Pudipeddi and Serajuddin (2005) recently compiled 81 solubility ratios for 55 different drugs. Their results, which parallel those presented here, show most of the solubility ratios were between 1 and 2 (84%); however, 9% of them had ratios greater than 3. Although the relative increase in solubility is modest, for water-insoluble drugs exhibiting dissolution rate limited absorption, this difference can be important for therapeutic activity.

SOLVATES AND HYDRATES OF DRUGS

Types of Solvates and Characterization Methods

Molecules from the crystallization solvent can become incorporated into the crystalline lattice of drugs during the synthetic process. These solvent molecules may participate in hydrogen bonding with the drug molecules, fill space in the unit cell, and facilitate closest packing arrangements. Hydrates can also form when drugs absorb water vapor from the atmosphere or are exposed to water during processing or when suspended in water.

Solvates are generally discovered by their physical property differences from nonsolvated forms. Buxton et al. (1988) reported a hygroscopic anhydrate and a nonhygroscopic hemihydrate of paroxetine hydrochloride. Techniques like loss on drying or TGA will detect general weight loss on heating a sample, and the solvent may be identified as water by Karl Fisher analysis or as organic solvents by gas chromatographic analysis of the evolved gas. DSC thermograms will typically show an endotherm before melting, owing to loss of the solvent molecules (Giron, 1995). Hotstage microscopy can be used to visualize this solvent loss by examining the sample under silicon oil during heating. Melting point, solubility, tableting behavior, dissolution rates, crystal habit, density, and hygroscopicity can also differ substantially between nonsolvated and solvated forms of the same drug. Khankari and Grant (1995) have reviewed the characterization methods for pharmaceutical hydrates and the physical properties affected by hydrate formation.

Single crystal X-ray analysis can often be used to localize the solvent molecules in the crystal lattice, which may be present in stoichiometric ratios or nonstoichiometrically. Byrn (1982) has classified solvates as polymorphic (desolvate to a new XRD pattern) or pseudopolymorphic (desolvate to a similar X-ray powder pattern). Nonstoichiometric solvates that desolvate to the same X-ray powder pattern are often caused by the presence of *channels* in the crystal that can take up varying amounts of water based on the vapor pressure. SQ33600 (Brittain et al., 1995) and cromolyn sodium (Cox et al., 1971) are examples of this type of solvate.

The majority of characterized solvates are stoichiometric, with either water or organic solvents present in a fixed ratio with the drug molecules. Glibenclamide was isolated as two nonsolvated polymorphs, a pentanol solvate, and a toluene solvate (Suleiman and Najib, 1989). Furosemide could form solvates with dimethylformamide or dioxane (Matsuda and Tatsumi, 1989). Haleblian and McCrone (1969) studied the solid forms of steroids, and found different dissolution rates for two monohydrates of fluprednisolone, a monoethanol and hemiacetone solvate of prednisolone, and two monoethanolates and a hemichloroform solvate of hydrocortisone. Other solvents that have been reported to form solvates with drugs include methyl ethyl ketone, propanol, hexane, dimethyl sulfoxide, acetonitrile, and pyridine. The potential toxicity concerns eliminate most of these from consideration as practical mechanisms of solubility enhancement for human therapeutics.

Stoichiometric hydrates are the most important solvates affecting the solubility of marketed pharmaceuticals. Hemihydrates, monohydrates, and dihydrates are the most common stoichiometric ratios of water incorporated into the crystalline lattice of drugs. Pfeiffer et al. (1970) have shown how different hydrates of cephalosporins could be isolated from solvent systems of varying water activity. Cephalexin has a monohydrate and a dihydrate form, which are stable under different relative humidity conditions. Cefazolin has a monohydrate, a sesquihydrate (1.5 moles water), and a pentahydrate form (Byrn and Pfeiffer, 1992). Jozwiakowski et al. (1996) have found that lamivudine