34a High Shear Wet Granulation: Scale-up Insights Derived from Granule Size and Porosity Measurements

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High shear wet granulation is routinely used in the pharmaceutical industry to improve flow and processing properties of fine powder blends. Scale-up from lab to commercial scale is often complicated by use of mixers with varying geometry and impeller design. Another complicating factor is that scale-up success is commonly measured several steps downstream of the high shear process (i.e. after milling or compression). In this study, granule size and porosity were measured immediately after gentle handling and drying of wet granules in an attempt to evaluate scale-up in the absence of downstream processing effects. Scale-up of a typical formulation was studied from lab (2,10L) to pilot/production (300,600L) scale across different mixer designs using constant impeller tip speed and similar agitation times. Granule properties at each scale were measured over a range of granulating fluid levels (GFL).

The results show that granule growth as measured by d10, d50, and d90 as a function of GFL was qualitatively similar across all scales and mixer designs. An exponential model provided a good fit to the growth curves giving an empirical representation of granule growth kinetics and indicating enhanced sensitivity with increasing GFL. At a given GFL, while d10 values were similar across scales, d50 and especially d90 progressively increased with scale. These results seem consistent with the widely accepted notion that more lump formation occurs at larger scales, likely a consequence of less effective mixing/binder dispersion. However, these results might also indicate that while the uptake of fine particles, as represented by d10, was similar across scales, there could be differences in granule breakage rates between scales. The increase in d90 with scale coincides with a decrease in the size of the chopper zone relative to total working volume in going from the smallest to largest mixer.

Granule porosity, as expected, steadily decreased with increasing GFL. Unlike granule size, porosity did not correlate strongly with mixer scale. The 600L results did show a steeper drop off in porosity with rising GFL, but this is believed to be primarily due to the more aggressive impeller blade design utilized in that particular mixer. The fact that changes to granule size and porosity did not mirror each other across scales suggests that granule growth and consolidation can be influenced by different factors and not always mutually controlled.