be administered by parenteral route or other specific routes for specificity of the desired activity). The typical parameter studies for solid dosage forms relate to the ability of a powder mix to flow well in manufacturing machines and to the intrinsic characteristics that make it compressible. Some examples of properties studied include crystal structures (polymorphs), external shapes (habits), compression properties, cohesion, powder flow, micromeritics, crystallization, yield strengths, effects of moisture and hygroscopicity, particle size, true bulk and tapped density, and surface area.

7.2.1 Particle Size Studies

The particle size of a new drug substance is a critical parameter, as it affects every phase of formulation and its effectiveness. Appropriate particle size is required to achieve the optimal dissolution rate in solid dosage forms and to control sedimentation and flocculation in suspensions. Small particle size (2–5 μm) is required for inhalation therapy. The content uniformity and compressibility are governed by the particle size. As a result, the preformulation studies must develop a specification of particle size as early as possible in the course of the studies and develop specifications that need to be adhered to, throughout the studies.

Conventional methods of grinding in mortar or ball milling (where sample quantity is sufficient; generally, it is not sufficient and is limited to about 25–100 mg) or micronization techniques are used to reduce the particle size. The method used can have significant effect on the crystallinity, polymorphic structures (often to amorphous forms), and drug substance stability and can range from discoloration to significant chemical degradation. Changes in polymorphic forms can be determined by performing X-ray powder diffraction (XRPD) before and after milling.

Micronization, where possible, allows an increase in the surface area to the maximum, which can have an impact on the solubility, dissolution, and, as a result, bioavailability. As the aim of most preformulation studies is to determine if a solid dosage form can be administered, knowing that the reduction of the particle size, where it changes the dissolution rates, can be pivotal in decision-making for the selection of dosage forms. In the process of micronization, the drug substance is fed into a confined circular chamber, where it is suspended in a high-velocity stream of air. Interparticulate collisions result in a size reduction. Smaller particles are removed from the chamber by the escaping air stream toward the center of the mill, where they are discharged and collected. Larger particles recirculate until their particle size is reduced. Micronized particles are typically less than 10 μm in diameter. In some instances, micronization can prove counterproductive, where it results in increased aggregation (leading to reduced surface area) or alteration of crystallinity, which must be studied by using methods such as microcalorimetry, dynamic vapor sorption (DVS), and inverse gas chromatography (IGC).

The introduction of DVS in 1994 revolutionized the world of gravimetric moisture sorption measurement, bringing the use of outdated, time-intensive, and labor-intensive desiccator into the modern world of cutting-edge instrumentation and overnight vapor sorption isotherms. With a resolution down to 0.1 μg, a 1% change in