300c Determination of the Coalescence Probability of Wet Granules by Mesoscale Modeling

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One of the outstanding problems in pharmaceutical granulation is the issue of product composition non-uniformity. The composition of granules -- in particular the relative amount of the API (active pharmaceutical ingredient) -- often reveals substantial variation across granule size classes. This may lead to a variation of API content in tablets, an undesirable and potentially dangerous situation. The aim of our work is to understand the fundamental causes of the composition non-uniformity via a combination of experiments, multi-dimensional population balance modeling, and particle-level simulations. In this paper we will address the specific problem of finding the relationship between granule composition (porosity, binder/solids ratio), binder properties (spreading rate and equilibrium contact angle on primary particles), and the probability of coalescence between two granules of different composition or between a granule and a primary particle. Knowledge of this relationship is a pre-requisite for multi-dimensional population balance modeling of granulation, and the testing of various hypotheses that have been proposed as the cause of composition non-uniformity, such as difference in the wettability of the API and excipient particles, or difference in their initial particle size.

We have recently developed computational methodology for the construction of "virtual granules" (see Figure 1a) by random sequential deposition of primary particles of arbitrary shape coupled with spreading and solidification of binder droplets on the particle assembly (Stepanek, 2004; Stepanek and Ansari, 2005). Using this methodology we have generated populations of granules by systematically varying the binder/solids ratio, and the liquid binder contact angle on the primary particles. For each volumetric binder/solids ratio and particle wettability, the corresponding porosity of the virtual granule was found as well as the fraction of particle surface covered by the binder. The necessary (though not sufficient) condition for coalescence during particle collision is that the two colliding objects meet each other in binder-wet regions. We have therefore conducted computational experiments of agglomerate-agglomerate and agglomerate-particle collisions, and recorded the probability of wet contact over a statistically large number of simulated collisions (an example of a typical result is shown in Figure 1b) as function of the composition and size of the colliding agglomerates. Interestingly, this probability does not always coincide with the fractional surface coverage, due to effects such as steric shielding of liquid forming capillary bridges (probability of collision smaller than expected from surface coverage), or imperfect spreading of droplets on the primary particles (larger probability than expected from surface coverage).

The obtained dependence of coalescence probability on granule composition was then used in a multi-dimensional population balance model to predict the composition distribution across size-classes and compared with experimental data from a fluid bed granulator for mannitol-HPC system.

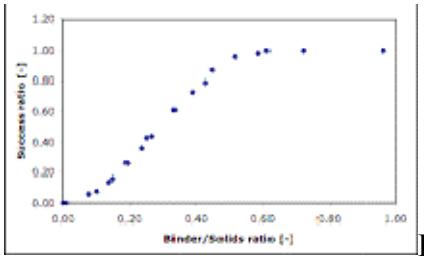
(a)  (b) 

Figure 1: (a) Three-dimensional computer model of a wet agglomerate, obtained by meso-scale simulation. (b) Calculated dependence of the probability that a wet surface is contacted during collision, as a function of the liquid binder to solids

ratio. **References:** F. Stepanek, 2004, Computer-aided product design: granule dissolution, *Chem. Eng. Res. Des.*, 82(A11):1458-1466.

F. Stepanek and M.A. Ansari, 2005, Computer simulation of granule microstructure formation, *Chem. Eng. Sci.*, 60: 4019-4029.