Solubility of Valdecoxib in the Presence of Glycerol, Propylene Glycol, and Poly(ethylene glycol) 400 at (298.15, 303.15, and 308.15) K

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This study investigated the solubilization of valdecoxib in aqueous solutions of glycerol, propylene glycol, and poly(ethylene glycol) 400 at (298.15, 303.15, and 308.15) K. The analysis of valdecoxib was carried out by UV spectral measurements at λ_{max} of 204 nm. The solubility of valdecoxib increased with increasing mass fraction of glycerol, propylene glycol, and poly(ethylene glycol) 400 at (298.15, 303.15, and 308.15) K. For poly(ethylene glycol) 400 + water mixtures, the solubility of valdecoxib was higher when compared to the glycerol + water and propylene glycol + water mixtures. The solubilization power of glycerol, propylene glycol, and poly(ethylene glycol) 400 at (298.15, 303.15, and 308.15) K was 1.1, 1.5, and 1.8; 2.6, 2.8, and 2.9; and 3.0, 3.5, and 3.9, respectively.

Introduction

Poor water solubility character of certain drugs has always presented a challenge to the formulation scientists while developing injectable formulations.[1−3] In such cases, the formulation scientist is forced to investigate several possible ways of improving drug solubility in water−cosolvent, water−surfactant, or water−carriers mixtures.[4−10] The use of cosolvents, carriers, and surfactants for the solubility enhancement of poorly water soluble drugs is thoroughly studied. It is found that these media are suitable for the enhancement of drug solubility.[2,4−10] The solubility data in a media based on water−cosolvent, water−carrier, or water−surfactant mixtures will help the formulation scientists while developing injectable formulations.[5−7]

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 squeeze out nonpolar solutes.[8−10] While developing injectable formulations for poorly water soluble drugs, ethanol, glycerol, propylene glycol, poly(ethylene glycol) 300, and poly(ethylene glycol) 400 are widely used excipients for the solubilization of drugs.[4]

Valdecoxib is a recently introduced nonsteroidal antiinflammatory drug used in the management of oesteoarthritis, pain, and dysmenorhea.[11] It is chemically designated as 4-(5-methyl-3-phenyl-4-isoxazolyl) benzenesulfonamide and is a diaryl-substituted isoxazole (see Figure 1). Valdecoxib has poor solublity in water (i.e., 10 μg/mL at 298.15 K).[11,12] Therefore, the design of an injectable formulation for valdecoxib is a challenging task, and it requires investigations on its solubility behavior in the presence of various solubilizing excipients that are used in the injectable formulations to select an appropriate media to enhance its solubility. In this paper, the solubility of valdecoxib is presented at (298.15, 303.15, and 308.15) K in binary mixtures of glycerol + water, propylene glycol + water, and poly(ethylene glycol) 400 + water. Analysis of valdecoxib was done with a UV spectrophotometer. Such a database is useful in developing injectable formulations containing valdecoxib.

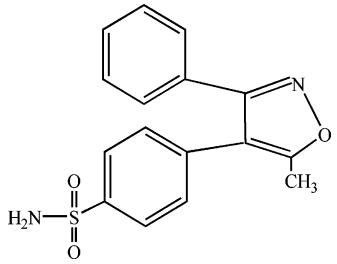

Figure 1. Structure of valdecoxib.

Experimental Section

Materials. Valdecoxib (99.6 % 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), and poly(ethylene glycol) 400 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, and poly(ethylene glycol) 400 + water were prepared by mass in 50 mL glass tubes. All the mass measurements were made on an electronic balance (Explorer, Ohaus, Switzerland) within the 0.01 mg.

The solubility of valdecoxib in various mass fraction compositions of glycerol (0, 10, 20, 30, and 100) % + water, propylene glycol (0, 20, 40, 60, 80, and 100) % + water, and poly(ethylene glycol) 400 (0, 15, 30, 45, 60, and 100) % + water mixtures were determined at (298.15, 303.15, and 308.15) K. The solubility study of valdecoxib in binary mixtures of glycerol, propylene glycol, and poly(ethylene glycol) 400 was determined by adding the excess amount of valdecoxib into the closed cap tubes containing various binary mixtures. These binary mixtures containing an

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Table 1. Solubility of Valdecoxib (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	10.25 ± 0.6	10.4± 0.2	11.1 ± 0.8
10	12.2 ± 0.5	13.3 ± 0.6	13.8 ± 0.3
20	16.2 ± 0.4	19.4 ± 0.5	23.7 ± 0.4
30	21.8 ± 0.8	29.7 ± 0.6	36.3 ± 0.7
100	50.4 ± 1.4	56.7 ± 2.5	60.3 ± 2.7
	Propylene Glycol (1) + Water (2)		
0	10.25 ± 0.6	10.4± 0.2	11.1 ± 0.8
20	41.3 ± 1.4	76.2 ± 1.7	118.3 ± 2.4
40	187.6 ± 2.5	391.2 ± 3.1	506.7 ± 2.9
60	650.2 ± 4.8	1027.0 ± 4.2	1267.8 ± 4.9
80	1038.6 ± 6.7	1765.6 ± 6.4	2524.5 ± 5.6
100	1434.4 ± 7.1	1925.7 ± 5.5	2936.8 ± 6.6
	Poly(ethylene glycol) 400 (1) + Water (2)		
0	10.25 ± 0.6	10.4 ± 0.2	11.1 ± 0.8
15	35.2 ± 0.9	66.2 ± 1.6	101.4 ± 1.9
30	107.7 ± 2.8	220.1 ± 4.7	298.8 ± 3.6
45	276.9 ± 4.3	551.3 ± 5.1	1142.3 ± 5.8
60	734.5 ± 5.2	1516.2 ± 6.0	2805.5 ± 5.9
100	2135.4 ± 6.1	2987.3 ± 5.7	4456.6 ± 7.0

[a] Mean ± SE, $n = 6$.

excess amount of the drug were shaken for 48 h using an automatic shaken 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 mixture was removed, passed through a 0.22 μm membrane filter (Millipore, USA), suitably diluted with the corresponding mass fraction of glycerol (0, 10, 20, 30, and 100) % + water or propylene glycol (0, 20, 40, 60, 80, and 100) % + water or poly(ethylene glycol) 400 (0, 15, 30, 45, 60, and 100) % + water mixtures, and then the valdecoxib content was determined by measuring the absorbance at 204 nm. The detection of valdecoxib was done with UV spectrophotometer (Shimadzu 16001, Japan). The λ_{max} of valdecoxib did not vary much in glycerol + water or propylene glycol + water or poly(ethylene glycol) + water mixtures; hence, we have used $\lambda_{max} = 204$ nm for all the binary systems to estimate the valdecoxib content. 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 are estimated to be ± 1.1 %.

Results and Discussion

Glycerol, propylene glycol, and poly(ethylene glycol) 400 are respectively used in the mass fraction range of (15 to 30) %, (10 to 80) %, and (18 to 67) % for the solubilization of drugs in injectable formulations. Therefore, this paper presents the solubility data of valdecoxib within the specified mass fraction compositions at (298.15, 303.15, and 308.15) K. These solubility data are useful while developing injectable formulations containing valdecoxib.

The experimental solubility data of valdecoxib in glycerol + water, propylene glycol + water, and poly(ethylene glycol) 400 + water mixtures at (298.15, 303.15, and 308.15) K are presented in Table 1. The graphical presentation is given in Figures 2, 3, and 4. The solubility of valdecoxib in water is very low (i.e., 10.25 μg/mL at T = 298.15 K).[7,11,12] The mixed-solvent systems in the present study include glycerol + water, propylene glycol + water,

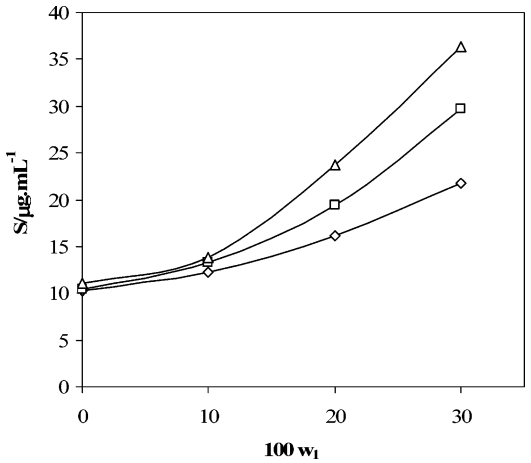

Figure 2. Solubility (S) of valdecoxib in glycerol (1) + water (2) mixtures: ◇, 298.15 K; □, 303.15 K; △, 308.15 K.

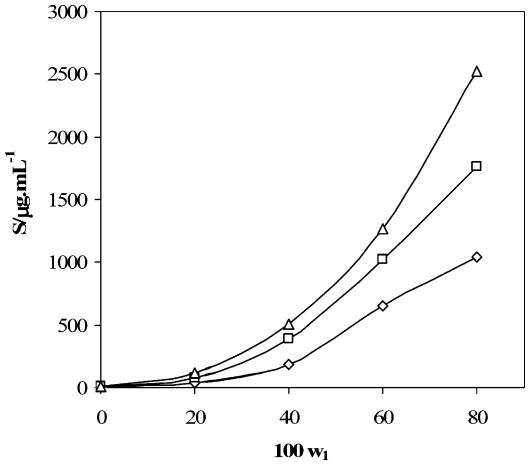

Figure 3. Solubility (S) of valdecoxib in propylene glycol (1) + water (2) mixtures: ◇, 298.15 K; □, 303.15 K; △, 308.15 K.

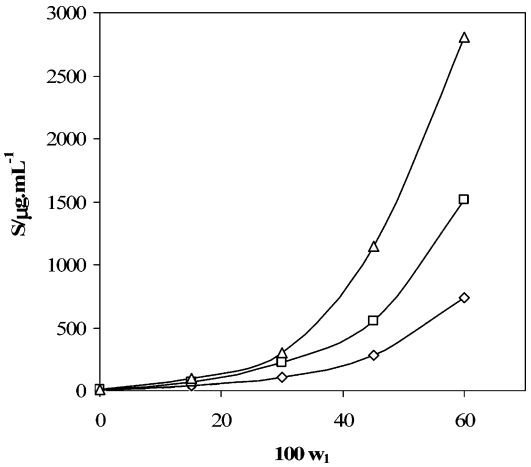

Figure 4. Solubility (S) of valdecoxib in poly(ethylene glycol) 400 (1) + water (2) mixtures: ◇, 298.15 K; □, 303.15 K; △, 308.15 K.

and poly(ethylene glycol) + water. From Figure 2, 3, and 4, it appears that aqueous solubility of the valdecoxib increased by the addition of glycerol, propylene glycol, and poly(ethylene glycol) 400 at (298.15, 303.15, and 308.15) K. 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, poly(ethylene glycol) 400 exhibited a higher solubilizing capacity for valdecoxib at (298.15, 303.15, and 308.15) K as compared to glycerol and propylene glycol.

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	1.1	0.06	0.99
	303.15	1.5	0.04	0.99
	308.15	1.8	0.07	1.01
propylene glycol	298.15	2.6	0.08	1.1
	303.15	2.8	0.07	1.2
	308.15	2.9	0.05	1.3
poly(ethylene glycol) 400	298.15	3.0	0.1	1.0
	303.15	3.5	0.08	1.1
	308.15	3.9	0.1	1.2

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

		($\Delta_{tr}G°$/kJ·mol^{-1})[a] at *T*/K		
cosolvent	$100w_1$	298.15	303.15	308.15
glycerol	10	−4.4 ± 20	−7.4 ± 1	−7.6 ± 1
	20	−11.4 ± 1	−18.7 ± 0.5	−26.5 ± 2
	30	−18.9 ± 1	−31.5 ± 0.7	−41.5 ± 2
	100	−39.8 ± 0.6	−50.9 ± 0.5	−59.2 ± 0.6
propylene glycol	20	−34.8 ± 20	−49.8 ± 1	−59.2 ± 1
	40	−72.7 ± 1	−90.7 ± 0.5	−95.5 ± 2
	60	−103.8 ± 1	−114.8 ± 0.7	−118.5 ± 2
	80	−115.5 ± 1	−128.4 ± 0.8	−135.7 ± 2
	100	−123.5 ± 0.6	−130.5 ± 0.5	−139.5 ± 0.6
poly(ethylene glycol) 400	15	−30.8 ± 20	−46.3 ± 1	−55.3 ± 1
	30	−58.8 ± 1	−76.3 ± 0.5	−82.3 ± 2
	45	−82.4 ± 1	−99.3 ± 0.7	−115.8 ± 2
	60	−106.8 ± 1	−124.6 ± 0.8	−138.3 ± 2
	100	−133.5 ± 1	−141.5 ± 1	−149.9 ± 1

[a] Mean ± SE, $n = 6$.

The solubilization of a nonpolar molecule in a cosolvent + water system is mainly governed by the hydrophobicity of the drug and cosolvent and the absorption or evolution of heat.[8] Dielectric constants of all the water + cosolvent mixtures (ϵ_{mix}) were calculated from the relation $\epsilon_{mix} = \epsilon_1\phi_1 + \epsilon_2\phi_2$, where ϕ is the volume fraction of the solvent and subscripts 1 and 2 represent water and cosolvent, respectively. The relative permittivity of water, glycerol, propylene glycol, and poly(ethylene glycol) 400 is 78.36, 42.5, 32, and 12.4, respectively ($T = 298.15$ K). The solubility of valdecoxib in water, glycerol, propylene glycol, and poly(ethylene glycol) 400 at 298.15 K is (10.2, 50.4, 1434.4, and 2135.4) μg/mL, respectively. It indicates that the solubility of valdecoxib decreases with an increase in the polarity of the solvents. In case of glycerol + water, propylene glycol + water, and poly(ethylene glycol) 400 + water mixtures, the solubility of valdecoxib increased with a decrease in the relative permittivity of the glycerol + water, propylene glycol + water, and poly(ethylene glycol) 400 + water mixtures.

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:[8,13−16]

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

where S_{mix} and S are the solubility of valdecoxib in glycerol + water, propylene glycol + water, and poly(ethylene glycol) 400 + water mixtures, and pure water, respectively. ϕ_2 is the volume fraction of the cosolvent, and Φ is the solubilization power of the cosolvent. The Φ value of glycerol, propylene glycol, and poly(ethylene glycol) 400 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 gives a quantitative estimate of the ability of the solvent to increase aqueous solubility of the valdecoxib. Solubilization power of the cosolvents tested in the present study increased slightly with an increase in the temperature of the dissolution media. Among the cosolvents tested, poly(ethylene glycol) 400 exhibited higher solubilization power at (298.15, 303.15, and 308.15) K when compared to glycerol and propylene glycol (see Table 2).

An indication of the process of transfer of valdecoxib from pure water to the glycerol + water, propylene glycol + water, and poly(ethylene glycol) 400 + water mixtures at (298.15, 303.15, and 308.15) K may be obtained from the values of Gibbs energy change. The Gibbs energy of transfer of valdecoxib from pure water to the glycerol + water, propylene glycol + water, and poly(ethylene glycol) 400 + water mixtures was calculated using the following equation (eq 2):[6,17]

$$\Delta_{tr}G° = -2.303RT \log\frac{S_o}{S_s} \quad (2)$$

where S_o/S_s is the ratio of molar solubility of valdecoxib in glycerol + water, propylene glycol + water, and poly(ethylene glycol) 400 + water mixtures to that in pure water. The obtained values of Gibbs energy for glycerol + water, propylene glycol + water, and poly(ethylene glycol) 400 + water mixtures are presented in Table 3. The data provide the information regarding the increased solubility of valdecoxib in the presence of glycerol, propylene glycol, and poly(ethylene glycol) 400 in water. Gibbs energy values were all negative for all the glycerol + water, propylene glycol + water, and poly(ethylene glycol) 400 + water mixtures tested at (298.15, 303.15, and 308.15) K, indicating the spontaneous nature of valdecoxib solubilization, which decreased with an increase in mass fraction of glycerol, propylene glycol, and poly(ethylene glycol) 400, demonstrating that the reaction became more favorable when the mass fraction of these cosolvents are increased. However, reaction conditions were more favorable in poly(ethylene glycol) 400 + water mixtures at (298.15, 303.15, and 308.15) K when compared to glycerol + water and propylene glycol + water mixtures.

Conclusions

It has been shown that the solubility of valdecoxib in water can be enhanced by the addition of glycerol, propylene glycol, and poly(ethylene glycol) 400 in water as well as by increasing the temperature of the dissolution media. The solubilizing power of the poly(ethylene glycol) 400 was higher when compared to glycerol and propylene glycol. This indicates that poly(ethylene glycol) 400 is an effective solubilizing agent while developing injectable formulations containing valdecoxib.

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