

granulation formulations) can result in granules for compression that provide tablet cores demonstrating

- Prolonged disintegration times (due to excessive hydrophobic layer build-up because of “overblending” with hydrophobic lubricants such as magnesium stearate) [81]
- Low hardness, which again is a symptom of too intimate a contact between granule, lubricant(s), and some intergranular disintegrants

The selection of blender and blending times can also impact the final granule with respect to active/excipient homogeneity and compressibility [17]. In the case of direct-compression formulations, overblending can result in demixing of active [82], in addition to prolonged, disintegration times and soft tablets [83]. Similarly, underblending can give rise to homogeneity and compressibility/encapsulation problems. Consequently, the formulation scientist must optimize the blending conditions during formulation development, with the realization that these may well vary from product to product.

Many pharmaceutical companies employ a perforated pan (e.g., Accela-Cota) coating system to film coat tablets. Sugar coating has almost entirely been eclipsed by film coating. Once again, it would be in the company’s best interests to ensure that the formulation scientist is provided with a smaller version [12- or 24-inch pan(s)] of the same equipment used in the production facility. In addition, environmental, safety, and cost concerns have necessitated the change to aqueous-based film-coating dispersions or water-soluble polymers from organic solvent-based coating solutions. However, the use of organic solvents may, in certain cases, be unavoidable.

ASSESSMENT OF THE FINAL FORMULATION AND EXHIBIT-BATCH PRODUCTION

The most promising formulation, selected based on consistent/satisfactory *in vitro* drug release over a broad hardness range, is then scaled up from an initial development batch size of 5000 units to approximately 20,000 units. Samples of the drug product (which may be in the form of uncoated/coated tablets or capsules) are then packaged in all possible configurations intended for future commercialization, and placed on “informal stability” (investigative stability assessment) together with the appropriate packaging(s) of innovator product, both of which have been analyzed for potency, degradation products, and dissolution profile. By so doing, it is possible to evaluate the comparative stability of the generic product against the product of original research.

“Informal stability” is carried out under “accelerated” conditions of elevated temperature/humidity (normally 40°C/75% relative humidity [RH]) and light (where applicable) for a period of 2 to 3 months. It is also useful to place the Reference Listed Drug (RLD or Brand) on accelerated stability. The generic product is analyzed at monthly intervals for active content/potency, and related substances/degradation products and dissolution profiles are generated. Should stability problems manifest with the generic product stored under a specific storage condition, then testing of the RLD stored under the same conditions can be extremely informative.