Solubility of Valdecoxib in the Presence of Poly(ethylene glycol) 4000, Poly(ethylene glycol) 6000, Poly(ethylene glycol) 8000, and Poly(ethylene glycol) 10 000 at (298.15, 303.15, and 308.15) K

Chenguang Liu, Kashappa Goud H. Desai,* and Chengsheng Liu

Life Science College, Ocean University of China, 5 Yushan Road, Qingdao 266003, China

The present study investigated the solubilization of valdecoxib in aqueous solution using poly(ethylene glycol) 4000, poly(ethylene glycol) 6000, poly(ethylene glycol) 8000, and poly(ethylene glycol) 10 000 at (298.15, 303.15, and 308.15) K. The analysis of valdecoxib is carried out by UV spectral measurements at $\lambda_{max} = 202$ nm. The aqueous solubility of valdecoxib could be enhanced by the addition of an increasing mass fraction of all of the poly(ethylene glycols) tested as well as by increasing the temperature of the dissolution media. The molecular weight of the poly(ethylene glycols) tested played an important role in valdecoxib solubilization in the aqueous medium. Among the poly(ethylene glycols) studied, poly(ethylene glycol) 4000 exhibited a higher solubilization potential than the others. Calculated Gibbs free energy values were all negative for all of the poly(ethylene glycol) + water mixtures at (298.15, 303.15, and 308.15) K, indicating the spontaneous nature of valdecoxib solubilization. In the case of poly(ethylene glycol) 4000 + water mixtures, the $\Delta_{tr}G°$ values decreased to a greater extent than those for the other carriers {poly(ethylene glycol) 6000, poly(ethylene glycol) 8000, and poly(ethylene glycol) 10 000) + water mixtures}, indicating that the reaction conditions were more favorable in poly(ethylene glycol) 4000 + water mixtures than in other carrier + water mixtures.

Introduction

Valdecoxib is a novel selective cyclo-oxygenase-2 inhibitor administered orally as an analgesic and anti-inflammatory drug. The chemical structure of valdecoxib is shown in Figure 1. It is chemically designated as 4-(5-methyl-3-phenyl-4-isoxazolyl) benzenesulfonamide and is a diaryl-substituted isoxazole. It is a white crystalline powder, relatively insoluble in water. The solubility of valdecoxib in water is 10 μg/mL ($T = 298.15$ K).[1−5] The pKa is around 10. Often such drugs show poor absorption and limited bioavailability. Hence, the poor aqueous solubility and/or dissolution rate of valdecoxib has presented a challenge to the development of a suitable formulation for oral administration.[1,3,5]

The improvement of pharmaceutical and biological availability of hydrophobic drugs is still a major technological problem, and several approaches have been attempted to overcome this drawback.[6] Among the strategies investigated for enhancing the solubility and/or dissolution properties of poorly water-soluble drugs, the solid dispersion technique in hydrophilic carriers has often been successfully applied.[7] The dispersion of poorly water-soluble drugs in an inert hydrophilic polymeric matrix in the solid state provided by the fusion, solvent, or solvent-fusion method leads to products referred to as oral solid dispersions.[7−9] The principal factors used to explain the improved solubility and/or dissolution rates of solid-dispersed drugs include the particle size decrease, reduction of aggregation and/or agglomeration phenomena, solubilizing effect of the carrier, improved wettability, and loss of crystallinity.[7] Among the vast number of hydrophilic carriers used to prepare solid-dispersed drugs, poly(ethylene glycols) with molecular weight ranging from 4000 to 10 000 are widely used in pharmaceutical industries because these offers numerous advantages over other carriers.[7,9,10−11] However, the selection of an effective hydrophilic carrier for preparing the oral solid-dispersed drug is mainly based on its ability to solubilize the hydrophobic drug in the aqueous medium.

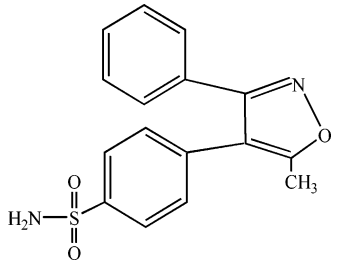

Figure 1. Structure of valdecoxib.

The solubility study of valdecoxib in the presence of poly(ethylene glycols) has not been studied. Therefore, the present study reports the solubility data of valdecoxib in the presence of the most widely used hydrophilic carriers (i.e., poly(ethylene glycol) 4000, poly(ethylene glycol) 6000, poly(ethylene glycol) 8000, and poly(ethylene glycol) 10 000) at (298.15, 303.15, and 308.15) K. Such a solubility database at different temperatures is useful in pharmaceutical industries while preparing the solid dispersion-based oral dosage forms containing valdecoxib. In addition, because these poly(ethylene glycols) are also used as solubilizing agents in liquid oral formulations, this database will also help us to select an appropriate poly(ethylene glycol)−water mixture and the temperature of the aqueous media while preparing the liquid oral formulations containing valdecoxib. An analysis of valdecoxib was done with UV spectrophotometry.

* Corresponding author. E-mail: kghdesai@yahoo.com.

10.1021/je049667h CCC: $30.25
Published on Web 12/08/2004

Table 1. Mass Fraction Solubility of Valdecoxib (*S*) in Polyethylene Glycol[a] (1) + Water (2) Mixtures at 298.15 K

	($S/\mu g \cdot mL^{-1}$)[b]			
	carrier			
$100w_1$	poly(ethylene glycol) 4000	poly(ethylene glycol) 6000	poly(ethylene glycol) 8000	poly(ethylene glycol) 10 000
0	10.25 ± 0.6	10.25 ± 0.6	10.25 ± 0.6	10.25 ± 0.6
1	23.0 ± 0.3	20.1 ± 0.4	17.3 ± 0.8	15.4 ± 0.4
2	27.6 ± 0.7	25.2 ± 0.6	21.4 ± 0.5	19.1 ± 0.5
5	31.0 ± 1.1	28.5 ± 0.3	25.6 ± 1.0	22.4 ± 0.6
10	38.4 ± 1.2	35.8 ± 1.3	31.1 ± 1.9	27.3 ± 1.7

[a] Poly(ethylene glycol) 4000, poly(ethylene glycol) 6000, poly(ethylene glycol) 8000, and poly(ethylene glycol) 10 000. [b] Mean ± SE, $n = 6$.

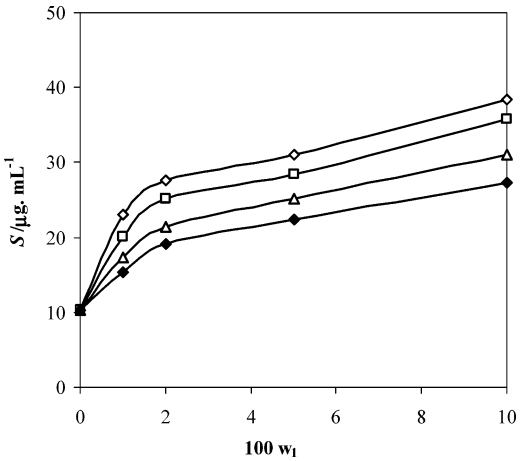

Figure 2. Mass fraction solubility *S* of valdecoxib in poly(ethylene glycol) (1) + water (2) mixtures at 298.15 K: ◇, poly(ethylene glycol) 4000; □, poly(ethylene glycol) 6000; Δ, poly(ethylene glycol) 8000; ◆, poly(ethylene glycol) 10 000.

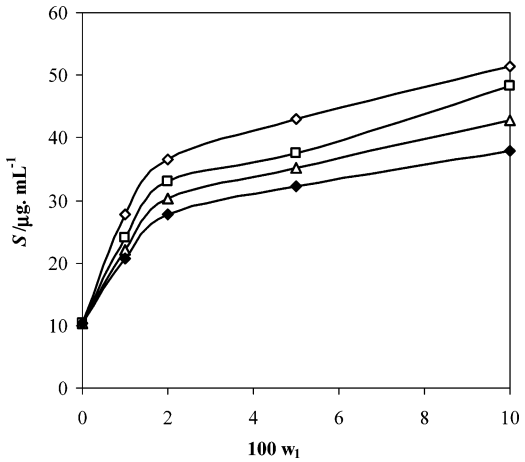

Figure 3. Mass fraction solubility *S* of valdecoxib in poly(ethylene glycol) (1) + water (2) mixtures at 303.15 K: ◇, poly(ethylene glycol) 4000; □, poly(ethylene glycol) 6000; Δ, poly(ethylene glycol) 8000; ◆, poly(ethylene glycol) 10 000.

Experimental Section

Materials. Valdecoxib (99.6% purity) was obtained as a gift sample from Cipla Ltd., Mumbai, India. Poly(ethylene glycol) 4000, poly(ethylene glycol) 6000, poly(ethylene glycol) 8000, and poly(ethylene glycol) 10 000 were purchased from Showa Chemicals Co., Tokyo, Japan. Ultrapure water (Millipore) was used throughout.

Methods. Solubility Experiments. Binary mixtures of poly(ethylene glycols) (i.e., poly(ethylene glycol) 4000, poly(ethylene glycol) 6000, poly(ethylene glycol) 8000, and poly(ethylene glycol) 10 000) + water were prepared in 50-mL glass tubes. The mass of these poly(ethylene glycols) taken in the 50-mL glass tube was calculated by subtracting the empty mass of the tube from the total mass of the glass tube with these poly(ethylene glycols). All of the mass measurements were taken on an electronic balance (Explorer, Ohaus, Switzerland) within an accuracy of 0.01 mg.

The solubility of valdecoxib was determined in five mass-fraction compositions of the above-mentioned binary mixtures of poly(ethylene glycols) (0, 1, 2, 5, and 10)% + water. The solubility of valdecoxib in the binary mixtures of poly(ethylene glycols) + water at (298.15, 303.15, and 308.15) K was determined by adding an excess amount of valdecoxib to the closed-cap tubes containing various binary mixtures. Poly(ethylene glycols) (i.e., poly(ethylene glycol) 4000, poly(ethylene glycol) 6000, poly(ethylene glycol) 8000, and poly(ethylene glycol) 10 000) + water mixtures were shaken for 72 h using an automatic shaking water bath (Jeio Tech, South Korea) at each temperature. The temperature was maintained at (298.15, 303.15, and 308.15) K within ±0.1 K at the desired temperature on a digital display. After 72 h, 5 mL of each binary mixture was

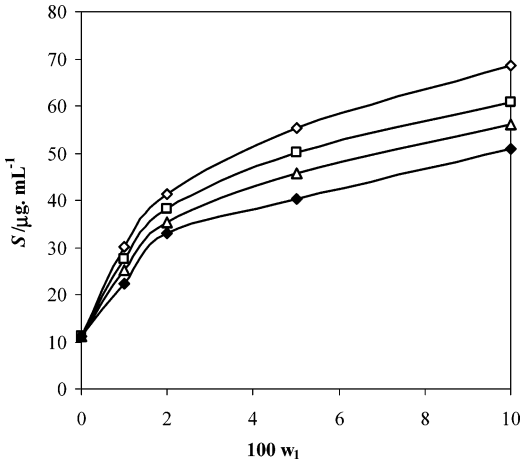

Figure 4. Mass fraction solubility *S* of valdecoxib in poly(ethylene glycol) (1) + water (2) mixtures at 308.15 K: ◇, poly(ethylene glycol) 4000; □, poly(ethylene glycol) 6000; Δ, poly(ethylene glycol) 8000; ◆, poly(ethylene glycol) 10 000.

removed, passed through a 0.22-μm membrane filter (Millipore), suitably diluted with a corresponding mass fraction composition of poly(ethylene glycol) (0, 1, 2, 5, and 10) % + water mixtures, and then the valdecoxib content was determined by measuring the absorbance at 202 nm. The detection of valdecoxib was done with UV spectrophotometry (Shimadzu 16001, Japan). The λ_{max} of valdecoxib did not vary much in all of the poly(ethylene glycol) + water mixtures, and hence, we have used $\lambda_{max} = 202$ nm for all of the binary mixtures to estimate the valdecoxib content. The solubility experiments were repeated six times ($n = 6$) in an identical manner. The variation in the solubility

Table 2. Mass Fraction Solubility of Valdecoxib (*S*) in Poly(ethylene glycol)[a] (1) + Water (2) Mixtures at 303.15 K

	$(S/\mu g \cdot mL^{-1})^b$			
	carrier			
$100w_1$	poly(ethylene glycol) 4000	poly(ethylene glycol) 6000	poly(ethylene glycol) 8000	poly(ethylene glycol) 10 000
0	10.43 ± 0.2	10.43 ± 0.2	10.43 ± 0.2	10.43 ± 0.2
1	27.7 ± 0.4	24.1 ± 0.7	22.1 ± 0.8	20.7 ± 0.6
2	36.5 ± 1.0	33.1 ± 0.6	30.2 ± 0.6	27.8 ± 0.4
5	43.1 ± 0.7	37.6 ± 0.8	35.2 ± 1.1	32.3 ± 0.7
10	51.4 ± 2.3	48.3 ± 0.5	42.8 ± 0.4	37.9 ± 1.2

[a] Poly(ethylene glycol) 4000, poly(ethylene glycol) 6000, poly(ethylene glycol) 8000, and poly(ethylene glycol) 10 000. [b] Mean ± SE, $n = 6$.

Table 3. Mass Fraction Solubility of Valdecoxib (*S*) in Poly(ethylene glycol)[a] (1) + Water (2) Mixtures at 308.15 K

	$(S/\mu g \cdot mL^{-1})^b$			
	carrier			
$100w_1$	poly(ethylene glycol) 4000	poly(ethylene glycol) 6000	poly(ethylene glycol) 8000	poly(ethylene glycol) 10 000
0	11.0 ± 0.4	11.0 ± 0.4	11.0 ± 0.4	11.0 ± 0.4
1	30.1 ± 0.3	27.6 ± 0.2	25.1 ± 0.4	22.4 ± 0.2
2	41.2 ± 0.5	38.2 ± 0.4	35.3 ± 0.7	33.1 ± 0.6
5	55.2 ± 0.8	50.2 ± 1.6	45.6 ± 1.1	40.3 ± 1.1
10	68.6 ± 0.9	60.9 ± 1.5	56.1 ± 1.2	50.8 ± 1.3

[a] Poly(ethylene glycol) 4000, poly(ethylene glycol) 6000, poly(ethylene glycol) 8000, and poly(ethylene glycol) 10 000. [b] Mean ± SE, $n = 6$.

Table 4. Thermodynamic Parameters of the Solubility Process of Valdecoxib in Poly(ethylene glycol)[a] (1) + Water (2) Mixtures at 298.15 K

	$(\Delta_{tr}G^o/kJ \cdot mol^{-1})^b$			
	carrier			
$100w_1$	poly(ethylene glycol) 4000	poly(ethylene glycol) 6000	poly(ethylene glycol) 8000	poly(ethylene glycol) 10 000
1	−21.5 ± 0.5	−17.2 ± 0.6	−11.5 ± 0.4	−8.6 ± 0.2
2	−26.0 ± 0.8	−22.9 ± 0.5	−16.9 ± 0.7	−14.0 ± 0.5
5	−28.9 ± 1.1	−25.9 ± 1.4	−21.4 ± 0.9	−18.0 ± 1.1
10	−34.3 ± 1.3	−31.7 ± 1.2	−26.2 ± 1.3	−22.9 ± 1.6

[a] Poly(ethylene glycol) 4000, poly(ethylene glycol) 6000, poly(ethylene glycol) 8000, and poly(ethylene glycol) 10 000). [b] Mean ± SE, $n = 6$.

Table 5. Thermodynamic Parameters of the Solubility Process of Valdecoxib in Poly(ethylene glycol)[a] (1) + Water (2) Mixtures at 303.15 K

	$(\Delta_{tr}G^o/kJ \cdot mol^{-1})^b$			
	carrier			
$100w_1$	poly(ethylene glycol) 4000	poly(ethylene glycol) 6000	poly(ethylene glycol) 8000	poly(ethylene glycol) 10 000
1	−29.6 ± 0.4	−25.4 ± 0.2	−21.9 ± 0.3	−19.9 ± 0.3
2	−37.8 ± 0.6	−34.9 ± 0.4	−31.3 ± 0.7	−28.8 ± 0.6
5	−42.8 ± 1.5	−38.7 ± 0.8	−35.9 ± 1.4	−33.3 ± 1.0
10	−48.1 ± 1.4	−46.3 ± 1.3	−41.8 ± 1.5	−38.1 ± 1.1

[a] Poly(ethylene glycol) 4000, poly(ethylene glycol) 6000, poly(ethylene glycol) 8000, and poly(ethylene glycol) 10 000. [b] Mean ± SE, $n = 6$.

values of valdecoxib at all temperatures ranged from 0.2 to 2.3 μg/mL. The temperature was maintained at (298.15, 303.15, and 308.15) K within ±0.1 K.

Results and Discussion

Poly(ethylene glycols) are polymers of ethylene oxide, with a molecular weight usually falling in the range of (200 to 300 000). For the manufacture of oral solid dispersions, poly(ethylene glycols) of molecular weight (4000 to 10 000) are frequently used because in this molecular weight range the water solubility is still very high but hygroscopy is not a problem. If a poly(ethylene glycol) with too low a molecular weight is used, then this can lead to a product with a sticky consistency that is difficult to formulate into a pharmaceutically acceptable product. Additional attractive features of these poly(ethylene glycols) include their ability to solubilize some hydrophobic compounds and also to improve compound wettability.[7]

The experimental solubility data of valdecoxib in poly(ethylene glycols) (i.e., poly(ethylene glycol) 4000, poly(ethylene glycol) 6000, poly(ethylene glycol) 8000, and poly(ethylene glycol) 10 000) + water mixtures at (298.15, 303.15, and 308.15) K are presented in Tables 1, 2, and 3, respectively. The phase solubility behavior of valdecoxib in the presence of increasing mass fractions (1, 2, 5, and 10)% of poly(ethylene glycol) 4000, poly(ethylene glycol)

Table 6. Thermodynamic Parameters of the Solubility Process of Valdecoxib in Poly(ethylene glycol)[a] (1) + Water (2) Mixtures at 308.15 K

	$(\Delta_{tr}G^o/\ kJ\cdot mol^{-1})^b$			
	carrier			
$100w_1$	poly(ethylene glycol) 4000	poly(ethylene glycol) 6000	poly(ethylene glycol) 8000	poly(ethylene glycol) 10 000
1	−36.8 ± 0.2	−33.1 ± 0.4	−26.0 ± 0.3	−22.1 ± 0.4
2	−47.8 ± 0.5	−44.5 ± 0.9	−38.0 ± 0.6	−35.8 ± 0.8
5	−58.0 ± 1.2	−54.1 ± 0.7	−46.9 ± 1.1	−42.7 ± 1.6
10	−65.6 ± 1.3	−60.8 ± 1.2	−54.2 ± 1.0	−50.8 ± 1.4

[a] Poly(ethylene glycol) 4000, poly(ethylene glycol) 6000, poly(ethylene glycol) 8000, and poly(ethylene glycol) 10 000. [b] Mean ± SE, $n = 6$.

6000, poly(ethylene glycol) 8000, and poly(ethylene glycol) 10 000 in water at (298.15, 303.15, and 308.15) K is presented in Figures 2, 3, and 4, respectively. The solubility of valdecoxib in water is very low (i.e., 10.25 μg/mL (T = 298.15 K)) because the valdecoxib, predominantly a nonpolar molecule, cannot effectively break into the lattice structure of the water; hence water solubility is low. From Figures 2, 3, and 4, it is very clear that the aqueous solubility of valdecoxib could be enhanced by the addition of an increasing mass fraction of all of the poly(ethylene glycols) studied. As the temperature of the dissolution media increased from (298.15 to 308.15) K, the solubility of valdecoxib could be further enhanced by several orders of magnitude.

Poly(ethylene glycols) increase the aqueous solubility of a poorly water soluble drug mainly by improving the wettability of the hydrophobic surface of the drug.[7] As mentioned earlier, poly(ethylene glycols) vary in their molecular weight in the range of (200 to 300 000). As the molecular weight increases, so does the viscosity of the poly(ethylene glycol). In the present study, poly(ethylene glycols) with molecular weights of (4000 to 10 000) are studied because these are widely used as carriers while developing the solid or liquid oral formulations. The results of the present study indicated that the solubility of valdecoxib decreases with an increase in the molecular weight of the poly(ethylene glycols) studied. For instance, poly(ethylene glycol) 4000 exhibited a higher solubilization potential at all temperatures when compared to poly(ethylene glycol) 6000, poly(ethylene glycol) 8000, and poly(ethylene glycol) 10 000. As the molecular weight of these poly(ethylene glycols) increases, the viscosity of the aqueous medium also increases, which might have retarded the dissolution of drug particles into the aqueous medium.

To understand the reaction conditions in all the poly(ethylene glycols) (i.e., poly(ethylene glycol) 4000, poly(ethylene glycol) 6000, poly(ethylene glycol) 8000, and poly(ethylene glycol) 10 000) + water mixtures, the obtained solubility data of valdecoxib at (298.15, 303.15, 308.15) K was fit to the following equation:

$$\Delta_{tr}G^\circ = -2.303RT \log \frac{S_o}{S_s}$$

An indication of the process of transfer of valdecoxib from pure water to poly(ethylene glycol) + water mixtures at (298.15, 303.15, and 308.15) K was obtained from the values of the Gibbs free energy change, where S_o/S_s is the ratio of the molar solubility of valdecoxib in poly(ethylene glycol) + water mixtures to that in pure water. The obtained values of the Gibbs free energy of poly(ethylene glycols) (i.e., poly(ethylene glycol) 4000, poly(ethylene glycol) 6000, poly(ethylene glycol) 8000, and poly(ethylene glycol) 10 000) + water mixtures at (298.15, 303.15, 308.15) K are given in Tables 4, 5, and 6, respectively. The data provide information regarding the increased solubility of valdecoxib in the presence of poly(ethylene glycols) in water. Gibbs free energy values were all negative for all poly(ethylene glycol) (i.e., poly(ethylene glycol) 4000, poly(ethylene glycol) 6000, poly(ethylene glycol) 8000, and poly(ethylene glycol) 10 000) + water mixtures tested, indicating the spontaneous nature of valdecoxib solubilization, and they decreased with an increase in their mass fraction. The $\Delta_{tr}G^\circ$ values for all of the poly(ethylene glycol) + water mixtures tested further decreased when the temperature of the dissolution media increased from (298.15 to 308.15) K. However, $\Delta_{tr}G^\circ$ decreases to a greater extent in the case of poly(ethylene glycol) 4000 + water mixtures when compared to poly(ethylene glycol) 6000 + water, poly(ethylene glycol) 8000 + water, and poly(ethylene glycol) 10 000 + water mixtures. The results of the solubility studies indicated that poly(ethylene glycol) 4000 is an effective and appropriate carrier for preparing valdecoxib−poly(ethylene glycol) 4000 oral solid dispersions as well as for drug solubilization in liquid oral formulations.

Conclusions

It has been shown that the solubility of valdecoxib in water can be enhanced by the addition of various mass fraction of poly(ethylene glycol) 4000, poly(ethylene glycol) 6000, poly(ethylene glycol) 8000, and poly(ethylene glycol) 10 000 as well as by increasing the temperature of the dissolution media. The enhanced solubility could be due to improved wetting of the hydrophobic surface of valdecoxib in water. The values of the Gibbs free energy indicated that reaction conditions were more favorable in poly(ethylene glycol) 4000 + water mixtures than in the other poly(ethylene glycol) + water mixtures tested. On the basis of the results of the present study, it can be emphasized that poly(ethylene glycol) 4000 is an effective solubilizing carrier for preparing oral solid dispersions and liquid formulations containing valdecoxib.

Literature Cited

(1) Needleman, P.; Isakson, P. C. The Discovery and Function of Cox-2. *J. Rheumatol.* **1997**, *24*, 2−7.

(2) Barden, J.; Edwards, J. E.; McQuay, H. J.; Moore, R. A. Oral valdecoxib and Injected Paracoxib for Acute Postoperative Pain: A Quantitative Systematic Review. *BMC Anesthesiol.* **2003**, *3*, 1−8.

(3) Ormrod, D.; Wellington, K.; Wagstaff, A. J. *Valdecoxib Drugs* **2002**, *62*, 2059−2071.

(4) Dannhardt, G.; Kiefer, W. Cyclooxygenase Inhibitors-Current Status and Future Prospects. *Eur. J. Med. Chem.* **2001**, *36*, 109−126.

(5) Liu, C.; Desai, K. G. H.; Liu, C. Solubility of Valdecoxib in the Presence of Ethanol and Sodium Lauryl Sulfate at (298.15, 303.15, and 308.15) K. *J. Chem. Eng. Data* **2004**, *49*, 1847−1850.

(6) Desai, K. G. H.; Kulkarni, A. R.; Aminabhavi, T. M. Solubility of Rofecoxib in the Presence of Methanol, Ethanol, and Sodium

Lauryl Sulfate at (298.15, 303.15, and 308.15) K. *J. Chem. Eng. Data* **2003**, *48*, 942−945.
(7) Leuner, C.; Dressman, J. Improving Drug Solubility for Oral Delivery Using Solid Dispersions. *Eur. J. Pharm. Biopharm.* **2000**, *50*, 47−60.
(8) Hoerter, D.; Dressman, J. B. Influence of Physiochemical Properties on Dissolution of Drugs in the Gastrointestinal Tract (review). *Adv. Drug. Delivery Rev.* **1997**, *25*, 3−14.
(9) Strickley, R. G. Solubilizing Excipients in Oral and Injectable Formulations. *Pharm. Res.* **2004**, *21*, 201−230.
(10) Mani, N.; Jun, H. W.; Beach, J. W.; Nerukar, J. Solubility of Guaifenesin in the Presence of Common Pharmaceutical Additives. *Pharm. Dev. Technol.* **2003**, *8*, 385−396.
(11) Tang, L.; Khan, S. U.; Muhammad, N. A. Evaluation and Selection of Bio-Relevant Dissolution Media for a Poorly water-Soluble New Chemical Entity. *Pharm. Dev. Technol.* **2001**, *6*, 531−540.

Received for review September 17, 2004. Accepted October 13, 2004.

JE049667H