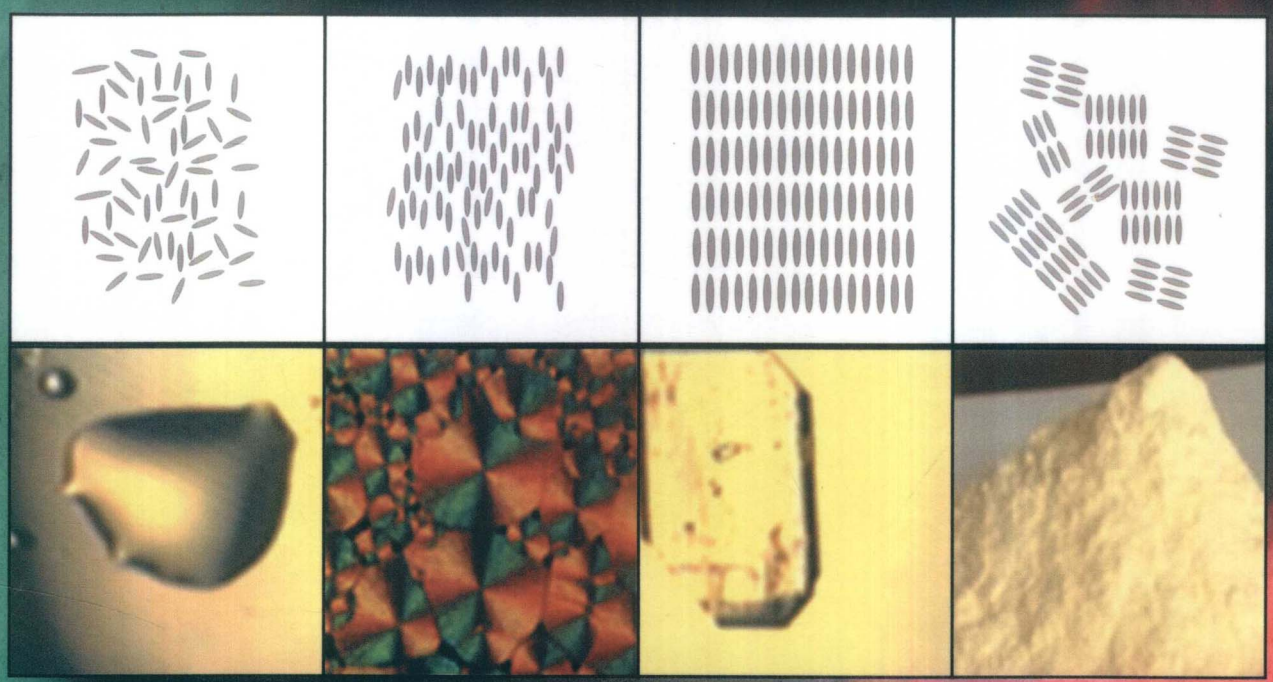
Solid-State Properties of Pharmaceutical Materials

Stephen R. Byrn • George Zografi • Xiaoming (Sean) Chen



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PREFACE

The aim of this book is to illustrate the importance of understanding the fundamental solid-state properties of pharmaceutical materials during the development of solid pharmaceutical products and to lay out general strategies for the physical characterization of solids using various analytical tools. Generally, great emphasis is understandably placed on the discovery of new active pharmaceutical ingredients (API) for the cure, treatment, and prevention of various acute and chronic diseases. However, it has been firmly established that the ability to obtain successful drug products in an efficient and timely manner strongly depends on the formulation and manufacture of stable and bioavailable drugs into useful products, where various physical and chemical characteristics play an essential role. In essence, it can be said, therefore, that a "drug" is more than a molecule, rather being part of a complex mixture of materials with physical chemical characteristics that can determine therapeutic success or failure.

The book is divided into four parts. The first part focuses on the various phases or forms that solids can assume, including polymorphs, solvates/hydrates, salts, cocrystals, amorphous forms, crystal mesophases, and nanocrystals, and various issues related to their relative stability and tendencies to undergo transformations. The second part focuses on the key methods of solid-state analysis such as X-ray crystallography, X-ray powder diffraction, thermal analysis, microscopy, vibrational spectroscopy, and solid-state NMR. The third part reviews critical physical attributes of pharmaceutical materials, mainly related to drug substances, including particle size/surface area, hygroscopicity, mechanical properties, solubility, and physical and chemical stability. The fourth part of the book builds on the first three parts to illustrate how an understanding of the various properties of pharmaceutical materials may be used for (1) the rational selection of drug solid form, (2) the analysis of mixtures of various solid forms within the drug substance and the drug product, (3) establishing rational protocols and strategies for carrying out efficient and successful product development, and (4) applications of appropriate manufacturing and control procedures, using Quality by Design, and other strategies that lead to safe and effective products with a minimum of resources and time.

Furthermore, we have attempted to design this book in such a way that it can be used by preformulation and formulation scientists, process engineers, analytical chemists, quality assurance and quality control managers, regulators, and other researchers, who all contribute to the drug development process. We hope that by presenting a mixture of fundamental solid-state science and its practical applications to the drug development process we will have helped all involved to gain a greater perspective of the importance of both aspects.

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SOLID-STATE PROPERTIES OF PHARMACEUTICAL MATERIALS

CONTENTS

1

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.

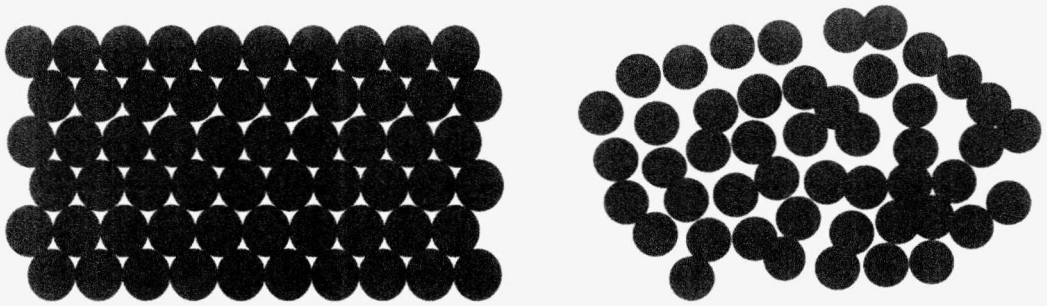


FIGURE 1.1 Idealized view of crystalline (left panel) and amorphous (right panel) material. In this two-dimensional figure, the molecules are viewed as circles.

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

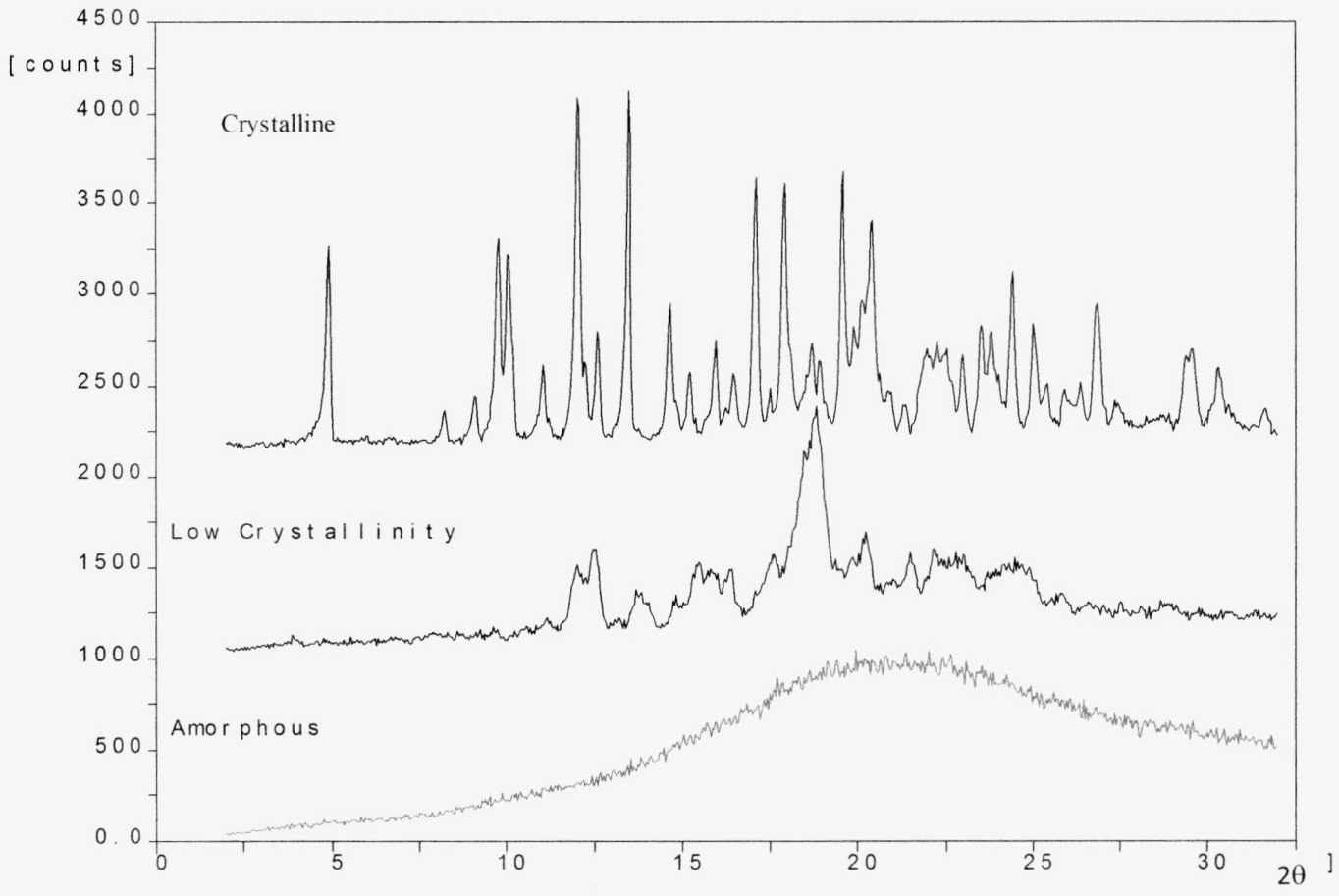


FIGURE 1.2 X-ray diffraction pattern of three samples, crystalline, low crystallinity, and amorphous.

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

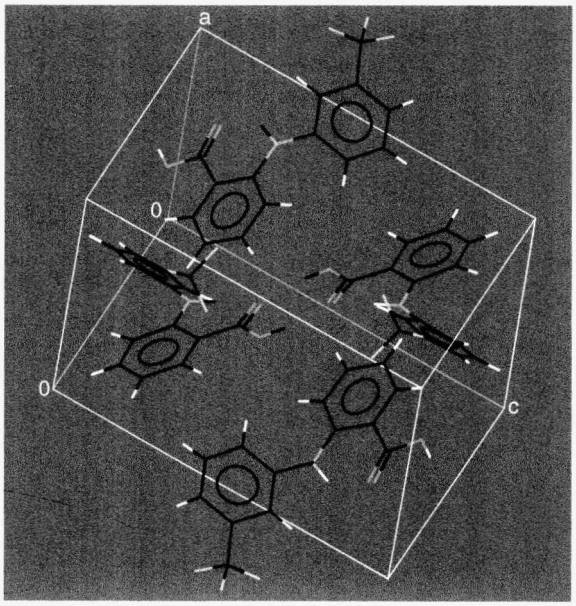
- *Polymorphs*: When two crystals have the *same chemical composition* but *different internal structure* (molecular packing), they are polymorphic modifications, or polymorphs (think of the three forms of carbon: diamond, graphite, and fullerenes). Polymorphs can result from different molecular packing, 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



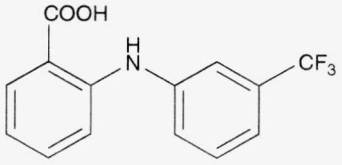


FIGURE 1.3 Single crystal structure the Form I polymorph of flufenamic acid (structure shown on the right panel).

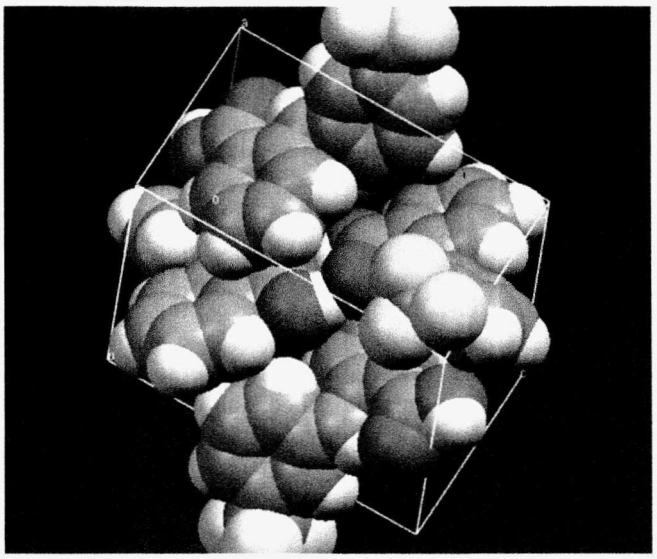


FIGURE 1.4 Space filling drawing of the unit cell of flufenamic acid Form I.

flow and the corresponding increase in molecular mobility can result in crystallization or increased chemical reactivity of the solid. Several historic papers describe some additional details of amorphous materials. Pikal and coworkers at Eli Lilly showed that amorphous materials can have lower chemical stability [3], and Fukuoka et al. showed amorphous materials had a tendency to crystallize [4]. Nevertheless, in some cases, amorphous forms have been historically used as products. An excellent example is novobiocin [5], which exists in a crystalline and an amorphous form. The crystalline form is poorly absorbed and does not provide therapeutic blood levels; in contrast, the amorphous form is readily absorbed and is therapeutically active. Further studies show that the solubility rate of the amorphous form is 70 times greater than the crystalline form in 0.1 N HCl at 25°C when particles <10 micron are used.

It is possible to make a "top 10" list of the differences between crystalline and amorphous materials. Crystalline materials have the following characteristics:

1. higher purity,
2. More physically and chemically stable, *crystalline hydrate > anhydrous crystal > amorphous*
3. lower solubility,
4. narrow and (usually) higher melting point range,
5. harder,
6. brittle – slip and cleavage,
7. directionally dependent properties – anisotropy,
8. less compressible,
9. better flow and handling characteristics, and
10. less hygroscopic.

From this list, it is clear that crystalline materials are generally more desirable unless they are so insoluble that they cannot be used as medicines.

Not only do polymorphs show different X-ray powder diffraction patterns but they also have different unit cells, and different properties including thermal properties [6]. Figure 1.5 shows the different crystal packing of the Forms I and II of sulfathiazole.

Additionally, polymorphs are characterized as monotropic or enantiotropic depending upon their thermal properties [9, 10].

- Monotropic polymorphs exist if the transition temperature between forms is greater than the melt. In monotropic polymorphs, one form is most stable throughout the temperature range.
- Enantiotropic polymorphs exist if the transition temperature between forms occurs before melting. In this case, one form is more stable at one temperature. At a

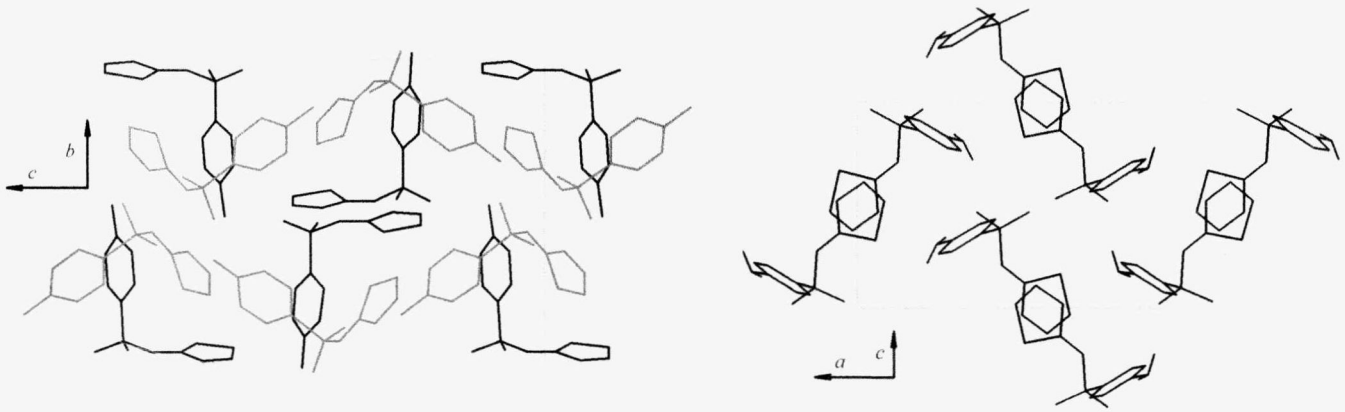


FIGURE 1.5 Crystal packing and unit cells (grey) of Forms I (left panel) and II (right panel) of sulfathiazole. The grey and black molecules in Form I indicate two unrelated molecules in the asymmetric unit. *Source*: Kruger and Gafner, 1971 [7, 8]. Redrawn from data published.

different temperature the other form is most stable. For flufenamic acid, Form I is most stable above the transition temperature of 42°C and Form III is most stable below the transition temperature. Practically, this means that slurrying at room temperature will convert Form I to Form III.

Crystalline solvates contain solvents regularly incorporated into the crystal lattice. When the solvent is water the solid form is called a hydrate. Solvates and hydrates do not have the same composition as unsolvated materials. Solvates and hydrates are sometimes referred to as pseudopolymorphs or solvatomorphs. Interestingly, it is possible for solvates and hydrates to be polymorphic. In such a case one has polymorphic solvates. Kuhnert Brandstatter in her 1971 book showed photomicrographs of 16 solvates of estradiol [11]. Figure 1.6 shows the crystal structure of caffeine monohydrate. The crystal of caffeine is built up by stacking the layers shown in Figure 1.6 on top of each other. Thus the hydrate molecules are in tunnels in this solid form.

It is important to note that the FDA (Food and Drug Administration) has defined polymorphs as "different crystalline forms of the same drug substance. This may include solvation or hydration products (also known as pseudopolymorphs) and amorphous forms. Per the current regulatory scheme, different polymorphic forms are considered the same active ingredients." Thus, for purposes of registration, scientists are directed to define polymorphs more broadly to include amorphous forms, solvates, and hydrates.

Cocrystals, that is, two component crystals, are another solid material of interest. Like solvates, the new crystalline

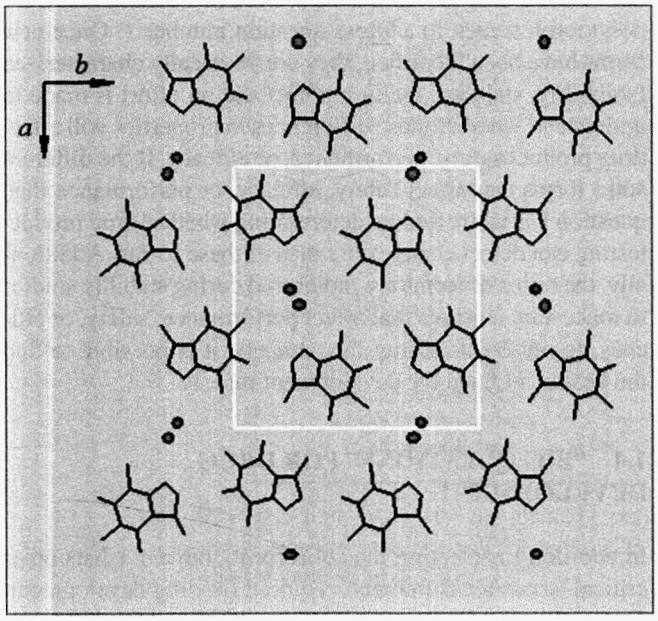


FIGURE 1.6 Projection of the crystal structure of caffeine hydrate on the *ab* plane. *Source*: Burger and Ramberger, 1979 [9, 10]. Reproduced with the permission of Springer.

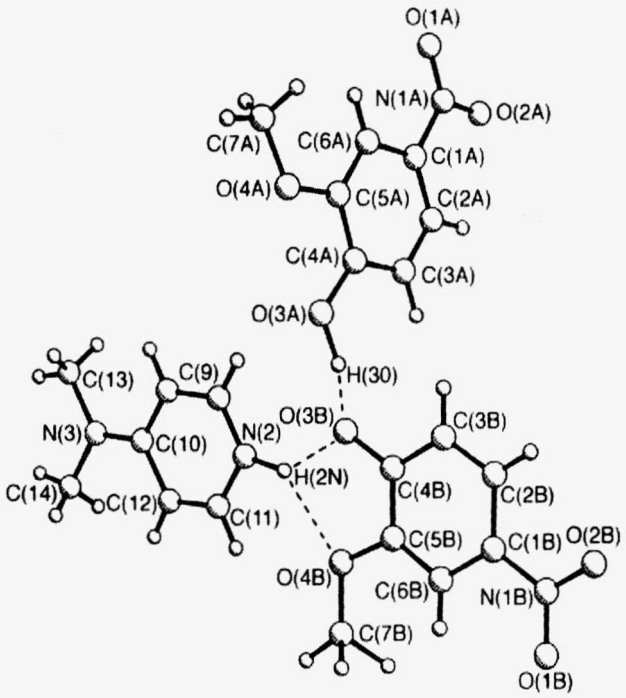


FIGURE 1.7 Crystal structure of a cocrystal (2-methoxy-4-nitrophenol-4-(dimethylamino) pyridine (2:1)). The unit cell parameters are $a = 6.880$, $b = 38.40$, $c = 8.454$, and the space group is $Pna2_1$. *Source*: Burger and Ramberger, 1979 [9, 10]. Reproduced with the permission of Springer.

structure imparts different properties including solubility, stability, and mechanical properties to the material. Of special interest are cocrystals with altered solubility or stability. Figure 1.7 shows the crystal structure of a cocrystal of phenol and 2-methoxy-4-nitrophenol–4-(dimethylamino)pyridine (2:1) [12]. The FDA has recently released a draft guidance defining cocrystals as "Solids that are crystalline materials composed of two or more molecules in the same crystal lattice."

Pharmaceutical salts are substances formed by a reaction of an acid and a base. The FDA has suggested the following definition of salts as "Any of numerous compounds that result from replacement of part or all of the acid hydrogen of an acid by a metal or a radical acting like a metal: an ionic or electrovalent crystalline compound. Per the current regulatory scheme, different salt forms of the same active moiety are considered different active ingredients." When a carboxylic acid reacts with an amine a salt is typically formed (Scheme 1.1). However, the degree of proton transfer can vary depending on the acidity and basicity of the reacting groups. The FDA definition seems to encompass all of these materials.

$$RCOOH + H_2N - R' \longrightarrow RCOO^- \cdots H_3N^+ - R$$

SCHEME 1.1