Application of model uncertainty analysis on the modelling of the drying behaviour of single pharmaceutical granules


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A shift from batch processing towards continuous processing is of interest in the pharmaceutical industry. However, this transition requires detailed knowledge of all consecutive continuous 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 under study. Since modelling efforts only started recently in this field, uncertainties about the model predictions are generally neglected. However, model predictions have an inherent uncertainty originating from uncertainty in input data, model parameters, model structure, boundary conditions and software. In this presentation, the model prediction uncertainty originating from parameter uncertainty will be illustrated for a model describing the continuous drying of pharmaceutical wet granules in a six-segmented fluidized bed drying unit, which is part of the full continuous from powder to tablet manufacturing line (Consigma,...). A validated model describing the drying behaviour of a single pharmaceutical granule in two consequent phases is used (Mortier et al., 2011).

First, an uncertainty analysis is performed based on the parameters that are directly linked to model assumptions and boundary conditions i.e. all particles are assumed to be spherical (Rp), have a certain porosity ($\varepsilon$) and have a certain gas flow rate passing their surface equal to an average gas flow rate (Vgas). The Generalised Likelihood Uncertainty Estimation (GLUE) (Beven, 2006) method is used to propagate uncertainty to the model output. Calculated model prediction uncertainties are shown in Figure 1. As expected, assumed prior parameter distributions have limited influence on uncertainty boundaries and confidence boundaries may slightly depend on the selected fit criterion and its threshold value. As a second step, the same analysis is performed on the most sensitive parameters since they have the largest influence on the model predictions. Finally, all mentioned uncertain parameters are taken into account and confidence boundaries are evaluated. These analyses give a realistic view on the prediction power of the models and can be very important when using models in scenario analysis, control and optimisation.

Figure 1 – Measurement data (points) and model prediction uncertainty boundaries.


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