

Two methods for the measurement of the dissociation pressure of a crystalline hydrate

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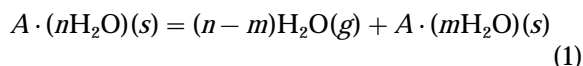
Abstract

Two methods for the measurement of the characteristic dissociation pressures of a system containing water vapor and two different crystalline hydrates of the pharmaceutical compound MK-0677 are described. One method involves the spectroscopic determination of water in gases equilibrated with the solids at controlled temperatures, using an infrared spectrometer. The second method utilizes the extrapolated onset temperature of the transition from one hydrate to the other at controlled humidities, as observed by differential scanning calorimetry. The methods give similar results for the system of interest. © 1997 Elsevier Science B.V.

Keywords: Vapor pressure; Dissociation pressure; Solvates; IR spectroscopy; Differential scanning calorimetry

1. Introduction

The phase rule [1] predicts the conditions under which the control of a certain number of intensive properties of an equilibrium system will result in fixation of all of the other intensive variables of the system. In its usual form the phase rule is expressed as the equation $F = C - P + 2$, where F is the number of degrees of freedom of the system (the number of intensive properties which must be fixed to form an invariant system), C is the number of components engaged in the equilibrium expression, and P is the number of phases present. Application of the phase rule to the dissociation of a hydrated material such as the equilibrium shown in Eq. (1) indicates one degree of freedom:



If a single intensive variable such as the temperature is fixed, all of the other intensive variables such as the dissociation pressure are also fixed. In Eq. (1) the equilibrium constant for the reaction is a function only of the water vapor pressure because solid materials are defined as having unit activity.

Hydrates and other solvates are frequently encountered in the development of pharmaceutical substances [2]. The characteristic dissociation pressures of these materials are important in the optimization of both process conditions for their isolation and storage conditions. The importance of the interactions between pharmaceutical substances and water to the development of a

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product has been reviewed [3]. For these reasons the dissociation pressure of a hydrated form of the drug substance MK-0677 (*N*-[1(*R*)-[(1,2-dihydro-1-methylsulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethoxy)ethyl]-2-amino-2-methylpropanamide methanesulfonic acid salt, Fig. 1) in equilibrium with a lower hydrate ($n = 3.5$, $m = 1$, Eq. (1)) was desired. Two methods were developed for this measurement: a spectroscopic method in which the infrared absorbances of the vapor in equilibrium with the hydrates was related to the dissociation pressure and a calorimetric method in which a known vapor pressure of gaseous water in contact with the solid was related to the temperature at which a thermal event was observed to occur.

Other techniques for evaluating vapor pressures of solvates, liquids, and volatile solids using one-way flow systems have been reported [4–6]. Dunn et al. [7] have reported a method of increasing the separation of endothermic dehydration events in the DSC analysis of hydrated calcium sulfates in cement by increasing the water pressure over the sample. Quantitative uses of vapor phase infrared analysis have been confined primarily to the study of environmental contaminants in stack effluents [8] although analysis of mixtures of halomethanes at a single temperature has been reported [9].

2. Experimental

2.1. Preparation of solids

The higher hydrate (3.5 H₂O) of MK-0677 was obtained by crystallization from a mixture of ethyl acetate, ethanol, and water (25:1.6:2.0, v/v/v) with cooling followed by filtration and removal of excess solvent by passing a stream of humidified nitrogen through the solid. The 3.5 hydrate was fully characterized by X-ray powder diffraction, thermogravimetric analysis, DSC and Karl Fisher titration.

2.2. Infrared vapor pressure measurements

The apparatus illustrated in Fig. 2 was constructed for the spectroscopic method. A Nicolet

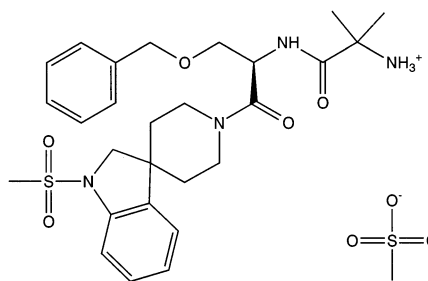


Fig. 1. MK-0677 (anhydrous).

Magna-550 Fourier-transform mid-infrared spectrometer with a TGA Interface gas cell was used. Spectra were collected at a resolution of 0.25 cm⁻¹ with 32 scans of the interferometer and triangular apodization. The optical bench of the spectrometer was purged with a flow of nitrogen which had been passed through a bed of anhydrous CaSO₄ and molecular sieves. The TGA interface consisted of an oven containing a two-pass infrared gas cell of approximately 20 cm path length. Nitrogen gas was pumped at a flow rate of approximately 20 ml min⁻¹ through an equilibration chamber containing either pure water (for construction of the standard curve) or the solid under study; the flow was recirculated. The pump head and equilibration chamber were immersed in

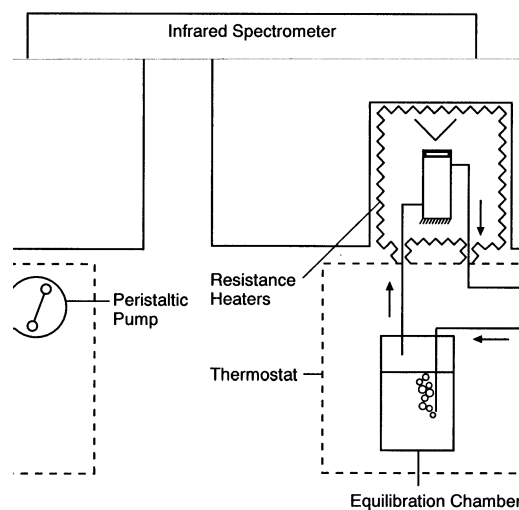


Fig. 2. Apparatus used to measure dissociation pressures using infrared absorbances.

a water–ethylene glycol thermostat. The oven containing the gas cell and the tubes carrying the flow to and from the gas cell were heated to 110°C to avoid condensation of water within the system and to avoid differences in the infrared absorbances produced by different rotational-vibrational populations at different temperatures. The temperature of the thermostat could be changed to obtain vapor pressures at various temperatures. The temperature of the thermostat was measured with a calibrated mercury-in-glass thermometer readable to 0.1°C.

The solid under study was prepared by placing the 3.5 hydrate in the equilibration chamber and removing a portion of the water by passing dry nitrogen through the material. The amount of water evolved was monitored gravimetrically.

Absorbances were obtained for the water line at 1696 cm⁻¹ by using peak height with baseline correction. Approximately 25 min circulation was required for the equilibrium vapor pressure to be achieved in the gas cell after a change in the temperature of the thermostat. Equilibrium was judged to have been reached when the absorbance varied by less than 0.001 in successive spectra collected 5 min apart. The imprecision of the absorbances is estimated to be $\pm 2.5\%$ based on the differences between absorbances collected at the same temperature at the beginning and the end of the experiment, which lasted approximately 5 h. Water vapor–liquid equilibrium data used in the standard curve were obtained from standard tables [10].

3. Differential scanning calorimetry measurements

The sample was weighed into open aluminum cups and placed in the sample chamber of a DuPont Instruments 910 differential scanning calorimeter (DSC). The sample chamber was continuously purged with nitrogen which had been saturated with water vapor by directing the flow through a gas washing bottle containing pure water. The partial pressure of water in the purge gas was controlled by placing the gas washing bottle in a water–ethylene glycol thermostat. The dew point of the equilibrated flow was measured

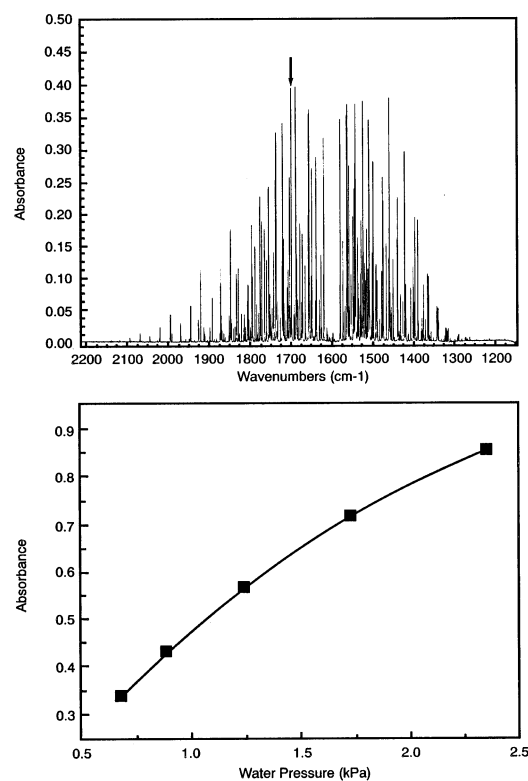


Fig. 3. (Top) Portion of the mid-infrared gas phase spectrum of water. The peak used in the infrared measurements is indicated. (Bottom) Standard curve for water used in the infrared method.

with a calibrated electronic hygrometer before passing into the DSC sample chamber. A sample of the higher hydrate was heated in the DSC at a heating rate of 1°C min⁻¹ under measured humidity conditions until a thermal event associated with evolution of water was observed; the temperature at which the thermal event began was recorded. Likewise samples of monohydrate (obtained during the dehydration experiment) were cooled at 1°C min⁻¹ until rehydration to the higher hydrate was detected. The heating and cooling programs were started at least 10°C below or above the transition temperature, respectively. Dehydration and rehydration transition temperatures were measured at different partial pressures of water in purge gas, which were obtained by changing the equilibration temperature of the thermostat. The DSC temperature-sensing ele-

Table 1

Dissociation vapor pressures of water determined for the transition $(3.5 \text{ H}_2\text{O}) \cdot \text{MK-0677} = 2.5 \text{ H}_2\text{O} + \text{H}_2\text{O} \cdot \text{MK-0677}$ as determined by infrared and DSC measurements

T (°C)	P(H ₂ O) (DSC dehydration) (kPa)	P(H ₂ O) (DSC rehydration) (kPa)	P(H ₂ O) (IR) (kPa)
42.93	2.75	—	—
38.98	2.15	—	—
35.09	1.68	—	—
30.75	1.28	—	—
24.57	0.84	—	—
41.95	—	2.75	—
38.46	—	2.15	—
34.52	—	1.68	—
29.30	—	1.28	—
22.86	—	0.84	—
39.9	—	—	2.12
34.9	—	—	1.58
30.1	—	—	1.16
25.1	—	—	0.86

ment was calibrated using the melting transition of indium.

4. Results and discussion

The two analytical methods developed differ in a fundamental way: in the spectroscopic method the temperature is held fixed and the vapor pressure allowed to assume its equilibrium value. In the DSC method the vapor pressure is fixed, but rather than allowing the temperature to reach an equilibrium value, the temperature is varied until a transition is detected. Thus the DSC method requires the rapid attainment of equilibrium for the accurate measurement of dissociation pressure.

A standard curve was generated with the infrared method using pure water which had been equilibrated at measured temperatures. Fig. 3 shows a portion of the infrared spectrum of water including the peak used in the measurements and the standard curve used. The nonlinear form of the standard curve was similar to that reported for carbon monoxide [8]. A third-order polynomial expression was fitted to the pressure-absorbance data and used to calculate experimental water vapor pressures from the absorbances recorded when the gas within the cell was equilibrated with

a mixture of the 3.5 hydrate and monohydrate, which was prepared by passing dry nitrogen through the equilibration chamber as described. Equilibrium water vapor pressures obtained with the mixture of hydrates are presented in Table 1.

Also presented in Table 1 are the temperature-pressure data obtained with the DSC method both for dehydration and rehydration. The close agreement of the onset temperatures of dehydration and rehydration at each partial pressure of water indicate that the 1°C min^{-1} heating rate is slow enough to obtain reliable results; any significant lag in the attainment of equilibrium would produce a significant difference in the onset temperatures.

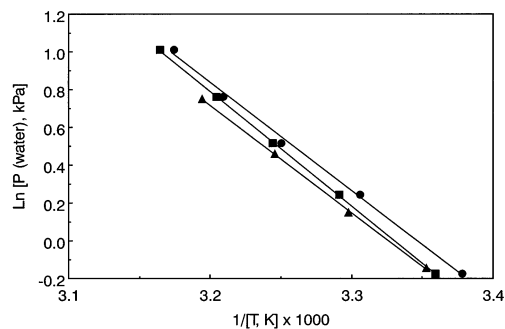


Fig. 4. van't Hoff plot of hydrate dissociation pressures as determined by infrared measurements (\blacktriangle), DSC dehydration measurements (\blacksquare), and DSC rehydration measurements (\circ).

Comparison of the results obtained with the calorimetric and spectroscopic techniques is shown in Fig. 4. Calculation of pressures from the linear least-squares formulae used to generate the solid lines in Fig. 4 shows agreement between the methods within approximately 0.25 kPa over the entire temperature range. Thus the methods provide very similar equilibrium dissociation pressures for the system under study.

In conclusion, two methods have been developed for the measurement of the characteristic dissociation pressures of hydrated materials as a function of temperature: a spectroscopic method and a calorimetric method. The methods give very similar results when applied to the equilibrium between two hydrated forms of MK-0677. The DSC method is expected to be applicable to any similar case in which equilibrium is attained rapidly. The spectroscopic method may be extended to other systems such as solvate equilibria or vapor–liquid equilibria, including systems in which two or more

volatile components are present in the gas phase.

References

- [1] A. Findlay, A.N. Campbell and N.O. Smith, *The Phase Rule and its Applications*, 9th edn, Dover, NY, 1951.
- [2] S. Byrn, R. Pfeiffer, M. Ganey, C. Hoiberg and G. Poochikian, *Pharm. Res.*, 12 (1995) 945–954.
- [3] C. Ahlneck and G. Zografi, *Int. J. Pharm.*, 62 (1990) 87–95.
- [4] G.P. Baxter and J.E. Lansing, *J. Am. Chem. Soc.*, 42 (1920) 419–426.
- [5] G.P. Baxter, F.K. Bezenberger, C.H. Wilson, *J. Am. Chem. Soc.*, 42 (1920) 1386–1393.
- [6] G.P. Baxter and W.C. Cooper, Jr., *J. Am. Chem. Soc.*, 46 (1924) 923–933.
- [7] J. Dunn, K. Oliver, G. Nguyen and I. Sills, *Thermochim. Acta*, 121 (1987) 181–191.
- [8] J. Bak and A. Larsen, *Appl. Spectrosc.*, 49 (1995) 437–443.
- [9] S. Milicev and T. Skapin, *Vibrational Spectrosc.*, 4 (1992) 9–13.
- [10] R.C. Weast and S.M. Selby (Eds.), *Handbook of Chemistry and Physics*, 48th edn, Chemical Rubber, Cleveland, Ohio, 1967, p. D-110.