Uncertainty analysis applied on drying model for pharmaceutical granules

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Introduction: Pharmaceutical processing

- Shift: from batch to continuous processing ongoing
  → Development of mechanistic models of multi-phase systems useful for
  - Understand the process (knowledge buildup)
  - Once understood, control the process
- Model: conceptualisation of reality → Assumptions and simplifications of the system → Model output uncertainty due to uncertainties in model structure, parameters and inputs
- Objective: quantify uncertainty through uncertainty analysis to investigate the prediction uncertainty induced by the main assumptions at the particle level and the most sensitive parameters using the GLUE methodology (see right)

Single particle drying model

A mechanistic model for single granules was calibrated and validated [1]

The drying process consisted of two distinct, sequential periods:
  - First drying period: fast drop in moisture content:
    \[ m_t = \frac{h_0(n - p_\infty)}{A} \]
  - Second drying period: slow evaporation:
    \[ m_v = \frac{h_0(R_{p,\infty} - R_{p,\infty})}{A} \exp\left(\frac{\beta t}{R_{p,\infty}}\right) \]

Results: Parameter set 1: \( \epsilon, V_0, R_p \)

Influence of ‘the particle assumptions’ on the model prediction: porosity (\( \epsilon \)), gas flow rate (\( V_0 \)), dry particle radius (\( R_p \))
A threshold value of 1.4 is used

Two-dimensional dottyplot of the fitting criterion: used to detect correlations between parameters

Conclusions:
  - \( \epsilon \) and \( R_p \): a distinct region within the prior distribution is obtained
  - \( V_0 \): with available experimental data not able to identify parameter value

Predictive Uncertainty boundaries:

Results: Parameter set 2: \( \beta_1 \) and \( \beta_2 \)

Influence of the most sensitive parameters on the model prediction
A threshold value of 3 is used (\( > 1.4: \) parameter set 1)

Conclusions:
  - \( \beta_1 \): a low value for wSSE is possible for any value
  - \( \beta_2 \): shape is inherently connected to drying process itself

Two-dimensional dottyplot:

Take home message

- Parameter space is assessed by evaluating simulations according to the likelihood, which is based on experimental data
- Additional insight in the model structure can be obtained by performing a GLUE analysis (correlations between parameters)
- The extension of the model to a batch of granules can be used to investigate the distribution of the moisture content, which is important for the subsequent tableting step


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