Application of Global Sensitivity Analysis As Preparatory Step for Reduction of a Drying Model of Pharmaceutical Granules

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Publication date:
2012

Document Version
Publisher's PDF, also known as Version of record

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Citation (APA):
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Thursday, November 1, 2012: 4:05 PM
Conference A (Omni )

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A shift from batch towards continuous manufacturing is nowadays gaining interest in the pharmaceutical industry (Leuenberger, 2001). However, this transition requires detailed knowledge of all consecutive unit operations in a continuous manufacturing line in order to design adequate control strategies for guaranteeing product quality at all time. One hereby relies on in-process measurements of critical process and product parameters and real-time adjustment of input variables. Given the complexity of the system, the knowledge development can be facilitated by developing mechanistic models of the multi-phase systems in the pressure (Mortier et al., 2011). The identifiability of using such models is partly based on the sensitivity analysis of the model parameters, as reviewed in the previous section. Sensitivity analysis techniques are used to rank the degrees of freedom according to their sensitivity (Saltelli et al., 2004; Saltelli et al., 2008). They represent the fraction of the variance observed in the MC results that can be accounted for by a single parameter variation. This contribution gives a detailed description of this GSA to illustrate its usefulness.

The Global Sensitivity Analysis (GSA) methodology used was a Monte Carlo (MC) simulation followed by a statistical analysis for both drying phases, since the behaviour of both phases is very different and might be sensitive to other model constituents. A Latin Hypercube sampling technique from uniform distributions was used to generate the degrees of freedom used in the MC simulation (McKay et al., 1979). Five degrees of freedom were preselected (gas temperature, gas flow rate, gas humidity, gas pressure and initial granule temperature). These were chosen on the basis of their sensitivity in a local sensitivity analysis (evidenced earlier in Mortier et al. (2012)) and the fact that they can be manipulated during the operation of the dryer. A preselection also keeps the sample size of the MC analysis reasonable (2000 samples were generated). An uncertainty range for each degree of freedom was determined based on physical limitations of the dryer and physical reality. Each combined set of degrees of freedom was evaluated (MC shot) and the growth term for the first and second drying phase was calculated.

Comparing the different sets of degrees of freedom it is obvious that the chosen combination of degrees of freedom for the sensitivity analysis has an influence on both drying time and behaviour. The output of the MC was further processed using a linear regression analysis at different time instants in both drying periods using the so-called Standardized Regression Coefficients (SRC) method (Saltelli et al., 2004; Saltelli et al., 2008).

As the drying model reaches no steady state, the moisture content for both drying phases has to be compared after a certain time has elapsed. The average moisture content for one simulation would be another way of selecting an output to perform the linear regression with the parameters that have been varied. For the first drying phase the output was evaluated after 3 s. An R² of 0.97 was obtained, which is above the recommended value of 0.7 indicating that the linear regression model explains a large portion of the observed variance induced by the variance in the degrees of freedom. The SRCs are a robust and reliable measure of sensitivity, even for non-linear models and are sensitive to the degrees of freedom according to their sensitivity (Saltelli et al., 2004; Saltelli et al., 2008). They represent the fraction of the variance observed in the MC results that can be explained by the variance imposed by the degree of freedom. The SRC of the gas temperature was found to be 0.93, clearly higher than the SRCs for the other degrees of freedom (ranging between 0.07-0.29). This indicates that gas temperature is by far the most influential degree of freedom in the first drying phase regardless of the values of the other degrees of freedom. For the second drying phase two time instants were selected: respectively 1 and 11 seconds after the start of the second drying phase. After 1 s the R was 0.75, while after 11 s the R dropped to 0.54 indicating strong non-linear behavior for which the applied GSA method is no longer valid (other GSA techniques should be used here, but this was considered to be outside the scope of this work). For this reason, the output after 1 s was used to rank the degrees of freedom. The gas temperature with an SRC of 0.87 was again found to be the most sensitive degree of freedom.

Since the gas temperature was found to be by far the most sensitive degree of freedom for both drying phases, this input...
variable was selected to perform the reduction of the full drying model.


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