

evaluation of the crystalline forms of API is important to avoid processing effects on crystal transformations and amorphous to crystalline transitions, which may have implications for finished product stability, dissolution behavior, and bioavailability. Before formulation development, it is important to establish the crystal properties of drug substances and critical excipients using x-ray powder diffraction and thermal analytical techniques. These techniques can also be used to monitor changes in crystallinity during processing and in the finished product on storage.

Moisture Sensitivity and EMC

Because water is typically used as the granulating medium, the binding property of moisture and equilibrium moisture content (EMC) of the formulation play a significant role in the granulation and drying processes. Hygroscopic materials such as polyethylene glycol, if present in large amounts in a formulation, are difficult to dry. In some instances, the hygroscopic nature of the drug may necessitate the use of special manufacturing facilities with strict humidity control. The EMC of major components generally dictates the final moisture content of the dried granules. The drying rate (drying curve) of a formulation can be theoretically estimated from the drying rate of the individual components. If the drug component is moisture sensitive, water should be avoided as the granulating medium. In such cases, ethanol or isopropanol may be used; however, the drying equipment (tray or fluid bed dryers) needs to be explosion proof because alcohols or other organic solvents have low flash points. Furthermore, the rate and extent of alcohol emission to the environment must be considered, because the Environmental Protection Agency has strict guidelines on alcohol emission that may vary from region to region.

Bulk and Tapped Densities of Major Components

The bulk and tapped densities of formulation components are easy to measure and provide valuable guidance for the flow property and in selection of the manufacturing equipment and processes. Low bulk and tapped densities indicate poor flowability of a material and require additional processing, such as roller compaction or wet granulation, to avoid production problems. Bulk densities of the major components affect the load size in the processing equipment (i.e., mixture and dryer) and govern the batch size. Equation 5.1 can be useful in estimating the batch size load from the bulk densities of the individual components:

$$B = 100 \times \{(a/D_a) + (b/D_b) + (c/D_c) + \dots\}/V \quad (5.1)$$

where B is the percentage load in the mixer; V is the working volume of the mixer (liters); a , b , and c are the weights of the major components in the batch (kg); and D_a , D_b , and D_c are the bulk densities of the components a , b , and c (kg/L). If the calculated value of B is about 50% to 105%, the batch size can be considered appropriate depending on the type of equipment used.

Flow Parameters

The flow characteristics of individual components and the blend remarkably affect the manufacturing process. In addition to bulk and tapped densities, other flow