SOLID-STATE PROPERTIES OF PHARMACEUTICAL MATERIALS

STEPHEN R. BYRN
GEORGE ZOGRAFI
XIAOMING (SEAN) CHEN

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SOLID-STATE PROPERTIES AND PHARMACEUTICAL DEVELOPMENT

1.1 INTRODUCTION

Solid-state chemistry and the solid-state properties of pharmaceutical materials play an ever increasing and important role in pharmaceutical development. There is much more emphasis on physical characterization since the release of the International Committee on Harmonization (ICH) Q6A guidance on specifications. This guidance directs the scientist to determine what solid form is present in the drug substance (active pharmaceutical ingredient [API]) and drug product. It directs the manufacturer to "know what they have." Additionally, the ICH Q8 guidance on development and the ICH Q9 guidance on risk management require a firm understanding of how the medicine was developed and any risks involved.

There are many more poorly soluble drugs under development. In many cases, the solid form of the API and the solid form and formulation in the drug product determine apparent solubility that in turn determines blood levels. That is, the formulation determines bioavailability and therapeutic response. In these cases, it is even more important to physically characterize the API form and the formulations. Furthermore, the vast majority of medicines (drug products) are solids and those drug products that are not solids often start with solid APIs. In addition to solubility and bioavailability, the solid form may affect stability, flow, compression, hygroscopicity, and a number of other properties.

This book focuses on solid-state properties of pharmaceutical materials and methods of determining these properties. The authors have made every effort to include examples and case studies in order to illustrate the importance of knowing what you have. This book will focus on solid-state properties and general strategies for physical characterization. Case studies and practical examples will be emphasized. In many respects, this book will illustrate that a medicine is more than a molecule. Additional goals include providing a full physical/analytical/operational definition of the different solid forms as well as other terms frequently used in pharmaceutical materials science including: polymorph, solvate, amorphous form, habit, nucleation, transformation, dissolution, solubility, and stability.

1.2 SOLID-STATE FORMS

Pharmaceutical materials can exist in a crystalline or amorphous state. Figure 1.1 illustrates the crystalline state as a perfectly ordered solid with molecules (circles) packed in an orderly array. Figure 1.1 illustrates an amorphous material as a disordered material with only short-range order. Crystalline materials give an X-ray diffraction pattern because Bragg planes exist in the material (see Figure 1.2). Amorphous materials do not give a diffraction pattern (Figure 1.2). Of course, there are many interesting cases where a pharmaceutical material shows an intermediate degree of order falling somewhere between the highly ordered crystalline state and the disordered amorphous state. From a thermodynamic point of view, crystalline materials are more stable but the rate of transformation of amorphous materials to crystalline materials can be highly variable [1].

Solid-State Properties of Pharmaceutical Materials, First Edition. Stephen R. Byrn, George Zografi and Xiaoming (Sean) Chen.

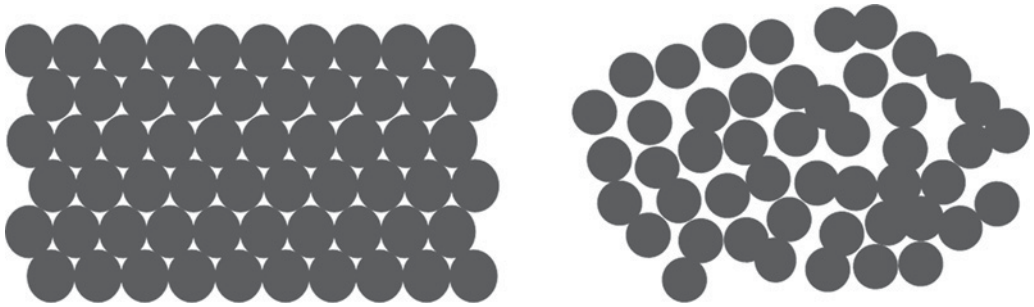


FIGURE 1.1 Idealized view of crystalline (left panel) and amorphous (right panel) material. In this two-dimensional figure, the molecules are viewed as circles.

Crystals of a pharmaceutical material from different sources can vary greatly in their size and shape. Typical particles in different samples may resemble, for example, needles, rods, plates, and prisms. Such differences in shape are collectively referred to as differences in morphology. This term merely acknowledges the fact of different shapes. It does not distinguish among the many possible reasons for the different shapes. Naturally, when different compounds are involved, different crystal shapes would be expected as a matter of course. When batches of the same substance display crystals with different morphology, however, further work is needed to determine whether the different shapes are indicative of polymorphs, solvates, or just habits. Because these distinctions can have a profound impact on drug performance, their

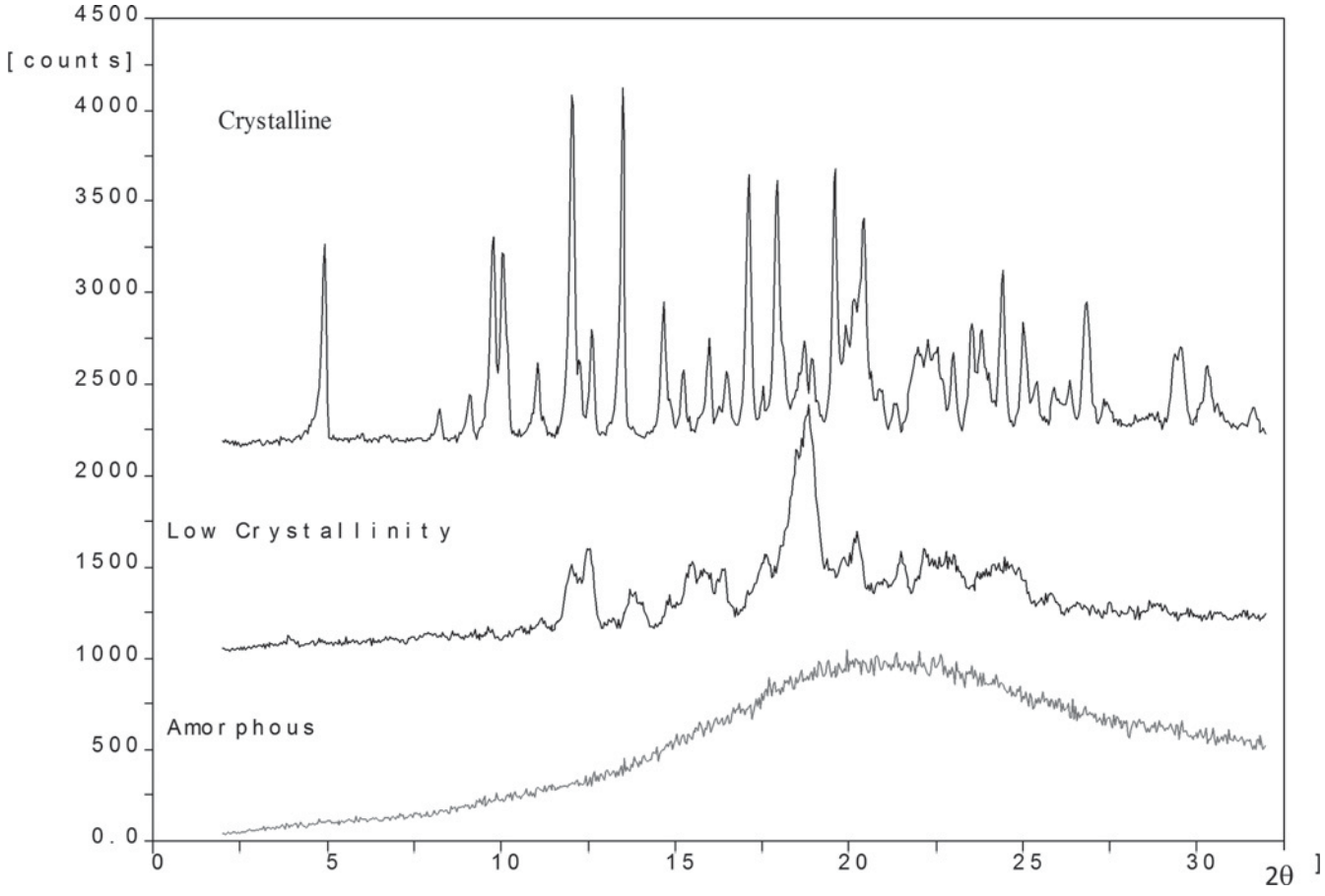


FIGURE 1.2 X-ray diffraction pattern of three samples, crystalline, low crystallinity, and amorphous.

careful definition is very important to our discourse. At this time, only brief definitions are presented.

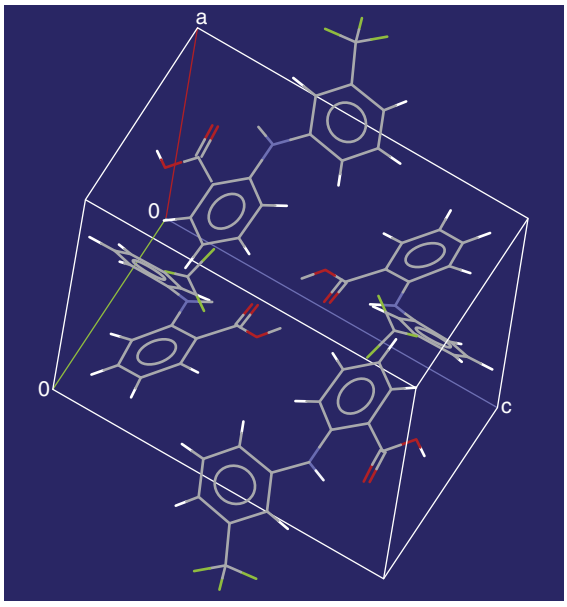
- *Polymorphs*: When two crystals have the *same chemical composition* but *different internal structure* (molecular packing), they are polymorphic modifications, or polymorphs (think of the three forms of carbon: diamond, graphite, and fullerenes). Polymorphs can result from different molecular packing, different molecular conformation, different tautomeric structure, or combinations of these.
- *Solvates*: These crystal forms, in addition to containing molecules of the same given substance, also contain *molecules of solvent* regularly incorporated into a unique structure (think of wet, setting plaster: $CaSO_4 + 2H_2O \rightarrow CaSO_4 \cdot 2H_2O$).
- *Habits*: Crystals are said to have different habits when samples have the *same* chemical composition and the *same* crystal structure (i.e., the same polymorph and unit cell) but display different shapes (think of snowflakes).

Together, these solid-state physical modifications of a compound are referred to as crystalline forms. When differences between early batches of a substance are found by microscopic examination, for example, a reference to "form" is particularly useful in the absence of information that allows the more accurate description of a given variant batch (i.e., polymorph, solvate, habit, or amorphous material). The term pseudopolymorphism is applied frequently to designate solvates. These solid-state modifications have different physical properties.

To put these important definitions into a practical context, we consider two cases (aspirin and flufenamic acid) in which a drug was crystallized from several different solvents and different-shaped crystals resulted in each experiment. Although sometimes dramatically different shapes were obtained upon changing solvents for the various crystallizations, the final interpretations in the two cases are different. For aspirin, X-ray powder diffraction showed that all crystals regardless of shape had the same diffraction pattern. Thus, the different shaped crystals are termed crystal habits. For flufenamic acid, the different shaped crystals had different X-ray powder diffraction patterns. Subsequent analysis showed that the crystals did not contain solvent. Thus these different crystals are polymorphs.

Further analysis of the crystals from this case provides the single crystal structure. The single crystal structure gives the locations of the atoms relative to a hypothetical unit cell. The unit cell is the smallest building block of a crystal. Figure 1.3 shows the unit cell of Form I of flufenamic acid. This unit cell contains four flufenamic acid molecules. Figure 1.4 shows a space-filling model of the contents of the flufenamic acid Form I unit cell. This figure illustrates Kitaigorodskii's close-packing theory, which requires that the molecules pack to minimize free volume [2].

Amorphous materials will be discussed in Chapter 6. In this introductory chapter as mentioned briefly above, amorphous materials have no long range order and are thermodynamically metastable. An amorphous solid is characterized by a unique glass transition temperature T_g, the temperature at which it changes from a glass to a supercooled liquid or rubbery state. When T rises above T_g, the rigid solid can



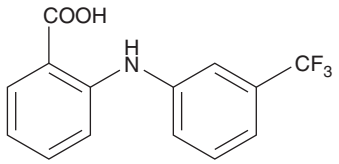


FIGURE 1.3 Single crystal structure the Form I polymorph of flufenamic acid (structure shown on the right panel).

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