of the hydrolysis rate will be, particularly when partial inclusion takes place. Inhibition of hydrolysis is expected when the ester function is included in the cavity protected from the attack of any reactive species.

Numerous examples of stability changes upon complexation have been reported in the literature (Albers and Muller 1995). However, because it is still rather difficult to predict the precise structure of the complexes, it is not possible at the current stage to predict how complexation should affect stability. For insoluble compounds that also have potential stability problems, a quick stability screening in the absence and presence of complexing agents may prove to be very useful. If complexing agents destabilize the compound, it will certainly make the complexation a less attractive option for solubilization.

SOLID STATE PROPERTIES

The solid state properties like crystallinity, polymorphism (crystal structure), shape (morphology), and particle size of drugs are important in the stability, dissolution, and processibility of drugs. Some commonly used methods in solid state studies include microscopy, hot stage microscopy with polarized light, X-ray powder diffraction (XRPD), thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), FT-IR/Raman, and solid state NMR.

Particle Size

It has been shown that dissolution rate, absorption rate, content uniformity, color, taste, texture, and stability depend to a varying degree on particle size and particle size distribution (Ravin and Radebaugh 1990). For poorly soluble drugs, bulk API having small particle size should be used to enhance *in situ* dissolution. In general, the particle size of API is recommended to reduce to 50% less than 10 μm and 90% less than 30 μm. From regulatory perspective, Sun et al. (2010) published a review on particle size specifications for solid oral dosage forms.

Particle size is very important because for most poorly soluble compounds, the absorption process is rate-limited by the dissolution rate in GI fluids. For example, digoxin exhibits a dissolution rate of limited absorption at particle sizes of greater than 10 μm in diameter because the poor driving force for dissolution supplied by the solubility, combined with the low surface area of drug at larger particle sizes, is insufficient to ensure timely dissolution (Dressman and Fleisher 1986). An increase in bioavailability with particle-size reduction also has been observed with griseofulvin. The extent of absorption of an oral dose increased 2.5 times when the surface area was increased approximately sixfold. Micronized griseofulvin permits a 50% decrease in dosage to obtain a satisfactory clinical response.

Because particle size reduction is often used as a mean of bioavailability enhancement, the effect of the micronization process on the physicochemical properties of the drug substance needs to be carefully studied. Increasing surface area by milling or other methods may lead to rapid degradation of a compound. Drug substances may also undergo polymorphic transformation during the milling process. Milling often causes crystalline material to convert, at least in part, to the amorphous form. The amorphous materials are frequently more hygroscopic and undergo more facile degradation reactions than their crystalline counterparts.

Besides stability concern from particle size reduction, the flowability of drug substances generally will decrease as particle size decreases, which makes it difficult to use direct compression in formulation design and process development. At high drug loading, the poor flowability from micronized API may also cause problems for both dry granulation and melt granulation. Considering the lipophilic property of insoluble drugs, even though reducing particle size can help improving dissolution rate, the sticking of API during compression may become a serious issue if using direct compression and dry granulation approaches.

Some of the most commonly used particle size determination methods in the pharmaceutical industry include sieving or screening, microscopy, sedimentation, stream scanning, and light