uniformity, improve blend flow, provide narrow particle size distribution, and densify the material. For water-insoluble compounds, the wet granulation process can be the process to modify intrinsic dissolution rates of the compounds. The mechanism to accomplish granulation involves powder mixing, binder addition in solution or liquid, wetting of powder mass and nucleation, growth of the granules, and densification of the powder and granule attrition and breakage. The resulting wet mass is further dried and processed downstream to a finished dosage form (Figure 23.4). Gokhale et al. (2005) classified the granulation process as (1) low-shear (PK blender with intensifier bar, planetary mixer, ribbon blenders, etc.) granulator, (2) moderate-shear granulator (fluid-bed granulation with rotor granulator), and (3) high-shear (HS) granulator (ULTIMAPROTM and GMXTM). The process variables affecting the quality of granules are (1) powder blend load, (2) impeller speed, (3) granulation liquid addition method and rate, (4) chopper speed, and (5) granulation time.

Process factors also need to be considered for this unit operation such as granulation liquid requirement for a particular blend mix. This largely depends on the blend characteristics, but in theory the liquid requirement is generally close to saturation. The saturation requirement largely depends on the blend composition. Lipps and Sakr (1994) concluded in their study that the insoluble fillers like dibasic calcium phosphate (DCP) and some grades of lactose can be granulated well below the 100% liquid saturation level. Physical characteristics of the drug and drug load, type of binder, binder solvent, types of excipients, and quantity play a critical role in overall granule characteristics.

It is important to recognize the differences in utilizing the wet granulation technique for water-soluble and water-insoluble API. Furthermore, concentration of the drug in the blend also plays an important role in these considerations. The water-soluble drugs may have the tendency to become solubilized during the granulation and recrystallize on drying. Hence, the volume of the granulation vehicle required in this case becomes a critical parameter in the development process. This is also important for water-insoluble compounds, as the solubilized compounds should be crystallized into the most stable crystal form that has lower aqueous solubility than the original form. In the case of water-insoluble drugs, controlled particle growth and dissolution profiles with content uniformity are challenging tasks. Chowhan (1998) studied the effect of API physical properties on the wet granulation process and resulting granulation. The change in the particle shape of the API was observed to go from spherical to plate structure resulting in the decreased compressibility of the granulation. In summary, for a wet granulation process the scientist must understand the various formulations, process and equipment variables, and the interdependencies of all variables impacting the downstream processing of the solid dosage forms.

For drying of the granulation in fluid-bed process, inlet air temperature, moisture carrying capacity of the air, air volume and velocity, atomization air pressure, liquid spray rate, product temperature, and exhaust air temperatures are the key process variables that dictate the rate of water removal. Examples of different techniques for drying the wet granulation include tray drying, fluid-bed drying, microwave drying, and radio frequency drying. It is important to recognize that the mechanism and principles for water removal differ from process to process. Tray drying seems to be the slowest process where water is removed from the static bed. This may also lead to migration of drug to the surface and has the potential for recrystallization (O'Connor and Schwartz, 1985). Fluid-bed drying tends to be a very efficient process; however, the process leads to loss of density in dried granulation owing to air fluidization of wet mass. This may be a limitation in high-dose scenario as the size of the tablet would tend to increase.

Schwartz (2002) suggests special consideration for the compression process. Press speed for material that compacts by plastic deformation, overmixing of lubricant in the force feeder, heat buildup on long compressions runs, material abrasiveness, and tooling care are important variables for consideration. Dwell time and compression and ejection forces are other variables identified for monitoring process.

Scientists have successfully utilized the cosolvent approach in developing soft gelatin formulations (Tabibi and Gupta, 2000). When the solubilization of an NCE in a definite concentration is accomplished, soft gelatin capsules can become a dosage form of choice. Once a cosolvent system