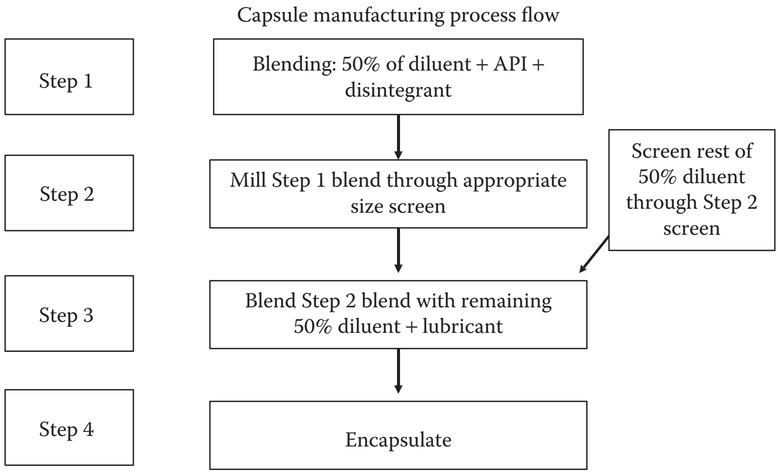

FIGURE 23.5 Example process flow for the encapsulation process.

techniques are available to manage some of the risks, they are best considered long-term strategies to consider these options on case-by-case basis.

Figures 23.3 through 23.5 illustrate the stepwise process flow typically utilized in wet and dry granulation techniques for the manufacture of tablet dosage forms. For capsules, the process tends to be simpler with utilization of first three steps from dry granulation followed by encapsulation in appropriate-size capsule shells. Depending on the batch size, a manual filler (e.g., Bonapace), semi-automatic encapsulator (e.g., Capsugel Ultra 8), or automated encapsulator (Zanasi, Macofar, etc.) could be utilized for manufacturing.

Alexander and Muzzio (2002) suggest that for scale-up of blending operation one must consider the geometry of the blenders, total number of revolutions, fill volume, and total blending time. In theory, blend uniformity is achieved by three essentially independent mechanisms: (1) convection, which causes the large particles to move in the direction of flow owing to blender rotation; (2) dispersion, which considers the random movement of particles due to collision or interparticle motion and generally parallel to the axis of rotation; and (3) shear, which refers to particle separation from large agglomerates. In most tumbling blend operations, the shear involved is relatively minimal, unless an intensifier bar is utilized.

Rekhi and Sidwell (2005) explain the theory of size reduction during the milling operation. The material being milled is subjected to one or more of four forces during milling: (1) shear (cutting forces), (2) compression (crushing forces), (3) impaction (the direct, high-velocity collision force), and (4) tension (forces that elongate or pull particles apart). Cleavage during milling occurs at the weakest point in the granules. The characteristics of the granules after size reduction depend mainly on the type of the mill used, impeller type and speed, screen size, and thickness. Mill selection in turn depends on the material characteristics and classification. Materials can be classified as hard, soft, fibrous, and intermediate on Moh's scale. The important material properties are toughness, brittleness, abrasiveness, cohesive/adhesiveness, melting point, agglomeration tendency, moisture content, flammability, toxicity, and reactivity. These properties must be considered when making a selection between high-energy or low-energy mill. In low-energy mills, the size reduction is accomplished primarily by shear and some attrition whereas in high-energy mills, the size reduction is achieved by high-velocity impact between the rapidly moving impeller/blades and the powder being milled. At times, wet milling of the agglomerates is performed to increase surface area and facilitate efficient drying as well as improve size uniformity and granule formation.

Granulation is a process of agglomeration where significant particle growth is accomplished in a powder blend by the addition of binder solution. The unit operation is intended to ensure content