

General principles of pharmaceutical solid polymorphism: a supramolecular perspective

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Abstract

The diversity of solid-state forms that an active pharmaceutical ingredient (API) may attain relies on the repertoire of non-covalent interactions and molecular assemblies, the range of order, and the balance between entropy and enthalpy that defines the free energy landscape. It is recognized that crystallization is associated with molecular recognition events that lead to self-assembly, and that pharmaceutical function and thermodynamic stability can be altered with a slight change in the interacting molecules or their molecular network motifs. Our current understanding of pharmaceutical solids in terms of molecular recognition and complementarity provides new insights into the design and function of single and fully miscible, multiple-component solids with varying degrees of order, from amorphous to crystalline states, and in this way is leading the path to supramolecular pharmaceuticals. This review describes pharmaceutical solids in terms of supramolecular chemistry and crystal engineering concepts, and discusses the events that control crystallization and solid phase transformations.

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Keywords: Supramolecular isomers; Supramolecular pharmaceuticals; Crystallization; Crystal engineering; Cocrystals; Solvates; Molecular dispersions

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1. Introduction

The diversity of pharmaceutical solid-state forms of the same molecules is based on a repertoire of non-covalent interactions that allows for control of chemical stability, dissolution, solubility and in some cases bioavailability of the active pharmaceutical ingredient (API) [1,2]. It also provides a means to study molecular recognition and supramolecular assemblies formed by non-covalent interactions (hydrogen bonds, van der Waals, π – π stacking, and electrostatic interactions) in relation to material properties [3–8]. Because of its

strength and directionality, the hydrogen bond has been the most important interaction in molecular recognition [9]. The field of crystal engineering has been inspired by molecular recognition concepts in biology and pharmacology, where recognition between molecules regulates behavior of a supramolecular assembly. We are indeed witnessing the era of supramolecular therapeutics and the design of supramolecular assemblies with fine-tunable pharmacologic activity [10]. The motivation behind crystal engineering lies in creating molecular assemblies to control solid-state function. In fact, progress over the past 20 years in crystal engi-

neering [5,6,8] has made possible the design of new pharmaceutical materials [11–13] and molecular level control of crystallization and phase transformations [14–18].

Advances in crystal engineering and supramolecular chemistry [8,19,20] invite us to consider new perspectives and perhaps definitions of the various solid-state forms that the same and/or different molecules may adopt in terms of molecular assemblies and architectures. Analogies between polymorphism and supramolecular isomers and networks have been suggested in the literature [8,14,21–23] and are described in Table 1. The diverse range of pharmaceutical solids can be classified in terms of structure and composition. A structural perspective is based on the extent to which molecular networks are ordered, with crystals having repeating molecular patterns and long-range order while amorphous or disordered solids have local molecular assemblies and lack long-range order. Thus amorphous and crystalline systems share the same intermolecular forces although the former will exhibit molecular assemblies that lack periodicity. In terms of compo-

sition, miscible, multi-component crystalline and amorphous pharmaceutical systems are built with molecules of different components where assemblies are formed by non-covalent forces, for example between molecules of API and another component. Single phase (miscible), multi-component systems in the amorphous state are referred to as molecular dispersions [24,25] and in the crystalline state as cocrystals [5,23,26].

Polymorphism in crystalline solids is defined as materials with the same chemical composition, different lattice structures and/or different molecular conformations [14,27–29]. Pseudopolymorphism is a term that refers to crystalline forms with solvent molecules as an integral part of the structure [2,30]. In a supramolecular sense, polymorphism is the existence of more than one type of network superstructure for the same molecular building blocks, and pseudopolymorphism is the case where the solvent is one of the molecular components of the network [8]. Thus polymorphism is regarded as a type of supramolecular isomerism and pseudopolymorphism as a type of cocrystal.

Table 1

Glossary of definitions incorporating terms used in supramolecular chemistry

Polymorphism (molecular crystals)

- ability of a substance to exist in different molecular arrangements and/or different molecular conformations

Conformational polymorphism

- formed by molecules that adopt different conformations in different crystal structures

Pseudopolymorphism

- when crystals of a compound include solvent molecules or solvates and are classified in terms of structure as
 - isolated lattice sites
 - lattice channels
 - metal–ion coordinated solvates

Supramolecular isomerism

- ability of a substance to exist in more than one type of network superstructure for the same molecular building blocks
- networks are generated by different supramolecular synthons or molecular assemblies (e.g. dimers and head to tail chains)

Conformational supramolecular isomerism

- formed by flexible molecular components that can lead to changes in architecture

Multiple-component solids (single phase)

- *solvates* are a special type of multi-component solids and are classified in terms of molecular networks where solvent molecules may be
 - an integral part of the network structure (cocrystal) and form at least a two-component crystal, or
 - may not directly participate in the network itself, as in open framework structures (clathrates)
- multi-component crystalline phases in general are formed with molecules of different substances, and are defined in terms of molecular cooperativity, non-covalent bonds, molecular networks and often hydrogen bond patterns
 - *cocrystals* when the molecular network is formed by different molecular building blocks
 - hydrogen bond links can be formed via neutral molecules, ionized molecules or inorganic ions resulting in a range of supramolecular networks

The implications of molecular self-assembly in the solid state go beyond crystal engineering and materials science since this ensemble of molecular interactions relates to physical and chemical properties that affect pharmaceutical performance. These effects are well documented in the literature and include mechanical behavior, physical and chemical stability, solubility, dissolution rate and in some cases bioavailability [1]. For instance, the development of solid-state forms for oral delivery with increased dissolution of highly lipophilic APIs with high intestinal wall permeability has generated intense interest [31]. Different strategies rely on non-covalently controlled phenomena to achieve this objective and include changes in intermolecular bonds, molecular networks, and extended architectures. The hydrogen bond is the most frequent connector found in molecular networks and analysis of geometries and patterns is often of great utility and is readily accessible from the Cambridge Structural Database [3,32]. Approaches to enhance solubility and dissolution rate of solids involve altering the molecular networks in two main ways: (1) by changes in supramolecular arrays of the same components (crystalline and amorphous states) and (2) by changes in molecular components of the network by means of non-covalent forces (cocrystals, solvates, salts). This diversity of networks leads to materials with different free energy states, thus their stability and delivery can be affected by crystallization to more thermodynamically stable forms.

It is recognized that the most thermodynamically stable form of an API may not always represent the

most desirable solid form to develop with respect to pharmaceutical function and that survival during its lifetime relies on thermodynamics, kinetics, and molecular recognition events, as shown in Fig. 1. This paper reviews polymorphism in terms of supramolecular chemistry concepts, discusses the factors that compete with or reinforce one another in the stabilization of and transition between solid-state forms with emphasis on crystalline states, and presents methods to prepare different solid forms and analyze their supramolecular arrays and energetics.

2. Thermodynamics

When a compound exists in various solid-state forms there are two important questions to address: (1) what is their relative thermodynamic stability, or the conditions and direction in which a transformation can occur, and (2) how long will it take for the transformation to reach equilibrium? Thermodynamics provides information about the first question and kinetics about the second.

The main approaches used to assess thermodynamic stability relationships of polymorphs are based on thermodynamic rules according to Burger and Ramberger [33] and free energy change–temperature diagrams [34]. While the former distinguishes between monotropic and enantiotropic systems, the latter in addition to this allows for calculation of the transition temperature. Thorough thermodynamic analysis of these systems has been published [28,29,35] and a

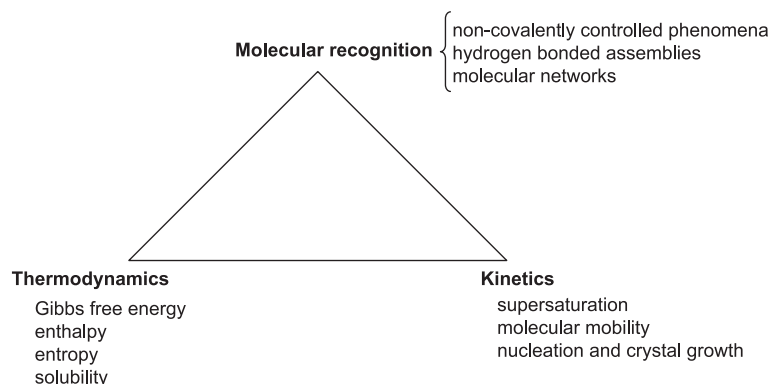


Fig. 1. Schematic diagram showing the phenomena that governs solid-phase transformations. It is important to consider how mechanical, thermal, and chemical (solvents, additives, impurities, relative humidity) stresses affect the competition among these processes.

crystalline states that have well defined G versus T curves.

Yu et al. [34,35] have shown that the ΔG versus temperature diagram provides the most complete and quantitative information about the stability relationship of polymorphs. The ΔG and its temperature dependence can be obtained from melting data (melting temperature, enthalpy of fusion), enthalpy of transformation if available, and/or solubility dependence on temperature data for the solid-state forms of interest (enthalpies of solution from van't Hoff plot). The melting data method requires less sample weight relative to the solubility method, however, it exposes the material to potential chemical degradation. While the solubility method offers the advantage of studying a range of temperatures and various solvents, there is the possibility for solution-mediated transformations or solvate formation during solubility measurement. Thus, instead of an equilibrium method for solubility measurement, a dynamic method is used for estimating the solubility of metastable solid states [38] and is referred to as metastable or kinetic solubility. The solubility can be estimated from the maximum concentration achieved during dissolution of excess solid in a solvent or from the initial intrinsic dissolution rate method [39,40].

The stability relationships for polymorphs of anhydrous carbamazepine, *P*-monoclinic and triclinic, can be determined from a ΔG versus temperature diagram based on melting and solubility data reported in the literature, according to the method described by Yu [35]. Consider for carbamazepine, *P*-monoclinic = III = A and triclinic = I = B. The change in free energy for the polymorphic transformation from polymorph A to B is given by:

$$\Delta G_0 = \Delta H_0 - T_{m,A} \Delta S_0 \quad (2)$$

where the subscript “0” indicates the value of the thermodynamic function at $T_{m,A}$, the melting point of form A. The same nomenclature used by Yu [35] is used in this example. The changes in enthalpy, ΔH , and entropy, ΔS , associated with the transformation are calculated from melting data according to the following equations:

$$\Delta H_0 = \Delta H_{m,A} - \Delta H_{m,B} + (C_{p,L} - C_{p,B})(T_{m,B} - T_{m,A}) \quad (3)$$

$$\Delta S_0 = \frac{\Delta H_{m,A}}{T_{m,A}} - \frac{\Delta H_{m,B}}{T_{m,B}} + (C_{p,L} - C_{p,B}) \ln \left(\frac{T_{m,B}}{T_{m,A}} \right) \quad (4)$$

where the term $(C_{p,L} - C_{p,B})$ is the difference between the heat capacities of form B and supercooled liquid at temperatures between $T_{m,A}$ and $T_{m,B}$ and the difference in heat capacity is assumed to be independent of temperature in the narrow temperature range typically observed for polymorphs ($T < 20$ K). Among the various methods proposed to calculate the value of this parameter [35,41] we will demonstrate the heat of transition (ΔH_t) calculation since solubility data as a function of temperature is often available for APIs. If ΔH_t is independent of T in the range of measurement then:

$$\Delta H_t = \Delta H_0 \quad (5)$$

where ΔH_t for a transition from A to B is given by:

$$\Delta H_t = \Delta H_S^B - \Delta H_S^A \quad (6)$$

ΔH_S^B and ΔH_S^A are the enthalpies of solution for polymorphs A and B and can be calculated from the solubility dependence on temperature according to the linear relationship given by a van't Hoff plot according to:

$$\ln(s) = -\frac{\Delta H_S}{RT} + c \quad (7)$$

where s is the solubility of a given polymorph at an absolute temperature T , R is the gas constant, and c is a constant. The van't Hoff plot has been successfully applied to APIs over narrow temperature ranges. The model derived by Grant and coworkers [42] for evaluation of the heat of solution can be applied over wider temperature ranges when the van't Hoff plot leads to non-linearity. These methods have been thoroughly reviewed elsewhere [28].

The value for $(C_{p,L} - C_{p,B})$ can then be calculated from substitution of ΔH_0 with ΔH_t and rearrangement of Eq. (3), which gives:

$$(C_{p,L} - C_{p,B}) = (\Delta H_t - \Delta H_{m,A} + \Delta H_{m,B}) / (T_{m,B} - T_{m,A}) \quad (8)$$

Thus ΔH_0 , ΔS_0 , and ΔG_0 can be evaluated from Eqs. (8), (3), (4) and (2). By assuming a non-linear or linear dependence of ΔG on temperature [35], ΔG for the polymorphic transition can be determined at other temperatures. The linear relationship is given by:

$$\Delta G(T) = \Delta G_0 - \Delta S_0(T - T_{m,A}) \quad (9)$$

In this way, a ΔG –temperature diagram can be obtained for a polymorphic pair from melting data.

The difference in the Gibbs free energy associated with the transformation of polymorph A to B can be calculated from solubility measurements of the two forms by the following relation

$$\Delta G = (G_B - G_A) = RT \ln \left(\frac{S_B}{S_A} \right). \quad (10)$$

This equation assumes that concentrations can be substituted for activities if the ratio of the activity coefficients of the two polymorphs is approximately 1. A complete discussion of this method is presented in other reviews [28,38]. The ΔG –temperature diagram based on the solubility method (Eq. (10)) can be combined and compared with that obtained from the melting data according to Eq. (9). This is shown for carbamazepine polymorphs below.

2.1.1. ΔG –temperature diagram for carbamazepine polymorphs

2.1.1.1. ΔG –temperature diagram from solubility data. Behme and Brooke [41] studied the *P*-monoclinic and triclinic carbamazepine polymorphs and measured solubilities as a function of temperature in 2-propanol. There has been confusion in the nomenclature of carbamazepine polymorphs in the literature and in the original report by Behme and Brooke [41]; values have been reported for the triclinic form and not trigonal [43,44]. A transition temperature of 346 K (73 °C) was calculated by extrapolation of the solubility lines from a van't Hoff plot, Fig. 3. Since this transition temperature is below the melting temperatures of each polymorph, III and I are enantiotropically related. Below 346 K, III has lower solubility and is thus more stable than I. The heats of solution in 2-propanol calculated from the slopes of the lines are 31.54 kJ/mol for III, and 28.01 kJ/mol for I. The heat

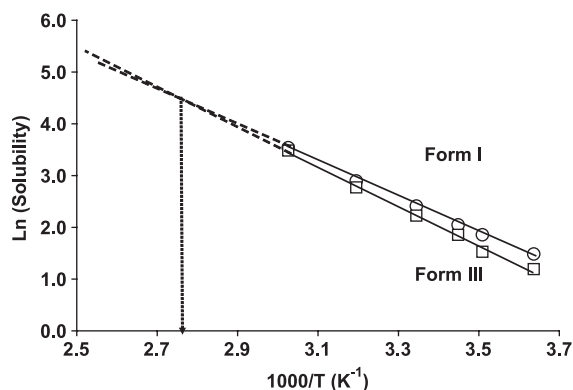


Fig. 3. The van't Hoff plot for the *P*-monoclinic (III) and triclinic (I) forms of carbamazepine in 2-propanol. Adapted from the data presented by Behme and Brooke [41].

of transition is then 3.53 kJ/mol. The ΔG –temperature diagram was calculated from Eq. (10) and is shown in Fig. 4.

2.1.1.2. ΔG –temperature diagram from melting data. The thermal analysis of carbamazepine polymorphs I and III [41] shows that form I melts at 189 °C and form III at 174 °C. DSC at slow heating rates shows that III transforms to I endothermically with a ΔH_t of 3.3 kJ/mol between 150 and 170 °C. From the melting data, ($\Delta H_{m,I}$ = 26.4 kJ/mol, $\Delta H_{m,III}$ = 29.3 kJ/mol) and from the solubility data, (ΔH_t = 3.53 kJ/mol), the value for ($C_{p,L} - C_{p,B}$) was calculated from Eq. (8) and ΔG_0 = −0.94 kJ/mol was obtained from Eq. (2). The ΔG values were calculated at other temperatures from Eq. (9) and are plotted in Fig. 4.

Extrapolation of ΔG obtained from solubility and melting data to $\Delta G = 0$, Fig. 4, shows a transition temperature of 353 K (80 °C) from the melt method compared with 346 K (73 °C) from the solubility method. This deviation is within the expected range of 7% [35].

2.2. Burger–Ramberger rules

Burger and Ramberger have described rules for the assignment of a given polymorphic pair as enantiotropic or monotropic [33]. Three particularly useful rules they proposed are the heat of transition, heat of fusion, and density rule [33,45,46]. The first two rules

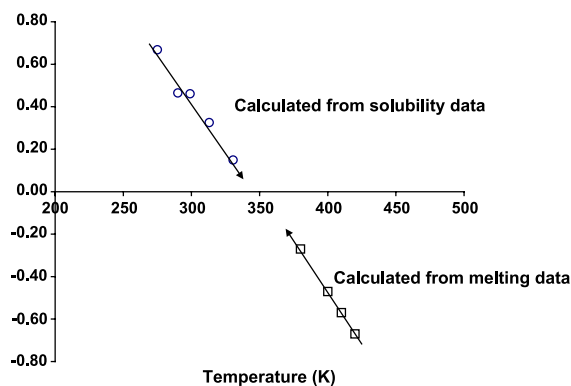


Fig. 4. The ΔG versus temperature diagram for carbamazepine polymorphs, *P*-monoclinic (III) and triclinic (I). This shows a transition temperature at $\Delta G=0$ and an enantiotropic relationship between these polymorphs. ΔG values were calculated from solubility and melting data according to the equations presented in the text.

require calorimetric measurements, which are conveniently carried out by DSC.

2.2.1. Heat of transition rule

If, at some temperature, an endothermic transition between crystal forms is observed then there is a transition point below this temperature and the two polymorphs are related enantiotropically. A polymorph pair is related monotropically if an exothermic transition is observed at some temperature and no transition occurs at a higher temperature. This latter case is exemplified by carbamazepine forms I (triclinic) and II (trigonal) [44]. An exothermic transition (-1.46 kJ/mol) occurs when form II transforms to form I between 140 and 160 °C demonstrating a monotropic relationship. The transition from form III (*P*-monoclinic) to I (triclinic) is endothermic [41] and according to these concepts it is an enantiotropic relationship. The transition temperature for this polymorphic pair has been calculated to be in the range of 73–80 °C from the ΔG – T diagram discussed in the previous section.

2.2.2. Heat of fusion rule

In cases where the rate of transformation is slow and DSC cannot measure the heat of transition, it is useful to apply the heat of fusion rule. In an enantiotropic system the higher melting polymorph will have the lower heat of fusion and if the higher melting polymorph has the higher heat of fusion the system is

monotropic. If the melting points of the polymorphs differ by more than 30 °C then the rule may not be valid and the higher melting polymorph could have the higher enthalpy of fusion in an enantiotropic system [47]. This rule is exemplified by nabumetone. Form I melts 15 °C higher than form II and possesses a higher heat of fusion (31.3 vs. 24.5 kJ/mol) as evidenced by DSC [48]. Therefore, the two polymorphs are related monotropically.

2.2.3. Density rule

Molecules in crystalline solids typically pack together to maximize intermolecular interactions. This is a manifestation of the general principle that, in the attractive regime, the more closely two atoms approach the lower their energy [49]. Therefore, the most stable polymorph of a compound lacking strongly directional intermolecular interactions at 0 K will be the one with the highest density [50]. Crystals whose packing structures are dominated by van der Waals interactions usually obey this rule. Form I of nabumetone has a density of 1.26 g/cm³ and the metastable form II possesses a density of 1.21 g/cm³ [48,51]. By contrast, crystals with hydrogen-bonded structures can adopt arrangements in which the most stable form has the lower density. Ritonavir is an example of this sort of exception to the density rule. In this system the more stable structure form II has a lower density (1.25 g/cm³) than form I (1.28 g/cm³) [52].

3. Kinetics

3.1. Interplay between kinetic and thermodynamic factors

While thermodynamics establishes the stability domains of the various solid states, once a metastable domain is encountered the kinetic pathways will determine which form will be created and for how long it can survive. To this end, it is essential to consider the structural elements of the molecular assembly processes that lead to crystallization and how they are controlled. Etter [53] considered the process of crystallization in terms of molecules arranging themselves into energetically suitable packing patterns by non-covalent forces, specifically hydrogen

bonds. A major conclusion of this work was to establish a connection between the molecular assembly processes that precede nucleation and the molecular arrays in the crystal state:

Molecule $\leftrightarrow$ Molecular assembly $\leftrightarrow$

Molecular network $\leftrightarrow$ Crystal

These findings motivated investigations on the supra-molecular aspects of crystallization processes and have found great utility in explaining the appearance or disappearance of polymorphs [14], the role that solvents and additives have on the directed nucleation of polymorphs [17,27,54], and the kinetic stability of metastable forms including amorphous solids [37].

The balance between the kinetic and thermodynamic factors is illustrated by the free energy–reaction progress diagram (Fig. 5) for a transition from the initial state G_i , to two different solid forms A or B. Form A is more stable and less soluble than B ($G_A < G_B$). G_i may represent a supersaturated solution in a multiple-component system, liquid or solid (molecular dispersion in amorphous system), or in the

case of a single component system an undercooled liquid (melt) or an amorphous solid. The reaction follows a path through an energy maximum between the initial and final states. This resistance to the transition from G_i to G_A or G_B arises because there is an energy barrier for molecular diffusion, molecular assemblies, and for the creation of an interface. For a chemical reaction in a homogeneous system, this energy maximum is the transition state and reflects elementary reactions, bimolecular or trimolecular, that yield products with new covalent bonds. In comparison, a crystallization event or phase transformation leads to heterogeneous systems in which a separate new phase is created from a supramolecular assembly by formation of non-covalent bonds.

A transition from the initial state G_i to state A or B will depend on the energy barrier and according to the reaction pathway in Fig. 5, the height of the energy barrier for structure A ($G_A^* - G_i$) is greater than that for B ($G_B^* - G_i$). Because the rate of nucleation is related to the height of the energy barrier on the reaction path, B will nucleate at a faster rate than A even though the change in free energy is greater for A ($G_A - G_i$) than for B ($G_B - G_i$). This is one of the possible behaviors that could be observed in the order of appearance of polymorphs and is referred to as Ostwald's law of stages. It states that “when leaving an unstable state, a system does not seek out the most stable state, rather the nearest metastable state which can be reached with loss of free energy” [55]. However, Ostwald's law of stages is not universally valid because the appearance and evolution of solid phases are determined by the kinetics of nucleation and growth under the specific experimental conditions [27,56,57] and by the link between molecular assemblies and crystal structure [16,58,59].

Crystallization involves both the nucleation and growth of a phase. Because of the key role of nucleation in the selective crystallization of polymorphs and the stabilization of metastable states, it will be discussed in this review. Studies of growth kinetics and crystal morphologies are useful in characterizing intermolecular interactions on specific crystal planes and as a consequence in identifying additives or solvents that may preclude or promote the crystallization of a particular polymorph. The reader is referred to references that address these concepts and strategies [15,17,18,27,54,60].

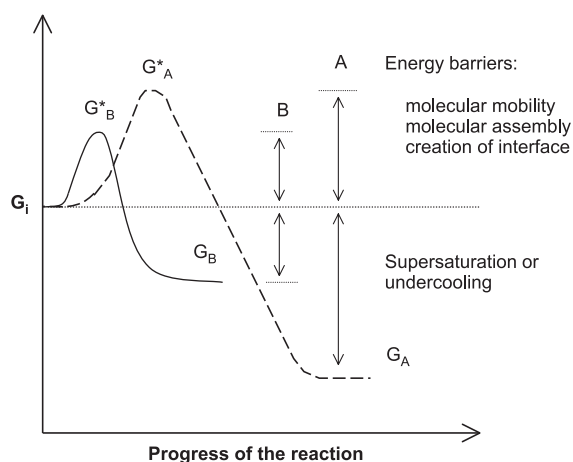


Fig. 5. Schematic diagram for a hypothetical transition from the initial state, G_i , to two different solid forms A or B, with free energies G_A and G_B . Form A is more stable and less soluble than B. A transition from the initial state G_i to state A or B will depend on the energy barrier and according to this reaction pathway the height of the energy barrier for structure A, ($G_A^* - G_i$) is greater than that for B, ($G_B^* - G_i$). Because the rate of nucleation is related to the height of the energy barrier on the reaction path, B will nucleate at a faster rate than A even though the change in free energy is greater for A ($G_A - G_i$) than for B ($G_B - G_i$).

3.2. Nucleation

Nucleation mechanisms can be divided into two main categories: homogeneous and heterogeneous (surface or interface catalyzed) [61–64]. Homogeneous nucleation rarely occurs in large volumes (greater than 100 μl) since solutions contain random impurities that may induce nucleation [65,66]. A surface or an interface of composition and/or structure different from the crystallizing solute may serve as a nucleation substrate, by decreasing the energy barrier for the formation of a nucleus that can grow into a mature crystal. Nucleation that is promoted by crystals of the crystallizing solute is known as secondary nucleation. These mechanisms are thoroughly discussed by Mullin [62], Myerson [64] and Zettlemoyer [61]. Nucleation mechanisms have been of great utility in controlling the nucleation and transformation of polymorphs and solvates, isolating metastable solid phases in confined spaces [51], directing nucleation of polymorphs using solid substrates that template certain crystal structures [27,67,68], and in controlling transformations during dissolution of metastable solid phases [18,40,69].

3.2.1. Homogeneous nucleation

Thermodynamic considerations for nucleation are based on the work of Gibbs [70], Volmer [71] and others, where the free energy change for an aggregate or molecular assembly undergoing a phase transition ΔG is given by:

$$\Delta G = \Delta G_V + \Delta G_S \quad (11)$$

where ΔG_S is the surface free energy change associated with the formation of the phase boundary (a positive quantity), and ΔG_V is the volume free energy change associated with the phase transition (a negative quantity). For homogeneous or heterogeneous nucleation:

$$\Delta G_V = -\alpha l^3 v^{-1} k_B T \ln\left(\frac{c}{s}\right) \quad (12)$$

where α is the volume–shape factor, l is the characteristic length, v is the molecular volume of the crystallizing solute, k_B is Boltzmann's constant, T is temperature, and c is solute concentration. This equation assumes that concentrations can be substi-

tuted for activities if the ratio of the activity coefficients at the supersaturated concentration and equilibrium concentration are approximately 1. For homogeneous nucleation:

$$\Delta G_S = \beta l^2 \gamma_{12} \quad (13)$$

where β is the area shape factor and γ is the interfacial energy per unit area between the crystallization medium, 1, and the nucleating cluster, 2. Consequently, the overall free energy change for nucleation is decreased by a large supersaturation ratio (c/s) and by a low interfacial energy.

The factors that regulate nucleation are best appreciated by considering the equation for the rate of homogeneous nucleation from liquid solutions:

$$\begin{aligned} J &= N_0 v \exp\left(\frac{-\Delta G^*}{k_B T}\right) \\ &= N_0 v \exp\left(\frac{-4\beta^3 v^2 \gamma_{12}^3}{27\alpha^2 (k_B T)^3 \left(\ln\left(\frac{c}{s}\right)\right)^2}\right) \end{aligned} \quad (14)$$

J is the number of nuclei formed per unit time per unit volume, N_0 is the number of molecules of the crystallizing phase in a unit volume, v is the frequency of atomic or molecular transport at the nucleus–liquid interface, and ΔG^* is the maximum in the Gibbs free energy change for the formation of a supramolecular array, at a certain critical size, l^* . The nucleation rate was initially derived for condensation in vapors by Becker and Döring [72], where the pre-exponential factor is related to the gas kinetic collision frequency. In the case of nucleation from condensed phases the frequency factor is also related to the diffusion process [73]. The value of l^* can be obtained by maximizing the free energy function with respect to the characteristic length:

$$l^* = \frac{2\beta v \gamma_{12}}{3\alpha k_B T \ln\left(\frac{c}{s}\right)} \quad (15)$$

For spherical clusters, $\alpha = 4\pi/3$ and $\beta = 4\pi$ based on the radius of the prenucleation molecular assembly, and therefore:

$$r^* = \frac{2v \gamma_{12}}{k_B T \ln\left(\frac{c}{s}\right)} \quad (16)$$

Considering these geometric factors, the rate for homogeneous nucleation of spherical assemblies is:

$$J = N_0 v \exp \left(\frac{-16\pi v^2 \gamma_{12}^3}{3(k_B T)^3 \left(\ln \left(\frac{c}{s} \right) \right)^2} \right) \quad (17)$$

Inspection of the equation above suggests that the nucleation rate can be experimentally controlled by the following parameters: molecular or ionic transport, viscosity, supersaturation, solubility, solid–liquid interfacial tension, and temperature. One can reach the conclusion that an increase in solubility, due to solid-state form or solvent change, will increase the nucleation rate because this will decrease the interfacial energy [74] and increase the probability of molecular collisions by increasing N_0 [15,59]. This behavior is also consistent with Ostwald's law of stages regarding the initial appearance and faster nucleation rate of the least stable solid phase as shown by the behavior outlined in Fig. 5. However, this dependence of nucleation on solubility will not be followed in the presence of strong solvent–solute interactions that interfere with the formation of molecular assemblies compatible with those in the crystalline state [59].

3.2.2. Nucleation in confined spaces

An important factor contributing to the nucleation mechanism and kinetics is the volume of solution in which nucleation occurs. The dispersal of a bulk liquid into a collection of small droplets has been shown to be an effective way of achieving large supersaturations or undercoolings [65,66]. Precipitation and solidification in small volumes (droplets) involving emulsions have been used to study homogeneous nucleation processes [75], for the control of purity, particle size, and morphology [76,77], and in capillaries for nucleation of metastable phases [51]. Dispersing a solution into small domains isolates heterogeneous nucleants, affects the cooperativity phenomena and makes nucleation more difficult.

3.2.3. Heterogeneous nucleation

Heterogeneous nucleation processes are of fundamental and practical importance in pharmaceutical systems since unintentionally or intentionally added surfaces or interfaces may promote nucleation of

different crystal structures. The reactivity of solid surfaces as heterogeneous nucleants has significant consequences in the isolation of the desired solid-state modification and in the control of conversions between these modifications, since the free energy required for the formation of two-dimensional nuclei is lowered by the presence of an appropriate substrate. Quantitatively this is described by the following equation [78]:

$$\Delta G_S = \gamma_{12} A_{12} + (\gamma_{23} - \gamma_{13}) A_{23} \quad (18)$$

where γ is the interaction energy per area as described earlier, A is the surface area of the interfaces, and the subscript 3 represents the substrate. The first term in this equation corresponds to homogeneous nucleation. This equation shows that the total change in surface free energy will be lowered and nucleation facilitated by favorable surface interactions between the aggregate (2) and the substrate (3) and unfavorable interactions between the crystallization medium (1) and the substrate (3), due to the negative value of the second term in Eq. (18).

These concepts have been applied to the directed nucleation of polymorphs [16,44,79–81] and provides us with the attractive possibility that “a library of organic seeds can be used to control polymorphism, or to search for unknown polymorphs” [82]. Molecular recognition phenomena based on this approach are experimentally more accessible than those based on solvent-selective polymorph crystallization.

The effectiveness of crystal seeding in controlling crystallization outcomes relies on the potential of solid surfaces to promote heterogeneous or secondary nucleation [62,63], while avoiding heterogeneous nucleation mediated by unknown contaminants. The effects of accidental heterogeneous nucleation have been reported in the crystallization of ritonavir polymorphs [52,83] where an insoluble degradation product promoted the nucleation of a more stable polymorph.

The consequences of heterogeneous nucleation are also important during the dissolution of metastable solid phases, since if unnoticed it may lead to erratic “dissolution behavior” due to fast transformation to a less soluble form. We and others have reported that surfaces of metastable anhydrous phases of theophylline [69,84] and carbamazepine [18,85] facilitate the nucleation of the stable hydrate forms during disso-

lution. The information gained from this type of study can be very useful in the design of methods to control crystallization during dissolution as well as during isolation of the desired solid form.

4. Molecular recognition

As has been discussed in the previous sections, without fulfilling the energy requirements dictated by thermodynamics a new phase will not be created, and without the formation of non-covalent bonds compatible with ordered molecular networks a crystal will not be formed. Thus the essential questions in the crystallization of desired polymorphs and stabilization of metastable phases including amorphous solids are: (1) how far is the system from equilibrium, (2) what is the molecular mobility, and (3) are molecular assemblies in the parent phase compatible with those in the crystal structures? The first has been addressed by the thermodynamic concepts and the second is relevant to crystallization from the solid state, and in particular disordered systems, since in the liquid state unless viscosity values are high, the rates of molecular motion are higher than for other events and are not rate limiting. The third can be addressed by studies of nucleation behavior of polymorphs in different solvents, in the presence of soluble additives and insoluble additives from the selective reactivity of surfaces. Advances of analytical methods to gain molecular level information have also provided impetus in addressing the molecular organization and identifying networks in fluid and solid pharmaceutical phases.

The approach of solvent selection for screening polymorphs relies on the diversity of molecular arrays that can be formed in the presence of other molecules competing with the self-recognition event that precludes nucleation. The effect of solvent on the rate of nucleation and order of appearance of polymorphs has been studied by considering the kinetic, thermodynamic and molecular assemblies of APIs, for example sulfamerazine [86], sulfathiazole [87], carbamazepine [88], and other compounds [16]. Grant and coworkers [86] have shown that the nucleation rate is a function of the balance between thermodynamics and strength of solvent–solute interactions, and that the fastest nucleation rates will be observed in solvents with a relatively high solubility but moderate solvent inter-

actions. Threlfall [57] has thoroughly considered thermodynamic factors and the conditions in which the solvent may or cannot affect polymorphic outcomes. Because of the interplay between thermodynamic factors (free energies, solubilities, concentrations, interfacial tensions), temperature, and molecular assembly in determining nucleation of a new phase, it is essential to consider the effects on thermodynamic factors when using solvents or surfaces to selectively nucleate polymorphs.

The relation between molecular assemblies and crystallization has also been of great interest in improving the stability of amorphous solids [37,89]. Since crystalline and amorphous phases share similar non-covalent bonds and differ in the range of disorder, the amorphous state may be considered as a precursor to the crystalline state. In this case the ease of nucleation is dependent on molecular mobility, in addition to the obvious thermodynamic and kinetic factors, and differences in the molecular motifs between the amorphous and crystalline states [37,89].

5. Single-component systems

5.1. Amorphous

Pharmaceutical glasses or amorphous solids present an attractive approach to drug delivery because of their improved bioavailability compared to their crystalline counterparts. Amorphous solids lack the three-dimensional long-range molecular order characteristic of crystals, but may exhibit short-range order [24,25,36]. Amorphous materials are further from equilibrium than crystalline materials, are higher energy states, and as expected have faster dissolution rates and kinetic or metastable solubilities relative to corresponding crystals [31]. Mechanical properties can also be affected by the extent of disorder [90].

Hancock and Parks [31] predicted metastable solubility values for amorphous forms to be between 10 and 1600 times that of the stable crystalline forms. The measured metastable solubility is usually considerably less due to the rapid crystallization when exposed to water vapor or dissolution media. In fact, they report measured kinetic solubilities for amorphous drug compounds of at least 14 times higher

than the thermodynamically stable crystalline state, whereas for polymorphs and solvates it could be about four times higher.

Amorphous phases can be prepared under conditions very far from equilibrium from various initial states: (a) the liquid state by fast precipitation achieved at high driving forces and at low temperatures to reduce mobility (quenching a melt by rapid cooling and fast evaporation or freezing of solvent in liquid solution) [36,37], and from (b) crystalline solids by milling or grinding at low temperatures [91] and by desolvation of crystalline materials [92]. Manufacturing processes commonly used to prepare amorphous materials include spray-drying, freeze-drying and melt extrusion. Pharmaceutical products reported in the USP/NF and Physician's Desk Reference containing amorphous components, APIs, and excipients often include tablets, capsules, suspensions, and powders. Insulin suspensions, for instance, for subcutaneous administration have been marketed with varying ratios of amorphous and crystalline insulin to control the rate of delivery.

Molecularly disordered solids experience translational motion and molecular mobility that do not occur in the crystalline state. This enhanced molecular mobility can also lead to physically and chemically reactive materials and to changes in pharmaceutical properties depending on the methods of preparation and storage as well as storage time. For example, it has been shown that amorphous cefamandole nafate prepared by freeze-drying and spray-drying has slightly different X-ray diffraction patterns [93] and amorphous tri-*O*-methyl-cyclodextrin prepared by milling and melt-rapid quench has different relaxation enthalpy rates and crystallization rates although the T_g and heat capacity values are similar [94]. This difference in properties for the same material has raised the question of whether there are different amorphous states. In a recent publication, Shalaev and Zografi discuss the differences between true polyamorphism and relaxation polyamorphism [37]. To our knowledge, true polyamorphism has not been reported for pharmaceutical materials and is defined as the existence of two distinct amorphous states involving a first-order transition and differs from the frequently observed relaxation states typical of amorphous materials. The latter behavior or relaxation polyamorphism is more frequently observed in pharmaceutical materi-

als and is a result of different kinetic states or continuous changes of amorphous systems.

Despite the long-range disorder of amorphous materials it has been found that there are regions of local order. Information about molecular assemblies and in particular hydrogen-bond patterns in low molecular weight organic glasses has been obtained by spectroscopic methods (infrared and Raman) [95]. Similarities between molecular assemblies in the amorphous and crystalline states have been related to the instability of the amorphous state and to the crystallization of different polymorphic forms [37,89]. Indomethacin has been shown to crystallize from the amorphous state in either the γ or α crystal forms depending on the temperature [96]. Temperatures $\leq T_g$ produce the γ polymorph whereas $T > T_g$ produce the α form. Raman and IR studies have shown that hydrogen-bond patterns of indomethacin in the amorphous state lead to crystallization of the polymorph with molecular assemblies similar to those in the glass [24]. Hydrogen-bond motifs found in crystalline monocarboxylic acids and in the α and γ indomethacin polymorphs are shown in Fig. 6. The dimer found in the γ form is the most common supramolecular synthon for monocarboxylic acid crystals [53].

Recent developments to probe molecular level interactions and mobility provide in-depth understanding of molecular relaxation and recognition processes that allow for better design and stability of disordered pharmaceutical dosage forms. Strategies to assess and predict the long-term stability and performance of amorphous systems rely on measurements

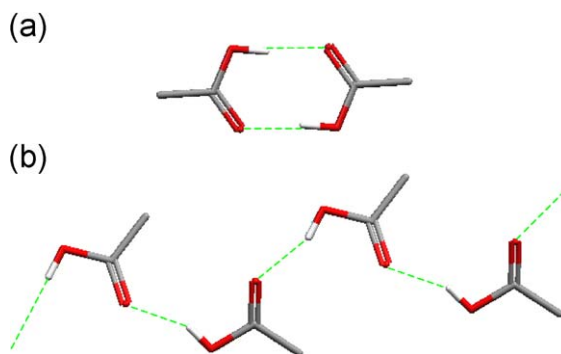


Fig. 6. Molecular assemblies of the carboxylic acid synthon (intermolecular connector) illustrating the hydrogen bond patterns that lead to two supramolecular isomers: (a) dimer and (b) head-to-tail chain.

that reflect (1) molecular mobility, such as enthalpy relaxation, viscosity, and solid-state NMR relaxation times and (2) intermolecular interactions such as infrared and Raman spectroscopies.

5.2. Crystalline

Structurally, crystalline polymorphs are characterized by varying degrees of changes in conformation and packing arrangement of molecules in the solid state. Often the key intermolecular interactions, both weak and strong, are preserved among forms, although it is difficult to predict when this will be the case for a given compound. For cases where obvious changes in conformation are observed, the designator “conformational polymorph” [1,2,29,97–99] is generally used. Differences in the packing of molecules with similar conformations have been termed by some investigators as “packing polymorphism” [1,29]. It is generally recognized that these designations, however, are artificial because virtually all polymorphs exhibit small differences in conformation among their modifications. However, it is important to note that polymorphs, which exhibit large differences in structure, do not necessarily have large differences in stability and vice versa.

5.2.1. Nabumetone

Nabumetone (RelafenTM), Fig. 7, is an anti-inflammatory, analgesic, and antipyretic therapeutic usually prescribed to patients with arthritis. This pharmaceutical crystallizes in two polymorphic forms. The commercial material (form I) is monoclinic with two unique molecules in the unit cell [48,51,100]. A second polymorph forms upon evaporation from small volumes of ethanol [48] or crystallization in capillaries (Section 7.2.2) [51]. This polymorph is also monoclinic, but possess only one asymmetric molecule in the unit cell (form II) [48,51]. Similar molecular conformations are adopted in both forms. However, the molecules in each structure adopt strikingly different arrangements in the lattice.

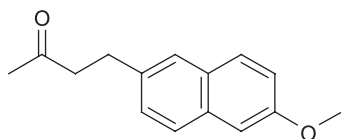


Fig. 7. Structure of nabumetone.

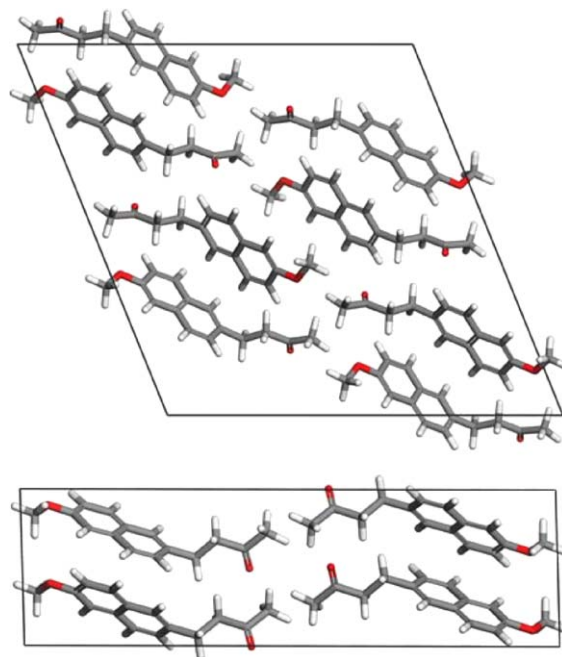


Fig. 8. Packing diagram of nabumetone polymorphs (top: form I, bottom: form II).

Form I assembles in a head-to-tail manner whereas form II packs in a tail-to-tail head-to-head fashion, Fig. 8. In form I weak intermolecular interactions, especially C—H···O close contacts, dominate the structure. By contrast, form II packs in a herringbone arrangement with several C—H··· π interactions.

5.2.2. Carbamazepine

Carbamazepine, Fig. 9, a pharmaceutical used in the treatment of epilepsy and trigeminal neuralgia, is a tetramorphic system possessing nearly identical molecular conformation and strong hydrogen bonding among its polymorphs. Investigations into the polymorphism of this drug began in the late 1960s and produced three forms; two of these were structurally

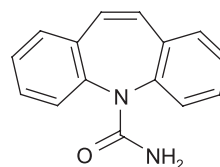


Fig. 9. Structure of carbamazepine.

characterized [101–103] in the 1980s and the structure of the third form was recently solved by single crystal X-ray diffraction [44]. Remarkably, after 30 years of study a fourth polymorph [104] was discovered by the technique of polymer heteronucleation (Section 7.2.5) [68]. All four polymorphs adopt an essentially identical anti-carboxamide dimer motif. This is in contrast to many other highly polymorphic systems, which display differences in either conformation or strong hydrogen bonding pattern (see sulfapyridine). The distinction among crystal forms lies in the packing of the dimer units. This is illustrated in the diagrams presented in Fig. 10. The triclinic (form I) and trigonal (form II) polymorphs pack in a similar manner. Both modifications form two C—H $\cdots$ O intermolecular interactions between an oxygen and two different hydrogen donors. These contacts take

place between a benzenic hydrogen and the oxygen of the urea. Forms III and IV also feature important C—H $\cdots$ O close contacts. However, these involve a hydrogen on the double bond of the azepine ring to the oxygen of the urea, which link adjacent dimers into infinite chains. The densities of the carbamazepine polymorphs cover a large range of values with form II possessing the lowest density of 1.24 g/cm³ and form III having the highest density of 1.34 g/cm³. The relative stabilities of the four polymorphs are in accordance with the density rule with the densest structure, form III, being the most stable (Section 2.2.3).

5.2.3. Sulfapyridine

Sulfapyridine is an anti-bacterial sulfonamide drug used to treat pneumonia and is known to crystallize

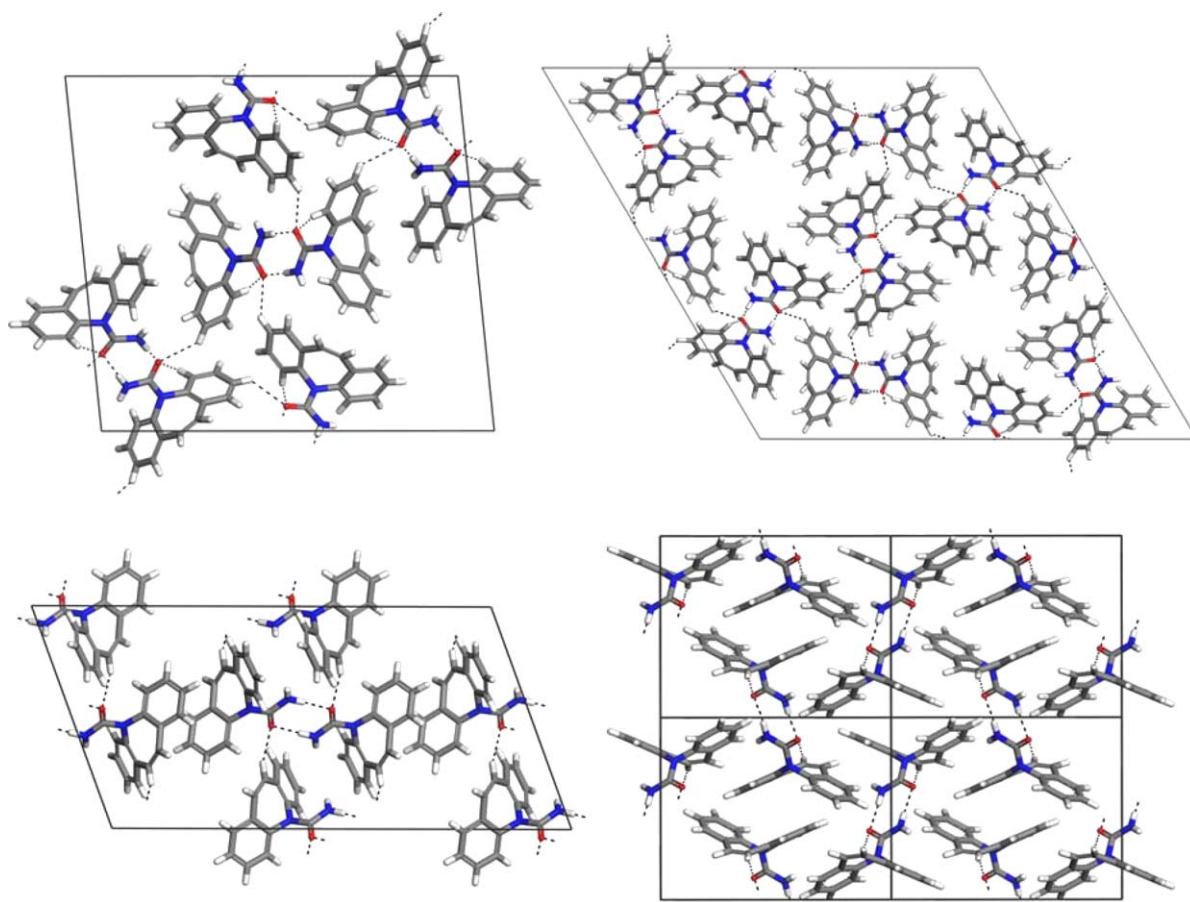


Fig. 10. Packing diagrams of carbamazepine polymorphs. From top left clockwise: form I, II, III, and IV.

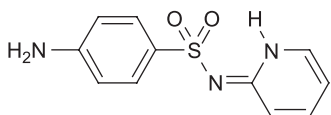


Fig. 11. Structure of sulfapyridine.

as at least seven polymorphs. Four of these forms (II–V) have been structurally characterized [105–107]. Polymorphism of this system was first reported in 1946, [108] when four polymorphs were identified by melting point and a fifth was found by optical crystallographic properties. Later thermal microscopy experiments on sulfapyridine revealed seven polymorphs [109]. However, it was not until 1984 that a single crystal structure of this compound had been solved [105]. Two additional polymorphs

were structurally characterized in 1985 and another was described in 1988 [106,107]. This system displays conformational polymorphism, which is exemplified by differences in the N–S–C–C torsion angle in the molecule, Fig. 11, that can be as large as 39° between forms. A single distinct molecular conformation is present in forms II–IV. However, form V is unique in the fact that it possesses two different conformers in the same unit cell. This difference is also apparent in the packing arrangement and hydrogen bonding schemes displayed by each modification, Fig. 12. Forms II, IV, and V exhibit a similar N–H $\cdots$ N hydrogen bonded dimer. These dimer units assemble in a different manner in each of the three polymorphs, while form III packs with an N–H $\cdots$ O intermolecular hydrogen bonded dimer.

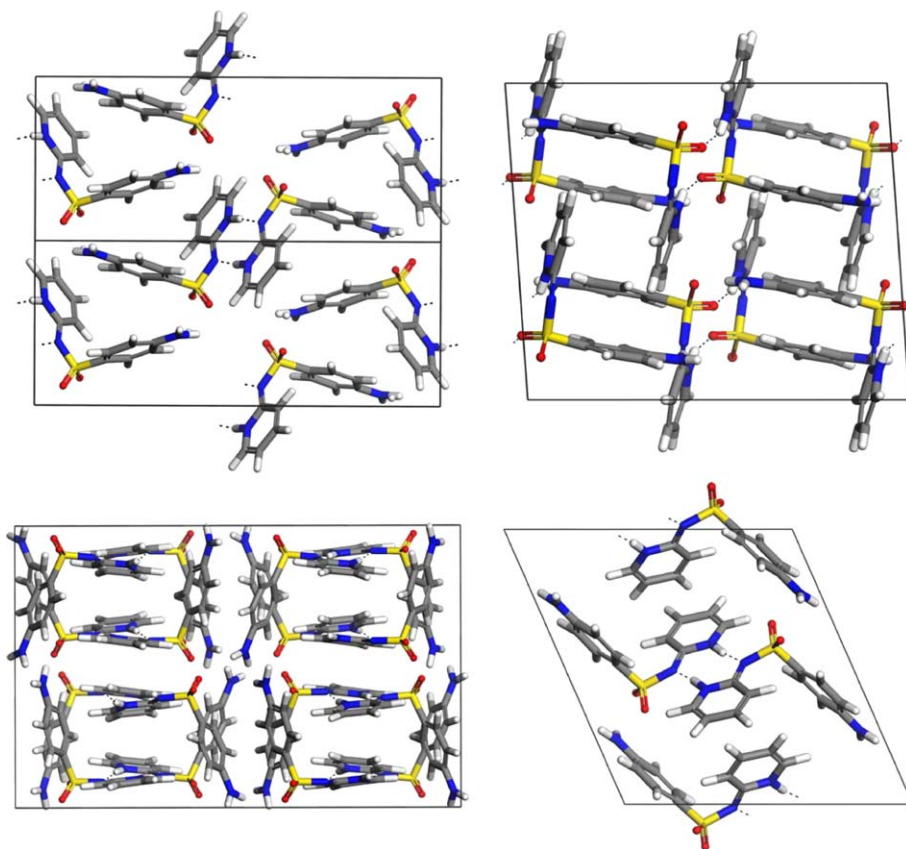


Fig. 12. Packing diagrams of sulfapyridine polymorphs. From top left clockwise: form II, III, IV, and V.

6. Multiple-component systems

Multi-component systems are molecular assemblies composed of an API and a complementary molecule (neutral or charged) such as solvent, excipients, and other substances. These solid-state supermolecules are assembled from specific non-covalent interactions between molecules, including hydrogen bonds, ionic, van der Waals and π – π interactions. Supramolecular synthons are the structural units that connect molecules to one another via these interactions. Thus, intermolecular interactions can be used as key molecular recognition elements in the design of amorphous or crystalline multiple-component systems and in the characterization of structures. It is important to recognize that amorphous and crystalline solids share the same intermolecular bonds and differ mainly in the range of disorder.

Etter derived guidelines for hydrogen bonding in crystals from analysis of hydrogen bond motifs that apply to the design of molecular assemblies [26,110]. The simplest of these rules states that all available proton donor and acceptor groups will be used in the hydrogen bond patterns of most organic molecules in the crystalline state [110]. Ideally, the hydrogen bond rules can be used as guidelines for the design of molecular assemblies if one is mindful of crystallization kinetics and thermodynamic properties.

6.1. Amorphous

Multiple-component systems can be prepared as amorphous molecular dispersions. Homogeneous dispersions of API and other substances offer the advantages of the higher energy amorphous state, such as improved dissolution rates and bioavailability. Components used in the formulation of solid dispersions include polymers such as polyethylene glycol (PEG) [111,112], polyvinylpyrrolidone (PVP) [24,113–116], polyvinylalcohol (PVA) [117], polyvinylpyrrolidone/vinylacetate (PVP/VA) copolymers [118,119], cellulose derivatives [120,121], polyacrylates and polymethacrylates [122,123]. In contrast to single-component amorphous solids, molecular dispersions can be designed with optimal stability and function. For instance, relaxation times, molecular mobility, and intermolecular interactions can be varied by the choice of components [37,118].

The stabilizing effects of PVP on amorphous molecular dispersions of organic substances have been explained in terms of hydrogen bonding patterns [24,118,119]. For instance, the ability of PVP to inhibit the crystallization of indomethacin at room temperature (30 °C) has been related to molecular mobility and intermolecular interactions. Vibrational spectroscopy results revealed that the hydrogen bonds responsible for dimer formation in indomethacin are disrupted, which are prerequisite to the formation of crystal nuclei [24,119]. The carboxylic acid of indomethacin instead forms a stronger hydrogen bond with the more basic amide carbonyl of the polymer. Since the local structure or heterogeneity of the molecular dispersion is apparently less ordered than that of amorphous indomethacin due to disruption of the dimer, it can be expected that the time scale for structural relaxation will be greater for the dispersion [37].

6.2. Crystalline

Crystal engineering offers a rational approach to the design of new compositions and crystal structures. Much as an organic chemist employs the covalent bond in the design of drug molecules, non-covalent bonds can be exploited in the design of supramolecular structures. Hydrogen bonded networks are the most commonly studied since a certain degree of reliability and predictability exists regarding the interaction of donors and acceptors [110]. However, additional interactions that also play significant roles in the creation of multi-component crystals include van der Waals, π – π stacking, and electrostatic interactions [2,9]. Molecular networks of these kinds are used in building cocrystals, solvates, hydrates, and salts and will be described herein.

6.2.1. Cocrystals: solvates

The drug development process exposes pharmaceutical solids to solvents, organic and aqueous solvents during crystallization, wet granulation, storage and dissolution, that can lead to the formation of solvated crystals by design or inadvertently. Crystalline forms of APIs with included solvent molecules differ in pharmaceutical performance—mechanical behavior, stability, dissolution and often bioavailability—from the unsolvated API crystal [124–126].

Choice of development of solvated or unsolvated form will depend on its pharmaceutical properties, how long it can survive and under what conditions. Thus of fundamental importance is the question of why some APIs form solvates and others do not.

The propensity of an API molecule to form solvates has been related to molecular structures, hydrogen bond patterns, and crystal packing [30,124–129]. The Cambridge Structural Database has been useful to analyze the nature of supramolecular networks in solvated crystals [30,128,129] and to identify molecular recognition events that lead to incorporation of solvents in crystal structures. Nangia and Desiraju [30] found that the propensity of organic solvents to be included in molecular crystals depends on their ability to effectively participate in hydrogen bonding, and that multi-point recognition via strong and weak hydrogen bonds between solvent and solute molecules facilitates solvate formation. They also recognize the importance of the kinetics and energetics of solvation and desolvation events during crystallization. Because formation of an unsolvated crystal by crystallization from solvent requires that solute–solvent interactions be replaced by solute–solute interactions, strong solute–solvent interactions may lead to nucleation of solvated crystals.

A survey of the 2002 Cambridge Structural Database (version 5.23) found that water is incorporated into organic crystals far more frequently than any other solvent. Of 257 000 entries for organic and metal organic compounds, 115 600 do not contain metal atoms, and of these, 10 000 are solvates. The frequency for the solvents incorporated into organic crystals is as follows: 5070 water, 356 ethanol, 745 methanol, 309 acetone, 137 DMSO and 274 THF. It is surprising that about 50% of the entries for solvates are hydrates because water is not a good solvent for many of these compounds and other solvents are commonly used for crystallization. This brief search reported here does not account for the frequency of use of solvents and the reader is referred to the work of Nangia and Desiraju for analysis on the frequency of formation of organic solvates [30].

Hydrated forms of pharmaceutical solids are also more common than solvates due to the abundance of water in the atmosphere, its small size, its ability to act as both a hydrogen bond donor and acceptor, and the water activity of solvents or vapor that APIs come in

contact with. A study of the environments of water molecules, hydrogen bonded to nitrogen and oxygen atoms, within organic hydrates using the Cambridge Structural Database revealed that water prefers to maximize its hydrogen bonding interactions within a hydrate structure [129]. In the most commonly found environment (38%) among the 3315 crystal hydrates investigated, water forms three hydrogen bonds (two to hydrogen and one to oxygen) with oxygen or nitrogen atoms of organic molecules. The second most commonly found environment (28%) for water shows tetrahedral coordination with two hydrogen atoms and two lone pairs. In another study Infantes and Motherwell [128] examined the patterns of water clusters within more than 1400 hydrated structures and classified them as discrete rings, chains, infinite chains, tapes and layer structures. The most frequent water motifs were discrete chains (61%), infinite chains (20%) and discrete rings (9%). The majority of discrete chains simply have a pair of water molecules joined through hydrogen bonds, while the majority of discrete rings have four water molecules. When solute molecules have acceptor/donor groups, a bridge between water molecules and organic molecules form an infinite network in one dimension, a tape.

Another classification of hydrates is based on general structural differences of water networks: I, isolated lattice site (discrete chains or rings); II, lattice channel (chain or tape structures); III, metal–ion coordinated hydrates [124,126]. Common analytical techniques can discern if water is loosely bound to the crystal surface, if it is hydrogen bonding to itself within the crystal lattice to form channels (class I) or if it predominantly interacts with other molecules within the lattice, such as the drug moiety or co-ion in the case of salts (class II–III). The channel hydrates (class II) can be further classified into (a) expanded channels, which expand or contract to form non-stoichiometric hydrates, (b) lattice planes, where water is localized in a two-dimensional order and (c) dehydrated hydrates, formed when dehydration leaves an intact anhydrous structure that is similar to that of the hydrate.

Niclosamide is an example that demonstrates the impact of intermolecular interactions on the structure of molecular assemblies and their influence on physical–chemical properties [130]. Molecular recognition

in these networks depends on hydrogen bonding between $\text{O}-\text{H} \cdots \text{O}$ moieties and has been described for three solvates of niclosamide: a dihydrate, a tetrahydrofuran (THF) solvate and a tetraethylene glycol (TEG) solvate. The relative strength of hydrogen bond donor and acceptor groups was correlated to structural architecture and thermal behavior, indicating desolvation pathways. Caira et al. [130] showed that in the niclosamide hydrate, water molecules occupy a channel and hydrogen bond with surrounding drug molecules (Fig. 13a). This arrangement falls

into the aforementioned class II structures. The strength of this assembly is confirmed by high dehydration onset temperatures (173 ± 5 and 201 ± 5 °C), and indicates that water and niclosamide are tightly bound. In contrast, the THF solvate undergoes rapid desolvation from molecular assemblies at 30 °C, which is 36 °C lower than the boiling point of THF. The instability of this system was explained by weak forces forming a continuous channel within the crystal structure, which facilitates migration of the solvent out of the lattice (Fig. 13b). The TEG solvate forms

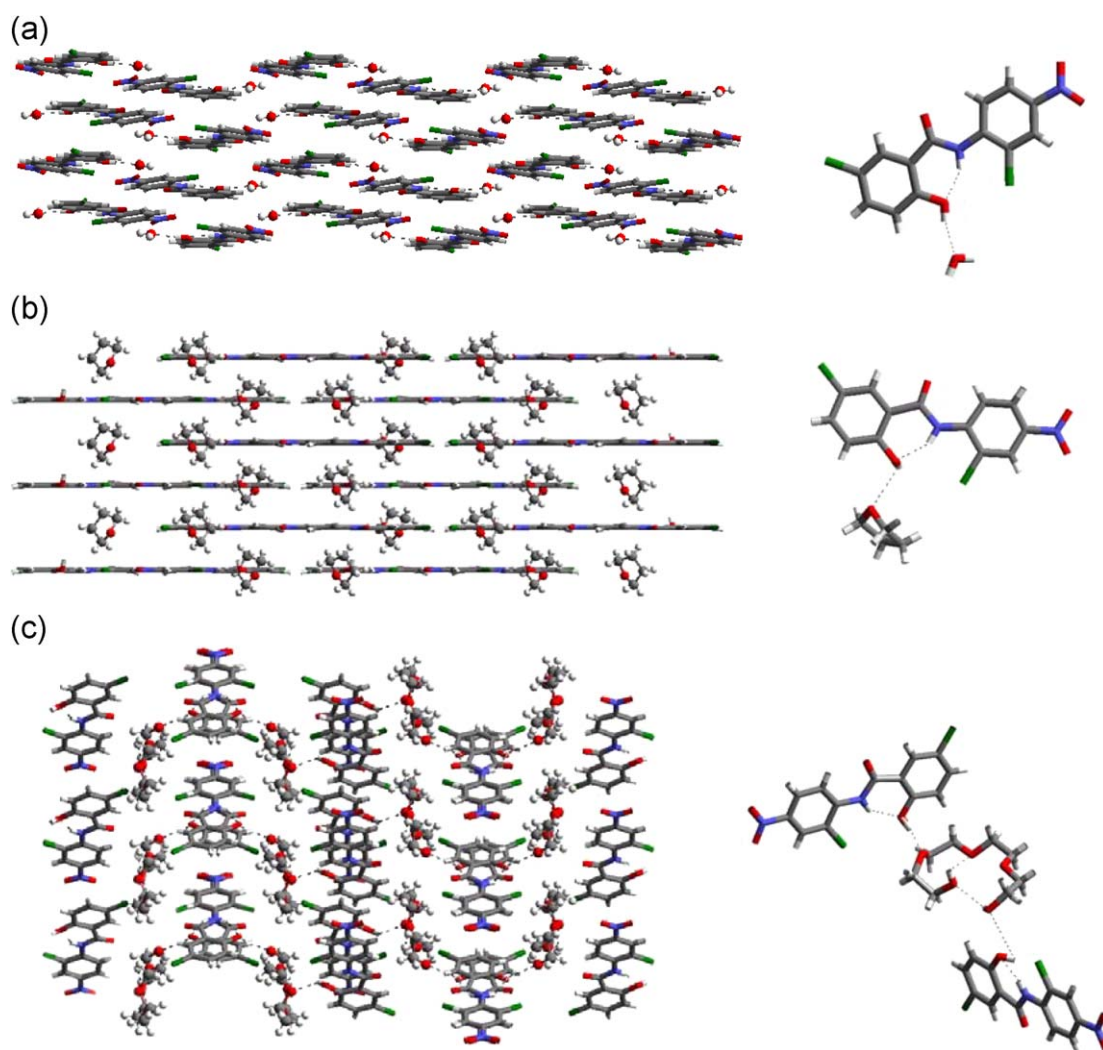
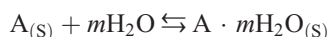


Fig. 13. Crystal structures and heterosynthons of niclosamide (a) monohydrate, (b) THF solvate, and (c) TEG solvate. Solvent molecules are represented as cap-stick models for clarity in the molecular packing diagrams. Adapted with permission from reference [13].

stronger hydrogen bonds relative to THF and thus shorter bond distances. The unit cell contains a 2:1 complex with TEG intercalating between layers of niclosamide (Fig. 13c). Hence, desolvation in this system is slower and occurs over a much wider temperature range (65–230 °C).

Understanding thermodynamic and kinetic factors that dictate the stability of a solid phase is essential in drug development, given that unexpected changes can result in erratic dissolution rates and variable bioavailabilities. For instance, carbamazepine and theophylline are marketed with the anhydrous forms which undergo transformation to the hydrate form during dissolution [15,18,40,69] and when the solid is exposed to moisture [131,132]. Transformation from an anhydrous to a hydrated state can be solution-mediated, where dissolution of the metastable phase and crystallization of the more stable hydrate form occurs via the solution phase, or a transformation can occur in the solid state by incorporating water into the crystal lattice [69,126]. Hydration and dehydration events are also influenced by the water activity in the liquid and vapor phases [133,134].

Khankari and Grant [125] have described the thermodynamics of hydrate equilibria, where the formation of hydrate crystals from an anhydrous phase is represented as:



$$K_h = \frac{a[A \cdot mH_2O_{(s)}]}{a[A_{(s)}]a[H_2O]^m} \quad (19)$$

where K_h is the equilibrium constant for the hydration/dehydration equation, m is the number of moles of water taken up by 1 mol of the anhydrous phase, $a[A \cdot mH_2O_{(s)}]$ is the thermodynamic activity of the hydrate, $a[A_{(s)}]$ the activity of the anhydrate, and $a[H_2O]$ is the water activity. Calculating the equilibrium constant for a process enables determination of the relative tendency for a transformation to occur. If pure solids of the hydrate and anhydrous phase represent the standard state of unit activity, then the equilibrium constant can be simplified into:

$$K_h = a[H_2O]^{-m} \quad (20)$$

The water activity, abbreviated a_w , in the crystallization solvent or in the vapor phase will determine the relative stability of a hydrate. Water activity can thereby be controlled by changing the composition of the solvent or by regulating relative humidity. For organic solvent/water mixtures, a_w values can be calculated from literature values of the mole fraction-based activity coefficient, γ_w , and the mole fraction of water in the mixture, x_w :

$$a_w = \gamma_w x_w \quad (21)$$

Studies have examined the influence of a_w in organic solvent/water mixtures on the physical stability of the solid phases of theophylline and ampicillin [133,134]. Water and water-miscible organic solvent mixtures of varying compositions were used to control a_w . Equilibrium water activity values were estimated for solid phases of these compounds. For example, theophylline anhydrate is in equilibrium with theophylline monohydrate when $a_w = 0.25$ and 25 °C. The higher the water activity, the greater the driving force for the transformation. In this study, Zhu and Grant concluded that water activity is the principal thermodynamic factor directing the crystallization of the anhydrate or hydrate phase from the solvent mixture and showed that the kinetics are faster in the liquid phase relative to the vapor phase, leading to shorter times to generate a phase diagram [133].

6.2.2. Cocrystals: neutral molecules

Multi-component networks can be assembled by applying a supramolecular heterosynthon approach based on hydrogen bonding patterns. Etter successfully prepared a wide array of cocrystals based on hydrogen bonding guidelines [4,26,110,135–137]. By choosing systems where the primary controlling features are hydrogen bond interactions, cocrystals of acyclic amides, diarylureas, nitroanilines and 2-aminopyrimidines were prepared by crystallization from organic solvents and in some cases by grinding a physical mixture of the components. Formation of cocrystals of API and excipient, or other component, provides the opportunity to design delivery systems at the molecular level and to enhance their pharmaceutical properties. In fact, we are witnessing the age of supramolecular therapeutics and the design of supra-

molecular assemblies with fine-tunable pharmacologic activity [10,138].

A supramolecular design strategy was recently used to prepare 13 new cocrystals of carbamazepine [13]. The crystal packing of carbamazepine in polymorphs and solvates shows the formation of dimers, with the carboxamide unit acting as both a hydrogen bond donor and acceptor (Fig. 14). Two design strategies were utilized using this moiety as the primary supramolecular synthon where interactions

either retain or disrupt the carbamazepine dimer formation. Fig. 14a–d shows how carbamazepine can form cocrystals with water, acetone, saccharin, or nicotinamide that retain the carboxamide dimer and hydrogen bond instead with available donor/acceptor groups. In contrast, formic acid and trimesic acid cocrystals of carbamazepine disrupt dimer formation (Fig. 14e–f). Given that these cocrystals significantly alter intermolecular associations and modify crystal packing, physical and pharmaceutical properties may

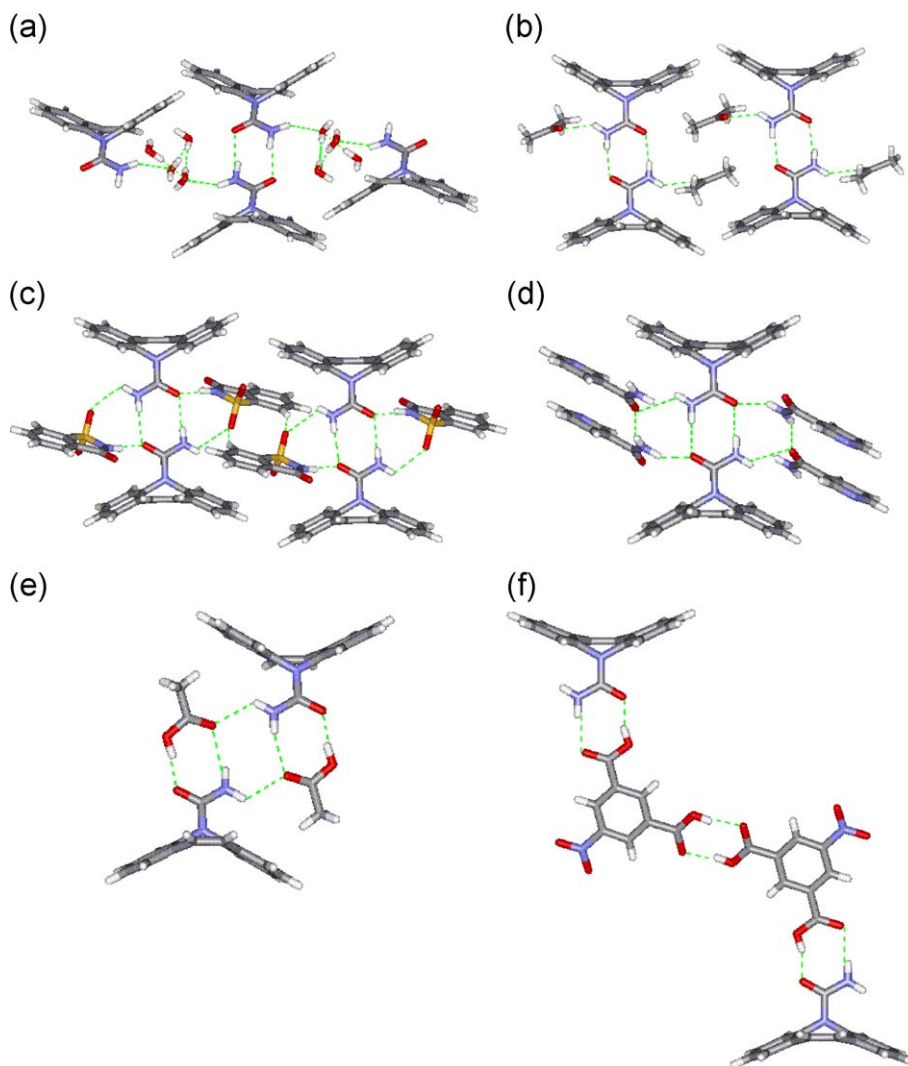


Fig. 14. Molecular assemblies in multiple-component crystals of carbamazepine: (a) hydrate, (b) acetone, (c) saccharin, (d) nicotinamide, (e) acetic acid, and (f) 5-nitroisophthalic acid. Adapted from reference [130].

be consequently affected. Current studies in our laboratories are addressing the pharmaceutical behavior of these materials.

Novel pharmaceutical phases have also been described for a series of cocrystals of acetaminophen [139], aspirin, ibuprofen, and flurbiprofen [12]. Formation of these cocrystals is dominated by non-covalent interactions. Five acetaminophen cocrystals were formed based on $\text{O}-\text{H}\cdots\text{O}=\text{C}$ or $\text{N}-\text{H}\cdots\text{O}=\text{C}$ interactions depending on the structural units present in component molecules. Additionally, $\pi-\pi$ stacking interactions were also involved in the formation of an acetaminophen–pyridine adduct. In the case of aspirin, ibuprofen, and flurbiprofen, carboxylic acid–pyridine supramolecular heterosynthons were applied in the preparation of solid-state complexes. As such, drug dimer formation between carboxylic acids was disrupted and three-component adducts with 2:1 stoichiometries were formed. The supramolecular assemblies of said compounds were different enough to affect physical properties, such as the melting point relative to the individual components.

The utility of cocrystals in providing crystal modifications, which beneficially alter pharmaceutical behavior, has been demonstrated for nicotinamide as well as insulin. Nicotinamide, a form of vitamin B-3, is very hygroscopic and completely deliquescent under high relative humidity. Crystalline adducts of nicotinamide [140,141], chloral or bromal hydrate [142], and cobalt or nickel chloride [143] improve the hygroscopic behavior of nicotinamide. Supramolecular networks between nicotinamide and higher fatty acids such as octadecanoic acid, form an inclusion compound based on associations between carbonyl and amide groups, limiting the ability of nicotinamide to associate with water [140].

NPH insulin is the most widely used insulin product, but it has limited duration of action. Brader et al. [11] prepared an extended-release cocrystalline insulin product that retains the favorable pharmaceutical properties of NPH. The cocrystal former selected is a less soluble insulin derivative which has a hydrophobic nature that alters molecular associations and imparts a decrease in solubility on the cocrystal causing it to dissolve slower than NPH. The appropriate ratio of components results in a continual release insulin cocrystal that extends the pharmacokinetic area under the curve from 12 to over 24 h.

6.2.3. Cocrystals: charged molecules

Pharmaceutical salts represent another class of multi-component systems characterized by electrostatic interactions. The primary motivation for the preparation of pharmaceutical salt forms is to improve the aqueous solubility of poorly soluble APIs with ionizable functional groups. The salt selection process has generally focused on salt forms that are 2 pH units away from the pK_a of the drug [144–146]. This technique does not, however, minimize trial and error. Alternatively, Kramer and Flynn [147] have shown that the pH–solubility profile of the basic or acidic drug can be used to extrapolate a pH_{max} , or pH of maximum solubility, above and below which either the salt or unionized drug will be the equilibrium species. Thus, a weakly basic drug will exist as the salt form when $\text{pH} < \text{pH}_{\text{max}}$ and as the free base when $\text{pH} > \text{pH}_{\text{max}}$. Based on the pH–solubility curve, one can then narrow down the type and number of salts that can be prepared [146].

The approach of supramolecular designs can also be used to prepare pharmaceutical salts. This technique has been successfully applied in the design of small organic molecules. For instance, eight dianion salts of pyromellitic acid have been reported [148], which employ negative charge assisted hydrogen bonds. The ionic $\text{O}-\text{H}\cdots\text{O}$ hydrogen bond between carboxylic groups is regarded as being stronger and more covalent in nature than similar types of interactions [149]. Formate and hydrogen glutarate salts of pyrimethamine, an antifolate drug for the treatment of malaria, are also described in the literature [150]. The carboxylate group of the respective anions interacts with the protonated pyrimidine moiety of the drug, with $\text{N}-\text{H}\cdots\text{O}$ hydrogen bonds serving as the primary association. As described herein, molecular recognition approaches have a wide range of application in drug development and dosage form stability.

7. Preparation of solid-state forms

7.1. Overview of solid-state preparation methods

Crystallization of APIs is most frequently carried out from solutions in the liquid state and strategies and concepts have been thoroughly reviewed in the literature [15,16,43,151]. Independent of the method and

the crystallizing medium, the process relies on the balance between molecular recognition, kinetics, and thermodynamics, as discussed in earlier sections.

The search and control of solid-state forms has motivated the development of new crystallization methods from liquid solutions, supercritical fluids, and solids via solvent-free methods. In liquid solutions, recent focus has led to the study of crystallization processes in confined spaces, for example in capillary tubes [51], and to the evolution of high-throughput methods that in addition to employing small volumes, test the ability of surfaces to nucleate polymorphs [68]. Other advances include crystallization from supercritical fluids where enhanced molecular diffusion and ease of solubility, control of temperature, pressure and solvents provide a means to carefully control polymorph selection [151]. Solvent-free methods have attracted attention in deliberately preparing multiple-component crystalline and amorphous phases by grinding, mixing, compressing, or heating. Several groups have reported cocrystal formation by simple grinding of a mixture of solid components. Frankenbach and Etter [53] showed that cocrystals of 3,5-dinitrobenzoic acid and 4-amino-benzoic acid with an extensive network of hydrogen bonds can be created by grinding. In some cases, crystals formed in solvent do not form by solid-state grinding and vice versa [152,153]. The use of mechanical force is attractive because of its low environmental impact and ease of preparation.

Solid phase transformations of APIs caused by mechanical stress are more frequently associated with the formation of amorphous states. This has attracted attention in the pharmaceutical area because of the unintentional transitions that occur during processing [1] and the significant increase in metastable, or kinetic, solubility of the amorphous state relative to the thermodynamically stable solubility of the crystalline state. The increase in metastable solubility as a result of amorphous formation by grinding has been shown for griseofulvin and glibenclamide [154,155]. Increases in steady-state concentration (c) relative to the solubility of the crystalline phase (s), as high as 14 for glibenclamide and 5 for griseofulvin, were observed by increasing the mass of drug added to the solvent during solubility measurements, Fig. 15. Awareness of this type of transformation is important when unexpected properties could compromise thera-

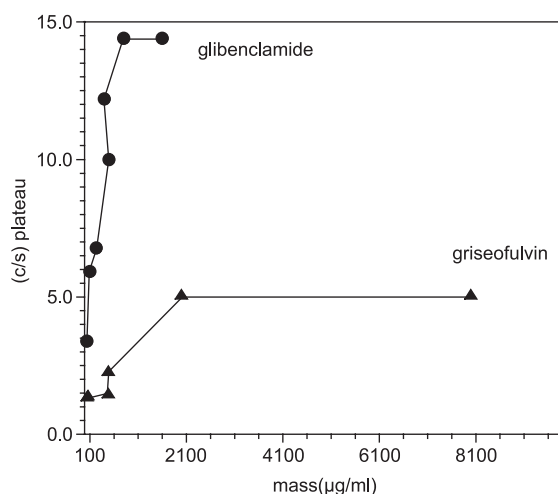


Fig. 15. Comparison of plateau supersaturations achieved by increasing the mass of amorphous glibenclamide (●) and griseofulvin (▲) in aqueous suspensions.

peutic outcomes. However, recent advances in understanding of molecular assemblies and mobility in amorphous states, provide significant opportunities to control the stability of disordered delivery systems [37,89,90].

7.2. New approaches

In general, scientists have yet to achieve a satisfactory degree of control over polymorphism and in particular there is no method to guarantee the production of even the most thermodynamically stable form of a compound. More problematic, and a commonly encountered task for pharmaceutical companies, is finding all forms of a compound that can exist under ambient conditions. When the crystal structures of polymorphs are already known then design of crystal growth accelerators or inhibitors is possible using additives [56,60,156] or monolayers [157]. These strategies are in general limited to crystallographically characterized compounds and are often system specific. The ultimate goal in the field is a universal approach that can produce all energetically reasonable polymorphs of a compound rapidly. Though a method for systematically exploring “polymorph space” [158] has not yet been demonstrated there are exciting recent developments in crystallization techniques that contribute toward this goal; five of these

are discussed here. Two of these methods, high throughput crystallization and capillary growth methods, are improvements on standard crystallization techniques. The remaining three techniques, laser-induced nucleation and heteronucleation by crystalline and polymeric surfaces, act by affecting the nucleation process.

7.2.1. High throughput crystallization methods

The number of possible temperature, concentration, and solvent combinations that should be sampled in searching for a new polymorph greatly exceeds what can be conveniently carried out on the bench top. In order to test thousands of conditions a high throughput process of crystal growth and analysis has been developed [159]. Robotic liquid handling prepares individual solutions, which are subjected to various crystallization conditions. Crystals are screened by a combination of optical image analysis and Raman microscopy to differentiate polymorphs. This strategy was initially applied to acetaminophen, a trimorphic system that has been scrutinized by numerous other investigators [160–163]. The results of the investigation yielded solvent mixtures for the selective production of acetaminophen forms I and II [164]. The analysis of patterns of polymorph generation under a multitude of crystallization conditions provides a roadmap to generating the desired form.

7.2.2. Capillary growth methods

Polymorph generation from solution is dependent upon supersaturation ratio. It is known that in order to access metastable forms of a compound a high supersaturation ratio is often required. In fact, in the regime where the most stable form is only slightly supersaturated most metastable forms are thermodynamically unable to crystallize. Crystallization from capillaries is ideal for producing an environment with high supersaturation because small volumes of solution isolate heterogeneous nucleants [65,66], and reduce turbulence and convection. A successful example of the application of crystallization in capillaries for polymorph generation is that of nabumetone [51] (Section 5.2). This metastable form [48,51] was accomplished by evaporation of a 1:3 water:acetone solution at room temperature inside a 1.0 mm capillary tube. An additional advantage of this approach is that the crystals can be analyzed by PXRD or single crystal

X-ray diffraction, the two most reliable techniques for polymorph differentiation, without removal from the crystallization vessel.

7.2.3. Laser-induced nucleation

Non-photochemical laser-induced nucleation (NPLIN) is a crystallization technique that has the potential to affect nucleation rate as well as polymorph produced. Initial experiments revealed dramatically increased nucleation rates for supersaturated urea solutions upon irradiation with plane-polarized light [165]. This is proposed to occur by alignment of the prenucleating clusters in the applied optical field and a correspondingly reduced entropic barrier to the free energy of activation for critical nucleus formation. In further investigations, it was demonstrated that the technique could provide polymorphic selectivity. NPLIN of supersaturated solutions of glycine preferentially yield the polar γ glycine polymorph [166]. In the absence of laser light the solution growth conditions produced the α polymorph. Although this method has not yet been applied to pharmaceuticals, the technique represents a promising area for polymorph selection and discovery.

7.2.4. Heteronucleation on single crystal substrates

Well-defined surfaces have long been employed in controlling crystallization [67]. In particular, inorganic and organic crystal surfaces have been used as substrates to direct crystallization of many compounds by an epitaxial mechanism [167]. In this process, the oriented growth of a substance on a surface occurs due to the alignment of their lattice parameters. An impressive example of epitaxial growth on an organic crystal surface is 5-methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile, ROY, which is a system with six structurally characterized conformational polymorphs [168–171]. Selection of the yellow needle polymorph of ROY occurs by sublimation on the (101) face of a pimelic acid single crystal. However, sublimation of ROY onto the (010) face of a succinic acid single crystal led to the concomitant formation [27] of three polymorphs: yellow needles, orange needles, and red plates. Notably, the red plates constitute a new, seventh, form of this compound. Extension of this method, by employing a combinatorial library of surfaces, has been proposed for polymorph discovery [82,170].

7.2.5. Polymer heteronucleation

The first combinatorial approach to controlling polymorphism that directly targets nucleation is the recently reported method of polymer heteronucleation [68]. In this method compounds are crystallized in the presence of a chemically diverse library of polymer heteronuclei by solvent evaporation, cooling, sublimation or other traditional crystallization techniques. The polymer acts as an additional diversity element to affect the crystallization outcome. This has the potential for controlling the formation of established forms as well as the discovery of unknown polymorphs without prior knowledge of solid-state structure. Application of this technique to acetaminophen identified, for the first time, conditions to produce the metastable orthorhombic polymorph from aqueous solution. In the absence of specific polymers, monoclinic forms exclusively. In addition to causing the selective growth of one polymorphic form instead of another, polymer heteronucleation was successful in producing a new form of an extremely well studied pharmaceutical. Over 30 years of study on the solid-state chemistry of carbamazepine had yielded three polymorphs. However, a fourth polymorph [104] was discovered using polymer heteronucleation that, remarkably, proved more stable than the well-studied trigonal form [44].

8. Structural and analytical techniques

Once a suspected new solid-state modification of a compound is discovered its classification as a polymorph must be demonstrated by series of analytical techniques [1,2,34,99,172–175]. The most definitive of these is single crystal X-ray diffraction because it directly determines differences in packing and conformation of molecules. Furthermore, intermolecular interactions in the solid are elucidated with atomic resolution providing a wealth of chemical data. However, it can be difficult to obtain high quality crystals of adequate size for this technique and, despite important advances in detector technology, single crystal X-ray diffraction remains relatively low throughput. An important feature of the technique is that it can rule out pseudopolymorphs. In cases where single crystals of sufficient quality for structural determination are not available, solvates and hydrates can often

be identified by thermogravimetric analysis (TGA) or by spectroscopic techniques such as infrared or Raman spectroscopy. Importantly powder X-ray diffraction (PXRD), the most reliable technique for rapid polymorph identification, cannot easily differentiate between true polymorphs and pseudopolymorphs. With this caveat, below we discuss several methods of identifying polymorphs in approximate order of their speed of application [176].

8.1. Microscopy

Generally polymorphs differ in morphology and this is an important preliminary analysis criterion for monitoring crystallizations. The shape of polymorph crystals can be observed by optical or scanning electron microscopy very rapidly and in combination with other analytical methods can provide differentiation among forms. However, it is usually difficult to determine if differences in morphology alone are caused by polymorphism or are simply a result of changes in growth conditions or solvent. Techniques including crystalline and polymer heteronucleation (Sections 7.2.4 and 7.2.5) that utilize one crystallization condition (solvent, temperature, etc.) provide a means of generating polymorphs without altering morphology making microscopy a fairly reliable primary screen in high throughput studies.

8.2. Vibrational spectroscopy

Most prominent among the vibrational spectroscopic methods for polymorph identification are infrared and Raman spectroscopy. Both techniques offer information on structure and molecular conformation in the solid state by probing vibrations of atoms. These methods are especially important for characterization of polymorphs because hydrogen-bonding patterns often differ among forms and the functional groups affected will display shifts of varying degrees, Fig. 16. Other information gained from vibrational spectroscopies, which can be helpful in distinction of polymorphs, includes low energy lattice vibrations caused by differences in crystal packing. This information is more readily obtained by Raman than by infrared spectroscopy because the former can measure lower frequency vibrational bands ($100\text{--}600\text{ cm}^{-1}$) routinely, Fig. 17. Infrared spectroscopy observes

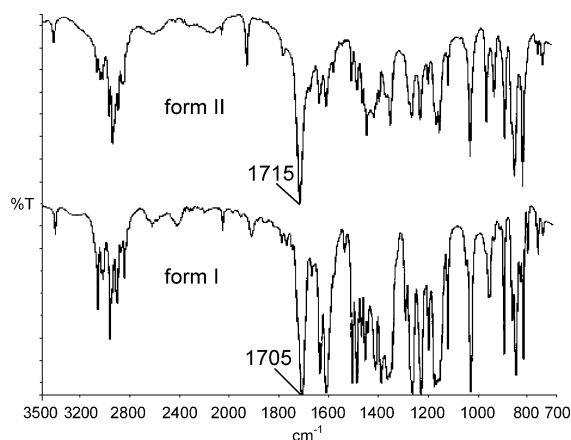


Fig. 16. FT-IR spectra of the two polymorphs of nabumetone. The carbonyl shift between the two forms is prominent indicating large differences in intermolecular interactions.

vibrational modes associated with the absorption of a compound in the infrared region of the spectrum, whereas, the Raman effect is based on the observation of scattered photons that occur as a result of the passage of light through a sample. Different selection rules apply in determining which vibrational modes are observed in each technique, although in the typical case of low symmetry molecules bands are observed at the same positions with both techniques and merely vary in intensity.

Infrared absorption spectroscopy has enjoyed the most use in polymorph investigations primarily because it is a robust technique available in most laboratories. Several limitations of the technique are worth considering especially for studies involving small quantities of sample or single crystals. These studies are most conveniently conducted by IR microscopy and this is the method of choice for studies on single crystals. However, an IR transparent substrate must be employed and it is difficult to collect spectra of all but the thinnest crystals due to transmittance issues. Substrate and sample transmittance issues can be circumvented by using attenuated total reflection (ATR) or diffuse-reflectance infrared (DRIFT) spectroscopy [177].

Raman spectroscopy provides similar chemical information to IR absorption spectroscopy [178,179]. However, when applied to investigations of polymorphism the Raman method has a number of important advantages. The technique is well suited for in situ

studies of polymorphism because it can perform measurements both behind glass and in water; conditions that cannot be accommodated by IR absorption measurements [180,181]. A Raman spectrometer interfaced to a microscope has an additional advantage of being able to pinpoint small crystalline samples, which do not have to be removed from crystallization vials for analysis, thus eliminating sample preparation. In addition, the spatial resolution of Raman microscopy ($\sim 1 \mu\text{m}$) is limited by the wavelength of the visible light probe rather than infrared radiation, making this technique suitable for examining minute sample quantities in complex matrices. Traditionally Raman spectrometers were exotic tools because they required expensive parts and exhibited low sensitivity. However, recent advances in detector technology and improved lasers are bringing this technique into the mainstream. Modern Raman spectroscopy is rapid and applicable to direct analysis in multi-well plates facilitating high throughput studies.

8.3. Powder X-ray diffraction

One of the most reliable techniques for polymorph differentiation is PXRD [182], which yields a fingerprint of a phase having numerous peaks whose positions correspond to periodic spacings of atoms in the solid state, Fig. 18. This experiment is one of the most important in the characterization of polymorphs because different lattice constants will, in

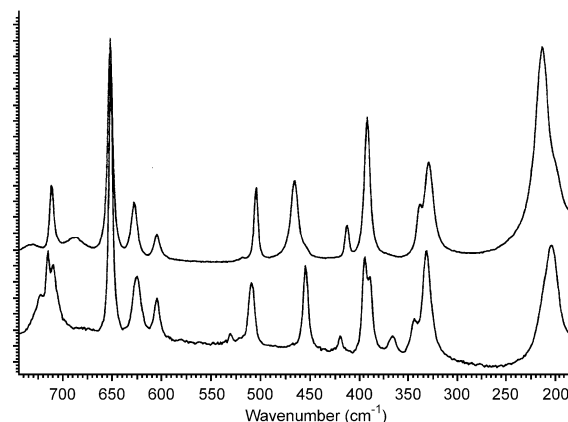


Fig. 17. Raman spectra overlay of selected region of monoclinic (top) and orthorhombic (bottom) polymorphs of acetaminophen. The low frequency region is easily accessed with this technique.

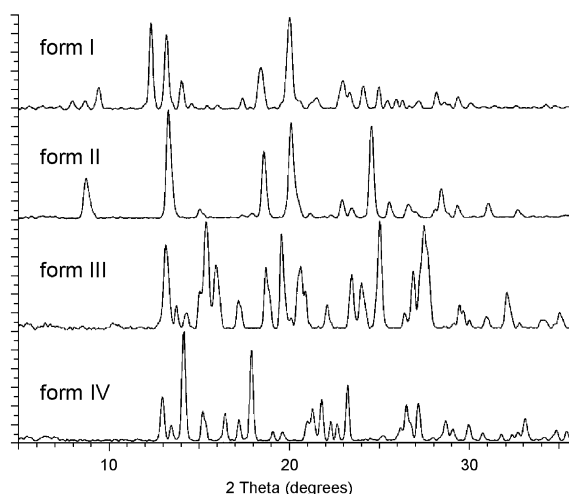


Fig. 18. PXRD comparison of the four polymorphs of carbamazepine. Dramatic differences in peak position are observed when comparing diffraction patterns making this an excellent technique for distinction among forms in a tetramorphic system.

general, give rise to different peak positions. Furthermore, the generally good separation between peaks in the diffractogram allows for quantitative analysis of mixtures of polymorphs using PXRD [2]. Unlike single crystal X-ray diffraction or vibrational spectroscopy, there is no chemical information apparent in the data. However, with additional effort lattice constants can often be extracted from the data. The cell volume can be compared to other crystalline forms and this information can be used to infer the presence of solvent molecules in the lattice or changes in density between polymorphs. In exceptional cases, high quality PXRD data can be employed to derive complete crystal structures and this technique of structure determination from powder diffraction (SDPD) is currently one of the exciting frontiers in structural chemistry [183,184]. Often synchrotron data is required to obtain satisfactory results with SDPD and the intensities of the peaks are critical [185].

New advances in PXRD technology have made it possible to obtain data at a rapid rate on small quantities (< 1 mg) of sample. Several diffractometer manufacturers have developed systems based on two-dimensional detectors with automated mapping stages geared for high throughput screening [186,187]. Furthermore, recent innovations have led to the design of

a novel batch crystallizer, which can be used in conjunction with dispersive X-ray diffraction to study solution crystallization in situ [188].

8.4. Thermal techniques

8.4.1. Differential scanning calorimetry and thermogravimetric analysis

The technique of differential scanning calorimetry (DSC) measures the amount of energy absorbed or released by a sample as it is heated, cooled or held at a constant temperature, Fig. 19 [189–193]. This energy is related to the difference in heat flow between a standard sample and the unknown. Integration of the area under the heat flow curve yields the enthalpy

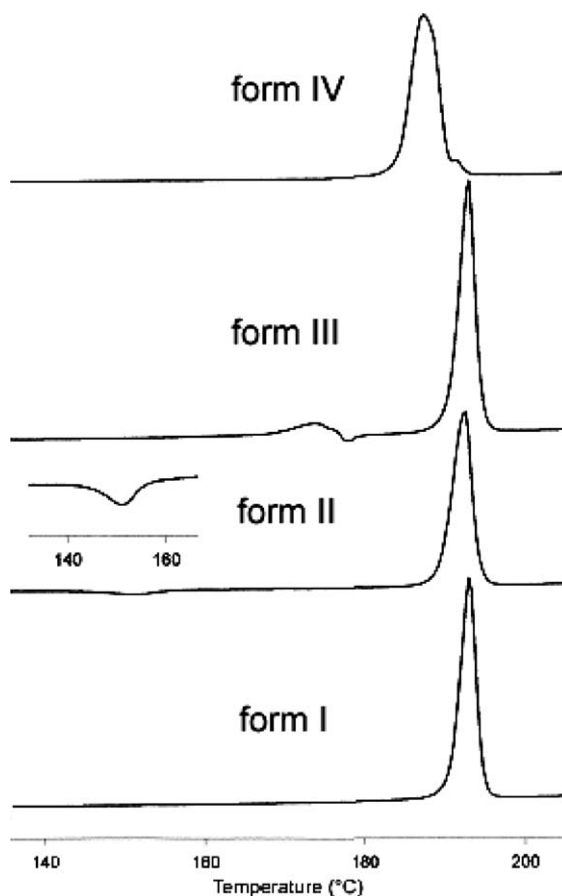


Fig. 19. DSC overlay of the four polymorphs of carbamazepine. These are readily distinguished by this method. These curves indicate that forms II, III, and IV transform to form I upon heating.

change associated with the thermal event of interest. Thermodynamic data that can be obtained by this method includes melting point, heat capacity, and heat of fusion as well as polymorphic transitions of a given compound if they occur below the melting point. DSC is essential in elucidating the stability relationships between polymorphs as outlined by the Burger–Ramberger rules (Section 2.2). However, DSC can be misleading in cases where sample decomposition occurs during heating. The decomposition product can recrystallize or alter the melting point of the pure compound. TGA can effectively detect decomposition that occurs with release of volatile products and this technique should generally be carried out to test for this possibility.

8.4.2. Hot stage microscopy

Hot stage microscopy is one of the oldest and most straightforward methods for studying phase transitions in crystals [109,194]. Varying the temperature of a substance while viewing it under a microscope, often through crossed polarizers, provides a wealth of information about melting/recrystallization behavior as well as solid-state transformations. Polymorphic transitions are often accompanied by a change in a crystal's birefringence so even subtle reorganizations in structure can cause large changes in optical properties. This technique also allows the detection of solvates by observing the evolution of a gas or liquid from a crystal. Novel polymorphs can be generated in this experiment either by high temperature transition of one form to another or by crystallization from the melt. Coupling hot stage microscopy with vibrational spectroscopy or DSC can further expand the utility of this method.

8.5. Nuclear magnetic resonance spectroscopy

Solid-state nuclear magnetic resonance (SS-NMR) spectroscopy [195,196] can be used to investigate polymorphism by probing the environments of atoms in the solid state; non-equivalent nuclei will resonate at different frequencies and these changes in chemical shift can often be connected with changes in conformation or chemical environment of the compound. SS-NMR is also useful because it is able to determine the number of crystallographically inequivalent sites in a unit cell. Unlike PXRD, SS-NMR spectroscopy is

well-suited to studying amorphous forms of pharmaceuticals and solvates that are usually trivial to detect. Collecting spectra at various temperatures is a powerful tool in understanding polymorphic transformations and molecular motion in the solid [2].

9. Summary and future directions

Recent advances in our understanding of supramolecular chemistry concepts coupled with the development of analytical methods to probe molecular assemblies in fluid and condensed phases have motivated molecular level design of pharmaceutical solids and better control of events that lead to crystallization. It is recognized that the interplay between molecular recognition, thermodynamics, and kinetics can be carefully controlled by the selection of appropriate conditions, molecular components, and functional groups to regulate crystallization outcomes and to optimize stability. Examples of molecular level control of crystallization from liquid and amorphous phases as well as crystal engineering design strategies to alter molecular network arrays, crystal structure, and composition of pharmaceutical solids have been presented. These developments are changing the language with which we describe pharmaceutical solids beyond general structural features to molecular recognition and molecular assemblies. They are also leading us to a deeper understanding of molecular organization, the design of molecular networks with fine-tunable properties, and the beginnings of supramolecular pharmaceuticals.

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