ELSEVIER

International Journal of Pharmaceutics 135 (1996) 151–160

international journal of pharmaceutics

Influence of water activity in organic solvent + water mixtures on the nature of the crystallizing drug phase. 1. Theophylline

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Received 6 November 1995; revised 22 January 1996; accepted 23 January 1996

Abstract

The hydration state of a hydrate depends on the water activity, a_w, in the crystallization medium. Selection of an appropriate ratio of water to cosolvent in the crystallization medium of a hydrate is critical and is often semi-empirical. This study attempts to elucidate this selection process by studying the conditions of physical stability of the solid phases of theophylline, which comprise an anhydrate and a monohydrate. A mixture of the anhydrate and the monohydrate may sometimes be obtained, if the system is not in equilibrium. The excess solid phase was characterized by powder X-ray diffractometry and the water content was measured by Karl-Fischer titrimetry. In contact with methanol + water or 2-propanol (isopropyl alcohol, IPA) + water mixtures, at $a_w < 0.25$, the anhydrate was the only solid phase at equilibrium, no matter which solid form was initially added. At $a_w > 0.25$ in either solvent mixture, the monohydrate was obtained as the most stable form at equilibrium. These results suggest (a) that water activity is the major factor determining the nature of the solid phase of theophylline which crystallizes from methanol + water or IPA + water mixtures and (b) that the system, theophylline anhydrate $\rightleftharpoons$ theophylline monohydrate, is in equilibrium at $a_w = 0.25$ and at 25°C. The solubilities of the two solid forms in each of the mixed solvent systems were also measured and are discussed. The concepts presented, tested and discussed may, in principle, be applied to any pharmaceutical system consisting of an anhydrate and a hydrate, or a lower hydrate and a higher hydrate.

Keywords: Theophylline; Anhydrate; Monohydrate; Methanol; 2-Propanol; Water activity; Crystallization; Solubility

1. Introduction

During the process of crystallization, solvent may become incorporated into the crystal structure. A hydrate forms when water is incorporated from the crystallization medium. The change in the thermodynamic activity of the drug due to hydration alters the pharmaceutically important properties, such as the solubility and the physical and chemical stability. The solubility of a drug usually influences its dissolution rate. The alter-

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PII S0378-5173(95)04466-3

ation in the dissolution rate and the stability as a result of hydration may, ultimately, modify the bioavailability and product performance (Shefter and Higuchi, 1963; Haleblian, 1975; Khankari and Grant, 1995). It is, therefore, of vital importance to control the phase transformation, including the anhydrate-hydrate or lower hydrate-higher hydrate phase transition, in the development and manufacture of pharmaceutical dosage forms (De Smidt et al., 1986; Rodriguez-Hornedo et al., 1992)

The formation of hydrated crystals from anhydrous crystals (Shefter and Higuchi, 1963; Grant and Higuchi, 1990) may be represented by the following equilibrium

$$\text{A(solid)} + m\text{H}_2\text{O} \rightleftharpoons \text{A}.m\text{H}_2\text{O(solid)}$$

$$K_h = \frac{a[\text{A}.m\text{H}_2\text{O(solid)}]}{a[\text{A(solid)}]a[\text{H}_2\text{O}]^m} \quad (1)$$

where K_h is the equilibrium constant for the process shown in Eq. 1, and $a[\text{A}.m\text{H}_2\text{O(solid)}]$, $a[\text{A(solid)}]$, and $a[\text{H}_2\text{O}]$ are the thermodynamic activities of the hydrate, the anhydrate, and water respectively. When $a(\text{H}_2\text{O}) = [a[\text{A}.m\text{H}_2\text{O(solid)}]/\{a[\text{A(solid)}]K_h\}]^{1/m}$, the anhydrate, A(solid), and water are in equilibrium with the hydrate, $\text{A}.m\text{H}_2\text{O}$(solid). When $a(\text{H}_2\text{O}) > [a[\text{A}.m\text{H}_2\text{O}$ (solid)]/$\{a[\text{A(solid)}]K_h\}]^{1/m}$, the hydrate, $\text{A}.m\text{H}_2\text{O}$ (solid), will be more stable than the anhydrate, A(solid). The anhydrate, A(solid), will be more stable than the hydrate, $\text{A}.m\text{H}_2\text{O}$(solid), in the inverse situation when $a(\text{H}_2\text{O}) < [a[\text{A}.m\text{H}_2\text{O}$ (solid)]/$\{a[\text{A(solid)}]K_h\}]^{1/m}$. Corresponding relations also hold for the phase transitions between different hydrates of a drug. If the standard states of unit activity of A(solid) and of $\text{A}.m\text{H}_2\text{O}$(solid) are represented by their pure solid phases, Eq. 1 simplifies to give Eq. 2.

$$K_h = a[\text{H}_2\text{O}]^{-m} \quad (2)$$

where m is the number of moles of water taken up by one mole of the anhydrate (or lower hydrate) in the stoichiometric equation. Thus, the hydration state of a hydrate depends on the water activity in the surrounding medium, for example, in the crystallization medium, which may consist of water and organic solvent mixture, or in the vapor phase in which the water activity can be controlled in a relative humidity chamber.

The water activity, $a[\text{H}_2\text{O}]$, which is abbreviation to a_w, in a crystallization medium can be controlled by changing the composition of an appropriate water + organic solvent mixture. The organic co-solvent should be water-miscible, such as methanol, ethanol, 2-propanol (isopropyl alcohol, IPA), acetone, acetonitrile, or dioxan. Values of the mole fraction-based activity coefficient, γ_w, in mixtures of each of these solvents with water are known (Gölles, 1961; Gölles, 1962; Udovenko and Mazanko, 1967; Sokolova and Morachevskii, 1967; Chirikova et al., 1966; Bacarella et al., 1956). Values of a_w in mixtures of organic solvent + water can be calculated from the literature values of γ_w and the mole fraction of water, x_w, in these mixtures by Eq. 3.

$$a_w = \gamma_w \cdot x_w \quad (3)$$

Values of a_w are fitted to a polynomial in x_w, which enables a_w to be estimated at any value of x_w in the organic solvent + water mixtures employed for the crystallization of a drug. The a_w value in mixtures of organic solvent + water will be modified by the presence of the dissolved drug and a suitable means must be used to evaluate this effect. The fundamental hypotheses in the present work are that, when a drug, which can form a hydrate, is crystallized from mixtures of organic solvent + water, (a) the water activity, a_w, in the mixtures is the major factor determining the nature of the anhydrate or hydrate phase that crystallizes and, (b) that the dissolved drug in the aqueous solvent mixtures influences a_w to a much smaller extent than does the organic solvent. For this concept to be useful, the organic solvent should not form a solid solvate nor a solid solvate-hydrate phase with the drug. The above hypotheses have been previously tested in preliminary studies with nedocromil sodium ($C_{19}H_{15}NO_7Na_2$) in IPA + water mixtures (Khankari and Grant, 1993) and with ampicillin in methanol + water mixtures at 25°C (Zhu and Grant, 1994). The work reported here is part of a continuing series of studies, in which the above hypotheses are further tested using theophylline, caffeine, carbamazepine, and nedocromil magne-

sium as model compounds. In the present work, a preliminary report of which has been presented (Yuen et al., 1995), theophylline, which exists as an anhydrate and a monohydrate, is crystallized from methanol + water and IPA + water mixtures. The main objective here is to investigate whether a_w is a major factor determining the nature of the anhydrate and hydrate phases of theophylline which crystallize from these two organic solvent + water mixtures. The second objective is to study the influence of solvent composition on the solubility of the theophylline phases.

2. Experimental

2.1. Materials

Theophylline anhydrate was obtained from Sigma Chemical Co. (St. Louis, MO), dried for 24 h in an oven at 100°C and stored in a desiccator over phosphorus pentoxide at room temperature. Theophylline monohydrate was prepared by crystallization from distilled water, which was supersaturated by dissolving the anhydrate. The monohydrate was dried at room temperature and stored over a saturated aqueous solution of ammonium chloride (relative humidity 79.5%). Ammonium chloride was obtained from EM Science (Gibbstown, NJ). Methanol and 2-propanol (isopropyl alcohol, IPA) were obtained from Fisher Scientific (Fair Lawn, NJ).

2.2. Methods

2.2.1. Solubility studies

The solubilities of theophylline anhydrate and monohydrate were each determined in methanol + water and IPA + water mixtures of various water activities. Excess theophylline (1 g) was equilibrated for up to 5 days with 10 g solvent mixture (methanol + water or IPA + water, each containing a different mole fraction of water, corresponding to a defined a_w value) in a 20-ml vial at 25°C. Equilibration was attained by shaking the vials in a temperature-controlled water bath. Samples (1 ml) were withdrawn, filtered, suitably diluted with water and analyzed by UV spectrophotometry (Beckman UV-64) at 270 nm. Equilibration was judged to have occurred when three successive measurements differed by not more than 1%.

2.2.2. Powder X-ray diffraction

The powder X-ray diffraction patterns of the theophylline solid phases were determined using a Siemens D-500 powder X-ray diffractometer, with Cu Kα radiation at 30 mA and 45 kV with 2θ increasing at the rate of 3°/min. Counts were accumulated for 1 s at each step. The sample was packed into an aluminum holder and the instrument was operated between an initial and a final 2θ-angle of 5° and 35°, respectively, in increments of 0.05° 2θ.

2.2.3. Karl Fischer titrimetry

The amounts of water, expressed as % w/w and as the number of moles per mole of anhydrous theophylline, in the solid phases were determined using a Mitsubishi Moisturemeter (Model CA-05, Mitsubishi Chemical Industries Limited, Tokyo, Japan). The sample (6–8 mg) was accurately weighed and quickly transferred to the titration vessel before measuring the water content.

2.2.4. Relative humidity measurement

The relative humidity of the vapor phase above saturated aqueous solutions of theophylline was measured by a Rotronic-Hygroskop BT (Rotronic Instrument Corp., Huntington, NY). At equilibrium, the relative humidity, expressed as a decimal fraction, is equal to a_w both in the vapor phase and in the solution.

3. Results and discussion

Values of γ_w in methanol + water and IPA + water mixtures have been previous reported (Gölles, 1961; Udovenko and Mazanko, 1967) as stated above. Fig. 1 shows values of a_w in methanol + water and IPA + water mixtures calculated using Eq. 2 and plotted against x_w. These a_w values were fitted to polynomials of the fourth degree in x_w, and were then used to esti-

mate the water activity at any value of x_w in methanol + water mixtures (Eq. 4) or in IPA + water mixtures (Eq. 5).Methanol + water mixtures:

$$a_w = 0.0056 + 1.398x_w - 0.647x_w^2 + 0.153x_w^3 + 0.0845x_w^4 \ (R = 0.9996) \quad (4)$$

IPA + water mixtures:

$$a_w = 0.0215 + 2.828x_w - 1.837x_w^2 - 2.380x_w^3 + 2.379x_w^4 \ (R = 0.9985) \quad (5)$$

The diagonal straight line in Fig. 1 shows the Raoult's law plot from which methanol + water and IPA + water mixtures give positive deviations. The greater deviation in IPA + water mixtures may be attributed to the larger hydrophobic interaction in the solution resulting from the greater volume and surface area of the cavity created in water by the larger alkyl group of the co-solvent.

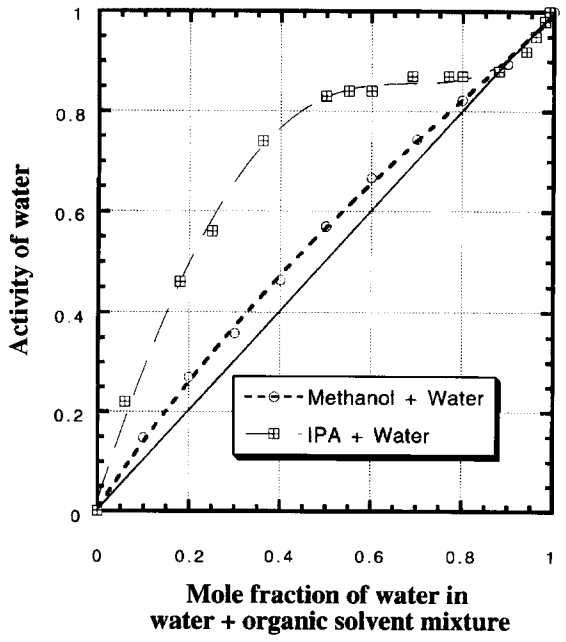

Fig. 1. Plot of the water activity versus the mole fraction of water in methanol + water and IPA + water mixtures at 25°C (data from Gölles, 1961; Udovenko and Mazanko, 1967). The diagonal straight line corresponds to ideal behavior according to Raoult's law.

A saturated solution of theophylline in water is in equilibrium with water vapor at the measured $a_w = 0.94$. Therefore, when the saturated solution ($a_w = 0.94$) is diluted infinitely with water ($a_w = 1.00$), a_w changes by only 6%. This relative small change in a_w appears to justify hypothesis (b) that the presence of theophylline, even at the solubility limit, has little effect on a_w in organic solvent + water mixtures.

Theophylline anhydrate or monohydrate was added to methanol + water or IPA + water mixtures of various compositions and equilibrated at 25°C for 5 days to determine the solubility. After equilibration, the excess solid was characterized by powder X-ray diffractometry. The water content of each phase was determined by Karl Fischer titrimetry. Theophylline anhydrate, theophylline monohydrate and mixtures of the above two forms in different proportions were obtained in the excess solid phase throughout the study. The powder X-ray diffraction patterns of the theophylline forms are shown in Fig. 2. Both the anhydrate and monohydrate forms are crystalline, as is evident from the presence of a number of diffraction peaks. The additivity of both the anhydrate and the monohydrate patterns in separate experiments was shown for mixtures of theophylline anhydrate and the monohydrate.

Theophylline anhydrate in contact with methanol + water mixtures for 5 days converted to the monohydrate at $a_w \geq 0.252$ and remained unchanged at $a_w < 0.227$ (Fig. 3, circles). In contact with IPA + water mixtures for 5 days, theophylline anhydrate completely converted to the monohydrate at $a_w \geq 0.749$ (Fig. 4, open circles). However, in contact with IPA + water mixtures for 5 days at $0.258 \leq a_w \leq 0.625$ (Fig. 4, full circles) the anhydrate was only partially converted to the monohydrate, since the X-ray patterns corresponded to mixtures of the anhydrate and the monohydrate, showing that equilibrium had still not been achieved. The water content of the excess solid phase increased with increasing a_w between 0.258 and 0.625, corresponding to increasing phase conversion of the anhydrate to the monohydrate (Fig. 4, full circles) and indicating that the higher the water activity, the greater the thermodynamic driving force and the greater the

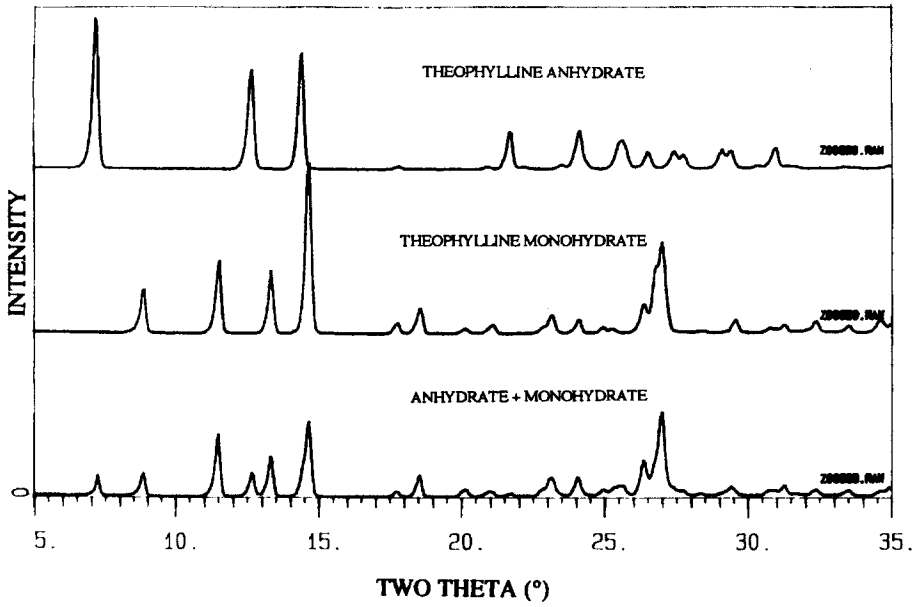

Fig. 2. Powder X-ray diffraction patterns of the two forms of theophylline investigated and of a mixture of the two forms.

rate of conversion. Since, at $0.258 \leq a_w \leq 0.625$, equilibrium was not achieved within 5 days (Fig. 4, full circles), the solid phases in contact with

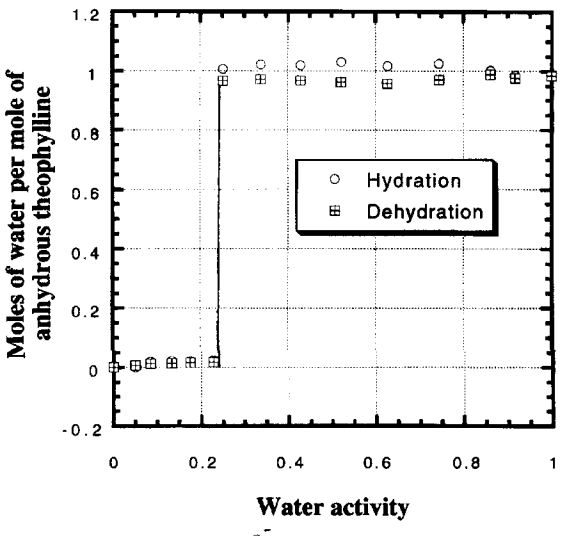

Fig. 3. Phase diagram after equilibration for 5 days showing the dependence of theophylline hydrate stoichiometry on water activity in methanol + water mixtures during theophylline hydration and dehydration processes at 25°C. Circles represent the fate of the anhydrate initially added. Squares represent the fate of the monohydrate initially added.

IPA + water mixtures within the range of $0.258 \leq a_w \leq 0.625$, were examined after 30 days by powder X-ray diffractometry and the water contents by Karl Fischer titrimetry. Within 30 days the phase conversion of the anhydrate to the monohydrate was complete (Fig. 5, circles).

Theophylline monohydrate in contact with methanol + water mixtures changed to the anhydrate at $a_w \leq 0.227$ but remained as the monohydrate at $a_w \geq 0.252$ (Fig. 3, squares). After being in contact with IPA + water mixtures for 5 days, the monohydrate partially dehydrated to the anhydrate at $a_w \leq 0.541$ (Fig. 4, full squares). After being in contact with IPA + water mixtures for 30 days (Fig. 5, squares), the partially dehydrated monohydrate (Fig. 4, full squares) completely changed to the anhydrate at $a_w \leq 0.171$ (Fig. 5, squares), while at $0.229 \leq a_w \leq 0.541$, the partially dehydrated monohydrate (Fig. 4, full squares) converted back to the monohydrate (Fig. 5, squares). These results suggest that theophylline changes form reversibly in response to a_w in the crystallization medium (Figs. 3 and 5), although equilibration in IPA + water mixtures takes between 5 and 30 days to achieve.

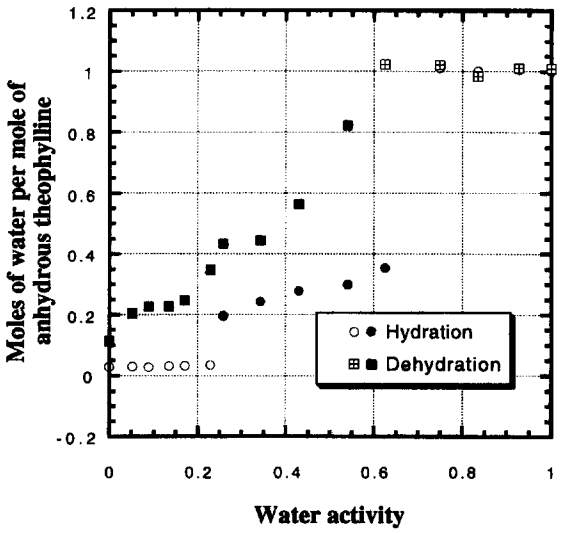

Fig. 4. Phase diagram after 5 days showing the dependence of theophylline hydrate stoichiometry on water activity in IPA + water mixtures during theophylline hydration and dehydration processes at 25°C (equilibrium not reached). Circles represent the fate of the anhydrate initially added. Squares represent the fate of the monohydrate initially added. Open circles and open squares represent a single phase, anhydrate or monohydrate, shown by powder X-ray diffraction. Full circles and full squares represent a mixture of the anhydrate and monohydrate shown by powder X-ray diffraction.

The water content of theophylline monohydrate, when added to an organic solvent + water mixture, contributes to x_w to a small extent and prevents the attainment of $a_w = 0$. The intrinsic water content in theophylline monohydrate could influence the water activity to a small but varying extent. This result may explain the discrepancy in water activity at which the monohydrate changes to the anhydrate ($a_w = 0.227$ in methanol + water mixture as compared with $a_w = 0.171$ in IPA + water mixture).

The phase transformation of theophylline anhydrate to the monohydrate is found to occur by a solvent-mediated process in which the anhydrate dissolves and creates the necessary supersaturation for the nucleation and growth of monohydrate crystals (De Smidt et al., 1986; Rodriguez-Hornedo et al., 1992). The kinetics of the transformation, anhydrate to monohydrate, for theophylline in water + organic solvent mixtures should take into consideration both the dissolution of the anhydrate phase and the nucleation and growth of the monohydrate phase. For theophylline in methanol + water mixtures, the equilibria were achieved within 5 days (Fig. 3), but in IPA + water mixtures the equilibria were not attained within 5 days (Fig. 4) but required 30 days (Fig. 5). Additional experiments, such as monitoring the concentration-time profiles during transformation, would be needed to explain why the kinetics of the phase transformation of theophylline anhydrate to the monohydrate is slower in IPA + water mixtures than in methanol + water mixtures.

In contact with IPA + water or methanol + water mixtures, the monohydrate was always present at equilibrium at $a_w > 0.25$. However, at $a_w < 0.25$ in either solvent mixture, the anhydrate form was the only solid phase obtained, no matter which solid form was initially added to the methanol + water or IPA + water mixtures. This observation indicates that equilibrium had been achieved with the more stable form. These results demonstrate the validity of hypothesis (a) that water activity is the major factor determining the nature of the theophylline phase, anhydrate or

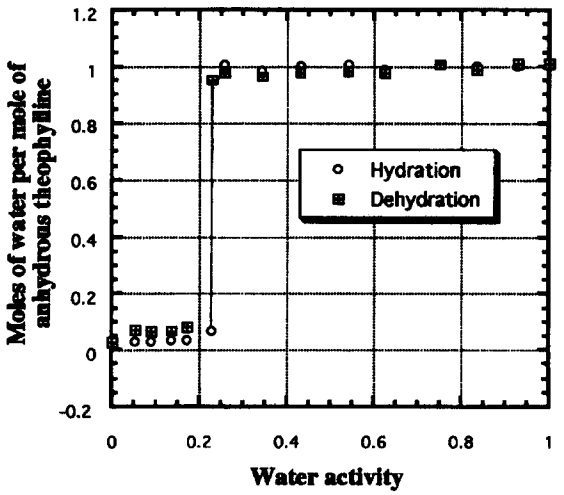

Fig. 5. Phase diagram after equilibration for 30 days showing the dependence of theophylline hydrate stoichiometry on water activity in IPA + water mixtures during theophylline hydration and dehydration processes at 25°C. Circles represent the fate of the anhydrate initially added. Squares represent the fate of the monohydrate initially added.

monohydrate, which crystallizes from methanol + water or IPA + water mixtures. At equilibrium, the a_w, at which theophylline anhydrate $\rightleftharpoons$ theophylline monohydrate, is found to be approximately 0.25. The stoichiometric number, m, in Eqs. 1 and 2 is unity. Substituting these values into Eq. 2 leads to $K_h = 4.0$. For the phase equilibrium between nedocromil sodium trihydrate and the heptahemihydrate, $a_w = 0.80$, $m = 4.5$ and $K_h = 2.7$ (Khankari and Grant, 1993). Similarly, for the equilibrium between ampicillin anhydrate and the trihydrate, $a_w = 0.34$, $m = 3$ and $K_h = 25.9$ (Zhu and Grant, 1994). Comparison of the respective K_h values enables the relative tendencies for the transition from the anhydrate to the hydrate or from the lower hydrate to the higher hydrate to be obtained for any pharmaceutical compound. Furthermore, these equilibrium constants apply in all liquid mixtures of water + organic solvents that are capable of providing these a_w values.

At $a_w = 0.25$, corresponding to $x_w = 0.2$ in methanol + water mixture and $x_w = 0.08$ in IPA + water mixture (Fig. 1), theophylline anhydrate is in equilibrium with theophylline monohydrate. Apparently, the phase transformation of theophylline anhydrate to the monohydrate occurs at a lower concentration of water in IPA + water mixture than in methanol + water mixture, yet the equilibrium water activity is essentially the same. This observation emphasizes the fact that the water activity in the crystallization medium is more important than water concentration in determining the nature of the phase (anhydrate or hydrate) that crystallizes.

Otsuka et al. (1990) studied the hydration behavior of two forms of theophylline anhydrate, Type I and Type II, at 35°C. Their Type I was obtained by recrystallization from distilled water at 95°C, whereas their Type II was obtained by dehydration of theophylline monohydrate of 100°C for 24 h, a more drastic treatment. Their reported powder X-ray diffraction patterns suggest that the crystal structures of Type I and Type II are identical with that of theophylline anhydrate. The observed difference in diffraction intensities with that of theophylline anhydrate. The observed difference in diffraction intensities may

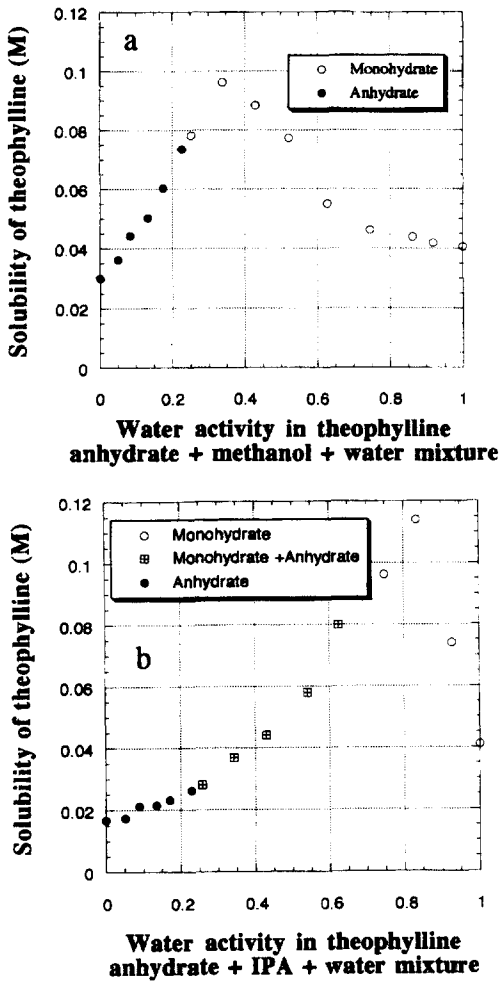

Fig. 6. Solubility profiles of theophylline anhydrate (initially added) as a function of water activity in (a) methanol + water mixtures and (b) IPA + water mixtures at 25°C. The legend designation of each data point refers to the solid phase obtained after 5 days. Full circles represent the formation of the anhydrate at equilibrium, open circles represent the formation of the monohydrate at equilibrium, and squares represents a mixture of both phases, not necessarily in equilibrium within 5 days.

be attributed to a preferred orientation effect due to differences in crystal habit. The reported powder X-ray diffraction pattern of Type I corresponds closely to that of the anhydrate employed in the present work (Fig. 2, top).

At 35°C in the presence of water vapor at various a_w values (which are equivalent to relative humidities, RH, expressed as decimal fractions),

Otsuka et al. (1990) found that the Type I anhydrate remains as the anhydrate at RH ≤ 0.82 but transforms to the monohydrate at RH ≥ 0.88. On the other hand, the Type II anhydrate remains as the anhydrate at RH ≤ 0.66 but transforms to the monohydrate at RH ≥ 0.75. The lower a_w ($=0.25$) for the solution phase transformation in the presence of organic solvent + water mixtures in the present work is mainly attributed to the attainment of true equilibrium, but not so in the vapor phase hydrations reported by Otsuka et al. (1990). However, a secondary factor may be the lower temperature employed in the present work. The different a_w (RH) values reported by Otsuka et al. (1990) may arise from the slower kinetics of hydration of the two other types of anhydrate. The fact that Type II, whose crystals contain cracks, is more readily hydrated than Type I, which gives more intense diffraction peaks, clearly points to kinetic factors in determining the observed hydrations of Otsuka et al. (1990).

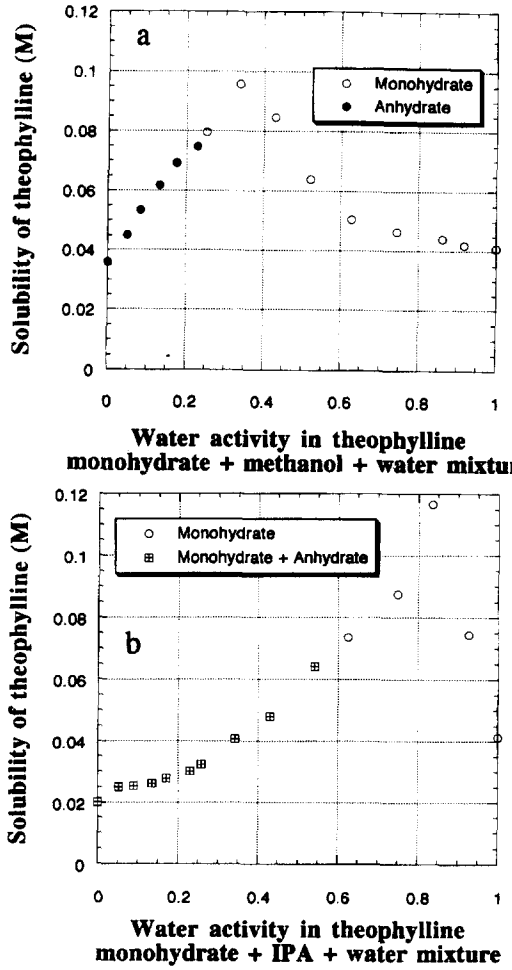

Fig. 7. Solubility profiles of theophylline monohydrate (initially added) as a function of water activity in (a) methanol + water mixtures and (b) IPA + water mixtures at 25°C. The legend designation of each data point refers to the solid phase obtained after 5 days. Full circles represent the formation of the anhydrate at equilibrium, open circles represent the formation of the monohydrate at equilibrium, and squares represents a mixture of both phases, not necessarily in equilibrium within 5 days.

The solubility of theophylline anhydrate in methanol + water mixtures, when plotted against a_w in these mixtures, increased to a maximum (0.0962 M at $a_w = 0.338$) and then decreased (Fig. 6a). IPA + water mixtures gave a similar pattern with a slightly higher maximum solubility (0.114 M at $a_w = 0.832$) (Fig. 6b). The solubility profiles of theophylline monohydrate in methanol + water and IPA + water mixtures (Fig. 7a,b) are similar to those of the anhydrate in the above two binary mixtures (Fig. 6a,b) and the a_w values at the maxima are identical. The ratio of the peak solubility of theophylline anhydrate to that of the monohydrate in both methanol + water and IPA + water mixtures is close to 1, indicating only a small difference between the thermodynamic activities of theophylline anhydrate and monohydrate at the above a_w values. These maxima have a complex thermodynamic origin, since they are a consequence of the influence of both enthalpy and entropy terms on the partial molar free energy of the solute (Gould et al., 1984; Grant and Higuchi, 1990).

These solubility maxima may be treated semi-empirically by regular solution theory (Gould et al., 1984) and by the extended solubility parameter approach (Martin et al., 1981). The original Hildebrand equation predicts that the solubility of a compound, for which the solubility parameter lies between the solubility parameters of the two solvents of a binary mixture, will exhibit a peak at which the solubility parameter of the mixed solvent, δ_1, equals that of the solute, δ_2. In a mixed solvent system, regular solution theory indicates that the solubility parameter, δ_1, should be represented by Eq. 6:

$$\delta_1 = \phi_a\delta_a + \phi_b\delta_b \quad (6)$$

where ϕ_a and ϕ_b are the volume fractions and δ_a and δ_b are the respective solubility parameters of the individual solvents (Snyder, 1980) in the binary liquid mixture. From the solubility parameter of each mixed solvent system at the composition giving the maximum solubility, the solubility parameter of theophylline, δ_2, was calculated to be 15.7 $cal^{1/2}cm^{-3/2}$ in methanol (δ_a = 14.5 $cal^{1/2}cm^{-3/2}$) + water (δ_b = 23.4 $cal^{1/2}cm^{-3/2}$) mixtures and 15.2 $cal^{1/2}cm^{-3/2}$ in IPA (δ_a = 12 $cal^{1/2}cm^{-3/2}$) + water (δ_b = 23.4 $cal^{1/2}cm^{-3/2}$) mixtures. These calculated solubility parameters, δ_2, for theophylline are appreciably larger than the value of 14 $cal^{1/2}cm^{-3/2}$ reported by Martin et al. (1981). The above calculations of the solubility parameter of theophylline employed the classical solubility parameter of water, δ_b = 23.4 $cal^{1/2}cm^{-3/2}$ (Hildebrand and Scott, 1962). This value accounts quite well for the solubility of water in paraffinic solvents (Black et al., 1948) at 25°C, partly because the solutions are so dilute that the solute-solvent interactions are dominated by London dispersion forces (Grant and Higuchi, 1990). However, Davis et al. (1972) have suggested that δ_b = 15.65 $cal^{1/2}cm^{-3/2}$ for water may better account for the solubility behavior of hydrocarbons and of the methylene group of other organic compounds, such as alkanols, in water at 25°C. Using δ_b = 15.65 $cal^{1/2}cm^{-3/2}$ for water, the solubility parameter of theophylline, δ_2, is calculated to be 14.7 $cal^{1/2}cm^{-3/2}$ in methanol + water mixtures and 13.0 $cal^{1/2}cm^{-3/2}$ in IPA + water mixtures. The differences between these calculated solubility parameters for theophylline and that derived by Martin et al. (1981) may be accounted for by differences in the relative emphasis of the hydrogen bonding and polar interaction in the ternary solutions, since regular solution theory in its simplest form is derived under the assumption that only London dispersion forces are the significant intermolecular interactions. These differences illustrate the difficulty of deriving reliable solubility parameters for polar solutes (Grant and Higuchi, 1990).

Pfeiffer et al. (1970) in their study of the pseudopolymorphism of cephaloglycine and cephalexin crystallized in several organic solvent + water mixtures observed a break in the solubility profile at that solvent composition at which one hydrate changes to another. Bogardus (1983) reported that the maximum in the solubility of cholesterol in water + glyceryl 1-monooctanoate mixtures coincided with the anhydrate-hydrate crystalline phase change of cholesterol. However, in the present study, the maximum solubility of theophylline occurred at a_w = 0.338, while phase transformation at equilibrium occurred at a_w = 0.25 in methanol + water mixtures. Similarly, in IPA + water mixtures, the maximum solubility of theophylline occurred at a_w = 0.832, but phase transformation occurred at a_w = 0.25. These discrepancies suggest that the maximum solubility and the change of crystal form of theophylline have different origins in these two binary solvent mixtures. The solubility maxima may reflect the sensitivity of the strong hydrogen bonding interactions in solution to a_w in each binary solvent system, methanol + water or IPA + water.

4. Conclusions

The first hypothesis (a) that "when a drug, which can form a hydrate, is crystallized from mixtures of organic solvent + water, the water activity, a_w, in the mixtures is the major factor determining the nature of the anhydrate or hydrate phase that crystallizes" is essentially correct for theophylline in water + methanol or water + IPA mixtures. The anhydrate is in equilibrium with the monohydrate at a_w = 0.25 in each of these solvent mixtures. Saturation of water with theophylline monohydrate reduces a_w by only 6%, confirming the second hypothesis (b) that "the dissolved drug in the aqueous solvent mixtures influences a_w to a much smaller extent than does the organic solvent".

The solubilities of theophylline anhydrate and monohydrate have maximum values (0.0962 M at a_w = 0.338) in methanol + water and (0.114 M at a_w = 0.832) in IPA + water mixtures. These a_w values do not correlate with a_w = 0.25 for the theophylline anhydrate-monohydrate equilibrium in either binary solvent mixture, emphasizing their different origins.

Acknowledgements

We thank the Pharmaceutical Research and Manufacturers of America Foundation, Inc. for an Undergraduate Research Fellowship in Pharmaceutics for Ceaminia Yuen.

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