Solubility of Rofecoxib in the Presence of Methanol, Ethanol, and Sodium Lauryl Sulfate at (298.15, 303.15, and 308.15) K†

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The poorly water-soluble anti-inflammatory rofecoxib is studied for solubility enhancement with the help of cosolvents such as methanol and ethanol as well as an anionic surfactant sodium lauryl sulfate (SLS) in water. The analysis of the drug is carried out by UV spectral measurements at λ_{max} of 285 nm. The effect of mass fraction of cosolvents and surfactant on the solubility of the drug is studied at (298.15, 303.15, and 308.15) K. Increased solubility of rofecoxib was observed by increasing the mass fraction of methanol and SLS in water at all the temperatures. In the case of the water + ethanol mixture, the solubility of rofecoxib was somewhat unusual; that is, solubility increased with increasing mass fraction of ethanol up to 80%, but solubility decreased in pure ethanol at all the temperatures. Experimental solubility data of rofecoxib were correlated with those calculated by a log−linear equation.

Introduction

The solubility of solid drugs in water is an important molecular/physical property that influences the pharmacokinetics such as release, transport, extent of absorption of drug in the body, and other pharmacodynamic properties of drugs.[1] Poor solubility of drug in water also affects the onset of action and achievement of therapeutic drug concentration in the blood.[2] Solubility and its enhancement in the presence of cosolvents, hydrophilic polymers, and surfactants are of interest to the pharmaceutical industry while formulating poorly soluble drugs for oral delivery.[3−6] Cosolvents such as propylene glycol, poly(ethylene glycol), and ethanol are commonly used in pharmaceutical formulations to increase the solubility of hydrophobic drugs. Surfactants can also be used to enhance the solubility of hydrophobic solutes by increasing the wettability of the solute. When a surfactant is placed in water, it forms micelles. A nonpolar drug will partition into the hydrophobic core of the micelle while polar tails will solubilize the complex.

Rofecoxib is a nonsteroidal anti-inflammatory drug (NSAID) used in the management of oesteoarthritis, pain, and dysmenorhea.[7−9] Rofecoxib, a methyl sulfonyl phenyl substituted furanone derivative (see Figure 1) that is structurally and functionally related to celecoxib, has poor solubility in water,[10] that is, 4.6 μg/mL at 298.15 K. In this paper, the solubility of rofecoxib is presented at (298.15, 303.15, and 308.15) K in binary mixtures of methanol + water, ethanol + water, and sodium lauryl sulfate (SLS) + water. These solvent mixtures have polarities between those of water and pure cosolvents.[11] Analysis of rofecoxib was done with a UV spectrophotometer. Such a database is useful in developing controlled release formulations containing rofecoxib.

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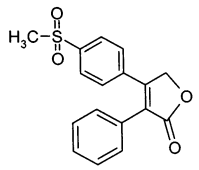

Figure 1. Structure of rofecoxib.

Experimental Section

Materials. Rofecoxib (99.4% purity) was obtained as a gift sample from Eros Pharma, Bangalore, India. Methanol, ethanol, and sodium lauryl sulfate were purchased from S.D. Fine Chemicals, Mumbai, India. Double-distilled water was used throughout, and its purity was checked by comparing its density and conductivity at 298.15 K with the literature values, which agreed well.

Methods. (a) Solubility Experiments. Different mass fraction aqueous mixtures of methanol and ethanol were prepared in 100 mL volumetric flasks. The mass of methanol or ethanol taken in the 100 mL volumetric flask was calculated by subtracting the empty mass of the flask from the total mass of the volumetric flask with methanol or ethanol. Sodium lauryl sulfate + water mixtures were prepared by adding the calculated mass of sodium lauryl sulfate into the 100 mL volumetric flasks. All the mass measurements were taken on a single pan Mettler microbalance (Model AE 240, Switzerland) within the accuracy ±0.01 mg.

A total of six compositions were used for mixing with rofecoxib in specially designed closed cap bottles. In each of these bottles, an excess amount of rofecoxib was added to ensure its maximum solubility. Mixtures were shaken thoroughly for 6 h at each temperature and allowed to stand to attain equilibrium as well as to settle completely the undissolved drug. The bottles were immersed in a stirred circulation, constant temperature water bath (Grants, model Y14, U.K.), the temperature of which was maintained at (298.15, 303.15, and 308.15) K. The temperatures

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Table 1. Solubility of Rofecoxib in Methanol (1) + Water (2) Mixtures at Different Temperatures

	solubility of rofecoxib[a] (μg/mL)		
$100W_1$	298.15 K	303.15 K	308.15K
0	8.19 ± 0.03	9.36 ± 0.10	11.18 ± 0.17
20	24.30 ± 0.46	29.65 ± 1.47	44.88 ± 0.32
40	132.3 ±0.3	156.2 ± 0.8	245.2 ± 16.9
60	538.3 ± 35.9	730.3 ± 10.9	973.5 ± 8.1
80	1220 ± 24	1509 ± 38	1977 ± 13
100	1400 ± 5	1961 ± 13	2751 ± 11

[a] Mean ± SE, $n = 6$.

Table 2. Solubility of Rofecoxib in Ethanol (1) + Water (2) Mixtures at Different Temperatures

	solubility of rofecoxib[a] (μg/mL)		
$100W_1$	298.15 K	303.15 K	308.15K
0	8.19 ± 0.03	9.36 ± 0.10	11.18 ± 0.17
20	25.26 ± 0.50	42.44 ± 5.91	55.61 ± 0.89
40	228.7 ± 4.4	306.6 ± 12.5	418.7 ± 13.4
60	633.5 ± 15.2	865.3 ± 8.9	1183 ± 2
80	879.2 ±13.9	1187 ± 30	1381 ± 65
100	390.5 ± 1.9	506 ± 10.8	614.4 ± 5.1

[a] Mean ± SE, $n = 6$.

were read within the accuracy ±0.1 K at the desired temperature on a digital display.

A 10 mL aliquot of the mixture was removed from the aqueous layer, and the absorbance was measured at 285 nm using a UV spectrophotometer (Anthelie, Secomam, France). The λ_{max} of rofecoxib did not vary much in methanol + water or ethanol + water mixtures, and hence, we have used $\lambda_{max} = 285$ nm for both the cosolvent systems to estimate the drug content. The standard curve for rofecoxib was established in methanol, ethanol, and SLS. From the slope of the straight line, the solubility of rofecoxib in the binary mixture was calculated.

(b) Partition Experiments. Benzene and water (each 25 mL) were taken in 100 mL volumetric flasks to which an excess amount of rofecoxib was added to ensure the maximum solubility in both the phases. Mixtures were shaken thoroughly for 6 h at each temperature and then allowed to stand to attain equilibrium as well as to separate both the phases and the undissolved drug completely. The flasks were previously immersed in a stirred circulation constant temperature water bath (Grants, model Y14, U.K.), the temperature of which was maintained at (298.15, 303.15, and 308.15) K within the accuracy ±0.1 K at the desired temperature.

Results and Discussion

Experimental solubility data of rofecoxib in water + methanol, water + ethanol, and water + SLS mixtures at different temperatures (298.15, 303.15, and 308.15) K are respectively presented in Tables 1−3, while graphical presentations are given in Figures 2−4. The solubility of rofecoxib is higher in pure methanol than in pure ethanol and pure water at all temperatures. The solubility increased by several orders of magnitude by increasing the mass fraction of methanol and also by increasing the temperature of the dissolution media (see Figure 2). In the case of the ethanol + water mixture, the solubility of rofecoxib increased with an increase in mass fraction of ethanol up to 80% in water, and it further decreased in pure ethanol, as shown in Figure 3.

As the alcohol (both ethanol or methanol) concentration increases in water, the dielectric constant and hydrogen-bonding interactions might decrease, but the specific interactions between solute and solvent molecules will increase. Interactions of aromatic rings and apolar groups of rofecoxib with water and alcohol molecules are of a complex character. Hence, it is difficult to correlate the unusual solubility behavior of rofecoxib in ethanol + water mixtures. Our experimental data confirm this. The process of solubilization in any media involves breaking of the interionic or intermolecular bonds in the solute, the separation of molecules of the solvent to provide free space in the solvent cage to accommodate the solute molecules, as well as the interactions between the solvent and the solute molecules or ions. Atoms and molecules are held together by various types of bonds (e.g., London forces, hydrogen bonds, dipole−dipole, etc.) that are intricately related to solubility.

In the case of a surfactant system, the solubility increased with increasing concentration of surfactant (SLS) at all the temperatures. Solubility data of rofecoxib in

Table 3. Solubility of Rofecoxib in SLS (1) + Water (2) Mixtures at Different Temperatures

	solubility of rofecoxib[a] (μg/mL)		
$100W_1$	298.15 K	303.15 K	308.15K
0	8.19 ± 0.031	9.36 ± 0.10	11.18 ± 0.17
0.5	42.90 ± 0.99	49.03 ± 0.85	54.30 ±0.99
1.0	86.08 ± 1.42	103.8 ± 11.4	105.5 ± 0.3
1.5	117.7 ± 1.1	144.8 ± 12.0	151.1 ± 3.4
2.0	145.7 ±1.1	187.3 ± 8.8	190.7 ± 6.0

[a] Mean ± SE, $n = 6$.

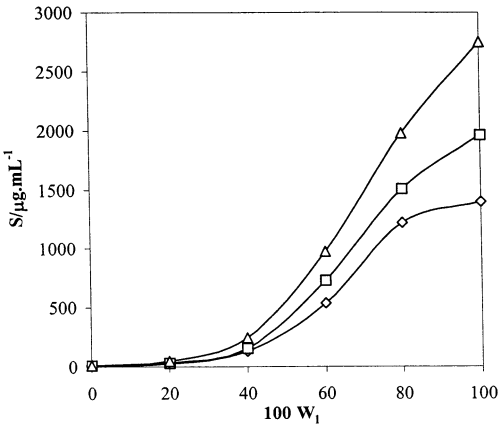

Figure 2. Solubility of rofecoxib in methanol (1) + water (2) mixtures at 298.15 K (◇), 303.15 K (□), and 308.15 K (△).

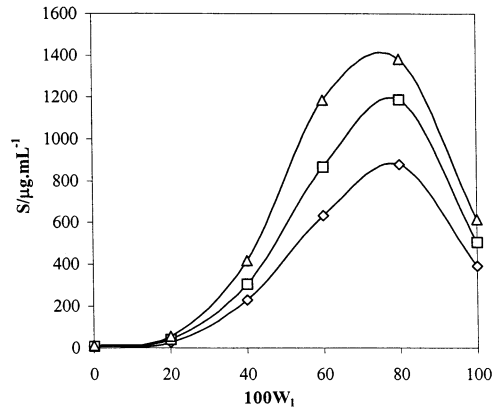

Figure 3. Solubility of rofecoxib in ethanol (1) + water (2) mixtures at 298.15 K (◇), 303.15 K (□), and 308.15 K (△).

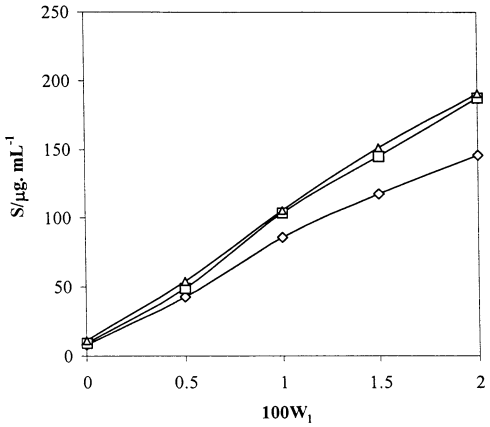

Figure 4. Solubility of rofecoxib in SLS (1) + water (2) mixtures at 298.15 K (◇), 303.15 K (□), and 308.15 K (△).

Table 4. Results of Partition Coefficient of Rofecoxib in Water + Benzene Mixtures at Different Temperatures

T/K	log K_{ow}[a]
298.15	2.361 ± 0.012
303.15	2.436 ± 0.017
308.15	2.511 ± 0.003

[a] Mean ± SE, $n = 3$.

various mass fractions of SLS are presented in Figure 4. However, the solubility of rofecoxib in SLS + water mixture did not significantly increase when compared to the case of methanol + water or ethanol + water mixtures.

The solubility of rofecoxib in the water + ethanol mixture was somewhat unusual; that is, the solubility increased with an increase in ethanol concentration in water up to 80%, but it decreased in pure ethanol. Thus, the solubilizing power of the cosolvent (ethanol) decreases at higher mass fraction of ethanol in water for rofecoxib. To explain these anomalies, the relationship (eq 1) developed by Yalkowsky and co-workers[12−14] for the prediction of the solubility of a solute in the presence of a cosolvent by using the solubilizing power of the cosolvent and the partition coefficient of the solute was used to calculate the solubility of rofecoxib.

$$\log S_{mix} = \log S_w + (s \log K_{ow} + t)f_c \qquad (1)$$

where S is the solubility of the solute, s and t are cosolvent constants that are solute independent, and K_{ow} is the partition coefficient of the active agent between the organic−water system. Rofecoxib is practically insoluble in octanol, and hence, in this research, we have calculated its partition coefficient in the water−benzene system at (298.15, 303.15, and 308.15) K. These data are presented in Table 4. As the temperature increases, the partition coefficient also increases due to the increased solubility of rofecoxib in benzene at higher temperatures.

Millard et al.[15] have fitted the wide range of solubilization power of ethanol and octanol water partition coefficient data of solutes to calculate the values of s and t, of eq 1. The reported values[15] of s and t are 0.93 and 0.4, respectively, for ethanol, and using these values, the solubility of rofecoxib was calculated. Predicted solubility data of rofecoxib in the ethanol + water cosolvent system are presented in Table 5. Deviations were calculated by comparing experimental values with the theoretically predicted values. Calculated values of deviations are also included in Table 5. If the experimental solubility of rofecoxib is higher than the predicted data, then deviations are negative and vice versa. Up to the mass fraction 60% ethanol in water, the calculated deviations are negative, indicating that the solubility of rofecoxib is more than the predicted solubility. This suggests that the solubilizing power of ethanol up to the mass fraction 60% in water for rofecoxib is more than the predicted data. However, beyond 60% mass fraction of ethanol, it decreases. It may be noted that deviations are positive for the mass fraction 80% ethanol in water for rofecoxib. This indicates that, at this concentration of ethanol, the solubilizing power of ethanol decreases for rofecoxib and, hence, the calculated values of deviations are positive.

Table 5. Solubility of Rofecoxib in Ethanol (1) + Water (2) Mixtures Calculated Using Eq 1 and Deviations by Comparing with the Experimental Values

	calc values of solubility of rofecoxib (mg/mL)			deviations		
$100W_1$	298.15 K	303.15 K	308.15 K	298.15 K	303.15 K	308.15 K
20	0.035	0.041	0.052	0.009	−0.001	−0.004
40	0.127	0.157	0.203	−0.102	−0.150	−0.215
60	0.413	0.527	0.704	−0.221	−0.339	−0.480
80	1.209	1.585	2.174	0.330	0.398	0.793

Conclusions

It has been shown that the solubility of rofecoxib in water can be increased by the addition of methanol, ethanol, and SLS in water. The solubility of rofecoxib in a water + ethanol mixture was increased up to the mass fraction 80% ethanol in water. Theoretically calculated solubility values of rofecoxib in water + ethanol mixtures at the mass fraction 80% ethanol are higher than the actual results, and hence, deviations are positive, indicating that as ethanol concentration increases (beyond the mass fraction 60%), the solubilizing power of ethanol decreases for rofecoxib.

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