product quality and the manufacturing process used to produce it [9,10]. Early formulation development and later scale-up trials should include such studies by intentionally selecting excipients covering normal variability in functional properties, for studying their impact on manufacturing and product CQAs. If such materials are not available from the excipient vendor, creative formulation approaches should be designed to incorporate this variability. For example, if a polymer matrix-based controlled release system is designed with a single specified viscosity grade, DOE studies may be performed with specific lots of polymer at the extremes of the viscosity range specified. If such lots are not available from the vendor, then DOE studies may be performed with mixtures of various viscosity grades to achieve the extremes of the specified viscosity range. A robust formulation and process design should be capable of handling typical lot-to-lot excipient variability. However, this should be studied upfront and critical material properties and their control strategy should be clearly identified.

### Particle Shape, Size, and Surface Area

Particle shape and size and the size distribution of APIs and excipients can significantly affect their flow behavior. This is especially significant for products intended for manufacturing using direct compression technology. Spherical particles are ideal for dry mixing, whereas rod- and needle-shaped particles are difficult to process in dry mixing. Most pharmaceutical components (drug and excipients) fall between these two extremes. It is important to perform a thorough microscopic evaluation of the API and other major components of the formulation. The shape, size, surface morphology, and relative amounts of these components should be considered in selecting the manufacturing process. It is also possible to modify particle characteristics of materials for ease in the manufacturing process. For example, Povidone K90 is available as flakes and powder. The powder form is suitable for dry mixing, whereas flakes can be used as a binder that is dissolved in the granulating medium.

### Solubility in Water and Granulating Fluid

If the manufacturing process utilizes the wet granulation method, the solubility of the drug and major excipients in the granulation fluid is critical. Water-soluble components will solubilize during a water-based granulation process and may form a dough-like mass that quickly results in overgranulation and makes drying difficult. If all components are water insoluble, the resulting granules will be soft due to poor binding, and the advantage of wet granulation to improve flowability and content uniformity may not be achieved. A powder mass containing a mixture of soluble and insoluble components in appropriate proportions provides excellent granules. For components that are susceptible to hydrolysis or require drying under milder temperatures, use of organic solvents such as ethanol or isopropanol may be the only alternative.

### Crystallinity and Polymorphism

Many pharmaceutical materials exist in multiple polymorphic crystalline forms. Depending on the crystallization solvent and conditions, the drug substance may also form hydrates or solvates, usually referred to as pseudo-polymorphs. A careful