stress, ranging from gentle sieving to micronization process. This can be determined using electric detectors to determine polarity as well as the electrostatic field. The electrostaticity results in significant changes in the powder flow properties.

Studies on tribo-electrification and potential charge buildup on equipment and particle surfaces and subsequent adhesion due to static charge often overlook the fact that all materials (whether they have a net surface charge or not) exhibit surface energy forces, that are very short range, but come into play once surfaces are "touching." These van der Waals forces are due to the dispersive and polar surface energies inherent at material boundaries. Dry powders with mass-median particle sizes larger than around 100 to 200 μm, seldom exhibit strong "cohesive" powder behavior, and such powders are usually described as "free flowing." As particle size decreases, however, 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 that are smaller than 2 to 20 μm, such forces can be strong enough to cause small amounts of plastic deformation on 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 comprised of finer particles are more cohesive, and, when very cohesive powders are placed in a rotating drum, they do not 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.

LX. CAKING

Powders cake due agglomeration as a result of factors such as static electricity, hygroscopicity, particle size, impurities of the powder and storage conditions, stress temperature, RH, and storage time, etc. 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 due to free liquid and bonds due to 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 above specially when exposed to moisture; the mechanisms involve moisture sorption due to surface sintering and recrystallization at well below the critical relative humidity. In most instances, increase in relative humidity begin to show some impact at values above 20% resulting in most dramatic effects above 75% to 80% relative humidity for powders that are subject to humidity effects.

LXI. 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. Whereas, 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.

Whilst 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 batches products because of some unrecorded conditions in the early phases of development. Related substances whether identified or not can significantly alter the predominance of a specific polymorph. To develop a reliable, commercial recrystallization process, the following scheme should be followed in the production of candidate drugs:

1. Selection of solvent system
2. Characterization of the polymorphic forms
3. Optimization of process times, temperature, solvent compositions, etc.
4. Examination of the chemical stability of the drug during processing
5. Manipulation of the polymorphic form, if necessary

Many analytical techniques have been used to quantitate mixtures of polymorphs, for example, XRPD has been used to quantitate the various polymorphs. Assay development requires creation of calibration curves and validation, which can be a difficult task where mixed polymorphs are present and requires study that there is no polymorphic transformation during analysis or change in the hydration of crystals, if that is also a concomitant problem. Whereas at the preformulation stage, the dosage form considerations are still developing, there is need to answer questions like how would a polymorph change should this be subject to manufacturing equipment stress like granulation or drying of granules, wet or dry granulation, and compression. In addition to the polymorphism of active drugs, the excipients like magnesium stearate can be present in various polymorphic forms that can significantly alter the behavior of active drug in the formulation stages. Studies using XRPD, IR, or SEM should be used for excipients as well as the active drug.

LXII. STABILITY STUDIES TO SELECT OPTIMAL DRUG AND EXCIPIENT COMBINATIONS

- Rapid screens of salts, solvates, hydrates, polymorphs and cocrystals.
- Large-scale preformulation and formulation studies.
- Characterization of polymers, food ingredients, and fine particles.
- Process optimization monitoring of surface and bulk chemistry.
- Quality control of incoming raw materials.
- Investigation of batch-to-batch variations in material formulations.
- At-line PAT support of production performance to specifications.

Whereas microcalorimetery remains the workhorse of studies, the use of inverse gas chromatography (IGC) is becoming more popular to determine the changes to drug substance upon micronization. The IGC differs from traditional gas chromatography insofar as the stationary phase is the