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## **Quality-by-Design Based Characterization of Pharmaceutical Processes by Means of Numerical Simulations**

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Fundamental scientific knowledge is required to develop and optimize pharmaceutical manufacturing processes that yield constantly high quality products and provide most cost efficient manufacturing strategies. In our work we present combined Quality-by-Design and computer simulation approaches (Discrete Element Method, DEM, and Computational Fluid Dynamics, CFD) to characterize three key unit operations of solid and liquid dosage form manufacturing, namely powder blending [1], tablet coating [2] and fluid mixing. The aim is to evaluate the impact of formulation parameters and process variables on process and product quality.

Understanding the variability of both material attributes and process parameters, as well as their overall impact on the unit operations are critical elements for QbD. In a first step, the QbD-methodology is systematically used to (1) establish the critical quality attributes representative for the selected dosage forms, (2) identify potentially critical input factors that may affect process and product quality and (3) risk-rank these factors to define activities for process characterization. Subsequently, computer simulation-based characterizations of the three unit operations are performed. For the blending process the concentration of the active pharmaceutical ingredient, as well as the mixing time are related to the blending uniformity. The film homogeneity on a single tablet is then analyzed as critical quality attribute for the coating unit operation. Finally, a functional design space (engineering design space) for a mixing tank is established. The computational data are used to map out three-dimensional knowledge spaces, leading finally to the definition of design spaces as subset of them. Based on these results, appropriate strategies for process control are presented as well.

- [1] Adam S, Suzzi D, Radeke C, Khinast JG. An Integrated Quality by Design (QbD) Approach towards Design Space Definition of a Blending Unit Operation by Discrete Element Method (DEM) Simulation. Submitted to Eur J Pharm Sci, 2010.
- [2] Suzzi D, Radl S, Khinast JG. Local Analysis of the Tablet Coating Process: Impact of Operation Conditions on Film Quality. Submitted to Chem Eng Sci, 2010.