369c Mathematical Modeling of Wet Granulation:

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Purpose: To develop basic mathematical models which can be used in future for simulation and scale-up of the wet granulation process in high shear or fluidized bed granulators.

Methods: A fundamental model of the wet granulation process should capture and combine the following three key features: 1.Population balancing of growth and breakage of different granules; 2. Hydrodynamic modeling of the gas -- solid mixture flow; 3. Modeling of contact mechanics and granule formation. For pharmaceutical application, the models should predict also the granule composition. In attempt to solve the above problem, we first generalized the volume approach of the rigorous population balances [1,2] and employed it for modeling of 2-component solid + binder or solid + solid granulation under ideal mixing conditions. For calculation of the coalescence kernel we employed the Kinetic Theory of Granular Flow (KTGF) for calculation of number of collisions $N_{i,j}$ between different classes of granules [3]. For the calculation of the number of successful collisions $N_{i,j}^{suc}$ we have proposed the relation

$$N_{i,j}^{suc} = b^{geom}\, b^{phys}\, N_{i,j}$$

where b^{geom} is the geometrical success factor giving the probability that colliding particles hit each other on the wet spot and b^{phys} is the physical success factor which accounts for the dissipation of kinetic energy by viscous forces and can be computed from relations proposed in [4]. For calculation of b^{geom} we used the results of mesoscale simulations of the granule formation [5]. For the evaluation of the average value of the time dependent $N_{i,j}$ we interactively employed the FLUENT multiphase model of granular flow in a pilot plant fluidized bed granulator. Granule breakage was neglected in the calculations but can be added without much complication.

Results: The developed models can predict both the size and composition of different granules. Preliminary theoretical results show that non-uniform granule composition can be caused by the granule -- formation mechanism (i.e. kernel) and also by the non-ideal mixing in the granulator. The model also successfully predicts some interesting phenomena observed experimentally, for example the induction (wetting) period without granule growth for binder solutions with low concentration of the active component, or granule segregation under non-ideal flow conditions in laboratory-scale granulators.

Conclusions: Combination of the population balances with hydrodynamic modeling of granular flow and with calculation of physically based coalescence kernels based on the KTGF and mesoscale modeling of granule formation is a promising tool for the analysis and design of pharmaceutical wet granulators.

References:

[1] Rajniak, P., & Chern, R.: Mathematical modeling of wet granulation: Combination of population balances and FLUENT granular model. Poster No.: T3160, AAPS Annual Meeting, Baltimore, 2004.

[2] Verkoeijen, D., Pouw, G.A., Meesters, G.M.H., & Scarlett, B.: Population balances for particulate processesÑa volume approach. Chem. Eng. Sci.57 (2002) 2287-2303.

[3] Goldschmidt, M.J.V. Hydrodynamic modelling of fluidized bed granulation, PhD thesis, Twente University, 2001.

[4] Liu, L.X., Litster, J.D., Iveson, S.M., & Ennis, B.J.: Coalescence of deformable granules in wet granulation processes. AIChE J. 46 (2000) 529-539.

[5] Stepanek, F., & Ansari, M.A.: Computer simulation of granule microstructure formation. Chem.Eng.Sci. 60 (2005) 4019-4029.