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Review

Factors affecting crystallization of hydrates

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Abstract

Objectives To provide a comprehensive understanding of the competing thermodynamic and kinetic factors governing the crystallization of various hydrate systems. The ultimate goal is to utilize this understanding to improve the control over the unit operations involving hydrate formation, as well as to optimize the bioavailability of a given drug product.

Key findings The thermodynamic and kinetic factors that govern hydrate crystallization are introduced and the current status of the endeavour to gain a mechanistic understanding of the phenomena that occur during the crystallization of different hydrate systems is discussed. The importance of hydrate investigation in the pharmaceutical field is exemplified by examining two specific hydrate systems: the polymorphic hydrate system and hydrates of pharmaceutical salts.

Summary This review identifies the factors that are of critical importance in the investigation of anhydrate/hydrate systems. This knowledge can be used to control the phase transformation during pharmaceutical processing and storage, as well as in building a desired functionality for the final formulation.

Keywords crystallization; hydrate; kinetics; salt; thermodynamics

Introduction

Hydrate is the most commonly identified solvate within small organic drug molecules. It has been estimated that at least every third drug compound can form a hydrate.[1] Hydrate formation or dehydration of a given hydrate may affect the performance of the final medicinal product. The bioavailability of a poorly water soluble compound is affected due to the difference in solubility and dissolution rate between the anhydrate and hydrate forms. In the manufacturing environment, processability can also be affected not only by solubility differences, but also by particulate level properties (i.e. different habits). Hydrate can also be part of the overall intellectual property protection strategy for a given compound. Therefore, it is very important to identify any possible hydrate form(s) in the early phases of the drug development process.

Water is frequently present in the manufacturing environment of pharmaceuticals, for example atmospheric water cannot be avoided and aqueous processing solutions are needed. Later processing phases may involve the use of heat, resulting in possible dehydration of any given hydrate. Though these phenomena are not thoroughly understood, it may result in an unstable product due to variation in hydrate content or uncontrolled hydrate formation and dehydration processes. The overall picture is further complicated when the conditions in the gastrointestinal tract are taken into consideration. The bioavailability of the final drug product can be affected by the in-situ processes involving hydrate formation in the biological environment.

These facts underpin the need for a thorough understanding of both the structural (crystallographic) aspects of hydrates and the mechanisms of hydrate formation. Development of functional medicinal products and, later, manufacturing of safe pharmaceuticals, requires control over these phenomena. This review will introduce the thermodynamic and kinetic factors affecting the crystallization of hydrates. Specific focus will be placed on two groups of hydrates, namely polymorphic forms of a given hydrate and hydrates of salt-forming compounds.

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Hydrate as a solid form

The nature of water incorporation in pharmaceutical hydrates

Given the diversity of pharmaceutical compounds, water can be incorporated into the crystal lattice in several ways. A practical approach to classify hydrates has been presented.[2,3] This classification system is based on common analytical techniques and divides the hydrates into three main classes.

The first class is called isolated site hydrates, and the characteristic for this structure is that the water molecules are not in contact with one another. Instead, they form hydrogen bonds and have van der Waals interactions with the drug molecule. These structures show sharp dehydration endotherms (indicated by sharp endothermic peaks in differential scanning calorimetry), narrow weight loss ranges (observed with thermogravimetric analysis) and sharp OH bands in infrared spectroscopy.

The second category is channel hydrates, which have crystal water molecules as chains along a given crystal axis. The water molecules form hydrogen bonds with the adjacent water molecules. These structures have sharp OH bands in infrared spectra at a relatively low frequency, but rather wide thermogravimetric analysis weight loss ranges and broad endothermic peaks in differential scanning calorimetry. The dehydration temperature is usually lower compared with isolated site hydrates. Also, upon dehydration, the water molecules can be removed without affecting the original hydrate structure. The void spaces left in the dehydrated desolvate can be filled again by another solvent while still retaining the initial crystalline structure. Cephalexin serves as one example. For the cephalexin acetonitrile solvate, the acetonitrile molecules can be substituted by water molecules without altering its crystalline structure substantially. The incorporated water molecules in the hydrate can again be displaced by acetonitrile while its structure is still maintained.[4,5] The channel hydrates can be further divided into two subclasses. Planar hydrates are defined as structures where the water of crystallization forms a two-dimensional plane. Some channel hydrates can expand their overall cell dimensions to take up additional water in non-stoichiometric amounts and are called expanded channels.[2] Others can retain their unit cell dimensions even after uptake of several molar equivalents of water.[6,7] For instance, topotecan HCl trihydrate can take up to two additional moles of water while retaining the same basic crystalline structure.[8]

The third class is called ion-associated hydrates, and they contain ion-coordinated water. High dehydration temperatures are typical for this class because of the strong bond strength of this type. An example of a drug from each class is given in Figure 1.

Pharmaceutical properties affected by hydrate formation

The incorporation of water into the crystal lattice leads to a change in intermolecular interactions within the hydrate crystal. As a result, a hydrate is more thermodynamically stable than anhydrate when the water activity is above the critical water activity for hydrate formation.[12] The fact that hydrate has a lower free Gibbs energy than anhydrate causes

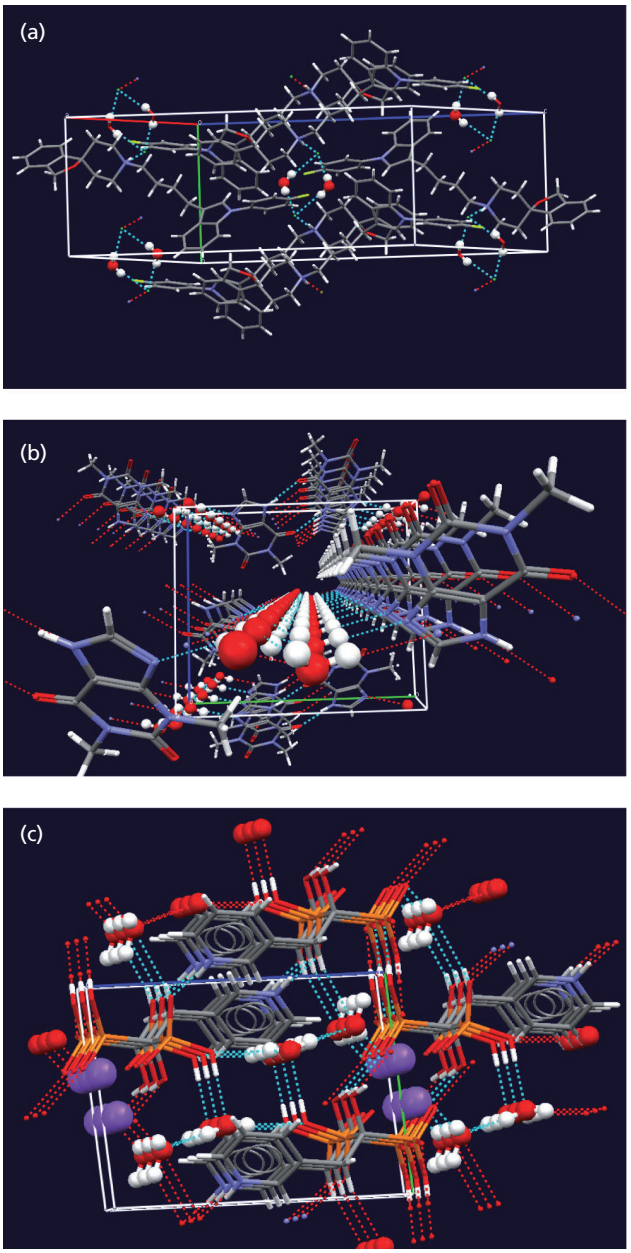

Figure 1 Hydrate examples for each classification. (a) Isolated site hydrate: siramesine hydrochloride.[9] (b) Channel hydrate: theophylline monohydrate (reference code THEOPH01).[10] (c) Ion-associated hydrate: risedronate sodium dihydrate (reference code WURPOO).[11]

it to have a lower solubility. Since solubility is a determinant of dissolution rate calculated according to the Noyes-Whitney equation, hydrates also have lower dissolution rates. The theoretical background for this is detailed in the following section, and examples illustrating the pharmaceutical implications of solubility and dissolution rate changes are demonstrated later. Therefore, a common understanding is that hydrates have poorer solubility and a poorer dissolution rate compared with anhydrates. In reality, dissolution is not a simple process when particulate properties such as particle size distribution/shape distribution, specific surface area and other surface properties

are also considered. Therefore, in spite of their lower solubilities, hydrates may have a better dissolution performance than their corresponding anhydrates. For instance, cefdinir monohydrate (product R93H batch 52734) had a faster and higher dissolution rate than its anhydrate (product R93 batch 54693) in both water and simulated gastric fluid media. The enhanced dissolution of hydrate was attributed to its smaller crystal size and also higher specific surface area.[13] Superior dissolution properties of hydrate compared with anhydrate have also been observed for some drugs, for example tranilast[14] and erythromycine.[15] The reasons for this were suggested to be the higher surface energy or lower hydrophobicity of the hydrate compared with the anhydrate. It should be noted that solubility can also be greatly affected by the dissolution media. Rifampicin monohydrate had lower solubility in water, but higher solubility in simulated gastric fluid than its corresponding anhydrate form.[16] Recent development in the field of dissolution testing has enabled simultaneous measurement of dissolution medium and solid state form during dissolution testing.[17–20] The improved dissolution approach has been implemented in a recent publication where carbamazepine anhydrate demonstrated a clearly higher initial dissolution rate in simulated intestinal fluid FaSSIF than in buffer. By a thorough analysis of the solid state data obtained during dissolution, it was found that a hydrogen bonding was formed between the drug and sodium taurocholate, a compound in FaSSIF. This inhibited the carbamazepine hydrate formation and thus provided its better dissolution behaviour.[21]

The influence of excipients on drug hydrate formation has not only been observed during dissolution, but also under other pharmaceutical relevant conditions for instance processing and storage. When a drug is processed or stored together with excipients under humidity, certain excipients can have the effect of preventing hydrate formation. The exact mechanism of action is however still unclear. Airaksinen *et al*.[22] suggested that the amorphous character of the excipient was important for its inhibition ability during wet granulation. Excipients having higher water absorptivity have greater inhibition ability. Specific drug–excipient molecular interactions, especially hydrogen bonding interactions, have also been attributed to be a major basis for the inhibition effect of excipients in several studies.[23–25] Qu *et al*.[26] have attempted to explain the effect of excipients from a crystallization perspective where they found that hydroxypropyl methylcellulose (HPMC) can selectively increase the solubility of carbamazepine dihydrate in an ethanol–water mixture, and thus reduces the driving force of the anhydrate–hydrate phase transformation.

Hydrate formation can also induce changes in mechanical properties including flow properties and compatibility. For example, carbamazepine anhydrate can show prism-like morphology, but it becomes needle shaped when forming hydrate. These needle-shaped crystals are known to have poor processability, including poor flowability, cohesiveness and compressibility.[27] Hydrate formation, however, can also have a positive impact. Hydrate crystals can facilitate tablet compaction,[28] produce tablets with higher tensile strength of compaction.[29,30] Sun and Grant[30] have suggested one explanation for the increased tensile strength by hydrate formation. A three-dimensional network could be formed between water and host (*p*-hydroxybenzoic acid) molecules in the hydrate crystal, and thus facilitate higher plastic deformation properties of the crystal and enhance bonding strength.[30]

Chemical stability is another essential aspect that needs to be considered, but few reported examples exist. Dihydroxyphenylalanine hydrate can be oxidized in air to phenylalanine, which has a lower chemical stability than anhydrate.[31] However, it has also been found that the crystalline water can play a role in protecting and stabilizing the chemical stability of a compound. Vitamin B12 (cyanocobalamine) hydrate (form A) is chemically more stable to light and heat than its anhydrate.[32]

Hydrate: fundamentals of crystallization

Thermodynamics of anhydrate/hydrate systems

Hydrate is the most widely encountered solvate. As described earlier, at least every third drug compound can form a hydrate.[1] However, each solid compound responds uniquely to the possible formation of hydrate, and hence generalizations of hydrate formation prediction are still not possible.[33] Infantes *et al*.[34] suggested that the presence of some polar chemical functional groups, for example COOH, can cause a significantly higher frequency of hydrated structures. Hydrates differ from polymorphs since the chemical composition is not the same for anhydrate and hydrate. The thermodynamic difference between anhydrate and hydrate, however, is similar to polymorphic systems, and can also be reflected by the Gibbs free energy analysis. The Gibbs free energy difference, ΔG, between the anhydrate and hydrate state is proportional to the ratio of the thermodynamic activities, a, and is approximately proportional to the ratio of the solubilities, x, in any given solvent:

$$\Delta G = RT \ln\left(\frac{a_2}{a_1}\right) = RT \ln\left(\frac{x_2}{x_1}\right) \quad (1)$$

where 1 and 2 denote the different phases (polymorphs or anhydrate/hydrate) of the crystals. For a polymorphic system, the value of the solubility ratio, and thus the Gibbs free energy difference, is defined by temperature and pressure. Therefore, the relative thermodynamic stability of the polymorphs is independent of the solvent.[35] For an anhydrate/hydrate system, the value of the solubility ratio and Gibbs free energy strongly depend on the water activity in the solvent, and the system is defined by temperature, pressure and water activity in the solvent. As a consequence, the relative stability of an anhydrate/hydrate system has to be specified with respect to both temperature and the water activity in the surrounding medium.

Grant and Higuchi[36] have established the following relationship to describe the equilibrium between a hydrate and an anhydrate:

$$\mathrm{A(solid)} + m\mathrm{H_2O} \leftrightarrow \mathrm{A \cdot mH_2O(solid)}$$

$$K_h = \frac{a[A \cdot mH_2O(solid)]}{a[A(solid)]a[H_2O]^m} \quad (2)$$

where K_h is the equilibrium constant for the process, $a[A{\cdot}mH_2O(solid)]$, $a[A(solid)]$ and $a[H_2O]$ are the thermodynamic activities of the hydrate, the anhydrate and water, respectively, and m is the number of water moles taken up by one mole of the anhydrate. When $a[H_2O] > \{a[A{\cdot}mH_2O(solid)]/[a[A(solid)]K_h]\}^{1/m}$, the hydrate is the more stable form. The anhydrous form will be more stable in the inverse situation. If the pure solids of anhydrate and hydrate are taken as the standard states (i.e. with unity activity), then Equation 2 can be simplified as: $K_h = a[H_2O]^{-m}$. Thus, the anhydrate/hydrate state of a crystalline solid depends on the water activity in the surrounding medium. The equilibrium water activity for anhydrate/hydrate at room temperature has been reported for theophylline,[37] ampicillin[38] and carbamazepine.[39,40]

Since the equilibrium constant K_h is a function of temperature, the relative stability between anhydrate/hydrate is also strongly affected by temperature. Thus an anhydrate/hydrate system is defined by both the temperature and the water activity in the surrounding medium. This leads to a significant difference in the behaviour of anhydrate/hydrate and polymorphic systems. At ambient pressure, the transition temperature between two enantiotropically related polymorphs is an inherent thermodynamic property of the system, which is independent of the surrounding medium, such as solvent. In contrast, the transition temperature between anhydrate/hydrate depends on the solvent compositions. In the example shown in Figure 2, the transition temperature between anhydrous carbamazepine form III and dihydrate is 64.5°C in water,[41] and this transition temperature decreased to 14.3°C in the water–ethanol mixture containing 31 mol% of water.[39,40] Another example is given for the anhydrous and dihydrate inosine, the transition temperature of the two forms changes from 10°C to 7°C and then to 3°C when the solvent shifts from pure water to water–acetone mixtures containing 80 wt% and 35 wt% water, respectively.[42] A similar observation has also been made for the anhydrous and monohydrate forms of nitrofurantoin in acetone–water solutions[43] and L-serine in methanol–water solutions.[44]

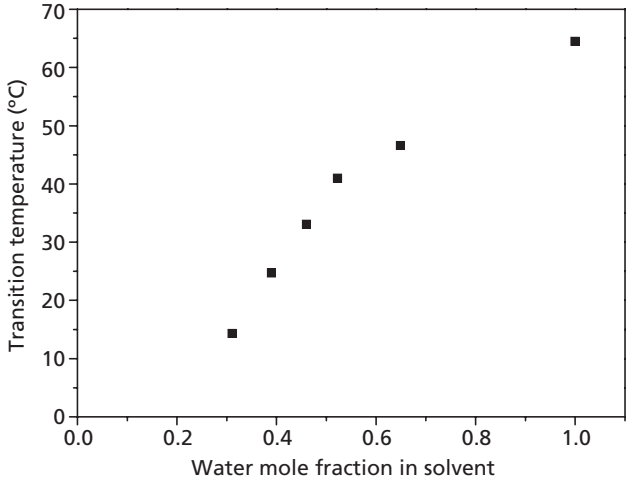

Figure 2 Transition temperature of anhydrous and dihydrate carbamazepine as a function of water fraction in water–ethanol mixtures.[39–41]

Crystallization of hydrates from aqueous solutions

Controlling the anhydrate/hydrate state of crystals in cooling crystallization

Crystallization of an anhydrate/hydrate system from aqueous solution is common in industry for various reasons. For the compounds that have significant temperature-dependent solubility, the final crystal product yield of a cooling crystallization can be increased by using a mixture of water and an organic solvent. One example is demonstrated in Figure 3 for the solubility of carbamazepine in absolute ethanol and an ethanol–water mixture. It is obvious that the yield of a cooling crystallization from 50°C to 35°C can be significantly increased by using an ethanol–water mixture containing 54 mol% of ethanol instead of absolute ethanol as the solvent. As reported in the literature,[39] the transition point of anhydrous and dihydrate carbamazepine in the ethanol–water mixture containing 54 mol% ethanol is 33°C, which means that replacing the solvent will not lead to undesired solid form change from the anhydrate to the dihydrate in the final product. Therefore, the economic efficiency of a crystallization process can be significantly improved by simply changing the solvent from absolute ethanol to an ethanol–water mixture.

At a given solvent composition, the thermodynamic behaviour of an anhydrate/hydrate system is similar to that of two enantiotropically related polymorphs, as shown in Figure 4. The crystallization of such a system is a complex process due to the fact that various fundamental mechanisms are involved in the process, such as the nucleation and crystal growth of the different solid forms, and the phase transformation between them. Although the solid–liquid equilibrium is defined by thermodynamics, kinetic factors play an important role in crystallization, and thus the prediction and control of the form of the crystals initially crystallized out from the solution is a complicated task. As shown in Figure 4, crystallization is completely thermodynamically controlled only in the shaded area. In this zone, only the stable form can be crystallized out. For the crystallization taking place outside the thermodynamically controlled area, the occurrence of nucleation for a particular solid form is the consequence of competition between

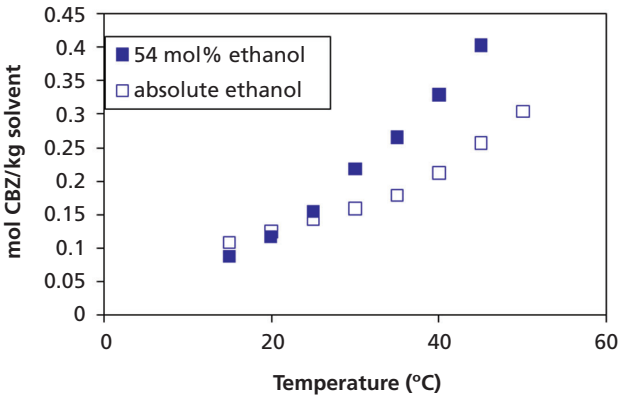

Figure 3 Solubility of carbamazepine in absolute ethanol and in a water–ethanol mixture containing 54 mol% ethanol. CBZ, carbamazepine.

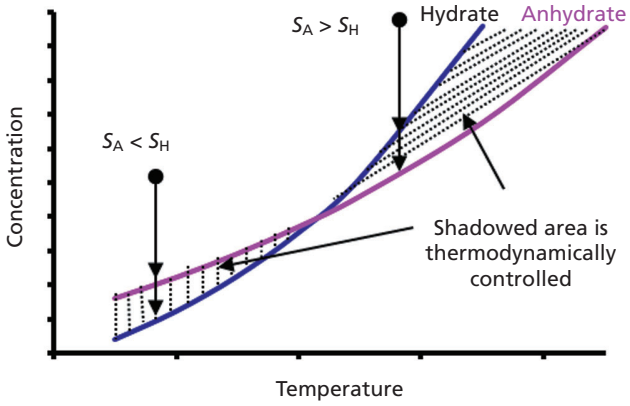

Figure 4 Solid–liquid equilibrium of an anhydrate/hydrate system at a certain solvent composition. S is the supersaturation ratio: $S = c/c^*$, where c is concentration and c^* is solubility.

kinetic and thermodynamic factors. On the one hand, the supersaturation level for the stable form is higher than that for the metastable form, on the other hand, the nucleation kinetics of the metastable form might be fast enough to overcome this supersaturation difference. The well-known Ostwald's rule of stages[45] predicts that the least stable form is produced first by spontaneous crystallization, since 'in the course of transformation of an unstable state into a stable one the system does not go directly to the most stable conformation but prefers to reach intermediate stages having the closest free energy to the initial state.' It has been observed that the occurrence of polymorphs during crystallization from solution quite often follows the Ostwald's rule of stages, where the least stable form first crystallizes out and then transforms to the more stable form. However, the crystallization of anhydrate/hydrate systems frequently show a behaviour contrary to the Ostwald's rule of stages where the most stable form crystallizes out directly, as shown in the cooling crystallization of inosine.[42] The two anhydrous polymorphs, α and β, are monotropically related, where β is the stable form, and the dihydrate inosine is enantiotropically related with the β form with a transition temperature of 10°C in pure water. The results of the cooling crystallization experiments performed at various temperature and supersaturation levels confirmed that, below the transition temperature, direct nucleation of the stable dihydrate always resulted, without any evidence of the appearance of any metastable forms. In contrast, nucleation of the dihydrate was not observed in the crystallizations performed above the transition temperature, and the appearance of polymorphs α and β was dependent on the structure of the molecular stacks in the solution, which is determined by the solvent–solute interaction. The inosine molecules are self-associated as dimers in aqueous solutions, and the aggregation of these α-like dimers formed the nuclei having the α structure. Interestingly, the nuclear magnetic resonance spectra revealed no apparent change in the nature of the solution dimers when the temperature decreased from 25°C to 7°C. The authors attributed the dominating nucleation of the dihydrate to the formation of the nuclei comprising dihydrate dimers stabilized by bound water molecules at temperatures below the transition temperature.[42] In one of our previous studies, we also observed that the stable form was always crystallized out in the cooling crystallization of carbamazepine from a water–ethanol mixture.[46] The anhydrous form III crystallized out at temperatures above the transition temperature, and the dihydrate form crystallized out when the crystallization was performed below the transition temperature. We have also observed the crystallization of the thermodynamically stable monohydrate of nitrofurantoin from water–acetone mixtures at temperatures below the transition point.[43] The direct nucleation of the thermodynamically stable hydrates below their transition point in aqueous solutions has been reported for other systems, such as the monohydrate citric acid[47] and hemipenta hydrate risedronate monosodium.[48] It has to be mentioned here that for the more complicated hydrate polymorphs, for which the hydrate itself can exist as more than one polymorph, the most stable hydrate polymorph does not necessarily have to be the first one to crystallize out.

Controlling the hydrate state of the crystals in antisolvent crystallizations

Another typical occasion for the crystallization of the anhydrate/hydrate system from aqueous solutions is the antisolvent crystallization, which is commonly used for compounds having high but weakly temperature dependent solubility in a given solvent (water or an organic solvent). The solubility of the target compound might be dramatically decreased by the addition of another solvent that is miscible with the original solvent. Water is used either as the original solvent[49] or as the antisolvent.[50–52] Most of the work reported in the literature has focused on the effects of the operation parameters, such as the temperature, addition mode and rate of the antisolvent, on the hydrate state of the crystals. It has to be emphasized here that the relative stability between the different hydrate states may also change during the crystallization process, since the water concentration in the solution changes during the whole crystallization process. For an antisolvent crystallization conducted by adding water to an organic solvent solution, the anhydrous form can be the stable one in the early stages of the batch, while the hydrate can become the stable form later on in the crystallization process. Therefore, in order to gain a deeper understanding of the crystallization behaviour of anhydrate/hydrate systems in antisolvent crystallization, the relative stability of the anhydrate/hydrate in the whole solvent composition range encountered in the antisolvent crystallization has to be fully investigated. The relative stability of the first nucleated crystals, that is whether nucleation occurs in the stable form or the metastable form in the environment (temperature and water activity), needs to be clearly elucidated.

Controlling antisolvent crystallization is much more complicated than with cooling crystallization due to the different way in which the supersaturation is generated. In cooling crystallization, the supersaturation is generated by cooling the solution by circulating a coolant through the jacket of the crystallizer, and thus the supersaturation is generated on the whole inner wall of the crystallizer. The supersaturation is usually even inside the whole crystallizer for laboratory scale crystallizations. However, the supersaturation for antisolvent crystallization is generated by pumping an antisolvent into the

crystallizer. When the antisolvent droplets fall into the solution, it may create a local zone near the feeding point where the concentration of the antisolvent is higher than that in the other zone of the crystallizer.[53] As a result, both the supersaturation level and the water concentration in the local zone near the feeding point are higher than the mean values in the whole crystallizer. This difference between the local concentration and the mean concentration depends on the feeding manner and feeding rate of the antisolvent and the mixing condition in the crystallizer. If water is used as the antisolvent, the water concentration in the feeding zone is higher than the mean water concentration in the crystallizer, and this concentration difference increases with increasing feeding rate of water. The situation will be reversed when an organic solvent is used as the antisolvent to induce the crystallization in an aqueous solution. The relative stability of the anhydrate/hydrate in the feeding zone might be different from that in the crystallizer generally, and this has to be taken into account when the crystallization behaviour of the anhydrate/hydrate system is investigated.

Solvent-mediated anhydrate/hydrate phase transformation

As shown above, the relative stability of the anhydrate/hydrate depends on both temperature and the water activity (water fraction) in the surrounding solvent. A solvent-mediated phase transformation will occur if the anhydrate or hydrate is brought to a circumstance where it is the metastable form (see Figure 2). In principle, there are many similarities between the fundamental mechanism of a solvent-mediated anhydrate/hydrate transformation and that of a polymorphic transformation. Both processes consist of the dissolution of the metastable form and the crystallization of the stable form. Depending on the relative kinetics of the dissolution of the metastable form and the crystallization of the stable form, the transformation can be dissolution controlled or crystallization controlled.[54,55] Usually the solvent-mediated phase transformation process starts from slurry consisting of the metastable solid phase and the solution, which is saturated with respect to the metastable form but supersaturated with respect to the stable form. As soon as the nuclei of the stable form are formed in the slurry, the growth of these nuclei will consume the supersaturation, and the solution becomes undersaturated with respect to the metastable form. The dissolution of the metastable form is thus driven by the undersaturation, which produces the supersaturation for the crystallization of the stable form. Obviously, the solvent-mediated phase transformation is driven by the solubility difference between the anhydrate and the hydrate, and thus the phase transformation rate increases with increased solubility difference, which can be caused by the change of temperature or water fraction in the solvent. On the other hand, an extremely slow phase transformation may occur at the circumstance near the transition points shown in Figure 2.

The presence of additives may have a distinct influence on the phase transformation of anhydrate/hydrate due to either the thermodynamic or kinetic effect. It has been reported that some surfactants can promote the phase transformation from anhydrate to hydrate in water.[56–59] Rodríguez-Hornedo and Murphy[58] observed that the surfactants changed the rate-controlling step from crystallization of dihydrate carbamazepine (CBZH) to the dissolution of anhydrous carbamazepine (CBZA) due to its facilitating effect on the surface-mediated nucleation of CBZH. This effect probably resulted from the adsorption of the surfactant at the CBZA crystal–solution interface and solubilization of CBZ in these adsorbed assemblies. This solubilization can lead to high interfacial concentration of CBZ on the surface of the dissolving CBZA crystals and offers a high driving force for the crystallization of CBZH on the CBZA surface. In addition to surfactants, cellulose and polymers have also been widely reported to affect the dissolution and phase transformation of pharmaceutical compounds. Hydroxypropyl methylcellulose was reported to be an inhibitor for the phase transition from anhydrate to hydrate[60] and a promoter for the dissolution of anhydrous carbamazepine.[61] The strong inhibiting effect of HPMC on the solvent-mediated phase transformation of CBZA to CBZH in ethanol–water mixtures was observed by Qu *et al*.[26] The mechanism of the inhibiting effect mainly resides in the thermodynamic factors. The presence of HPMC selectively increased the solubility of CBZH and consequently reduced the solubility difference between CBZA and CBZH. This resulted in a decreased supersaturation during the phase transformation. It was found that the effect of HPMC on the nucleation and growth kinetics of CBZH crystals was not pronounced.

The solvent-mediated anhydrate/hydrate or polymorphic phase transformation in a suspension turnover experiment can be simulated by modelling approaches, including population balance equations and kinetic equations. The kinetics of the fundamental processes during the transformation, such as the dissolution of the metastable form, the secondary nucleation and growth of the stable form, have to be taken into account when modelling. Modelling cannot be separated from practical experiments. The parameters used in the kinetic equations often need to be estimated from the in-line experimentally obtained values, such as solid phase composition, solution concentration and particle size distribution.[62–65] Solvent-mediated anhydrate/hydrate or polymorphic phase transformation may happen during the dissolution test, which usually exerts a significant influence on the obtained dissolution rate profile. In such cases, the hydrodynamic conditions in the dissolution testing apparatus are of essential importance and therefore have to be taken into account in the modelling of the dissolution process and the solid phase transformation process.[20]

Examples of two specific hydrate systems

Polymorphism within a specific hydrate

Polymorphic hydrate can be defined as two or more hydrates having the same chemical composition and same molar ratio of water in the crystalline lattice, differing only in their crystal packing arrangements. The work published on crystallization of polymorphic hydrates[66–69] is limited compared with that published on anhydrate polymorphs.

As stated earlier, properties such as mechanical properties and physical and chemical stability are often different between a hydrate and its corresponding anhydrate, which

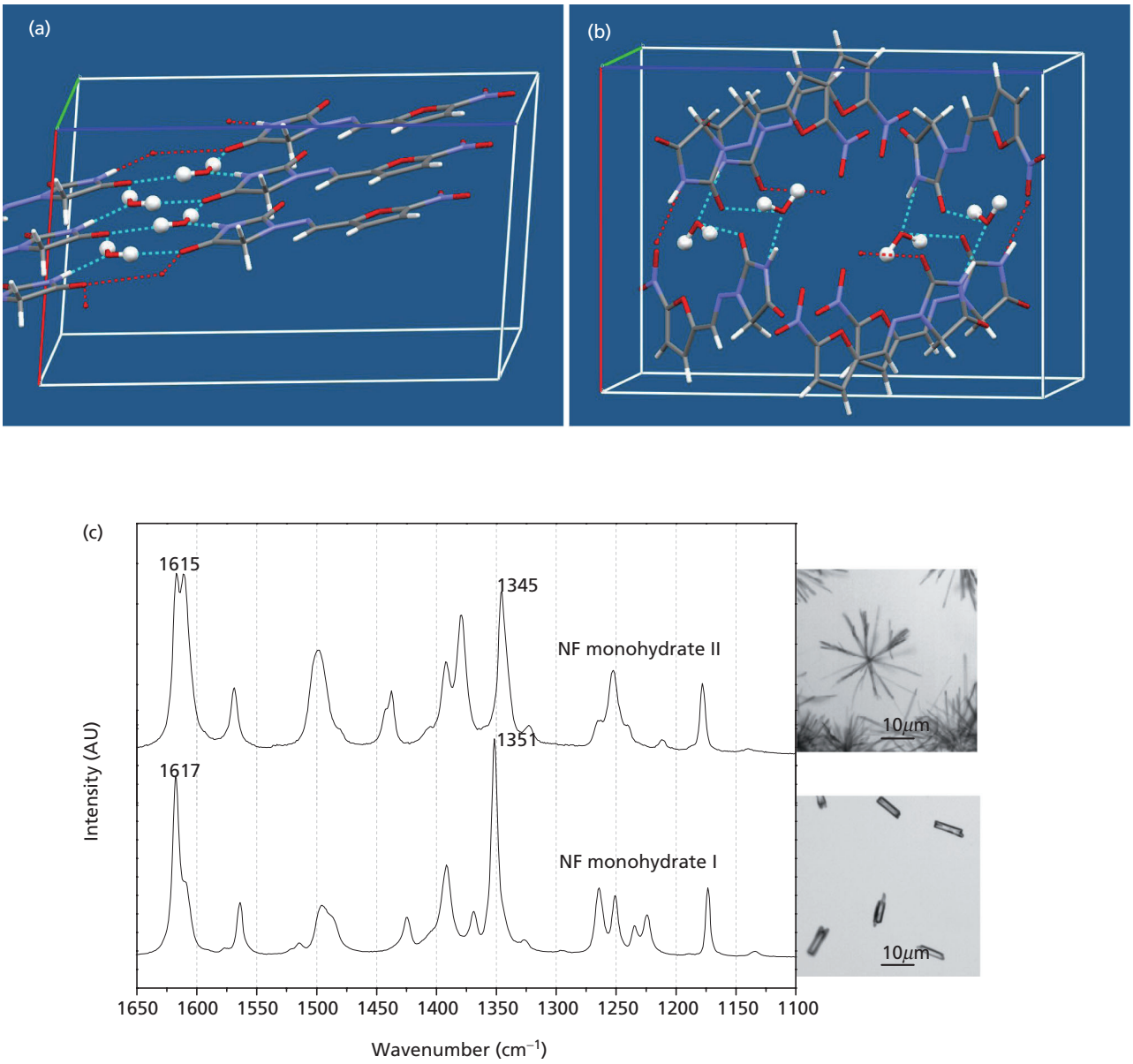

Figure 5 Typical crystal morphology and H bonds of nitrofurantoin monohydrates and corresponding Raman spectra. NF, nitrofurantoin. (a) NF monohydrate I. (b) NF monohydrate II. (c) Raman spectra of monohydrates I and II.

makes screening and stabilization of the selected form crucial. The same applies to the hydrate polymorphs. Different polymorphs of hydrate are also found to exhibit different properties. In the case of olanzapine, three polymorphs of the dihydrate, dihydrate D, B and E exist. Dihydrate D is the most thermodynamically stable form and has the most efficient crystal packing and hence the highest density. The thermal stability of both metastable dihydrates B and E are relatively lower compared with dihydrate D.[70] Another example is niclosamide, having two polymorphs of the monohydrate, stable hydrate H_b and unstable H_a. The aqueous solubility of the stable monohydrate is one-third less than that of the metastable monohydrate.[71] This relatively large difference in their solubility, and thus their Gibbs free energy, indicates a strong tendency for metastable niclosamide HY_a to convert to HY_b in aqueous condition. Therefore HY_a may achieve higher solubility when used in an aqueous formulation, but there is a risk of it converting to the stable hydrate HY_b.

There follows a specific example based on crystallization of two polymorphs of nitrofurantoin monohydrate. These two monohydrates (monohydrate I and II) have the same stoichiometry, but differ in their crystal packing arrangements. Figure 5a and b show the crystal structure of monohydrate I and II, respectively. The typical crystal morphology of these two monohydrates, along with the corresponding Raman spectra, is shown in Figure 5c. The existence of these two polymorphic nitrofurantoin hydrates was discovered in 1993, and though a large number of publications have reported on hydrate II,[69,72–78] little is known about monohydrate I.[43,79]

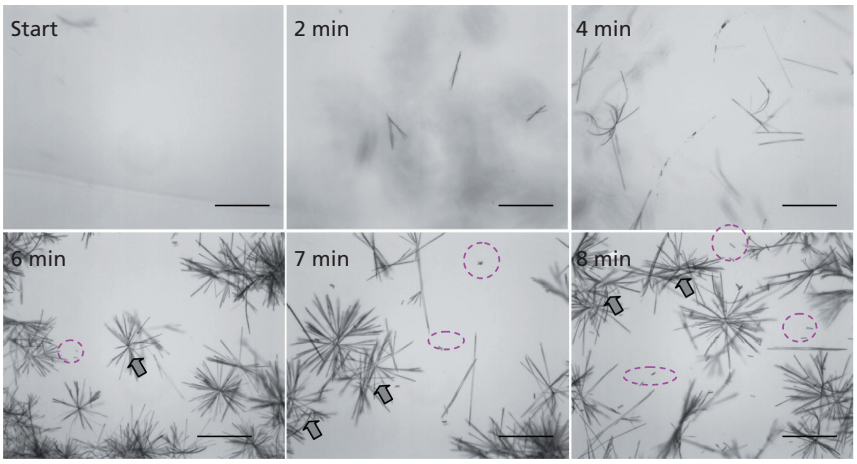

Figure 6 Crystallization of nitrofurantoin observed under light microscopy. Nitrofurantoin was crystallized from an acetone–water mixture containing 0.67 mole fraction of water. Horizontal scale bars: 50 μm. The time point at which each picture was taken is indicated. Examples of hydrate I crystals are encircled; and examples of hydrate II clusters are indicated by an arrow. Phase identification of hydrate forms was based on Raman microscopy results.

Although the nitrofurantoin monohydrate I can be prepared separately, it has mainly been observed to be crystallized concomitantly with monohydrate II via evaporative crystallization. As shown in Figure 6, monohydrate II (needle shaped) appeared immediately following solvent evaporation, while the plate morphology crystals (monohydrate I) started forming at around 6 min. At 8 min, both needle clusters and plates were crystallized. Hydrate I had much slower nucleation and growth rates than hydrate II during evaporative crystallization.

Cooling crystallization with and without the seeds of monohydrate I was also performed. It was again observed that the nucleation and growth of needle monohydrate II was very fast once the solution had cooled to the metastable zone limit. No monohydrate I was crystallized in any of these experiments and even seeding with monohydrate I failed to initiate its nucleation. Seeding has been proved to be an effective way of controlling the polymorphism of the crystal product, since the presence of a particular polymorphic crystal's surface in a supersaturated solution can usually facilitate the nucleation of this seeded crystal form. However, the crystallizations seeded with monohydrate I yielded monohydrate II crystals, among which the hydrate I seeds can be identified with a Raman microscope. The failure of the seeding method in the polymorphic control of the nitrofurantoin hydrates was attributed to the fact that the barrier of the secondary nucleation of monohydrate I was much higher than the barrier of the primary nucleation of monohydrate II. Seeding the supersaturated solution at 36°C or 37°C with monohydrate I did not induce the secondary nucleation of monohydrate I, since the supersaturation level was much lower than the metastable zone limit of the secondary nucleation of monohydrate I. As a result, the supersaturation increased with cooling and eventually reached the metastable zone limit of the monohydrate II, where the spontaneous nucleation of monohydrate II occurred.[43,80]

The solubility tests of these two monohydrates at room temperature (around 23°C) revealed that the difference in aqueous solubility, and thus free energy between these two hydrates, is rather small (110 $\pm$ 4 μg/ml and 131 $\pm$ 12 μg/ml for hydrates II and I, respectively,[79]). Therefore, when the nucleation and growth of monohydrate II was dominant, crystallization of pure monohydrate I was difficult to achieve. This explained the failure to produce monohydrate I through both cooling crystallization and cooling crystallization seeded with monohydrate I crystals. The crystallization of the nitrofurantoin monohydrate I represents a challenging issue in polymorphism control. Further systematic research is needed in this area to allow full exploration of the crystallization of polymorphic hydrate systems.

Hydrates of pharmaceutical salts

Pharmaceutical salts and pharmaceutical hydrates have been studied extensively as individual research topics as they are both of paramount importance in the development and manufacturing of pharmaceuticals. However, the combined phases (hydrates of pharmaceutical salts) have received much less attention, even though such solid phases are commonly encountered. In a study by the Cambridge Structural Database,[81] it was found that 29.9% of 6608 investigated pharmaceutical salts were able to exist as hydrates, which would justify this class of pharmaceutical solids receiving further attention.

Salt formation is widely utilized in the pharmaceutical industry because it offers a means of altering the physicochemical characteristics of an ionizable drug without modifying its chemical structure.[82] In particular, the higher solubility and hence increased dissolution rate of salts encourages companies to perform salt screens for weakly acidic or weakly basic compounds.[82–84] A salt system is composed of a drug and a counterion held together by ionic bonding.[85] Thus, a salt, like a hydrate, represents a two-component system. If hydrate formation of a pharmaceutical salt takes place, a three-component system arises, which provides the resulting solid phase with new properties.

Structure and bonding in hydrates of pharmaceutical salts

The organization of drug molecules and counterions in salt hydrates differ between salt hydrates of acidic and basic drugs.[31] The most common salts of acidic drugs are those that contain metallic cations (as opposed to organic bases).[83,84] Thus, hydrates of salts of pharmaceutical acids belong to a great extent to the metal ion-coordinated hydrates according to the hydrate classification proposed by Morris.[3] The coordination tendency of the metal ion is satisfied by linkages to suitable ligands found in the crystal structure, such as carboxylate, alcohol, carbonyl, amide, sulfonate and water.[31] As discussed below, this kind of organization does not apply to salt hydrates of basic drugs.

The predominant metal ion used in pharmaceutical salts is the sodium ion.[81,83] In 1974, sodium salts comprised 61.97% of all cationic salts, whereas other popular metal ions such as potassium and calcium comprised 10.82% and 10.49%, respectively.[83] The metal ion-coordinated hydrates of *p*-aminosalicylic acid[86] (PAS) exemplifies the structural relationship between the drug molecule, the metal ion and water in metal ion coordinated hydrates. The sodium salt of PAS is a dihydrate, in which each sodium ion is coordinated to two water molecules. In the calcium salt, which is a trihydrate, two calcium ions share six water molecules and four PAS molecules, the sixfold coordination of the calcium being maintained by PAS molecules bridging the calcium ions. The magnesium salt had the simplest structure of the hydrates, with one magnesium ion coordinated to two PAS molecules and four water oxygens to make up its six coordinations. Within this series, it was found that the tendency to form hydrates increased with increasing ionic potential of the counterions.[86] The propensity of divalent ions to form higher hydrates has also been observed for nedocromil; the magnesium salt can exist as penta, hepta and decahydrates,[87] and the zinc salt as penta, hepta, and octahydrates.[88] For the PAS series, it was also found that the water molecules in the divalent salts were more tightly bound, resulting in greater stability towards dehydration, which may affect the stability of the salt hydrate during processing and storage.[86]

The most commonly used counterion for salts of basic compounds is the chloride ion, which in a recent study of the Cambridge Structural Database was found to account for 2874 hits out a total of 6021 salts.[81] The chloride ion is often bonded to amine moieties of the drug molecule, and the water molecules of hydrochloride hydrates tend to be extensively involved with any hydrogen bond donors and acceptors in the structure.[31] A specific example is siramesine hydrochloride.[9] In the anhydrate structure of this salt, the chloride ion is ionically bonded to the ammonium nitrogen. In the monohydrate, water is incorporated into the crystal packing through hydrogen bonds to the chloride ion. Each chloride ion accepts hydrogen bonds from two different water molecules, and thus water does not interact directly with the drug molecules. In a study of the hydrochloride salts of morphine and naloxone, it was found that in the crystal packings of the anhydrates, the chloride ions were connected to the drug molecules, whereas in the hydrate packings, the chloride ions were hydrogen bonded to water and not connected to the drug molecules. Besides the bonding to the chloride ion, the water molecules in the hydrates were also connected to the drug molecules. These observations lead to the conclusion that chloride ions always take part in the hydrogen bonding networks of hydrochloride salts and that they prefer to bridge to water rather than nitrogen. Furthermore, it was suggested that the introduction of water or counterions such as chlorine generate structures with higher dimensional hydrogen bonding networks than the corresponding anhydrate or free base structures.[89]

Influence of salt hydrates on pharmaceutical manufacturing and release

Many of the effects of hydrate formation on the physicochemical properties of pharmaceutical salts are essentially analogous to the effects on non-salts. Examples of where hydrate formation had a positive impact include moricizine hydrochloride hemihydrate[90] and LY334370 hydrochloride dihydrate.[91] The intrinsic dissolution rates of these hydrates were higher than those of their anhydrate salt counterparts. Furthermore, a tetrahydrate of diclofenac sodium was found to exhibit better flowability than the anhydrate salt, mainly due to lower cohesivity of the hydrate particles.[92]

However, hydrates of salts do exhibit distinct features that are not applicable to non-salt hydrates. For a non-salt hydrate system containing drug molecules and water molecules, the conversion between anhydrate and hydrate can be studied in order to gain control over the events taking place during processing and release of the drug substance.[93,94] For a salt hydrate containing ionized drug molecules and charged ions besides water molecules, conversion of the salt form to the free acid or base form can also occur, and the effect on processing and release may be equally substantial.[84,85,95] The solubility of an ionizable compound changes with pH. The pH solubility profile is based on the Henderson-Hasselbalch relationship, which relates the solubility of the completely 'un-ionised' compound (S_0, intrinsic solubility) to both the solubility measured at a given pH (S) and the pK_a of the compound:

$$S = S_0\left[1+10^{(pK_a-pH)}\right] \quad \text{for a monobasic compound} \quad (3)$$

$$S = S_0\left[1+10^{(pH-pK_a)}\right] \quad \text{for a monoacidic compound} \quad (4)$$

The pH solubility profile of a weakly basic drug is shown in Figure 7. The pH_{max} is defined as the point of maximum solubility, and below this pH the solid phase in equilibrium with the solution is the salt. Above the pH_{max}, the solid phase in equilibrium with the solution is the free base. For a weakly acidic drug, the pH solubility profile is the mirror image of the profile shown in Figure 7.[82–85]

The solubility of the free acid or base form is lower than the solubility of their corresponding salt forms, and therefore transformation to the free form may have a dramatic effect on the release properties of salt hydrates. In the following case, examples will be presented where transformation of salt hydrates to the free form have played an important part with respect to drug release. These examples underline the

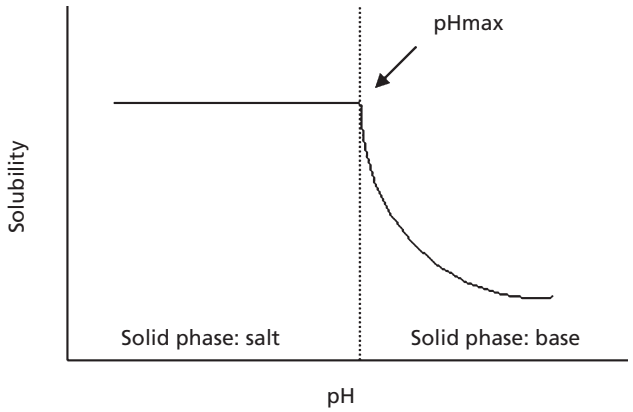

Figure 7 pH solubility profile for weakly basic drugs.

importance of investigating the solid state as well as the solution state properties of hydrates of pharmaceutical salts.

Diclofenac sodium (DS) is a non-steroidal anti-inflammatory drug that is marketed in an anhydrous form. Besides the anhydrous form, the salt has been shown to exist as a trihydrate, two different tetrahydrate forms and a pentahydrate.[96] In an investigation of the release properties of six different prolonged release products of DS, it was found that even identical formulations showed very dissimilar release profiles.[97] Furthermore, samples of industrial scale lots of DS have shown batch-to-batch variations with poor consistency in the IR spectra and thermal behaviour.[92,97] This has led to an investigation of the storage stability of DS, in which it was found that storage at 25°C and 59% relative humidity for 60 days resulted in water uptake and conversion of the anhydrate salt to the tetrahydrate form designated DSH.[92] Thus, DS may convert to DSH during storage at ambient conditions.

Intrinsic dissolution rate studies of DS and DSH in various media showed that the drug precipitated as the free acid at certain pH values, but that the propensity to precipitate was not the same for DS and DSH. At pH 6.8, a layer of insoluble free acid formed on the surface of the DSH tablet, limiting the percentage dissolved to 50% of the drug content. This was not observed with the DS tablet, which converted entirely to DSH1 (another tetrahydrate form) and released 90% of the drug content within 2 h. At pH 4.5, an insoluble layer of free acid was again formed on the surface of the DSH tablet, whereas DS transformed entirely to the free acid. At pH 1.2, both forms transformed entirely to the free acid. The different propensities to transform to free acid were attributed to a higher wettability of DS compared with DSH, which resulted in better release profiles of DS compared with DSH.[92] Thus, in terms of drug release the anhydrate sodium salt of diclofenac is more favourable than the hydrate sodium salt; however, the hydrate salt is the more stable form at ambient conditions (stable for a minimum of 2 years).[92,96]

Siramesine hydrochloride is a poorly water soluble drug that can exist in an anhydrous and a monohydrate form.[9] The solubilities and the powder dissolution rates of the two salt forms have been determined at pH 3.4 (below pH_{max}) and 6.4 (above pH_{max}) to study the influence of solid form on the pH-dependent transformation of salt to its free base (Figure 8). At pH 3.4, no transformation to the base was observed and the dissolution rates of the anhydrate and monohydrate salts were comparable. The solubility of the anhydrate salt at this pH was about twice that of the monohydrate salt, but the monohydrate salt had a higher specific surface area, resulting in similar dissolution profiles. At pH 6.4, precipitation of the free base took place in the dissolution vessels of the anhydrate salt, but not in the vessels of the monohydrate salt. This resulted in a more favourable dissolution profile of the monohydrate salt, which reached a higher percentage dissolved value than the anhydrate salt. The explanation given for the different propensities of the salt forms to transform to the free form is that crystals of the anhydrate salt act as nucleation substrates for the base form, which nucleate and grow from the surface of the anhydrate crystals. Due to the different crystal packing of the monohydrate salt, the surface chemistry of this form is different from that of the anhydrate salt form, and hence the hydrate salt crystals did not facilitate nucleation and growth of the free base to the same extent as the anhydrate salt crystals. This may have implications for the in-vivo release and absorption of this drug since it is poorly water soluble, and dissolution rate may be the rate limiting step controlling bioavailability.[98]

Summary

This review identifies the factors that are of critical importance in the investigation of anhydrate/hydrate systems. This knowledge can be used to control the phase transformation during pharmaceutical processing and storage, as well as in building a desired functionality for the final formulation. Although the thermodynamic difference between an anhydrate and its corresponding hydrate follows Gibbs free energy analysis, where the Gibbs free energy difference between the anhydrate and hydrate state is proportional to the ratio of their thermodynamic activities and is approximately proportional to the ratio of their solubilities in any given solvent, similar to the thermodynamic difference between two polymorphs in the anhydrate polymorphic systems, the relative stability of an anhydrate/hydrate system is much more difficult to predict. The anhydrate/hydrate transformation is influenced by both the temperature and water activity in the surrounding medium. This clearly creates challenges in controlling the anhydrate/hydrate system since the active pharmaceutical ingredient is often exposed to varied pharmaceutical processing and storage conditions, including stress related to temperature, solvent and pressure. Excipients can interact with the active pharmaceutical ingredient, and thus have an influence on its stability. The picture becomes even more complex when the hydrate can exist as two or more different polymorphic forms. Crystallization of polymorphic hydrate systems has demonstrated behaviour against the Ostwarld's rule of stages, where the most stable form crystallizes out directly without the appearance of the metastable form.

Furthermore, hydrates of pharmaceutical salts, as a special hydrate system, can have not only anhydrate–hydrate transformation but also transformation of the salt to its free acid or base form. Since the free form is less soluble than the salt form, the transformation from salt to free form is often undesirable. Also, as exemplified before, the propensity to trans-

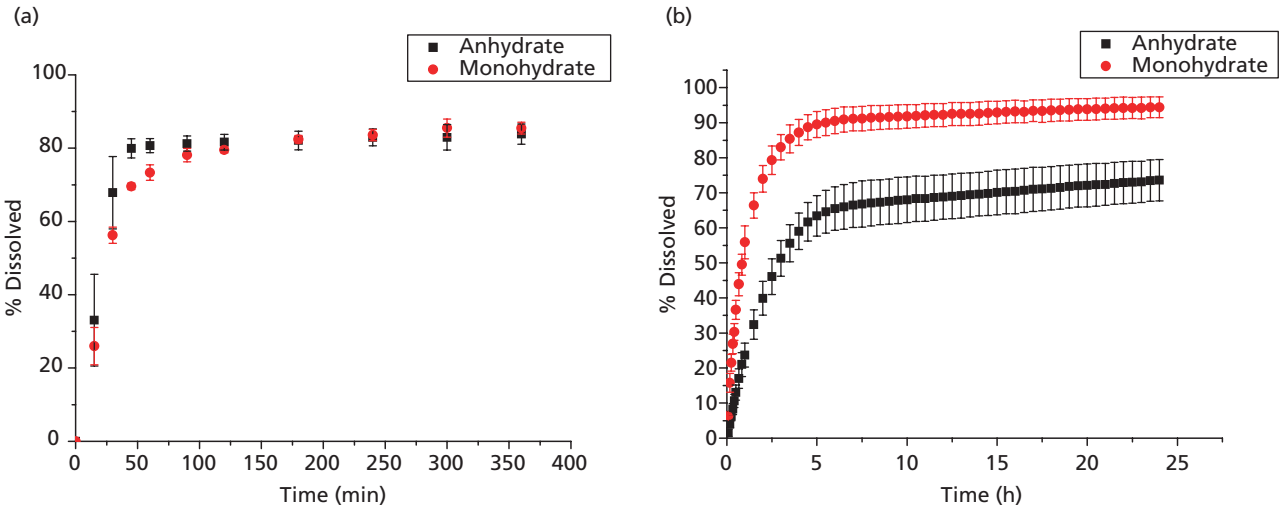

Figure 8 Dissolution rates of siramesine hydrochloride anhydrate and monohydrate. (a) Dissolution of siramesine hydrochloride anhydrate and monohydrate in pH 3.4 ($n = 3$). (b) Dissolution of siramesine hydrochloride anhydrate and monohydrate in pH 6.4 ($n = 3$).[98]

form to the free form may be different for the anhydrate salt and the hydrate salt of a given active pharmaceutical ingredient, depending on the different structural arrangements in the corresponding crystals. Hence, the release properties may vary depending on whether the anhydrate salt or the hydrate salt is applied. However, further investigation is necessary to determine the exact underlying mechanism behind the difference in transformation propensity between the anhydrate and hydrate salt to the free form.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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