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Thermochimica Acta 248 (1995) 61–79

thermochimica acta

Pharmaceutical hydrates

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Received 2 April 1994; accepted 7 April 1994

Abstract

A hydrate is a solid adduct containing both the parent compound (e.g., the anhydrate of a drug or excipient) and water. This review discusses only the crystalline stoichiometric hydrates in which the environment of the water molecules exhibits various defined patterns, and emphasizes pharmaceutical hydrates and their behavior. The presence of the water molecules influences the intermolecular interactions (affecting the internal energy and enthalpy) and the crystalline disorder (entropy), and hence influences the free energy, thermodynamic activity, solubility, dissolution rate, stability, and bioavailability. In addition, many solid-state properties are altered, including mechanical behavior, such as tableting, grinding, and product performance. The physicochemical characterization of hydrates is included in a flow chart of questions to be answered as part of a "decision tree" during the process of product development. Pharmaceutical hydrates may be characterized by a variety of complementary physicochemical methods most of which are well-known. This review details the characterization of hydrates by solid-state nuclear magnetic resonance spectroscopy, Raman spectroscopy, and isothermal microcalorimetry, and considers a variety of pharmaceutical examples.

Keywords: Bioavailability; Dehydration; Drug; Hydrate; Pseudo-polymorphism; Stability

1. Introduction

Pharmaceutical solids may come in contact with water during processing steps, such as crystallization, lyophilization, wet granulation, aqueous film-coating or

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SSDI 0040-6031(94)01952-5

spray-drying. Moreover, 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 and 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. The former is dependent on the specific surface area while the latter is independent of the specific surface area of the solid [1].

With some crystalline solids, solvent in the surrounding medium may become incorporated into the crystal lattice of the compound in stoichiometric proportions. These molecular adducts are termed solvates. Hydrates are formed when water is the solvent of crystallization. In hydrates water occupies definite positions in the crystal lattice, usually by forming hydrogen bond(s) and/or coordinate covalent bond(s) with the anhydrate drug molecules. This article discusses only the crystalline stoichiometric hydrates in pharmaceutical solids.

Incorporation of the solvent molecules into the crystal lattice produces a new unit cell different from that of the anhydrate and, consequently, the physical properties of the solvate may differ from those of the anhydrate. This effect is analogous to polymorphism, a term which indicates the existence of at least two different crystal structures of the same chemical substance, although solvates are strictly molecular adducts. To distinguish solvates from polymorphs, the term pseudopolymorphs has been applied to solvates [2]. Like many other chemical compounds, however, certain solvates may themselves exhibit polymorphism, as in the case of fluprednisolone monohydrate [3], succinyl sulfathiazole monohydrate [4], and nedocromil sodium monohydrate [5]. It is important to emphasize that the two crystal forms must have the same stoichiometry in order to be termed polymorphs.

2. Nature of the water molecule environment in hydrates

The water molecule H_2O behaves as if it consists of a tetrahedral distribution of two positive and two negative regions of charge. On each negatively charged region, the water molecule interacts with its neighbors via a coordinate covalent (dative) bond or by accepting a hydrogen bond. On each positively charged region the water molecule interacts with its neighbors via a donated hydrogen bond. Thus, the neighbors of a water molecule in a hydrate include electron acceptor groups (or proton donors), such as M^{n+}, R–OH, R_1R_2NH, and electron donor groups (or proton acceptors), such as $R-COO^-$, $R-O^-$, Cl^-. The neighbors of a water molecule may include other water molecules suitably oriented for hydrogen bond formation. The water molecule may also participate in the various types of van der Waals' interaction (dipole–dipole, dipole-induced dipole and dispersion forces).

Some of the numerous possible environments of a water molecule in a hydrate are presented in Fig. 1. Wells [6] has proposed a classification of water molecules in hydrates based on the number of nearest H_2O neighbors. Fig. 1 shows that a water molecule in a hydrate may have (a) four, (b) three, (c) two, (d) one or (e) zero water molecules as nearest neighbors. When several types of water molecule occur in the same crystal structure, finite or infinite hydrogen-bonded water

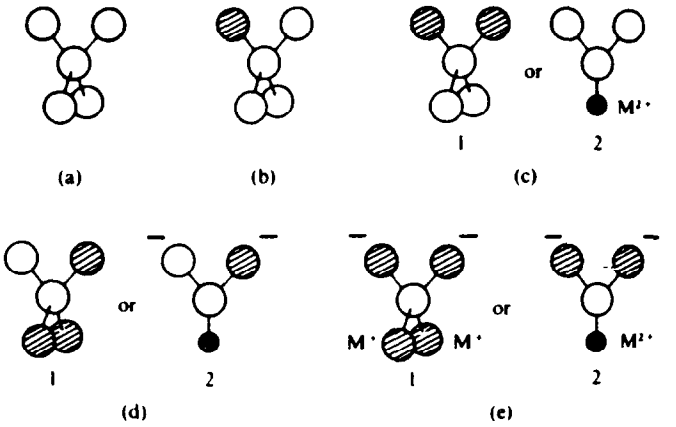

Fig. 1. Environment of water molecules in hydrates. The non-shaded larger circles represent water molecules, the smaller shaded circles represent multivalent metal ions, and the larger shaded circles represent univalent metal ions or any electron accepting (or proton donating) groups or electron donating (or proton accepting) groups other than water. (Reproduced from Ref. [6] with the permission of the copyright owner, Clarendon Press, Oxford, UK.)

networks may be formed [7]. Thus, water molecules in Fig. 1(a) and (b) will yield all possible types up to and including three-dimensional water networks; Fig. 1(c) occurs in rings or chains of water molecules ($n$mers, $3 \leq n \leq$ infinity); Fig. 1(d) occurs in pairs (dimers) of water molecules, while Fig. 1(e) represents a single (monomer) water molecule (associated with metal ions in the case of salt hydrates).

3. Reasons for the differences in the physical properties of hydrates

Incorporation of the water molecule(s) in the crystal lattice of the anhydrate or a lower hydrate changes the dimensions, shape, symmetry and capacity (number of molecules, z) of the unit cell. As a result, the anhydrate and each hydrate of a given chemical compound exhibit different physical properties as described below [8].

A change in the volume of the unit cell upon hydration corresponds to a change in the molar volume and hence to a change in the density of the substance. Incorporation of water molecules into the crystal lattice of the anhydrate or of the lower hydrate alters the following behavior of the crystals: (a) the interaction of the electron vibrations with light quanta changing the refractive index; (b) the interactions of the molecular motions with heat quanta changing the thermal conductivity; (c) the movement of the electrons in an electric field changing the electrical conductivity. Formation of additional bonds between the host molecules and the water molecules and changes in the bonding between the host molecules themselves alter the cooperativity of the molecules in the crystal lattice and hence alter the melting point.

Fig. 2 summarizes the effect of hydration of a drug on its physical properties [5]. Incorporation of the water molecule(s) into the crystal lattice of the anhydrate or of a lower hydrate changes the intermolecular interactions within the solid and

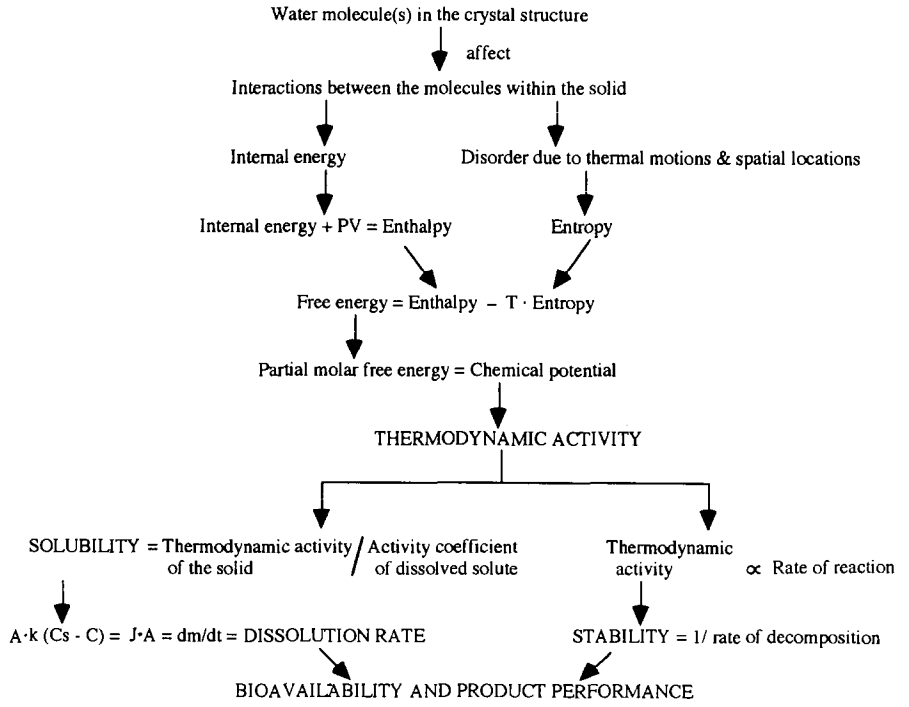

Fig. 2. Effect of hydration on the physical and pharmaceutical properties of a drug. A is the area of the solid exposed to the dissolution medium, k is the mass transfer coefficient, C_s is the solubility of the solid, C is the concentration dissolved, J is the intrinsic dissolution rate and dm/dt is the dissolution rate of the solute.

hence modifies the internal energy and therefore the enthalpy of the solid. As a result of hydration of the solid, changes in the shape and symmetry of the unit cell alter the entropy of the solid. These changes in the enthalpy and entropy result in changes in the free energy and chemical potential of the solid. Finally, the modification of the chemical potential changes the fugacity and therefore the thermodynamic activity of the solid.

4. Pharmaceutical implications of the differences in the physical properties of hydrates

4.1. Applications of pharmaceutical hydrates

The change in the thermodynamic activity of the solid due to hydration alters its pharmaceutically important properties, such as the solubility and the physical and chemical stability (Fig. 2). The change in the solubility of a drug usually changes its dissolution rate. The alterations in the dissolution rate and the stability of a drug

may, ultimately, modify its bioavailability and product performance. Some of these pharmaceutical consequences which result from the differences in the physical properties of hydrates are discussed in the following section.

4.2. Solubility

The solubility of an anhydrate form of a crystalline nondissociating organic compound A in water [4,9] is proportional to the equilibrium constant K_s in the equilibrium

$$\mathrm{A(solid)} \overset{K_s}{\rightleftharpoons} \mathrm{A(aqueous)} \tag{1}$$

The solubility depends on temperature, pressure and the nature of the solid form (hydrate or anhydrate) and is approximately proportional to the thermodynamic activity of the latter. The equilibrium solubility of a hydrate of A, i.e. of $\mathrm{A} \cdot m\mathrm{H_2O}$, in water is similarly proportional to the equilibrium constant K'_s in the equilibrium

$$\mathrm{A} \cdot m\mathrm{H_2O(solid)} \overset{K'_s}{\rightleftharpoons} \mathrm{A(aqueous)} + m\mathrm{H_2O} \tag{2}$$

The formation of hydrated crystals from anhydrous crystals is represented by the equilibrium

$$\mathrm{A(solid)} + m\mathrm{H_2O} \overset{K_h}{\rightleftharpoons} \mathrm{A} \cdot m\mathrm{H_2O(solid)} \tag{3}$$

$$K_h = \frac{a[\mathrm{A} \cdot m\mathrm{H_2O(solid)}]}{a[\mathrm{A(solid)}]a[\mathrm{H_2O}]^m} \tag{4}$$

where K_h is the equilibrium constant for the process shown in Eq. (3), and $a[\mathrm{A} \cdot m\mathrm{H_2O(solid)}]$, $a[\mathrm{A(solid)}]$, $a[\mathrm{H_2O}]$ are the thermodynamic activities of the hydrate, the anhydrate and water, respectively. The hydrate $\mathrm{A} \cdot m\mathrm{H_2O}$ will be more stable than the anhydrate A(solid) when $K_h > 1$, that is, when $a(\mathrm{H_2O}) > [a[\mathrm{A} \cdot m\mathrm{H_2O(solid)}]/\{a[\mathrm{A(solid)}]K_h\}]^{1/m}$. Corresponding relations hold for the various hydrates of a drug.

A rule applying to solubility behavior is that the anhydrous form of a substance is always more soluble in water than the corresponding hydrate(s) which crystallized from water at the same temperature [4,10]. Because the hydrate has already interacted intimately with water, the free energy released on crystal dissolution and the further interaction with water is less for the hydrate than for the anhydrate. Fig. 3 compares the aqueous solubilities of the hydrate and the anhydrate forms of theophylline at various temperatures [11] and shows that the aqueous solubility of the anhydrous theophylline is consistently higher than that of the theophylline monohydrate below 60°C.

Because Eq. (1) is given by adding Eqs. (2) and (3)

$$K_h = K_s/K'_s \tag{5}$$

and

$$\Delta G^{\ominus}_h = -RT \ln K_h = -RT \ln(K_s/K'_s) \tag{6}$$

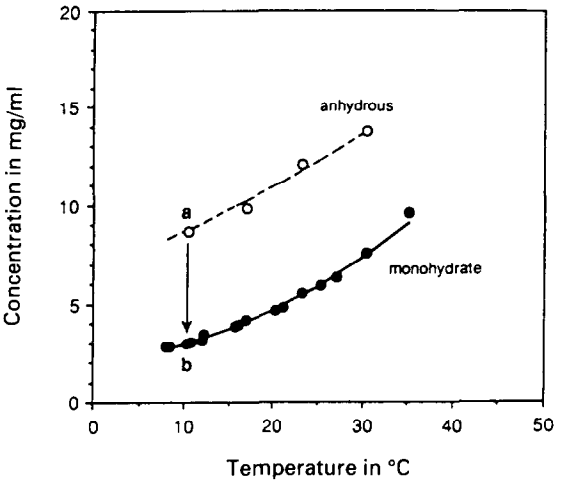

Fig. 3. Solubility dependence on temperature, for anhydrous and monohydrate theophylline in phosphate buffer (pH 6). Points a and b represent the concentration range in which the phase transformation was studied. (Reproduced from Ref. [11] with the permission of the copyright owner, Elsevier Publishers B.V., Amsterdam, Netherlands.)

where $\Delta G_h^{\ominus}$ is the standard free energy of hydration which is represented by Eq. (3), R is the gas constant and T is the absolute temperature. The value of $\Delta G_h^{\ominus}$ can be calculated from the solubilities of the anhydrous and the hydrated forms of the drug in place of K_s and K_s', respectively. The corresponding standard enthalpy and entropy of hydration, $\Delta H_h^{\ominus}$ and $\Delta S_h^{\ominus}$, can be calculated from the temperature dependence of the solubility ratio (K_s/K_s') using the van't Hoff isochore equation.

An application of the theory discussed above is illustrated in Fig. 4 and Table 1. Fig. 4 shows that the van't Hoff-type plot for the anhydrous and hydrated forms of theophylline and Table 1 shows the thermodynamic quantities calculated for anhydrate–hydrate systems of theophylline and glutethimide [4]. In Table 1 the enthalpy of solution ΔH_s is more endothermic for the hydrate than for the anhydrate of each drug, corresponding to a negative value for the enthalpy of hydration, ΔH_h. Similarly, the standard Gibbs free energy of solution, $\Delta G_s^{\ominus} = -RT \ln(\text{solubility})$, is less negative for the hydrate (solubility $\propto K_s'$) than for the anhydrate (solubility $\propto K_s$), corresponding to a negative value for the standard Gibbs free energy of hydration $\Delta G_h^{\ominus}$ for each drug. The standard entropy of hydration $\Delta S_h^{\ominus}$ is negative, indicating that the hydration process is enthalpy-driven for each drug.

4.3. Dissolution rate

If dissolution is a transport-controlled (usually a diffusion rate-controlled) process, the intrinsic dissolution rate J of a solid, which is the rate of dissolution per unit surface area (i.e. the mass flux), is given by

$$J = (\mathrm{d}m/\mathrm{d}t)(1/A) = k(C_s - C) \tag{7}$$

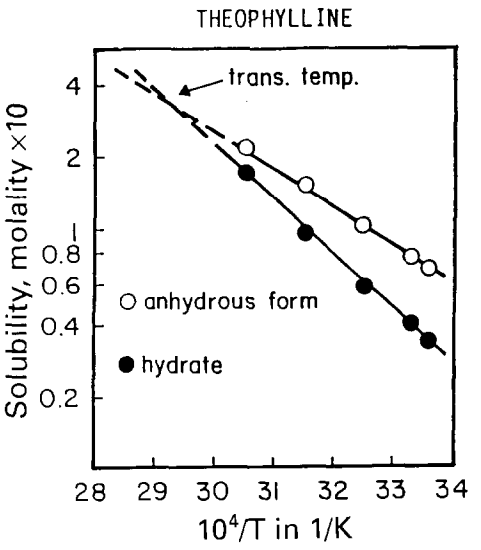

Fig. 4. van't Hoff-type plot of molal solubility (mol kg $^{-1}$, log scale) against the reciprocal of the absolute temperature for the anhydrous and hydrated forms of theophylline in water. (Reproduced from Ref. [4] with the permission of the copyright owner, American Pharmaceutical Association, Washington DC, USA.)

Table 1
Thermodynamic values calculated from van't Hoff solubility–temperature plots for anhydrous–hydrated systems of theophylline and glutethimide.

Compound	Transition temp./°C	ΔH_s/(cal mol^{-1}) [a]		ΔH_h/(cal mol^{-1}) [b]	$\Delta G_h^{\ominus}$/(cal mol^{-1})	$\Delta S_h^{\ominus}$/(cal K^{-1} mol^{-1}) [d]	
		Hydrate	Anhydrate			at 25°C [e]	at transition temp [f]
Theophylline	73	10 700	7400	−3300	−410	−10.0	−9.5
Glutethimide	52	11 700	9700	−2000	−280	−5.8	−6.1

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[a] Heat of solution in water. [b] Heat of hydration = ΔH_s of the anhydrate $-\Delta H_s$ of the hydrate. [c] Standard Gibbs free energy of hydration = $-RT$(solubility of the anhydrate/solubility of the hydrate). [d] Standard entropy of hydration = $(\Delta H_h - \Delta G_h^{\ominus})/T$. [e] At $T = 298.15$ K (25°C). [f] At the transition temperature, where $\Delta G_h = 0$.

where A is the area of the solid exposed to the dissolution medium, k is the mass transfer coefficient, C_s is the molar solubility of the solid, C is the molar concentration dissolved and dm/dt is the dissolution rate. The mass transfer coefficient $k = D/h$, where D is the diffusivity of the solid and h is the thickness of the diffusion layer which depends on the geometry of the system and agitation conditions. Under sink conditions, i.e. when $C_s \gg C$, Eq. (7) can be written as

$$J = kC_s \tag{8}$$

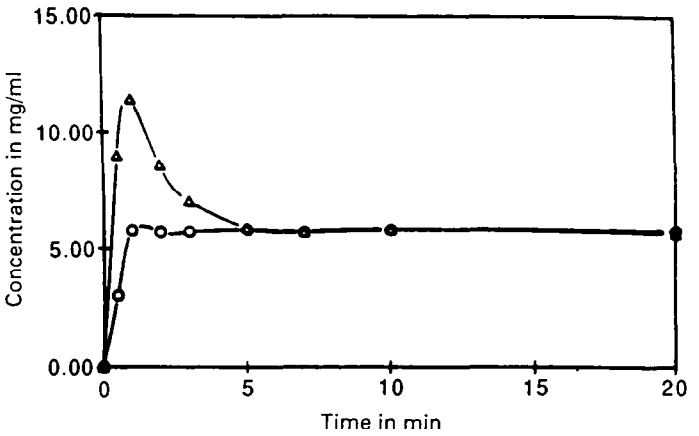

Fig. 5. Concentration profile during dissolution of anhydrous and monohydrate theophylline crystals at 23°C; △, anhydrate; ○, monohydrate. (Reproduced from Ref. [16] with the permission of the copyright owner, Marcel Dekker, New York, USA.)

As discussed earlier, the aqueous solubility C_s of the anhydrate is greater than that of its hydrate form at temperatures at which the hydrate crystallizes from water. Consequently, according to Eq. (8), under the same transport rate-controlled conditions, i.e. for the same value of k, the dissolution rate of the anhydrate is greater than that of the corresponding hydrate [5,12–15]. Fig. 5 illustrates the different dissolution behavior of theophylline monohydrate and anhydrate at 23°C [16]. The results show a significant difference in the initial dissolution rate of the monohydrate compared to the anhydrate. During dissolution of the theophylline anhydrate, the solution becomes supersaturated with respect to the hydrated form, which precipitates and grows until the concentration reaches the solubility of the monohydrate crystal form.

It is often difficult to determine the aqueous solubility of the metastable forms because, upon equilibration, the metastable forms may undergo spontaneous transformation to the thermodynamically stable form. In this case the solubility of the metastable form may be estimated from its initial intrinsic dissolution rate [14]. If the mass transfer coefficient of the drug from the metastable form (Form A) and the thermodynamically stable form (Form H), under identical hydrodynamic conditions are assumed to be equal, then Eq. (8) leads to

$$\frac{J_H}{J_A} = \frac{C_{s_H}}{C_{s_A}} \tag{9}$$

where J_H and J_A are the mass fluxes for Forms H and A respectively and C_{s_H} and C_{s_A} are the solubilities of the thermodynamically stable form and the metastable form, respectively. Thus, knowing the values for J_H, J_A and C_{s_H}, the value for C_{s_A} can be calculated from Eq. (9). This concept is illustrated in Fig. 6 which presents the concentration profile during the dissolution of disks of the anhydrous and monohydrate theophylline at 23°C [16].

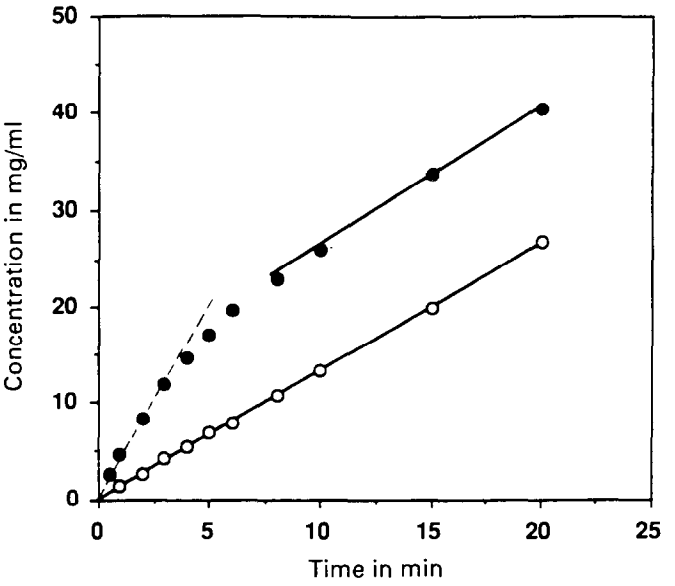

Fig. 6. Concentration profile during intrinsic dissolution of anhydrous and monohydrate theophylline from a disk at 23°C; ●, anhydrate; ○, monohydrate. (Reproduced from Ref. [16] with the permission of the copyright owner, Marcel Dekker, New York, USA.)

4.4. Bioavailability

The differences in the solubility and the dissolution rate of the anhydrate and the hydrate may alter the bioavailability of the drug. Poole et al. [17] studied the physicochemical factors influencing the absorption rate of the anhydrous and trihydrate forms of ampicillin. When the anhydrate and the trihydrate were administered as an oral suspension or as a capsule to dogs and to humans, the blood serum concentrations of ampicillin produced by the anhydrate were found to give higher peaks which occurred earlier than those produced by the trihydrate (Fig. 7). It was deduced that these differences in the blood serum concentrations of ampicillin were the result of differences in the aqueous solubility of the anhydrate and of the trihydrate. On account of the similar solubilities of the anhydrate and the trihydrate in dilute hydrochloric acid, Hill et al. [18] suggested that the differences in bioavailability are related to formulation factors.

Three crystal modifications of nitrofurantoin (two anhydrates and a monohydrate) have been studied [19]. Gouda et al. [20] and Ebien et al. [21,22] reported that the dissolution rate and bioavailability of nitrofurantoin commercial tablets in humans decreased after 1–8 weeks of storage at different relative humidities at higher temperatures. Gouda et al. [20] concluded that the dissolution rate decreased through the agglomeration of the mixture of powders in the preparation. However, the possibility of crystallographic transformation was not investigated. In order to clarify the decreased dissolution rate of nitrofurantoin preparations after storage

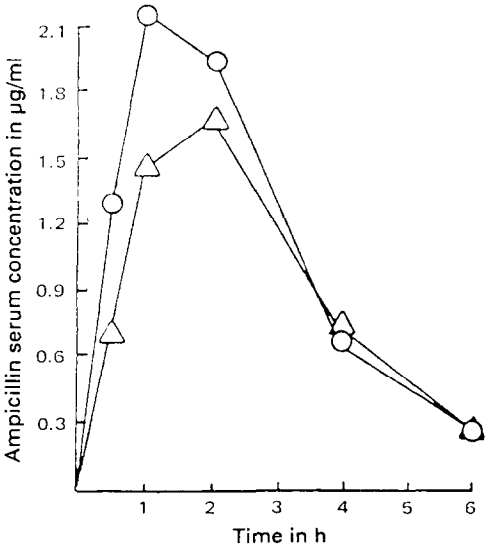

Fig. 7. Mean blood serum concentrations of ampicillin in human subjects after oral administration of 250 mg doses of oral suspension: ○, anhydrate; △, trihydrate. (Reproduced from Ref. [17] with the permission of the copyright owner, Excerpta Medica, New Jersey, USA.)

under high humidity conditions, Otsuka et al. [23] analyzed the physicochemical stability of the anhydrate and the monohydrate under high and low humidity conditions. Otsuka et al. [23] concluded that crystallographic phase changes of the drug can occur during the storage period at relatively high or low humidities and suggested that these crystallographic phase changes may be among the most important factors controlling the bioavailability of the preparation. Similarly, the erratic bioavailability of theophylline [24] or of carbamazepine [25] from solid dosage forms has been attributed to the phase change corresponding to hydrate formation during dissolution.

4.5. Physical stability of suspensions

The mean particle size diameter and the particle size distributions of suspended insoluble drugs are important considerations in formulating physically stable pharmaceutical suspensions [26]. A change from one pseudopolymorphic form to the thermodynamically stable crystal form or a change in the crystal habit due to the degree of hydration of the drug may induce crystal growth in the suspensions which may lead to caking and deflocculation of the suspensions [27–30].

Metronidazole benzoate can exist as an anhydrate and as a monohydrate [29]. The monohydrate is the thermodynamically stable form in water below 38°C. Hoelgaard and Møller [29] showed that the phase transition of the anhydrate to the monohydrate is followed by a drastic increase in the particle size causing physical instability of the suspension. Supensions containing the monohydrate result in a physically stable suspension when stored below the transition temperature at about 38°C.

Anderson and Bundgaard [31] reported that the phase transition in metronidazole benzoate suspension can be inhibited by formation of an inclusion complex of the drug with β-cyclodextrin. Through complexation, the marked crystal growth resulting from the phase transition is inhibited.

Similar results have been reported in the case of carbamazepine. Anhydrous carbamazepine transforms to the hydrate in aqueous suspensions. New crystals grow by the whisker mechanism [32] and the transformation takes about 1 h [33].

4.6. Chemical stability

Some solid-state oxidation reactions of crystal solvates require prior desolvation [34]. Byrn [34] suggested that stabilization of such compounds could be accomplished by preventing desolvation. Dihydrophenylalanine, when crystallized from dilute 80% ethanol, yielded prism-shaped anhydrate crystals which were found to be stable to oxidation. However, crystallization of dihydrophenylalanine from a saturated solution, in either 80% ethanol + water or in methanol + ethyl acetate, yielded needle-shaped hydrate crystals which were oxidized by air at 100°C giving 70% phenylalanine in 10 min. Similarly, the pseudopolymorphic solvate of hydrocortisone 21-*t*-butyl acetate was found to be more sensitive to oxidation by air than the polymorphic solvate or non-solvate of the drug [35]. The hydrated form of vitamin B_{12}(cyanocobalamine) is chemically more stable to light and heat than the anhydrous form [36].

4.7. Tabletting

Hydrates form an integral part of many solid dosage forms, either in the form of excipients, such as magnesium stearate, lactose, glucose, dextrose or calcium diphosphate, or in the form of an active ingredient, such as cephalosporins, ampicillin or theophylline [37] and the other drugs discussed in the present review. York [38] has pointed out the importance of studying pseudopolymorphism in pharmaceutical excipients.

Lerk et al. [39] studied the binding capacities of α-D-glucose dehydrated at temperatures from 60 to 135°C. Fig. 8 shows that the crushing strength of tablets, compressed from fully dehydrated α-D-glucose monohydrate, increases with the increasing dehydration temperature. The authors suggest that the increased binding capacity of the particles is due to the change in the texture of the particles upon thermal dehydration.

Commercial magnesium stearate exhibits batch-to-batch differences in its physical properties. Several of these differences, most notably differences in moisture content, have been shown to correlate with the ability of the compound to act as a lubricant [40–44]. Variations in the physical properties of magnesium stearate batches due to hydrate formation have been shown to affect the mechanical failure properties of powder beds [45] and tablet die wall friction [46]. Ertel and Carstensen [40] examined the lubricant properties of three batches of commercial magnesium stearate and three hydrates of pure magnesium stearate and concluded

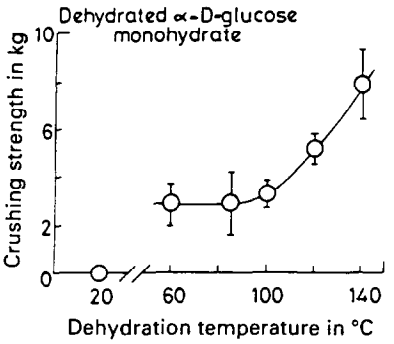

Fig. 8. Crushing strength of tablets, compressed from fully dehydrated α-D-glucose monohydrate, treated at different temperatures. (Reproduced from Ref. [39] with the permission of the copyright owner, The Royal Pharmaceutical Society of Great Britain, London, UK.)

that the lubricant properties of pure magnesium stearate are influenced by the crystal structure of the compound, specifically the crystal spacing which is dependent on the hydration state.

Otsuka et al. [47] investigated the effects of tabletting pressure of hydration kinetics of theophylline anhydrate tablets. The results showed the hydration of the theophylline tablets decreased with increased tabletting pressure and that the tablets expanded 11–17% in volume during hydration to the monohydrate.

According to an announcement made by the Food and Drug Administration [48], the anticonvulsant drug carbamazepine can lose up to one third of its effectiveness when stored in humid conditions (such as bathrooms). Lowes [49] reported that a pseudopolymorh of the drug, the dihydrate form, was produced when three anhydrous carbamazepine tablet formulations were stored at ambient or at elevated humidity conditions. The formation of the dihydrate was found to be influenced by tablet composition and by manufacturing conditions.

4.8. Grinding

The physical manipulation, such as grinding, of a pharmaceutical compound may exert a substantial influence on its solid-state properties. Otsuka and Kaneniwa [50] studied the effects of grinding on the physicochemical properties of cephalexin and showed that a noncrystalline (i.e. amorphous) form was obtained upon grinding the drug for 4 h. Furthermore, the dehydration point and the decomposition point of the ground cephalexin were depressed by about 25°C and 30°C, respectively. When similar studies were carried out on cephalothin sodium [51], the results showed that the degree of crystallinity of the drug decreased with increased grinding time. The authors suggested that the hygroscopicity and the chemical stability of cephalothin sodium in the solid state are closely related to the crystallinity.

Table 2 lists the hydrolysis rate constants for the solid-state decomposition of 4-methoxyphenyl aminoacetate hydrochloride under various conditions of admix-

Table 2
Degradation rate constants for the solid-state decomposition of 4-methoxyphenyl aminoacetate hydrochloride (MPAA) under various conditions of admixture and storage with α-lactose monohydrate

Condition	Rate constant/ ($min^{-1} \times 10^5$)
MPAA; 39°C; 10% RH	5.9
MPAA; 37°C; 80% RH	11.6
MPAA + α-lactose monohydrate (gently mixed); 37°C; 80% RH	25.5
MPAA + α-lactose monohydrate (lactose ground for 10 min then gently mixed); 37°C; 80% RH	46.7
MPAA + α-lactose monohydrate (mixture ground for 10 min); 37°C; 80% RH	50.4

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ture and storage with α-lactose monohydrate [52]. The data show that the rate of hydrolysis was substantially increased by gentle mixing of 4-methoxyphenyl aminoacetate hydrochloride with α-lactose monohydrate. The degradation rate was further increased when the lactose was ground for 10 min prior to gentle mixing, suggesting that the degradation is promoted by the release of water from the α-lactose monohydrate.

5. "Decision tree" when working with pharmaceutical hydrates

The discussion in the preceding section emphasizes the importance of characterizing the pharmaceutical hydrates so that the problems of phase transformation affecting the physical and/or chemical stability, bioavailability and processing during product development can be avoided. Consequently, during the development of a dosage form, it is essential to investigate whether the solid under consideration forms a hydrate(s) and, if so, to determine the conditions of temperature and water activity under which the different pseudopolymorphs of the drug are thermodynamically stable.

Fig. 9 shows a decision tree or a flow chart [1] which provides a set of questions which need to be asked during the process of product development in order to set appropriate analytical specifications and controls. Fig. 9 also lists the solid-state analytical techniques that can be used to answer the questions presented. In order to verify whether or not the substance is likely to exist as a solvate, it is crystallized from solvents with varying polarity. As an alternative to varying the polarity of the solvent the water activity of the solvent medium may be varied using mixtures of water with a suitable organic solvent [5]. The crystallized solid is analyzed by the methods listed in Fig. 9 to reveal its composition and stoichiometry. If the presence of a hydrate is affirmative, then important physical properties, such as the dissolution rate, solubility, and stability of the crystal forms are determined and compared with those of the anhydrate or of another hydrate of the same compound. If the

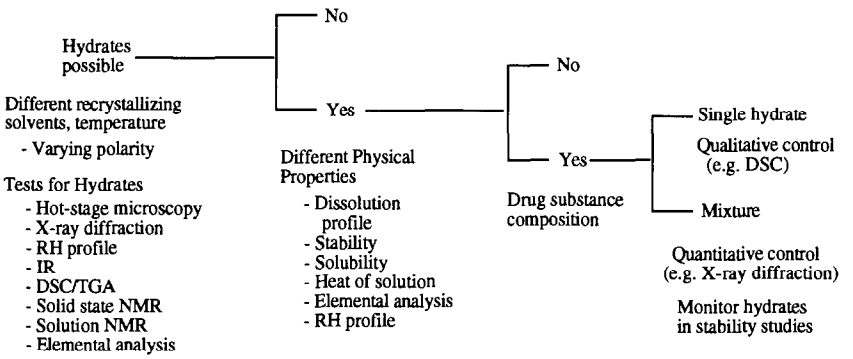

Fig. 9. "Decision tree", when working with pharmaceutical hydrates. (Reproduced from Ref. [1] with the permission of the copyright owner, Dr. Stepen R. Byrn, Purdue University, West Lafayette, IN, USA.

physical properties of the hydrate and of the anhydrate or those of two or more hydrates of the same substance are found to be significantly different from each other, then the composition of the pure drug substance and that of the final product has to be monitored to ensure the presence of a single crystal form.

6. Methods employed for the characterization of hydrates

6.1. Common, well-established methods

The established frequently-used techniques for the characterization of hydrates, include hot-stage microscopy [2,53], X-ray powder diffractometry [16,34], differential scanning calorimetry [54–57], thermogravimetric analysis [54–56,58], Karl Fischer titrimetry [58], infrared spectroscopy [16,34], single crystal X-ray analysis, [34], and solution calorimetry [59]. Because these methods have been extensively reviewed, including the reference cited, they will not be discussed in this article. However, some of the newer methods will be presented.

6.2. Solid-state nuclear magnetic resonance spectroscopy (solid-state NMR)

Solid-state NMR can be used in pharmaceutical research for the characterization of polymorphs and pseudopolymorphs, especially hydrates. On account of the incorporation of water molecule(s) into the crystal lattice, the molecular environment of the various nuclei, such as carbon, may be different in a hydrate than in the corresponding anhydrate. This leads to a different chemical shift interaction for each nucleus and, consequently, to a different isotropic chemical shift for the same nucleus in the two different pseudopolymorphs [60].

Byrn et al. [61] reported the solid-state ^{13}C NMR spectrum for the different hydrates of cefazolin and compared it with the solution ^{13}C NMR spectrum. Each crystal form exhibited a characteristic NMR spectrum indicating that solid-state NMR spectroscopy can be used to determine qualitatively which hydrate is present.

Similarly, Martinez et al. [62] applied solid-state ^{13}C NMR in their investigation of the solid-state chemistry of cefaclor dihydrate and found the results to be consistent with the intermolecular interactions in the crystal structure.

Suryanarayanan and Wiedmann [63] used solid-state NMR for the quantitation of the relative amounts of carbamazepine anhydrate and carbomazepine dihydrate in a mixture. In this study, high-resolution NMR spectra were obtained by means of cross polarization, dipolar coupling and magic angle spinning techniques. Although the NMR spectra for the two crystal forms appeared to be the same, the proton relaxation time of the dihydrate was shorter than that of the anhydrate. Consequently, a delay time of 10 s between pulses resulted in signals only from the dihydrate (Fig. 10) in mixtures of the dihydrate and the anhydrate. This apparent difference in the proton relaxation time was utilized for quantitative purposes after construction of a standard curve. By employing glycine as an internal standard and by measuring the peak area of the dihydrate, the amount of dihydrate in a mixture of the two crystal forms was determined.

Solid-state NMR spectroscopy may be termed a bulk technique, because the signal is independent of particle size. Furthermore, the signal is directly proportional to the number of nuclei once the acquisition parameters have been established. Establishing the experimental conditions and correctly assigning the signals in the spectrum, however, can be a time-consuming, although rewarding, process.

6.3. Raman spectroscopy

Low frequency lattice vibrations (10 to 150 cm^{-1}), which correspond to librations and to translations of the entire molecule, are easily accessible only to Raman spectroscopy [64]. Because the different crystal forms, including hydrates, of a compound yield different vibrational spectra, Raman spectroscopy can be used to characterize and to identify the solid phases of a substance.

Bellows et al. [64] characterized the two anhydrous polymorphs and the trihydrate of ampicillin by laser Raman spectroscopy. The results showed that each crystal form of ampicillin exhibits a characteristic pattern that is different from that of the other crystal forms. Thus, Raman spectroscopy can be used as an identification technique for hydrates.

Some of the advantages of Raman spectroscopy [65] are small sample size, short experimental time and no special requirement for sample preparation. However, the technique is more suitable for concentrated species rather than for those present in small amounts, such as impurities. Furthermore, the measured relative intensities do not provide quantitative information on the concentrations of the various species. Therefore, Raman spectroscopy cannot be used as a substitute for other conventional techniques in the characterization of hydrates.

6.4. Isothermal microcalorimetry

Most of the physical and chemical processes involve changes in the heat content, i.e. enthalpy [66,67]. These enthalpy changes can be used as a measure of the rates

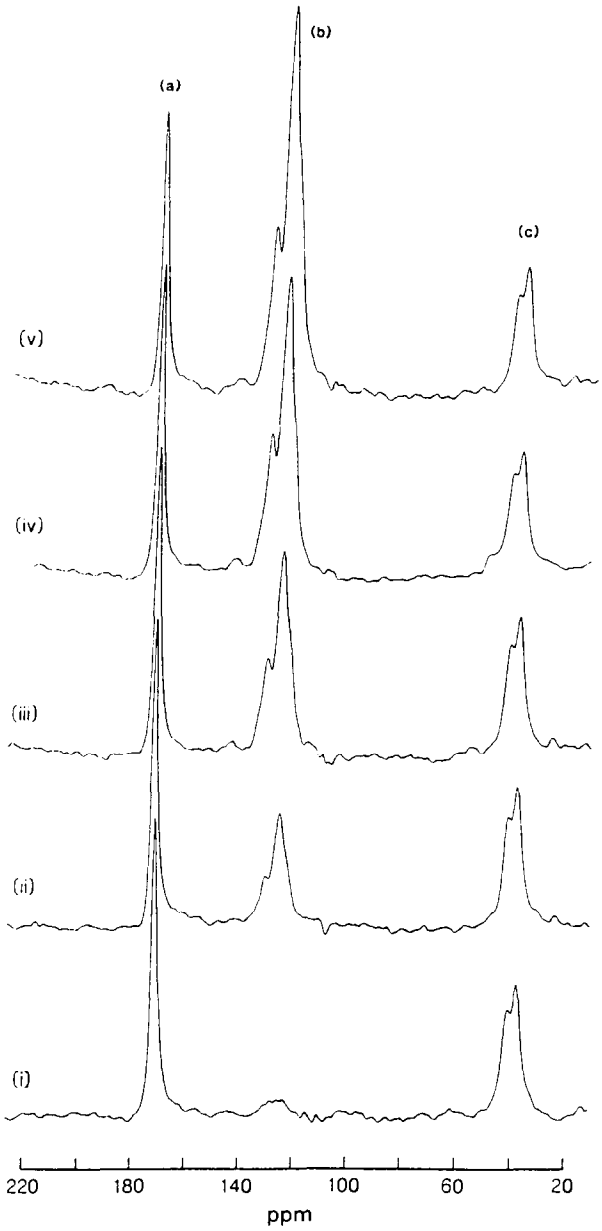

Fig. 10. ^{13}C spectra of mixtures of carbamazepine anhydrate (I), carbamazepine dihydrate (II) and glycine. The peak assignments are (a) the carbonyl carbon of glycine, (b) all carbons of II, and (c) the α-carbon of glycine. The mole fraction of II in the mixtures increases from spectrum (i) to spectrum (v). (Reproduced from Ref. [63] with the permission of the copyright owner, Plenum Publishing Corporation, New York, USA.)

of reactions. In an isothermal heat-conduction microcalorimeter, the heat produced by a sample is exchanged with the surroundings at a rate that is proportional to the reaction rate. Thus, the monitored signal is the rate of exchange of heat and is recorded as a function of time to yield a curve that is a continuous representation of the reaction rate. The magnitude of the signal is proportional to the sample size and to the overall enthalpy change of the reaction. The integrated curve yields the total heat evolved or absorbed in the reaction and thus affords the extent of reaction. A high-sensitivity isothermal calorimeter is capable of detecting very small heat flows (± 50 nW) produced or absorbed by a sample system [68] and thus, measures the thermal activity, i.e. the rate of heat production, with a sensitivity of about 10^4 greater than is possible with a conventional differential scanning calorimeter [69].

Angberg et al., in a series of publications [70–74], evaluated the use of heat-conduction microcalorimetry in pharmaceutical stability studies. In one of the publications [72], the incorporation of hydrate water into anhydrous lactose was investigated. The results showed that, with the help of microcalorimetry, it was possible to detect the hydration process of anhydrous lactose after only 1 day of storage at 58% RH. Furthermore, for a sample stored at 94% RH for 112 days, the high-sensitivity microcalorimeter could detect the continuation of the lactose hydration process which appeared to be complete by the conventional DSC technique.

Pikal and Dellerman [69] tested the stability of cephalosporins in the solid state and in aqueous solution by high-sensitivity isothermal calorimetry. The results showed that, for the crystalline solids and for the amorphous solids with low to moderate moisture content, the heat of reaction is roughly independent of temperature, water content, and polymorphic form. All the amorphous solids, and the crystalline non-stoichiometric hydrate of ceftazidime, showed decreased stability at high water content because water can be a reactant in the decomposition of cephalosporins [75].

Microcalorimetry is a sensitive and non-destructive technique in which no special sample preparation is necessary. Moreover, the heat flow measurements can be continuously monitored. However, due to parallel processes, the heat flow curves for mixed and complex systems may be difficult to interpret [67].

7. Conclusions

Hydrates form an integral part of many pharmaceutical dosage forms. In this review the role of hydrates in the formulation and processing of pharmaceutical dosage forms has been discussed. The reasons for the differences in the physical properties of hydrates, the pharmaceutical implications of these differences and some of the methods of characterization of hydrates are presented. It is evident that hydration or dehydration of a pharmaceutical solid during formulation development or in a final dosage form may adversely affect the physical, chemical and/or biological performance of a pharmaceutical product. Therefore, a thorough fundamental knowledge of the solid-state chemistry of a drug and that of the excipients

included in a formulation is most important for the successful design of a dosage form.

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