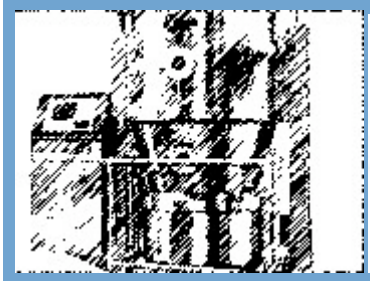
OWI-Consulting Inc
Onsite with Insight

Insight




Written by David M. Jones

Spring, 2009 Volume 7

Troubleshooting is Inevitable: Factors That May Help to Identify the Root Cause for Problems in Fluid Bed Spray Granulation.

The variables in the fluidized bed spray granulation process influence granule properties such as particle size distribution and bulk (and tap) density, metrics that are valuable tools in product and process understanding as well as in retrospective (or reactive) troubleshooting. These attributes are likely to impact tablet properties such as hardness, friability, disintegration and possibly dissolution rate. Unfortunately, beyond the process validation activities, in too many instances simple metrics such as particle size distribution (both before and after any milling or sizing step) and bulk and tap densities are not routinely recorded as in-process parameters. They may be taken under protocol up to that point, but to avoid the potential that a specification may eventually be required (possibly leading to granulation batch rejections on an arbitrary basis), these metrics are often eliminated from the batch records for routine production. This is unfortunate. If a production batch exhibits failures such as delamination of tablets or friability, the troubleshooter must work from the tablet press backwards. Granulation machine parameters may give insight into the root cause and the properties of the granules themselves will likely help to confirm the findings. The fluid bed spray granulation process should take place slowly and deliberately, building granules to the desired size range by the precise control of critical process parameters (CPP). A subsequent milling step should NOT substantively alter the particle size distribution of the dried granulation. It should merely shift the small fraction (typically less than 5%) of oversized granules into the size range of the aggregate. It should also not be of a type that is aggressive or milling may dramatically affect the performance of the granulation on a tablet press. By nature, fluid bed granules are porous and friable in comparison to those made using a high shear granulator. They do not need the force of a high shear mill to break the oversize agglomerates. In fact, a high shear mill may do a considerable amount of damage to the granules, causing an unnecessary amount of fines and this would almost certainly impact the tableting properties. A comparison of the particle size distributions taken before and after the milling step will expose the magnitude of the impact of the mill.

A poorly functioning spray nozzle will typically cause a combination of fines and coarse, dense granules. It does so as a consequence of non-uniformity of droplets – the majority is a fine mist, but there is likely to be a component of very large droplets (exceeding 50 microns) that form granules with nearly liquid centers. The resulting particle size distribution may be bimodal. The consequent dense granules will result in non-uniformity of moisture distribution because they possess little interstitial porosity. Internal moisture cannot move to the surface for evaporation. The surfaces may dry and ‘case harden’ making it all the more likely that the moisture will become entrapped. In some cases the wet granules will blind the screen during the final milling step. In others the mill will grind them finer and mask their existence. In either case, there is a strong possibility that their presence will have an adverse impact on tableting properties. It may seem that taking the moisture content of granules of various sizes would be an effective metric for identifying this problem. However, by the time the batch has been blended and tabletted, the moisture will have equilibrated in the aggregate and the disparity shadowed. If the problem is seen in a particular granulation batch, moistures should be taken as soon as the batch has finished. In a dried granulation, the high density of these granules may be revealed in the particle size distribution as a rogue peak, and bulk and tap density numbers for the aggregate will likely increase.