scattering. The microscopic method measures the dimensions from two-dimension information, and the Malvern method measures the dimensions from three-dimension information. The measured particle size with different methods may be different sometimes; for example, for needle shape drug, the microscopic method gives larger API size than the Malvern method.

Moisture Content and Hygroscopicity

The effects of moisture content in drug substances and finished dosage form have been widely studied. Static moisture content can be determined by many methods like Karl Fisher titration, loss on drying (LOD), and TGA. Dynamic hygroscopicity of a drug substance has been classified into four categories: non-hygroscopic, slightly-hygroscopic, moderately-hygroscopic and very-hygroscopic (Callahan et al. 1982). Hygroscopicity can be measured with DVS or VTI, by checking drug weight gain/loss at room temperature through at least two cycles of relative humidity gradient between 0% and 90%. At each incremental relative humidity, the drug sample needs to be suitable to ensure the moisture sorption/desorption near completion. For hygroscopic drugs, it is recommended to store them in hermetically sealed containers, with desiccators. A good point for insoluble drugs is that most of them are relative less hygroscopic.

For those drugs with both anhydrous and hydrous forms, they may hydrate/dehydrate during storage and processing. During dehydration, some drugs may convert to an amorphous form, and even have stability problems. Because of the significant solubility difference between the anhydrous and hydrous forms, the transformation may affect the therapeutic effects as well. Therefore, it is critical to study the relationship between the anhydrous and hydrous forms to avoid undesired crystal transformation for both drug substances and finished dosage during storage and processing.

Salt and/or Polymorph Selection

Salt selection may help to improve various properties of drug substance like bioavailability, stability, and manufacturability. Salt screen is often conducted in parallel to the polymorph screen in case a scalable crystallization process for the drug is not found. The importance of polymorphism in pharmaceuticals cannot be overemphasized. Some crystal structures contain molecules of water or solvents, known as hydrates or solvates, respectively, and they are also called as pseudopolymorphs. Identifying all relevant polymorphs and solvates at an early stage of development for new chemical entities has become a common practice in the pharmaceutical industry. For poorly soluble compounds, understanding their polymorphic behavior is even more important since solubility, crystal shape, dissolution rate, and bioavailability may vary with the polymorphic form. Conversion of a drug substance to a more thermodynamically stable form in the formulation can significantly increase the development cost or even result in product failure.

Preformulation should include rigorous studies to determine the number of polymorphs that exist, relative degree of stability of the various polymorphs, solubilities, method of preparation of each form, effect of micronization and tableting, and interaction with formulation ingredients. A conceptual approach to the characterization of pharmaceutical solids (Byrn et al. 1995), presented in the form of a series of decision trees, suggested a sequence for collecting data on a drug substance that will efficiently answer specific questions about solid state behavior in a logical order. These decision trees, although not a requirement by the FDA, should serve as a good strategic tool to organize the gathering of information early in the drug development process.

The importance of controlling the crystal form of a drug substance is also well recognized by the FDA. The FDA's guidance on abbreviated new drug applications (ANDAs) Pharmaceutical Solid Polymorphism states that *appropriate* analytical procedures should be used to detect polymorphic, hydrated, or amorphous forms of the drug substance. The guidance also states that it is the applicant's responsibility to control the crystal form of the drug substance, and if bioavailability is affected, to demonstrate the suitability of the control methods. Recently,