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

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This study investigated the solubilization of valdecoxib in aqueous solution using ethanol as a cosolvent and sodium lauryl sulfate as a surfactant at (298.15, 303.15, and 308.15) K. The analysis of valdecoxib is carried out by UV spectral measurements at a λ_{max} value of 201 nm. Preliminary investigations indicated both ethanol and sodium lauryl sulfate are respectively an effective cosolvent and surfactant for the solubilization of valdecoxib. The aqueous solubility of valdecoxib could be enhanced significantly by using ethanol as a cosolvent at various concentrations as well as by increasing the temperature of the dissolution media. The solubility of valdecoxib increased with increasing mass fraction of ethanol up to 80%, but solubility decreased in pure ethanol at all the temperatures. Experimental solubility data of valdecoxib were correlated with those calculated by a log-linear equation. Calculated Gibbs free energy values were all negative for all the ethanol + water mixtures at (298.15, 303.15, and 308.15) K, indicating the spontaneous nature of valdecoxib solubilization. In the case of sodium lauryl sulfate + water mixtures, the solubility of valdecoxib linearly increased with increasing mass fraction of sodium lauryl sulfate in water at all the temperatures.

Introduction

Together with the permeability, the solubility behavior of a drug is a key determinant of its oral bioavailability.[1,2] There have always been certain drugs for which solubility has presented a challenge to the development of a suitable formulation for either oral or injectable administration.[3] With the recent advent of high throughput screening of potential therapeutic agents, the number of poorly soluble drug candidates has risen sharply and the formulation of such drugs for either oral or injectable delivery now presents one of the most frequent and greatest challenges to formulation scientists in the pharmaceutical industries.[4]

The widely used excipients to solubilize drugs in oral and injectable dosage forms include water soluble organic solvents and surfactants.[5] Of the water-soluble organic solvents, poly(ethylene glycol) (PEG) 400, ethanol, propylene glycol, and glycerin have been commonly used in the commercially available solubilized oral formulations.[5,6] The frequently used surfactants in commercially available solubilized oral formulations include polysorbate 20 (Tween 20), polysorbate 80 (Tween 80), sodium lauryl sulfate, and sorbiton monooleate (Span 80).[5] However, the selection of either water-soluble organic solvent or surfactant is based on their ability to solubilize poorly soluble drug in an aqueous medium.[5,6]

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most widely used therapeutic agents, primarily for the treatment of pain and inflammation, especially arthritis.[7,8] Recently introduced NSAIDs are celecoxib, rofecoxib, valdecoxib, and paracoxib.[9] These NSAIDs are poorly soluble in water.[9] The very poor aqueous solubility of these drugs, however, gives rise to difficulties in the design of pharmaceutical formulations (oral or injectable). Valdecoxib is one of the recently introduced NSAIDs used in the management of oesteoarthritis, pain, and dysmenorhea.[10] Valdecoxib is chemically designated as 4-(5-methyl-3-phenyl-4-isoxazolyl)benzenesulfonamide and is a diaryl substituted isoxazole (see Figure 1). It has poor solubility in water, that is, 10 μg/mL at 298.15 K.[9−11] Therefore, the design of a formulation for valdecoxib is a challenging task and it requires preliminary investigations on its solubility behavior in the presence of effective cosolvent and surfactant in order to select an appropriate medium to enhance its solubility. The solubility study of valdecoxib has not received much attention so far. In this paper, the solubility of valdecoxib is presented at (298.15, 303.15, and 308.15) K in binary mixtures of ethanol + water and sodium lauryl sulfate + water. Ethanol and sodium lauryl sulfate were found to be an effective water-soluble organic solvent and surfactant, respectively, since they were found to have a higher solubilizing ability than other water-soluble organic solvents (PEG 400, propylene glycol, and glycerol) and surfactants (Tween 20, Tween 80, and Span 80). Analysis of valdecoxib was done with a UV spectrophotometer. Such a database is useful in developing oral or injectable formulations containing valdecoxib.

Experimental Section

Materials. Valdecoxib (99.6% purity) was obtained as a gift sample from Cipla Ltd., Mumbai, India. Ethanol and sodium lauryl sulfate were purchased from Showa Chemicals Co., Tokyo, Japan. Ultrapure water (Millipore, U.S.A.) was used throughout.

Methods. Solubility Experiments. Binary mixtures of ethanol + water and sodium lauryl sulfate + water were prepared in 50 mL glass tubes. The mass of ethanol 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 ethanol. Sodium lauryl sulfate + water mixtures were prepared by adding the calculated mass of sodium lauryl sulfate into the 50 mL glass tubes. All the mass measurements were taken on an electronic balance (Explorer, Ohaus, Switzerland) within an accuracy of 0.01 mg.

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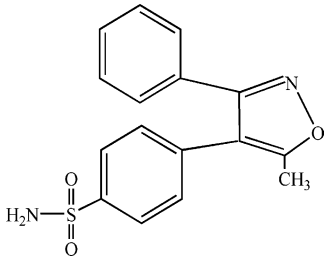

Figure 1. Structure of valdecoxib.

The solubility of valdecoxib was determined in six mass fraction compositions of ethanol (0, 20, 40, 60, 80, and 100)% + water and five mass fraction compositions of sodium lauryl sulfate (0, 0.25, 0.5, 0.75, and 1.0)% + water. The solubility study of valdecoxib in binary mixtures of ethanol and sodium lauryl sulfate was determined by adding an excess amount of valdecoxib into the closed-cap tubes containing various binary mixtures. The ethanol + water and sodium lauryl sulfate + water mixtures were shaken for 24 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 24 h, 5 mL of each binary mixture was removed, passed through a 0.22 μm membrane filter (Millipore, U.S.A.), and suitably diluted with a corresponding mass fraction of the ethanol (0, 20, 40, 60, 80, and 100)% + water or sodium lauryl sulfate (0, 0.25, 0.5, 0.75, and 1.0)% + water mixtures, and then, the valdecoxib content was determined by measuring the absorbance at 201 nm. The detection of valdecoxib was done with a UV spectrophotometer (Shimadzu 16001, Japan). The λ_{max} value of valdecoxib did not vary much in ethanol + water or sodium lauryl sulfate + water mixtures, and hence, we have used λ_{max} = 201 nm for both the binary systems to estimate the valdecoxib content. The standard curve for valdecoxib was established in ethanol and sodium lauryl sulfate. From the slope of the straight line, the solubility of valdecoxib in each binary mixture of ethanol + water and sodium lauryl sulfate + water was calculated. The repeated solubility experiments (n = 6) showed a variation of 0.2% to maximum 15% in the solubility values of valdecoxib at all the temperatures.

Results and Discussion

Cosolvent addition is a highly effective technique for enhancement of the solubility of poorly water-soluble drugs.[12,13] 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 squeeze out nonpolar solutes.[14] The small nonpolar hydrocarbon region in the cosolvent can reduce the ability of the aqueous system to squeeze out nonpolar solutes.

In the present study, preliminary investigations were conducted on the solubility behavior of valdecoxib in the presence of widely used cosolvents. These preliminary investigations indicated that ethanol is an effective and appropriate cosolvent for valdecoxib solubilization, since it exhibited a higher solubilizing capacity when compared to other cosolvents. Therefore, detailed solubility data were then obtained only with the ethanol + water system at (298.15, 303.15, and 308.15) K and such a database is useful while preparing the oral or injectable formulations containing valdecoxib.

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

	S^a/μg mL^{-1}		
	T/K		
$100w_1$	298.15	303.15	308.15
0	10.25 ± 0.6	10.4 ± 0.2	11.1 ± 0.8
20	125 ± 3	223 ± 4	248 ± 4
40	3092 ± 4	4180 ± 5	5698 ± 4
60	6639 ± 5	9791 ± 5	14 334 ± 5
80	14 289 ± 6	16 133 ± 7	20 973 ± 1
100	9645 ± 7	13 557 ± 15	15 491 ± 1

[a] Mean ± SE, n = 6.

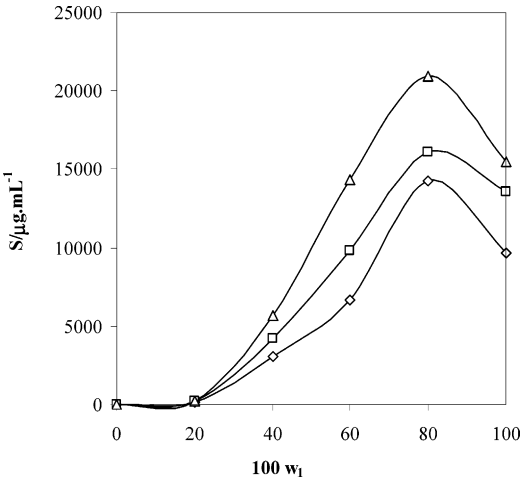

Figure 2. Solubility (S) of valdecoxib in ethanol (1) + water (2) mixtures: ◇, 298.15 K; □, 303.15 K; Δ, 308.15 K.

The experimental solubility data of valdecoxib in ethanol + water mixtures at (298.15, 303.15, and 308.15) K are presented in Table 1, while a graphical presentation is given in Figure 2. The solubility of valdecoxib in water is very low, that is, 10.25 μg/mL (T = 298.15 K). This is because the valdecoxib, being predominantly a nonpolar molecule, cannot effectively break into the lattice structure of the water; hence, the water solubility is low. The mixed-solvent system in the present study includes ethanol−water. From Figure 2, it is very clear that the aqueous solubility of the valdecoxib increased remarkably by the addition of cosolvent (ethanol). As the temperature of the dissolution media increased from (298.15 to 308.15) K, the solubility of valdecoxib increased further by several orders of magnitude. However, the solubility enhancement by ethanol was somewhat unusual; that is, the solubility increased with an increase in the ethanol mass fraction in water up to 80%, but it decreased in pure ethanol. At 80% ethanol concentration, the aqueous solubility of the valdecoxib was increased by 1394-, 1545-, and 1898-fold at (298.15, 303.15, and 308.15) K, respectively. Similar unusual drug solubility behavior has also been previously reported for rofecoxib.[4]

The solubilization of a nonpolar molecule in a cosolvent−water system is mainly governed by the hydrophobicity of the drug and cosolvent, dielectric constant of the cosolvent−water mixture, and absorption or evolution of heat.[5,12] In the present study, the solvent with a higher drug solubility in the pure state is referred to as the stronger solvent (ethanol) and the other as the weaker solvent (water). Dielectric constants of the mixtures were calculated from the relation $\epsilon_{mix} = \epsilon_{ws}f_{ws} + \epsilon_{ss}f_{ss}$, where ϵ and f are the dielectric constant and volume fraction, respectively, and the subscripts mix, ws, and ss represent volumes for the

Table 2. Parameters Obtained from the Linear log S_{mix} vs V_{ss} Plot

	T/K		
parameter	298.15	303.15	308.15
solubilization power of ethanol (Φ)	4.0	4.01	4.15
correlation (R^2)	0.9292	0.9073	0.9017
intercept	1.31	1.43	1.47

mixtures, weaker solvent, and stronger solvent, respectively. The dielectric constants of water and ethanol are 78.36 and 24.3, respectively (T = 298.15 K). The solubility of valdecoxib in water and ethanol at 298.15 K is (10.2 and 9644) μg/mL, respectively. It indicates that the solubility of valdecoxib decreases with an increase in the polarity of the solvents. In the case of ethanol + water mixtures, the solubility of the valdecoxib increased with a decrease in the dielectric constant of the ethanol + water mixture up to a certain concentration of ethanol (mass fraction of 80%), beyond which the solubility decreased. This effect occurs because drugs have some degree of polar character as well and maximum solubilization is a function of the relative polarity of the solute and the solvent. Moreover, factors other than the polarity of the solute and the solvent are also involved.

The logarithmic relation between the total drug solubility in a mixed-solvent system and the volume fraction of the stronger solvent can be described by eq 1.[12,13]

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

where S_{mix} and S are the solubility of valdecoxib in ethanol + water mixtures and pure water, respectively. V_{ss} is the volume fraction of the ethanol, and Φ is the solubilization power of the ethanol. The Φ value was obtained from the linear log S_{mix} versus V_{ss} plot, and the parameters obtained from this plot are presented in Table 2. The solubilization power of the ethanol (Φ) gives a quantitative estimate of the ability of this solvent to increase the aqueous solubility of the valdecoxib. The solubilization power of the ethanol for valdecoxib increased slightly with an increase in the temperature of the dissolution media.

The following equation (eq 2) was used in this study to calculate deviations from linearity:

$$\log Sc = \phi \log Sn + (1 - \phi) \log Sw \quad (2)$$

where Sc is the calculated valdecoxib solubility, Sn is the solubility of the valdecoxib in the pure ethanol, Sw is the equilibrium valdecoxib solubility in water, and ϕ is the volume fraction of the ethanol.[15] Deviations of the observed solubility (ln Sc) values from the log-linearity relationship for valdecoxib in ethanol−water mixtures at (298.15, 303.15, and 308.15) K are presented in Figure 3. The solubility of valdecoxib in ethanol + water mixtures produced negative deviations from linearity in (20 to 80)% mass fraction of ethanol. However, negative deviation values were higher at a low mass fraction of ethanol of (20 to 40)% when compared to a higher mass fraction of ethanol of (60 to 80)%. Tailing of deviations toward a positive trend beyond the mass fraction 80% ethanol indicates that the solubilizing power of the ethanol for valdecoxib decreased beyond the mass fraction 80% ethanol in water.

An indication of the process of transfer of valdecoxib from pure water to the ethanol + water mixtures at (298.15, 303.15, and 308.15) K may be obtained from the values of the Gibbs free energy change. The Gibbs free energy of transfer of valdecoxib from pure water to the ethanol + water mixtures may be calculated using the following equation (eq 3).[6]

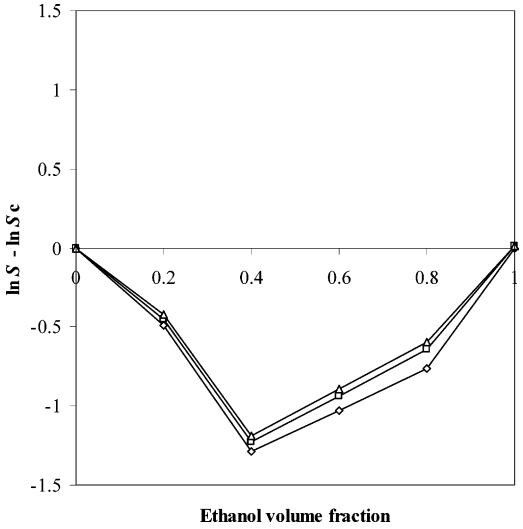

Figure 3. Deviations of observed solubility (ln Sc) values from the log-linearity relationship for valdecoxib in ethanol + water mixtures: ◇, 298.15 K; □, 303.15 K; Δ, 308.15 K.

Table 3. Thermodynamic Parameters of the Solubility Process of Valdecoxib in Ethanol (1) + Water (2) Mixtures at Different Temperatures

	$\Delta_{tr}G°$ [a]/kJ mol^{-1}		
	T/K		
$100w_1$	298.15	303.15	308.15
20	−62.5 ± 20	−91.8 ± 1	−109.0 ± 1
40	−142.8 ± 1	−179.8 ± 0.5	−218.7 ± 2
60	−161.8 ± 1	−205.3 ± 0.7	−251.0 ± 2
80	−181.1 ± 1	−220.3 ± 0.8	−264.3 ± 2
100	−108.7 ± 0.6	−123.2 ± 0.5	−144.6 ± 0.6

[a] Mean ± SE, n = 6.

$$\Delta_{tr}G° = -2.303RT \log \frac{S_0}{S_s} \quad (3)$$

where S_0/S_s is the ratio of the molar solubility of valdecoxib in ethanol + water mixtures to that in pure water. The obtained values of the Gibbs free energy are presented in Table 3. The data provide the information regarding the increased solubility of valdecoxib in the presence of ethanol in water. The Gibbs free energy values were all negative for all ethanol + water mixtures tested at (298.15, 303.15, and 308.15) K, indicating the spontaneous nature of valdecoxib solubilization, and it decreased with an increase in mass fraction of ethanol up to 80%, demonstrating that the reaction became more favorable when the mass fraction of ethanol increased from (20 to 80)%. The $\Delta_{tr}G°$ values of the pure ethanol at (298.15, 303.15, and 308.15) K were of increased values when compared to those of low mass fraction ethanol (20 to 80)% + water mixtures, indicating that the reaction conditions were less favorable for valdecoxib solubilization in pure ethanol than the other ethanol + water mixtures.

Water-miscible surfactant molecules contain both a hydrophilic and 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.[5] The

Table 4. Solubility (*S*) of Valdecoxib in Sodium Lauryl Sulfate (1) + Water (2) Mixtures at Different Temperatures

	$S^a/\mu g\ mL^{-1}$		
	T/K		
$100w_1$	298.15	303.15	308.15
0	10.25 ± 0.6	10.4 ± 0.17	11.05 ± 0.7
0.25	99.4 ± 1.8	113.8 ± 1.3	135 ± 2.1
0.5	191 ± 2.6	219.1 ± 1.6	255.1 ± 2.6
0.75	319.9 ± 1.6	371.3 ± 1.5	424.7 ± 5.3
1.0	418 ± 3.2	496.9 ± 3	553.1 ± 5.2

[a] Mean ± SE, $n = 6$.

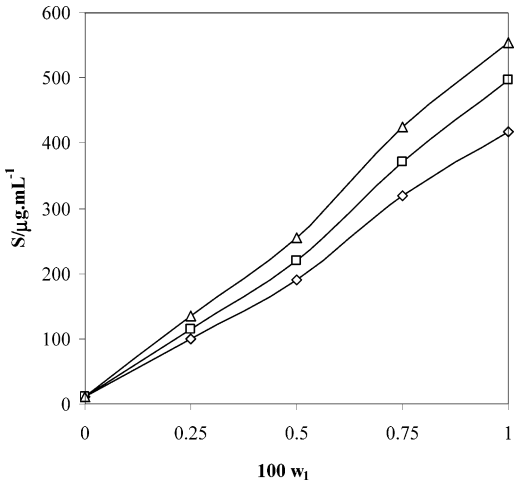

Figure 4. Solubility (*S*) of valdecoxib in sodium lauryl sulfate (1) + water (2) mixtures: ◇, 298.15 K; □, 303.15 K; Δ, 308.15 K.

Table 5. Parameters of the Linearity Plot of Valdecoxib Solubility (mg/mL) vs the Concentration of Sodium Lauryl Sulfate (mg/mL)

	T/K		
parameter	298.15	303.15	308.15
solubilizing efficiency of sodium lauryl sulfate (slope)	0.043	0.052	0.057
correlation (R^2)	0.9979	0.9978	0.9978

solubility of valdecoxib in sodium lauryl sulfate + water mixtures at (298.15, 303.15, and 308.15) K is presented in Table 4, while a graphical presentation is given in Figure 4. At a maximum mass fraction (1%) of sodium lauryl sulfate in water, the solubility of valdecoxib increased up to 40-, 48-, and 51-fold at (298.15, 303.15, and 308.15) K, respectively. To analyze the linearity in the solubility enhancement of valdecoxib with an increasing mass fraction of sodium lauryl sulfate in water, the solubility of valdecoxib (mg/mL) was plotted against the concentration of sodium lauryl sulfate (mg/mL). The slope obtained from this curve gives an estimation of the solubilizing efficiency of the sodium lauryl sulfate at different temperatures. The parameters obtained from the linearity plot are presented in Table 5. The data show that the solubility of the valdecoxib is proportional to the concentration of sodium lauryl sulfate in the water and the solubilizing efficiency of the sodium lauryl sulfate increased with an increase in temperature of the dissolution media. As reported by others,[16] the solubility of a poorly water-soluble drug in a surfactant medium often has a linear relationship with the concentration of the surfactant in the medium above the critical micelle concentration (cmc). Since the lowest sodium lauryl sulfate concentration tested (0.25%) is still above the cmc of sodium lauryl sulfate (0.023%), the linear relationship is expected.[16]

Conclusions

It has been shown that the solubility of valdecoxib in water can be enhanced by the addition of ethanol and sodium lauryl sulfate in water. The solubility of valdecoxib in ethanol + water mixtures increased up to the mass fraction 80% ethanol in water. Deviations of observed solubility values from the log-linear relationship were negative up to the mass fraction 80% ethanol in water, indicating that the solubilizing power of ethanol decreases beyond the mass fraction 80%. The solubility of valdecoxib in water could be increased linearly with an increase in the mass fraction of sodium lauryl sulfate in water.

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