Polymorphism in Pharmaceutical Solids

edited by
Harry G. Brittain
Discovery Laboratories, Inc.
Milford, New Jersey

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Effects of Pharmaceutical Processing on Drug Polymorphs and Solvates

Harry G. Brittain

Discovery Laboratories, Inc.
Milford, New Jersey

Eugene F. Fiese

Pfizer Central Research
Groton, Connecticut

I. INTRODUCTION

In the previous chapters, the structural origin, energetics, and thermodynamics of polymorphs and solvates have been largely described for pure chemical entities. In most of the studies reported, the compounds were intentionally converted among various polymorphic forms for the purpose of study. In the present chapter, we will discuss the *unintentional* conversion of polymorphs and the desolvation of hydrates upon exposure to the energetics of pharmaceutical processing. Environments as harsh as 80°C and 100% RH for up to 6 h are not unusual during the routine manufacture of dosage forms. As previously noted, the various crystalline polymorphs frequently differ in their heats of fusion by as little as 1 kcal/mol, with the transition temperature being well below the boiling point of water. In the case of hydrates, removal of water from the crystal lattice requires more energy but is very much dependent on the temperature and humidity history of the sample.

In this chapter we will discuss the effects of pharmaceutical processing upon the crystalline state of polymorphic and solvate systems. Given the degree of attention lavished on drug substances that is required by solid-state pharmaceutical [1] and regulatory [2] concerns, it is only logical that an equivalent amount of attention be paid to processing issues. A variety of phase conversions are possible upon exposure to the energetic steps of bulk material storage, drying, milling, wet granulation, oven drying, and compaction. In this setting, an environment as harsh as 80°C and 100% RH for up to 12 h is not unusual,

and the mobility of water among the various components must be considered.

II. PRODUCTION AND STORAGE OF BULK DRUG SUBSTANCE

The first processing opportunity to effect a change in polymorphic form or solvate nature is with the final crystallization step in the synthesis of the bulk drug substance. Crystallization is thought to occur by first forming hydrogen-bonded aggregates in the solution state, followed by the buildup of molecules to produce a crystal nucleus. A number of parameters are known to affect the crystallization process, including solvent composition and polarity, drug concentration and degree of supersaturation, temperature and cooling rate during the crystallization process, presence of seed crystals and/or nucleation sites, additives that influence crystal habit or add strain to the crystal lattice, agitation, pH, and the presence of a salt-forming molecule. It is evident that ample opportunity exists for the appearance of a polymorphic change when a process is scaled up, or moved to a new site, or run by a new operator.

Since the discovery chemist would have been able to make gram quantities of a quasi-crystalline drug substance, logic holds that the process chemist should be able to make kilograms of the same substance in a GMP manufacturing setting. While Mother Nature and equilibrium may have been fooled at the bench-top (where reaction steps are short and yield is improved through the use of anti solvents), longer processing times and improvements in purity usually mean that thermodynamic equilibrium will be achieved for the first time at the scale-up stage. On the other hand, the need for high yield frequently is the chief motivating force early in a development program, so even the first scale-up phase often fails to produce the thermodynamically preferred polymorph. Eventually, either at the first scale-up site or when the process is moved to a new site, the thermodynamically preferred form will appear. This observation has been attributed to Gay-Lussac, who noted that unstable forms are frequently obtained first, and that these subsequently transform to stable forms.

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