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Scale-up: Issues to consider when scaling from the lab into pilot sized Wurster equipment.

As mentioned in the previous Insight (August 1, 2008), the use of DoE (design of experiments) during the early stages of formulation and process development will help to clarify which of the process variables impact CQA (critical quality attributes). A second benefit is that it essentially forces development staff into keeping as many of the process variables at a consistent value such that the list of variables to be studied is minimized. This discipline is especially important for scale-up to pilot and production sized equipment, where differences in nozzle size, bed depth, particle trajectory and mass effects are intrinsic and essentially unpredictable at the smaller scale.

A common misconception in scale-up is that fluidization in a larger piece of equipment automatically and dramatically results in increased attrition of the substrate. Consequently, and without experimentation to confirm otherwise, a very conservative process air volume is selected for the onset of fluidization. As coating or layering progress, the air volume, spray rate and temperature are stepped upward (sometimes frequently), most often in tandem. If this step-wise ramping consumes a good deal of the overall process time, unraveling it via DoE will be nearly impossible - all of these variables are confounding. In reality, a generalization can be made: coated material is always stronger than uncoated core, therefore, the goal is to get a layer of coating applied *as quickly as possible.* Additionally, the real source of attrition is not fluidization, but the interface between the fluidizing substrate, and the supersonic atomizing air. The substrate accelerates to about 5-10 m/sec where the atomizing air velocity is 300+ m/sec for most nozzles operating at a pressure of 2 bar or higher. It should be noted that pilot and production scale Wursters use a spray nozzle that consumes a large amount of compressed air in order to provide small droplets at the considerably faster spray rate than that used in the R&D lab machine. Consequently, the kinetic energy is much greater.

Heat and mass transfer are also the responsibility of the fluidization air. The evaporation rate governed by the exit air relative humidity threshold of the coating liquid will dictate the rate of solid addition to the core, so there are significant benefits both functionally and economically to using aggressive air flows. In summary, most processes are not adversely affected by keeping the process air volume at a high and constant value for the onset and duration of the process. If experimentation demonstrates some sensitivity, a slightly lower air flow may initially (for 30 minutes or less).

For drug layering onto non-pareil sugar seeds, a stepped increase (typically 3-4 steps) in spray rate within the first 2 hours is common. However, it should be done without using a decreased process air volume. For film coating, constant spray rate, atomizing air pressure, process air temperature and volume are strongly recommended. In this manner, DoE can be applied easily – within a batch, there are no changes made, even for a high weight gain (more than 20%).

What should be evident is that scaling from any of the lab sized Wursters to the pilot scale 18" Wurster is the true 'scale-up', presenting the most significant challenges. Thereafter, production equipment typically incorporates multiples of the partitions and spray nozzles used in the 18" Wurster. In reality, this 'scale-up' should be referenced as a 'scale-out'. Parameters such as process air volume, atomizing air pressure (and volume), spray rate and temperatures derived for the 18" Wurster are typically replicated on a per partition basis in the production equipment. Hardware components are also duplicated – the spray nozzle, partition diameter and orifice plate configurations (permeability in both the up and down bed regions) are the same in both scales of equipment. Partition length is nominally longer therefore the increase in bed depth is usually inconsequential provided that the 18" Wurster was used at or near its working capacity.

The next Insight will delve into considerations for determining the domain for scale-up and a DoE in pilot and production scale equipment.

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