Development of critical quality attributes control strategies in a continuous high shear wet granulation process

N. Nicolaï1,2, T. De Beer2, K.V. Gernaey2 and I. Nopens1
1BIOMATH, Department of Mathematical Modelling, Statistics and Bioinformatics, Faculty of Bioscience Engineering, Ghent University, Coupure Links 653, 9000 Ghent, Belgium
2Laboratory of Pharmaceutical Process Analytical Technology, Department of Pharmaceutical Analysis, Faculty of Pharmaceutical Sciences, Ghent University, Harelbekestraat 72, 9000 Ghent, Belgium
3Department of Chemical and Biochemical Engineering, Technical University of Denmark, Building 229, 2800 Kgs. Lyngby, Denmark
niels.nicolai@UGent.be

Transition towards continuous production has gained serious attention from the pharmaceutical industry as well as its regulatory authorities, mainly because of its economic, product related and environmental benefits. Clearly, such manufacturing systems require a combination of advanced process measurement tools, a thorough understanding of the process dynamics and an effective yet robust control strategy allowing real-time release. Therefore, continuous manufacturing in the pharmaceutical industry demands a well-advised plan of action.

In this study, the focus is on an innovative continuous from-powder-to-tablet production line used for secondary manufacturing of pharmaceutical tablets, ConsiGma™. Recent advances in both process analysers as well as the ongoing development of validated mechanistic models for the granulation and drying sub-processes, have paved the way for closed-loop control of the considered continuous wet granulation and drying line. Typically, this line comes with a regulatory control layer capable of controlling nine univariate critical process parameters (e.g. drying temperature, screw speed and air flow rate). However, critical quality attributes (e.g. granule size distribution, granule shape, density and residual moisture content), i.e. the variables directly related to the quality of the product itself, are not measured nor controlled in real-time, hence nullifying most of the advantages of continuous processing. Therefore, the purpose of current research is to extend the regulatory control layer of the system by adding additional control loops which allow for direct control of product quality related properties.

A first step towards this objective was the identification of all control relevant product variables and the selection of a suitable operating point in the accompanying design space. Subsequently, the dynamic behaviour of the system around this operating point needs a thorough investigation in order to develop suitable multiple-input multiple-output (MIMO) control strategies (e.g. decentralised control and decoupled control) using computer-aided design tools.

The ultimate goal of this ongoing study is the development of a system-wide supervisory control layer capable of controlling the different sub-processes as one integrated system. Eventually, this could unlock the full potential of the considered continuous manufacturing line as well as continuous production in the pharmaceutical industry as a whole.