surface energies inherent at material boundaries. Dry powders with mass-median particle sizes larger than around 100–200 μm seldom exhibit strong "cohesive" powder behavior, and such powders are usually described as "free flowing." However, as the particle size decreases, the amount of surface area per unit mass increases, and surface energy forces have a greater influence on bulk powder flow characteristics. For contacting particles smaller than 2–20 μm, such forces can be strong enough to cause small amounts of plastic deformation on the particle surfaces near the points of contact—even with no applied external loads. The bulk behavior of such fine powders can be dominated by their "cohesivity." It is well known that powders composed of finer particles are more cohesive, and, when very cohesive powders are placed in a rotating drum, they neither usually flow easily nor do they form a smooth top surface. Instead, cohesive powders build up large overhanging "chunks" that can break off and collapse or cascade in random avalanches onto the material further down the slope. Placing the rotating drum in a centrifuge at an elevated *g*-level can cause a "nonflowable" cohesive powder to flow.

7.2.10 Caking

Powders cake as a result of agglomeration, owing to factors such as static electricity, hygroscopicity, particle size, impurities of the powder, storage conditions, stress temperature, RH, storage time, and so on. The mechanisms involved in caking are based on the formation of five types of interparticle bonds, such as bonding resulting from mechanical tangling, bonding resulting from steric effects, bonds via static electricity, bonds as a result of free liquid, and bonds caused by solid bridges. During the process of micronization, the formation of localized amorphous zones can lead to caking, as these zones are more reactive to factors described earlier, especially when exposed to moisture. The mechanisms involve moisture sorption as a result of surface sintering and recrystallization at well below the critical RH. In most instances, the increase in RH begins to show some impact at values >20%, resulting in most dramatic effects above 75%–80% RH for powders that are subject to humidity effects.

7.2.11 Polymorphism

Because polymorphism can have an effect on so many aspects of drug development, it is important to fix the polymorph (usually the stable form) as early as possible in the development cycle. Although it is not necessary to create additional solid-state forms by techniques or conditions unrelated to the synthetic process for the purpose of clinical trials, regulatory submission of a thorough study of the effects of solvent, temperature, and possibly pressure on the stability of the solid-state forms is advised. A conclusion that polymorphism does not occur with a compound must be substantiated by crystallization experiments, from a range of solvents. This should also include solvents that may be involved in the manufacture of the drug product, for example, during granulation.

As it is hoped that the issue of polymorphism is resolved during prenomination and early development, it can remain a concern when the synthesis of the drug is scaled up into a larger reactor or transferred to another production site. It is not unlikely that a metastable form identified in prenomination may not be reproduced in later batch