as a pure material. Interestingly, the 1:1 coamorphous blend released both drugs in a synchronized manner. The coamorphous systems were stored under dry conditions at 4°C and 25°C for 21 days, following which, only the 1:1 mixture retained the amorphous state. Löbmann et al. (2012) also investigated a coamorphous mixture of simvastatin and glipizide. Once again the coamorphous mixtures showed improved stability compared to the individual amorphous forms; however, improved stability was determined to be a result of glipizide acting as an anti-plasticizer rather than a molecular interaction of the two compounds. Similar studies have been conducted investigating coamorphous systems, including Allesø et al. (2009), who demonstrated that an amorphous mixture of cimetidine and naproxen enhanced the dissolution rate of both drugs and Chieng et al. (2009) who found that a mixture of indomethacin and ranitidine created a highly stable amorphous binary mixture.

Viscosity agents have been added to suspensions to retard crystallization in much the same manner that they are used to prevent crystallization to a more stable polymorph. Mullins and Macek (1960) found that suspensions of amorphous novobiocin lasted 22 days at 37°C and 6 months at 25°C before converting to the crystalline compound. By adding 1% methyl cellulose to the suspension, they were able to extend this to more than 1 year at 37°C, making a viable drug product when stored at room temperature. Amorphous formulations that utilize polymers to improve both solubility and physical stability are still susceptible to recrystallization in the solid dispersion. Yang et al. (2010) has developed a numerical model to predict the recrystallization kinetics of an efavirenz-PVP system.

There are drug substances that have only been isolated in the amorphous state owing to bulky side chains that prevent effective packing into the crystalline lattice. In this case, the danger of crystallization later in development can be minimized by stressing the drug to show that it cannot readily be made to crystallize. The usual situation is that the drug substance can form a low-energy stable crystal form, and in fact, this may be a large contributing factor to its poor aqueous solubility. The use of any amorphous drug requires study and application of the principles outlined earlier so that inadvertent crystallization of the dosage form does not occur between manufacture and patient use.

STRATEGY FOR WATER-INSOLUBLE DRUG FORMULATION USING METASTABLE SOLIDS

The use of alternate solid-state forms (crystalline polymorphs, crystalline solvates, or amorphous states) is a viable means to increase the dissolution rate, apparent solubility, or oral bioavailability of a poorly soluble drug substance. Because of the possibility of conversion to more stable forms, these metastable forms should be used only if sufficient solubility is not obtained with the lowest energy crystalline form. The technique is most useful for solid dosage forms, where the chance of converting to more stable modifications is greatly reduced versus solution dosage forms. The first step in taking advantage of these possibilities is to characterize fully the potential crystal forms of the drug and the glass transition temperature of its amorphous form, if this is being considered. The decision trees presented by Byrn et al. (1995) can be helpful in identifying the types of preformulation studies needed to address adequately the phase purity and the conditions of stability for each form. If the metastable forms give an enhancement of solubility that is therapeutically important, stress testing should be done to understand the rate and conditions required for conversion. Storage temperature/humidity, initial water content, and processing variables should be examined to ensure that the chosen solid form could be reliably made into a stable dosage form. If a stable hydrate exists and this form is acceptable, this should be used to prevent physical changes later when the dosage form encounters water. If required, means of stabilizing the metastable form against crystallization of the stable crystal form can be studied. If these experiments show that the metastable form cannot be prevented from converting over the product shelf life, it is best to utilize one or more of the other techniques in this book for solubility enhancement.