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A thermodynamic study of the solubility of theophylline and its hydrate

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Summary

The solubilities of theophylline and theophylline hydrate as a function of temperature are determined in the temperature range 288–365K. The solubility as a function of temperature can be described by $\ln X = 10.0 - 5178.3 \cdot 1/T$ for theophylline hydrate and a polymorph of theophylline. A number of other thermodynamic parameters are determined by means of differential scanning calorimetry and vapour pressure studies. The conversion of theophylline hydrate into theophylline and a saturated solution occurs at 337.0K, the transition enthalpy being 11.2 $kJ \cdot mol^{-1}$. The melting temperature and the enthalpy of melting of theophylline are 543.7K and 31.2 $kJ \cdot mol^{-1}$, respectively; the enthalpy of sublimation at 421K is 126 $kJ \cdot mol^{-1}$. These parameters are used to calculate the δ-values of theophylline and theophylline hydrate, which are found to be 14.0 s.u. [1] and 13.2 s.u., respectively. The validity of all data is discussed in relation to an 'extended' Hildebrand-Scatchard equation for theophylline, derived by Martin et al. (1980).

Introduction

Several publications concerning drug release from non-aqueous suspensions have appeared in the past few years (e.g. Crommelin and de Blaey, 1980a and b; Schoonen et al., 1979; Fokkens and de Blaey, 1982). Most of these studies were carried out in a model apparatus in which a suspension is on top of an aqueous

[1] s.u. = solubility units = $cal^{0.5} \cdot cm^{-1.5} \cdot mol^{-0.5}$

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phase. The release rate of the drug from the suspension into the aqueous phase is determined by taking samples from the aqueous phase and analyzing them. In such a release process one of the following 3 steps is rate limiting, i.e. sedimentation of the particles in the suspension, passage through the non-aqueous phase/aqueous phase interface or dissolution of the drug particles hanging at this interface.

The drug release process has been studied either by changing the composition of the suspension (Crommelin and de Blaey, 1980a and b) or by changing the composition of the aqueous phase (Fokkens and de Blaey, 1982). In studying the influence of the pH of the aqueous phase on the release rate of theophylline suspended in liquid paraffin (Fokkens and de Blaey, 1983) we observed that sometimes a cake of theophylline formed in the interfacial layer. This caking phenomenon was independent of the pH of the aqueous phase and occurred only in dissolution-limited release processes. Microscopial observations showed that the cake consisted of crystalline needles, although the suspended drug was powdered anhydrous theophylline. A decrease in the release rate of the drug from the suspension was observed during the 'caking process'. Hence it was postulated that the cake consisted of a (pseudo)-polymorph of theophylline, e.g. theophylline hydrate, although from the work of Moës (1981) one can conclude that there is no significant difference between the solubility of theophylline and theophylline hydrate. The purpose of our study was to determine some thermodynamic properties of theophylline and theophylline hydrate, which would enable us to elucidate the precise nature of the cake.

Theory

In the past few years a number of research papers on the prediction of solubilities of drugs in various dissolution media have been published (see e.g. Martin et al., 1980; Martin et al., 1981; Yalkowsky and Valvani, 1980); these predictions are based on the Hildebrand-Scatchard equation for regular solutions

$$\ln X = -\frac{\Delta H_f}{RT} \cdot \left(\frac{T_m - T}{T_m} \right) - (\delta_1 - \delta_2)^2 \frac{V_2 \cdot \phi_1^2}{RT} \qquad (1)\ ^2$$

The first term on the right-hand side of the equation represents the ideal solubility, and the second term is a 'correction' for the difference in interaction forces (van der Waals interactions) between drug–drug, solvent–solvent and drug–solvent molecules. However, when hydrogen-bonding occurs between solute and solvent Eqn. 1 may not be used, and so far there is no fundamental theory which has general validity and which describes such irregular solutions. An attempt was made by Martin and co-workers (Martin et al., 1980; Adjei et al., 1980; Martin and Carstensen, 1981; Martin et al., 1981) to use an empirically extended Hildebrand-Scatchard

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[2] For an explanation of the symbols used, see 'List of symbols'.

equation to describe the solubility of a number of compounds that form irregular solutions with various mixtures of solvents:

$$\ln X = -\frac{\Delta S_m^f}{R}\ln\frac{T_m}{T} - \frac{V_2 \cdot \phi_1^2}{RT}\left(\delta_1^2 + \delta_2^2 - 2W\right) \qquad (2)$$

W is the empirically calculated interaction energy between solute and solvent of the irregular solution; for the theophylline/water system Martin et al. (1980) calculated W to be 365 $(s.u.)^2$.

From Eqns. 1 and 2 it is obvious that the solubility of a compound depends among other things on parameters related to the nature of the solute, i.e. T_m, ΔH_m, V_2 and δ_2. The molar volume of the solute as a supercooled liquid, V_2, is often calculated using the group contribution method described by Fedors (1974). The δ_2-value can be determined from solubility measurements of the drug in mixtures of solvents having various δ-values (see e.g. Martin et al., 1980; Martin et al., 1981) or can be calculated using the following equation

$$\delta = \left(\frac{\Delta H_{vap} - RT}{V}\right)^{0.5} \qquad (3)$$

When δ is calculated using Eqn. 3, both ΔH_{vap} of the dissolved compound and the molar volume as a supercooled liquid, V, at temperature T have to be known. ΔH_{vap} is the difference between ΔH_{sub} and ΔH_m, and V can be calculated after Fedors (1974). If ΔH_{sub} is known at a certain temperature it can be calculated at the desired temperature by correcting it for the ΔC_p, i.e. $(C_p^g - C_p^s)$. When all the parameters mentioned in Eqn. 1 or Eqn. 2 have been determined it is possible to predict the solubility of a compound as a function of temperature.

Generally, however, values mentioned above are obtained at rather high temperatures (over 373K) and are used to predict solubilities, e.g. at room temperature, so one has to take into account that the crystal structure of the compound involved can be different at these various temperatures; if it is different, then the predicted solubility will deviate from the observed solubility.

Theophylline exists in both the hydrate and the anhydrous form. Shefter and Higuchi (1963) showed that theophylline [3] is metastable in contact with water at temperatures below a transition temperature of 346K (T_{tr}), which implies that below T_{tr} monohydrous theophylline is stable and above T_{tr} theophylline is stable. This implies that thermodynamic values measured above T_{tr} are sometimes used to predict the solubility at temperatures below T_{tr} and hence data determined for theophylline are used to predict the solubility of theophylline hydrate. So, in order to make a correct extrapolation of the data obtained at temperatures above T_{tr}, it is necessary to know the equilibria of theophylline and theophylline hydrate in relation to temperature.

The following schemes represent phase reactions for theophylline, theophylline

[3] Whenever theophylline is mentioned in the text, we mean the anhydrate.

hydrate and water. Theophylline will be denoted as Tp, the hydrate by Tp · 1aq and a saturated solution of theophylline in water by sln(Tp,x,T) meaning that the solution contains (1 − x) moles of water and x moles of theophylline at temperature T. Below the transition temperature:

(I) $Tp \cdot 1aq(s) \rightarrow Tp(s) + H_2O(g) \quad \Delta H'$

(II) $xTp \cdot 1aq(s) + (1 - 2x)H_2O(l) \cdot \rightarrow sln(Tp,x,T) \quad \Delta H'_{sol}$

At the transition temperature:

(III) $(1 - x)Tp \cdot 1aq(s) \rightleftarrows (1 - 2x)Tp(s) + sln(Tp,x,T_{tr}) \quad \Delta H_{tr}$

Above the transition temperature:

(IV) $xTP(s) + (1 - x)H_2O(l) \rightarrow sln(Tp,x,T) \quad \Delta H^0_{sol}$

(V) $sln(Tp,x,T) \rightleftarrows xTP(s) + (1 - x)H_2O(g) \quad \Delta H^0$

(VI) $Tp(s) \rightleftarrows Tp(l) \quad \Delta H_m$

(VII) $Tp(s) \rightleftarrows Tp(g) \quad \Delta H_{sub}$

Both T_{tr} and the enthalpy changes involved in these phase reactions can be determined by means of DSC and vapour pressure studies. The data obtained with vapour pressure measurements are plotted in a so-called Clausius-Clapeyron plot ($\ln P/P_0$ vs $1/T$) (see Fig. 2). From the difference in slopes, i.e. the difference between the enthalpy of the vaporization of water from the hydrate and the enthalpy of the vaporization of water from the saturated solution (Schemes I and V, respectively), one calculates the enthalpy of transition, ΔH_{tr} (De Kruif et al., 1982). The transition temperature is found from the intersection of the two vapour pressure curves. The vapour pressure data are fitted using the following equation (Clarke and Glew, 1966):

$$R \cdot \ln\frac{P}{P_0} = -\frac{\Delta G^0(\theta)}{\theta} + \Delta H^0(\theta) \cdot \left(\frac{1}{\theta} - \frac{1}{T}\right) + \Delta C_p^0(\theta) \cdot \left\{\frac{\theta}{T} - 1 + \ln\left(\frac{T}{\theta}\right)\right\} \qquad (4)$$

The dissolution enthalpies of both theophylline and theophylline hydrate are obtained from a van't Hoff plot which presents the natural logarithm of the mole fraction of dissolved drug vs $1/T$ (Schemes II and IV). A van't Hoff plot constructed in this way is expected to show two curves with an intersection at T_{tr}. The mole fraction of the dissolved drug as a function of temperature is fitted to

$$\ln X = \frac{\Delta S_{sol}}{R} - \frac{\Delta H_{sol}}{R} \cdot \frac{1}{T} \qquad (5)$$

Differential scanning calorimetry is used to obtain ΔH_{tr} and T_{tr} as well as ΔH_m and T_m (Schemes III and VI, respectively)

Once the various parameters described above have been determined it is possible to test the validity of Eqn. 2 and it may then be possible to predict the solubility of theophylline and theophylline hydrate as a function of temperature.

Materials and methods

Materials

Theophylline monohydrate was obtained from a commercial source and conformed to the European Pharmacopoeia standard. The anhydrous form was obtained from the hydrate by one of the following two methods.

(a) Drying at 120°C for at least 24 h. The drug was allowed to cool in a desiccator over silica gel. The absence of water was checked by weighing and DSC-measurements (see also Methods (a)). The anhydrous theophylline obtained in this way was used for solubility experiments and for some DSC-measurements.

(b) Sublimation ($P = 10^{-2} Pa$; $T = 430K$). This was done as a routine procedure in order to purify the drug for the vapour pressure studies. The anhydrous theophylline obtained in this way was also used for some DSC-measurements.

The buffer components used for the preparation of a phosphate buffer (pH = 5.0) were of reagent grade. The phosphate buffer was prepared by adding 4 N phosphoric acid to a 0.1 M phosphate buffer with pH = 7.0.

Methods

(a) Differential scanning calorimetry (DSC)

DSC measurements were carried out in closed aluminium pans on a DSC-II (Perkin Elmer); the whole procedure was controlled by a microprocessor (Apple II). The microprocessor was also used for data acquisition and for the calculation of the final results. The melting enthalpy, ΔH_m, of theophylline and the melting temperature, T_m, were determined (temperature scan was 510–560K).

The phase transition enthalpy, ΔH_{tr}, of the conversion of the monohydrate into the anhydrate and a saturated solution (Scheme III) was measured by heating the monohydrate from 310 to 365K. The transition temperature was read from the DSC-curves.

The heating rate was always 5 $K \cdot min^{-1}$; the DSC-apparatus was calibrated with Indium ($\Delta H_m = 3.2426$ $kJ \cdot mol^{-1}$).

(b) X-ray diffraction

Powder X-ray diffraction measurements were done in a temperature range of approximately 300–355K. Photographs were taken with a Guinier-Simon camera (Enraf Nonius, Delft, The Netherlands); the film speed was 2 mm/h. The radiation source was $CuK_{\alpha 1}$; the heating rate of the sample was 12 K/h.

(c) Vapour pressure studies

Vapour pressure-static. The water vapour pressure over the system theophylline · 1aq (s) – theophylline (s) – water (vap) and theophylline (sat. solution) was determined by a static method involving the use of a capacitance manometer (MKS Instruments) type 90H. The experimental set-up and the measuring procedure have been described in detail previously (De Kruif et al., 1981).

Vapour pressure-dynamic. The vapour pressure as a function of temperature of solid theophylline was determined by a simultaneous torsion/mass loss effusion apparatus (De Kruif and Van Ginkel, 1977). The stainless steel effusion cell used had two circular orifices of 1 mm diameter, 20 mm apart.

(d) Solubility measurements

The solubilities of theophylline and theophylline hydrate in approximately 0.1 M phosphate buffers (pH = 5.0) were determined using various methods.

(1) Solubilities of theophylline hydrate were determined as a function of temperature in a temperature range of 288–298K by shaking an excess of drug (about 10 g) with about 50 ml of buffer. This process was carried out in 100 ml flasks, placed in a temperature-controlled (T ± 0.1K) shaking water-bath. Samples were taken after 16, 24 and 48 h; they were filtered through a 0.22 μm membrane filter and analyzed

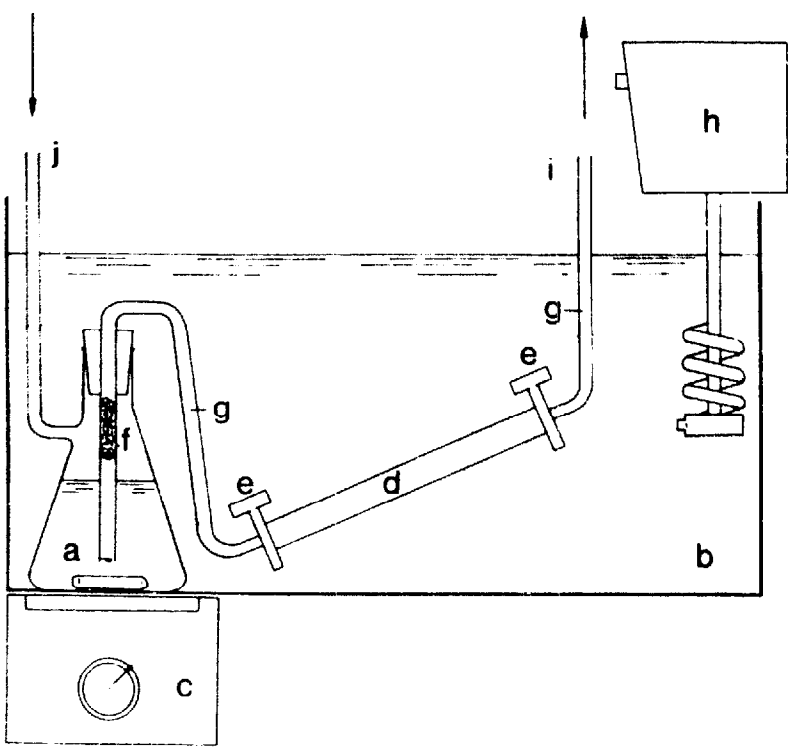

Fig. 1. Apparatus used to determine solubilities in the temperature range 290–364K. a, glass glask; b, water-bath; c, magnetic stirrer; d, glass tube; e, stop cocks; f, cotton wool; g, vacuum tubes; h, thermostat; i, to vacuum pump; j: open tube.

spectrophotometrically (Pye Unicam-1750) at 266.4 nm (the isobestic point) after suitable dilution. The same method was used for theophylline and for theophylline hydrate.

(2) Weighed amounts of drug were dispersed in known volumes of buffer in glass flasks. The flasks were placed in a water-bath and their contents were stirred vigorously with magnetic stirrers. The temperature of the water-bath was raised slowly (about 1K/h) and the solubility of the drug in relation to temperature was determined by observing the temperature at which the drug was completely dissolved. This method was used in the temperature range 293–363K with theophylline as the dispersed drug.

(3) In order to determine the solubility at high temperatures an apparatus as shown in Fig. 1 was used. The drug was dispersed in buffer in the glass flask (a); both drug and buffer had the same temperature. The flask was closed and immediately put into the constant-temperature water-bath (b). The contents of the flask were mixed vigorously with a magnetic stirrer (c) and after a certain period of equilibration (generally about 3 h), a sample was sucked into the glass tube (d) through a tube containing cotton wool, whereupon the stop cocks on both sides of the tube (d) were closed. Usually a duplicate sample was sucked into a second glass tube (not drawn) a few hours later. The glass tubes were then taken from the water-bath and cleaned carefully on the outside. After the tubes had been dried their weight was determined and the content of each tube was then put into a 1000 ml flask and each tube was rinsed with a 0.1 N sodium hydroxide solution. The solution in each flask was then diluted with water until the flask contained 1000 ml. After further suitable dilution the amount of drug was determined spectrophotometrically and the mole fraction X of the drug in solution was calculated by subtracting the amount of drug in the tube from the total weight of the contents. The solubility of the drug can be calculated using the following equation:

$$C_s = \frac{X \cdot M_2 \cdot 1000}{M_1} \qquad (6)\ ^4$$

Method no. 3 was used for both forms of theophylline, i.e below T_{tr} (temperature range 290–337K) the dispersed drug was the monohydrate and above T_{tr} (temperature range 337–364K) it was theophylline. A summary of the experimental conditions in the various methods used is given in Table 1.

Results and discussion

X-ray diffraction studies showed that the reversible transition of theophylline in theophylline hydrate and a saturated solution occurred at 337K. Once T_{tr} was

[4] This equation can be used for theophylline because the mole fraction of dissolved drug is negligible compared to the mole fraction of solvent.

TABLE 1

SUMMARY OF THE EXPERIMENTAL CONDITIONS IN RELATION TO THE SOLUBILITY METHODS USED

Method	Amount of drug	Tp	Tp·1aq	Temperature range (K)
I	excess	+	+	288–298
II	exactly weighed	+	–	290–364
III	excess	–	+	290–337
		+	–	337–364

known, the other parameters necessary for the prediction and/or determination of the solubility of theophylline and theophylline hydrate were measured.

Differential scanning calorimetry measurements were carried out on both theophylline and theophylline hydrate. The results are summarized in Table 2. The results given in Table 2 show that both the melting temperature and the enthalpy of melting are in good agreement with the literature data of 540–545K and 29.7 $kJ \cdot mol^{-1}$, respectively (European Pharmacopoeia, 1980; Martin et al., 1980, respectively). The transition temperature read from the DSC-curves is in excellent agreement with the T_{tr} found with the X-ray diffraction measurements.

A number of the parameters mentioned above were also determined using fundamentally different techniques, i.e. vapour pressure studies. The values obtained for T_{tr} and ΔH_{tr} (337K and 11.4 $kJ \cdot mol^{-1}$, respectively) in these studies are essentially the same as those found with DSC and X-ray diffraction. The data obtained with the vapour pressure (static) studies are given in Table 3 and plotted in a so-called Clausius-Clapeyron plot (Fig. 2). As mentioned in 'Materials and methods', two different vapour pressure techniques were used; the overall results are summarized in Table 4. The mean enthalpy of sublimation determined by vapour pressure studies (dynamic) is 126.1 $kJ \cdot mol^{-1}$ at T = 421K. So for the calculation of the δ-value of the drug, at e.g. T = 298K, ΔH_{sub}(421K) has to be corrected for the ΔC_p, i.e. $(C_p^g - C_p^s)$, in order to obtain ΔH_{sub}(298K). The ΔC_p is generally between -50 and -100 $J \cdot K^{-1} \cdot mol^{-1}$, which leads to an estimated value of 135 $kJ \cdot mol^{-1}$ for ΔH_{sub}(298K). From the work of Shefter and Higuchi (1963) it can be concluded that below T_{tr} theophylline hydrate is the stable modification of the drug in an aqueous medium; therefore one has to calculate the δ-value of the hydrate in order to predict the correct solubility of the drug in water below the transition tempera-

TABLE 2

RESULTS OBTAINED FROM DIFFERENTIAL SCANNING CALORIMETRY MEASUREMENTS

T_{tr} (K)	ΔH_{tr} ($kJ \cdot mol^{-1}$)	T_m (K)	ΔH_m ($kJ \cdot mol^{-1}$)
337.0 ± 1.3	11.1	543.7 ± 0.5	31.2 ± 1.5
n = 5	n = 2	n = 5	n = 3

TABLE 3

EXPERIMENTAL RESULTS OF WATER VAPOUR PRESSURE OVER Tp HYDRATE AND Tp SATURATED SOLUTION

Theophylline · $1H_2O$			Theophylline (sat. soln.)		
T (K)	P (Pa)	Δln P ($\times 10^2$)	T (K)	P (Pa)	Δln P ($\times 10^2$)
314.82	5758	−0.12	339.76	26027	0.35
319.92	8072	0.32	343.51	30689	0.44
312.45	4978	1.29	347.20	35348	−1.22
297.12	1614	−1.10	350.75	41424	−0.22
288.32	822	0.79	355.36	50296	0.33
273.15	218	−0.08			
303.87	2681	−0.42			
324.21	10530	−0.27			
329.32	14390	−0.39			
331.69	16620	−0.09			
335.14	20400	0.23			

ture. Therefore the ΔH_{vap} mentioned in Eqn. 3 equals $\Delta H_{sub}(298K) - (\Delta H_m + \Delta H_{tr})$. If the molar volume of theophylline and theophylline hydrate is taken to be 124 cm^3 (Martin et al., 1980), the δ-value of theophylline hydrate at T = 298K is 13.2 s.u. and the δ-value for theophylline at T = 298K is 14.0 s.u. Martin et al. obtained a δ-value (T = 298K) of 14.0 s.u. which is exactly the same as the value calculated here for theophylline. Although it seems that all data necessary for the calculation of ln X, using Eqn. 2, are known, it is still not permissible to use this equation for the prediction of the solubility of the hydrate; Martin et al. (1980) calculated the empirically determined interaction factor, W, using the ΔH_m determined for theophylline. Eqn. 2 may be used to predict the solubility of the anhydrate in water, but since below T_{tr} the solubility of theophylline cannot be determined experimentally using the normal techniques (see Shefter and Higuchi, 1963), it is useless to solve Eqn. 2, since it has no practical validity. However, Eqn. 2 can be rewritten to make it applicable for the prediction of the solubility of theophylline hydrate ($\Delta H'_m = \Delta H_m + \Delta H_{tr}$):

$$\ln X_2^1 = -\frac{\Delta H'_m}{RT_m} \cdot \left(\frac{T_m - T}{T}\right) - \left(\delta_1^2 + \delta_2^2 - 2W\right) \cdot \frac{V_2 \Phi_1^2}{R \cdot T} \qquad (7)$$

Therefore the value of W can be determined empirically if the solubility at one temperature is known. Hence the solubility has to be determined first, both above and below the transition temperature. From the data given above it is obvious that T_{tr} is 337.0K.

This value of T_{tr} is not in agreement with the transition temperature of 346K predicted by Shefter and Higuchi (1963); they predicted T_{tr} using a van't Hoff plot representing ln X vs 1/T. They determined T_{tr} from the point of intersection of the

TABLE 4

EXPERIMENTAL RESULTS AT θ; COEFFICIENTS OF EQN. 4

Substance	Method	T_1 (K)	T_2 (K)	θ (K)	$\Delta G^0(\theta)$ ($J \cdot mol^{-1}$)	$\Delta H^0(\theta)$ ($kJ \cdot mol^{-1}$)	$\Delta C_p^0(\theta)$ ($J \cdot K^{-1} \cdot mol^{-1}$)
Theophylline·$1H_2O$	static	273	335	298.15	−18531 ± 20	55.8 ± 0.2	−51.4 ± 9.3
Theophylline (sat. soln.)	static	339	355	348.66	−30573 ± 20	42.4 ± 0.4	–
Theophylline (solid)	torsion	404	434	421.27	3209 ± 200	124.5 ± 2	–
Theophylline (solid)	mass loss	404	434	421.46	3211 ± 200	127.6 ± 2	–
Theophylline (solid) [a]	mean	404	434	421.37	3210 ± 200	126.1 ± 2	–

[a] Mean value of simultaneous torsion and mass loss effusion experiment.

TABLE 5

RESULTS OF THE SOLUBILITY EXPERIMENTS. A = METHOD I; B = METHOD II; C = METHOD III

A		B		C	
$10^3 \cdot T^{-1}$ (K^{-1})	ln X	$10^3 \cdot T^{-1}$ (K^{-1})	ln X	$10^3 \cdot T^{-1}$ (K^{-1})	ln X
3.456	−7.740	3.3962	−7.447	3.447	−7.842
3.411	−7.657	3.2944	−7.075	3.447	−7.791
3.388	−7.559	3.1954	−6.560	3.307	−7.262
3.357	−7.476	3.0965	−5.990	3.307	−7.218
		3.0372	−5.669	3.254	−6.983
		3.0017	−5.450	3.117	−6.205
		2.9512	−5.187	3.116	−6.206
		2.9235	−4.985	2.99[illegible]	−5.426
		2.8633	−4.692	2.991	−5.517
		2.8110	−4.419	2.914	−5.121
		2.7567	−4.182	2.910	−5.101
		2.7349	−4.005	2.872	−4.867
				2.872 *	−4.913
				2.858	−4.879
				2.833 **	−4.694
				2.825	−4.648
				2.817 *	−4.673
				2.805 **	−4.584
				2.788	−4.549
				2.771	−4.402
				2.761	−4.394
				2.745 *	−4.258
				2.742 *	−4.207

* pH of the aqueous phase is 2.
** Equilibration time over 1 week.

curves of theophylline hydrate and theophylline; however, the curve of theophylline was based on only a few data points, and was extrapolated over rather a long temperature range, so the T_{tr} determined in this way could not be very accurate.

On the basis of the data given above we constructed a van't Hoff plot (ln X vs 1/T), expecting to find two straight lines with a point of intersection at $1/T = 1/337K^{-1}$ and a difference in slopes of about 11.2 $kJ \cdot mol^{-1}$. The results of the various solubility experiments are given in Table 5 and are plotted in Fig. 3.

From Fig. 2 it can be seen that there is no clear point of intersection; so the results of the solubility experiments are not as expected. It seems as if only one stable form of theophylline exists in water (or buffer) in the temperature range 293–365K. The line equation obtained from all solubility data presented in Table 5 (least-squares regression method) is given in Eqn. 8.

$$\ln X = 10.0 - 5178.3 \cdot \frac{1}{T} \tag{8}$$

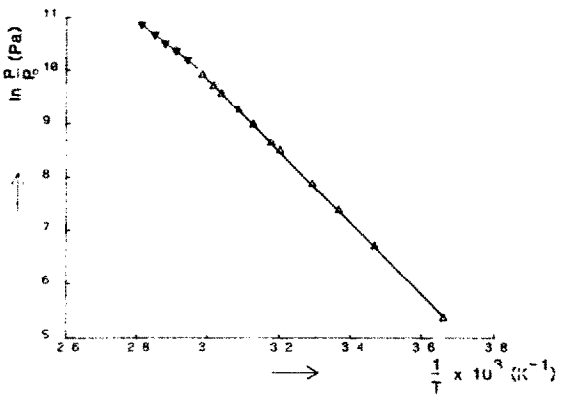

Fig. 2. Clausius-Clapeyron plot of the water vapour pressure data. △ theophylline hydrate; ▼ saturated solution of theophylline. The data are given in Table 3.

It was Cammenga [5] who pointed out that when theophylline is prepared by drying theophylline hydrate, at e.g. 383K, a polymorph of theophylline is formed. We confirmed his statement by performing X-ray diffraction studies; it should be noted that the formation of the stable theophylline from the polymorph occurs very slowly (a few hours at approximately 350K). Since the drug was always dried at 383K and was used almost immediately, it is obvious that the solubility data measured above T_{tr} represent the solubility of the polymorph. The ΔH_{sol} for both theophylline hydrate and the polymorph calculated from the solubility data below and above T_{tr} show no significant difference: 43.2 ± 1.4 kJ · mol^{-1} and 41.6 ± 1.4 kJ · mol^{-1} for

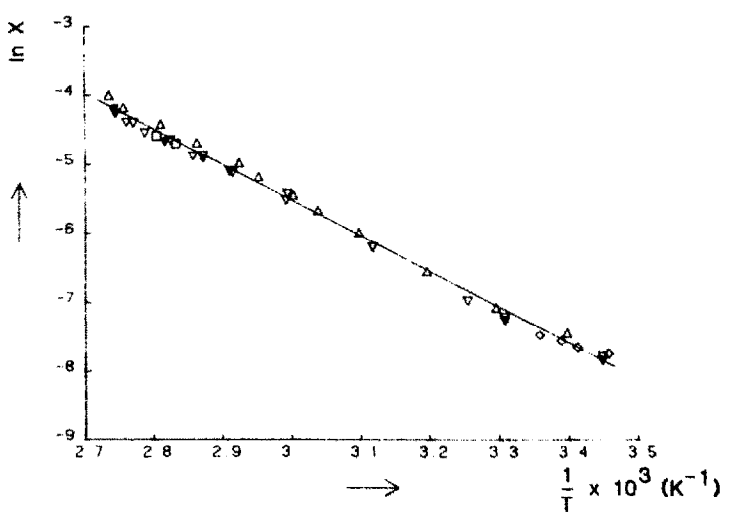

Fig. 3. Van't Hoff plot representing the mole fraction of theophylline or theophylline hydrate vs 1/T; the symbols used refer to the various methods used. ◇, method 1; △, method 2; ▽, method 3; ▼, method 3, pH of the aqueous phase = 2; □, method 3, equilibration time over 1 week.

[5] Cammenga, personal communication.

the hydrate and the polymorph, respectively. Thus Eqn. 8 is valid over the temperature range studied, which implies that the W value, at e.g. 298K, can now be calculated with the help of Eqn. 7, using $\delta_1 = 23.45$ s.u., $\delta_2 = 13.2$ s.u. (see above) and $\Delta H'_m = 42.4$ kJ · mol^{-1}, on the assumption that Φ_1^2 equals 1. The value of the interaction energy W (298K) now becomes 326 (s.u.)^2. This value for W differs, as expected, from the W-value calculated by Martin et al. (1980). So Eqn. 2 can be used to predict the solubility of theophylline setting W to 365 (s.u.)^2 and Eqn. 7 can be used to determine the solubility of theophylline hydrate (below T_{tr}) setting W to 326 (s.u.)^2.

As pointed out in the Introduction, we are interested in the crystallization process that occurs when amorphous particles of theophylline make contact with water. From the results given above we conclude that in such a process theophylline hydrate crystallizes when the temperature is below T_{tr}. However, when the temperature at which a solubility experiment is carried out is higher than the transition temperature, it is expected that the actual solubility will depend on the pre-treatment of the drug used.

From the results and discussion given above we conclude that for certain compounds the solubility as a function of temperature can be predicted using Eqn. 2 or Eqn. 8. The advantage of Eqn. 2, over Eqn. 8 is that W can be related to δ (Martin et al., 1980). However, one has to be sure that the crystal form of the compound does not change in the investigated temperature range. Whenever a conversion of a modification of a compound into another modification occurs, one has to determine the relevant thermodynamic parameters of both forms of the compound involved in order to be able to predict a correct solubility. As pointed out above, rather large changes in the solubility of theophylline can occur, which might be important, i.e. in formulation procedures.

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List of symbols

C_s	saturation concentration (g/kg)
$\Delta C_p^0(T)$	heat capacity of vapour minus condensed phase at temperature T(kJ · K^{-1} · mol^{-1})

$\Delta G^0(T)$	Gibbs' energy of vapour minus condensed phase at temperature T(kJ · mol^{-1}) for a standard pressure of 1 Pa
$\Delta H^c(T)$	enthalpy of vapour minus condensed phase of compound c at temperature T(kJ · mol^{-1})
$\Delta H_F = \Delta H^c_m$	melting enthalpy of compound c (kJ · mol^{-1})
ΔH_{tr}	transition enthalpy of the transition of monohydrous theophylline in theophylline and a saturated solution (kJ · mol^{-1})
ΔH_{sub}	sublimation enthalpy of anhydrous theophylline (kJ · mol^{-1})
ΔH^c_{sol}	dissolution enthalpy of compound c (kJ · mol^{-1})
ΔH_{vap}	vaporization enthalpy of theophylline (kJ · mol^{-1})
ΔS_{sol}	dissolution entropy (kJ · K^{-1} · mol^{-1})
M_1	relative molecular mass of the solvent
M_2	relative molecular mass of the drug
P	vapour pressure measured (Pa)
P_0	reference vapour pressure (1 Pa)
R	gas constant (8.314 J · K^{-1} · mol^{-1})
T	temperature (K)
T_m	melting temperature of theophylline (K)
T_{tr}	temperature of the conversion of monohydrous theophylline into theophylline and a saturated solution (K)
Tp	theophylline
Tp · 1aq	monohydrous theophylline
V_2	molar volume of the drug as 'supercooled liquid' at temperature T (cm^3)
X	mole fraction of drug
δ_1, δ_2	solubility parameters of solvent and solute, respectively (J$^{0.5}$ · mol$^{-0.5}$ · cm$^{-1.5}$)
Φ_1	mole fraction of solvent
θ	reference temperature (usual midrange temperature) (K)
(s)	solid
(l)	liquid
(g)	gas
(diss)	dissolved

s = subscripts: 1—refers to the solvent
2—refers to the drug

c = compound: 0—refers to theophylline
1—refers to theophylline hydrate

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