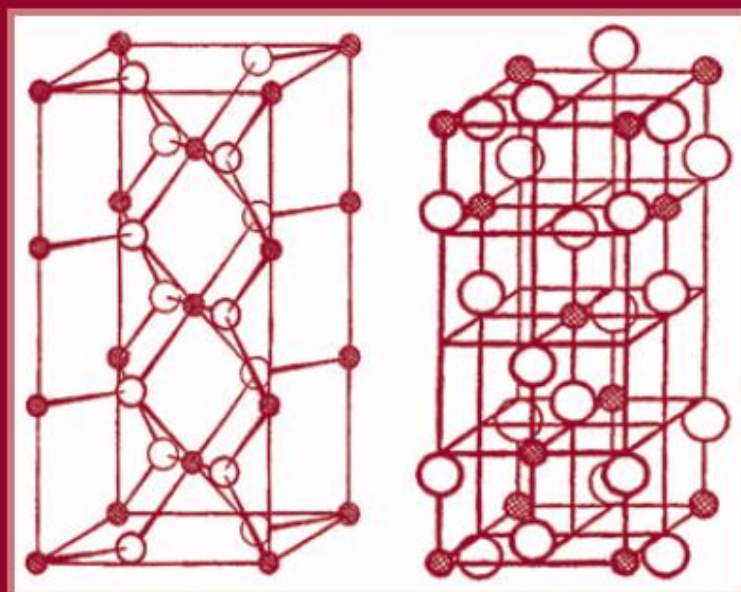


DRUGS AND THE PHARMACEUTICAL SCIENCES

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SECOND EDITION

Polymorphism in Pharmaceutical Solids



edited by
Harry G. Brittain

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

When kept in a closed system and allowed to equilibrate, the air above a mass of crystals will attain the RH value that stems from equation (3). These micro-environmental RH values are important to keep in mind when considering the shelf life of dosage forms and their packaging, because the water content of any free volume of air will equilibrate with the drug product. What makes matters worse is the exponential temperature dependence of the RH. As a general rule of thumb, the partial vapor pressure of water drops by a factor of two for every 11.1°C. Therefore, in a closed system, the RH rises by a factor of two for the same drop in temperature.

Although for polymorphs, phase interconversions are mostly temperature controlled, solvatomorphs are also highly sensitive to the activity of the solvents involved, as well as to the phase identity of the solvent. Even though thermodynamics might favor a solid–solid phase transition, it frequently happens that the reaction is kinetically unfavorable, and hence, some metastable polymorphs can be maintained for years without any evidence for formation of the stable polymorph. However, when these metastable forms are exposed to even the smallest amounts of solvent, the interconversion process can take place very rapidly.

Nývlt discussed the kinetics of this mechanism, and called it a solid–liquid–solid phase transformation (12). Boerrigter et al. encountered this process in their investigations on their research of epitaxial polymorphic growth of a model steroid compound and showed that a tiny amount of acetone present in the system catalyzed recrystallization of the metastable phase. To emphasize that the molecules involved must pass through a temporary state of dissolution rather than a melt they redubbed the term to be more specifically a solid–solute–solid phase transition (13). In short, the mechanism is explained as a molecular level layer of solution that traverses through the crystal. Keeping this in mind, when a certain crystalline form undergoes a phase transition after a solvent is introduced that does not necessarily mean that a solvatomorph was formed. It is equally possible that a metastable form recrystallized into a more stable solvent-free form.

Hydrates represent a special case of solvatomorphs because water raises no issues regarding toxicity and is usually of no concern in the approval of drug products. On the other hand, water is the only solvent that is present in ambient conditions, and its uptake and possible equilibria between hydrate forms represents a concern for processing, packaging, and storage. For practical purposes it is therefore important to determine the relative stabilities of solvatomorphs. Relative stability studies for solvatomorphic systems are no different than those for anhydrous polymorphic systems, except that the activity of the solvent must be taken into account.

By far the most instructive information about the relative stability of polymorphs and solvatomorphs can be gathered from a G – T diagram (free energy vs. temperature). Figure 4 shows such a diagram taken from a recently published paper in which Griesser and coworkers diligently analyzed the behavior of three polymorphs of (*R*)-cinacalcet hydrochloride using a plethora of analytical techniques (14). G – T cannot, of course, be measured directly, and it must be determined from data gathered from various experiments, typically a combination of differential scanning calorimetry (DSC) and hot-stage microscopy that identify the thermal energy exchange during phase transitions. Because the solid forms cannot be forced to interconvert between all phases at any given temperature actual data can only be measured on a limited number of events. The thick arrows represent actual data of temperature and enthalpy exchange, whereas the curves were later deduced from

sublimation, vaporization, desolvation, solid–solid phase transitions, and chemical degradation) as well as exothermic processes (i.e., crystallization and oxidative decomposition). Thermal methods are routinely used for the characterization of polymorphs, and in light of the experimental simplicity, often constitute the first line of techniques used to understand the polymorphic space of a system.

Differential Scanning Calorimetry (DSC)

In DSC, which is the most widely used technique for thermal characterization of pharmaceuticals, the analyte is subjected to a controlled temperature program and the temperature and the heat flow associated with a thermally induced transition is measured.

DSC has been developed along two lines: power-compensation DSC and heat-flux DSC. In power-compensation DSC, separate heating elements are in contact with the sample and reference cells, with the rate of heating by these elements being controlled and measured. Thus the sample and reference are maintained at the same temperature and the heat flow required to accomplish this is measured. The other methodology is that of heat-flux DSC, where the sample and reference cells are heated by the same element, and one monitors the direction and magnitude of the heat being transferred between the two.

A detailed theory of DSC is outside the scope of this chapter and has been discussed elsewhere (1,2). Briefly, the basic principle behind a change in the baseline of a typical DSC plot (power vs. temperature), signifying a thermal event, is a change in the heat capacity of the system under investigation. The basic equation (4) describing the relationship between the heat flux (Q) associated with a thermal event and the heat capacity (C_p) of the system under investigation is given by:

$$(dQ/dt) = C_p(dT/dt) \quad (1)$$

where dQ/dt represents power at the constant heating or cooling rate, dT/dt . DSC plots are obtained as the differential rate of heating [in units of watts (joules/second) or calories/second] against temperature, and thus represent direct measures of the heat capacity of the sample. The area under a DSC peak is directly proportional to the heat absorbed or evolved by the thermal event, and integration of these peak areas yields the heat of reaction (in units of calories/seconds · gram or joules/seconds · gram).

The effectiveness of DSC to detect various polymorphic forms is illustrated in Figure 1 (7). Profiles 1, 2, and 3 (from top) show the reversible transitions between the enantiotropically related forms I and III. The fourth DSC curve shows the melting of form II followed by crystallization and melting of form I. The bottom DSC profile is a heating curve of a mixture of forms II and III, which shows the respective melting endotherms but no transition to form I. This was tentatively attributed to the absence of form I seeds in the mixture of forms II and III, which were concomitantly crystallized as opposed to the pure forms (profiles 1–4), which were crystallized separately using different methods.

Standard Reference Materials (SRMs) are available from the National Institute of Standards and Technology for calibration of temperature and enthalpy of fusion for differential scanning calorimeters. Indium (SRM 2232; melting temperature = 156.6°C; enthalpy of fusion = 28.5 J/g), tin (SRM 2220; melting point = 232.0°C; enthalpy of fusion = 60.2 J/g), and gallium (SRM 2234; melting temperature = 29.8°C;

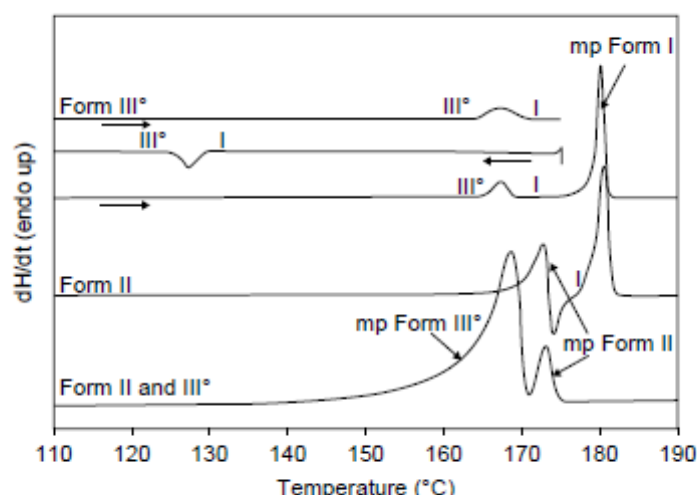


FIGURE 1 DSC profiles of cinacalcet hydrochloride polymorphs. The first (heating), second (cooling), and third (heating) profiles (*from top*) show the solid–solid transition (i.e., III° $\rightarrow$ I); the fourth profile shows melting of form II followed by crystallization and melting of form I; the fifth profile is a heating curve of a mixture of form II and form III° showing respective melting endotherms but no transition to form I signifying absence of form I seeds. Note: The direction of endotherm is *up*. Source: From Ref. (7).

enthalpy of fusion = 80.1 J/g) are suitable as calibration standards over the range of temperatures of interest in pharmaceutical analyses. Because DSC is also used at sub-ambient temperatures for the characterization of frozen solutions, mercury (SRM 2225; melting temperature = -38.9°C ; enthalpy of fusion = 11.5 J/g) is a suitable calibration standard. Heat capacity calibration in a DSC is usually carried out with synthetic sapphire (SRM 720), copper (SRM RM5), polystyrene (SRM 705a), or molybdenum (SRM 781D2).

Depending on the protocol used for temperature programming, a DSC experiment could be classified as being conventional, modulated, or accelerated (also known as Hyper-DSC®). In the conventional mode, the heating rate is constant and typically ranges from $0.1^{\circ}\text{C}/\text{min}$ to $20^{\circ}\text{C}/\text{min}$. The majority of DSC experiments are carried out in the conventional mode and may require optimization of the sample pan configuration (discussed later) and the experimental parameters to obtain the desired information (3). In Table 1, the effects of operational parameters are outlined.

In modulated DSC (MDSC), a changing (modulated) heating rate is superimposed on a constant average heating rate. The modulation is described by a frequency, determined by specific amplitude ($\pm^{\circ}\text{C}$) and period (seconds), such as $\pm 0.5^{\circ}\text{C}$ every 60 seconds, with the choice of the amplitude and period being dictated by the nature of the transition (8–10). The advantage of MDSC over conventional DSC is that it can separate the reversible heat flow from the non-reversible heat flow (Fig. 2). Reversible heat flow corresponds to events that respond to the changing heating rate (e.g., heat capacity change, melting). On the other hand, non-reversible heat flow events (e.g., crystallization or decomposition) are not affected by changing heating rates.

TABLE 1 Influence of Operational Parameters on the Outcome of DSC Experimental Results

	Effects
Sample size	
Large	Advantages (i) Non-homogeneous samples (ii) Detects "weak" transitions Disadvantages (i) Broad peaks (ii) Temperature of the event may be inaccurate (iii) Poor resolution (iv) Requires slow heating rate
Small	Advantages (i) Sharp peaks (ii) Increased resolution (iii) Permits faster heating rate Disadvantages (i) Decreased sensitivity
Heating rate	
Fast	Advantages (i) Increased sensitivity Disadvantages (i) Decreased resolution (ii) Decreased temperature accuracy
Slow	Advantages (i) Increased resolution Disadvantages (i) Decreased sensitivity

Source: Adapted from Ref. (2).

MDSC has found limited utility in the characterization of polymorphs (11,12). However, the inherent capability of this technique to separate overlapping melting and crystallization events has been demonstrated for the polymorphs of tristearin (13,14). MDSC is especially suited for the characterization of amorphous materials (15,16), and has enabled the quantification of amorphous content in a partially crystalline material (17). Because crystallinity differences could affect material performance, it is important that analysts are aware of low levels of lattice disorder in highly crystalline materials that were brought about by processing and storage conditions. Saklatvala et al. investigated two batches of an investigational crystalline drug, which showed pronounced differences in their stability and water sorption profiles, and MDSC enabled detection and quantification of the amorphous content in the batch characterized by the lower chemical stability and the increased propensity to take up water (18).

Hyper-DSC® uses accelerated heating rates (up to 500°C/min) in order to selectively investigate phase transitions. The high heating rates result in selective inhibition of transitions that would normally take place over the longer timescales