Solubility of Rofecoxib in the Presence of Aqueous Solutions of Glycerol, Propylene Glycol, Ethanol, Span 20, Tween 80, and Sodium Lauryl Sulfate at (298.15, 303.15, and 308.15) K

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The solubility data of rofecoxib in various mass fraction compositions of cosolvents (glycerol, propylene glycol, and ethanol) + water and surfactants (Span 20, Tween 80, and sodium lauryl sulfate) + water at (298.15, 303.15, and 308.15) K are presented. The analysis of rofecoxib was done by high-performance liquid chromatography. The solubility of rofecoxib increased with increasing mass fraction of cosolvents and surfactants at (298.15, 303.15, and 308.15) K. For ethanol + water mixtures, the solubility of rofecoxib was higher when compared to the glycerol + water and propylene glycol + water mixtures. The solubilization power of glycerol, propylene glycol, and ethanol at (298.15, 303.15, and 308.15) K was 0.81, 0.87, and 0.88; 2.2, 2.3, and 2.4; and 3.4, 3.6, and 3.8, respectively. In case of surfactants, sodium lauryl sulfate exhibited higher solubilizing efficiency at (298.15, 303.15, and 308.15) K than Span 20 and Tween 80.

Introduction

Studies on the solubility of poorly water-soluble drugs in water in the presence of cosolvents and surfactants gives important information with regard to its molecular/physical property that influences the pharmacokinetics such as release, transport, extent of absorption of drug in the body, and other pharmacodynamic properties.[1−3] In particular, poor solubility of a drug affects its onset of action and achievement of therapeutic drug concentration in the blood.[1] 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, topical, and injectable delivery. Moreover, solubility data of a drug in cosolvent + water, hydrophilic polymers + water, and surfactants + water mixtures are always useful while analyzing the pharmaceutical formulations.[4,5] Cosolvents such as glycerol, propylene glycol, poly(ethylene glycol) 400, and ethanol are commonly used in pharmaceutical formulations to increase the solubility of hydrophobic drugs. Surfactants (Span 20, Tween 80, and sodium lauryl sulfate) are also used to enhance the solubility of hydrophobic solutes by increasing the wettability of the solute.[6]

Rofecoxib is a nonsteroidal anti-inflammatory drug (NSAID) used in the management of oesteoarthritis, pain, and dysmenorhea. Rofecoxib, a methyl sulfonyl phenyl substituted furanone derivative (see Figure 1) that is structurally and functionally related to celecoxib, has poor solubility in water (i.e., 4.6 μg/mL at 298.15 K).[7−9] In this paper, solubility data of rofecoxib are presented in the presence of various mass fraction compositions of glycerol, propylene glycol, ethanol, Span 20, Tween 80, and sodium lauryl sulfate in water at (298.15, 303.15, and 308.15) K.

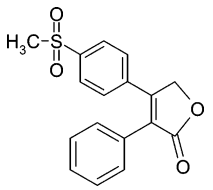

Figure 1. Structure of rofecoxib.

Glycerol, propylene glycol, and ethanol were used as cosolvents; Span 20, Tween 80, and sodium lauryl sulfate were used as surfactants. Analysis of rofecoxib was done by high-performance liquid chromatography (HPLC). Such a database is useful in developing oral, topical, and injectable formulations containing rofecoxib.

Experimental Section

Materials. Rofecoxib (99.2 % purity and molecular weight 314.36) was obtained as a gift sample from Cipla Ltd., Mumbai, India. Glycerol (99.8 % purity), propylene glycol (99 % purity), ethanol, Span 20, Tween 80, and sodium lauryl sulfate were purchased from Showa Chemicals Co., Tokyo, Japan. Ultrapure water (Millipore, USA) was used throughout.

Methods: Solubility Experiments. Binary mixtures of glycerol + water, propylene glycol + water, ethanol + water, Span 20 + water, Tween 80 + water, and sodium lauryl sulfate + water were prepared by mass in 50 mL glass tubes. All the mass measurements were made on an electronic balance (Explorer, Ohaus, Switzerland) within 0.01 mg. The uncertainty in the mass fraction compositions of cosolvents and surfactants is estimated to be ± 0.01 %.

The solubility of rofecoxib in various mass fraction compositions of cosolvents (glycerol, propylene glycol, and ethanol (0, 10, 20, 30, 40, and 100) % + water) and surfactants (Span 20, Tween 80, and sodium lauryl sulfate (0, 1, 2, 5, and 10) % + water) were determined at (298.15,

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

	(S/μg·mL^{-1})[a] at T/K		
$100w_1$	298.15	303.15	308.15
	Glycerol (1) + Water (2)		
0	8.2 ± 0.1	9.4 ± 0.1	11.2 ± 0.2
10	12.1 ± 0.4	13.3 ± 0.3	15.0 ± 0.6
20	13.8 ± 0.3	15.2 ± 0.5	17.4 ± 0.8
30	15.8 ± 0.4	18.1 ± 0.7	21.4 ± 0.9
40	18.4 ± 0.5	22.1 ± 0.8	25.5 ± 0.8
100	70.6 ± 2.0	95.3 ± 1.3	118.1 ± 1.1
	Propylene Glycol (1) + Water (2)		
0	8.2 ± 0.1	9.4 ± 0.1	11.2 ± 0.2
10	20.3 ± 0.3	25.1 ± 0.6	28.8 ± 0.8
20	30.8 ± 0.4	36.0 ± 0.8	42.1 ± 0.9
30	48.6 ± 0.9	60.0 ± 1.8	66.3 ± 1.2
40	70.1 ± 0.8	85.2 ± 2.2	97.5 ± 2.1
100	170.8 ± 3.2	190.6 ± 3.1	226.5 ± 1.8
	Ethanol (1) + Water (2)		
0	8.2 ± 0.1	9.4 ± 0.1	11.2 ± 0.2
10	23.4 ± 0.3	35.3 ± 2.2	44.2 ± 1.6
20	33.3 ± 0.5	54.0 ± 5.9	82.0 ± 0.9
30	82.1 ± 1.4	121.4 ± 2.7	197.3 ± 2.9
40	228.7 ± 4.4	306.6 ± 2.5	418.7 ± 3.4
100	395.5 ± 3.5	510.4 ± 3.3	624.3 ± 4.2

[a] Values are expressed as mean ± standard error, n = 6 (replication).

303.15, and 308.15) K. The solubility study of rofecoxib in binary mixtures of glycerol, propylene glycol, ethanol, Span 20, Tween 80, and sodium lauryl sulfate was determined by adding the excess amount of rofecoxib into the closed cap tubes containing various binary mixtures. These binary mixtures containing an excess amount of rofecoxib were shaken for 48 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 48 h, 5 mL of each binary mixtures was removed and passed through a 0.22 μm membrane filter (Millipore, USA), suitably diluted with corresponding mass fraction of cosolvents (0, 10, 20, 30, 40, and 100) % + water or surfactants (0, 1, 2, 5, and 10) % + water mixtures, and then the rofecoxib content was determined by a HPLC method as reported.[10] The detection of rofecoxib solubility was carried out by injecting 20 μL pf test solution into a HPLC system (1100, Hewlett-Packard, USA) using a C18 column (5 μm, 200 × 4.6 mm). A mixture of acetonitrile and water (1:1) was used as the mobile phase at a flow rate of 1.0 mL/min. The wavelength used for the detection of rofecoxib was 254 nm. The electronic balance (Explorer, Ohaus, Switzerland) had a range of measurement of up to 100 g with an uncertainty of ± 0.01 mg. Uncertainty of temperature maintained by water bath was found to be ± 0.1 K. The uncertainty in the solubility values due to uncertainties in the temperature measurements and weighing procedure, and instabilities of the water bath is estimated to be ± 1.5 %.

Results and Discussion

The experimental solubility data of rofecoxib in cosolvents (glycerol, propylene glycol, and ethanol) + water mixtures at (298.15, 303.15, and 308.15) K are presented in Table 1. The solubility of rofecoxib in water is very low (i.e., 8.2 μg/mL (T = 298.15 K)). The mixed-solvent systems in the present study include glycerol + water, propylene glycol + water, and ethanol + water. From Figures 2, 3, and 4, it is very clear that aqueous solubility of the rofecoxib increased remarkably by the addition of cosolvents (glycerol, propylene glycol, and ethanol). The solubility of rofecoxib increased with an increase in the mass fraction of glycerol, propylene glycol, and ethanol. The solubility of rofecoxib also increased when the temperature of the dissolution media increased from (298.15 to 308.15) K. However, the solubility of rofecoxib in ethanol + water mixtures was higher at all the temperatures tested when compared to glycerol + water and propylene glycol + water mixtures. This indicates that ethanol is a suitable cosolvent

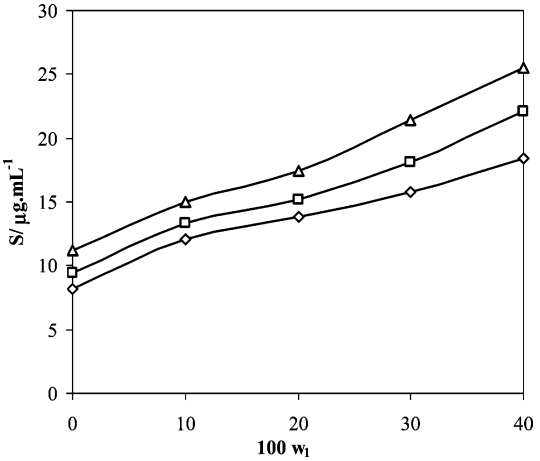

Figure 2. Solubility (S) of rofecoxib in glycerol (1) + water (2) mixtures: ◇, 298.15 K; □, 303.15 K; Δ, 308.15 K.

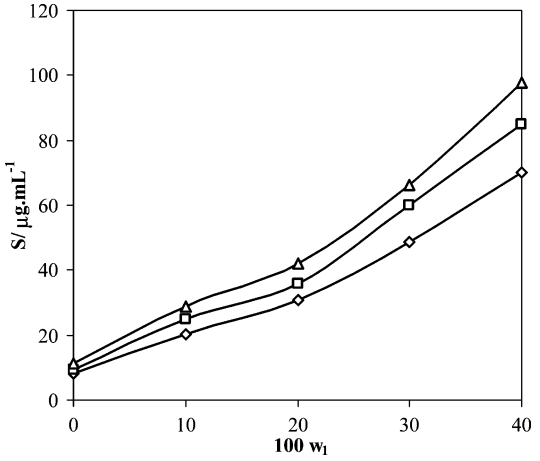

Figure 3. Solubility (S) of rofecoxib in propylene glycol (1) + water (2) mixtures: ◇, 298.15 K; □, 303.15 K; Δ, 308.15 K.

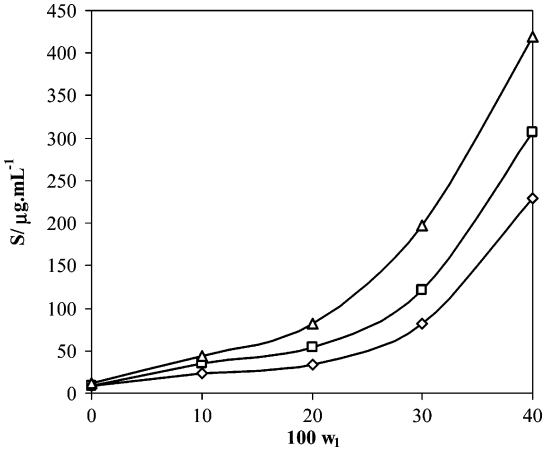

Figure 4. Solubility (S) of rofecoxib in ethanol (1) + water (2) mixtures: ◇, 298.15 K; □, 303.15 K; Δ, 308.15 K.

Table 2. Solubilization Power Parameters of Cosolvents Obtained from the Linear Log S_{mix} vs ϕ_2 Plot

solvent	T/K	solubilization power (Φ)	standard deviation	intercept
glycerol	298.15	0.81	0.02	0.95
	303.15	0.87	0.03	1.0
	308.15	0.88	0.01	1.1
propylene glycol	298.15	2.2	0.03	0.99
	303.15	2.3	0.02	1.0
	308.15	2.4	0.03	1.1
ethanol	298.15	3.4	0.06	0.92
	303.15	3.6	0.05	1.0
	308.15	3.8	0.03	1.1

for the solubilization of rofecoxib. Cosolvent addition is a highly effective technique for enhancement of solubility of poorly water-soluble drugs. Cosolvents are organic compounds that are substantially miscible with water. Cosolvents have small hydrocarbon regions. Since these regions are nonpolar and they do not interact strongly with water, they can reduce the ability of the aqueous system to constrict nonpolar solutes.

The logarithmic relation between total drug solubility in a water + cosolvent system and the volume fraction of the cosolvent can be described by eq 1:[11−13]

$$\log S_{mix} = \log S + \Phi\phi_2 \quad (1)$$

where S_{mix} is the solubility of drug in cosolvent + water mixtures, S is the solubility of drug in pure water, ϕ_2 is the volume fraction of the cosolvent, and Φ is the solubilization power of the cosolvent. In the present study, the Φ value of glycerol, propylene glycol, and ethanol was obtained from the linear log S_{mix} versus ϕ_2 plots. The parameters obtained from these plots are presented in Table 2. The solubilization power (Φ) values give a quantitative estimate of the ability of the solvent to increase aqueous solubility of the rofecoxib. Solubilization power of the glycerol, propylene glycol, and ethanol increased slightly with an increase in the temperature of the dissolution media. Among the cosolvents tested, ethanol exhibited higher solubilization power at (298.15, 303.15, and 308.15) K when compared to glycerol and propylene glycol (see Table 2). This indicates that ethanol is a suitable cosolvent for the solubilization of rofecoxib.

Water-miscible surfactant molecules contain both a hydrophilic and a hydrophobic portion and can solubilize many poorly water-soluble drugs. Surfactants can also self-assemble to form micelles once the surfactant monomer concentration reaches the critical micelle concentration. Thus, surfactants can solubilize drug molecules by either a direct cosolvent effect or by uptake into micelles. The solubility of rofecoxib in Span 20 + water, Tween 80 + water, and sodium lauryl sulfate + water mixtures at (298.15, 303.15, and 308.15) K is presented in Table 3, while graphical presentations are given in Figures 5, 6, and 7. The solubility of rofecoxib increased with increasing mass fraction of Span 20, Tween 80, and sodium lauryl sulfate at (298.15, 303.15, and 308.15) K. However, sodium lauryl sulfate exhibited a higher solubilization potential at all the temperatures tested than Span 20 and Tween 80. To analyze the linearity in the solubility enhancement of rofecoxib with an increasing mass fraction of Span 20, Tween 80, and sodium lauryl sulfate in water, the solubility of rofecoxib (mg/mL) was plotted against the concentration of surfactant (mg/mL). The slope obtained from this curve gives an estimation of the solubilizing efficiency of the surfactant at different temperatures. The parameters obtained from the linearity plot are presented in Table 4.

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

	(S/μg·mL^{-1})[a] at T/K		
$100w_1$	298.15	303.15	308.15
	Span 20 (1) + Water (2)		
0	8.2 ± 0.1	9.4 ± 0.1	11.2 ± 0.2
1	13.2 ± 0.2	14.7 ± 0.3	17.2 ± 0.1
2	14.8 ± 0.1	17.5 ± 0.2	20.0 ± 0.2
5	20.3 ± 0.3	25.2 ± 0.5	30.4 ± 0.6
10	44.2 ± 2.2	51.2 ± 2.1	59.9 ± 1.1
	Tween 80 (1) + Water (2)		
0	8.2 ± 0.1	9.4 ± 0.1	11.2 ± 0.2
1	25.2 ± 1.1	30.3 ± 2.3	37.1 ± 2.1
2	31.2 ± 2.2	38.4 ± 1.5	48.6 ± 2.4
5	64.2 ± 1.7	72.3 ± 3.1	84.5 ± 2.8
10	146.4 ± 4.2	158.3 ± 5.2	185.6 ± 3.1
	Sodium Lauryl Sulfate (1) + Water (2)		
0	8.2 ± 0.1	9.4 ± 0.1	11.2 ± 0.2
1	125.2 ± 2.6	151.3 ± 3.4	190.5 ± 1.8
2	183.3 ± 3.1	217.8 ± 3.5	313.6 ± 3.4
5	456.4 ± 3.6	523.2 ± 4.3	680.2 ± 4.1
10	937.4 ± 2.5	1010.4 ± 5.5	1160.1 ± 5.2

[a] Values are expressed as mean ± standard error, n = 6 (replication).

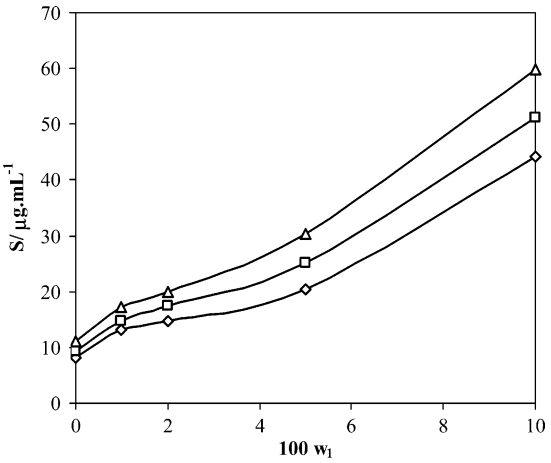

Figure 5. Solubility (S) of rofecoxib in Span 20 (1) + water (2) mixtures: ◇, 298.15 K; □, 303.15 K; Δ, 308.15 K.

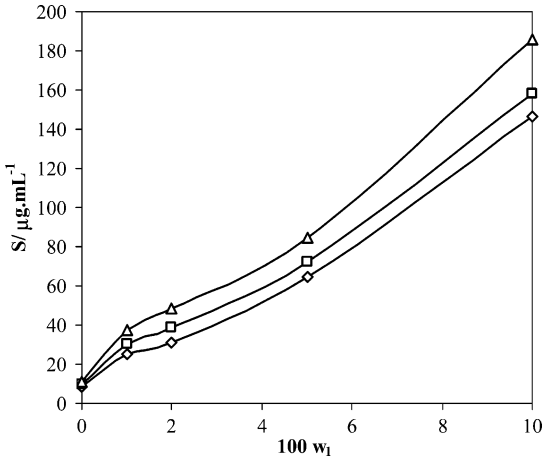

Figure 6. Solubility (S) of rofecoxib in Tween 80 (1) + water (2) mixtures: ◇, 298.15 K; □, 303.15 K; Δ, 308.15 K.

The data show that the solubility of the rofecoxib is proportional to the concentration of Span 20, Tween 80, and sodium lauryl sulfate in water. However, solubilizing efficiency of sodium lauryl sulfate is higher than that of Span 20 and Tween 80. The solubilization efficiency of

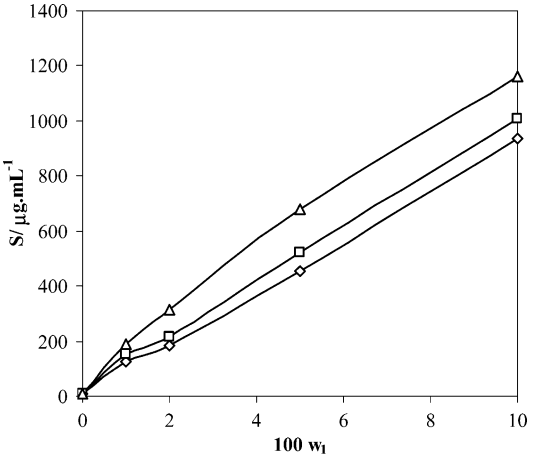

Figure 7. Solubility (*S*) of rofecoxib in sodium lauryl sulfate (1) + water (2) mixtures: ◇, 298.15 K; □, 303.15 K; Δ, 308.15 K.

Table 4. Parameters of the Linearity Plot of Rofecoxib Solubility (mg/mL) vs Concentration of Surfactant (mg/mL)

solvent	*T*/K	solubilization efficiency (slope)	correlation coefficient	intercept
	298.15	0.003	0.9623	0.0078
Span 20	303.15	0.004	0.9794	0.0091
	308.15	0.005	0.9848	0.010
	298.15	0.014	0.9873	0.0064
Tween 80	303.15	0.015	0.9892	0.0098
	308.15	0.017	0.9872	0.0131
	298.15	0.092	0.9984	0.011
sodium lauryl	303.15	0.099	0.9984	0.027
sulfate	308.15	0.113	0.9913	0.065

surfactants also increased with an increase in temperature of the dissolution media.

Conclusions

It has been shown that the solubility of rofecoxib in water can be enhanced by the addition of glycerol, propylene glycol, and ethanol in water as well as by increasing the temperature of the dissolution media. The solubilizing power of the ethanol was higher when compared to glycerol and propylene glycol. This indicates that ethanol is an effective solubilizing agent while developing formulations containing rofecoxib.

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