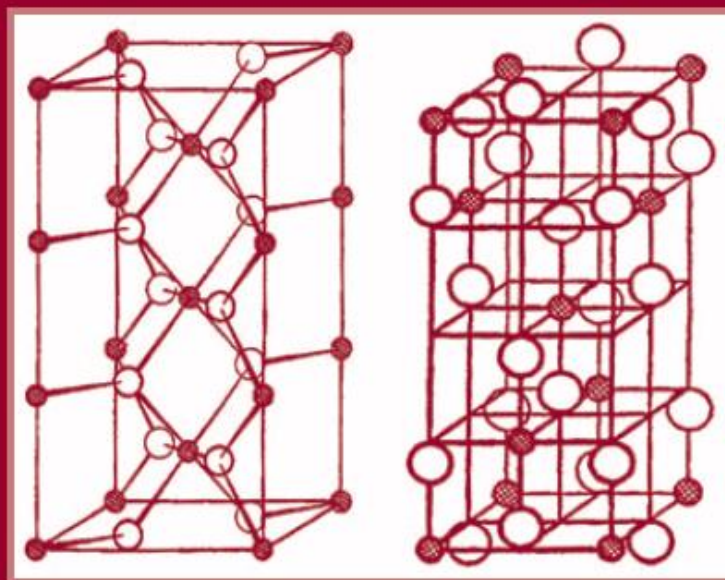


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Polymorphism in Pharmaceutical Solids



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Theory and Principles of Polymorphic Systems

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INTRODUCTION

With the discovery by Bragg that one could use the angular dependence of scattering of X rays from a crystalline solid to determine the structure of that solid (1), structural science has played a large role in the fields of chemistry and physics. Very early in the 19th century, it had become known that many compounds were capable of exhibiting the phenomenon of *dimorphism*, and could be crystallized into solids having different melting points and crystal habits. For example, the α - and β -forms of potassium ethyl sulfate were found to exhibit different solubilities and eutectic temperatures in their phase diagram (2). The existence of a thermally induced phase transition between the anhydrous and monohydrate forms of 5-nitrosalicylic acid was deduced from the temperature dependence of its solubility (3).

As the techniques of structure elucidation grew in their sophistication, the crystallographic basis of dimorphism became firmly established. The X-ray crystallographic technique enabled workers to determine the dimensions and angles associated with the fundamental building blocks of crystals, namely, the unit cell. At the same time it also became recognized that crystalline solids were not limited to one or two crystal forms, and that many solids were capable of being isolated in multitudes of crystalline forms.

During the very first series of studies using single-crystal X-ray crystallography to determine the structures of organic molecules, Robertson reported the structure of resorcinol (1,3-dihydroxybenzene) (4). This crystalline material corresponded to that ordinarily obtained at room temperature, and was later termed the α -form. Shortly thereafter, it was found that the α -form underwent a transformation into a denser crystalline modification (denoted as the β -form) when heated to about 74°C, and that the structure of this newer form was completely different (5). A summary of the unit cell parameters reported for both forms is provided in Table 1. The α -form features a relative open architecture that is maintained by a spiraling array of hydrogen bonding that ascends through the various planes of the crystal. The effect of the thermally induced phase transformation is to collapse the open arrangement of the α -form by a more compact and parallel arrangement of the molecules in the β -form. This structural change causes an increase in crystal density on passing from the α -form (1.278 g/cm³) to the β -form (1.327 g/cm³).

The term *polymorphism* has come to denote those crystal systems for which a substance can exist in structures characterized by different unit cells, but where each of the forms consists of exactly the same elemental composition. For a long time, the term *pseudopolymorphism* was used to denote other crystal variations where the crystal structure of the substance is defined by still other unit cells where these unit cells differ in their elemental composition through the inclusion of one or more

TABLE 1 Summary of the Unit Cell Parameters Associated with the two Polymorphs of Resorcinol (4,5)

Polymorphic form	α -form	β -form
Crystal class	Orthorhombic	Orthorhombic
Space group	<i>Pna</i>	<i>Pna</i>
Number of molecules per unit cell	$Z = 4$	$Z = 4$
Unit cell axis lengths	$a = 10.53 \text{ \AA}$ $b = 9.53 \text{ \AA}$ $c = 5.66 \text{ \AA}$	$a = 7.91 \text{ \AA}$ $b = 12.57 \text{ \AA}$ $c = 5.50 \text{ \AA}$
Unit cell angles	$\alpha = 90^\circ$ $\beta = 90^\circ$ $\gamma = 90^\circ$	$\alpha = 90^\circ$ $\beta = 90^\circ$ $\gamma = 90^\circ$

molecules of solvent, and more recently this term has become replaced by the term *solvatomorphism*. The crystallographic origins and consequences of polymorphism and solvatomorphism have been the focus of several monographs and reviews (6–12), recent annual reviews (13–15), and will be discussed in great detail in one of the later chapters in this book.

The existence of different crystal structures of the various polymorphs of a substance often causes these solids to exhibit a variety of different physical properties, many of which are listed in Table 2. Because of differences in the dimensions, shape, symmetry, capacity (number of molecules), and void volumes of their unit cells, the different polymorphs of a given substance have different physical properties arising from differences in molecular packing. Such properties include molecular volume, molar volume (i.e., molecular volume multiplied by Avogadro's number), density, refractive index along a given crystal axis, thermal conductivity, electrical conductivity, and hygroscopicity. Differences in melting points of the various polymorphs arise from differences of the cooperative interactions of the molecules in the solid state compared with the liquid state. Also observed are differences in spectroscopic properties, kinetic properties, and some surface properties. Differences in packing properties and in the energetics of the intermolecular interactions (i.e., thermodynamic properties) among polymorphs give rise to differences in mechanical properties.

These differences in physical properties among the crystal forms of a polymorphic system have become extremely interesting to pharmaceutical scientists because their manifestation can sometimes lead to observable differences that have implications for processing, formulation, and drug availability (16–21). For such situations, the regulatory concerns can often become critically important, and can determine the path of development for a given drug substance (22). Consequently, an entire field of characterization techniques for the evaluation of pharmaceutical solids has arisen, and its degree of sophistication continues to grow (23–29).

Once the phase space of a substance has been determined, and the scope of possible polymorphic or solvatomorphic forms is established, it becomes critical to determine the boundaries of stability for the different forms and how they might be interconverted. At the very least, one must determine which crystal form is the most stable state, because unless mitigating circumstances dictate otherwise, that form would be the one to be chosen for continued development.

TABLE 2 Physical Properties that Differ Among Crystal Forms of a Polymorphic System

Packing properties	Molar volume and density Refractive index Conductivity: electrical and thermal Hygroscopicity
Thermodynamic properties	Melting and sublimation temperatures Internal or structural energy Enthalpy Heat capacity Entropy Free Energy and Chemical Potential Thermodynamic Activity Vapor Pressure Solubility
Spectroscopic properties	Electronic state transitions Vibrational state transitions Nuclear spin state transitions
Kinetic properties	Dissolution rate Rates of solid-state reactions Stability
Surface properties	Surface free energy Interfacial tensions Crystal habit
Mechanical properties	Hardness Tensile strength Compactibility, tableting Handling, flow, and blending

THERMODYNAMICS OF POLYMORPHIC SYSTEMS

Before a discussion of the thermodynamics associated with systems capable of being crystallized in more than one form can be undertaken, a number of fundamental principles regarding the interactions that can take place in solid systems must be set out. In such discussions, one often uses thermodynamics to treat an *ideal* system, which may be taken as approximating some type of limiting condition. Real systems are often difficult to treat, but ideal systems are useful in that their boundaries can be used to deduce simple laws that are often sufficiently accurate to be practically useful. The following discussion has been distilled from several standard texts on thermodynamics and chemical equilibrium (30–34).

Systems are said to possess *energy*, and interacting systems exhibit simultaneous changes in observable properties that are accompanied by changes in energy. The energy of a system therefore implies the power to interact but also is a description of the results of interaction in terms of changed properties. To the thermodynamic scientist, these properties are usually descriptions in which the system exchanges energy with some standard system, although the properties can also be defined with respect to another member of the system. The changes of interest most pertinent to the present discussion involve changes in *potential* energy, or energy stored in a system as a result of how it came into that state. For example, the transformation of a substance from one physical phase to another involves the transfer of energy in the form of heat. Only changes or differences in energy are empirically measurable, because the

Solvates also include crystal structures where the solvent is not incorporated stoichiometrically into the crystal structure, but is accommodated by affinity at the surface, or in voids or channels in the structure (Fig. 1B). Where solvent is located at the surfaces, it may usually be driven off at temperatures slightly above the solvent boiling point, and the thermal stability will be the primary factor determining whether or not the structure is disrupted. Solvation by incorporation into voids or channels is more akin to solid solution formation, whereby the solvent acts as a solute in the host matrix of the crystalline substrate. In these cases, desolvation may or may not result in structural disruption, depending on both the thermal stability and the extent of the mechanical effects of removing solvent molecules from the depths of the lattice structure. In these cases, desolvation usually occurs at temperatures considerably higher than the solvent boiling point (often up to 30K higher), because of capillary effects in channels and geometric blocking of solvent release. It should be noted, however, that the arrangement of solvent molecules in channels also occurs quite commonly in stoichiometric solvatomorphs (15), by virtue of the crystallographic geometry, and the identification of solvent molecules within channels does not, in itself, characterize the solvate type.

"True" solvates are not polymorphic with the corresponding non-solvated forms, because the chemical constitutions are different. The term "solvatomorph" can be used to designate the fact that they represent alternative structures that are not polymorphic (14). As a general rule, solvates are not favored for pharmaceutical development, except for hydrates and occasionally ethanolates, because of the toxicity and undesirability of ingesting most solvents. Hydrates are often, although by no means universally, less soluble in aqueous media than the corresponding anhydrous forms (4).

Salt forms of drug substances are often employed to enhance their aqueous solubilities. Table 1 shows published data on the number of drug salts available in the 1990s (16). It can be seen that the number of salts with acidic counter-ions (anions) represents about 75% of the total from both sources. There are several reasons for this. First, most APIs contain basic nitrogen functions in their free base forms. Second, the list of anions that are suitable in terms of both appropriate pK_a values and pharmacological safety is much more extensive than the corresponding list of bases. Many nitrogenous bases exert biological and pharmacodynamic effects, and most inorganic cations are either toxic or exert essential biological functions, and in this latter case the dosing of additional quantities may restrict the scope of administration of the drug. Even so, the proportion of cations that are inorganic is considerably higher than the corresponding ratio for anions in both data sets recorded in Table 1. Table 2 gives the frequency distribution of the most common

TABLE 1 Reported Number of Drugs Available as Salts, and the Distribution of Acidic (Anionic) and Basic (Cationic) Counter-ions (16)

Source	No. of drug salts		No. of counter-ions (CIs)	
	with acid CI	with basic CI	Acidic	Basic
Index Nominum, 1995	1346	474	108	37
Rote Liste, 1999 (Germany)	612	208	55	21

TABLE 2 Distributions of Salts with the Most Frequently Occurring Acidic (Anionic) and Basic (Cationic) Counter-ions

Acidic (anionic) counter-ions			Basic (cationic) counter-ions		
Anion	Percentage of total		Cation	Percentage of total	
	Ref. (16)	Ref. (17)		Ref. (16)	Ref. (17)
Hydrochloride	36.2	42.1	Sodium	14.8	17.5
Sulfate	5.2	10.1	Potassium	2.9	4.9
Tartrate	3.3	2.6	Calcium	3.6	1.7
Hydrobromide	4.4	1.4	Magnesium	1.6	
Maleate	3.3	2.3	Meglumine	1.0	
Mesylate	3.3	1.2	Ammonium	0.9	
Phosphate	2.0	3.1	Aluminium	0.8	
Acetate	1.8	3.2	Zinc	0.5	
Citrate	3.0	0.8	Piperazine	0.5	
Pamoate	1.5	0.3	Tromethamine (Tris)	0.5	
Nitrate	1.3	0.8	Lithium	0.5	
Lactate	1.1	1.0	Choline	0.4	
Fumarate	1.1	0.6	Diethylamine	0.4	
Hydroiodide	1.3		4-Phenylcyclohexylamine	0.3	
Methylsulfate	1.1		Benzathine	0.3	
Succinate		1.1			
Propionate		1.0			
Carbonate		0.5			
Gluconate		0.5			
Aspartate		0.3			
Saccharate		0.3			
Besylate		0.3			
Valerate		0.3			

salt-forming acidic and basic counter-ions, as percentages of the total (acids + bases), calculated using data from two sources (16,17). It is clear from these data which counter-ions are used predominantly, although the detailed figures vary according to the data that has been sampled for the two compilations.

Figure 2 shows examples of the solubilization by salt formation of two candidate drug compounds, both of which were virtually insoluble as free bases, with data points effectively lying on the baselines of the charts (18). On solubility grounds alone, Figure 2A shows a clear preference for the edisylate (ethanedisulfonate) salt, although the solubility of 1.7mg/mL is not high in absolute terms. Much higher solubilities are exhibited by the salts in Figure 2B, up to 10mg/mL for the three most soluble forms. A recent investigation of salts with the saccharate anion has identified solubility enhancements of 600, 40, and 3, respectively, for halperidol, mirtazepine, and quinine (19). However, it cannot be assumed that all salts will confer enhanced solubility, and salts can often have lower solubilities than the corresponding free bases. Salt screens are frequently carried out to identify the most suitable counter-ions, as will be described below.

revert to crystalline forms over a period of time. The rate at which such changes occur is of critical importance, and methods developed for stabilizing and formulating amorphous drugs are usually designed to minimize and slow down such interconversions, both in storage and in use. A result such as that in Figure 5C, with interconversion over 20 minutes at 45°C, indicates that such reductions in solubility could occur in vivo (37°C) over the time scale of absorption of the drug, which could end up deposited in the digestive tract as a poorly soluble and slowly absorbed crystalline form.

OVERVIEW OF METHODS FOR PRODUCING SOLID FORMS

The ways in which the various solid forms above may be prepared will be outlined in the following sections in a method-based structure, whereby those methods employed most extensively will be described first and in most detail. The last 10 years or so has seen an explosion in the range and types of method used to prepare solid forms that has been fuelled by the burgeoning interest in polymorphism and solid form diversity and the consequent requirement to prepare and manufacture targeted solid forms consistently and reliably. The traditional crystallization methods have been developed by understanding and controlling their functions, and have been augmented by a number of innovative new techniques to improve both their form selectivity and the range of polymorphs and other solid forms that can be prepared (35).

For preparing crystalline forms, crystallization from solution is by far the commonest method used in the pharmaceutical industry today. Crystallization from melts is rarely employed, mainly because of the limitation of thermal stability of API compounds and the small scales of production. Pharmaceutical production is usually at relatively small scale, with processes carried out batchwise in multi-purpose plants under conditions that are specific for a given product and manufacturing process. Furthermore, synthesized organic compounds are usually prepared in a solution, and crystallization is most commonly employed as the method by which solid material is recovered from the solution of the final synthesis step. Although the logistics and procedural details are different, the same underlying principles govern crystallization as a production method and its use in investigative work, including polymorph searching and single-crystal preparation for X-ray structure determination. Moreover, the production of a specific polymorph identified in such investigations may require the method by which it was obtained to be translated to a preparative or production environment, and this knowledge transfer will be greatly assisted by a sound understanding of the principles that underlie the method by which it was obtained.

As a general principle, slow crystallization and transformation processes operated under mild conditions with moderate driving forces are more likely to produce stable crystalline polymorphs, whereas rapid processes employing dynamic and extreme conditions with large driving forces will produce metastable and unstable crystalline forms and amorphous solids. This principle is illustrated in Figure 6 for a selection of preparation methods, compiled by the author based on a recent similar idea (35,36). The relationship between the speed at which a process operates and the outcome is well represented by the antisolvent mediated processes, using bulk addition and diffusion. These operate on the same principle, but with very different rates of antisolvent addition. Diffusion is a method that introduces

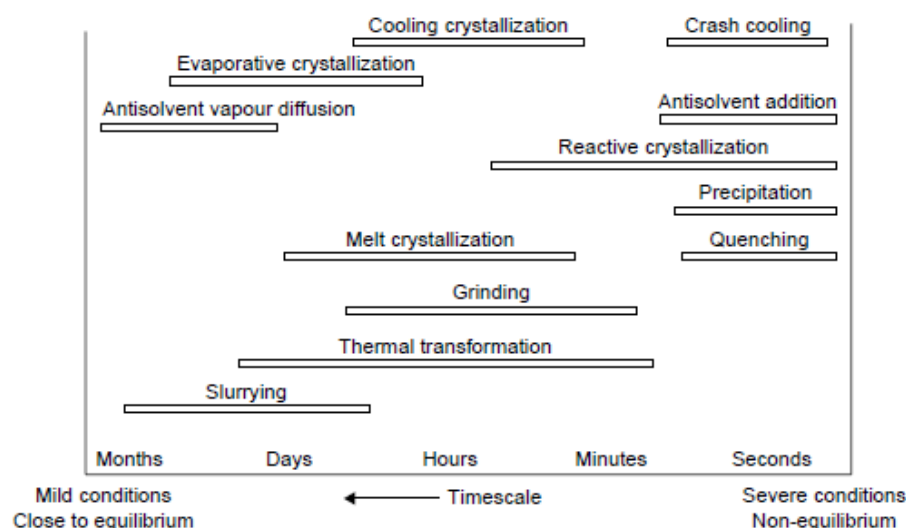


FIGURE 6 A selection of methods for producing crystalline forms. Longer running procedures favor stable polymorphs, whereas more rapid methods are more likely to yield less stable forms (35,36).

the antisolvent slowly, that is used in the slow growth of single crystals, whereas bulk antisolvent addition will cause a solute to crash out of solution, and is often used where other milder crystallization methods fail.

CRYSTALLIZATION FROM SOLUTION

As mentioned above, crystallization from solution is by far the commonest crystallization method used as a process for product recovery in the pharmaceutical industry. In this context, it simultaneously fulfills two essential functions:

1. Purification of the high-value pharmaceutical product, and separation from reaction by-products.
2. Consolidation of the product into a specified crystalline form with consistent and well-characterized physical properties.

Ideally, crystallization will be carried out starting with the solution from the final reaction step of product preparation or manufacture. Often, however, isolation of crude product is carried out using a method that maximizes yield but does not crystallize well, which does not purify effectively or give rise to a good crystalline form. In these cases, recrystallization is often employed to carry out the purification and consolidation functions.

Crystallization to produce specific polymorphs follows the same set of principles as those used in designing processes to manufacture crystalline products, and a basic understanding of these principles can greatly aid the design of a crystallization screen for polymorphs or of a process by which a particular polymorph,

stable or metastable, can be prepared consistently. Some of the general principles, applying to all solution crystallizations, will be outlined in the section "Cooling Crystallization," for which they are easiest to formulate and understand. In the following sections, we will show how they can be extended to alternative methods of crystallization from solution.

Although following the same principles, crystallizations carried out for investigative purposes such as polymorph screening are subject to fewer constraints and limitations than processes in manufacture, although these limitations may subsequently come to bear if the process has to be adapted for production of the identified polymorph. For example, investigative crystallizations do not need high yields, because small quantities of a polymorph product can usually be isolated and identified. Also, it is possible to employ a diversity of methods in investigative work that are not scaleable and adaptable to larger scale, or for which such adaptations may be expensive. Conversely, there are also methods that are operated much more conveniently at larger scale, such as processes involving supercritical fluids.

Cooling Crystallization

Cooling crystallization from solution is usually the method of first choice, both for investigative crystallization in the laboratory and for manufacture at large scale. Its advantages are that it is easy to carry out and reproduce, it is generally well understood, and it may be reasonably scaled up in most cases. In practice, there are often limitations to cooling crystallization at large scale, in particular, the preference for natural cooling limits the rate at which cooling can be applied. In the laboratory, however, cooling rates can be set flexibly and accurately, depending on the purpose for which the crystallization is carried out and the product properties that are required.

There are a number of excellent texts that cover the principles of cooling crystallization comprehensively (37–39), and they are only outlined briefly here to serve the matter in hand, viz. the use of cooling crystallization to prepare polymorphs and other variable solid forms. Nevertheless, a sound understanding of the principles of crystallization is essential if solid-form searching is to be designed in an efficient and comprehensive manner. For a given crystallizing compound and solvent, the first requirement is knowledge of the solubility curve. This is best illustrated by reference to Figure 7, which shows the aqueous solubilities of some common inorganic salts as a function of temperature, from readily available data (40). CuSO_4 shows a steady increase in solubility with temperature, and may be crystallized by cooling the solution to give blue crystals of the stable pentahydrate $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$. Examination of the curve reveals that cooling a solution from 90°C to 10°C could result in recovery of 64% of the dissolved solid, if the crystallization proceeds to equilibrium. On the other hand, NaCl shows only a very slight increase in solubility with temperature, and cooling from 90°C to 10°C could produce only a maximum of 5% of the dissolved solute as solid. Cooling crystallization from water is unsuitable for NaCl, and industrial processes for its preparation rely on other methods, principally evaporative crystallization. The solubility curve for Na_2SO_4 shows a discontinuity at 32°C, which corresponds to the transition of the most stable solid phase at equilibrium with the solution from the decahydrate $\text{Na}_2\text{SO}_4 \cdot 10\text{H}_2\text{O}$ to the anhydrous salt. Although the most stable phase at the crystallization temperature will be favored thermodynamically under these conditions, it will not necessarily be obtained for the reasons discussed below.

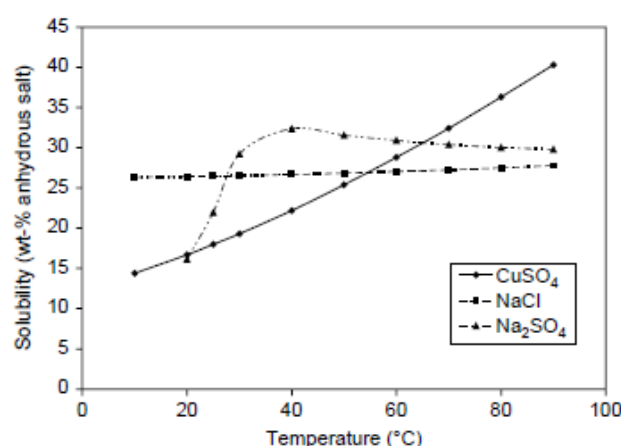


FIGURE 7 Solubility curves for the dissolution of simple inorganic salts in water (40). CuSO_4 may be crystallized from water by cooling, whereas NaCl may not. Na_2SO_4 exhibits a change in the most stable solid phase at 32°C , which is manifested as a discontinuity in the solubility curve.

Extensive solubility data is not usually available when approaching the crystallization of a new compound in form screening, but an indication as to whether cooling crystallization is a feasible option can be obtained from two data points corresponding to the solubilities at low and high temperature for the solvents under consideration. A compound that shows a marked solubility increase at the higher temperature may, in principle, be crystallized by cooling. For form screening purposes, the crystallization yield does not have to be high, and cooling crystallization may be employed provided that a reasonable supersaturation level, say 15% to 20%, can be achieved by cooling the solution. For production, yields will normally need to be higher than this, and in such cases cooling will have to be supplemented by other means of removing solid from solution, such as evaporation or an antisolvent.

The solubility curve is fixed by the thermodynamic relationship between the solid and the solution, and represents the condition that the chemical potentials of the dissolved solute and the solid at equilibrium with the solution are equal. The Gibbs Phase Rule stipulates that, for any given temperature, there will be a unique and determined concentration corresponding to equilibrium. The other component of the route map for a cooling crystallization is the metastable zone width (MZW), illustrated in Figure 8. An initially undersaturated solution at point A is cooled at a constant rate of temperature decrease, following the horizontal arrow. On crossing the solubility line at B the solution becomes supersaturated, but no solid separates at this point. At C, crystal nucleation occurs. Substantial crystallization occurs beyond this point by both the growth of the nuclei formed at C and by further nucleation and growth, and the conditions return toward equilibrium on the solubility line at D. Taking a range of temperature-concentration starting points A, represented as points below and to the right of the solubility curve in Figure 8, the supersolubility curve represents the locus of the points at which nucleation first

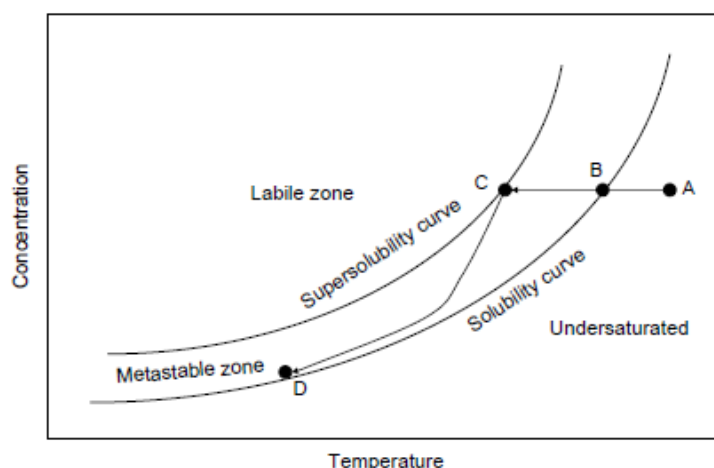


FIGURE 8 The metastable zone in cooling crystallization. Cooling a solution from A induces supersaturation at B, and nucleation at C. The region BC in which the solution is supersaturated but no nucleation occurs is the metastable zone. Beyond the nucleation point, crystal growth and further nucleation occurs until equilibrium is attained at D.

occurs for a given set of crystallization conditions, including cooling rate. The width of the metastable zone (MZW), represented by BC, is a measure of the difficulty in crystallizing a given substance due to the kinetics of inducing nucleation.

Unlike the solubility curve, the supersolubility curve and MZW are dependent on the conditions employed for crystallization, in particular, the cooling rate. Because crystal nucleation has a kinetic component associated with the ordering of molecular clusters into structured crystal nuclei, higher rates of cooling will give rise to wider metastable zones. MZW can vary from 2 to 5 K for simple inorganic salts to tens of degrees for complex organic molecules. The MZW represents the level of supersaturation driving force and departure from equilibrium at which nucleation and crystallization take place, and this can substantially affect polymorph selectivity. Operation close to equilibrium with narrow metastable zones will favor the formation of relatively stable solid forms, because stable crystalline solids are generally less labile than unstable and amorphous forms, and the lower driving forces and more extended timescales associated with working close to equilibrium generally favor their formation.

A further factor that can affect polymorph selectivity in cooling crystallization is enantiotropy, and this is illustrated in Figure 9 for the simple case of a dimorphic system in which the transition temperature T_i lies within the operating temperature range of the crystallization (41). Form II is stable below T_i , form I above T_i . Cooling from point A, the metastable zone of form I is traversed and crystallization is nucleated while the solution remains undersaturated with respect to form II. Point B represents the limit of this condition; the nucleation of form I occurs at the saturation point of form II. At C, the solution first becomes supersaturated with respect to form I, but in this case saturation with respect to form II occurs before the form I

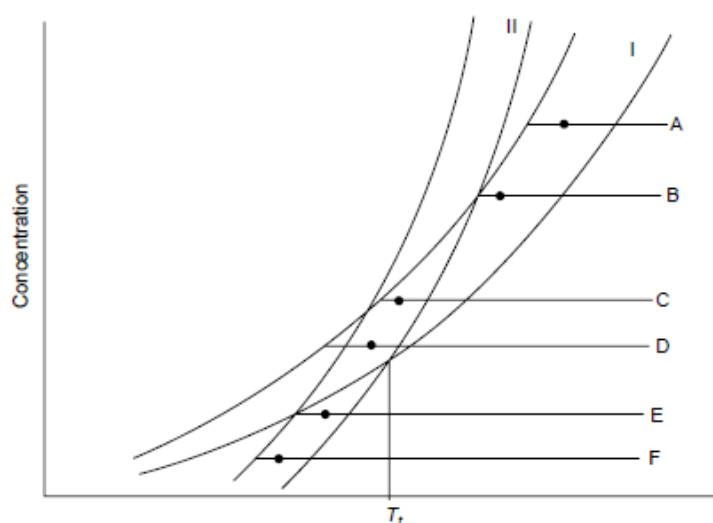


FIGURE 9 Solubility and metastable zones for the cooling crystallization of a dimorphic compound with a transition temperature within the crystallization region. Selecting the start and end temperatures A–F will determine the crystal forms obtained. Source: Adapted from Ref. (41). Abbreviation: T_t , transition temperature.

metastable zone limit is reached. Thus, crystallization of form I will occur from a solution that is also supersaturated with respect to form II, and there is the possibility of cross-seeding and producing a mixture of the two forms. At D, a mixture of forms is even more likely. Points E and F represent the converse of B and A, respectively, and indicate the conditions under which form II may be prepared. Figure 9 illustrates the importance of varying the crystallization conditions, in this case the temperature, in any search for polymorphs. Given that such searches are usually conducted to discover what forms can be prepared, the existence of characteristics such as enantiotropy will not be known at the time such searches are undertaken.

Figure 10 illustrates a situation where further unstable polymorphs exist along with the enantiotropic dimorphic relationship of Figure 9, and how these forms may be accessed by using extreme crystallization conditions, in this case cooling rate (41). Under slow cooling, forms III and IV will never occur because the solute will crystallize as forms I and/or II depending on the temperature conditions. Increasing the cooling rate will “stretch” the metastable zone to encompass a larger area of the concentration–temperature continuum. Unstable forms will have high solubilities, and this extension of the metastable zone, as shown in Figure 10, will eventually lead to the conditions for their crystallization falling within the metastable zones of the more stable forms. Under these conditions, the unstable forms are more likely to form because they are generally more labile than the more stable forms, as is reflected in their relatively narrow metastable zones within this area of the concentration–temperature plane.

Table 4 lists solvents commonly used in the crystallization of pharmaceuticals, in decreasing order of their boiling points. Comprehensive polymorph screening will involve a larger and wider range of solvents that are not necessarily safe and suitable for use in processing but rather give the maximum range and diversity of interactions and effects on the solute that is being crystallized. Data from a search of the CCDC database (in March 2008) of their frequency of occurrence is also given, but this information must be treated with some caution. Although the searches were carried out using the common synonyms of the solvents (e.g., 2-butanone/methyl ethyl ketone/MEK, chloroform/trichloromethane), the "hits" include structures in which the "solvent" moiety forms part of the crystal structure, and in these cases may or may not be considered part of the solvent. For pyridine and cyclohexane, these structures or their derivatives occur very frequently in the crystal structures prepared, and their categorization as a "solvent" does not seem appropriate. THF (tetrahydrofuran) also occurs frequently in this way, and most of the solvents in Table 4 participate in at least a few of the structures reported. The distinction between this type of structure and a solvate, where the solvent molecule forms part of the crystal structure but is deemed to constitute a distinct and separate molecular species, can be a fine one. Also, Table 4 has been compiled using all entries in the database, many of which are organometallic, and how representative this selection is of pharmaceutical products is difficult to judge. Searching with exclusions does not seem to be justified, as organometallics arise quite often as therapeutic compounds, for example, as cytotoxic compounds used in cancer chemotherapy.

The need to utilize a diversity of solvents in polymorph and other solid-form screening was recognized early on (42), and the selection of suitable lists of solvents has now become a matter of considerable scientific sophistication. In the 1990s, the selection of suitable solvents was approached predictively using group contribution methods such as UNIFAC (43), and this has now evolved into more sophisticated packages (44) such as the NRTL-Segment Activity Coefficient (SAC) model that is now implemented in commercially available software (45). Mixtures of solvents are commonly employed to modify and optimize the solvent properties, including solute solubility, polarity, and hydrogen-bonding donor and acceptor properties.

Several effects on crystallization and polymorph selection can be mediated by the solvent selection, the simplest of which is an effect of temperature. The temperature range in which a solvent can be used is limited by its boiling point (Table 4), and by the solubility profile of the solute. In enantiotropic systems, the polymorph that is crystallized may depend on the crystallization temperature by the principles discussed in the section "Cooling Crystallization" and Figure 9. McCrone, writing in 1957 (9), describes the use of high-boiling solvents such as benzyl alcohol and nitrobenzene for the recrystallization of metastable forms on a hot stage. For the API buspirone hydrochloride, a higher or a lower melting form resulted according to whether the crystallization was carried out above or below 95°C (46). Recrystallization from xylene (boiling point 137–140°C) converted the lower boiling form to the higher boiling form. This can be explained by enantiotropy, whereby the lower melting form becomes the more stable below the transition temperature, but crystallization is strongly influenced by the kinetics of nucleation and crystal growth and does not always give rise to the most stable form.

The freeze-crystallization of mannitol was found to be influenced by both the initial mannitol concentration and by the rate of freezing (47). In the range of 2.5–15%, the δ -polymorph was favored by higher concentrations, whereas the

the semi-synthetic macrolide antibiotic dithromycin crystallizes in at least nine stoichiometric solvate forms (137), six of which are isomorphic. With water, it is not unknown for hydrates to form from water present as impurity in a different solvent, as is illustrated by the large number of hydrates reported in Table 4 (for discussion, see section "Effects of Solvent"). Also, pharmaceutical solids may come into contact with water during a wide range of processing steps including lyophilization, wet granulation, aqueous film coating, or spray drying. They may be exposed to water during storage in an atmosphere containing water vapor, or in a dosage form consisting of materials that contain water (e.g., excipients) that are capable of transferring it to other ingredients. Water may be adsorbed onto the solid surface and/or may be absorbed in the bulk solid structure.

Hydrates can exhibit polymorphism, and some substances form a series of hydrates with differing levels of hydration. Nitrofurantoin forms two monohydrates with different packing arrangements and temperatures and enthalpies of dehydration (138), and amiloride hydrochloride dihydrate has been obtained as two polymorphic forms (139). Scopolamine hydrobromide has been isolated as a hemihydrate, a sesquihydrate, and a trihydrate, all with the same molecular geometries and unit cell parameters (140). Ouabaine has been crystallized at a range of hydration levels, with the most stable form changing with temperature (141).

Hydrates can be prepared most simply by recrystallization from water, or from a solvent mixture that contains water. For example, trazodone hydrochloride tetrahydrate has been prepared by dissolving the anhydrate in hot distilled water, allowing the solution to remain at room temperature overnight, and storing the collected crystals at 75% relative humidity and 25°C until they reached constant weight (142). Sorbitol provides another example where slow cooling of a saturated aqueous solution yields long thin needles of sorbitol hydrate (143). Acemetacin monohydrate has been obtained by slow evaporation from a mixture of acetone and water at room temperature (144).

Stable hydrates can also be obtained by suspending the anhydrous material in water. Aqueous suspensions of anhydrous metronidazole benzoate are metastable, and storage at temperatures lower than 38°C leads to monohydrate formation accompanied by crystal growth (145). When suspended in water, anhydrous carbamazepine is transformed to the dihydrate (146).

Simply exposing an anhydrous powder to high relative humidity can sometimes lead to formation of a hydrate. On exposure to a relative humidity of 100%, dexmedetomidine hydrochloride is converted to the monohydrate (147). Droloxifene citrate is an example of a compound that is not very hygroscopic and yet still forms a hydrate (148). Sorption of water only occurs when the anhydrate form is exposed to atmospheres with relative humidity above 85%. However, the monohydrate can be formed by exposing the anhydrous form to 98% relative humidity for 10 days at 24°C.

Investigations of the formation of co-crystal hydrates of theophylline and caffeine by grinding methods (149) have demonstrated different outcomes according to the methods used. The methods were: (1) grinding together "neat" solids using hydrated form(s) of one or both reactants, and (2) liquid-assisted grinding of anhydrous starting materials in the presence of liquid water. The first method can either result in an anhydrous co-crystal, as with caffeine, or steer the reaction to a co-crystal hydrate, as with theophylline. The ability to prepare an anhydrous co-crystal from a hydrated starting material may be valuable if the co-crystal has

- The solvatomorph could be the only crystalline form suitable for crystal structure determination of the drug substance by means of single-crystal X-ray diffraction study.
- The solvatomorph could be useful in a desolvated form that facilitated its dissolution.
- The solvatomorph could constitute new intellectual property, and thus be patentable.

Without a doubt, water is the solvent that forms the largest number of pharmaceutically useful solvatomorphic solids, and it has been estimated that approximately one-third of drug substances are capable of forming crystalline hydrates (4). Owing to its small size that enables it to fill structural voids and because of its multidirectional hydrogen-bonding capability, water is an ideal agent for the linking of drug molecules into stable crystal structures (3). The mere presence of water in a system is not a sufficient reason to anticipate formation of a hydrate species, because the activity of water in the crystallizing medium determines whether a given hydrate species will form (5). Because water is such a ubiquitous substance, it is not surprising that the most important type of solvatomorphism involves the incorporation of water into crystal lattices.

The potential pharmaceutical impact of changes in hydration state of crystalline drug substances and excipients exists throughout the development process. The behavior of hydrates has become the object of increasing attention over the last decades, primarily due (directly or indirectly) to the potential impact of hydrates on the development process and dosage form performance. Substances may hydrate or dehydrate in response to changes in environmental conditions, processing, or over time, if they exist in a metastable thermodynamic state (6).

Often it may turn out not be practical or possible to maintain the same hydrate species of a compound during scale-up activities that was originally isolated during the discovery "bench" scale synthesis. The choice of counterions required to produce a more soluble salt form may also be dictated by the extent and type of hydration observed for a given salt, and/or by the moisture level that may be safely accommodated by the dosage form (7).

The physicochemical stability of the compound may raise issues during preformulation. Some hydrated compounds may convert to an amorphous form upon dehydration, and some may become chemically labile. This is true of cephadrine dihydrate, which dehydrates to become amorphous and then undergoes subsequent oxidation. Other compounds may convert from a lower to higher state of hydration yielding forms with lower solubility. In any case, the resulting "new" forms would represent unique entities that, depending on the dosage form, might have to be maintained throughout the manufacturing process and in the clinic, and would impact on the regulatory status of the compound. Most often this demands that the form (usually crystalline) be identified and characterized with respect to handling conditions during the early pre-IND stage of the development process.

As dosage form development proceeds, changes in hydration state can result in variable potencies depending on handling conditions during weighing steps, the kinetics of the hydration/dehydration process, and the environmental conditions during processing. Differences in powder flow can result from changes in crystal form and/or morphology that may accompany the hydration/dehydration process. This can affect content uniformity in solid processing either in the mixing process or during

Sisir Bhattacharya**Department of Pharmaceutics, University of Minnesota, Minneapolis, Minnesota, U.S.A.***Harry G. Brittain***Center for Pharmaceutical Physics, Milford, New Jersey, U.S.A.***Raj Suryanarayanan***Department of Pharmaceutics, University of Minnesota, Minneapolis, Minnesota, U.S.A.***INTRODUCTION**

The different physical forms of a compound can exhibit pronounced differences in physicochemical properties. The term "physical form" encompasses polymorphs, solvates (also referred to as solvatomorphs), the non-crystalline (amorphous) form, and partially crystalline forms. Although numerous analytical techniques are available to characterize the physical forms of pharmaceutical compounds, this chapter will focus on thermal and crystallographic characterization techniques. While discussing the analytical techniques and their applications, we will use the term "polymorphism" in its broadest sense, with the understanding that with appropriate modifications, the techniques can often be extended for the characterization of the other physical forms of pharmaceuticals. Although crystallography (through crystal structure) provides the most definitive evidence of polymorphism, thermoanalytical, spectroscopic, and microscopic techniques are often used in a complementary fashion for the characterization of polymorphs.

Comprehensive and in-depth discussions of different thermoanalytical techniques can be found in the literature (1,2), and this chapter will specifically discuss the applications of thermoanalytical and crystallographic techniques in the characterization of pharmaceuticals. The specific thermoanalytical techniques to be discussed are differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), and hot-stage microscopy (HSM). Several recent reviews and book chapters have covered this topic, and the examples presented are designed to complement the information in the literature (1–4). In the second part of the chapter, applications of X-ray powder diffractometry (XRD) (5,6) are provided. Finally, applications of variable-temperature XRD (VT-XRD) are discussed, specifically to monitor phase transitions as a function of temperature.

THERMOANALYTICAL TECHNIQUES

Thermal analysis methods can be conveniently defined as those techniques in which some property of the analyte is measured as a function of an externally applied temperature. In most applications, one effects a linear increase in the temperature of the sample while the property of interest is recorded on a continuous basis. Thermoanalytical methods are used to monitor endothermic processes (i.e., melting, boiling,

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the crystal lattice. To measure a powder pattern, a randomly oriented powdered sample is prepared in an effort to expose all the planes in the lattice. The scattering angle is determined by slowly rotating the sample and measuring the angle of diffracted X rays (typically using a scintillation detector) with respect to the angle of the incident beam. Alternatively, the angle between sample and source can be kept fixed, while moving the detector to determine the angles of the scattered radiation. Knowing the wavelength of the incident beam, the spacing between the planes (identified as the *d*-spacings) is calculated using Bragg's Law.

The XRD pattern will therefore consist of a series of peaks detected at characteristic scattering angles. These angles, and their relative intensities, can be correlated with the computed *d*-spacings to provide a full crystallographic characterization of the powdered sample. After indexing all the scattered lines, it is possible to derive unit cell dimensions from the powder pattern of the substance under analysis. For routine work, however, this latter analysis is not normally performed, and one typically compares the powder pattern of the analyte to that of reference materials to establish the polymorphic identity. Because every compound produces its own characteristic powder pattern owing to the unique crystal structure, powder XRD is clearly the most powerful and fundamental tool for polymorphic identity of an analyte.

The United States Pharmacopeia contains a general chapter on XRD (61), which sets the criterion that identity is established if the scattering angles in the powder patterns of the sample and reference standard agree to within the calibrated precision of the diffractometer. It is noted that it is generally sufficient that the scattering angles of the ten strongest reflections obtained for an analyte agree to within either ± 0.10 or $\pm 0.20^\circ 2\theta$, whichever is more appropriate for the diffractometer used. Older versions of the general test contained an additional criterion for relative intensities of the scattering peaks, but it has been noted that relative intensities may vary considerably from that of the reference standard, making it impossible to enforce a criterion based on the relative intensities of corresponding scattering peaks.

For identification purposes, it is usually convenient to identify the angles of the 10 most intense scattering peaks in a powder pattern, and to then list the accepted tolerance ranges of these based on the diffractometer used for the determinations. Useful tabulations of the XRD patterns of a number of compounds have been published by Koundourellis and coworkers, including 12 diuretics (62), 12 vasodilators (63), and 12 other commonly used drug substances (64).

The literature abounds with countless examples that illustrate how powder diffraction has been used to distinguish between polymorphs. It is safe to state that one could not publish the results of a phase characterization study without the inclusion of XRD data. Nowhere is this more crucial than in intellectual property controversies, where the different XRD patterns of polymorphs are used for patentability purposes. For example, two polymorphic forms of ibandronate sodium have been the subject of two United States patent applications (65), and although the XRD patterns of these are somewhat similar (Fig. 11), a sufficient number of differences in scattering peak angles exist so as to permit their identification. In the patent applications, some of the claims define the two polymorphs on the basis of five characteristic XRD scattering peaks, which enables one to tabulate the data and determine whether or not a given sample of ibandronate sodium is within the scope of these XRD claims.

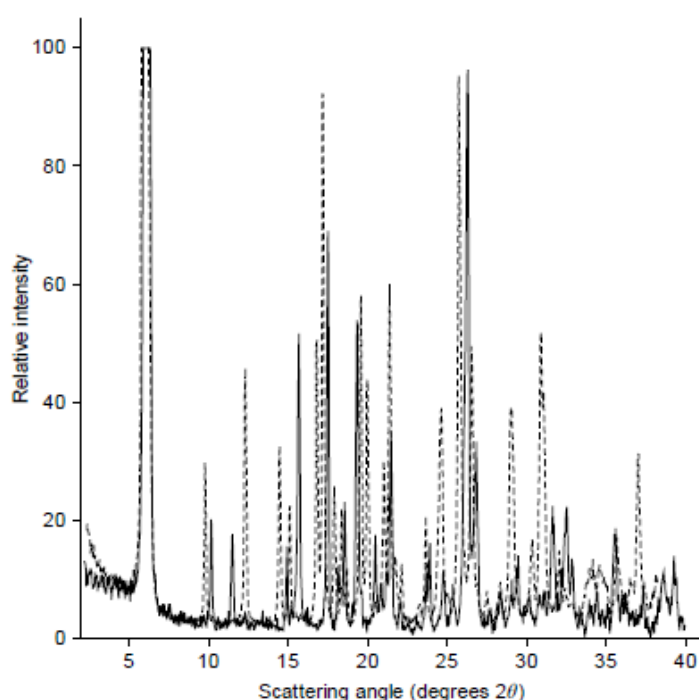


FIGURE 11 X-ray powder diffraction patterns of ibandronate sodium, Form A (solid trace) and Form B (dashed trace). The patterns have been adapted from data in United States patent applications 2006/0172975 and 2006/0172976 (65).

Once the characteristic XRD patterns of one or more analytes have been established, it is usually possible to develop methods for phase quantification. The methodology is based on the premise that each component will contribute to the overall scattering by an amount that is proportional to its weight fraction in a mixture, and that the powder pattern of each analyte contains one or more peaks whose scattering angle is unique to that analyte. Quantitative analysis typically requires the use of reference standards that contribute known scattering peaks at appropriate scattering intensities. This can be achieved through the use of internal standards, where one would mix reference materials such as elemental silicon or lithium fluoride into the sample matrix.

Although simple intensity correction techniques can be used to develop suitable quantitative XRD methods, the introduction of more sophisticated data acquisition and handling techniques can greatly improve the quality of the developed method. For instance, improvement of the powder pattern quality through use of the Rietveld method has been used to evaluate mixtures of two anhydrous polymorphs of carbamazepine and the dihydrate solvatomorph (66). The method of whole pattern analysis developed by Rietveld (67) has found widespread use in crystal structure refinement and in the quantitative analysis of complex mixtures.

For example, it has been observed that milled melt-quenched samples crystallize much more readily than do unmilled samples (82). It has been suggested that mechanical stress such as milling introduces "high energy sites" or nuclei, which can lead to crystallization.

Another factor that needs to be considered is the importance of the surface area of the powder to the phenomenon of surface crystallization. It has been demonstrated that the growth rate of crystals at the surface is much faster than the bulk growth rate (81). The implication of this observation is that solids with a higher surface area may be more prone to crystallization, and thus this might be one reason that milled samples crystallize faster.

As described above, it is very difficult to predict the crystallization tendency of amorphous solids, and therefore, experimental measurements of physical stability need to be made. Crystallization rates are normally measured using techniques such as XRPD, DSC, or spectroscopy. Given that crystallization may be slow under ambient conditions, it is obviously desirable to use accelerated stability testing conditions to evaluate the crystallization potential of an amorphous formulations. There are several factors that may complicate extrapolations of crystallization rates at high temperatures/relative humidities to ambient conditions. The crystal phase resulting from devitrification may not be the same for the different experimental conditions. For example, indomethacin crystallizes predominantly as the gamma polymorph at lower temperatures and relative humidities, and as the alpha form at higher temperatures and relative humidities (83,84).

In addition, the temperature dependence of the crystallization rate may not follow a simple Arrhenius-type relationship. This may result from crystallization of different polymorphs as mentioned above or from a non-Arrhenius dependence of molecular mobility on temperature as discussed earlier. Additional factors that have to be considered are changes in growth mechanism close to T_g as discussed previously and the effects of water content, which will be discussed in more detail below.

Based on the preceding discussion, it is clearly very difficult to predict precise crystallization rates under a given set of experimental conditions either from data obtained under accelerated stability conditions or from some experimentally measured property of the amorphous solid. However, given that different compounds have very different crystallization tendencies, it is still useful to assess crystallization tendency under a variety of conditions. Clearly, a compound that is stable under extreme conditions will be a viable candidate for formulation in an amorphous state. For compounds having a moderate tendency to crystallize, a measure of the effect of moisture and temperature on crystallization tendencies may help to determine if packaging could reduce the crystallization tendency and provide storage stability.

STABILIZATION AGAINST CRYSTALLIZATION: AMORPHOUS SOLID DISPERSION TECHNOLOGY

Single-component amorphous drugs often display physical instability over the intended shelf life of the product, and so polymeric crystallization inhibitors are frequently added to improve the physical stability. In order to be an effective inhibitor of bulk crystallization, the polymer must form an intimate mixture with the drug substance, resulting in a miscible, single-phase, amorphous solid dispersion. Molecular mixtures of amorphous solids are also generated in freeze-dried

biological products where sugars are added to improve the stability of proteins, and for polymeric film coatings where small molecules are added to the coating to act as plasticizers and to improve mechanical properties.

Several methods can be used to prepare amorphous solid dispersions, which involve destroying the crystal structure of the drug and mixing the resultant liquid with the polymer. One common method entails dissolution of crystalline drug and polymer in a solvent, followed by drug substance solvent removal. This process is typically carried out using techniques such as rotary evaporation, spray drying, freeze drying, air drying, or vacuum oven drying. Another common method entails heating the crystalline drug and polymer mixture to a temperature above the melting point of the drug and processing the mixed molten mass by means of melt extrusion. It has also been reported that solid dispersions can sometimes be prepared by co-milling the drug and the polymer (85). If crystallization is avoided during the preparation stage, and the drug and polymer remain intimately mixed, the system is said to have formed a miscible, single-phase, amorphous solid dispersion.

If miscibility is achieved, the behavior of the drug in the solid dispersion will be altered relative to that of the pure amorphous drug, and the properties of the solid dispersion will depend on the individual component properties as well as on the composition. There are several polymers that can be used to form solid dispersions, although it has been observed that some drug-polymer combinations are miscible whereas other systems are immiscible. From a theoretical perspective, molecular level mixing will only be achieved if the intermolecular interactions between the drug and the polymer are sufficiently favorable to overcome the cohesive interactions in the pure amorphous phases and crystallization of either component is avoided.

Derivatized cellulose polymers such as hydroxypropyl methylcellulose and the vinylpyrrolidone family of polymers [including poly(vinylpyrrolidone) and poly(vinyl-pyrrolidone-co-vinyl acetate)] have been found to be miscible with a variety of drug substances. In contrast, polymers or drugs containing strong cohesive interactions may not mix with chemically dissimilar components. For example, the ionic polymer, Eudragit E100 (which is a cationic methacrylate polymer), is only partially miscible with the itraconazole (86). Ibuprofen has been found to be largely immiscible with dextran (87), which is able to form extensive cohesive hydrogen bonding interactions.

ESTABLISHING MISCIBILITY

Determining the miscibility of the binary system can be challenging. For miscible systems, it would be expected that the glass transition temperature of the amorphous mixture is intermediate to that of the pure component T_g values. Thus, if a high T_g polymer is mixed with a low T_g drug substance, the T_g of the dispersion will increase with an increasing amount of polymer. An example is shown in Figure 17, where the T_g as a function of polymer concentration is shown for the felodipine-PVP solid dispersion system.

Assuming that two components are miscible, there are theoretical ways to predict the T_g of the mixture as a function of composition. The Gordon-Taylor equation is one of the most commonly used approaches for pharmaceutical systems (89), and assumes that the two components are miscible at all compositions and that the free volumes of the components are additive (90). The T_g of mixture, T_{g12} is then defined as