Solubility of Carbamazepine (Form III) in Different Solvents from (275 to 343) K

Wenju Liu,[†] Leping Dang,[†] Simon Black,[‡] and Hongyuan Wei*[,†]

School of Chemical Engineering and Technology, Tianjin University, Tianjin 300072, People's Republic of China, and Process Research & Development, AstraZeneca, Macclesfield, SK10 2NA, U.K.

Using a laser monitoring technique, the solubilities of carbamazepine (form III) in methanol, ethanol, 1-propanol, 2-propanol, tetrahydrofuran (THF), and 1-butanol were determined by the synthetic method from (275 to 343) K. A laser technique is used to determine the dissolution of particles. Results are correlated by semiempirical equations, which show a good fit to the experimental data.

Introduction

Carbamazepine (CBZ) with the chemical name 5*H*-dibenz-(*b*,*f*)azepine-5-carboxamide (CAS No. 298-46-4, Figure 1) is a white or almost white powdered crystal and a first-generation anticonvulsant drug that has been used to treat partial seizures, trigeminal neuralgia, manic−depressive illness, and explosive aggression for nearly 40 years. Four well-characterized anhydrous polymorphs and a dihydrate as well as other solvates of CBZ have been reported in the literature.[1,2]

Different polymorphs of CBZ can be crystallized from different solvents.[3,4] Among all CBZ published anhydrous polymorphs, form III is the form used in the marketed tablets and the most stable form at room temperature and at temperatures up to 78 °C[3] and could be crystallized from various solvents with high dielectric constants. So, the solubility of CBZ (form III) in pure solvents is of great importance in manufacturing and purifying processes. Up to now, only a few solubilities of CBZ (form III) in ethanol, ethanol with additives, and ethanol−water mixtures have been reported.[5−8]

In this work, the solubilities of CBZ (form III) in methanol, ethanol, 1-propanol, 2-propanol, tetrahydrofuran (THF), and 1-butanol were measured by a synthetic method between (275 and 343) K at atmospheric pressure. A laser monitoring observation technique was used to determine the solubility. This study forms part of a larger project on the use of solubility data to design crystallization processes.

Experimental

Materials. A white crystalline powder of CBZ ($C_{15}H_{12}N_2O$, molecular weight 236.27), form III (measured by X-ray powder diffraction), was obtained from Suzhou Hengyi Pharmaceutical Co. Ltd., China, with a melting point of 193 °C measured with a NETZSCH DSC-204 differential scanning calorimeter. Its purity was more than 99 % (determined by UV referred to the Chinese Pharmacopoeia), and the material was stored in a desiccator and used without treatment. The methanol, ethanol, 1-propanol, 2-propanol, tetrahydrofuran, and 1-butanol (purchased from Tianjin Kewei Chemical Reagent Co., China) used for experiments were of analytical reagent grade. Their purities are better than 99 %.

* Corresponding author. Phone: +86-22-27405754. Fax: +86-22-27400287. E-mail: wenjuliu@tju.edu.cn.
[†] Tianjin University.
[‡] AstraZeneca.

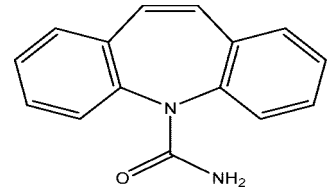

Figure 1. Structure of carbamazepine.

Apparatus and Procedure. Solubility was measured by the synthetic method.[9,10] The measuring principle and setup were similar to that described in the literature.[11] The laser monitoring technique was used to measure solubilities of CBZ (form III) in different solvents at a constant temperature. The laser system consists of a laser generator, a photoelectric transformer, and a digital light-intensity display. Solutions under measurement are in a 100 mL jacketed glass vessel, where a desired value of temperature of the measured solution within stability of ± 0.05 K was maintained by circulating water from a water bath with a digital thermoelectric controller (type CKW-2200, China) with an uncertainty ≤ 0.5 %. Temperatures were measured with a mercury-in-glass thermometer with an uncertainty of ± 0.05 K. Continuous stirring was achieved with a magnetic stir bar. A condenser was connected with the vessel to prevent the solvents from evaporating. Masses of solute and solvents are weighed using an analytical balance (type FA2004, China) with an accuracy of ± 0.1 mg.

First, predetermined known masses of CBZ (form III) and solvents were transferred into the jacketed vessel. Then, the contents of the vessel were stirred until the temperature fluctuation varies within 0.05 K. A known mass of solute was added so that it did not exceed the solubility too much. Then, known amounts of either solute or solvent by mass were added. When the last portion of solids disappeared, the light penetrating the vessel reached its maximum, and the total amounts of solute and solvent were obtained. The saturated mole fraction solubility of solute x_1 can be obtained as follows

$$x_1 = \frac{m_1/M_1}{m_1/M_1 + m_2/M_2} \tag{1}$$

where m and M represent mass and mole mass and subscripts 1 and 2 represent solute CBZ (form III) and solvents, respectively. The same solubility experiment was conducted two more times. The uncertainty of the experimental solubility values was

10.1021/je8002157 CCC: $40.75
Published on Web 08/05/2008

Table 1. Mole Fraction Solubilities of Carbamazepine (Form III), x_1, in Methanol, Ethanol, 1-Propanol, 2-Propanol, 1-Butanol, and Tetrahydrofuran

T/K	$10^4 x_1^{\text{exptl}}$	$10^5(x_1^{\text{exptl}} - x_1^{\text{calcd}})$	T/K	$10^4 x_1^{\text{exptl}}$	$10^5(x_1^{\text{exptl}} - x_1^{\text{calcd}})$
		Methanol			
276.80	64.00	−29.15	311.40	185.8	−41.42
285.05	87.90	19.53	320.70	252.9	24.74
290.30	103.0	22.49	326.80	299.0	−8.542
301.50	141.4	1.862			
		Ethanol			
278.80	30.90	−69.23	305.70	71.90	63.10
283.35	38.20	−13.88	312.70	82.60	−6.708
287.70	42.00	−2.130	319.00	98.70	−74.32
292.20	48.00	20.66	329.75	164.7	−44.31
295.80	53.90	41.15	338.16	257.8	34.06
301.10	64.90	77.43			
		1-Propanol			
279.90	26.00	20.98	316.00	108.7	−19.13
292.00	43.50	42.90	329.30	190.7	−102.1
301.80	62.40	29.66	339.00	315.6	30.30
		2-Propanol			
285.10	18.30	−11.19	311.55	60.90	16.96
290.50	26.50	19.54	319.36	81.00	−1.416
298.00	36.00	21.99	329.33	114.0	−64.81
303.60	42.50	−2.493	337.54	169.2	37.72
		1-Butanol			
285.15	−42.44	−27.45	317.60	117.6	16.62
291.55	−25.38	−10.46	323.90	149.4	39.16
297.85	−20.99	−6.609	328.80	182.6	93.12
305.94	−41.65	−28.79	343.64	286.1	−52.18
311.45	90.80	−17.06			
		Tetrahydrofuran			
278.35	106.6	−13.60	303.75	176.3	−7.345
286.64	125.3	−13.63	311.45	206.3	1.538
289.55	135.0	9.930	326.43	268.9	−87.89
295.55	152.6	19.29	330.46	306.3	56.08

about 0.5 %. The uncertainty in the solubility values result from the uncertainties in the temperature measurements, weighing procedure, and temperature of the water bath (with uncertainty ± 0.1 K).

Results and Discussion

The results of carbamazepine (form III) solubility in different solvents are listed in Table 1. Figure 2 gives the plot of the solubility of carbamazepine (form III) in these solvents at a temperature range of about (275 to 343) K. The temperature-dependent solubility can be correlated by a semiempirical equation[12]

$$\ln x_1 = A + \frac{B}{T/\text{K}} + C \ln T/\text{K} \tag{2}$$

where T is absolute temperature and A, B, and C are all empirical constants. Correlated values of A, B, and C of different solvents are listed in Table 2 together with the relative root-mean square deviation (σ), which is defined as the following

$$\sigma = \left[\frac{1}{N}\sum_{i=1}^{N}\left(\frac{x_{1,i}^{\text{exptl}} - x_{1,i}^{\text{calcd}}}{x_{1,i}^{\text{exptl}}}\right)^2\right]^{1/2} \tag{3}$$

where N is the number of experimental points; $x_{1,i}^{\text{calcd}}$ is the solubility calculated from eq 2; and $x_{1,i}^{\text{exptl}}$ is the experimental value of solubility.

From Table 2, it can be seen that the parameter C in eq 2 has a positive value. This corresponds to lower heat capacities of the carbamazepine in solution in these solvents than in the solid phase. Figure 2 shows that the calculated values are in good agreement with the experimental ones. In Figure 3, the solubilities of carbamazepine in ethanol in this work and in the

Table 2. Parameters of Equation 2 for Carbamazepine (Form III) in Different Solvents

solvent	A	B	C	$10^2\sigma$
methanol	−104.95	2201.0	16.359	2.28
ethanol	−582.86	23760	87.392	8.93
1-propanol	−234.61	6986.9	36.137	6.02
2- propanol	−96.424	846.14	15.428	4.67
1-butanol	−106.71	1690.2	16.826	6.02
tetrahydrofuran	−86.789	2193.7	13.214	1.55

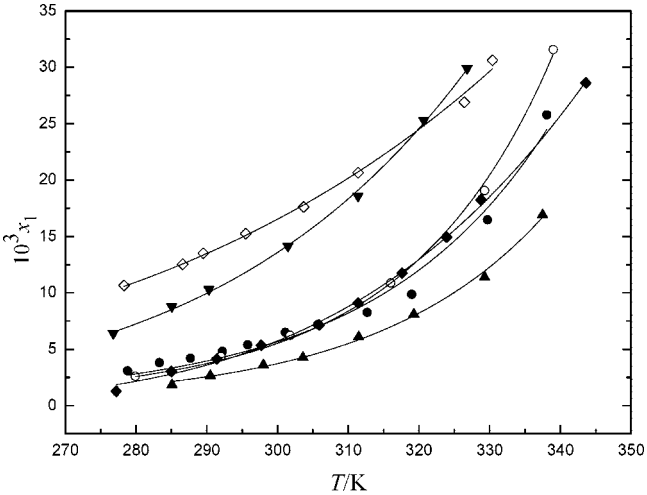

Figure 2. Mole fraction solubility of carbamazepine, x_1, in different solvents: ▼, methanol; ●, ethanol; ○, 1-propanol; ▲, 2-propanol; ◆, 1-butanol; ◇, THF. Curves are data fits using eq 2 and the parameters in Table 2.

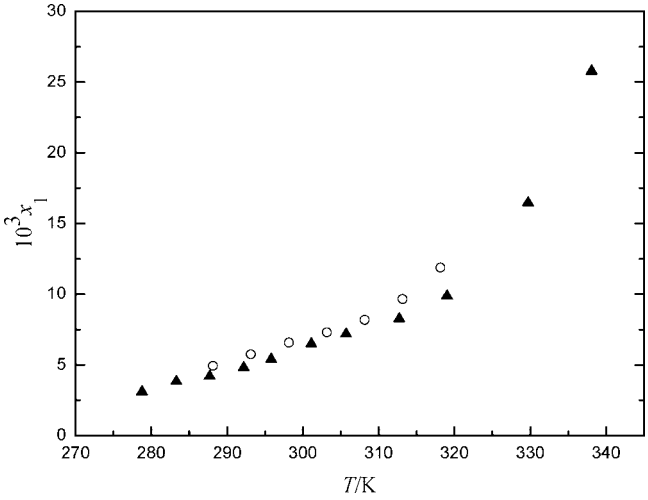

Figure 3. Mole fraction solubility of carbamazepine, x_1, in ethanol: ▲, the experimental data; ○, the data in the literature.[6]

literature[6] are compared. The data in this work are a little lower than that in the literature. In general, the data in this work were in reasonable agreement with the data in the literature especially in the range of (287 to 305) K.

Effect of Polymorphism and Solvates on the Data. One possible source of systematic error in experiments of this type is conversion of the solid to a different polymorph or a solvate during the experiment. As the temperature was always below 78 °C, conversion of form III to another true polymorph is not possible. A polymorph screen of carbamazepine[3] discovered solvates in several solvents but not in methanol, ethanol, or tetrahydrofuran. Other alcohols were not investigated. The good fit and absence of any inflection points in the solubility data suggest that no transformations to solvates occurred during this study. The crystals obtained from methanol, ethanol, 1-propanol, 2-propanol, and 1-butanol were CBZ polymorph III (confirmed by XRD) with a blocklike shape, which indicated that no solvates were formed. For tetrahydrofuran, abundant CBZ was added at 50 °C under constant stirring for 2 h. The shape of the undissolved CBZ was still blocklike, which showed that no solvates were formed.

Conclusion

The solubilities of carbamazepine (form III) in methanol, ethanol, 1-propanol, 2-propanol, tetrahydrofuran (THF), and 1-butanol were determined using laser monitoring techniques. The results show that solubility in the six selected solvents increases as temperature rises, but the increment with temperature varies according to different solvents. Also, it can be seen that carbamazepine dissolved much more in methanol and tetrahydrofuran than in the other four solvents. According to the values of the relative root mean square deviation (σ), it can be seen that the solubilities of carbamazepine in the solvents under consideration can be fitted with eq 2 very well (with the range from 1.55 % to 8.93 %), indicating that the correlated equation in this work could provide essential data for manufacturing and purifying processes of carbamazepine in industry.

Literature Cited

(1) Lang, M.; Kampf, J. W.; Matzger, A J. Form IV of Carbamazepine. *J. Pharm. Sci.* **2002**, *91*, 1186–1190.
(2) Grzesiak, A. L.; Lang, M. D.; Kim, K.; Matzger, A. J. Comparison of the Four Anhydrous Polymorphs of Carbamazepine and the Crystal Structure of Form I. *J. Pharm. Sci.* **2003**, *92*, 2260–2271.
(3) Getsoain, A.; Lodaya, R. M.; Blackburn, A. C. One-solvent Polymorph Screen of Carbamazepine. *Int. J. Pharm.* **2008**, *348*, 3–9.
(4) Hilfiker, R.; De Paul, S. M.; Szelagiewicz, M. Approaches to Polymorph Screening. *Polymorphism*; Wiley-VCH Verlag: Weinheim, 2006.
(5) Bettini, R.; Bonassi, L.; Castoro, V.; et al. Solubility and conversion of carbamazepine polymorphs in supercritical carbon dioxide. *Eur. J. Pharm. Sci.* **2001**, *13*, 281–286.
(6) Qu, H.; Marjatta, L. K.; Kallas, J. Solubility and stability of anhydrate/hydrate in solvent mixtures. *Int. J. Pharm.* **2006**, *321*, 101–107.
(7) Qu, H.; Louhi-Kultanen, M.; Kallas, J. Additive Effects on the Solvent-Mediated Anhydrate/Hydrate Phase Transformation in a Mixed Solvent. *Cryst. Growth Des.* **2007**, *7*, 724–729.
(8) Murphy, D.; Rodríguez-Cintroń, F.; Langevin, B.; Kelly, R. C.; Rodrígúez-Hornedo, N. Solution-mediated phase transformation of anhydrous to dihydrate carbamazepine and the effect of lattice disorder. *Int. J. Pharm.* **2002**, *246*, 121–134.
(9) Nyvlt, J. *Solid−Liquid Equilibria*; Czechoslovak Academia of Sciences: Praha, Czechoslovakia, 1997.
(10) Jiang, Q.; Gao, G.-H.; Yu, Y.-X.; Qin, Y. Solubility of Sodium Dimethyl Isophthalate-5-sulfonate in Water and in Water + Methanol Containing Sodium Sulfate. *J. Chem. Eng. Data* **2000**, *45*, 292–294.
(11) Zhang, C.; Wang, J.; Wang, Y. Solubility of Ceftriaxone Disodium in Acetone, Methanol, Ethanol, N,N-Dimethylformamide and Formamide between 278 and 318 K. *J. Chem. Eng. Data* **2005**, *50*, 1757–1760.
(12) Mullin, J. W. *Crystallization*, 3rd ed.; Butterworth-Heinemann: Oxford, 2000.

Received for review March 27, 2008. Accepted June 20, 2008. The authors are grateful to AstraZeneca UK Limited and National Nature and Science Foundation of China (NSFC) for their financial assistance in this project.

JE8002157