reference for the calculation of the RMSE for the other grid sizes assuming it to be the pseudo-analytical solution. The RMSE was calculated as the mean of the RMSE on the first three moments. This was done using $\Phi_{KO}$ as flux limiting function. The effect on the calculation time
of the decrease in $N$ was also investigated. In figure 8.4 the RMSE and the calculation time are visualised. Starting from a value of 300 for $N$ the curve of the RMSE flattens and there is almost no improvement. The increase in the calculation time is obvious.

In table 8.3 the scaled calculation time is listed for all simulations with different grid sizes, where the calculation time is normalised with respect to the smallest obtained value (i.e. for the case of $N = 50$). Also, the calculation time for a grid size of 2,000 is mentioned. The calculation time is scaled to allow better comparison of calculation times obtained with different solution techniques. It is obvious that the calculation time increases with $N$. The calculation time is however not linearly dependent on $N$. Comparing a grid size of 2,000 with a grid size of 200 gives a reduction of the calculation time with more than 99.8%. At $N = 300$, a reduction of 99.5% is obtained.

Comparing the effect of different grid sizes on the prediction of the moments and the number density for a $\kappa$-value of $1/3$, the following conclusions can be made: As $N$ increases, the height of the peak at the start of $m_0$ decreases (Fig. C.1 (Appendix C)). During the first stages of the drying process, a significant difference can be observed between the moment predictions, especially for coarse grids ($N < 250$). The time needed for $m_0$ to reach steady state gradually increases for lower $N$. In figure C.1 (Appendix C) the first moment is presented for different grid sizes. For $N < 250$, significantly deviating behaviour is observed, whereas the other grid sizes display more or less the same trend. In figure C.2 (Appendix C) the number density is presented after 300 s. The width of the distribution increases clearly with decreasing $N$-value. This is also true for $N > 250$. However, these deviations do not seem to significantly impact the lower integral moments of the distribution. Depending on what one’s interest is, one needs to be careful in choosing $N$. A value larger than 2,000 might even be required. The standard deviation, as a measurement of the
8.4. Results

Table 8.3: Scaled calculation time for the HRFV-scheme using different $N$-values for $\kappa = 1/3$ (reference is $N = 50$, simulation time of 400s)

<table>
<thead>
<tr>
<th>$N$</th>
<th>Scaled calculation time</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,000</td>
<td>1.21 $\times 10^4$</td>
</tr>
<tr>
<td>500</td>
<td>190</td>
</tr>
<tr>
<td>450</td>
<td>147</td>
</tr>
<tr>
<td>400</td>
<td>112</td>
</tr>
<tr>
<td>350</td>
<td>79.1</td>
</tr>
<tr>
<td>300</td>
<td>56.4</td>
</tr>
<tr>
<td>250</td>
<td>34.7</td>
</tr>
<tr>
<td>200</td>
<td>20.3</td>
</tr>
<tr>
<td>150</td>
<td>10.71</td>
</tr>
<tr>
<td>100</td>
<td>4.27</td>
</tr>
<tr>
<td>50</td>
<td>1</td>
</tr>
</tbody>
</table>

Width of the distribution decreases clearly with increasing values of $N$ (Fig. C.3 (Appendix C)). For small values of $N$ (< 200) the curve of the standard deviation shows some sharp peaks at later time steps.

Influence of the flux limiting function for the HRFV-scheme for a $\kappa$-value of 1/3

The influence of the flux limiting function is investigated in more detail for an $N$-value of 300, as finer grids did not improve the results significantly. In figure 8.5 (Left) the 0th moment is presented. Only for the early time steps a difference can be noticed. The number density is also affected by this and at 300s the width is the smallest when using $\Phi_{R,s}$, followed by $\Phi_{KO}$, $\Phi_{VL}$ and $\Phi_{R,m}$ (Fig. 8.5 (Right)).

In figure 8.6 the standard deviation is presented in function of time for the different flux limiting functions. The difference in width of the distribution is clearly visible. The width of the distribution using $\Phi_{R,s}$ as flux limiting function is smaller compared to the others.

In Table 8.4 the scaled calculation time is listed. The sequence of the calculation time is the same as that of the standard deviation (i.e. shorter calculation times coincide with larger final standard deviation).

PBM solution using the HRFV-scheme with highest accuracy for a $\kappa$-value of -1)

A similar evaluation ($N = 2,000$) was performed for a $\kappa$ value of -1 without any flux limiting function. In this case, the result is similar (Fig. 8.7). Again
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Figure 8.5: $m_1(t)$ (Left) and $n(R_w)$ at 300 s (Right) for the HRFV-scheme with $\kappa = 1/3$ and $N = 300$ with different flux limiting functions

Figure 8.6: Standard deviation for the HRFV-scheme with $\kappa = 1/3$ and $N = 300$ with different flux limiting functions

Table 8.4: Scaled calculation time for the HRFV-scheme using different flux limiting functions ($N = 300$) (reference is $\Phi_{R,m}$, simulation time of 400 s)

<table>
<thead>
<tr>
<th>$N$</th>
<th>$\kappa = 1/3$</th>
<th>$\kappa = -1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Phi_{KO}$</td>
<td>4.00</td>
<td>3.94</td>
</tr>
<tr>
<td>$\Phi_{VL}$</td>
<td>2.46</td>
<td>2.49</td>
</tr>
<tr>
<td>$\Phi_{R,m}$</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>$\Phi_{R,s}$</td>
<td>4.76</td>
<td>4.82</td>
</tr>
</tbody>
</table>

there is some dynamic behaviour at the start for $m_0$ (Fig. 8.7). For $m_1$ an initial increase can be observed, which is physically not possible as the moisture content should decrease continuously in time (Fig. 8.7). The number density at
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different time steps showed negative values, which is physically impossible and is caused by numerical instability (Fig. 8.8). This renders these simulations highly uncertain.

The standard deviation is presented in figure 8.9. Near the end of the simulation, values of the standard deviation keep decreasing, meaning that the width of the distribution becomes smaller and smaller. This phenomenon is likely caused by the occurrence of negative values for the number density and is very likely a numerical artefact.

In investigating the impact of lowering the grid size indicated that the oscillation in the number density at a certain time point was lower for small values of N. However, the negative values for the number density did not disappear. Due to the uncertainty of these simulations, this method was not further investigated.

Figure 8.7: \( m_0(t) \) (Left) and \( m_1(t) \) (Right) for the HRFV-scheme with \( \kappa = -1 \) and \( N = 2,000 \)

Figure 8.8: \( n(R_w) \) at different time instants for the HRFV-scheme with \( \kappa = -1 \) and \( N = 2,000 \) with the focus on the bimodal distribution (the value for \( R_w \) decreases in time)
Influence of the flux limiting function for the HRFV-scheme for a $\kappa$-value of -1

Different flux limiting functions are tested for an $N$-value of 300. The results are presented in figures 8.10 and 8.11. It is obvious that the negative values for the number density disappear when a flux limiting function is implemented. The difference between the methods is limited for $m_0$. Again the width of the distribution after 300 s is dependent on the flux limiting function. Comparing the calculation time of the different flux limiting functions, mentioned in table 8.4, it is clear that the sequence of the calculation time is the same as that of the standard deviation.

In figure 8.11, the standard deviation is presented for the different scenarios.

Figure 8.10: $m_1(t)$ (Left) and $n(R_w)$ at 300 s (Right) for the HRFV-scheme with $\kappa = -1$ and $N = 300$ with different flux limiting functions
8.4. Results

The influence of the flux limiting function on the width of the distribution is significant.

![Graph showing standard deviation for different flux limiting functions.](image)

**Figure 8.11:** Standard deviation for the HRFV-scheme with $\kappa = -1$ and $N = 300$ with different flux limiting functions

**PBM solution using MOC with highest accuracy**

Figures 8.12 and 8.13 show the result for the MOC-method using $N = 1,000$. For the normalised $m_0$ a clear peak can be seen at the start, and as time evolves the curve shows a further dynamic behaviour, which becomes more significant at the end (Fig. 8.12). In fact the value for $m_0$ should stay fixed at 1. Deviations mean that mass leaks have occurred. $m_1$ decreases over the whole time range, which is expected as the moisture content decreases (Fig. 8.12). The width of the number density at different time steps is only slightly different, but does not change much over time (and as such also not the height of the peak) (Fig. 8.13). In the right part of figure 8.13 the focus is on the bimodal behaviour at the transition of the first drying phase to the second drying phase. This effect is important to explain the increase of the standard deviation at the start of the drying process.

In figure 8.14 the evolution of the standard deviation is presented as a function of time. At the end the increase in width is limited in comparison with the increase for the HRFV-scheme.

**Investigation of grid coarseness for the MOC**

Also for MOC the effect of $N$ was investigated. Due to the moving domain the grid size can be much smaller compared to the HRFV-scheme. In this case the grid size comprised values ranging from 10 to 1,000 (Table 8.5). The decrease in RMSE with increasing $N$ is presented in figure 8.15, also showing a signif-
Figure 8.12: $m_0(t)$ (Left) and $m_1(t)$ (Right) for the MOC with $N = 1,000$

Figure 8.13: $n(R_w)$ at different time instants for MOC with $N = 1,000$ (the value for $R_w$ decreases in time)

Figure 8.14: The standard deviation of the distribution as a function of time for the MOC
8.4. Results

icant increase in calculation time. The decrease in RMSE is calculated using $N$ equal to 1,000 as the reference case.

The scaled calculation time is mentioned in Table 8.5. It is obvious that the calculation time increases with $N$, but no linear dependency occurs.

For $m_0$ a clear peak can be seen at the start for each grid size (Fig. C.4). This peak does not disappear for larger $N$, but decreases significantly. At the end a constant difference can be seen between the grid sizes. For $m_1$ only a clear difference can be detected at the start when comparing different grid sizes (Fig. C.4 (Appendix C)). The number density after 300 s is almost the same for all grid sizes, but the curve for $N$ equal to 10 is less smooth (Fig. C.5 (Appendix C)). The overall model behaviour seems to remain unchanged as of $N = 100$, which seems the optimal value for this solution.

**Figure 8.15:** The RMSE and the calculation time for increasing values of $N$ for the MOC

**Table 8.5:** Scaled calculation time for MOC using different $N$-values (reference is $N = 10$, simulation time of 400 s)

<table>
<thead>
<tr>
<th>$N$</th>
<th>Scaled calculation time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,000</td>
<td>$6.34 \times 10^3$</td>
</tr>
<tr>
<td>500</td>
<td>$1.54 \times 10^3$</td>
</tr>
<tr>
<td>400</td>
<td>$1.06 \times 10^3$</td>
</tr>
<tr>
<td>300</td>
<td>594</td>
</tr>
<tr>
<td>200</td>
<td>263</td>
</tr>
<tr>
<td>100</td>
<td>68.1</td>
</tr>
<tr>
<td>50</td>
<td>18.1</td>
</tr>
<tr>
<td>40</td>
<td>11.76</td>
</tr>
<tr>
<td>30</td>
<td>7.02</td>
</tr>
<tr>
<td>20</td>
<td>3.36</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
</tr>
</tbody>
</table>
Comparison and conclusion for the methods based on discretisation of the domain

It is interesting to compare the HRFV schemes mutually and with the MOC in terms of the number density, the width of the distribution, the calculation time and the moment dynamics. Without implementing a flux limiting function in the HRFV scheme the result is significantly different (occurrence of negative values for the number density when \( \kappa \) equal to -1). However, after implementation of a flux limiter in both HRFV schemes still some differences can be observed. The sequence of the magnitude of the standard deviation is comparable for both \( \kappa \)-values (Fig. 8.6 and 8.11). Comparing the absolute values for the width of the distribution it is obvious that the result using \( \Phi_{VL} \) and \( \Phi_{KO} \) are closer to each other for a \( \kappa \)-value of -1 compared to a \( \kappa \)-value of 1/3. For \( \Phi_{VL} \), \( \Phi_{R,m} \) and \( \Phi_{R,s} \) the width is almost identical for both \( \kappa \)-values. The ranking of the calculation times is the same for both \( \kappa \)-values (Table 8.4).

The number density after 300 s is, similar to the standard deviation, only significantly different between both \( \kappa \)-values for \( \Phi_{KO} \) (Fig. 8.5 and 8.10). Next, the HRFV scheme using \( \Phi_{KO} \) (as proposed by Qamar et al. [Qamar et al., 2006]) and \( \Phi_{R,s} \) (which results in the distribution with the lowest standard deviation) can be compared with MOC. This was done using a grid size of 300 for the HRFV scheme, as there is almost no improvement in the RMSE when a finer grid is used (Fig. 8.4). For MOC \( N \) was set equal to 100, since a finer grid has almost no influence on the number density at 300 s (Fig. S7).

In figure 8.16 the zeroth moment is presented. The result for the HRFV scheme is somewhat different compared to MOC. At the start both methods gave an increase followed by a decrease. However, the result for the HRFV scheme remains stable after the initial dynamic behaviour whereas the result for the MOC fluctuates also at later time points. The \( m_1 \) should decrease from the start, which happened for MOC but this is not the case for the HRFV scheme (Fig. 8.16). The results for the higher order moments are presented in figure C.6 (Appendix C). For \( m_2 \) till \( m_5 \) a small bump can be observed in the beginning for the HRFV scheme, while this is not the case for the MOC.

In figure 8.17 the initial distribution is presented. The results for both flux limiting functions used in the HRFV scheme gave of course the same result, but as the discretisation of the domain is different for the MOC a small difference could be expected. At 120 s a clear difference in the width and height of the peak can already be detected. Where the solution is a sharp peak for the MOC the HRFV schemes give a curve which is much wider and exhibits a
8.4. Results

Figure 8.16: Comparison of $m_0(t)$ (Left) and $m_1(t)$ (Right) for the different solution methods using discretisation

lower peak. At larger time instants (320 and 400 s) the distributions resulting from the HRFV scheme become wider and wider whereas that of the MOC almost remains unaltered.

In figure 8.18 the standard deviation is presented. It is obvious that the width of the distribution is strongly dependent on the solution method. While the increase in the standard deviation is limited for the MOC the increase for the HRFV scheme is more pronounced. The distribution at the end is clearly smaller when the MOC is used. For the HRFV scheme the width of the distribution is strongly dependent on the grid size (Fig. C.4 (Appendix C)). An almost identical curve for the standard deviation could be obtained when $N$ would be chosen around 2,000. However, this requires significantly longer calculation times. But based on this fact, it could be concluded that the MOC approximates the number density more precisely, as a similar result would have been obtained when the accuracy of the HRFV scheme would have been increased (by increasing $N$).

The calculation time is definitely different for all methods. Whereas only 21 s were required for the MOC the HRFV schemes took 284 and 277 s for $\Phi_{KO}$ and $\Phi_{R,s}$ respectively.

Based on the performance of the distinct discretisation methods and the calculation time, the MOC seems to be the preferred method for the PBM at hand. The HRFV scheme with a $\kappa$-value of -1 without flux limiting function leads to negative values for the number density, which is not desirable. Increasing $N$ did not give better results compared to small values of $N$, and in fact the oscillation was even lower for low values of $N$. 

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Figure 8.17: $n(R_w)$ at $t = 0$ s (initial condition) (Upper left), $t = 120$ s (Upper right), $t = 320$ s (Lower left) and $t = 400$ s (Lower right) for the HRFV-scheme with $\kappa = 1/3$ ($\Phi_{KO}$ and $\Phi_{R,s}$ and the MOC-method

Figure 8.18: Comparison of the standard deviation for the different solution methods using discretisation
8.4. Results

8.4.4 Quadrature Method of Moments (QMOM)

The QMOM is investigated with the PD and the Chebyshev algorithms respectively. The same simulation parameters were used as for the discretisation methods, and the grid size to calculate the initial distribution in terms of \( n \) was set to 500. For this method a large \( N \) for the calculation of the initial distribution gives more accurate values for the initial moments, but has no influence on the total calculation time. For the other solution methods the grid size for the initial distribution is chosen according to the grid size used during calculation. In this case the number of moments that are calculated is varied between 3 and 7.

The results for the PD algorithm are presented in figure 8.19 for the first three moments and in figure C.7 (Appendix C) for the higher order moments. With the PD algorithm it was possible to calculate 7 moments. The difference between the higher moments when 3 or more moments are calculated is minimal. Also the increase in calculation time is limited when increasing the number of moments (Table 8.6).

Using the Chebyshev algorithm the number of moments was limited to 3 due to infinity problems. The moments are presented in figure C.8 (Appendix C). Upadhyay concluded that the Chebyshev algorithm can be used for very high order moments to obtain accurate high order quadratures [Upadhyay, 2012]. However, based on the presented results the PD algorithm was able to calculate at least 7 moments, whereas the Chebyshev algorithm failed after more than 3 moments. Moreover, the calculation time when using the Chebyshev algorithm was 6 times larger compared to the PD algorithm.

**Table 8.6:** Scaled calculation time for QMOM using the PD-algorithm (reference is \( n_{Mom} = 7 \), simulation time of 400 s)

<table>
<thead>
<tr>
<th>( n_{Mom} )</th>
<th>Scaled calculation time</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>0.33</td>
</tr>
<tr>
<td>4</td>
<td>0.49</td>
</tr>
<tr>
<td>5</td>
<td>0.65</td>
</tr>
<tr>
<td>6</td>
<td>0.88</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
</tr>
</tbody>
</table>

Comparing MOC (discretisation) and QMOM-PD (moments-based method)

Two different types of solution methodologies are compared, one is based on discretisation (MOC), while the other is based on moments (QMOM-PD). For the MOC \( N \) was set to 100. To compare the discretisation methods with the method of moments the moments were calculated from the number density at
each time step. The zeroth moment shows a difference between the discretisation method and the method of moments (Fig. 8.20). The MOC results in a sharp peak at the start and a bump at the end. For $m_1$ a difference is observed at the start, but the trend for both methods is the same (Fig. 8.20). The detailed part of the figure shows that the method of moments develops approximately the same. The same conclusion can be drawn for $m_2$ (Fig. C.9 (Appendix C)). The other moments give approximately the same result (Fig. C.9 (Appendix C)). In fact it can be concluded that both methods would end up with the same results in terms of the moments.

The calculation time for the method of moments is significantly lower (Table 8.7), but the result is only a set of moments compared to the full number density for the discretisation methods. It is important to mention that QMOM-PD is very fast to run, i.e. it took only half a second to run the simulation. As such, it is an interesting tool to extend with other models, such as CFD models. In the literature several methods for the reconstruction of the moments are available [John et al., 2007].
8.5 Conclusion

Figure 8.20: Comparison of $m_0(t)$ (Left) and $m_1(t)$ (Right) for the MOC-method with QMOM-PD

Table 8.7: Scaled calculation time to compare a discretisation method with a method using moments (reference is QMOM-PD, simulation time of 400 s)

<table>
<thead>
<tr>
<th>Method</th>
<th>Scaled calculation time</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOC</td>
<td>45.6</td>
</tr>
<tr>
<td>QMOM-PD</td>
<td>1</td>
</tr>
</tbody>
</table>

8.5 Conclusion

The implementation of the reduced drying model in a PBM enables to calculate the evolution of the moisture content for a batch of granules. The PBE was solved using different solution methodologies:

- The HRFV-scheme with a $\kappa$-value equal to $1/3$ calculates the number density accurately using a grid size higher than 300. A grid size of 50 results in a significant difference in the moments. However, the width of the number density decreases when a larger grid size is used. A grid size of 300 was chosen for further research. The choice of the flux limiting function does not have a large influence on the result, only the calculation time can be reduced by approximately a factor of 5 using $\Phi_{R,m}$ instead of $\Phi_{R,s}$. Using a $\kappa$-value equal to -1 without any flux limiting function it was not possible to calculate the distribution correctly, as negative values for the number density occur. This problem can be solved by implementing a flux limiter.
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- The MOC, which uses a moving grid, requires a lower grid size to obtain a smooth curve for the number density. Here, a grid size of 100 was sufficient.

- Comparing the methods using a discretisation of the domain it can be concluded that the MOC is much faster than the HRFV scheme with a $\kappa$-value of 1/3. The MOC uses a moving grid, and as such the grid size can be taken lower and still the result will be accurate.

- The QMOM with the PD algorithm is able to calculate at least 7 moments. The increase in calculation time is limited when increasing the number of moments. When using the Chebyshev algorithm it is only possible to calculate 3 moments, which contradicts the result presented by Upadhyay [2012].

- QMOM is significantly faster than the discretisation methods but no number density is obtained as a result. Several reconstruction methods exist but when using such methods the computation time increases again.

The PBM model with the implemented empirical drying model allows to calculate the evolution of the moisture content during drying. The model can now be used to compute the evolution of the moisture content distribution for different initial distributions, different particle sizes and different gas temperatures. The model can be used to investigate the effect of the change in gas temperature during drying, and as such to develop some guidelines about the set-up of the dryer. However, before using the model for process control and defining the Design Space, a validation should be carried out using experimental data. However, this is outside the scope of this thesis.

The modelling approach used here, which consists of first setting up and calibrating/validating a drying model for a single particle, followed by model reduction and inclusion in a PBM can definitely be generalized. However, the model formulation of the PBM might turn out to differ from case to case, as well as the obtained parameter values.
CHAPTER 9

Global Sensitivity Analysis applied to a drying model for a population of granules


Abstract:
Mechanistic models for pharmaceutical processes are becoming more important due to the shift towards continuous production processes. During a model building procedure a GSA is a powerful tool to explore the sensitivity in the parameter space. The analysis is performed on a PBM-model describing the drying behaviour of a population of granules. The granule radius and gas temperature were found to be most sensitive. The former indicates that granulator performance impacts drying behaviour, the latter is informative with respect to the variables that primarily need to be controlled during continuous operation. Several GSA techniques were analysed and compared with respect to the correct conclusion and computational load.

9.1 Introduction

In chapter 5 the incentives to perform a sensitivity analysis were already provided, as well as the differences between a Local Sensitivity Analysis (LSA) and a Global Sensitivity Analysis (GSA). Moreover, several GSA techniques were introduced. In chapter 5 the analyses are done on the single particle drying model describing the drying behaviour of one single pharmaceutical granule. The performance of a GSA on a PBM-model is quite innovative as it has not
been reported in the literature. A GSA requires one single output value for each Monte Carlo simulation, but in the case of a PBM model the output is a number density distribution at each time step.

9.2 Objectives

In this chapter different GSA techniques are analysed and compared for the PBM model describing the drying behavior of a population of wet granules as developed in chapter 8. The PBM model is investigated through a GSA in order to improve the available level of process knowledge. Indeed, the knowledge gained by performing a GSA can later on be used when developing a suitable control strategy of the drying process during continuous operation. The analysis is performed for six factors, and more details about the choice of the factors used in the GSA can be found in the section 9.3. The objective of this sensitivity analysis is to investigate which factors have the largest influence on the moisture content distribution properties of the particles which is predicted by the PBM. This will provide useful information with respect to developing control strategies for this unit process when used in the continuous application.

9.3 Materials & methods

The GSA was performed for the one-dimensional PBM model, which is extensively described in chapter 8. However, in this chapter the reduced model, function of both the gas temperature as well as the gas velocity was used (Chapter 7, section 7.4.3). The PBM model describing the drying behaviour of pharmaceutical granules is given by:

\[
\frac{\partial}{\partial t} n(R_w, t) + \frac{\partial}{\partial R_w} \dot{R}_w(R_w, Y)n(R_w, t) = 0
\]  

(9.1)

with \(n(R_w, t)\) the number density, \(Y\) the continuous phase vector, which includes \(T_g\) and \(V_g\). \(\dot{R}_w(R_w, Y)\) equals respectively \(G^*_{r,1}(R_w, T_g, V_g)\) and \(G_{r,2}(R_w, T_g)\) for the first and the second drying phase. These growth terms are respectively given by:

\[
G^*_{r,1}(R_w, T_g, V_g) = (v_1 V^2_g + v_2 V_g + v_3) G_{r,1}(R_w, T_g)
\]  

(9.2)

\[
G_{r,1}(R_w, T_g) = A + B R_w + C e^{D R_w}
\]  

(9.3)

\[
R_w = \frac{R_w - R_p}{R_{w,0} - R_p}
\]  

(9.4)
9.3. Materials & methods

\[ G_{r,2}(R_{w,nor}, T_g) = A'(R_{w,nor})^{B'} + C' \left( 1 + D' R_{w,nor} \right)^{E'} + R_f'(A'0.5^{B'} + C' \left( 1 + D'0.5 \right)^{E'}) \]  

(9.5)

\[ R_{w,nor} = \frac{R_w}{R_p} \]  

(9.6)

where \( v_1, v_2 \) and \( v_3 \) are empirical coefficients to incorporate the gas velocity dependency, \( A, B, C, D, A', B', C', D' \) and \( R_f' \) are empirical coefficients, which are dependent on \( T_g \), and \( R_{w,0} \) is the initial (wet) radius.

The MOC, which uses moving grid, is used to solve the PBE [Qamar and Warnecke 2007]. This solution method gave the best results taking both the accuracy and computational load into account (Chapter 8). A grid size of 100 was used for the calculations.

As most [GSA] techniques require one single value as output value for each Monte Carlo simulation, it was decided to perform two analyses. A first one on the standard deviation of the distribution at the end of the drying process (\( \sigma_d \)), whereas a second one focuses on the mean of the distribution at the end of the drying process (\( \mu_d \)). Other output values can also be investigated, but since the product quality at the end of the process is the main point of interest for pharmaceutical production processes, these two output values seemed to be reasonable choices.

The factors used in the GSA are chosen based on the operation of the fluidized bed dryer of the ConsiGma\textsuperscript{TM} (extensively described in chapter 3). The wet granules are fed into one of the six segments during a certain filling period \( t_{fil} \), after which the next segment is filled. After the filling period the wet granules are further dried, where the total drying time includes \( t_{dry} \) and is indicated as \( t_{dry} \). This means that some granules are dried longer compared to others, i.e. the drying time varies between \( t_{dry} - t_{fil} \) and \( t_{dry} \). The factors used in the GSA are the gas temperature \( T_g \), the gas velocity \( V_g \), the particle radius \( R_p \), the initial moisture content of the wet granules as a factor \( R_{w,0,fac} \) (i.e. \( R_{w,0} = R_{w,0,fac} R_p \)), \( t_{fil} \) and \( t_{dry} \). The range of these factors used in the simulations is presented in table 9.1.

<p>| Table 9.1: Factors used in the GSA for the PBM model |
|------------------------|------------------|</p>
<table>
<thead>
<tr>
<th>Factor</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>( T_g )</td>
<td>25-45(^\circ)C</td>
</tr>
<tr>
<td>( R_p )</td>
<td>0.3-1.4 mm</td>
</tr>
<tr>
<td>( V_g )</td>
<td>200-400 m(^3)/h</td>
</tr>
<tr>
<td>( R_{w,0,fac} )</td>
<td>1.015-1.030</td>
</tr>
<tr>
<td>( t_{fil} )</td>
<td>60-400 s</td>
</tr>
<tr>
<td>( t_{dry} )</td>
<td>600-1800 s</td>
</tr>
</tbody>
</table>
9.4 Results

9.4.1 Dotty plots

One dimensional dotty plots are constructed. These present the output of the GSA with respect to the factor value, to understand the input-output relations. Dotty plots are created using 5,000 samples generated by Sobol sampling. For both outputs, i.e. $\mu_d$ and $\sigma_d$ at the end of the process, a threshold value is selected. Below this value the simulation is considered as 'behavioural' (i.e. good with respect to chosen quality objective), while in the other case it is a 'non-behavioural' simulation. For the mean $\mu_d$ a threshold value of 1.4% is selected, which is identical as in the case where a GSA is applied on the single particle drying model. For pharmaceutical applications the granules do not need to have the same moisture content. A distribution of the granule moisture content at the end of the drying process is even beneficial for the subsequent tableting step. The threshold value for the standard deviation $\sigma_d$ is therefore chosen as $0.1 \times 10^{-5}$.

The results for the mean are presented in figure 9.1 and only the factors exhibiting a clear trend are shown. It is obvious that a high gas temperature is beneficial to lower the moisture content, as the evaporation rate is higher. The smaller the particle radius, the higher the evaporation, and as such the lower the mean moisture content. The influence of the gas velocity, the initial moisture content and the filling time is found marginal. The drying time has a more pronounced influence, however, also this factor is less important compared to the gas temperature and the particle radius.

Potential correlations between factors can be detected by constructing two-dimensional dotty plots (Fig. 9.2). An even distribution of behaviours and non-behaviours across the two-dimensional factor space means that both factors have no influence on the output, and no correlations between the factors can be detected. Looking at the dotty plot at the intersection of the particle

![Figure 9.1: One-dimensional dotty plot of $\mu_d$ for the PBM-model. The 'behaviours' are situated below the black line. The factors without any trend are not visualized](image-url)
9.4. Results

radius and the drying time, it is obvious that a high value for the particle radius can be compensated by a high value for the drying time.

The same analysis can be made for the standard deviation of the distribution.

Figure 9.2: Two-dimensional dotty plots of $\mu_d$ for the PBM-model for all factor combinations. Factor combinations with a low value for the mean are considered as behavioural.

In figure 9.3 the results are presented for the factors with a trend (note that the $y$-axis is logarithmic). The gas temperature has a clear influence on the final standard deviation: the higher the gas temperature, the faster the evaporation rate and the wider the distribution. The particle radius, the gas velocity and the initial moisture content have no pronounced influence on the output. But whereas the filling time has no significant effect on the mean of the distribution, and as such on the evaporation rate, the influence on the standard deviation is obvious. The higher the filling time, the wider the distribution, which could be expected from experience. The influence of the drying time is quite limited: if the drying time is lower, the standard deviation seemed to be somewhat higher.

The two-dimensional dotty plots for the final standard deviation of the number density distribution are interesting to detect correlations between the factors.
9.4.2 Contribution to Sample Mean/Variances (CSM/CSV) plot

The data generated to create the dotty plots were further analyzed by creating CSM and CSV plots. The analysis was done using 5,000 samples. Based on the CSM, the particle radius is the most influential parameter for $\mu_d$, followed by the gas temperature (Fig. 9.5). The concavity of the curves can be used to understand input-output relations. As the curve of the particle radius is situated below the bisector, this means that for increasing values of the particle radius, the mean of the distribution increases. This could also be concluded based on the dotty plot (Fig. 9.2). The mean of the distribution is the most unevenly distributed for the particle radius (Fig. 9.5), i.e. the variance in the mean of the distribution is most pronounced for the particle radius, which was also clearly visible in the dotty plot (Fig. 9.1 and 9.2).

The standard deviation of the final distribution is most influenced by the gas temperature, followed by filling time (Fig. 9.6). Also the drying time and the particle radius are influential factors. Whereas an increasing value for the gas temperature leads to an increasing value for the standard deviation, and increasing drying time decreases the width of the distribution. The variance is the most unevenly distributed for the gas temperature, followed by the filling time (Fig. 9.6).
9.4. Results

Figure 9.4: Two-dimensional dotty plots of $\sigma_d$ for the PBM-model for all factor combinations. Factor combinations with a low value for the mean are considered as behavioural.

Figure 9.5: The CSM (Left) and the CSV (Right) plot of $\mu_d$ for the PBM-model using Sobol sampling.
Chapter 9. GSA applied to a PBM-model

Figure 9.6: The CSM (Left) and the CSV (Right) plot of $\sigma_d$ for the PBM-model using Sobol sampling

9.4.3 Regression-based sensitivity analysis

The regression-based sensitivity analysis is performed on the 5,000 samples generated for the doty plots. For the raw output data on the mean of the distribution an $R^2_Y$ of 0.99 is obtained, and the rank transformation has no influence on the coefficient of determination (0.99) (Table 9.2). $R_p$ is clearly the most sensitive factor, followed by $T_g$. The same conclusion could be drawn from the CSM plot. For the case with the standard deviation the rank transformation has an effect on the coefficient of determination, however, in both cases the $R^2_Y$ is high enough to draw conclusions. The gas temperature is the most influential factor for the width of the distribution. In fact, the same order of significance is valid for the case with and without rank transformation for both outputs. However, the difference between $R^2_Y$ for the standard deviation forms an indicator of the non-linearity of the model. The SRRCs have no quantitative value compared to the SRCs, but can only be used to rank the input factors.

Table 9.2: Results of the regression-based method for the PBM-model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SRC$_{\mu_d}$</th>
<th>SRRC$_{\mu_d}$</th>
<th>SRC$_{\sigma_d}$</th>
<th>SRRC$_{\sigma_d}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_g$</td>
<td>0.2034</td>
<td>0.1953</td>
<td>0.7211</td>
<td>0.8184</td>
</tr>
<tr>
<td>$R_p$</td>
<td>0.9738</td>
<td>0.9751</td>
<td>0.1700</td>
<td>0.1805</td>
</tr>
<tr>
<td>$V_g$</td>
<td>2.4961e-4</td>
<td>2.4058e-4</td>
<td>5.0140e-4</td>
<td>4.6201e-4</td>
</tr>
<tr>
<td>$R_{w,0,fac}$</td>
<td>2.1012e-4</td>
<td>3.5198e-5</td>
<td>0.0016</td>
<td>0.0017</td>
</tr>
<tr>
<td>$t_{fil}$</td>
<td>0.0078</td>
<td>0.0074</td>
<td>0.4527</td>
<td>0.4926</td>
</tr>
<tr>
<td>$t_{dry}$</td>
<td>0.0540</td>
<td>0.0517</td>
<td>0.1583</td>
<td>0.1531</td>
</tr>
<tr>
<td>$R^2_Y$</td>
<td>0.99</td>
<td>0.99</td>
<td>0.78</td>
<td>0.97</td>
</tr>
</tbody>
</table>
9.4. Results

9.4.4 Variance-based sensitivity analysis

The sensitivity indices, computed based on the method proposed by Saltelli et al. [2010], are presented in table 9.3. For this analysis 1,000 samples were generated. The sum of $S_{i,\mu d}$ corresponds to 0.99, which indicates that the input factors as such are responsible for almost all variance in the model output. The particle radius is obviously the most sensitive factor, and the same conclusion could be drawn as for the CSM plot. The gas temperature has a limited effect on the mean moisture content.

The sum of the first order indices is 0.86 for the standard deviation, meaning that interactions between the input factors are responsible for only 14% of the variance in the model output. For $S_{i,\sigma d}$ the highest value corresponds to parameter $T_g$, followed by $t_{fill}$. The sensitivity of $t_{dry}$ and $R_p$ is somewhat comparable. The same conclusions could be drawn as from the CSV plot. Taking interactions between factors into account, still $T_g$ is the most important factor. As the difference between $S_{i,\sigma d}$ and $S_{Ti,\sigma d}$ is low for $t_{dry}$, this factor is almost not involved in interactions with other factors. This is reasonable, as the drying time indicates only the end of the drying process, but has no influence on the process itself.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>$S_{i,\mu d}$</th>
<th>$S_{Ti,\mu d}$</th>
<th>$S_{i,\sigma d}$</th>
<th>$S_{Ti,\sigma d}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_g$</td>
<td>0.0441</td>
<td>0.0495</td>
<td>0.5900</td>
<td>0.7245</td>
</tr>
<tr>
<td>$R_p$</td>
<td>0.9451</td>
<td>0.9488</td>
<td>0.0322</td>
<td>0.0521</td>
</tr>
<tr>
<td>$V_g$</td>
<td>-7.2737e-7</td>
<td>7.5451e-8</td>
<td>-3.3177e-5</td>
<td>1.3572e-6</td>
</tr>
<tr>
<td>$R_{w,0,fac}$</td>
<td>-9.1197e-6</td>
<td>3.7276e-7</td>
<td>7.7727e-5</td>
<td>5.5935e-6</td>
</tr>
<tr>
<td>$t_{fill}$</td>
<td>7.7140e-5</td>
<td>9.9028e-5</td>
<td>0.1923</td>
<td>0.3434</td>
</tr>
<tr>
<td>$t_{dry}$</td>
<td>0.0030</td>
<td>0.0047</td>
<td>0.0462</td>
<td>0.0506</td>
</tr>
<tr>
<td>Sum</td>
<td>0.9921</td>
<td>0.8607</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In table 9.4 the results of the different methods are summarized. The ranking is identical for all techniques. As the data to create the dotty plots is further used for the CSM and CSV plots and the regression-based analysis, the same number of samples is used, i.e. 5,000 samples. For the variance-based analysis only 1,000 samples are used. The mean of the moisture content distribution is mostly influenced by the particle radius of the granules. However, this factor is primarily determined by the preceding unit process, i.e. the granulation step. The gas temperature is also influential, and has both an effect on the mean value as well as the
standard deviation of the distribution. As such, this factor is the key to control the specs of the distribution during operation, and should be included in a control strategy to ensure that the final quality of the dried product meets the specifications.

Table 9.4: Comparison of different GSA techniques for the PBM-model

<table>
<thead>
<tr>
<th>Technique</th>
<th>$k$</th>
<th>$N$</th>
<th>Most sens. factors for $\mu_d$</th>
<th>Most sens. factors for $\sigma_d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSM plot</td>
<td>6</td>
<td>5,000</td>
<td>$R_p-T_g$</td>
<td>$T_g-t_{fil}$</td>
</tr>
<tr>
<td>SRC</td>
<td>6</td>
<td>5,000</td>
<td>$R_p-T_g$</td>
<td>$T_g-t_{fil}$</td>
</tr>
<tr>
<td>SRRC</td>
<td>6</td>
<td>5,000</td>
<td>$R_p-T_g$</td>
<td>$T_g-t_{fil}$</td>
</tr>
<tr>
<td>$S_i$</td>
<td>6</td>
<td>1,000</td>
<td>$R_p-T_g$</td>
<td>$T_g-t_{fil}$</td>
</tr>
<tr>
<td>$S_{Ti}$</td>
<td>6</td>
<td>1,000</td>
<td>$R_p-T_g$</td>
<td>$T_g-t_{fil}$</td>
</tr>
</tbody>
</table>

9.5 Discussion

During operation of the ConsiGma\textsuperscript{TM} the dryer unit is filled with a batch of particles. In order to control the moisture content of the granules leaving the dryer, the operator should play with the particle radius and the gas temperature. The particle radius is obviously an input to the drying process and should be controlled by the granulator prior to the drying step. However, it is known that breakage occurs during fluidized bed drying, and this will off course influence the particle radius (Chapter 11).

The standard deviation of the moisture content distribution of the dry granules can be altered by adapting the filling time. As the gas temperature has also a significant impact on the width of the moisture content interval, a balance should be found between the drying time and the width of the interval when changing the gas temperature during operation. Furthermore, for a population of granules the gas velocity has no influence on the drying behaviour, neither on the mean moisture content nor on the interval in moisture content, and as such, it can be used to control the fluidization behaviour of the granules without affecting the drying behaviour. But as the gas velocity will have an impact on the breakage rate of the granules during drying, the gas velocity will have indirectly an influence on the drying rate of the granules.

9.6 Conclusion

The particle radius has a large influence on the drying rate, however, this factor is mostly determined by the granulation step. On the other hand the gas temperature, which is also an influential factor, can be used to direct the process during operation as it has influence on both the mean moisture content,
9.6. Conclusion

as well as on the width of the moisture content distribution. The interval in moisture content is also determined by the filling time.
Chapter 9. GSA applied to a PBM-model
CHAPTER 10

Comparison of techniques for reconstruction of a distribution from moments in the context of a pharmaceutical drying process


Abstract
The use of moment-based methods to solve a Population Balance Model(ing) (PBM) induces the need to reconstruct a distribution from the moments for system analysis. Several reconstruction methods are investigated (i.e. parameter fitting methods and the method of splines), compared with each other as well as with the result of a non-moment-based solution method for the PBM. The finetuning of the parameters for the method of splines was very important for the final result as well as for the computational time. An additional parameter, i.e. a different value for the first and the last interval for tol_red, was introduced to improve the result and speed up the calculation. None of the parameter fitting methods was able to correctly predict several peaks in the final distribution. In contrast, the method of splines was able to reconstruct the distribution even without prior knowledge. However, prior knowledge about the distribution does facilitate the finetuning.

10.1 Introduction
The MOM is a commonly used solution technique for PBEs, a variant of this method, i.e. QMOM was also applied in chapter 8. However, after the calculation of the moments it is difficult to interpret them as such with respect to ac-
Chapter 10. Reconstruction of a distribution from moments

tual changes in the distribution. Therefore, a reconstruction of these moments to recover the underlying distribution is appealing and in some cases needed in order to draw conclusions with respect to system behaviour. In mathematics, the reconstruction of a function from a given number of moments is known as the finite-moment problem [John et al., 2007]. Hulbert and Katz [1964] were among the pioneers describing this problem. In some cases the knowledge of the lower-order moments gives direct insight in important properties of the system, e.g. many physical and optical properties of aerosols [McGraw et al., 1995] [McGraw et al., 1998]. Several reconstruction techniques are available, using for instance linear or nonlinear inversion approaches. However, in most cases a large number of moments are required. Additionally, the reconstruction techniques often suffer from solution multiplicity and ill-conditioned problems [Aamir et al., 2009]. Only a limited number of reconstruction methods able to reconstruct the distribution from a finite number of moments have been described. A perfect reconstruction should mathematically rely on an infinite number of moments. But, even in this case, knowing all moments is only enough if the class of functions used to reconstruct the distribution is restricted adequately [John et al., 2007]. Certain size distributions are not uniquely determined by their integral moments, let be by their lower-order moments. For instance, for the log-normal distribution an infinite number of dissimilar distributions can be created from a specific median and geometric standard deviation [White, 1990]. The same situation applies for the modified \( \gamma \)-distribution and the non-negative integral moments [McGraw et al., 1998]. McGraw et al. refer to isomomental distributions as distributions which have identical moments but are different [McGraw et al., 1998]. As such, this can be a problem in situations where the case is characterized and the evolution is represented in terms of the moments.

Laguerre polynomials were used by Hulbert and Katz [1964] for reconstruction of the distribution from the moments, though this produced strong oscillations in the PDF. This is because Laguerre polynomials can have both positive and negative values, while size distributions are limited to positive values. As such, these polynomials can represent all functions defined over the domain \([0, \infty]\). Wulkow found that the approximation of the distribution of a discrete weighted Galerkin PBM requires 20-50 Laguerre terms [Wulkow, 1996].

The requirement for reconstructing a distribution with a finite number of moments is an \textit{a priori} restriction of the class of basis functions [John et al., 2007]. The available number of moments restricts the number of parameters of the function used to describe the distribution. In general, a very simple function is assumed for the distribution, which requires only a limited number of moments. These approximate distribution functions can be Gaussian, log-normal, \( \gamma \)-function, etc. Also the weighted sum of different distributions can be
used, in this case the weighting can be done by orthogonal polynomials [Aamir et al., 2009]. Next to the problem of finding a unique solution of these inverse problems, there is also no systematic methodology for the choice of these basis functions.

Discrete methods based on time-dependent updating of the distribution together with computation of the moments is used because of the numerical efficiency, ease of implementation, flexibility, straightforwardness, relatively low calculation time and suitability for on-line applications. However, the method is not sufficient for all physical processes affiliated to chemical engineering [Giaya and Thompson, 2004]. Giaya and Thompson [2004] used this method to recover the crystal size distribution for a batch cooling crystallizer. This method has some clear advantages, and a good agreement was found between this method and the numerical solution of the PBM (using a solution method based on discretisation for the PBE), but it relies on simplifications and hypotheses [John et al., 2007].

The reconstruction can also be based on the 'statistically most likely' distribution [Pope, 1979] [Baldyga and Orciuoli, 1999] as used by Sanyal et al. [2005]. In this case the number density function $n(L)$ is determined by:

$$n(L) = e^{\sum_{i=0}^{N-1} A_i L^i}$$  

(10.1)

where the coefficients $A_i$ should be determined using the moments [Sanyal et al., 2005]. In fact no suitable orthogonal basis set for the space of distribution functions exists and a set of moments does not lead to a unique distribution. An insight in the form of the distribution should be available from either theory or experiments [Diemer and Olson, 2002].

In contrast, John et al. [2007] proposed a highly flexible algorithm based on low-order splines, in which no prior assumptions on the shape and support of the distribution are required. Another advantage is that the number of moments used for the reconstruction can be easily increased [John et al., 2007]. The method is described in detail in section 10.3.2 Gupta et al. [2014] used the method to estimate the PDF and tested both unimodal and multimodal PDFs. Unimodal distributions could be successfully reconstructed by means of the Cornish-Fisher expansion series as well as the spline-based method, which was somewhat more accurate. However, for multimodal distributions only the spline-based method yielded good results.

10.2 Objectives

The objective of this chapter is twofold, (1) comparing different reconstruction methods and (2) comparing the distribution obtained after reconstruction of
the moments with the result obtained by directly solving the PBE using a solution method that yields the entire number distribution. For the comparison of different reconstruction methods, comparison is made between parameter fitting methods and the method of splines.

10.3 Materials & methods

10.3.1 Population Balance Model (PBM)

The PBE used to generate the moments is equation 10.2 (more details can be found in section 8.4.1), which describes the evolution of the moisture content for a population of wet pharmaceutical granules.

$$\frac{\partial}{\partial t} n(R_w, t) + \frac{\partial}{\partial R_w} \dot{R}_w(R_w, Y)n(R_w, t) = 0$$  \hspace{1cm} (10.2)

Two methods are used to solve the equation, i.e. the MOC and the QMOM using the PD-algorithm. More details about these methods can be found in section 8.3.

10.3.2 Reconstruction methods

Methods based on parameter fitting

When a priori knowledge of the shape of the distribution is available, reconstruction by parameter fitting to a simple function can be useful. The solution speed and ease of computation are clearly advantages, but on the other hand the method is limited to simple shapes. The requirement of a priori knowledge about the distribution is another serious drawback. Some insight into a suitable set of basis functions is required to obtain a reasonable result. Several mathematical functions are used which can be constructed with a small number of low-order moments, i.e. Gaussian, log-normal, β-function, etc. [Heinz, 2003] [Mersmann, 2001]. This technique is used frequently for reconstruction [Öncil et al., 2006] [Fox, 1998] [Ramkrishna, 2000]. The choice of a specific MOM, QMOM or more recently DQMOM has no influence on the need and the choice of the reconstruction method. In most cases parameter fitting leads to a monomodal PSD, and a multimodal PSD can be reconstructed by using a superposition of single peak reconstructed PSDs [John et al., 2007]. The Gaussian function is the most commonly used basis function, and widely used in different domains (natural sciences, social sciences, etc.). However, the symmetric behaviour of this function can create negative values for the internal coordinate. A limited amount of particles with negative internal coordinate can
be removed, but this is not always possible and, as such, it can lead to non-physical properties \cite{Baldyga and Bourne 1999}. The half-normal distribution contains only the positive internal coordinate, because it neglects the negative half of the curve. The log-normal function is an option when a symmetric distribution is not sufficient. This basis function can display a long tail in the direction of the larger particle sizes \cite{John et al. 2007}. The $\gamma$-function is a flexible function due to the skewness and kurtosis values, which are both dependent on the moment-values \cite{Diemer and Olson 2002}. When the standard deviation equals the mean, the $\gamma$-function becomes an exponential function \cite{Diemer and Olson 2002}. The $\beta$-function is even more flexible than the $\gamma$-function, and as such widely applied in engineering applications. The Rayleigh function, again an asymmetric function, is mostly used in radioactivity and wind energy technology. The Poisson distribution is a discrete function, meaning that it can only be used when the internal coordinates are chosen from discretized values. The use of these parameter fitting methods consists of calculating some general properties from the distribution based on a limited set of lower order moments \cite{John et al. 2007}:

\begin{align*}
\bar{x} &= \mu_1 / \mu_0 \\
c_v &= \sqrt{\frac{\mu_0 \mu_2}{\mu_1^2}} - 1 \\
\sigma &= \bar{x} c_v
\end{align*}

with $\bar{x}$ the mean internal coordinate, $c_v$ the coefficient of variation, $\sigma$ the standard deviation and $\mu_0$, $\mu_1$, $\mu_2$ respectively the 0th, 1st and 2nd integral moment.

The functions used in this study are \cite{John et al. 2007}:

\begin{align*}
f_G(x) &= \frac{1}{\sigma \sqrt{2\pi}} e^{-\frac{(x-\bar{x})^2}{2\sigma^2}} \\
f_{HN}(x) &= \frac{2 \phi e^{-x^2 \phi^2 / \pi}}{\pi}, \quad \phi = \sqrt{\frac{\pi - 2}{2\sigma^2}} \\
f_{LN}(x) &= \frac{1}{x \ln \sigma_g \sqrt{2\pi}} e^{-\ln^2(x/\bar{x}_g)/(2 \ln^2 \sigma_g)}, \quad \bar{x}_g = \frac{\bar{x}}{e^{0.5 \ln^2 \sigma_g}}, \quad \sigma_g = e^{\ln(c_v^2 + 1)} \\
f_\gamma(x) &= \frac{\mu^\mu e^{\mu - \mu x / \bar{x}}}{\Gamma(\mu) \bar{x}^\mu}, \quad \mu = \frac{\bar{x}^2}{\sigma^2}, \quad \Gamma(\mu) = \int_0^\infty z^{\mu - 1} e^{-z} \, dz \\
f_\beta(x) &= \frac{x^{\alpha - 1} (1 - x)^{\beta - 1}}{B(\alpha, \beta)}, \quad \alpha = \bar{x} \left( \frac{\bar{x}(1 - \bar{x})}{\sigma^2} - 1 \right), \\
\beta &= (1 - \bar{x}) \left( \frac{\bar{x}(1 - \bar{x})}{\sigma^2} - 1 \right), \quad B(\alpha, \beta) = \frac{\Gamma(\alpha) \Gamma(\beta)}{\Gamma(\alpha + \beta)}
\end{align*}
Chapter 10. Reconstruction of a distribution from moments

\[ f_{EX}(x) = \frac{e^{-\frac{x}{\bar{x}}}}{\bar{x}} \quad (10.11) \]

\[ f_{RA}(x) = \frac{x e^{-0.5 x^2/s^2}}{s^2}, \quad s = \bar{x} \sqrt{2/\pi} \quad (10.12) \]

with \( f_G, f_{HN}, f_{LN}, f_\gamma, f_\beta, f_{EX} \) and \( f_{RA} \) respectively a Gaussian, a half-normal, a log-normal, a \( \gamma \)-, a \( \beta \)-, an exponential and a Rayleigh function.

Reconstruction by splines

The reconstruction of a PSD-distribution can also be done by using splines (linear, quadratic or cubic; \( l \in \{1, 2, 3\} \)) [John et al., 2007]. Consider \( L \) moments and \( n + 1 \) discrete points \( (x_1 < x_2 < \cdots < x_{n+1}) \) on the \( x \)-axis. A spline, piecewise polynomial, \( s^{(l)}(x) \), of degree \( l \) is:

- a polynomial of degree \( l \) in each subinterval \([x_i, x_{i+1}] \) (\( i = 1 \ldots n \))
- \((l-1)\)-times continuously differentiable in \([x_1, x_{n+1}]\)

The method of splines makes no \textit{a priori} assumption about the shape of the function \( f(x) \), since the ultimate shape will be approximated by a piecewise polynomial function. The coefficients of these polynomials are determined by solving an ill-conditioned linear system of equations. Initially, a rough estimation of the interval where \( f \) has positive values is needed, but this interval is iteratively adapted in the algorithm. The final interval should be as small as possible. The number of moments can be chosen arbitrarily, but the moments should be reliable, because small changes in the moments can have a major influence on the reconstruction [John et al., 2007].

Here, the equations for the cubic splines will be given as an example, i.e. \( l \) equals 3. If \([a, b]\) is the interval at the start, with \( a = x_1 < x_2 < \cdots < x_{n+1} = b \), then the onset is:

\[ s_i(x) = \sum_{j=0}^{3} s_{i,j} (x-x_i)^j, \quad x \in [x_i, x_{i+1}], \quad i = 1 \ldots n \quad (10.13) \]

In this equation there are \( 4n \) unknown coefficients \( s_{i,j} \) which should be determined using properties of splines and boundary conditions. Using cubic splines involves some regularity assumptions:

\[ s_i'(x) = \sum_{j=1}^{3} s_{i,j} j(x-x_i)^{j-1} \quad (10.14) \]

\[ s_i''(x) = \sum_{j=2}^{3} s_{i,j} j(j-1)(x-x_i)^{j-2} \quad (10.15) \]
10.3. Materials & methods

with \( s'_i(x) \) and \( s''_i(x) \) the first and second derivative of \( s_i(x) \). As \( f(x) \) is a PDF, it is assumed that \( f(x) \) vanishes identically outside \([x_1, x_{n+1}]\). Here, a smooth transition is assumed at the boundaries of the interval, which means:

\[
s_1(x_1) = 0, \quad s'_1(x_1) = 0, \quad s''_1(x_1) = 0 \quad (10.16)
\]

Combining equations 10.16 and 10.13 leads to:

\[
s_1(x_1) = s_{1,0} = 0, \quad s'_1(x_1) = s_{1,1} = 0, \quad s''_1(x_1) = 2s_{1,2} = 0 \quad (10.17)
\]

At \( x_{n+1} \) the following is valid:

\[
s_n(x_{n+1}) = 0, \quad s'_n(x_{n+1}) = 0, \quad s''_n(x_{n+1}) = 0 \quad (10.18)
\]

leading to:

\[
\begin{pmatrix}
1 & x_{n+1} - x_n & (x_{n+1} - x_n)^2 & (x_{n+1} - x_n)^3 \\
0 & 1 & 2(x_{n+1} - x_n) & 3(x_{n+1} - x_n)^2 \\
0 & 0 & 2 & 6(x_{n+1} - x_n)
\end{pmatrix}
\begin{pmatrix}
s_{n,0} \\
s_{n,1} \\
s_{n,2} \\
s_{n,3}
\end{pmatrix}
= 0 \quad (10.19)
\]

Other boundary conditions can be implemented, for instance a linear spline or quadratic spline at the first and last interval.

The required continuity of \( s^{(3)}(x) \) at \( x_{i+1} \) (\( i = 1 \ldots n - 1 \)) is:

\[
s_{i}(x_{i+1}) = s_{i+1}(x_{i+1}) \quad (10.20)
\]

This gives \( n - 1 \) equations:

\[
\begin{pmatrix}
1 & x_{i+1} - x_i & (x_{i+1} - x_i)^2 & (x_{i+1} - x_i)^3 & -1
\end{pmatrix}
\begin{pmatrix}
s_{i,0} \\
s_{i,1} \\
s_{i,2} \\
s_{i,3} \\
s_{i+1,0}
\end{pmatrix}
= 0 \quad (10.21)
\]

The same requirement is valid for the first and second derivative of \( s^{(3)}(x) \) at \( x_{i+1} \) (\( i = 1 \ldots n - 1 \)), leading to another \( 2(n - 1) \) conditions:

\[
\begin{pmatrix}
1 & 2(x_{i+1} - x_i) & 3(x_{i+1} - x_i)^2 & -1
\end{pmatrix}
\begin{pmatrix}
s_{i,1} \\
s_{i,2} \\
s_{i,3} \\
s_{i+1,1}
\end{pmatrix}
= 0 \quad (10.22)
\]
Chapter 10. Reconstruction of a distribution from moments

\[
\begin{pmatrix}
2 & 6(x_{i+1} - x_i) & -2
\end{pmatrix}
\begin{pmatrix}
s_i^0 \\
s_i^1 \\
s_i^2 \\
s_i^3 (i+1)^0
\end{pmatrix} = 0
\quad (10.23)
\]

Combining all requirements for the splines gives 3n + 3 conditions for 4n unknown coefficients. The known moments are required to determine the other \( L = n - 3 \) coefficients. For this, the \( k \)th moment of \( s^{(3)} \) \((k \in \mathbb{N})\) is given by:

\[
\int_{x_1}^{x_{n+1}} x^k s^{(3)} \, dx = \sum_{i=1}^{n} \int_{x_i}^{x_{i+1}} x^k s_i(x) \, dx = \sum_{i=1}^{n} \sum_{j=0}^{3} s_{i,j} \int_{x_i}^{x_{i+1}} x^k (x - x_i)^j \, dx
\]

Introducing the following symbols:

\[
I_1 = \frac{x_{i+1}^{k+1} - x_i^{k+1}}{k+1}, \quad I_2 = \frac{x_{i+1}^{k+2} - x_i^{k+2}}{k+2}, \\
I_3 = \frac{x_{i+1}^{k+3} - x_i^{k+3}}{k+3}, \quad I_4 = \frac{x_{i+1}^{k+4} - x_i^{k+4}}{k+4}
\]

the result of equation 10.24 is:

\[
\int_{x_1}^{x_{n+1}} x^k s^{(3)} \, dx = \sum_{i=1}^{n} \left[ I_1 s_i^0 + (I_2 - x_i I_1) s_i^1 + (I_3 - 2x_i I_2 + x_i^2 I_1) s_i^2 \right. \\
\left. + (I_4 - 3x_i I_3 + 3x_i^2 I_2 - x_i^3 I_1) s_i^3 \right]
\]

Equation 10.26 has to correspond with the \( k \)th moment \( \mu_k \) of \( f(x) \), for \( k = 0, 1 \ldots \)

This 4n X 4n linear system can be solved to obtain all unknown coefficients. However, the system is ill-conditioned and the condition number grows rapidly towards infinity as the number of moments increases. The condition number is a measurement of how sensitive the system (here a linear system) is towards changes or errors in the input. A large condition number means that the system is almost singular, while a condition number close to one corresponds to the case where the inverse can be computed with good accuracy. Also, the final reconstruction should only contain non-negative values, as it is a PDF.

Therefore, the method computes the solution iteratively starting from an initial reconstruction \( f^{(0)}(x) \) in an initial interval \([x_{1}^{(0)}, x_{n+1}^{(0)}]\). Let \( f^{(k)}(x) \) be a computed reconstruction in \([x_{1}^{(k)}, x_{n+1}^{(k)}]\). Each subinterval is divided into 10 equidistant subsubintervals with \( x_{ij} \) as nodes \((i = 1 \ldots n, \ j = 1 \ldots 10)\). An
10.3. Materials & methods

extra condition is implemented for the current reconstruction:

\[
 f_{\text{max}}^{(k)} := \max \left\{ \max_{i=1...n, j=1...10} \left\{ \left| f^{(k)}(x_{ij}) \right|, \left| f^{(k)}(x_{n+1}) \right| \right\} \right\} \tag{10.27}
\]

After a reconstruction is calculated, the values of \( f^{(k)}(x) \) are examined in the first and last subinterval (for each node in the subinterval, 11 values in \([x_1^{(k)}, x_2^{(k)}]\) and \([x_n^{(k)}, x_{n+1}^{(k)}]\) in order to resize the interval. The following criterion is verified (here mentioned for the right boundary):

\[
 \left( \sum_{j=1}^{10} \left[ \left( f^{(k)}(x_{nj}) \right)^2 + \left( f^{(k)}(x_{n/1}) \right)^2 \right] \right)^{1/2} \leq \text{tol}_{\text{red}} f_{\text{max}}^{(k)} \tag{10.28}
\]

If equation 10.28 is fulfilled, \( x_{n+1}^{(k+1)} \) becomes \((x_n^{(k)} + x_{n+1}^{(k)})/2\), otherwise the boundary remains unchanged, i.e. \( x_{n+1}^{(k)} \). After defining the interval for the next iteration, the nodes are redistributed equidistantly within the new interval.

To avoid the problem of ill-conditioning and negative values for the PDF all values of \( f^{(k)}(x) \) at \( x_i \) (\( i = 1...n+1 \)) and at the midpoints \( (x_{i6} = (x_i + x_{i+1})/2, i = 1...n) \) are inspected:

\[
 f_{\text{min, max}}^{(k)} := \min_{j=1,...,d} f_{\text{max}}^{(j)}, \frac{f^{(k)}(x_i)}{f_{\text{min, max}}} \geq \text{tol}_{\text{neg}}, \frac{f^{(k)}(x_{i6})}{f_{\text{min, max}}} \geq \text{tol}_{\text{neg}} \tag{10.29}
\]

with \( \text{tol}_{\text{neg}} \leq 0 \). This means that the reconstruction might be more negative between the nodes and the midpoints of the subintervals. Quite often, better results can be obtained by choosing a very small negative value for \( \text{tol}_{\text{neg}} \) [John et al., 2007]. Another solution to solve the ill-conditioning problem consists of regularizing the linear system of equations by neglecting small singular values. To compute the least-square solution of the linear system \((Ax=b)\) a pseudo-inverse routine is used. All singular values lower than a tolerance value \( \text{tol}_{\text{sing}} \) are treated as zero. The strategy consists of starting with a very small value as initial tolerance (for instance \(10^{-36}\)), after each redistribution of the nodes \( \text{tol}_{\text{sing}} \) is set to this initial value. However, if the criterion 10.29 is not fulfilled, the singular value \( \sigma \) of \( A \) with \( \sigma > \text{tol}_{\text{sing}} \) which is close to \( \text{tol}_{\text{sing}} \) is sought (\( \tilde{\sigma} \)).

By setting \( \text{tol}_{\text{sing}} = (\sigma + \tilde{\sigma})/2 \), \( \tilde{\sigma} \) is ignored in the next computation.

The differentiability of splines is a prerequisite for having enough equations to determine the coefficients. However, for the PSD the continuity is the only important condition. Therefore, these equations are multiplied by \( \omega^i \), with \( i \) the order of the differentiability condition. This scaling effect results in first neglecting the equations of higher differentiability in the removal of the singular values [John et al., 2007].
The drawbacks of this algorithm are problems when encountering non-smooth distributions and multimodal distributions. The use of a non-equidistant grid and an adaptive criterion for positioning the nodes dynamically in an appropriate manner are described by de Souza et al. [2010]. Using this algorithm the accuracy of the reconstruction increases with the number of moments. Also the process is sufficiently robust to tolerate some error in the moment values. In this chapter the original algorithm described by John et al. [2007] was implemented and used.

10.4 Results

The PBE was solved for a dry particle radius \( R_p \) of \( 6 \times 10^{-4} \) m and at a gas temperature of 55 °C. A normal probability density function was used as initial distribution with standard deviation \( \sigma \) of \( 3 \times 10^{-6} \) and mean \( \mu \) of 1.02 times \( R_p \):

\[
n_0 = \frac{1}{\sigma \sqrt{2\pi}} e^{-\frac{(R_w - \mu)^2}{2\sigma^2}}
\]  \( (10.30) \)

The MOC was used to compare because it is a solution method which calculates the entire number density distribution. In this case a value of 100 was used for the grid size.

10.4.1 Method of splines

Different values for the parameters in the algorithm were tested and evaluated. Each time step the initial interval for the algorithm was set to \([0, \text{max}(R_w)]\). The parameters were determined by running several simulations using the initial condition as test case, because for the initial condition both the number density in function of the internal coordinate \( R_w \) and the moments are available.

In table 10.1 the nominal values for different sets of \( \text{tol}_{\text{red}} \) are mentioned. It was decided to test also cases with two different values for \( \text{tol}_{\text{red}} \), one for the boundary at the lower values of the internal coordinate (\( \text{tol}_{\text{red},\text{left}} \)), and one for the higher values (\( \text{tol}_{\text{red},\text{right}} \)). Set A till D have an identical value for both \( \text{tol}_{\text{red},\text{right}} \) and \( \text{tol}_{\text{red},\text{left}} \), whereas for set E and F the values were chosen differently. In the last column the number of iterations \( n_{\text{it}} \) required to reconstruct one single distribution from its moments is mentioned.

The result is presented in figure 10.1. It is clear that \( \text{tol}_{\text{red}} \) has a significant impact on the final PDF. For set D and F the result is identical, but all other sets give another result. Because the initial condition is known (Eq. 10.30), it is obvious that set E corresponds to the correct situation. It is remarkable that it is the situation which requires the least number of iterations (Table
10.4. Results

Table 10.1: Algorithm settings for $tol_{\text{red}}$ for the method of splines ($l = 3$)

<table>
<thead>
<tr>
<th>Set</th>
<th>$tol_{\text{red, left}}$</th>
<th>$tol_{\text{red, right}}$</th>
<th>$n_{\text{it}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>$5 \times 10^{-1}$</td>
<td>$5 \times 10^{-1}$</td>
<td>306</td>
</tr>
<tr>
<td>B</td>
<td>$1 \times 10^{-1}$</td>
<td>$1 \times 10^{-1}$</td>
<td>365</td>
</tr>
<tr>
<td>C</td>
<td>$1 \times 10^{-2}$</td>
<td>$1 \times 10^{-2}$</td>
<td>855</td>
</tr>
<tr>
<td>D</td>
<td>$1 \times 10^{-3}$</td>
<td>$1 \times 10^{-3}$</td>
<td>893</td>
</tr>
<tr>
<td>E</td>
<td>$1 \times 10^{-1}$</td>
<td>$1 \times 10^{-2}$</td>
<td>110</td>
</tr>
<tr>
<td>F</td>
<td>$1 \times 10^{-2}$</td>
<td>$1 \times 10^{-1}$</td>
<td>658</td>
</tr>
</tbody>
</table>

In fact the result can be explained: the function of the value at the left side is to control the movement at the lower values of $R_w$. A high value for $tol_{\text{red, left}}$ enables a faster shift from low to high values of $R_w$ at the left side of the distribution. When $tol_{\text{red, left}}$ is lower than $tol_{\text{red, right}}$ the distribution will shift more in the direction of the lower moisture content. Set E, the correct distribution, is the only set where $tol_{\text{red, left}}$ is higher than $tol_{\text{red, right}}$. It is clear that during drying the moisture content will drop, but the final reconstruction should describe the 'real' distribution of the wet radius. A too high value at the right side, forces $R_w$ too much to the lower moisture content and was not able to describe the initial moisture content.

A new set of tests was performed while varying the value of $tol_{\text{neg}}$. In table 10.2, the different values for $tol_{\text{neg}}$, which are tested, are mentioned.

The results for set A till F are identical, a small deviation can be detected
Table 10.2: Sets for tol\_neg for the method of splines (l = 3)

<table>
<thead>
<tr>
<th>Set</th>
<th>tol_neg</th>
<th>n_it</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>10^{-1}</td>
<td>110</td>
</tr>
<tr>
<td>B</td>
<td>10^{-2}</td>
<td>110</td>
</tr>
<tr>
<td>C</td>
<td>5 \times 10^{-3}</td>
<td>110</td>
</tr>
<tr>
<td>D</td>
<td>10^{-3}</td>
<td>110</td>
</tr>
<tr>
<td>E</td>
<td>5 \times 10^{-4}</td>
<td>110</td>
</tr>
<tr>
<td>F</td>
<td>10^{-4}</td>
<td>110</td>
</tr>
<tr>
<td>G</td>
<td>0</td>
<td>117</td>
</tr>
</tbody>
</table>

for set G (Fig. not shown). It was decided to fix tol\_neg to a value of -5 \times 10^{-3}. For tol\_sing the value as proposed by John et al. [2007] was used. The nominal values for the parameters that are used for the remainder of the analysis are given in table 10.3.

The method of splines was compared using linear, quadratic and cubic splines (l \in \{1, 2, 3\}). The result is presented in figure 10.2 and the result obtained using MOC is also included in the figure. At 0 s the reconstruction using linear splines results in negative values for the number density, which is impossible for a PDF (Fig. 10.2). Using quadratic splines the maximum of the number density is located at a value for R_w which is far too low. The result using cubic splines corresponds the most with the MOC result. The result after 5 and 10 s is already a lot more comparable for different values of l (Fig. 10.2). At later time steps there is again much more deviation between the result using linear, quadratic and cubic splines and between the reconstruction using splines and MOC. However, the peak of the number density is more or less located at the same value for the internal coordinate.

The result of the reconstruction is also influenced by the number of moments used. The number of moments was therefore increased from 3 till 7 using cubic splines. At 0 s 3 and 4 moments is clearly not enough (Fig. 10.3). The result with 5 moments is already more satisfactory, but the peak is still located at a wrong position. Using 7 moments the result is comparable to MOC. However, the maximum value of the peak is higher. After 5 s the result for 3 and 4 moments is still very different compared to more moments and MOC (Fig. 10.3).
10.4. Results

Figure 10.2: Reconstruction using linear \((l = 1)\), quadratic \((l = 2)\) and cubic \((l = 3)\) splines at different time steps using 7 moments.

At 10 s the result with 4 moments is also comparable with MOC, which is also the case when using more moments (Fig. 10.3). At the end of the drying process (400 s) the peak is for almost every reconstruction located at the same \(R_w\), but the height of the peak is clearly larger for MOC (Fig. 10.3).

10.4.2 Comparison between method of splines and parameter fitting

The reconstruction using the method of splines with cubic splines, 7 moments and the parameters mentioned in table 10.3 is compared using different basic functions for parameter fitting. As the \(\gamma\)- and the \(\beta\)-function give 'Not a number' values, these methods were eliminated for further research. For the \(\gamma\)-function \(\Gamma(\mu)\) is equal to infinity with the calculated results of the moments, as \(\mu\) is a high value (Eq. 10.9). The same is valid for \(\Gamma(\alpha)\), \(\Gamma(\beta)\) and \(\Gamma(\alpha + \beta)\) (Eq. 10.10).

The results for the other methods are presented in figure 10.4. The position where the number density reaches a maximal value is indicated with a vertical line. The maximum values for the exponential and the half-normal reconstruction is always located at 0.

At the start (0 s) the best reconstruction should be found with the Gaussian
function, as this distribution was used to construct the initial condition (Fig. 10.4). But also the log-normal distribution gave good results, in addition to the method of splines. The peak using the Rayleigh basic function is located at a lower moisture content than the Gaussian and log-normal function and the reconstruction using the method of splines, but still better than the other functions. However, the width is much larger. At 5, 10 and 50 s the same is valid (Fig. 10.4). However, at 50 and 100 s the log-normal and the Gaussian distribution overestimated the moisture content. At 100 s the estimation using the Rayleigh basic function is even better than using the log-normal or Gaussian distribution. In fact it can be seen that the Rayleigh function locates the maximum of the number density more or less always at the same position, i.e. there is only a limited movement towards the lower moisture content.

In figure 10.5 the result is presented after 6 s. The drying process consists of two different drying phases; the first drying phase is characterized by a fast evaporation rate, and the second by a much slower evaporation rate (Chapter 4). As a consequence the distribution consists of 2 peaks when some particles
10.4. Results

Figure 10.4: Reconstruction using method of splines and parameter fitting at different time steps. For all methods the maximum value of the number density is indicated with a vertical line.

are in the first drying phase, while others are already in the second drying phase. This happens for this case after about 6 s. It is clear that only the method of splines is somehow able to detect the two peaks.

Figure 10.5: Reconstruction at 6 s using method of splines and parameter fitting
10.5 Discussion

Based on the evaluation and comparison of different reconstruction methods one can conclude that none of the methods is able to reconstruct the distribution perfectly. However, depending on the level of desired accuracy and the available a priori knowledge one of the discussed methods can be sufficient for the intended purpose. The methods based on parameter fitting are or can be useful when the underlying distribution is known. Attention should be paid when the distribution is used to monitor the process, as the possibility exists that a deviation of the process from normal behaviour is detected. In contrast, the method of splines is able to reconstruct multimodal distributions and as such the method is wider applicable. However, in order to obtain satisfactory results the method requires a finetuning of the parameters of the algorithm. Simply using the default parameter values can significantly impact the calculation time and the final result.

The number of iterations to obtain the final distribution is quite high for the spline-based method. As a consequence the method is not very useful when the distribution is required at different time steps. Indeed, when the PBM-model is used for process follow-up, it is recommended to use a non-moment based solution method for the PBE. This is due to the fact that the combined calculation time of a moment-based method in conjunction with the method of splines will be higher compared to another non-moment based solution method. Only in the case that one is just interested in the final distribution, the combination of a moment-based solution method and the method of splines is recommended. However, when a PBM-model is combined with a CFD-model a moment-based method is desired in order to have a reasonable calculation time. In this case the best solution to obtain a distribution is the method of splines.

10.6 Conclusion

Several reconstruction methods are available to create the PDF using moments. However, each method has advantages and disadvantages. Parameter fitting of basis functions is fast, but a good knowledge of the distribution is required in order to get a good estimation of the PDF. Therefore, this method is not ideal to track the distribution when several processes influence the behaviour of particles. In contrast, the method of splines can track the distribution quite well, but requires more computational time and a finetuning of the parameters of the algorithm. Finetuning of these parameters does not only influence the number of iterations which are required for the reconstruction, but also influences the final reconstructed PDF. For the problem mentioned here the nominal value for $\text{tol}_\text{neg}$ was less crucial compared to $\text{tol}_\text{red}$. Interestingly, the introduction of
10.6. Conclusion

a different $t_{\text{red}}$-value for the first and last interval had a remarkable influence on the final reconstruction. When the 'real' distribution is not known, some insight in the process will be required to choose a value for $t_{\text{red}}$ or values for $t_{\text{red, right}}$ and $t_{\text{red, left}}$. The order of splines ($l$) also influences the final reconstruction, and in our case using linear splines resulted in negative values for the number density. The method of splines also requires more moments for obtaining good results: when only 3 or 4 moments were used the result was not satisfactory, and in this case using parameter fitting with a Rayleigh, log-normal or Gaussian basic function yielded better results.

It was clear that the method of splines was the only method able to detect bi-modal behaviour. In summary, the method of splines is the preferred method in the case that no information about the final distribution is available. There is always a probability that several peaks prevail, which none of the other methods is able to detect.
Chapter 10. Reconstruction of a distribution from moments
CHAPTER 11

A two-dimensional PBM for continuous drying of a population of granules including drying and breakage: A simulation study

Abstract:
The one-dimensional PBM model describing the drying behaviour (Chapter 8) is extended to a two-dimensional PBM model to include the breakage occurring during the drying of particles in a fluidized bed. Therefore, a simulation study on breakage mechanisms has been performed. Three different breakage mechanisms, i.e. two granule breakage kernels and one surface breakage kernel, have been implemented and the influence of the involved parameters on the breakage rate has been analysed. First, a stand-alone one-dimensional breakage PBM model was solved. The formation of two equal fragments leads to clear peaks occurring at a size equal to half of the size of the mother particle. This is obviously different for uniform binary breakage where a smooth shift towards the lower size classes occurs. In the case of erosion fines are produced, and a peak appears at the lowest size class. Secondly, the drying was added to end up with a two-dimensional PBM model. In the case of the uniform binary breakage kernel the effect of breakage was clear, i.e. the width of the peak of the moisture content is remarkably larger due to breakage. The effect is less significant for the formation of two equal fragments.

11.1 Introduction

Drying of wet pharmaceutical granules implies several problems. During batch production bottlenecks include the time and the product quality after drying [Nieuwmeyer et al, 2007a]. Fluidized bed drying processes are fast, but the size reduction due to attrition is disadvantageous, as the resulting fines are con-
Chapter 11. A two-dimensional PBM: Drying and breakage

Considered as a product quality diminishing side effect [Nieuwme
er et al., 2007a][Nieuwme
er et al., 2007b]. Verkoeijen et al. [2002] described several break-ge mechanisms depending on the extent and the direction of the applied force (Fig. 11.1). Attrition is understood as the process whereby the original granule becomes more spherical due to the removal of sharp edges and other surface asperities. In this case fine dust is produced. The same is valid for wear, but in this case the shape remains almost identical, it is only a polishing of the original granule. When larger pieces are generated, the process is termed as abrasion, the original granules becomes smoother and more spherical. Due to fragmentation the granule is divided into several fragments. Chipping is the process whereby the original granule becomes rougher and less spherical, the pieces that break off are smaller compared to the pieces formed by fragmentation. In the case of attrition, wear and abrasion fine dust is formed during breakage, these mechanisms are further termed 'surface breakage'. The cases of fragmentation and chipping are referred as 'granule breakage'.

Research results showed that the moisture content has an influence on the strength of the granules, and a maximum strength was found for a moisture content between 20 and 25%. By using an image analysis technique it was found that breakage is mainly caused by attrition at higher moisture contents, whereas fragmentation is the main effect at lower moisture contents [Verkoeijen et al., 2002]. The formation of fines is important as it can affect the flowability of the granules [Nieuwme
er et al., 2007b] and/or the in-homogeneity [van den Dries et al., 2003].

Mathematical models describing breakage during drying can only be rarely found in literature. For single particles a theoretical drying model was proposed by Mezhericher et al. [2008a].

**Figure 11.1:** Different breakage mechanisms
11.2 Objectives

In this chapter a one-dimensional PBM which describes the drying of wet pharmaceutical granules is extended towards a two-dimensional PBM. The second internal coordinate is chosen as the size of the granules. Several theoretical breakage kernels were implemented. The effect of the kernels and the parameters of the kernels were analysed in a stand-alone breakage PBM model, i.e. a one-dimensional PBM model. The interaction between the PSD and the drying behaviour was investigated by using the two-dimensional PBM.

11.3 Materials & methods

11.3.1 Two-dimensional Population Balance Model (PBM)

The one-dimensional PBM described in chapter 8 was extended towards a two-dimensional PBM. The resulting PBE becomes:

\[
\frac{\partial}{\partial t} n(R_w, V, t) + \frac{\partial}{\partial R_w} R_w(R_w, Y) n(R_w, V, t) = \int_V^\infty \beta(V, v) S(v, X) n(R_w, v, t) dv - S(V, X) n(R_w, V, t) 
\]

(11.1)

where \( n(R_w, V, t) \) is the number density distribution, the term \( S(v, X)n(R_w, v, t) \) is the rate of breakage of particles of size \( v \) with \( S(v, X) \) the breakage rate coefficient, \( \beta(V, v) \) represents the fragment distribution function due to breakage of particles with size \( v \) and \( \beta(V, v)dv \) the number of particles produced with a mass between \( V \) and \( V + dv \) due to breakage of a granule with size \( v \). \( Y \) represents the continuous phase vector, which includes the gas temperature \( T_g \) in this case study. \( X \) refers to a vector including all factors influencing the breakage rate. \( V-v \) represents the size of a particle in terms of the volume.

In this study the breakage rate coefficient, also referred to as 'selection kernel', is dependent on the current size of the granule, \( v \), and \( X \). Possible factors which can have an influence on the breakage rate are the gas velocity \( V_g \), the moisture content of the granule \( X \), the formulation of the pharmaceutical powder, the granulation liquid, etc.

11.3.2 Solution of the two-dimensional PBE

The two-dimensional PBE (Eq. 11.1) is solved by first solving the homogeneous equation over a certain time step

\[
\frac{\partial}{\partial t} n(R_w, V, t) + \frac{\partial}{\partial R_w} R_w(R_w, Y) n(R_w, V, t) = 0
\]

(11.2)
and adding the breakage afterwards [Ma et al., 2002]. The homogeneous equation is solved using the HRFV-scheme (Section 8.3.1). The MOC is not used because of the moving grid. As particles that break need to be assigned to the corresponding moisture content, a moving grid is not possible. The breakage term is solved using the fixed pivot technique as presented by Kumar and Ramkrishna [1996]. Therefore, the breakage part of the continuous equation is first integrated over a discrete interval \( V_i - V_{i+1} \), leading to:

\[
\frac{dN_i(R_w, t)}{dt} = \int_{V_i}^{V_{i+1}} dV \int_v^\infty \beta(V, v) S(v, X) n(R_w, v, t) dv \\
- \int_{V_i}^{V_{i+1}} dV S(V, X) n(R_w, V, t)
\]  

(11.3)

The birth term due to the breakage \( R_{Bb} \) of larger particles is modified to:

\[
R_{Bb} = \int_{x_i}^{x_{i+1}} a(V, x_i) dV \int_v^\infty \beta(V, v) S(v, X) n(R_w, v, t) dv \\
+ \int_{x_{i-1}}^{x_i} b(V, x_i) dV \int_v^\infty \beta(V, v) S(v, X) n(R_w, v, t) dv
\]  

(11.4)

where \( v_i = (x_{i+1} + x_i)/2 \). The reasoning behind this modification lays in the fact that all properties should be preserved. This means that particles of size \( V \) in size range \([x_i, x_{i+1}]\) are represented by assigning fractions \( a(V, x_i) \) and \( b(V, x_i) \) to particle populations at \( x_i \) and \( x_{i+1} \) respectively. In this contribution only two general properties are preserved.

As particles are assumed to be concentrated at representative size, \( x_i \), the number density can be written as:

\[
n(R_w, V, t) = \sum_{k=1}^{M} N_k(R_w, t) \delta(V - x_k)
\]  

(11.5)

which can be substituted in equation (11.4)

\[
R_{Bb} = \sum_{k \geq i} S(x_k, X) N_k(R_w, t) \int_{x_i}^{x_{i+1}} a(V, x_i) \beta(V, x_k) dV \\
+ \sum_{k \geq i} S(x_k, X) N_k(R_w, t) \int_{x_{i-1}}^{x_i} b(V, x_i) \beta(V, x_k) dV
\]  

(11.6)

Equation (11.6) can be simplified by substitution of \( a(V, x_i) \) and \( b(V, x_i) \). This simplification is based on the fact that the formation of a particle of size \( V \) in size range \( x_i, x_{i+1} \), due to breakup, is represented by assigning fractions
11.3. Materials & methods

\( a(V, x_i) \) and \( b(V, x_{i+1}) \) to particle population at \( x_i \) and \( x_{i+1} \), respectively.

\[
R_{Bb} = \sum_{k \geq i}^{M} n_{i,k} S(x_k, X) N_k(R_w, t) \quad (11.7)
\]

where \( n_{i,k} \) is interpreted as the contribution to the population at the \( i^{th} \) representative size due to the breakage of a particle of size \( x_k \), and is given by:

\[
n_{i,k} = \int_{x_i}^{x_{i+1}} \frac{V}{x_{i+1} - x_i} \beta(V, x_k) dV + \int_{x_{i-1}}^{x_i} \frac{V - x_{i-1}}{x_i - x_{i-1}} \beta(V, x_k) dV \quad (11.8)
\]

which is obtained by simplification in order to have exact preservation of numbers and mass. The first and second integral are zero for respectively \( i = k \) and \( i = 1 \). The death term can be written as:

\[
R_{Db} = \int_{V_i}^{V_{i+1}} S(V, X) n(R_w, V, t) dV \quad (11.9)
\]

Combining equations 11.9 and 11.5 gives rise to:

\[
R_{Db} = S(x_i, X) N_i(t) \quad (11.10)
\]

Eventually resulting in the discrete equation for pure breakage:

\[
\frac{dN_i(R_w, t)}{dt} = \sum_{k \geq i}^{M} n_{i,k} S(x_k, X) N_k(t) - S(x_i, X) N_i(t) \quad (11.11)
\]

11.3.3 Breakage kernels

Several theoretical breakage kernels are investigated, i.e. two granule breakage kernels and one surface breakage kernel. The formation of two equal fragments, which is a granule breakage kernel, was the first kernel of interest:

\[
\beta(V, v) = \begin{cases} 
2, & V = \frac{v}{2} \\
0, & \text{otherwise}
\end{cases} \quad (11.12)
\]

Another kernel, again a granule breakage kernel, that has been investigated is a uniform binary breakage kernel:

\[
\beta(V, v) = \frac{2}{v} \quad (11.13)
\]

In this case it is equally likely to form a child particle of any size, whereas the breakage in two equal fragments leads to two daughter particles with the same
A third kernel is a surface breakage kernel where particles with the lowest size are formed due to the erosion of the larger sizes:

$$\beta(V, v) = \begin{cases} 
1, & V = 1, v - 1 \\
0, & \text{otherwise}
\end{cases} \quad (11.14)$$

A selection function $S(V)$, independent from the time and other variables, was chosen. Several forms of selection kernels are available (Table 11.1) [Vanni, 2000]. For simplified analysis of particulate systems size independent kernels are frequently used, when the focus is more on a qualitative agreement between experimental data and theory. The power law expression is used for more accurate predictions, and for such an analysis $k_1$ is situated between $1/3$ and $2$ [Chen et al., 1990]. Only in a limited amount of cases an exponential kernel is adopted [Vanni, 2000], and with this kernel it is possible to increase the breakage rate of the larger particles.

<table>
<thead>
<tr>
<th>Selection kernels $S(V)$</th>
<th>$k_0$</th>
<th>$k_0 V^{k_1}$</th>
<th>$k_0 e^{k_1 V}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size independent kernel</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Power law kernel</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exponential kernel</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 11.3.4 Simulation parameters

For the simulations the two-dimensional space had to be discretised, and a uniform grid has been chosen. The grid for the moisture content is divided into 100, while a grid size of 200 is chosen for the size of the particles. For the moisture content the discretisation domain ranged from 0 till 1.03 times the particle size (i.e. $R_{w, fac}R_p$). The size of the particles ranged from 100 to 1,000 µm, which is translated to the corresponding volume of the particles (assuming spherical particles). The gas temperature, necessary to compute the drying behaviour, was set at 55 °C.

As initial condition a two-dimensional Gaussian function is used for the simulations:

$$n_0 = \frac{1}{2\pi\sigma_{R_w} \sigma_V} e^{-\left(\frac{(R_w - \mu_{R_w})^2}{2\sigma_{R_w}^2} + \frac{(V - \mu_V)^2}{2\sigma_V^2}\right)} \quad (11.18)$$

where $\sigma_{R_w}$ and $\sigma_V$ are respectively the standard deviation of the initial Gaussian function for $R_w$ and $V$ and $\mu_{R_w}$ and $\mu_V$ the mean of the initial Gaussian function for $R_w$ and $V$ (Fig. 11.2).

The parameters of the initial distribution are mentioned in Table 11.2 (Fig.
11.4. Results

11.4.1 Stand-alone breakage PBM-model

The formation of two equal fragments

In a first set of simulations the power law selection kernel (Eq. 11.16) was used as selection kernel. The result for $k_0$ equal to $10^{-21}$ and $k_1$ equal to 1 after 500 s is presented in figure 11.3. These parameters are chosen after some trial and error simulations to get a first idea about suitable values for the parameters. As time evolves the wet granules break up and several peaks at a lower granule size appear. The result after 1,000 s shows a further break up of the wet granules (Fig. 11.3).

In figure 11.4 the number density is presented at different time steps in function of the volume of the granule. Here, the sum is taken of all particles regardless of the moisture content. The influence of the breakage on the PSD...
Figure 11.3: Number density distribution for the formation of two equal fragments and the power law selection kernel \(k_0 = 10^{-21}, k_1 = 1\) after 500 s (Left) and 1,000 s (Right)

is obvious. As in this case a particle breaks up in two equal fragments, a new particle appears at a size half of the size of the mother particle. This is the reason for the appearance of peaks with a size between 1.5 and 2, and an even smaller peak with a size between approximately 0.8 and 1.

The effect of \(k_0\) and \(k_1\) is investigated by using several parameter sets, which are listed in table 11.3. A higher value for these parameters will result in more breakage. But as \(k_1\) occurs in the exponent of equation 11.16 a higher output sensitivity can be expected. Therefore, the range of \(k_0\) has been chosen for each value of \(k_1\) independently in order to get a minimum breakage however
without having too much breakage.

In the left part of figure 11.5 the total number of granules $N$ is presented in

**Table 11.3:** Used parameter sets for the power law selection kernel for stand-alone formation of two equal fragments

<table>
<thead>
<tr>
<th>Set</th>
<th>$k_0$</th>
<th>$k_1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$10^{-23}$</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>$10^{-22}$</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>$10^{-21}$</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>$10^{-31}$</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>$10^{-30}$</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>$10^{-29}$</td>
<td>2</td>
</tr>
</tbody>
</table>

function of time for $k_1$ equal to 1. The influence of parameter $k_0$ is obvious, where a higher value for $k_0$ increases the break up significantly. The corresponding figures of the number density at 1,000 s are presented in the right part of figure 11.5. Dependent on the value of $k_0$ the number of granules in the lower size classes is remarkably higher.

The result for $k_1$ equal to 2 is presented in figure 11.6. In this case the differences between the different values of $k_0$ are much more pronounced (taking the limits of the $y$-axis into account).

The results for the size independent kernel (Eq. 11.15) are not shown but identical to the results for the power law selection kernel (Eq. 11.16).
Figure 11.6: Comparison of the total number of granules $N$ for the formation of two equal fragments and the power law selection kernel ($k_1 = 2$)

Uniform binary breakage

In figure 11.7 the three-dimensional plots are presented with values of $10^{-22}$ for $k_0$ and 2 for $k_1$ for the power law selection kernel. Based on some first trial and error simulations the order of magnitude of the parameters was chosen. After 500 s the breakage is already pronounced, and after 1,000 s even more particles were broken. It is clear that the breakage mechanism is different compared to the formation of two equal fragments. No single peaks occur at lower size classes, but a more smoother shift towards the lower sizes occurs.

In figure 11.8 the number density is presented at different time steps in function of the volume of the granule. Again the smoother shift towards the

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11.4. Results

lower size classes can be observed, in comparison with the case where two equal fragments are formed during breakage.

The effect of $k_0$ and $k_1$ is investigated by using several parameter sets. As the

![Figure 11.8: Total number of particles $N$ per granule size for uniform binary breakage and the power law selection kernel ($k_0 = 10^{-22}, k_1 = 2$) at several time steps](image)

same conclusions could be drawn as for the formation of two equal fragments, but these results are not shown.

**Erosion**

In figure [11.9] the three-dimensional plots are presented with values of $10^{-30}$ for $k_0$ and 2 for $k_1$ for the power law selection kernel. The fines, produced due to breakage, occur at a moisture content of 0%, because it is assumed that these fines are dry. After 500 s a peak is already visible at the lowest size class, and this peak becomes even larger after 1,000 s.

11.4.2 Two-dimensional PBM with breakage and drying of granules

The formation of two equal fragments

The two-dimensional PBM-model for the drying-breaking case was solved for $k_0$ equal to 1 and $k_1$ equal to $10^{-21}$, the same case which is discussed in detail in section [11.4.1]. In figure [11.10] the three-dimensional plots are presented. After 100 s a small peak at a lower particle size appears. Also the decrease of the moisture content is obvious. After 300 and 500 s the breakage is already more pronounced and after 1,000 s the particles are dry. Again it is clear that the second peak occurs at a size which is half of the size of the particles that
Figure 11.9: Number density distribution for erosion and the power law selection kernel \((k_0 = 10^{-21}, k_1 = 1)\) after 500 s (Left) and 1,000 s (Right) were present at the start of the simulation.

The total number of particles per moisture content class shows the clear

Figure 11.10: Number density distribution for the formation of two equal fragments and the power law selection kernel \((k_0 = 10^{-21}, k_1 = 1)\) including drying after 100 s (Upper left), 300 s (Upper right), 500 s (Lower left) and 1,000 s (Lower right)
11.4. Results

decrease of the moisture content during drying (Fig. 11.11).

\[ \text{Figure 11.11: Total number of particles } N \text{ per moisture content class for the formation of two equal fragments and the power law selection kernel (} k_0 = 10^{-21}, k_1 = 1 \text{) at several time steps} \]

**Uniform binary breakage**

For this case the simulation was done with $10^{-22}$ for $k_0$ and 2 for $k_1$ (which is the same as for the case with only breakage). The results after 100 s, 300 s, 500 s and 1,000 s are presented in figures 11.12. After 100 s some breakage can be observed, and the peak has already shifted towards a lower moisture content. After 300 s more breakage has occurred, and it is clear that the smaller particles are drying faster compared to the original larger particles. Particles with a $R_w$ of 0 are completely dry, and such particles are clearly visible after 500 s. Here, the difference in drying rate between the small and the large particles is obvious. All particles are dry after 1,000 s.

In figure 11.13 the total number of particles in each moisture content class is presented. The shift towards a lower moisture content is obvious. The longer the drying time, the wider the peak due to the breakage of particles as smaller particles dry faster compared to larger particles. This effect is much more pronounced compared to the previous case, i.e. the formation of two equal fragments.

**Erosion**

The simulation has been performed with values of $10^{-30}$ for $k_0$ and 2 for $k_1$. The three-dimensional plots after 100 and 500 s are presented in figure 11.14. The shift towards the lower moisture content is visible. A peak at the lowest size class appears due to the formation of fines.
Figure 11.12: Number density distribution for uniform binary breakage and the power law selection kernel ($k_0 = 10^{-22}$, $k_1 = 2$) including drying after 100 s (Upper left), 300 s (Upper right), 500 s (Lower left) and 1,000 s (Lower right)

Figure 11.13: Total number of particles $N$ per moisture content class for uniform binary breakage and the power law selection kernel ($k_0 = 10^{-22}$, $k_1 = 2$) at several time steps
11.5 Discussion

This study focuses on the numerical simulation of breakage during drying of wet pharmaceutical granules. Three mechanisms of breakage (i.e. the formation of two equal fragments, uniform binary breakage and erosion) have been implemented and investigated. However, there was no experimental data available yet for calibration. Theoretical kernels were also used for the rate of breakage.
Experimental data could reveal that other breakage mechanisms occur during drying, e.g. fragmentation in more fragments. However, the validation of the breakage mechanisms will be challenging, as several mechanisms can occur simultaneously. This is a general problem which has also been observed in crystallization processes where a PBM potentially includes growth, agglomeration, breakage, dissolution etc.

Moreover, during drying the moisture content of the granules decreases and the breakage mechanism might be different for wet and dry granules. It can be expected that the rate of breakage will be higher for dry granules and that the production of fines will therefore be higher. The fluidization pattern, which will be investigated using CFD (Part IV), is influenced by the gas velocity. A dependency of the rate of breakage on the gas velocity can also be expected, which is translated into the selection kernel in the PBM.

The validation of PBM kernels is very complicated, therefore, in most cases theoretical kernels are used (i.e. for aggregation, breakage, etc.) when simulating the process. Breakage kernels based on the physical mechanisms occurring during breakage are seldom used. However, using the PBM model for gaining process knowledge is dangerous when relying on these theoretical kernels. The true breakage mechanisms are only described by these kernels, but the real process is not modelled.

11.6 Conclusion

A theoretical study on the breakage mechanisms which can occur during drying has been performed. The differences between the mechanisms of breakage were clear. In the case of the formation of two equal fragments, clear peaks occur at a size equal to half of the size of the mother particles. Uniform binary breakage leads to a smoother shift towards the lower size classes. In the case of surface breakage (p.e. erosion) fines are produced corresponding to formation of particles in the smallest size classes.

The effect of breakage on the drying rate was most pronounced for uniform binary breakage, where the moisture content peak width is larger due to breakage. This effect is less significant for the case where two equal fragments are produced due to breakage.
PART IV

Computational Fluid Dynamics to study the flow pattern of fluidizing particles
In part IV a preliminary study is discussed which investigates the flow pattern of particles in a fluidized bed. This is done using Computational Fluid Dynamics (CFD).
CHAPTER 12

A Computational Fluid Dynamics (CFD) model for the flow pattern in a fluidized bed dryer: Preliminary results

Abstract:
The flow pattern of particles in the fluidized bed system of the ConsiGma™ has been investigated using Computational Fluid Dynamics (CFD). Some preliminary results are provided. First, a gas-phase simulation was performed. Next, after reaching a convergent solution, the solids were added into the flow domain. Up till now, the simulation results show that particles are escaping from the domain. This needs further attention in future research.

12.1 Introduction

Particle drying using continuous fluidized bed systems has great potential in pharmaceutical applications since it provides a number of advantages such as large heat capacity inside a bed, rapid heat and mass transfer rate and relatively short drying time [Hegedus and Pintye-Hódi, 2007]. The choice of the technique for drying wet granules might influence the properties of the granules (particles) and, hence, the further downstream processing. While modelling the fluidized bed drying process of wet granules, two distinct processes need to be accounted for. First, granules are drying, a process which is significantly influenced by the local conditions of the gas (velocity, vapour pressure). Secondly, the granules are fluidized in the dryer, thereby exhibiting a certain fluidization pattern which depends on the gas flow rate. Particle drying makes it even more difficult to characterize the fluidization behaviour of powders since the drying itself will influence the fluidization behaviour. During drying, the moisture content drops, which improves the fluidization. Using the classification
of Geldart, it is known that particles can shift from a Geldart C type of powder to Geldart B powders during drying. In order to capture detailed spatial behaviour of the system, the flow of the particles needs to be analysed. CFD has become a powerful tool for research and development in multiphase flow systems. Since computational resources have increased substantially at sharply decreasing costs, detailed computational information about the flows can nowadays be obtained even at a fraction of the cost of the corresponding experiments [van den Akker, 2006]. The Eulerian-Eulerian multiphase model incorporated in CFD codes has been used in this study to predict gas-solid flow behaviour. Dutta et al. [2009] studied the behaviour of gas-solid fluidized beds with an Eulerian-Eulerian model approach. The estimated time average bed expansion ratio and cross-sectional void profiles compared well with corresponding values of experimental data. Wang et al. [2007] proposed an approach to investigate the drying characteristics of a batch fluidized bed dryer based on a three-phase model and CFD simulation using Fluent®. Ronsse et al. [2007] described the use of a combined PBM and thermodynamic model to describe a batch topspray fluidized bed coating process. Therefore, the domain was discretised into different control volumes, in which the dynamic heat and mass balances for air, water vapour, core particles and coating material were established. A validation has been performed and it could be concluded that the proposed model is sufficiently reliable for the prediction of steady-state behaviour.

12.2 Objectives

The purpose of this study is to simulate transport phenomena during the drying process of pharmaceutical granules in a fluidized bed dryer using a CFD approach. Moreover, it is assumed to predict qualitative and quantitative behaviour of the flow patterns and particle mixing using Fluent® CFD code.

12.3 Gas-solid flow model

12.3.1 Multiphase hydrodynamic model

The gas phase is assumed to be incompressible. The hydrodynamic model for multiphase flow is based on the generalization of the Navier-Stokes equations using the so-called Eulerian-Eulerian approach [Anderson and Jackson, 1967]. Mass and momentum balances are solved for each phase. The KTGF [Lun et al., 1984] Gidaspow [1994] originating from the theory for non-ideal dense gases developed by Chapman and Cowling [1970] is used to close the solid-phase equations. Table 12.1 summarises the basic transport equations for the fluid and particulate phase. The continuity equations neglect mass transfer between
12.3. Gas-solid flow model

both phases. The terms at the right hand side of the momentum equations account for the effects of pressure, shear, gravity and momentum transfer between the gas and solid phase. Lift forces are neglected as well as virtual mass forces since the phase densities differ by a factor $> 10^3$. $\mu_s$ is the solids shear viscosity and has three contributions. The first term ($\mu_{s, col}$) accounts for the collision between particles while the second ($\mu_{s, kin}$) and the third ($\mu_{s, fr}$) term represent the kinetic contribution and frictional viscosity, respectively. The latter is included to account for the generation of stresses due to friction between particles in dense flow. The solids bulk viscosity, $\xi_s$, accounts for the resistance of the particles to compression and expansion. The solids pressure, $P_s$, is assumed to consist of two separate contributions: a kinetic term, which dominates in the dilute flow regime and a collisional term, which becomes important in the dense phase regime. The Syamlal and O’Brien [1989] model is used for the inter-phase momentum exchange coefficient.

The solid phase constitutive equations require the calculation of the granular temperature, $\Theta_s$, for which an additional transport equation has to be solved. The first term in the transport equation corresponds to the production of fluctuating kinetic energy by the effective shear stresses and the second term represents the dissipation of kinetic fluctuation energy due to the inelastic collision of particles [Lun et al., 1984]. The last term in the equation of the granular temperature transport equation represents the energy exchange between both phases. The restitution coefficient for particle–particle collisions, $e_{ss}$, is fixed at 0.9 for all the simulations in the present study. This value is in line with previous literature studies [Rong et al., 1999] [Tsuji et al., 2008] for both glass and polymer particles.

Table 12.1: Summary of conservation and constitutive equations

<table>
<thead>
<tr>
<th>Equation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuity equation:</td>
<td>$\frac{\partial}{\partial t} (\varepsilon_i \rho_i) + \nabla (\varepsilon_i \rho_i \mathbf{v}_i) = 0$</td>
</tr>
<tr>
<td>Momentum equation for gas phase:</td>
<td>$\frac{\partial}{\partial t} (\varepsilon_g \rho_g \mathbf{v}_g) + \nabla (\varepsilon_g \rho_g \mathbf{v}_g \mathbf{v}_g) = -\varepsilon_g \nabla P + \nabla \tilde{\tau}_g + \varepsilon_g \rho_g \mathbf{g} - \beta (\mathbf{v}_g - \mathbf{v}_s)$</td>
</tr>
<tr>
<td>Momentum equation for solid phase:</td>
<td>$\frac{\partial}{\partial t} (\varepsilon_s \rho_s \mathbf{v}_s) + \nabla (\varepsilon_s \rho_s \mathbf{v}_s \mathbf{v}_s) = -\varepsilon_s \nabla P - \nabla P_s + \nabla \tilde{\tau}_s + \varepsilon_s \rho_s \mathbf{g} + \beta (\mathbf{v}_g - \mathbf{v}_s)$</td>
</tr>
<tr>
<td>Gas-phase shear stress tensor:</td>
<td>$\tilde{\tau}_g = \varepsilon_g \mu_g \left( \nabla \mathbf{v}_g + \nabla \mathbf{v}_g^T \right)$</td>
</tr>
<tr>
<td>Solid-phase shear stress tensor:</td>
<td></td>
</tr>
</tbody>
</table>

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Table 12.1: Summary of conservation and constitutive equations

\[ \overline{\tau}_s = \varepsilon_s \mu_s \left( \nabla \overline{v}_s + \nabla \overline{v}_s^T \right) + \varepsilon_s \left( \xi_s - \frac{2}{3} \mu_s \right) \nabla \overline{v}_s \overline{I} \]  
(12.5)

Gas phase turbulence equations:

k-equation:

\[ \frac{\partial}{\partial t} (\varepsilon_g \rho_g k_g) + \nabla \cdot (\rho_g \overline{v}_g k_g) = \nabla \cdot \left( \varepsilon_g \mu_{t,g} \sigma_c \nabla k_g \right) + \varepsilon_g G_{k,g} - \varepsilon_g \rho_g \varepsilon_g + \varepsilon_g \rho_g \Pi_{k,g} \]  
(12.6)

\[ \varepsilon_g \text{-equation:} \]

\[ \frac{\partial}{\partial t} (\varepsilon_g \rho_g \varepsilon_g) + \nabla \cdot (\rho_g \overline{v}_g \varepsilon_g) = \nabla \cdot \left( \varepsilon_g \mu_{t,g} \sigma_c \nabla \varepsilon_g \right) + \varepsilon_g \rho_g \varepsilon_g k_g \left( C_{1g} G_{k,g} - C_{2g} \rho_g \varepsilon_g \right) + \varepsilon_g \rho_g \Pi_{\varepsilon,g} \]  
(12.7)

Solid phase kinetic fluctuation energy:

\[ \frac{3}{2} \left[ \frac{\partial}{\partial t} (\varepsilon_s \rho_s \Theta_s) + \nabla \cdot (\varepsilon_s \rho_s \overline{v}_s \Theta_s) \right] = \left( -P_s \overline{I} + \overline{\tau}_s \right) : \nabla \overline{v}_s + \nabla \left( k_s \Theta_s \right) - \gamma_{\Theta_s} + \phi_{\Theta_s} \]  
(12.8)

Solids collision viscosity \([\text{Syamlal et al.} \ [1993]]\):

\[ \mu_{s,\text{col}} = \frac{4}{5} \varepsilon_s \rho_s d_p g_{o,ss} \left( \frac{\Theta_s}{\pi} \right)^{1/2} \]  
(12.9)

Solids kinetic viscosity \([\text{Syamlal et al.} \ [1993]]\):

\[ \mu_{s,\text{kin}} = \varepsilon_s \rho_s d_p \sqrt{\sigma_s \pi} \left[ 1 + \frac{2}{5} \varepsilon_s g_{o,ss} \left( 1 + e_{ss} \right) \right] \]  
(12.10)

Solids frictional viscosity \([\text{Schaeffer} \ [1987]]\):

\[ \mu_{s,\text{fr}} = \frac{P_s \sin \varphi}{2 \sqrt{I_2 D}} \]  
(12.11)

where \( \varphi \) is the angle of internal friction

Solids bulk viscosity \([\text{Lun et al.} \ [1984]]\):

\[ \xi_s = \frac{3}{2} \varepsilon_s \rho_s d_p g_{o,ss} \left( 1 + e_{ss} \right) \left( \frac{\Theta_s}{\pi} \right)^{1/2} \]  
(12.12)

Solids pressure:

\[ P_s = \varepsilon_s \rho_s \Theta_s + 2 \rho_s \left( 1 - e_{ss} \right) \varepsilon_s^2 g_{o,ss} \Theta_s \]  
(12.13)

Radial distribution function \([\text{Ogawa et al.} \ [1980]]\):
12.3. Gas-solid flow model

Table 12.1: Summary of conservation and constitutive equations

\[ g_{o,ss} = \left[ 1 - \left( \frac{\varepsilon_s}{\varepsilon_{s,\text{max}}} \right)^{1/3} \right]^{-1} \]  \hspace{1cm} (12.14)

Drag function (Syamal and O’Brien [1989]):
\[ \beta = \frac{3\varepsilon_s\varepsilon_g\rho_g C_D}{4v_{t,s}^2d_p} \left( \bar{v}_s - \bar{v}_g \right) \]  \hspace{1cm} (12.15)

with \( C_D = \left( 0.63 + \frac{4.8}{\sqrt{Re_s/v_{t,s}}} \right) \)

Granular temperature transport equation:
\[ \left( -P_s \bar{I} + \bar{\bar{T}}_s \right) : \nabla \bar{v}_s - \gamma \Theta_s - 3\beta \Theta_s = 0 \]  \hspace{1cm} (12.16)

Dissipation of kinetic fluctuation energy:
\[ \gamma \Theta_s = \frac{12(1-\varepsilon_{ss}^2)g_{o,ss}}{d_p\sqrt{\pi \rho_s \varepsilon_s^{3/2} \Theta_s^{1/2}}} \]  \hspace{1cm} (12.17)

12.3.2 Turbulence modeling

Based on the standard \( k-\epsilon \)-model, which is de facto a two-equation model that involves the transport equation for the turbulent kinetic energy \( k \) and its dissipation rate \( \epsilon \) [Jones and Launder 1972], a \( k-\epsilon \) dispersed turbulence model for multiphase flow is used. The use of the multiphase \( k-\epsilon \) dispersed turbulence model is appropriate when there is only one continuous primary phase with dilute or a semi-dilute concentration of the secondary phase(s) and the material density ratio of the phases is high, which is the case in the present study.

The Stokes number, which is a dimensionless number corresponding to the behaviour of particles suspended in a fluid flow, being much less than 1 due to a high particle Reynolds number, does not allow the kinetic energy of the particles to depart significantly from that of the gas, thereby further justifying the choice of the dispersed turbulence model. Three time scales are of importance for dispersed phase turbulence [Simonin and Viollet 1990]: the time scale of the energetic turbulent eddies \( \tau_{\epsilon, g}^t \), the time scale of the inertial effects of the continuous phase on the dispersed phases \( \tau_{g,s}^F \) and the time scale of the eddy particle interactions \( \tau_{g,s}^\Pi \). \( \Pi_{kg} \) and \( \Pi_{eg} \) represent the influence of the dispersed secondary phase(s) on the continuous gas phase. They are modeled following Elgobashi and Abou-Arab [1983], while \( \bar{v}_g \) is the corresponding gas velocity.

The constants used in the \( k-\epsilon \) dispersed gas phase turbulence model are mentioned in table 12.2. Turbulence prediction in the dispersed phase (solid phase kinetic fluctuation energy) is achieved by an extension of the obtained results, using the Tchen theory of dispersion of particles by homogeneous and steady turbulent fluid motion [Hinze 1959]. The drag force has a significant influence on the stability and heat/mass transfer characteristics of the flow [Yin and Sundaresan 2009].
Table 12.2: Constants used in the $k$-$\epsilon$ dispersed gas phase turbulence model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_1$</td>
<td>1.44</td>
</tr>
<tr>
<td>$C_2$</td>
<td>1.92</td>
</tr>
<tr>
<td>$C_\mu$</td>
<td>0.09</td>
</tr>
<tr>
<td>$\sigma_k$</td>
<td>1.0</td>
</tr>
<tr>
<td>$\sigma_\epsilon$</td>
<td>1.3</td>
</tr>
</tbody>
</table>

12.3.3 Boundary conditions

The simulations are transient in nature to obtain time-continuous information of the gas-solid hydrodynamics inside the dryer. At the high gas velocities investigated, the flow is expected to be turbulent and a Reynolds-averaged approach is taken. The turbulence model used is the standard $k$-$\epsilon$ with standard wall functions. The turbulent intensity is assumed to be 5% of the inlet flow. Isothermal conditions are assumed throughout. At the outlet of the dryer, atmospheric pressure is imposed. A no-slip wall boundary condition is applied for the gas phase, while for the solids phase a free-slip wall boundary condition is used. It is noteworthy to mention that Reuge et al. [2008] reported that both free-slip and partial-slip wall boundary conditions give almost identical results for Geldart B particles in a fluidized bed.

12.3.4 Numerical procedure

A finite volume method, capable of handling complex geometries, is applied. The discretization of the convective fluxes is first-order upwind. A first-order implicit unsteady formulation using the Phase-Coupled SIMPLE algorithm [Vasquez and Ivanov 2000] is used to solve the equations. Three-dimensional (3D) simulations were performed, as it is necessary to obtain an accurate picture of the hydrodynamic flow patterns inside the dryer.

12.4 Problem description

A schematic representation of the fluidized bed dryer, i.e. the ConsiGma™, is shown in figure [12.1]. It is important to note that the fluidized bed dryer is a six-segmented system. Only one sixth of the total volume is used for the simulations, corresponding to one of the segments. An axisymmetric section is simulated to avoid high computational time without compromising on the intrinsic flow details. The perforated plate keeps the granules (particles) on the freeboard (see zone 1) without falling into the zone under the plate, while at the same time it allows for the free flow of gas (air) through the inlet into...
the dryer.

The mesh is built in ICEM CFD® software and consisted of $1.53 \times 10^6$ polyhedral cells, based on a mesh dependency check (results not shown). The advantages that polyhedral meshes have shown over some of the tetrahedral or hybrid meshes is the lower overall cell count, almost 3-5 times lower for unstructured meshes than the original cell count. The size of grid was refined in the region close to inlet, outlet, and walls where a larger gradient in pressure and/or velocity is expected. The entire fluid domain can be seen in figure 12.2 while figure 12.3 shows the individual domain for a better understanding of the geometry. Similar to the real scenario, there are two inlets namely, pressure inlet from the bottom and mass flow inlet (from the top) and a single top outlet. The gravitational force acts in the negative $y$-axis. Each adjacent fluid domain is connected through interfaces. In reality, the dryer is filled with particles for a certain period, i.e. the filling period $t_{fil}$, which is followed by a pure drying period (i.e. no filling).

12.5 Results & discussion

In the first stage, only gas-phase simulations were performed. The total volumetric flow rate from the bottom inlet is $360 \, \text{m}^3/\text{h}$. As the investigated flow domain (chamber) is one-sixth of the original volume, the mass flow rate (for one simulating chamber) at the bottom was accordingly calculated to be $0.02 \, \text{kg/s}$. The simulation was started in transient mode with a step size of 0.001 s, and as the solution reached convergence, it was shifted to steady-state. For a proper visualization of the flow profiles, three planar sections namely, plane 1, plane 2 and plane 3, perpendicular to each other along the $XY$-axis, were made in the
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Figure 12.2: Mesh of the entire fluid domain, i.e. one segment of the six-segmented drying unit of the ConsiGma\textsuperscript{TM}

Figure 12.3: Details of the mesh of the entire fluid domain
12.5. Results & discussion

geometry as shown in figure \[12.4\].

The steady-state profiles of the gas velocity magnitude for plane 1 and plane 2 are shown in figure \[12.5\]. As expected, the distribution of the gas velocity is uniform through the perforated plate. In the beginning, only gas-phase simulations were performed for a grid independency study and to see the stability of the numerical solution. Note that the top outlet is exposed to atmospheric pressure. However, a slight pressure difference at the bottom can be observed due to the presence of the porous plate.

From the gas-phase converged solution, the solid particles were added into the flow domain. In the experimental case, the solids are allowed to drop from the top inlet by gravity. However, this was impossible to achieve through numerical simulation as the solution became extremely unstable. It was therefore decided to already add an equivalent amount of solids in the fluidized bed. For this, a solid volume fraction of 0.1 which amounts to a mass of solid particles of 1 kg was patched in the solids inlet (Zone 1 in fig. \[12.1\]) at any time. The particle diameter and density were assumed to be 800 μm and 1,500 kg/m³ respectively. With this, it is assumed that once the fluidization starts the hydrodynamic profile of the simulation would closely mimic the real case scenario. The simulation was started in transient with a step size of 0.0001 s. With such a sufficiently low time step, the solution progressed well in the beginning. As expected, the fluidization slowly starts and thereby the solids start getting unpacked and begin to fluidize in the bed. The profile of the solids velocity (for plane 1) at 0.1 s is shown in figure \[12.6\] where it can be seen that the air velocity tries to carry the solid powders towards the higher zones of the dryer. However, some solid powders are observed to be slowly entrapped in thin layers along the perforated plate, at the initial stage of flow (Fig. \[12.7\] which could be detrimental to the stability of the numerical solution. In spite of this behaviour, the simulation
Chapter 12. CFD to study the fluidization pattern

Figure 12.5: Steady-state profile of the gas velocity magnitude for plane 1 and 2

was continued keeping the same time step size.

Figure 12.8 shows the solids velocity profile inside the bed at 0.5 s in plane 1. The arrow indicates a recirculation pattern caused by the air containing the solid particles. Since the solid phase is denser than air, the particles recirculate slower. At the bottom, some solids are still observed to be entrapped by the perforated plate. The fixed height of the domain with exit to atmospheric pressure causes air recirculation with a high momentum. Unfortunately, this behaviour led to the abortion of the simulation, as the higher momentum of air causes the escape of solid powder out of the domain.

In figure 12.9 and 12.10 the profiles of the volume fraction at 0.5 s are presented for different planes. It is obvious that after 5 s particles are fluidizing in the domain.

In short, the solid particles were seen exiting from the domain (Fig. 12.11) which is unacceptable when compared to the behaviour observed in the real case scenario. It must be noted that at any point of the simulation, it is expected that the amount of the solid granules in the fluidized bed is at least 1 kg. This was unfortunately not the case for the fluidized bed beyond 0.5 s in the simulation as the air entrained the solid particles out of the flow domain.
12.6. Conclusion

The gas-solid simulation, compared to the gas-only simulation presented new challenges. As such, several strategies are being considered to solve the present
Figure 12.8: The solids velocity profile inside the bed at 0.5 s in plane 1. Detailed view of the bottom of the bed at the right

problem without hampering the final objective of the simulation. It includes either increasing the height of the domain, or reducing the mass flow of air at the bottom inlet to maintain the quantity of solid powder in the domain. Another solution using a User Define Function (UDF) for a degassing boundary condition needs to be explored. This means that when the gas reaches the top boundary, the mass sink 'eats' only the air - or primary phase, while acting as a free-slip wall to solids so that the secondary phase cannot escape. Keeping this in mind, an efficient strategy needs to be formulated to continue with the simulation, without compromising realistic system behaviour.
12.6. Conclusion

Figure 12.9: Solids volume fraction inside the bed at 0.5s for different planes perpendicular to the distributor plate

Figure 12.10: Solids volume fraction inside the bed at 0.5s for plane 3
Chapter 12. CFD to study the fluidization pattern

Figure 12.11: Solid particles escaping from the domain
### Table 12.3: Notation

<table>
<thead>
<tr>
<th>Notation</th>
<th>Description</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{1,2}$</td>
<td>Empirical constants</td>
<td>-</td>
</tr>
<tr>
<td>$C_D$</td>
<td>Drag coefficient</td>
<td>-</td>
</tr>
<tr>
<td>$C_f$</td>
<td>Friction coefficient</td>
<td>-</td>
</tr>
<tr>
<td>$C_{\mu}$</td>
<td>Empirical constant</td>
<td>-</td>
</tr>
<tr>
<td>$d_p$</td>
<td>Particle diameter</td>
<td>m</td>
</tr>
<tr>
<td>$e_{ss}$</td>
<td>Solids-solids restitution coefficient</td>
<td>-</td>
</tr>
<tr>
<td>$g$</td>
<td>Gravitational acceleration</td>
<td>m/s²</td>
</tr>
<tr>
<td>$g_{o,ss}$</td>
<td>Radial distribution function</td>
<td>-</td>
</tr>
<tr>
<td>$G_{k,g}$</td>
<td>Rate of production of the turbulent kinetic energy</td>
<td>...</td>
</tr>
<tr>
<td>$I$</td>
<td>Unity tensor</td>
<td>-</td>
</tr>
<tr>
<td>$I_{2D}$</td>
<td>Second invariant of the deviatoric stress tensor</td>
<td>s⁻²</td>
</tr>
<tr>
<td>$k$</td>
<td>Turbulent kinetic energy</td>
<td>J/kg</td>
</tr>
<tr>
<td>$k_{\Theta_s}$</td>
<td>Diffusion coefficient of granular temperature</td>
<td>kg/s m</td>
</tr>
<tr>
<td>$P$</td>
<td>Pressure</td>
<td>N/m² or Pa</td>
</tr>
<tr>
<td>$Pr$</td>
<td>Prandtl number</td>
<td>-</td>
</tr>
<tr>
<td>$Re_s$</td>
<td>Relative Reynolds number</td>
<td>-</td>
</tr>
<tr>
<td>$t$</td>
<td>Time</td>
<td>s</td>
</tr>
<tr>
<td>$\vec{v}$</td>
<td>Velocity vector</td>
<td>m/s</td>
</tr>
<tr>
<td>$v_{t,s}$</td>
<td>Solids tangential velocity</td>
<td>m/s</td>
</tr>
<tr>
<td>$v_{r,s}$</td>
<td>Solids radial velocity</td>
<td>m/s</td>
</tr>
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#### Greek symbols

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta$</td>
<td>Interphase momentum exchange coefficient</td>
<td>kg/m³s</td>
</tr>
<tr>
<td>$\gamma_{\Theta_s}$</td>
<td>Collisional dissipation of energy</td>
<td>kg/m³s³</td>
</tr>
<tr>
<td>$\phi_{\Theta_s}$</td>
<td>Transfer of kinetic energy</td>
<td>kg/m³s³</td>
</tr>
<tr>
<td>$\varepsilon$</td>
<td>Turbulence dissipation rate</td>
<td>m²/s³</td>
</tr>
<tr>
<td>$\varepsilon_\iota$</td>
<td>Gas, solids volume fraction</td>
<td>-</td>
</tr>
<tr>
<td>$\varepsilon_{s,max}$</td>
<td>Solids packing limit</td>
<td>-</td>
</tr>
<tr>
<td>$\xi_s$</td>
<td>Solids bulk viscosity</td>
<td>kg/ms²</td>
</tr>
<tr>
<td>$\Theta_s$</td>
<td>Granular temperature of the solids</td>
<td>m²/s²</td>
</tr>
<tr>
<td>$\mu$</td>
<td>Shear viscosity</td>
<td>kg/ms</td>
</tr>
<tr>
<td>$\mu_{s,col}$</td>
<td>Collisional solids shear viscosity</td>
<td>kg/ms</td>
</tr>
<tr>
<td>$\mu_{s,fr}$</td>
<td>Frictional solids shear viscosity</td>
<td>kg/ms</td>
</tr>
<tr>
<td>$\mu_{s,kin}$</td>
<td>Kinetic solids shear viscosity</td>
<td>kg/ms</td>
</tr>
<tr>
<td>$\mu_t$</td>
<td>Turbulent viscosity</td>
<td>Pa s</td>
</tr>
<tr>
<td>$\rho$</td>
<td>Density</td>
<td>kg/m³</td>
</tr>
<tr>
<td>$\sigma$</td>
<td>Turbulent Prandtl number</td>
<td>-</td>
</tr>
<tr>
<td>$\tau$</td>
<td>Stress tensor</td>
<td>kg/ms²</td>
</tr>
</tbody>
</table>

#### Subscripts

<table>
<thead>
<tr>
<th>Subscript</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$g$</td>
<td>gas</td>
</tr>
<tr>
<td>$i$</td>
<td>gas/solid</td>
</tr>
<tr>
<td>$s$</td>
<td>solid</td>
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</table>
Chapter 12. CFD to study the fluidization pattern
PART V

Monitoring of a continuous drying process using a mass & energy balance
In part V the automatically collected in-line real-time univariate data is processed by means of both mass & energy balances. These balances are useful to monitor the drying process without the need for extra sensors.
Analysing drying unit performance in a continuous pharmaceutical manufacturing line by means of mass & energy balances


Abstract:
The current trend in the pharmaceutical industry to move from batch-wise to continuous production processes strengthens the need for monitoring and controlling the process in-line. The ConsiGma\textsuperscript{TM} continuous tableting line collects data of the different subunits in real-time, but these are generally not really used. In this chapter the data of the six-segmented fluidized bed dryer in the line are used for the development and evaluation of a mass and energy balance. The objectives are twofold: (1) prediction of the moisture content of the granules leaving the dryer solely based on the currently logged data and (2) prediction of the gas outlet temperature to check the mass balance. Once a validated system is established the gas temperature in different horizontal sections of the drying unit can be predicted. Calculations are also used to identify flows in the system and to propose alternative sensor locations. A calibration is performed in order to predict the evaporation rate. The balances were able to predict both the moisture content of the granules at the end of the drying process and the gas outlet temperature quite accurately. Combining the gathered information with the height of the bed in the fluidized bed this can be used to predict the gas temperature in different horizontal sections of the dryer. An extra sensor measuring the gas temperature and the humidity
at the wet transfer line would increase the accuracy of the calculations. An extra gas velocity sensor at the outlet would be useful to incorporate an extra supervision of the calculations.

## 13.1 Introduction

### 13.1.1 State of the art process monitoring and controlling in pharmaceutical industry

One recent trend in pharmaceutical manufacturing is the shift from batch-wise to continuous production processes, not only in the synthesis of small molecules [Plumb, 2005] [Cervera-Padrell et al., 2012], but also in formulation [Vervaet and Remon, 2005] [Leuenberger, 2001a]. The traditionally applied batch processes mostly rely on off-line post-process time-consuming and less efficient laboratory testing to evaluate the quality of the product. Continuous production processes, relying on in-line measurements and real-time adjustment of sensitive process variables would be a major step forward towards more efficient production routines. A batch is well defined, and as such it is easy to perform a quality assurance, since a batch can simply be accepted or rejected based on a quality assessment. But since quality is only checked after the process has ended in traditional manufacturing, it is impossible to control the process on the basis of such measurements. A bad batch is simply lost. However, monitoring the process during operation allows interfering during production (i.e. process control) which is more economical as the loss in off-spec product is limited [Plumb, 2005] [Leuenberger, 2001b]. A general problem within the pharmaceutical industry are the strict regulations. Once a process is approved by the regulatory authorities, it is generally accepted that it is almost impossible to change something in the way of processing without re-documentation and re-approval [Plumb, 2005]. The FDA intended to promote innovation by publication of the PAT guidance. An important concept is QbD, defined as 'a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management' [ICH, 2010].

The equipment to produce tablets in a continuous mode is to date limited. The ConsiGma™ continuous tabletting line (Collette™, GEA Pharma Systems, Wommelgem, Belgium) enables the production of tablets from powders in 20 minutes. It consists of the ConsiGma™ high shear granulator and fluidized bed dryer, combined with the GEA Courtoy MODUL P rotary tablet press [GEA, 2010]. Lödige Process Technology has the CWG line which is a continuous wet granulation line and is also a complete system from raw material dosing till tableting [lod, 2010] (Chapter 2 section 2.3). In this work, the focus
13.1. Introduction

is on the continuous fluidized bed drying system of the ConsiGma™ continuous tableting line. Real-time on-line measurements are continuously logged. The logged data will be processed using a mass and energy balance in order to monitor the process in real time.

Several in-line measurement tools are available for the monitoring and control of pharmaceutical manufacturing processes. In-line measurements provide real-time data about a process, and can thus be used as inputs to control the process operation. Process analyzers can be divided into the univariate (such as temperature, pressure, gas velocity, etc.) and multivariate process measurements, which provide biological, physical, chemical, etc. characteristics of the material. The determination of the moisture content of solids during processing can be achieved using several techniques. However, a lot of techniques that are currently available are not appropriate for use under harsh process conditions. Time domain reflectometry and transmissometry, capacitance probes, electrical resistance measurements, microwave spectrometry are all sensitive to the bulk density of the monitored system [Portoghese et al., 2008]. Other techniques are not able to measure the moisture content accurately due to the presence of hydrogen atoms in any other substance than water. This is the case for Nuclear Magnetic Resonance (NMR) or neutron absorption. Besides moisture content, NIRS is also able to provide information related to particle size. An advantage of the technique is its non-destructive nature. Moreover, NIRS is available against a reasonable cost, is fast, and is relatively immune to changes in bulk density caused by granule growth [Frake et al., 1997] [Sarraguça et al., 2010]. Frake et al. [1997] described NIRS as an in-line tool to obtain the granule moisture content and particle size of a fluidized bed granulation process. It allows modification of process conditions during operation as well as end-point identification. However, attention should be paid to prevent the formation of solid deposits on the probe [Portoghese et al., 2008]. Chablani et al. [2011] used NIRS to measure the granules’ moisture content produced using the ConsiGma™. The application of NIRS as a PAT tool during continuous manufacturing is promising. Besides NIRS spectroscopy, several other PAT tools have been examined for moisture content assessment during processing of pharmaceutical solids. Portoghese et al. [2008] described the use of triboelectric probes to measure solid moisture content during fluidization. Being inexpensive, very sensitive probes without requiring any maintenance makes them attractive. Microwave Resonance Technology (MRT) has been implemented in fluidized bed dryers and provides precise and accurate results for the granule moisture content independent of product density [Buschmüller et al., 2008]. The technique was validated using reference methods (Loss On Drying (LOD), Infra-red light) and Karl Fisher titration. Wang et al. [2009] used ECT for the on-line measurement of the solid moisture content in a batch.
Chapter 13. Monitoring by using mass & energy balance

fluidized bed dryer. The measured value can be used for implementation of a closed-loop control strategy. Including in-line monitoring obviously requires extra probes and software for data processing, and as such extra costs. In some cases the pharmaceutical production equipment already has sensors in place, without using them for specific monitoring or control tasks. Hence, with no extra cost these data can potentially be sufficient for monitoring and controlling the process, hereby guaranteeing product quality.

13.1.2 Error propagation of measured model input variables into model output variables

Any measured variable is prone to measurement errors and contains an inherent uncertainty. This will have an impact when using these measurements in further calculations (e.g. mass balance checks, computing control actions, etc.). An error propagation enables the operator to quantify the cumulative effect of errors in the input data. Another option would be the use of more accurate sensors to minimise the error on calculated output. Moreover, the quest for more accurate sensors results often in more expensive sensors, which is of course important in a production process.

In control applications, one can use data reconciliation techniques in order to reduce the impact of erroneous data [Vachhani et al., 2005], whereas uncertainty propagation can be used for calculations based on the raw data. Error propagation is a methodological tool to quantify the uncertainty on a model output, given the source of uncertainty and its specifications (e.g. variance) are known. Typically this is done by construction of output uncertainty boundaries. The uncertainty on parameters and variables is hereby propagated to the output. Different methods are available depending on the model (non-)linearity. Simple linear models can use classical error propagation techniques. More complex models can make use of linear error propagation or differential analysis. Uncorrelated inputs for the uncertainty propagation have an advantage as the covariance can be discarded from the evaluation [Helton and Davis, 2003]. For complex non-linear models, a Monte Carlo based method can be used [Helton and Davis, 2003]. The latter method uses repeated calculation of the output, while varying the input [Anderson, 1976]. In a first step, all sources of uncertainty should be identified, whereas in the next step these uncertainties should be quantified [Herrador and González, 2004]. The uncertainty limits can be based on the measurement error of the used sensors, or by using previously quantified confidence intervals. The input is then randomly selected from its error PDF using a sampling scheme (e.g. random or LHS-sampling). The calculated outputs will also be distributed, which allows defining an output uncertainty distribution. The drawback of the Monte Carlo method is the number of iterations (i.e. Monte Carlo shots) that should be carried out (in the order
of hundreds to thousands depending on the number of sources of uncertainty considered) before the variance of the output distribution is known accurately [Anderson, 1976]. This makes the technique computationally expensive, especially for complex models.

13.2 Problem statement & objectives

As indicated in section [13.1.1] process monitoring is mostly done by using off-line time-consuming measurements or by implementation of extra sensors. The automatically collected in-line real-time univariate data is nowadays logged, but is typically not used for process monitoring and/or controlling.

The main objective of this work is the use of a combined mass and energy balance to estimate the moisture content of granules at the end of the drying process in a six-segmented fluidized bed dryer, being part of a full continuous pharmaceutical from powder-to-tablet manufacturing line. The energy balance is made to compare the experimental gas outlet temperature with the calculated one as a validation of the balances. In the calculations error propagation is accounted for in order to consider uncertainty. Once the balances are validated a prediction of the gas temperature in different horizontal sections of each drying segment can be made. Furthermore, the study can be used to identify errors in the system and to propose an alternative sensor location.

13.3 Materials & methods

13.3.1 Experimental data collection

The automatically in-line logged data of the ConsiGma™ are available from two different production lines, one located at the Laboratory of Pharmaceutical Process Analytical Technology (Ghent University, Ghent, Belgium) and the other located at GEA Pharma Systems (Wommelgem, Belgium). Several datasets were available but only the results of two datasets (Table 13.1) are presented. The results of other datasets were similar and did not provide extra information, and were therefore not included.

For dataset A, only one segment was filled with wet granules, this data was

<table>
<thead>
<tr>
<th></th>
<th>System</th>
<th>Remark</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Ghent</td>
<td>Only one segment is filled - Calibration dataset</td>
</tr>
<tr>
<td>B</td>
<td>Wommelgem</td>
<td>Dataset with the full operating system</td>
</tr>
</tbody>
</table>

Table 13.1: Overview of the data used in the mass/energy analysis

collected at the system located in Ghent. The formulation of the dry premix
consisted of theophylline anhydrate (Farma-Quimica sur SL, Malaga, Spain) (30%, w/w), lactose monohydrate 200 M (DMV fonterra) (67.5%, w/w) and PVP (Kollidon 30, BASF, Burgbernheim, Germany) (2.5%, w/w). This premix was granulated with a 0.5% (w/v) SLS solution (Fagron, Waregem, Belgium) in distilled water at a barrel temperature of 25°C. SLS was added to improve the wettability of the dry premix. The screw speed was held constant at 950 rpm, the powder mass flow at 17.5 kg/h, the liquid mass flow at 32 g/min. The ConsiGma™ standard screw configuration was used. The data were continuously logged for several hours (during 8h), whereby the dryer is loaded with wet granules at certain moments, and is empty in between. One single experiment is defined between two periods where the dryer is empty, and an example is provided in figure 13.4. These experiments are executed over a period of several days (each day one run of around 8h).

Dataset B contains data of the full operating system, where all six segments were continuously filled with wet granules. As such a real-time situation is mimicked. The data are collected from the system situated at GEA Pharma Systems. The formulation consisted of two active ingredients (a slightly soluble API in a high dose and a soluble API in a lower dose), powdered cellulose, maize starch, pregelatinized starch and sodium starch glycinate. The dry ingredients were granulated with distilled water at a barrel temperature of 25°C and a screw speed of 900 rpm. The powder mass flow was kept at 20 kg/h, and the liquid mass flow at 50 g/min. During tableting magnesium stearate was added as lubricant. Johnson & Johnson (Janssen-Cilag, Italy) delivered all ingredients for the production.

For both datasets the residual moisture content after drying was measured using Karl Fisher titration using a V30 volumetric KF titrator (Mettler Toledo, USA). Prior to the titration of the granules, they are stirred and dissolved (methanol (Hydranal, Sigma Aldrich, Germany)) during 5 minutes. As Karl Fisher titration measures the combination of the bound water and the free water, the moisture content of the dry premix should be subtracted from the measured data to coincide with the calculated moisture content based on the mass balance (referred to as the corrected value ($X_{KF,corr}$)). For dataset A the moisture content at the end of the drying process ($X_{end,KF}$) is measured for each experiment, so just before the dryer is emptied.

### 13.3.2 Processing of experimental data

The experimental data were processed off-line, i.e. the data were extracted from the production line via a SCADA system and made available in Excel worksheets. The mass and energy balances were developed in Matlab®, and the data processing was not done on a real-time base. As the data is available in real-time, and considering that the calculation time is very short, in a later
stage the data processing can almost certainly be executed during the operation of the drying process.

### 13.3.3 Error propagation via Monte Carlo simulation

The error propagation is performed for the dataset where all six segments of the dryer are filled (dataset B). The sampling of the input for the Monte Carlo simulation is done with Sobol sampling \[^{[Sobol'] 1979}\]. In total 21 uncertain variables, which are continuously measured in the six-segmented dryer, are in a first step identified as uncertain and thus part of the error propagation. This includes measurements of temperature, pressure, gas flow rate, etc. An uncertainty level of 2% is selected as measurement error, so the \([P - 1\%, P + 1\%]\) (with \(P\) the measured value). Two extra uncertain inputs are included in the error propagation, which are the parameters of the calibration, performed in section 13.4.2 for reasons explained later on. For these inputs the 95% confidence interval of the coefficients are calculated, which is given by:

\[
[c_i - w_i, c_i + w_i]
\]  

(13.1)

where \(c_i\) is a parameter of the submodel and \(w_i\) is the half-width of a 2-sided confidence interval based on a specified level of significance, \(\alpha\). \(w_i\) is calculated according to:

\[
w_i = t_{df}^\alpha se_i
\]

(13.2)

with \(t_{df}^\alpha\) the \(t\)-value of the student's \(t\) distribution with \(df\) degrees of freedom for error and \(se_i\) is the standard error for the \(i^{th}\)-coefficient. A sample size of 25,000 is used for the Monte Carlo simulation. The generated output is analysed by calculating the mean, the standard deviation and the 95% confidence interval. This is done for the moisture content at the end of the drying process, as well as for the outlet gas temperature.

### 13.4 Results

#### 13.4.1 Deriving the energy and mass balance for the fluidized bed dryer

During operation of the ConsiGma\textsuperscript{TM} 61 univariate variables are continuously measured and logged. The available information includes pressure, temperature, flow rate, humidity, etc. for the different compartments of the continuous line. During fluidized bed drying of wet granules, several processes (evaporation, conduction/convection, heating, filtration) take place, which lead to a decrease of the drying air temperature \((T_g)\) in the dryer and an increase of the
humidity of the incoming drying air ($RH_g$) while passing through the drying unit. Given the measured variables and knowing the processes qualitatively, it should be possible to predict the moisture content of the outgoing drying air. This allows prediction of the average drying rate as well. A complete mass and energy balance is thus set up for the six-segmented fluidized bed dryer. This requires in a first step the definition of the physical properties of the in- and outgoing gas, liquid and solid streams of the subprocess (i.e. the six-segmented dryer), where the full process can be seen as the whole from-powder-to-tablet manufacturing line. The inputs, outputs and initial conditions of the subprocess should be known and one should be able to quantify them. Once these balances are closed and validated under a set of relevant experimental conditions, they can be used to determine the final moisture content of the granules and the temperature profile of the drying air in the dryer. For the latter each drying cell is divided in several horizontal sections. The combination of the temperature profile in each drying cell with knowledge about the trajectory followed by granules throughout the dryer, which can be investigated by a CFD-model (Part IV), is useful to calculate the drying behaviour of particles. A combination of the description of the spatial behaviour of the granules with a PBM-model would be very useful to understand the process in the fluidized bed dryer in more detail (Part III). Figure 13.1 presents the inlets and outlets of the dryer unit.

**Mass balance**

The moisture content of the wet granules, introduced in the dryer, can be calculated based on the amount of liquid and solids introduced in the granulator as the entire mass is transported from the granulator to the drying unit. The humidity, temperature and pressure of the incoming and outgoing gas are measured (Fig. 13.1), which enables to calculate the amount of water in the gas entering and leaving the dryer. The resulting steady-state mass balance is given by:

$$m_{wat,g,inlet} + m_{wat,gran,0} + m_{wat,g,WTL} = m_{wat,g,outlet} + m_{wat,gran,end} \quad (13.3)$$

where $m_{wat,g,inlet}$ and $m_{wat,g,outlet}$ are the mass of water in respectively the incoming gas stream and the outgoing gas stream, $m_{wat,gran,0}$ and $m_{wat,gran,end}$ are the mass of water in respectively the incoming (initial moisture content of the granules) and outgoing granules (resulting moisture content of the granules at the end of the drying process) and $m_{wat,g,WTL}$ represents the mass of water in the gas entering the dryer via the wet transfer line together with the wet granules (Fig. 13.1). The difference between the water content of the gas entering and leaving the dryer should theoretically equal the amount of water
13.4. Results

Figure 13.1: Boundaries of the mass and energy balance for the dryer unit. On the left, a representation of the way the fluidized bed dryer system operates is shown, supplemented with the measured variables. The question mark indicates that these 2 variables are not measured. On the right the mass balance is schematically represented.
evaporated during drying \( (m_{\text{vap}}) \). As it is a continuous drying process, the unit of these variables is per unit of time (kg/h). The amount of water in the incoming and outgoing gas and the gas of the wet transfer line is calculated based on RH\(_g\), \( T_g \) and \( P_g \). The relative humidity (RH\(_g\)) (a measured variable) in % is expressed as:

\[
RH_g = \frac{e_w}{e_w^*} \times 100 = \frac{\rho_w}{\rho_{w,s}} \times 100
\]  
(13.4)

with \( e_w \) the partial pressure of water vapour (Pa), \( e_w^* \) the saturated vapour pressure of water (Pa), \( \rho_w \) the vapour density (kg/m\(^3\)) and \( \rho_{w,s} \) the vapour density at saturation (kg/m\(^3\)). The saturated vapour pressure of water (Pa) can be calculated using [Landolt-Börnstein]:

\[
e_w^* = \frac{e^{77.3450+0.0057T_g-7235/T_g}}{T_g^{8.2}}
\]  
(13.5)

with \( T_g \) the dry bulb temperature of the moist air (K) (fitted to the experimental data of Landolt-Börnstein (1960)). Another alternative relation, which also takes the pressure into account, was presented by [Buck 1981]:

\[
e_w^* = 6.1121\left(1.0007 + 3.46 \times 10^{-6} P_g\right) e^{17.502 T_g/(240.97+T_g)}
\]  
(13.6)

where \( P_g \) is the absolute pressure in hPa. This last relation is used for the calculations. Using the ideal gas law \( \rho_w \) can be calculated:

\[
\rho_w = \frac{e_w m}{RT_g}
\]  
(13.7)

with \( R \) the universal gas constant (J/mol/K) and \( m \) the molar mass of water (18.01528 g/mol). The water content of gas \( m_{\text{wat,g}} \) (kg/h) can be calculated by:

\[
m_{\text{wat,g}} = \rho_w V_g
\]  
(13.8)

with \( V_g \) (m\(^3\)/h) the gas flow rate.

The humidity and the gas temperature of the gas entering the dryer via the wet transfer line are not measured. However, it is assumed that the humidity is high as this gas flow is in contact with the granulator. The temperature is assumed to be a normal ambient temperature. The assumed corresponding values were taken as 30% for the RH\(_{g,WTL}\) and 20°C for \( T_{g,WTL} \).

The total gas flow rate leaving the dryer is calculated based on conservation of mass. As the amount of air entering and leaving the dryer are equal (in kg/s), this amount can be used to calculate the gas flow rate leaving the dryer as the relative humidity RH\(_{g,\text{Outlet}}\), the gas temperature \( T_{g,\text{Outlet}} \) and the pressure \( P_{g,\text{Outlet}} \) of the gas flow leaving the dryer are measured.
13.4. Results

The partial pressure of dry air (Pa) is calculated by:

\[ P_{DA} = P_g - e_w \]  

(13.9)

The density of humid air (kg/m\(^3\)) is given by:

\[ \rho_{HA} = \frac{P_{DA}/R_d + e_w/R_v}{T_g} \]  

(13.10)

with \(R_d\) the specific gas constant for dry air (287.058 J/kg/K) and \(R_v\) the specific gas constant for water vapour (461.495 J/kg/K). The knowledge of the density of humid air enables one to calculate the mass of humid air \((m_{HA})\):

\[ m_{HA} = \rho_{HA} V_g \]  

(13.11)

The mass of dry air is computed by:

\[ m_{DA} = m_{HA} - m_{wat,g} \]  

(13.12)

An overview of the different equations used to calculate \(m_{wat,g}\) and \(m_{DA}\) is given in table 13.2.

**Energy balance**

While passing the drying unit the temperature of the gas decreases. When the complete energy balance is made, it should be possible on the one hand to calculate the gas temperature at the outlet taking all sinks of energy into account. This calculated value can be compared with the measured value in order to check the accuracy of the balance. On the other hand, this obtained knowledge can be used to determine the spatial profile of the temperature in a segment of the dryer. This information is useful when the trajectory of granules into a segment of the dryer is known. The combination of both yields the temperature profile that granules undergo during drying. Several heat sinks can be distinguished: energy required to evaporate the water in the granules, energy loss through the wall of the dryer, energy required to heat the granules entering the dryer and energy loss due to passing the filter.

1. Energy required for the evaporation of water from the wet granules: The energy required to evaporate water \((Q_{vap} \text{ (kJ/h)})\) is calculated by:

\[ Q_{vap} = \Delta H_{vap} m_{vap} \]  

(13.13)

with \(\Delta H_{vap}\) the heat of evaporation (2257 kJ/kg).

2. Energy loss through the wall of the dryer: The wall of the dryer consists...
Table 13.2: Schematic overview of equations to calculate $m_{\text{H}_2}$ and $m_{\text{O}_2}$.
of stainless steel, which is a good conductor of heat. As the dryer is not insulated, some heat will be lost through the wall. To determine the amount of energy lost through the wall, the dryer was split into three parts. One part under the distributor plate, where it is assumed that the temperature is equal to $T_{g,\text{inlet}}$, one part in the middle, at the level of the six segments, and one part where all six segments are joining again. As the temperature of the gas is measured in each cell separately at only one location, it is assumed that the temperature equals these values in the entire segment. For the upper part of the dryer the mean of the temperature in the six cells is used.

For each part the heat transfer is calculated using an overall heat transfer coefficient, which takes the conduction through the wall and the convection outside the dryer into account. It is assumed that there is no barrier inside the dryer for heat transfer, meaning that the temperature at the wall equals the temperature in the middle of the dryer. As the gas flow inside the dryer is high, and since there is a lot of turbulence, this assumption is reasonable. At the outer side of the wall free convection occurs with air as fluidum (Fig. 13.2).

The overall heat transfer coefficient $U$ (W/m$^2$/K) is calculated by:

$$U = \frac{1}{1 + 1/h + \Delta x/\lambda} \quad (13.14)$$

with $h$ the convective heat transfer coefficient (W/m$^2$/K), $\Delta x$ the thickness of the wall (m) and $\lambda$ the thermal conductivity (W/m/K). It is assumed that $h$ and $\lambda$ equal respectively 8 W/m$^2$/K and 16.3 W/m/K.

The heat transfer due to conduction and convection ($Q_{\text{con}}$) can be calculated by:

$$Q_{\text{con}} = U A \Delta T_{\text{con}} \quad (13.15)$$
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with $A$ the surface area of the wall ($m^2$) and $\Delta T_{\text{con}}$ the temperature difference between the inside and the outside of the dryer.

3. Energy required for heating up the granules: Since the granules originating from the granulator are at a lower temperature than the drying air temperature, 'as such' some energy is required to heat them up. Wet granules consist of water and solid material, and both need to be heated. The energy required to heat up material ($Q_{\text{heat}}$ (kJ/h)) is:

$$Q_{\text{heat}} = m_m c_{p,m} \Delta T_{\text{heat}}$$  \hspace{1cm} (13.16)

with $m_m$ the mass of the material being warmed, $c_{p,m}$ the specific heat of the material (kJ/kg/K) and $\Delta T_{\text{heat}}$ the difference between the temperature of the particles originating from the granulator and the temperature in the cell. Here, it is assumed that the temperature of the particles at the end of the drying process equals the temperature in the cell. The specific heat of water $c_{p,\text{wat}}$ is calculated by Perry and Green [2007]:

$$c_{p,\text{wat}} = \frac{(2.7637 \times 10^2 - 2.0901 T + 8.1250 \times 10^{-3} T^2 - 1.4116 \times 10^{-5} T^3 + 9.3701 \times 10^{-9} T^4)/M_w}{1,000} \hspace{1cm} (13.17)$$

with $M_w$ molecular weight of water ($18.015 \times 10^{-3}$ kg/mol) and $T$ the temperature in K. The temperature to calculate the specific heat of water is assumed to equal the temperature of the granulator barrel. The specific heat of the solids is assumed to equal $1.252 \times 10^{-3}$ kJ/kg/K.

4. Energy loss due to passing the filter: Depending on the experimental conditions a lower or higher pressure difference sets in over the filter. Due to this increasing pressure difference the energy ($Q_{\text{fil}}$ (kJ/h)) needed to pass the gas through the filter increases.

$$Q_{\text{fil}} = \Delta P_{\text{fil}} V_g$$  \hspace{1cm} (13.18)

with $\Delta P_{\text{fil}}$ the pressure difference over the filter. Two filters are being passed by the gas and $V_g$ is the volume of the gas passing the filter (gas flow rate) (m$^3$/h).

5. Complete energy balance: The total energy required during drying is the sum of $Q_{\text{vap}}$, $Q_{\text{con}}$, $Q_{\text{heat}}$ and $Q_{\text{fil}}$ (Table 13.3). The sum of the four energy sinks should balance with the energy that is released due to the cooling of the gas from the inlet temperature to the outlet temperature (source of energy):

$$Q_{\text{air}} = m_{\text{air}} c_{p,\text{air}} \Delta T_{\text{air}}$$  \hspace{1cm} (13.19)
13.4. Results

with $m_{\text{air}}$ the mass of air being cooled during drying, $c_{p,\text{air}}$ the specific heat of air (kJ/kg/K) and $\Delta T_{\text{air}}$ the temperature difference between the incoming and outgoing gas.

The energy balance can be used to calculate the temperature at the outlet of the dryer based on the amount of evaporated water, the temperature at the inlet and the temperature in each cell of the dryer.

<table>
<thead>
<tr>
<th>Table 13.3: Schematic overview of the energy balance</th>
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<tr>
<td>Sinks</td>
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<td>-------</td>
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<td>$Q_{\text{con}}$</td>
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<tr>
<td>$Q_{\text{heat}}$</td>
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<tr>
<td>$Q_{\text{fil}}$</td>
</tr>
<tr>
<td>Sources</td>
</tr>
</tbody>
</table>

13.4.2 Dataset A

Dataset A consists of several runs of experimental data, each collected on a distinct day. During these runs the gas inlet temperature is not constant. Figure 13.3 presents an example of the inlet gas temperature $T_{g,\text{inlet}}$ dynamics used for one day of experiments.

The humidity data of the drying air at the inlet $RH_{g,\text{inlet}}$ are presented in figure 13.4. The dependency of the humidity of the drying air on temperature is clearly visible. The higher the drying air temperature, the lower the corresponding value for the relative humidity. In figure 13.4 the measured relative
humidity at the outlet $RH_{g,\text{outlet}}$ is presented. The peaks coincide with the time when the dryer unit is filled with wet granules. Each peak corresponds to one experiment.

The calculated mass flux of water in the gas phase at the inlet $m_{\text{wat,g,IN}}$ (sum

![Graph showing RHg,inlet and RHg,outlet](image)

**Figure 13.4:** $RH_{g,\text{inlet}}$ (Left) and $RH_{g,\text{outlet}}$ (Right) for dataset A. The humidity at the inlet is changing due to the change in $T_{g,\text{inlet}}$. An example of one experiment is indicated in the figure of $RH_{g,\text{outlet}}$. The humidity of the gas is increasing when a drying cell is filled with wet granules of $m_{\text{wat,g,inlet}}$ and $m_{\text{wat,g,WTL}}$) and outlet are presented in figure 13.5. The water content of the gas at the outlet is remarkably higher compared to the inlet, which is to be expected as the difference between both should represent the evaporation rate $m_{\text{vap}}$. However, when the dryer unit is empty between the experiments (e.g. time points 1.8 to 2 in figure 13.4), the calculated mass of water of the gas at the outlet and inlet should normally be equal. This appears not to be the case and an 'offset' (difference between $m_{\text{wat,g,IN}}$ and $m_{\text{wat,g,outlet}}$ for an empty dryer) is observed. Moreover, this offset seems to be correlated with the gas inlet temperature $T_{g,\text{inlet}}$. For the periods where the dryer is empty, the offsets were calculated and plotted against $T_{g,\text{inlet}}$ (Fig. 13.5).

Based on this a relation between the offset and $T_{g,\text{inlet}}$ is established. This relation could be established both for the different runs together, i.e. taking all data points (further referred to as case 1), as well as separately, i.e. for each run another relation (further referred to as case 2) (i.e. for each day (run) another relation is made between the offset and the gas inlet temperature). The result of the linear regression for case 1 is presented in figure 13.5 and results in:

$$\text{offset} = 0.0187 T_{g,\text{inlet}} - 0.3763 \quad (13.20)$$

with $[0.0175 0.0199]$ and $[-0.4416 - 0.3111]$ the confidence intervals (significance level of 5%) for the coefficients. The $R^2$ of the linear regression equals

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Figure 13.5: $m_{\text{wat,g,IN}}$ and $m_{\text{wat,g,outlet}}$ (Left) for dataset A, where the difference between both should be approximately zero when the dryer is empty. On the right figure the offset (difference between $m_{\text{wat,g,IN}}$ and $m_{\text{wat,g,outlet}}$ for an empty dryer) in function of the gas inlet temperature $T_{g,\text{inlet}}$ is presented. The offset is calculated based on the calibration dataset. The linear regression for case 1, where the data points for all runs are used, is shown.

0.95 (Case 1), the $R^2$ for the linear regression for the independent runs (Case 2) varied between 0.87 and 1. Performing a linear regression for the different runs separately allows to calculate the moisture content of the granules at the end of the drying process more accurately for each experiment, however, the drawback is that the calibration is based on less data points. The offset seemed to be a general problem for all collected datasets (of which only two are discussed), no matter in which system the experiments were performed (cfr. Ghent or Wommelgem). As such, it was decided to perform one calibration (Case 1) and use the linear regression for all datasets. But both cases (Case 1 and 2) are used for dataset A in order to compare the results. The cause for this offset remains unclear.

Based on the liquid and solid addition to the granulator the moisture content of the granules entering the dryer can be calculated. Using the calculated evaporation rate, based on the properties of the gas entering and leaving the drying unit, the moisture content of the granules leaving the dryer is computed. Here, the evaporation rate is corrected for the above discussed offset. As one of the objectives is to monitor the moisture content of the granules leaving the dryer by using the real-time in-line measurements, it is important that the calculated moisture content is close to the moisture content measured by Karl Fisher titration (validation). The results are presented in table 13.4 for case 1 and 2 ($X_{\text{end,cal,1}}$ and $X_{\text{end,cal,2}}$ respectively). $X_{\text{end,KF}}$ and $X_{\text{end,KF,corr}}$ are respectively the mean of three Karl Fisher measurements and the corrected value. The standard deviation ($\sigma_{X_{\text{end,KF}}}$) is also calculated and listed in table.
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13.4 The experiments with an overprediction are indicated in bold, whereas the predictions with an underprediction are given in italics. The best result (Case 1 or 2) for each experiment is underlined. The scenario with the different linear regressions yields the best result. However, as the linear regression will be used for all datasets, collected on both the system in Ghent as in Wommelgem and operating in such a way that only one segment is filled with wet granules or for the full operating system, the linear regression of case 1 will be implemented in the mass and energy balance. This regression is more generally applicable as it is based on more data points, collected over several days.

13.4.3 Dataset B

When collecting dataset B, the full dryer equipment is used in a continuous operation (6 h run), and the set of process parameters are not changed during operation. Figure 13.6 presents the measured temperature at the inlet $T_{g,inlet}$ and shows that after the initial dynamic behaviour the temperature is close to the set point of 45°C.

The measured outlet temperature $T_{g,outlet}$ is obviously lower than $T_{g,inlet}$, as well as the calculated mean temperature over the six segments ($T_{g,mean}$) (Fig. 13.7). The gas temperature measured in the six cells is also added in figure 13.7. The gas temperature decreases in the cell when wet granules are filled in the segment. During drying the gas temperature increases again as less and less energy is required for evaporation of water. Based on these measurements the process in each segment can be followed, however, the moisture content of the drying air is not measured in each cell. The latter would provide extra information about the process and could be used to detect problems during operation. At the outlet a convolution of two sinusoidal functions with different frequencies and amplitudes can be observed for $T_g$, and an explanation for this behaviour is mentioned in the discussion (Section 13.5.1). However, it is noteworthy that it took almost 1.5 h until $T_{g,outlet}$ reached a steady-state value.

Figure 13.6: $T_{g,inlet}$ for dataset B. After a short transient the set point is reached.
Table 13.4: Moisture content of the granules at the end of the drying process for dataset A (Bold indicates an overprediction, italics an underprediction, underlined the best result). $X_{end,KF,corr}$ represents the corrected value (dry premix correction), which is the target for our calculations. $X_{end,cal,1}$ and $X_{end,cal,2}$ are the calculated values for respectively case 1 and case 2.

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<th>$\sigma_{X_{end,KF}}$</th>
<th>$X_{end,KF,corr}$ (%)</th>
<th>$X_{end,cal,1}$ (%)</th>
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of around 28°C (dynamic behaviour). At the early start it is obvious that the drying air temperature at the outlet is higher, as there is only one segment in which particles are being dried. Only after all segments have been filled with particles, the drying air temperature could reach a dynamic steady-state. Also, at the end of the 6 hour process the drying air temperature increased again, as the experiment was stopped and particles were no longer filled in the dryer. The drying air temperature measured in each segment follows a cyclic behaviour. The six-segmented dryer is operating in a continuous way, i.e. one segment is filled, while in the other segments granules are being dried. $T_{g,\text{mean}}$ is remarkably higher compared to $T_{g,\text{outlet}}$, which could be related to the location of the sensors, and/or the presence of filters between the drying unit itself and the outlet.

The measured relative humidity at the inlet ($RH_{g,\text{inlet}}$) and at the outlet ($RH_{g,\text{outlet}}$) is presented in Figure 13.8. The relative humidity at the inlet was around 10%, and only at the start the humidity was clearly higher. At the outlet the humidity increases: as in the beginning of the experiment it took some time until all segments are filled, and quite a steep increase was observed. However, it took again some time until a steady-state was reached. The cyclic behaviour, also present in the gas outlet temperature, is clearly visible here as well.

In Figure 13.9 the pressure difference over the filters is shown. A steady increase in pressure difference is obvious. This is understandable as more and more dust is stacked into the filters. This increase will contribute to the difference between $T_{g,\text{mean}}$ and $T_{g,\text{outlet}}$.

Figure 13.10 presents the gas flow rate at the inlet and the outlet, and obviously the flow is higher at the outlet. The flow at the outlet is firstly the combination of the flow at the bottom of the dryer and the wet transfer line.
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Figure 13.8: RH\textsubscript{g,inlet} (Left) and RH\textsubscript{g,outlet} (Right) for dataset B. After some dynamic behaviour at the start the humidity stays around 10\% for RH\textsubscript{g,inlet}. The cyclic behaviour of RH\textsubscript{g,outlet} is clearly visible.

Figure 13.9: \(\Delta P\textsubscript{fil}\) over the filters for dataset B. An increase in \(\Delta P\textsubscript{fil}\) is obvious.

Moreover, due to a difference in temperature, pressure and water content the gas flow rate at the top can differ from the bottom of the dryer.

In figure 13.11 the evaporation rate is presented, calculated using the linear regression (see equation 13.20). The increase and decrease of \(m\textsubscript{vap}\) at the start and the end of the run, respectively, are clearly visible. At the start one segment is filled after the other which causes the gradual increase of \(m\textsubscript{vap}\), and the same reasoning is valid at the end.

Based on the liquid and solid addition to the granulator the moisture content of the granules entering the dryer was calculated. Using the calculated (and corrected-validated) evaporation rate the moisture content of the granules leaving the dryer is computed (Fig. 13.12). It is impossible to calculate the moisture content of the granules for each cell separately as only the cumulative humidity of the gas leaving the dryer is measured. Karl Fisher titration measures a value.
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Figure 13.10: $V_{g,inlet}$ and $V_{g, outlet}$ for dataset B. $V_{g, outlet}$ is calculated since this variable is not measured.

Figure 13.11: $m_{vap}$ for dataset B. The calculation of $m_{vap}$ is based on the measured variables of the drying air.

of 13% for the initial moisture content and 1.35-1.45% for the residual moisture content. In figure 13.12 the moisture content of the granules entering the dryer ($X_0$) and leaving the dryer ($X_{end}$) is presented. The calculated mean over a time span of 2h equals 13.05% for $X_0$ and 1.37% for $X_{end}$, values which are in very good agreement with the Karl Fisher results.

The experimental outlet drying air temperature $T_{g, outlet, exp}$ is compared with the calculated temperature $T_{g, outlet, cal}$ in figure 13.12. In general the experimental and calculated results coincide well, and the overall cyclic behaviour is captured in the calculations. However, at a smaller scale the peaks of the calculation do not coincide with the experimental results. The combination of the outlet gas temperature and the humidity causes the fluctuation in the $\rho_{HA}$ of the gas at the outlet. This strong fluctuation causes the fluctuation in $T_{g, outlet, cal}$, and causes the shift in the time instants of the peaks. The calcu-
13.4. Results

Figure 13.12: $X_0$ and $X_{\text{end}}$ (Left) and $T_{g,\text{outlet},\text{exp}}$ and $T_{g,\text{outlet},\text{cal}}$ (Right) for dataset B. $X_0$ and $X_{\text{end}}$ are calculated based on properties of the input of the granulator and the $m_{\text{vap}}$. Both $T_{g,\text{outlet},\text{exp}}$ and $T_{g,\text{outlet},\text{cal}}$ display a cyclic behaviour, however at a smaller scale the peaks do not match entirely.

Lated mean temperature is 28.20°C.

Finally, an uncertainty propagation was performed on this dataset. The standard deviation for the moisture content $X_{\text{end}}$ is 0.2371. The resulting 95% confidence interval is [0.9383 1.8382]. The experimentally measured moisture content is clearly situated in the confidence interval. For the gas temperature the standard deviation is 0.2115, and the 95% confidence interval [27.7994 28.6021]. The result for the confidence interval of the gas temperature at the outlet is presented in figure 13.13. The confidence interval is small, and the experimentally measured temperature does not fall in the interval.

Figure 13.13: $T_{g,\text{outlet},\text{exp}}$ and 95% confidence interval for dataset B
13.5 Discussion

13.5.1 Use of in-line data for process monitoring of the ConsiGma™

The use of the standard logged data and a mass and energy balance can be compared with the use of expensive sensors, which are typically not standard available in most industrial pharmaceutical equipment. The use of the univariate data enables us to determine directly the end of the drying process by monitoring of the temperature profile of the different segments of the dryer, however, as it is not always desired to dry the granules till a moisture content of 0%, these profiles are not always sufficient. The use of a mass balance would be a powerful tool to quantify the moisture content of the granules at the end of the process. Moreover, the implementation of the balances in a real-time system enables the operator to follow up the process in a better way. A deviation in the gas outlet temperature gives the operator an indication that something is changing, but the calculated evaporation rate gives more information about the drying process itself, as it takes the properties of the inlet gas into account. Combining the information about the moisture content with an appropriate controller in order to increase or decrease the evaporation rate would be a major step forward towards improved process control of the drying process. However, the implementation of a controller requires more information about the drying process, and for this reason mechanistic models are a powerful tool. The use of balances has been compared by Fonteyne et al. [2014] with classical methods, i.e. end-point detection using indirect parameters, such as the product temperature or the humidity of the outlet drying air and with in-line moisture and solid state determination by means of PAT tools (Raman and NIRS). Both Raman and NIRS spectroscopy were successfully applied for the real-time monitoring of the drying process. Based on the NIRS-based Partial Least Squares (PLS) model, the drying process end-point could be predicted and was proven to be superior to conventional end-point determination.

There could be concluded that the calculated moisture content of the granules at the end of the drying process was lower than the result obtained by Karl Fisher titration. The granules are brought into the dryer using a transfer line, which is in contact with the granulator, and where the humidity of the gas is high. Together with these granules, water-rich air is introduced into the dryer, but no sensors are located at this inlet to measure the humidity and the gas temperature. As a consequence, an assumption has to be made about the humidity and the gas temperature. To calculate the amount of water evaporated during drying, it is assumed that the difference between the water content of the gas at the inlet and the outlet is only related through the drying process.
13.5. Discussion

However, in our case an unknown process takes place which resulted in a higher moisture content of the drying gas at the outlet compared to the inlet for an empty dryer. This means an overprediction of the evaporation rate, which is solved by implementing a correction term, but needs further investigation. With this correction reasonable results could be found for several data sets, of which part of them are presented. This means that mass and energy balances are a powerful tool to monitor the process without the need for extra sensors or time-consuming off-line experiments. An important conclusion is that it is very important not to trust the available data blindly, but perform basic reconciliation checks. In this case the problem with the data was revealed by making a mass and energy balance.

An important issue is the unequal behaviour of the different cells. This is clearly visualised by the sinusoidal function with lower frequency (Fig. 13.7). The higher frequency sinusoidal behaviour corresponds with one filling period (i.e. 180 s for dataset B), whereas the lower frequency sinusoidal behaviour corresponds with the total cell cycle (i.e. six times the filling period or 1080 s for dataset B). As the cells do not operate similarly, the relative humidity at the outlet is fluctuating according to which cell is in a certain state of the cycle (Fig. 13.8). For instance, each time that cell 1 is filled with wet granules more water is evaporated and $RH_{g,\text{outlet}}$ is higher.

A good prediction of the gas outlet temperature gives the opportunity to use this information and to combine with the trajectory that particles are following during fluidization. The study about the flow of particles can be done using CFD (Part IV), which is also able to predict the bed height of the granules. The gas temperature is not uniform in the dryer, but decreases due to several sinks (Section 13.4.1 and fig. 13.14). The bed height will determine in which section of the segment the gas temperature will decrease fast, as the heat for evaporation is the largest sink. The bed height can, together with assumptions about the uniformity of particles, be able to predict the amount of heat loss in different horizontal sections of the dryer. Another solution to calculate the gas temperature in different horizontal sections or in more detail at all locations is the use of a combined CFD-PBM model. Before the combination can be realized, a thorough validation of both models is necessary. Nevertheless, the combined model will be computationally very expensive. The use of the developed energy balance can give a first insight in the gas temperature at different locations without the need for a validated PBM model and the combined model.

As indicated extra sensors at the wet transfer line would give the opportunity to eliminate the assumptions about the humidity and the gas temperature. Furthermore, the possibility to measure the humidity and the temperature of the outlet air from each segment of the dryer would even provide additional
information about the process. The calculation of the evolution of the moisture content during drying would give the operator the freedom to interfere within the process in a more accurate way.

13.5.2 Prerequisites, assumptions and shortcomings when using mass & energy balances

However, using measurements to follow the process dynamics and perform process control in continuous production processes requires detailed information and has also some shortcomings. A mass and energy balance requires first of all the definition of the subprocesses, and all inlets and outlets should be known if it is an open process. However, there should be data available to quantify the important variables. Furthermore, assumptions will typically need to be made in order to simplify the process, and these assumptions should be carefully checked in order to justify them.

- The exact location of sensors should be known in order to (1) know which processes have to be taken into account and (2) to be sure that the measurements deal with the mentioned flow. For instance, the water content of the gas is dependent on the gas temperature ($T_g$), the pressure ($P_g$) and the volume of the gas ($V_g$). If not all sensors are located at the same location, the water content of the gas can not be determined correctly. Moreover, a sensor which is in contact with the material will produce other results compared to a sensor in contact with the gas phase.

- The presence of filters is important to include pressure drops or pressure rises, which results in an energy release or uptake.
13.6 Conclusion

- A mass and energy balance requires the knowledge of all inputs and outputs of the subprocess. If there is a lack in measurements at the boundaries of the subprocess the mass balance will be incorrect, leading to under- or overestimation of the calculated output variable. As such it is important to check the balances with validation experiments \textit{a priori} (i.e. before the use in industrial applications) and/or to include a real-time validation of the measurements by performing basic checks (e.g. comparing measured with calculated variables).

- An important shortcoming of mass and energy balances is their inability to assist in gaining detailed insight in the process since they are very crude. More detailed mechanistic models are very powerful tools to understand the process in more detail, and understand input-output relations. With the balances the influence of changing input variables during operation can not be investigated as the effect of the input variables on the output variable of interest, i.e. the moisture content, is not known. Once the effect of the input variables on the output variable of interest is known, the operator has freedom to change the inputs during operation in order to end up with the desired end quality.

13.6 Conclusion

The automatically collected in-line real-time data of the ConsiGma\textsuperscript{TM} continuous tableting line, and more specifically the fluidized bed dryer unit, is processed. The use of a mass and energy balance enables to monitor the process without the need for extra sensors or time-consuming off-line experiments. However, a calibration in order to predict the moisture content of the granules leaving the dryer was necessary. This was done by implementation of a linear regression to calculate the evaporation rate. The observed difference in water content of the gas at the inlet and the outlet for an empty dryer remains unsolved. For dataset B the experimental results, measured by Karl Fisher titration, and the calculated results were in very good agreement. The error propagation performed on the data was of interest to calculate the confidence interval on the calculated values and investigate whether measurement errors could explain the observed deviations between calculations using balances and actual measurements.

Mass and energy balances are powerful to monitor the process on-line, however gaining more detailed insight in the process is impossible. For the latter, mechanistic models remain necessary.
Chapter 13. Monitoring by using mass & energy balance
PART VI

Conclusions & Perspectives

White box

Supervisory control
The work presented in previous parts showed how models can be applied to describe the drying behaviour of pharmaceutical granules in a fluidized bed being part of a fully continuous pharmaceutical manufacturing process. In the following, the main conclusions of the work performed till now are listed. Finally, a number of suggestions for future research are given.
General conclusions

The main objective was the development of a mechanistic model for a fluidized bed drying process used in a continuous tablet manufacturing process, which has been approached in a step-wise manner. The step-wise approach is reflected in the different parts of this thesis, as well as in the different sections of the conclusions (Fig. 1.2).

14.1 Single particle drying model

A drying model describing the drying behaviour of single pharmaceutical granules has been developed. Pharmaceutical drying processes take place in two separate drying phases, which is translated into two submodels. In a first drying phase the weakly bound water at the surface of the granule is evaporated, while the water inside the wet granule is evaporated during the second drying phase. The submodel for the second drying phase includes an empirical power coefficient, i.e. $\beta$. Its influence on the drying behaviour was proved by a Local Sensitivity Analysis (LSA). Experimental data was collected to calibrate and validate this parameter. Several candidate model structures were analysed to describe the dependency between $\beta$ and the gas temperature using different model selection criteria, of which some take the model complexity into account. The same correction term which is available for the Akaike's Information criterion (AIC), to correct for small sample sizes, was included in the Bayesian Information Criterion (BIC), the Final Prediction Error (FPE) and the Khinchin’s law of Iterated Logarithm Criterion (LILC). However, after comparing the different criteria, no consensus could be found, but as most of the checks point towards the exponential model structure, the exponential relation was selected as the final model structure. As such, two empirical coefficients, i.e. $\beta_1$ and $\beta_2$ (the coefficient in the exponent) were added to the
drying model.

Next, the single particle drying model was further analysed using a Global Sensitivity Analysis (GSA) and an uncertainty analysis. These two tools enable the modeller to get more insight into the process and use the gained information to perform model reductions, prediction of uncertainty, etc. Several GSA techniques were compared using one output, i.e. the time to reach a moisture content of 1.4%. To tackle the large number of factors involved in the drying model, a Morris screening was used as starting point. This method is less computationally expensive compared to other methods, because less simulations are required to draw conclusions. Based on the Morris screening 10 out of the 23 factors were selected for further analyses. The Contribution to Sample Mean (CSM) plot revealed the importance of $\beta_2$ and the gas temperature. The regression-based sensitivity technique could only be used using the rank transformed output, as the $R^2_Y$ on the raw output was lower than 0.7, i.e. the threshold value to provide a reliable ranking of the factors. The $R^2_Y$ of 0.62 for the raw output data is an indication of the non-linearity of the drying model. The Standardized Rank Regression Coefficient (SRRC) was the highest for $\beta_2$, followed by the initial moisture content, represented by $R_{w,0,fac}$. The variance-based technique judges the sensitivity of the factors based on the first order indices ($S_i$) and the total effect of the factors ($S_{Ti}$). The sum of $S_i$ is 0.8, meaning that 20% of the variance in the model output is due to interaction between the factors. The difference between $S_i$ and $S_{Ti}$ and a different ranking between both forms a measure for non-linearity. Both indices stress the importance of $\beta_2$ and the gas temperature, which is an identical conclusion as for the CSM plot. A different ranking is found for the SRRCs where the impact of $R_{w,0,fac}$ is erroneously increased due to the rank transformation. Moreover, the variance-based technique provides information about the model and the underlying process. The difference between $S_i$ and $S_{Ti}$ for $R_{w,0,fac}$ is an indication that this factor is involved in interaction with other factors. $S_i$ equals 0.73 for $\beta_2$, meaning that 73% reduction in variance can be obtained if the value for $\beta_2$ can be fixed. Based on the GSA it can be concluded that the gas velocity and the porosity of the granules have almost no influence on the drying time. The importance of the gas velocity is negligible as the hindrance that the water vapour experiences when moving through the pores is the limiting factor in the second drying phase. The influence of the porosity on the drying time is quite unexpected.

An uncertainty analysis was performed in order to quantify the uncertainty about the model prediction. Therefore, a Generalised Likelihood Uncertainty Estimation (GLUE) analysis was performed on the validated drying model, which enables the modeller to incorporate the information about the experimental data in the assessment of the uncertain model predictions and to find a
balance between model performance and data accuracy. The analysis was done for two cases, one to detect the prediction uncertainty from the main assumptions at the particle level, i.e. the particle radius, the porosity of the particles and the gas flow rate, and a second one on the most sensitive parameters, i.e. $\beta$ and the gas temperature. As the gas temperature can be set accurately by the operator, this parameter was excluded from the analysis. Finally, both cases were combined. The gas velocity is clearly not identifiable and has almost no influence on the model output, which was earlier confirmed by the GSA. All behavioural parameter combinations have a value of the particle radius smaller than the previously assumed calibrated value of 0.6 mm. However, the irregular shape of the particles is not taken into account in the model, where all particles are assumed to be spherical. Moreover, by performing a GLUE analysis additional insight in the model structure could be obtained. The shape of the area of the behavioural runs for the particle radius and the porosity indicates that the amount of water in the particle determines if a fit is qualified as behavioural or non-behavioural.

Finally, the single drying particle model has been reduced to an empirical model in order to extend the model towards a population of particles using Population Balance Model[ling] (PBM). A procedure for the model reduction has been developed and applied to the validated drying model. The starting point was a GSA to detect the most sensitive degrees of freedom. Subsequently, simulations of the complex model were used to develop the reduced model. The result is a model describing the decrease of the moisture content in function of the gas temperature and the gas velocity.

In summary, for the first time a mechanistic model for drying of single granules has been calibrated for pharmaceutical applications using specifically collected experimental data. Several advanced modelling tools were applied to the model shedding more light on the process behaviour. This was the first time they were applied in the context of a pharmaceutical production process.

### 14.2 Population Balance Modelling (PBM) for the drying of pharmaceutical granules

A PBM model describing the drying behaviour of a population of wet granules has been developed. The use of PBM models to describe the drying behaviour is innovative for the pharmaceutical industry, where most processes are a black-box. Therefore, the reduced drying model has been implemented as a growth term in the Population Balance Equation (PBE). Several solution methods to solve the PBM are compared w.r.t. the accuracy and the computational effort. The High Resolution Finite Volume (HRFV) scheme was analysed for two different $\kappa$-values and different flux limiting functions.
A $\kappa$-value of $1/3$ calculates the number density distribution accurately using a grid size higher than 300. The results for different flux limiters were not significantly different, however, the influence on the calculation time was pronounced. Without any flux limiting function a $\kappa$-value of -1 leads to negative values in the number density distribution, which is very likely a numerical artifact. The implementation of a flux limiter could solve this problem. The Method of Characteristics (MOC), another method based on discretisation, which uses a moving grid, requires a larger grid to obtain a smooth number density distribution. Moreover, the calculation time for the latter method is remarkably lower compared to the HRFV scheme. The Quadrature Method of Moments (QMOM), a moment-based solution technique, was tested with two algorithms. The Product-Difference (PD)-algorithm was able to calculate at least 7 moments, whereas the Chebyshev algorithm could only calculate 3 moments. Nevertheless, the calculation time is obviously lower compared to the discretisation methods, but no number density is obtained as a final result. As such, results are less intuitive to interpret and it is more difficult to draw conclusions.

The developed PBM model can be used to compute the evolution of the moisture content distribution for different initial distributions, different particle sizes, different gas temperatures and different gas velocities. Moreover, a supply of wet granules during drying can be implemented in order to simulate a continuously drying process. The effect of the different inputs on the drying model can be investigated and used to develop guidelines about the set-up of the dryer. This innovative approach enables the pharmaceutical industry to test a lot of scenarios without the need to collect experimental data.

A GSA was performed on the PBM model using 6 factors which are chosen based on the operation of the fluidized bed dryer of the ConsiGma™. This was done using two outputs, i.e. the mean of the moisture distribution at the end of the drying process and the standard deviation of the moisture distribution. The ranking for the different methods (i.e. the CSM-plot, the regression-based and the variance-based technique) was identical. There was no effect on the ranking of the factors by performing a rank transformation on the raw data using the regression-based method, and in both cases the $R^2$ was high enough to draw conclusions. The difference between $S_i$ and $S_Ti$ for the drying time shows the limited influence on the drying process itself. The particle radius was the most sensitive factor, followed by the gas temperature, for the mean of the moisture content distribution. The width of the distribution was mostly influenced by the gas temperature and the filling time. An important conclusion is that the gas temperature is the key to control the specs of the distribution, as it has both an influence on the drying rate as well as on the width of the distribution. This is important information in view of developing control strategies.
The use of a moment-based solution method induces the need to reconstruct a distribution from the moments after solving the PBM-model. The parameter fitting methods, which require \textit{a priori} knowledge about the underlying distribution, were not sufficient to reconstruct the distribution, as in this case it was impossible to track the bimodal distribution. The method of splines was able to predict the peaks of the distribution quite correctly. However, a finetuning of the parameters was found to be required in order to end up with a reliable result as well as for the computational time. Also in this case prior knowledge is useful, as it facilitates the finetuning. To track the moisture content distribution, $\text{tol}_\text{neg}$ was less crucial compared to $\text{tol}_\text{red}$. The introduction of a different $\text{tol}_\text{red}$-value for the first and last interval had a remarkable influence on the final reconstruction. The final reconstruction is also influenced by the order of splines, linear splines lead to negative values for the number density distribution and is as such insufficient. The use of more moments improved the result significantly, in the case of only 3 or 4 moments, the result was even better using some functions of the parameter fitting method.

A preliminary simulation study has been performed to simulate breakage during the drying of wet granules. Three different breakage kernels were implemented in the PBE which has been solved using the fixed pivot technique. The mechanisms are analysed w.r.t. the introduced parameters of the kernels and compared with each other by solving the stand-alone breakage PBM-model. Later on the two-dimensional PBM-model has been solved, including as well the drying of the wet granules. Two granule breakage kernels were investigated, i.e. the formation of two equal fragments and uniform binary breakage. The difference between both was obvious, whereas the first leads to peaks at half the size of the mother granule, the second one leads to a smooth shift towards the lower size classes. The result of the erosion kernel, i.e. a surface breakage kernel, was the production of fines, which appear in the lowest size class. The drying rate was clearly different when adding uniform binary breakage, where the standard deviation of the number density distribution is larger due to breakage. In the case of the formation of two equal fragments the effect is less remarkable.

In summary, a theoretical PBM-model describing the drying behaviour of wet pharmaceutical granules has been developed. This innovative approach enables the pharmaceutical industry to run several scenarios. However, a thorough validation is required, which opens the door to system optimisation using scenario analysis. The extension to a two-dimensional PBM-model including drying and breakage gives the opportunity to gain more insight in the interplay between drying and breakage.
14.3 Computational Fluid Dynamics (CFD) to study the flow pattern in a fluidized bed

A preliminary study about the flow pattern of granules in the fluidized bed system of the ConsiGma™ has been performed. The challenging geometry of the dryer leads to difficulties during the development of a Computational Fluid Dynamics (CFD)-model. First, a (single) gas-phase simulation was performed until convergence, after which the solids were added into the flow domain. The combined gas-solid simulation results show that particles are escaping from the domain, which needs attention in future research.

14.4 Monitoring a fluidized bed drying process using mass and energy balances

The fluidized bed drying process of the ConsiGma™ has been analysed using mass and energy balances in order to monitor the process in real-time. This is increasingly important, especially in the context of continuous operation, due to the need to guarantee the product quality of the produced pharmaceuticals. The automatically collected in-line real-time univariate process data is generally not really used, but is a cheap way to monitor the process in comparison with the use of extra sensors to collect for instance spectral data. The data is processed using a mass and energy balance in order to predict the moisture content of the granules leaving the dryer. Additionally, the gas outlet temperature has been predicted and compared with the measured one. The latter is interesting since it yields an on-the-spot check point of the mass balance. Moreover, once the system is validated it can be used to predict the gas temperature in different horizontal sections of the drying unit, which means that an idea about the variation of the gas temperature experienced by the particles during drying is obtained. Finally, the calculations can be used to identify flows in the system and to propose alternative sensor locations. The calculations have been performed for several datasets, but only two of them were discussed. A calibration step was necessary in order to predict the evaporation rate correctly, since the calculated evaporation rate was higher than zero for an empty dryer. Till now, the reason for this gap has not been found, but will be investigated later on. After calibration, the balances were able to predict both the moisture content of the granules at the end of the drying process and the gas outlet temperature quite accurately.
14.5 Overall conclusion

The use of mechanistic models in the pharmaceutical industry is innovative. Whereas traditionally the processes used in the pharmaceutical industry are a black-box, these mechanistic models, when validated, are useful to get more insight in the process. Moreover, the pharmaceutical industry can use these models to test several scenarios without the need to collect experimental data. The latter is not only time-consuming but also an expensive way of gathering knowledge.
Chapter 14. General conclusions
The knowledge gaps and promising research paths that were identified throughout this work are listed below:

- Till now the single particle drying model has been calibrated and validated using one model formulation. It can be expected that the drying behaviour will be dependent on the formulation, at least to some extent. Therefore, in the future different formulations will be investigated and based on the varying raw material and wet granule properties a classification will be made in order to end up with a number of classes. The classification of the formulations can be done on the basis of a number of properties, (1) the properties of the raw material, e.g. the density of the powder, the flowability of the powder, the wettability of the powder, the spectral properties, etc. and (2) the properties of the wet granules, e.g. the density of the wet granules, the spectral properties, the process parameters used during granulation, etc. Afterwards the experiments to calibrate the drying model can be repeated for each class. Dependent on the differences in drying behaviour it can be decided to calibrate the empirical coefficient, i.e. $\beta$, again, or a correction term can be introduced. Another solution is to adapt directly the PBM-model in order to circumvent the need to perform several model reductions. Moreover, up till now only one value for the gas velocity, i.e. $200 \text{m}^3/\text{h}$, has been tested as with the low number of particles used in the experiments it was impossible to use a higher gas velocity. The reasons for this were multiple. First, the particles get stuck in the filters during the high fluidization. Second, particles were lost during the transfer and in the product control hopper. However, other equipment can be tested and compared with the already collected experimental data. A good agreement between both devices can provide the opportunity to test higher gas velocities without
using the ConsiGma™ and still end up with reliable results. A large dependency on the gas velocity is, however, not expected as the barrier for drying is the diffusion of the water vapour through the holes in the particle during the second drying phase.

- The PBM model needs a thorough validation. The one-dimensional PBM model for drying can not be validated as a stand-alone model, as breakage occurs simultaneously. A first comparison of the experimental drying rate and the calculated drying rate was not satisfactory. However, the growth term is based on the single particle drying model, which has only been calibrated for one formulation and one gas velocity. Both were different from the experiments used for the calibration of the single particle drying model. The breakage kernels as implemented in the PBM model can be validated by performing several experiments. For example, the influence of the gas velocity can be observed by setting the gas temperature at a very low value. By doing this, it can be assumed that the moisture content of the granules remains constant. Experiments with particles of different moisture content should be performed, as it can be expected that the moisture content will have an influence on both the breakage mechanism (i.e. fragmentation or erosion) as well as on the breakage rate. Also the size and shape of particles can influence the breakage. Up till now, all models assume a spherical shape of the particles.

- The preliminary results of the CFD work should be further investigated and compared with experimental data. Eventually, the use of a high speed camera could be helpful. Some basic experiments were already performed in order to test the use of a high speed camera to collect data. However, due to the small available area to take pictures of the fluidizing particles only part of the flow pattern can be visualised. Other possibilities to collect experimental data should be explored.

- The introduction of the correction term in the mass and energy balance is an artificial way in order to end up with a reliable solution. However, more work has to be done in order to find the reason for the leak in the mass balance. A thorough calibration and check up of the sensors is one of them. Moreover, extra sensors can be implemented in order to have multiple checks during the calculation. For instance an extra gas velocity sensor at the outlet would be useful, as up till now the gas velocity at the outlet is calculated using a mass balance. However, no information is available about the amount of gas leaving the drying unit via the outlet for the dry granules. An extra sensor at the wet transfer line, which measures the gas temperature and the humidity would increase the accuracy of the calculations. By implementing them and comparing with the already
gathered results one can obtain an indication of the error.

- Once a validated CFD model has been established, this can be combined with the predictions of the gas temperature in different horizontal sections of a segment in the dryer. The latter is based on the mass and energy balances. The knowledge about the trajectory of the granules through the bed and the ambient conditions at each point would lead to a better prediction of the drying behaviour of these granules using PBM.

- The mechanistic models are a first step in the development of control strategies, which rely on on-line measurements and real-time adjustment of sensitive input variables. These control strategies should ensure that the process stays within the Design Space in order to guarantee the end-product quality at all times. Moreover, the model, once validated, can also be used to help to determine the Design Space.

- The fluidized bed drying process is only one of the several unit operations during the continuous production of pharmaceutical tablets. To guarantee the quality of the produced tablets, all subprocesses need to be understood in detail. Hence, similar model-based analyses are required for all unit processes in the process train. Moreover, in order to control the full from-powder-to-tablet line these different models needs to be combined and/or the information needs to be transferred from one model to another, i.e. the output of the model of the previous unit process is the input for the model of the next unit process. The transfer of the wet granules via the wet transfer line will have to be investigated. Experimental data should reveal to which extent breakage occurs in the wet transfer line. This enables the operator to adjust the continuous process during operation in order to stay within the Design Space.
Chapter 15. Perspectives & future work
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Summary

The current interest from the pharmaceutical industry to shift to continuous production processes enhances the need for detailed process understanding. In contrast to batch production processes, which rely usually on off-line post-process time-consuming and less efficient laboratory testing to evaluate the quality of the product, continuous production processes should be controlled on a real-time in-line basis. The latter requires both an in-line monitoring as well as an in-line directing in order to ensure the process stays within the Design Space at all time. The Design Space is a central concept of the Process Analytical Technology (PAT) guidance, and defines the multidimensional combination and interaction of input variables and process parameters which ensure that the end-product quality is guaranteed. The Design Space has to be validated and approved by the regulators, but once approved it is allowed to move freely within the Design Space without post approval of the regulatory agencies. However, in order to develop the Design Space, detailed process knowledge is required, which can be gathered both experimentally as well as model-based. Mechanistic models attempt to describe the process physically, and once validated, process understanding can be gained. Furthermore, the use of modelling tools such as scenario analysis, Global Sensitivity Analysis (GSA), and uncertainty analysis allows further system exploration. In contrast, relying solely on the collection of experimental data to define the Design Space is time-consuming and costly, due to the large amount of required energy and/or material, and because equipment is typically not available for production (loss of production capacity) when used in the frame of experiments.

This PhD dissertation deals with the development of a mechanistic model describing the drying process in a fluidized bed being part of a full continuous from-powder-to-tablet manufacturing line, i.e. the ConsiGma™ (GEA Pharma Systems, Collette™, Wommelgem, Belgium). Later on, this model can help with the development of the Design Space.

A step-wise procedure was used to model the drying process in the fluidized bed unit. First, the drying behaviour of one single pharmaceutical granule was investigated. Experimental data was collected to reveal the drying behaviour.
of one single particle. Two phases could be distinguished; the weakly bounded water is evaporated at a high rate in the first few seconds, whereas in the next phase the evaporation rate is much lower. This is translated to a drying model consisting of two submodels. The submodel for the second drying phase contains an empirical power coefficient which was calibrated and validated using independent experimental data. Additional tools have been used to further explore the drying process, i.e. a GSA and a Generalised Likelihood Uncertainty Estimation (GLUE) uncertainty analysis. Whereas the first tool resulted in a ranking of the input variables in order of decreasing significance, in general the second tool provided information about the uncertainty of the predicted output variable. The gas temperature was an influential factor for the drying process, which is important with regard to the development of control strategies. The influence of the gas velocity is negligible for the drying of one single granule in constant ambient conditions. Therefore, the gas velocity was determined as the input variable to guide the fluidization behaviour. Subsequently, a model reduction of the full drying model was performed, using the information of the GSA which resulted in an empirical reduced model. This model could be solved with a relatively low computational effort and is, therefore, useful to implement in and/or combine with other models.

The extension from one particle towards a population of particles was made using Population Balance Modeling (PBM), which is a tool to model the interaction between particles and between particles and the ambient environment. A one-dimensional PBM model describing the evolution of the moisture content for a group of particles, filled in one segment of the dryer during a certain period, was implemented. Several solution techniques for the Population Balance Equation (PBE) were compared. The discretisation techniques resulted in a number density distribution at each time step, but required more calculation time compared to the moment-based techniques. A first discretisation technique, the High Resolution Finite Volume (HRFV) method, was implemented with several flux limiting functions, which were necessary to avoid negative values for the number density and suppress wiggles. The importance of these functions was proven by comparing the accuracy of the simulation results. The Method of Characteristics (MOC), another discretisation technique, required less calculation time, due to the moving grid, whereas the accuracy of the result was comparable with the HRFV scheme. The moment-based solution method resulted in a set of moments instead of a number density distribution at each time step. The Quadrature Method of Moments (QMOM) was used with two different algorithms, i.e. the Product-Difference (PD) and the Chebyshev algorithm. It could be concluded that the PD algorithm performed better compared to the Chebyshev algorithm. The drawback of the moment-based
techniques was the interpretation of the result, i.e. a set of moments. Several reconstruction methods were available to reconstruct the underlying number density distribution based on these moments. However, this led to an additional deviation from the real solution, and moreover, the method of splines, which has been proven as the preferred reconstruction method, required a large computational effort. Based on a GSA applied on the one-dimensional PBM model it could be concluded that the gas temperature was the key to control the specs of the distribution, as it had both an influence on the drying rate as well as on the width of the distribution.

Experimental data revealed that granules broke up during drying. Therefore, the one-dimensional PBM model was extended with an additional internal coordinate, i.e. the size of the granules, resulting in a two-dimensional PBM model. This model was able to predict both the moisture content distribution as well as the PSD during drying. Several breakage mechanisms (i.e. surface and granule breakage) were investigated theoretically. The rate of breakage was varied by changing the parameters of the respective kernel. The effect of breakage on the drying behaviour was analysed, and it was concluded that the effect was most pronounced in the case of uniform binary breakage.

A preliminary study to investigate the flow pattern of fluidizing particles using Computational Fluid Dynamics (CFD) was performed. First a gas-only simulation was performed. Starting from the converged solution for the gas-phase, the solid particles were added into the flow domain. This resulted in the escape of particles from the domain, a phenomenon which needs to be further investigated.

The real-time in-line measurements continuously logged during operation of the ConsiGma™ were processed by means of a mass and energy balance. Based on these balances the moisture content of the granules leaving the drying unit could be predicted. A good agreement with an off-line Karl Fisher titration was found. Moreover, the predicted and measured gas temperature at the outlet were compared, which is an internal check of the balances. It could be concluded that the drying process can be monitored during operation using these balances without the need to use additional sensors.

In general, the first parts of this thesis, i.e. the development of mechanistic models, increased the knowledge about the drying process, whereas the last part covered the monitoring of the drying process. Both are needed to develop a well-functioning controller of the fluidized bed drying process which can guarantee the end-product quality of the dry granules.
Besides the main outcomes of this thesis, i.e. knowledge buildup by using mechanistic models, the application of a set of powerful model analysis tools to support mechanistic model development (e.g. sensitivity and uncertainty analysis), and the demonstration of the use of mass and energy balances for on-line monitoring of the drying process, several research needs and perspectives were identified. One of the promising perspectives is the modelling of the full continuous tableting line. Therefore, the coupling between the different units and the reduction of the complex mechanistic models of the subunits is needed, which will of course be challenging. A model of the full production line is the first step towards enhanced quality control strategies relying on in-process measurements and real-time adjustment of critical process variables.
Samenvatting

Tegenwoordig is er veel interesse vanuit de farmaceutische industrie om over te schakelen van batch naar continue productiesystemen waardoor de nood aan gedetailleerde proceskennis wordt versterkt. In tegenstelling tot batch productiesystemen, die meestal steunen op off-line laboratorium testen om de kwaliteit van het product te evalueren, dienen continue productiesystemen gecontroleerd te worden op real-time basis. Dit vereist zowel in-line metingen als in-line sturing om ervoor te zorgen dat het proces op elk moment in de 'Design Space' blijft. De Design Space is een centraal concept van de Proces Analytische Technologie (PAT) richtlijnen. De Design Space wordt gedefinieerd als de multidimensionale combinatie en interactie van inputvariabelen en procesparameters om ervoor te zorgen dat de eindkwaliteit van het product gegarandeerd is. De Design Space dien t gev alideerd en go edgek eurd te w orden do or de regelgevende overheden, echter, eens goedgekeurd is het toegestaan vrij te bewegen in de Design Space zonder bijkomende goedkeuring. Om de Design Space te ontwikkelen is gedetailleerde proceskennis nodig, die zowel modelmatig als experimenteel kan vergaard worden. Mechanistische modellen trachten het proces fysisch te beschrijven, en eens gevalideerd, kan snel proceskennis verkregen worden. Bovendien kan het systeem verder geanalyseerd worden door gebruik te maken van verschillende hulpmiddelen, zoals scenario analyse, Globale Sensitiviteitsanalyse (GSA) en onzekerheidsanalyse. In tegenstelling tot deze modelmatige aanpak, is het definiëren van de Design Space op basis van experimentele data tijdrovend en kostelijk, omwille van de vereiste hoeveelheid aan energie en/of materiaal. Daarnaast is de uitrusting ondertussen meestal niet beschikbaar voor productie waardoor het verzamelen van experimentele data dus ook een verlies aan productiecapaciteit betekent.

Dit doctoraat omvat de ontwikkeling van een mechanistisch model dat het droogproces beschrijft in een wervelbed dat onderdeel is van een volledig continue van-poeder-tot-tablet productielijn, nl. de ConsiGma™ (GEA Pharma Systems, Collette™, Wommelgem, België). Dit model kan dan helpen bij het ontwerpen van de Design Space.

Een stapsgewijze procedure werd gebruikt om het droogproces in de wervelbed-
eenheid te modelleren. Eerst en vooral, werd het drooggedrag van één enkele farmaceutische granule onderzocht. Uit experimentele data is gebleken dat het droogproces via twee fasen verloopt. In de eerste seconden wordt het zwak gebonden water aan een hoge verdampingssnelheid verwijderd, waarna in de tweede droogfase de verdampingssnelheid veel lager is. Het submodel voor de tweede droogfase bevat een empirische machtscoëfficiënt die werd gekalibreerd en gevalideerd gebruik makend van onafhankelijke experimentele data. Verschillende hulpmiddelen werden gebruikt om het droogproces verder te verkennen, nl. een GSA en een GLUE onzekerheidsanalyse. Hier geeft de eerste tool aanleiding tot een ranking van de inputvariabelen in afnemende sensitiviteit en geeft de tweede tool informatie omtrent de onzekerheid van de voorspelde output. De gastemperatuur werd geïdentificeerd als de meest invloedrijke factor voor het droogproces wat belangrijke informatie is met betrekking tot de ontwikkeling van controlestrategieën. Tevens bleek dat de invloed van de gassenheid verwaarloosbaar is voor het drooggedrag van één enkele granule in constante omgevingscondities. Vandaar dat de gassenheid bestempeld werd als de variabele om het wervelgedrag te sturen. Vervolgens werd op basis van de informatie uit de GSA een modelreductie uitgevoerd die resulteerde in een empirisch gereduceerd model. Dit model kon opgelost worden met een relatief lage computationele vereiste en is daardoor (beter) bruikbaar om te implementeren en/of te combineren met andere modellen.

De uitbreiding van één partikkel naar een groep van partikels gebeurde door middel van Populatie Balans Modellen (PBM). Dit is een tool om de interactie tussen partikels onderling en tussen partikels en de omgeving te modelleren. Een één-dimensionaal PBM model werd ontwikkeld, dat de evolutie van de vochtigheid beschrijft van een groep van partikels die gevuld worden in één segment van de droger gedurende een zekere periode. Verschillende oplossings-technieken voor de Populatie Balans Vergelijking (PBE) werden vergeleken. De discretisatiemethoden resulteerden in een aantallen-gebaseerde distributie op elke tijdstip, maar vereisten meer rekentijd in tegenstelling tot de moment-gebaseerde technieken. Een eerste discretisatiemethode, de 'High Resolution Finite Volume' (HRFV) methode, werd geïmplementeerd met diverse flux-limiterende functies om negatieve waarden voor de aantallen-gebaseerde distributie en sterke schommelingen in het resultaat te vermijden. Het belang van deze functies werd bewezen door de accurateheid van de simulatieresultaten te vergelijken. De 'Method of Characteristics' (MOC), een andere techniek gebaseerd op discretisatie, vereiste minder rekentijd omwille van het bewegend grid. De moment-gebaseerde oplossingstechniek resulteerde in een set van momenten in tegenstelling tot een distributie op elke tijdstip. De 'Quadrature Method of Moments' (QMOM) werd geïmplementeerd met twee verschillende
Summary - Samenvatting

algortimes, nl. het 'Product-Difference' (PD) en het Chebyshev algoritme. Er kon geconcludeerd worden dat de performantie van het PD-algoritme beter was. Het nadeel van de moment-gebaseerde technieken is de interpretatie van de resultaten, nl. een set van momenten. Er bestaan verschillende reconstructietechnieken die in staat zijn om de onderliggende distributie te reconstrueren gebruik makend van de momenten. Dit geeft echter aanleiding tot een verdere afwijking van de echte oplossing, en bovendien vereiste de 'Method of Splines', de beste reconstructietechniek, een grote computationele kracht. Gebaseerd op de GSA, toegepast op het één-dimensionale PBM-model kon er geconcludeerd worden dat de gastemperatuur de sleutel is om de eigenschappen van de distributie te controleren; het heeft zowel een invloed op de droogsnelheid als op de breedte van de distributie.

Uit experimentele data is gebleken dat granulaten ook opbreken tijdens het drogen. Daarom werd het één-dimensionale PBM-model uitgebreid met een bijkomende interne coördinaat, nl. de grootte van de granulaten, resulterend in een twee-dimensionaal PBM-model. Dit model was in staat zowel de vochtigheidsdistributie als de deeltjesgrootedistributie tijdens het drogen te voorzien. Verschillende brekingsmechanismen (nl. oppervlaktebreking en partikelbreking) werden theoretisch onderzocht. De snelheid van breking werd gevarieerd door de waarden van de parameters van de verantwoordelijke kernel te veranderen. Het effect van de opbreking op het drooggedrag werd geanalyseerd. Er kon besloten worden dat het effect het sterkst was in het geval van uniforme opbreking in twee delen.

Een eerste studie om het stromingspatroon van wervelende partikels te analyseren werd uitgevoerd gebruik makend van Numerieke Stromingsmechanica (CFD). Eerst werd een simulatie uitgevoerd met enkel een gasfase, waarna vanaf de geconvergereerde oplossing, vaste partikels werden toegevoegd aan het stromingsdomein. Dit gaf aanleiding tot een verlies van partikels, een fenomeen dat verder onderzocht dient te worden.

De real-time in-line metingen die continu worden gedrogen tijdens de werking van de ConsiGma™ werden verwerkt, gebruik makend van een massa- en energie-balans. Gebaseerd op deze balansen kon de vochtigheid van de granulaten die de droogtheid verlaten, voorspeld worden. Een goede overeenkomst met een offline Karl Fisher titratie werd gevonden. Bovendien kon de voorspelde en de gemeten gastemperatuur aan de uitgang worden vergeleken, wat een interne controle is van de balansen. Er kon geconcludeerd worden dat het droogproces kan opgevolgd worden tijdens de productie gebruik makend van deze balansen zonder de nood aan extra sensoren.

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Naast de belangrijkste uitkomsten van deze thesis, nl. kennis vergaren door gebruik te maken van mechanistische modellen, de toepassing van een set van krachtige hulpmiddelen om het model te analyseren die de ontwikkeling van mechanistische modellen ondersteunt (vb. sensitiviteitsanalyse en onzekerheidsanalyse), en het gebruik van een massa- en energiebalans voor on-line opvolging van het droogproces, werden verschillende onderzoeksnoten en toekomstperspectieven geïdentificeerd. Eén van de beloftevolle perspectieven is de modellering van de volledige continue tabletterlijn. Dit vereist de koppeling van de verschillende eenheden en de reductie van de complexe mechanistische modellen van deze onderdelen, wat uiteraard een uitdagende taak zal zijn. Een model voor de volledige productielijn is de eerste stap naar een doorgedreven controlestrategie gebaseerd op in-process metingen en een real-time aanpassing van de kritische procesvariabelen.
Appendices

Appendix A: Model reduction of the first drying phase of the single particle drying model

A model reduction procedure is developed, which starts with a GSA to detect the most sensitive degrees of freedom. For the drying behaviour in the first drying phase, this results in the gas temperature, followed by the gas velocity. Subsequently, the drying model was simulated for a number of gas temperatures. Based on these results, a model structure was proposed, which contains some empirical coefficients.

For the first drying phase, the curves display an exponential behaviour at fixed gas temperatures (Fig. 7.3). The data obtained at a gas temperature of 55 °C were used as a starting point (base case). The non-linear behaviour on a log-scale suggested that also other terms should be taken into account. A pure exponential behaviour results in a linear equation on a log-scale.

\[ y = ae^{bx} \quad (15.1) \]
\[ \log(y) = \log(a) + \log(e)bx \quad (15.2) \]

First, \( R_w \) was normed in order to simplify the adaptation of the reduced model to other particle sizes and initial moisture content (Eq. 7.4), after which the first and higher order derivatives of the simulated \( G_{r,1} \) with respect to \( R_w \) (same procedure as equation 7.2) were taken. The second order derivative of the data showed a linear trend on a log-scale. Hence, the proposed expression for describing the growth term for the first drying phase was equation 7.3.

A first estimate of the different coefficients was based on the first till third
Appendix

derivative of the growth function:

\[
\frac{dG_{r,1}(R_{w,nor})}{dR_{w,nor}} = B + C \, D \, e^D \, R_{w,nor} \tag{15.3a}
\]

\[
\frac{d^2G_{r,1}(R_{w,nor})}{dR_{w,nor}^2} = C \, D^2 \, e^D \, R_{w,nor} \tag{15.3b}
\]

\[
\frac{d^3G_{r,1}(R_{w,nor})}{dR_{w,nor}^3} = C \, D^3 \, e^D \, R_{w,nor} \tag{15.3c}
\]

Using this approach coefficient \( D \) could be obtained for each simulation at a different gas temperature by dividing equation [15.3c] by equation [15.3b]. Once \( D \) is determined, a step-wise approach can be used to obtain estimates of the other coefficients. \( C \) can be easily determined from equation [15.3b] or [15.3c]. Subsequently, coefficient \( B \) can be obtained by calculating the offset between the first derivative and equation [15.3a]. The same procedure was followed for determining coefficient \( A \), but through comparing the original data of the growth with equation [7.3]. Subsequently, the values of the obtained coefficients were optimised using an optimization algorithm (i.e. fminsearchbnd3 in Matlab®). This procedure can be repeated for all gas temperatures. Finally, coefficient \( D \) was determined in function of the gas temperature using a polynomial fit. The order of the polynomial was fixed at 2. The higher the order, the more accurate the polynomial will describe the behaviour, but the more parameters will be introduced. Some outliers were detected (numerical errors resulting from the computation of derivatives) and removed, after which the polynomial fit was repeated for the smoothed data. The resulting polynomial is shown in figure A.1 (Eq. 7.8). The reason for the peak in the curve is that the value at this point has no influence as coefficient \( C \) is zero at this point.

Using the fixed relation between coefficient \( D \) and the gas temperature, the other coefficients were optimised again. This was done because a deviation in the polynomial with respect to the fitted coefficient can be caught by adopting this approach. The relation between \( D \) and \( T_g \) is a fit and will not give exactly the correct value for each \( T_g \). To ensure that the final reduced model is able to calculate the growth term as reliably as possible, the coefficients are optimised again by minimizing the error between the simulated result and the reduced model (using fminsearchbnd3 from Matlab®). Afterwards, a relation between coefficient \( C \) and the gas temperature was established (Fig. A.1) (Eq. 7.7). In a similar step-wise fashion, coefficients \( B \) and \( A \) were optimised and a polynomial was fit to relate the optimised value and the gas temperature (Fig. A.1) (Eq. 7.6 and 7.5). As the polynomial for \( A \) was determined in the final step, the order was chosen somewhat higher.

The resulting gas temperature dependent functions are summarized in table 7.3 where \( T_g \) represents the gas temperature in °C.
Appendix B: Model reduction of the second drying phase of the single particle drying model

The same procedure as for the first drying phase, explained in the previous appendix, has been used to develop an empirical model for the second drying phase.

The behaviour of the second drying phase is different (Fig. 7.7). Again, the data at a gas temperature of 55 °C were used for the base case. The growth of the second drying phase showed a symmetric shape around a normalized radius $R_{w,nor}'$ of 0.5. Therefore it was hypothesized to use the same function for both parts which could be easily added together. The curve also showed an infinite behaviour when $R_{w,nor}'$ was approaching zero or one. Therefore the most convincing hypothesis was to use a generalized hyperbolic function $(A' R_{w,nor}' B')$ for describing the curve for low values of $R_{w,nor}'$. For values higher than a normalized radius of 0.5 a similar equation was used to fit the
data, namely \( C' \left( 1 + D' R_{w, nor}^' \right)^{E'} \). By combining the previous functions, the data could be described in an appropriate way:

\[
G_{r,2}(R_{w, nor}, T_g) = A' (R_{w, nor}^')^{B'} + C' \left( 1 + D' R_{w, nor}^' \right)^{E'}
\]  
(15.4)

Using all simulated data (at different gas temperatures) and testing global optimization algorithms for all coefficients, the obtained curves of the coefficients in function of the gas temperature were not smooth at all, but it could be concluded that coefficients \( B' \) and \( E' \) could be approached by -1 in a first attempt. With this information coefficients \( A' \), \( C' \) and \( D' \) were subsequently optimised (with fminsearchbnd3 in Matlab\textsuperscript{®}). First, the relation between \( A' \) and \( C' \) and the gas temperature was determined (Eq. 7.11 and 7.13). Because these relations are always an approximation, coefficient \( D' \) is optimised, before its relation with the gas temperature is determined (Eq. 7.14). After this step coefficients \( a'_1, a'_2, c'_1, c'_2, d'_1 \) and \( d'_2 \) were optimised simultaneously. Using these relations for the coefficients an offset was found between the simulated result and the empirical model. The maximum value of the growth function for different gas temperatures varied between \(-1.181 \times 10^{-10}\) and \(-3.383 \times 10^{-5}\). As a result of the large range of values, it is not possible to minimize directly the difference between the simulated data and the empirical model. Therefore, a relative adaptation was introduced to remove the offset, resulting in equation 7.9. \( R'_f \) was determined for each simulated data point and in a next step also fitted in function of the gas temperature (Eq. 7.16). Using the calibrated \( R'_f \) relation coefficients \( a'_{11}, a'_{21}, c'_{1}, c'_{2}, d'_{1} \) and \( d'_{2} \) were optimised again. In a next step coefficient \( B' \) and \( E' \) were optimised and the relation between them and the gas temperature was determined (Eq. 7.12 and 7.15). However, coefficient \( B' \) and \( E' \) display a strong correlation. Finally, all coefficients were optimised. The resulting equations are given in table 7.4.

**Appendix C: Additional figures to compare the different solution methods for the one-dimensional PBM-model (Chapter 8)**
Figure C.1: $m_0(t)$ (Left) and $m_1(t)$ (Right) for the HRFV-scheme with $\kappa = 1/3$ and $\Phi_{KO}$ as flux limiting function for different grid sizes ($N$)

Figure C.2: $n(R_w)$ at 300 s for the HRFV-scheme with $\kappa = 1/3$ and $\Phi_{KO}$ as flux limiting function for different grid sizes ($N$)

Figure C.3: The standard deviation for the HRFV-scheme with $\kappa = 1/3$ and $\Phi_{KO}$ as flux limiting function for different grid sizes
Figure C.4: $m_0(t)$ (Left) and $m_1(t)$ (Right) for the MOC for different grid sizes ($N$)

Figure C.5: $n(R_w)$ at 300 s for the MOC for different grid sizes ($N$) MOC
Figure C.6: Comparison of $m_2(t)$ (Upper left), $m_3(t)$ (Upper right), $m_4(t)$ (Lower left) and $m_5(t)$ (Lower right) for the different solution methods using discretisation
Figure C.7: $m_3(t)$ (Upper left), $m_4(t)$ (Upper right), $m_5(t)$ (Lower left) and $m_6(t)$ (Lower right) for the QMOM using the PD-algorithm
Figure C.8: $m_0(t)$ (Upper left), $m_1(t)$ (Upper right) and $m_0(t)$ (Lower) for the QMOM using the Chebyshev algorithm
Figure C.9: Comparison of $m_2(t)$ (Upper left), $m_3(t)$ (Upper right), $m_4(t)$ (Lower left) and $m_5(t)$ (Lower right) for the MOC-method with QMOM-PD
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Poster + short oral presentation:


3. 5th International Conference on Population Balance Modelling, September 11-13, 2013, Bangalore, India: Scenario Analysis on a PBM describing the drying behaviour of wet pharmaceutical granules.

Poster:

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Curriculum vitae

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