TABLE 19.2
Properties of Drug Substances Dependent on the Solid State

Dissolution rate	Solubility
Chemical stability	Bioavailability
Melting point	Flowability
Particle size/shape	Compressibility
Hygroscopicity	Density
Filterability	Suspension viscosity
Tablet hardness	Color

in the literature as depending on the solid state of the drug. Some of these may provide significant advantages in drug development. Form I of celiprol HCl is much less hygroscopic than the form II polymorph (Narurkar et al., 1988). Form A chlorpropamide forms tablets with greater hardness than those of form C under identical compression forces (Matsumoto et al., 1991). Phenobarbitone also has crystalline forms that differ in compressibility profiles (Shell, 1963). The two polymorphs of methylprednisolone have different chemical stability profiles when exposed to identical temperatures and humidities of storage (Munshi and Simonelli, 1970). Crystal size and shape can alter the filterability or syringeability of suspensions, and affect the weight uniformity of tablets and capsules.

While there are numerous examples of miscellaneous physical property differences between different solid phases of the same drug substance, the excess free energy of metastable states is the most important. The higher energy state, a consequence of decreased crystal lattice energy, produces a greater molecular mobility and thermodynamic escaping tendency in metastable solids. This leads to faster dissolution rates and greater solubilities, which can have formulation and therapeutic implications for pharmaceuticals. Drugs with poor aqueous solubility are more likely to show enhanced bioavailability when metastable solids are used, because their oral absorption tends to be dissolution limited.

Advantages of Using Metastable Solids

Dissolution Rate Improvement

The Noyes–Whitney equation for the dissolution of solids into a solvent (Noyes and Whitney, 1897) can be used to calculate the rate of drug concentration (C) increase with time (t):

$$\frac{dC}{dt} = AK(C_s - C_b) \tag{19.2}$$

where A is the surface area of the solid exposed to solvent, C_s is the saturation concentration or apparent solubility, C_b is the bulk solution concentration, and K is a constant including the diffusion coefficient of the solute, the thickness of the unstirred diffusion layer, and the volume of solvent. Rotating die methods have been developed, such as the Wood's die apparatus, which maintain a constant surface area during the initial phase of dissolution experiments. Under sink conditions, where $C_s \gg C_b$, and with constant surface area (A), the intrinsic dissolution rate (IDR) can be obtained. The IDR (units mg/cm^2/min) is directly proportional to solubility, and depends on the intrinsic dissolution properties of the drug in the media, not the dissolution method:

$$\text{IDR} \approx K(C_s) \tag{19.3}$$