Water-Insoluble Drug Formation

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Alteration of the Solid State of the Drug Substance: Polymorphs, Solvates, and Amorphous Forms

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The maximum solubility of a drug substance is a function of the nature of the solid phase in equilibrium with a specified solvent system at a given temperature and pressure. Solubility is an equilibrium constant for the dissolution of the solid into the solvent and thus depends on the competition of solute:solvent interactions and solid:solid interactions. Alteration of the solid phase of the drug substance can influence its solubility and dissolution properties by affecting the molecular interactions in the solid.

A crystal of higher free energy will yield an apparent higher solubility than a lower energy stable crystal form of the same molecular structure. In the lowest energy solid state, the energetically favorable solid:solid interactions reduce the escaping tendency of the molecules, and thus fewer molecules dissolve in a given solvent under the same set of environmental conditions. Crystalline polymorphs, solvates and hydrates, and amorphous forms of drug substances have been used to change the thermodynamic driving force for dissolution and to increase the apparent solubility of poorly soluble drugs.

Unlike solubilization techniques that change the nature of the solvent environment (cosolvent systems, emulsions, micellization) or the chemical identity of the dissolved solute (salt formation, complexation, pro-drugs), manipulation of the solid state of the drug substance results in only a transient change in the system. Since the solvent

and the chemical form are identical, the system will ultimately revert to the lowest-energy solid phase in equilibrium with the solvent, with the lowest solubility. Crystal growth and dissolution have been used to assign relative physical stability for polymorphs by observing the direction of the transformation under a microscope under controlled temperature in contact with a solvent. The rate of transformation in contact with a solvent is normally too fast to consider solution or suspension dosage forms of metastable solids. Systems with unusually large energy barriers, slow reversion kinetics, or excipients to retard crystallization can be useful in limited circumstances.

The most practical use of this technique is to alter the solid phase in dry dosage forms where molecular mobility is greatly reduced. Metastable forms of solid drugs are often stable to physical transformation in the time context required for marketable formulations. Tablets, capsules, lyophilized powders, granules for constitution, and other solid dosage forms are ideal systems for incorporation of metastable solid phases. In most cases, the brief exposure to gastrointestinal (GI) fluids does not result in conversion to the lower solubility form prior to generating the desired enhanced effect. Solid-state transformations and transformations induced by adsorbed water during long-term storage can still be problematic. Any consideration of formulating metastable solid phases must balance the expected gain in efficacy with the potential for reversion to the less-favorable form prior to patient use. This involves both an understanding of the phase diagrams (which forms are physically stable under which conditions) and the physical principles governing transformation kinetics.

In this chapter, the theoretical and practical considerations for the use of metastable solids in formulations to gain a solubility or dissolution-rate advantage are explored. Experiments are suggested that identify the potential solid forms of the drug and elucidate the potential advantages and disadvantages. Specific examples of the degree of enhancement that can be expected and special considerations for each type of solid are covered (polymorphs, solvates, and amorphous forms).

THEORETICAL AND PRACTICAL CONSIDERATIONS

Importance of the Solid State of the Drug

Origin of the Effect of Solid State on Solubility

When a medicinal chemist discovers a new chemical entity (NCE) with a desired pharmacological effect, structure-activity relationships are used to optimize the series for activity. Aqueous solubility, partition coefficient, crystallinity, melting point, particle size, and hygroscopicity, all of interest to the formulator of this NCE, will also vary within the series of drug candidates. Because the biological activity is often estimated by target enzyme binding studies in very dilute media, solubility may not be optimized simultaneously. If an ionizable drug candidate is selected, the choice of free acid/base form versus the salt forms again produces a myriad of possible physical properties. The alteration of solubility by judicious choice of the salt was covered in a

previous chapter. In many cases the chosen salt or acid/base can crystallize in a variety of possible arrangements, each of which has the possibility of different physical properties. This includes the possibility of polymorphs, solvates, or noncrystalline (amorphous) forms. Thus, the solid phase chosen for development is the third decision made by the pharmaceutical scientists that has a major impact on the ultimate physical properties of the NCE, including the solubility. In a typical development program, the number of candidates decreases at each stage:

Stage I. Selection of best chemical structure (100–1000)

Stage II. Selection of acid/base/salt form (3–25)

Stage III. Selection of solid phase for development (1–3)

Each of these stages produces molecules of varying solubility by virtue of a change in the crystalline lattice, the last stage being the only one in which the chemical identity or counterion identity is unchanged.

Yalkowsky (1981) has developed equations describing solubility as a function of both hydrophobicity and crystal lattice forces. This has led to the observation that melting point or heat of fusion, both a function of the strength of forces holding molecules together in the solid state, can correlate with solubility within a homologous series. This is because the disruption of the crystal forces is a necessary prerequisite to the release of individual molecules into the solvent for dissolution. Grant and Higuchi (1990) summarized correlations in the case of diphenylhydantoin derivatives and substituted pteridines in their book on organic compound solubility. Wells (1988) has noted that in the series of phenols with hydroxy substituents, the high-melting para-form (hydroquinone) has a much lower solubility than the ortho- or meta-derivatives. Morelock et al. (1994) have used melting points and retention times to correlate with aqueous solubility in a series of reverse transcriptase inhibitors. They have found this useful in selecting the drug candidate that can possess optimum biological parameters and in guiding the further synthetic effort. The same factors can govern the solubility differences between drug-salt forms or solid phases, since, fundamentally, the change is brought about by a difference in solid:solid forces in each case. Wells (1988) has shown that riboflavin polymorphs follow a similar inverse correlation with melting point. Form III melts at 180° to 185°C and is soluble to greater than 1000 mg/mL in water. Forms I and II melt at 270° to 290°C and have solubilities of less than 100 mg/mL.

The success of altering solubility by manipulating the solid phase of the drug depends on which factor dominates the aqueous solubility behavior, the hydrophobicity, or the lattice forces. When the molecule is too lipophilic to have adequate aqueous solubility, cosolvents, pro-drugs, or emulsions are effective in increasing the solubility. Altering the solid state in this case may have little effect on its solubility, since poor aqueous solubility is due to the molecular lipophilicity. In contrast, cosolvents and emulsions do not have much impact if the reason for low solubility is the stability of the crystal lattice. When a drug has low solubility and a high melting point (>250°C), it is likely that disruption of the lattice is needed to increase the effective

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