plan based on the mixer type and geometry. The drug content assay of the sampled blend must meet preestablished criteria.

Wet Granulation

The wet granulation process offers several advantages over dry blending. Wet granulation provides effective distribution of low-dose actives, increased densification of low bulk density materials, and improved flowability and compressibility of the final blend. Although several wet processes are feasible, granulation employing low/high shear mixers and a fluid bed are more often used in the pharmaceutical industry and will be discussed here.

Low shear granulation employs mechanical agitation at slow speed, such as in ribbon and paddle mixers, planetary mixers, orbiting screw mixers, and sigma blade mixers, or rotating granulators such as twin-shell blenders with an intensifier bar/spray head combination. These granulators usually produce fluffier granules with lower bulk density compared with high shear granulation, which may be the desired property for some products. Important factors to consider during scaling up in rotating blenders include liquid addition rate, spray droplet size, intensifier bar/spray head design, and shell and intensifier bar rotation speeds.

Successful scale-up in mechanically agitated low shear mixers depends on the ability to monitor the granulation process during liquid/binder addition and subsequent wet massing. Researchers have suggested several techniques, such as infrared moisture sensors, torque measurement, current monitoring, and power consumption, to detect granulation endpoint. Luenberger [32] identified five distinct phases during wet granulation in a planetary mixer using a power consumption meter and stated that useful granules could be produced during the third phase. Landin et al. [33] and Faure et al. [34] used the concept of relating power consumption to several process and formulation variables in scaling up granulations in planetary mixers. The variables evaluated were impeller rotation speed and dimensions, wet mass density and consistency (measured using a mixer torque rheometer), and fill ratio (height of wet mass/bowl diameter). Using data obtained for mixers of different sizes, they came up with a relationship between the power number (Np) and Reynolds number (Re), Froude number (Fr), and the bowl fill ratio, that is, $Np = f$ (Re, Fr, fill ratio). The Reynolds number represents the ratio of dynamic to viscous forces, whereas the Froude number represents the ratio of dynamic force in the mixer to the gravitational force. This relationship is useful in predicting consistent granulation endpoints during scale-up [33,34].

Wet granulation in high shear mixer granulators is the method of choice due to shorter process time, superior granule properties, and process reproducibility. High shear granulation offers several advantages, including densification of low bulk density materials, lower binder requirement, control over porosity of granules, and easy cleaning. Several designs of bowls, impellers, and choppers are available from different manufacturers. The most common design has the impeller shaft rotating in the vertical plane. The impeller could be bottom driven inside a fixed bowl, such as in Diosna, PMA/Fielder, and VG/Powrex (Glatt) mixers. In a variation of this design, the impeller and chopper are top driven inside a detachable bowl, such as in Collette-Gral, GMX/Vector, Huttlin, and Bohle mixers. Several of these granulators are