Solubility of Rofecoxib in the Presence of Mannitol, Poly(vinylpyrrolidone) K30, Urea, Polyethylene Glycol 4000, and Polyethylene Glycol 6000 at (298.15, 303.15, and 308.15) K

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The present study investigated the solubilization of rofecoxib in aqueous solution using mannitol, poly(vinylpyrrolidone) K30, urea, poly(ethylene glycol) 4000, and poly(ethylene glycol) 6000 at (298.15, 303.15, and 308.15) K. The analysis of rofecoxib is carried out by high-performance liquid chromatography (HPLC). The aqueous solubility of rofecoxib could be enhanced by the addition of increasing mass fraction of all of the hydrophilic carriers tested except mannitol as well as by increasing the temperature of the dissolution medium. Among the hydrophilic carriers studied, urea exhibited a higher solubilization potential than the other carriers. Calculated Gibbs free energy values were all negative for all of the hydrophilic carriers + water mixtures at (298.15, 303.15, and 308.15) K, indicating the spontaneous nature of rofecoxib solubilization. In the case of urea + water mixtures, the $\Delta_{tr}G°$ values decreased to a greater extent than those for the other carriers (mannitol, poly(vinylpyrrolidone) K30, poly(ethylene glycol) 4000, and poly(ethylene glycol) 6000) + water mixtures, indicating that the reaction conditions were more favorable in urea + water mixtures than in other carriers + water mixtures.

Introduction

For poorly soluble, highly permeable (class II) drugs, the rate of oral absorption is often controlled by the solubility/dissolution rate in the gastrointestinal tract. Therefore, together with permeability, the solubility/dissolution behavior of a drug is a key determinant of its oral bioavailability. There have been numerous efforts to improve the drug solubility/dissolution rate. These include (1) use of hydrophilic carriers; (2) solubilization in surfactants; (3) use of cosolvents; (4) use of a prodrug; and (5) manipulation of drug crystallinity. The most promising methods for promoting the solubility/dissolution rate are the use of cosolvents and hydrophilic carriers. The solubility of drugs in aqueous mixed hydrophilic carriers or cosolvents often exhibits a maximum as a function of composition.[1,2]

In the pharmaceutical industry, the development of a suitable oral formulation for a poorly soluble drug is often governed by its solubility/dissolution behavior in the presence of various hydrophilic carriers. Using hydrophilic carriers, the widely prepared oral solid formulations are solid dispersion-based systems. In an aqueous medium, hydrophilic carriers enhance drug solubility by either improving the wettability of a hydrophobic surface of the drug or by the formation of complexes with the drug. The dispersion of a poorly soluble drug in hydrophilic carriers in the solid state obtained by melting, grinding, solvent, or spray-drying methods leads to products referred to as solid dispersions. The use of hydrophilic carriers for drug solubilization is a convenient and highly effective technique. In the case of solid dosage forms, possible mechanisms of an increased solubility/dissolution rate for a poorly water-soluble drug by these hydrophilic carriers include the reduction of crystallite size, a solubilization effect of the carrier, the absence of aggregation of drug crystallities, improved wettability and dispersibility of a drug from the dispersion, dissolution of the drug in the hydrophilic carrier, conversion of the drug to the amorphous state, and finally, the combination of the above-mentioned methods.[3−6] Therefore, the use of hydrophilic carriers for the solubilization of a poorly soluble drug remains one of most effective technique because it involves simple operative procedures. However, appropriate and effective carriers can be selected only by performing preliminary studies on its solubility behavior in the presence of carriers at different temperatures.

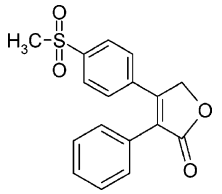

Figure 1. Structure of rofecoxib.

Rofecoxib is a selective cyclo-oxygenase-2 inhibitor administered orally as a analgesic and antiinflammatory drug. The chemical structure of rofecoxib is shown in Figure 1. Rofecoxib, a methyl sulfonyl phenyl-substituted furanone derivative (Figure 1) that is structurally and functionally similar to celecoxib, has poor solubility in water (i.e., 4.6 μg/mL at 298.15 K[7−9]). This very poor aqueous solubility and wettability of rofecoxib gives rise to difficulties in the design of oral formulations and leads to variable bioavailability.[7] To design an efficient formulation, the determination of the solubility behavior of the drug in the presence of widely used hydrophilic carriers or cosolvents or surfactants is essential and will help us to choose the most effective carrier or cosolvent or surfactant for drug solubilization.[10] Such studies give useful information about the efficacy of drug molecules both in vitro and in vivo.[7,10]

The solubility behavior of rofecoxib in the presence of cosolvents and a surfactant has been reported.[7] However,

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Table 1. Solubility of Rofecoxib (*S*) in Mannitol, Poly(vinylpyrrolidone) K30, Urea, Polyethylene Glycol 4000, and Polyethylene Glycol 6000 (1) + Water (2) Mixtures at 298.15 K

	$S/\mu g \cdot mL^{-1}$[a]				
	carrier				
$100w_1$	mannitol	poly(ethylene glycol) 6000	poly(ethylene glycol) 4000	poly(vinyl-pyrrolidone) K30	urea
0	8.2 ± 0.1	8.2 ± 0.1	8.2 ± 0.1	8.2 ± 0.1	8.2 ± 0.1
1	13.7 ± 0.2	14.5 ± 0.2	17. 1 ± 0.4	18.1 ± 0.2	19.2 ± 0.2
2	14.0 ± 0.1	15.3 ± 0.2	20.2 ± 0.3	23.8 ± 0.8	38.7 ± 0.4
5	14.2 ± 0.3	18.1 ± 0.4	24.6 ± 0.5	60.1 ± 2.2	61.5 ± 0.5
10	14.3 ± 0.1	20.0 ± 0.6	46.9 ± 1.3	90.3 ± 3.6	95.6 ± 4.5

[a] Mean ± SE, $n = 6$.

Table 2. Solubility of Rofecoxib (*S*) in Mannitol, Poly(vinylpyrrolidone) K30, Urea, Polyethylene Glycol 4000, and Polyethylene Glycol 6000 (1) + Water (2) Mixtures at 303.15 K

	$S/\mu g \cdot mL^{-1}$[a]				
	carrier				
$100w_1$	mannitol	poly(ethylene glycol) 6000	poly(ethylene glycol) 4000	poly(vinyl-pyrrolidone) K30	urea
0	9.5 ± 0.2	9.5 ± 0.2	9.5 ± 0.2	9.5 ± 0.2	9.5 ± 0.2
1	14.3 ± 0.3	15.5 ± 0.1	18.2 ± 0.3	19.6 ± 0.1	23.4 ± 0.3
2	14.4 ± 0.2	16.4 ± 0.3	21.6 ± 0.2	25.3 ± 0.6	45.6 ± 0.2
5	14.5 ± 0.1	19.2 ± 0.3	26.8 ± 0.54	70.3 ± 3.2	80.6 ± 5.6
10	14.7 ± 0.2	21.3 ± 0.8	57.5 ± 3.1	108 ± 4.6	120.2 ± 6.5

[a] Mean ± SE, $n = 6$.

its solubility behavior in the presence of hydrophilic carriers has not been studied so far. Therefore, in this paper, we report the solubility data of rofecoxib in the presence of the most widely used hydrophilic carriers (i.e., mannitol, urea, poly(vinylpyrrolidone) K30, poly(ethylene glycol) 4000, and poly(ethylene glycol) 6000) at (298.15, 303.15, and 308.15) K. Such a solubility database at different temperatures is useful in pharmaceutical industries while preparing the oral (liquid or solid) dosage forms containing rofecoxib. An analysis of rofecoxib was done by an HPLC method.

Experimental Section

Materials. Rofecoxib (99.6% purity) was obtained as a gift sample from Natco Pharmaceuticals, Hyderabad, India. Mannitol, urea, poly(vinylpyrrolidone) K30, poly(ethylene glycol) 4000, and poly(ethylene glycol) 6000 were purchased from Showa Chemicals Co., Tokyo, Japan. Ultrapure water (Millipore) was used throughout.

Methods. Solubility Experiments. Binary mixtures of mannitol, urea, poly(vinylpyrrolidone) K30, poly(ethylene glycol) 4000, and poly(ethylene glycol) 6000 + water were prepared in 50-mL glass tubes. The mass of these carriers 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 carriers. All of the mass measurements were made on an electronic balance (Explorer, Ohaus, Switzerland) within an accuracy of 0.01 mg.

The solubility of rofecoxib was determined at five mass fractions of above-mentioned binary mixtures of hydrophilic carriers (0, 1, 2, 5, and 10 mass) % + water. The solubility of rofecoxib in binary mixtures of mannitol, urea, poly-(vinylpyrrolidone) K30, poly(ethylene glycol) 4000, and poly(ethylene glycol) 6000 + water at (298.15, 303.15, and 308.15) K was determined by adding an excess amount of rofecoxib to the closed cap tubes containing various binary mixtures. These binary mixtures containing an excess amount of rofecoxib 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 removed, passed through a 0.22-μm membrane filter (Millipore), and suitably diluted with the correspondings mass fraction of the hydrophilic carriers (0, 1, 2, 5, and 10) % + water mixtures, and then the rofecoxib content was determined by HPLC (1100, Hewlett-Packard) using the C18 column (5 μm, 200 × 4.6 mm^2) method. A mixture of acetonitrile and water (1:1) was used as the mobile phase at a flow rate of 1.0 mL/min. The detection of rofecoxib was done by using a UV detector at 254 nm.[11] The solubility experiments were repeated six times (n = 6) in an identical manner. The variation in the solubility values of rofecoxib at all temperatures ranged from (0.1 to 6.6) μg/mL. The temperature was maintained at (298.15, 303.15, and 308.15) K within ±0.1 K.

Results and Discussion

The experimental solubility data of rofecoxib in the hydrophilic carriers mannitol, urea, poly(vinylpyrrolidone) K30, poly(ethylene glycol) 4000, and poly(ethylene glycol) 6000) + 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 rofecoxib in the presence of increasing mass fractions of (1, 2, 5, and 10) % mannitol, urea, poly-(vinylpyrrolidone) K30, poly(ethylene glycol) 4000, and poly(ethylene glycol) 6000 in water at (298.15, 303.15, and 308.15) K is presented in Figures 2, 3, and 4, respectively. The experimental solubility of rofecoxib in water is very low (i.e., 8.2 μg/mL at T = 298.15 K) because the rofecoxib, predominantly a nonpolar molecule, cannot effectively break into the lattice structure of the water; hence, the water solubility is low. From Figures 2, 3, and 4, it is very clear that the aqueous solubility of rofecoxib could be enhanced by the addition of increasing mass fractions of all of the hydrophilic carriers studied except mannitol. As the temperature of the dissolution media increased from (298.15 to 308.15) K, the solubility of rofecoxib could be further enhanced by several orders of magnitude.

Table 3. Solubility of Rofecoxib (*S*) in Mannitol, Poly(vinylpyrrolidone) K30, Urea, Polyethylene Glycol 4000, and Polyethylene Glycol 6000 (1) + Water (2) Mixtures at 308.15 K

	$S/\mu g \cdot mL^{-1}$[a]				
	carrier				
$100w_1$	mannitol	poly(ethylene glycol) 6000	poly(ethylene glycol) 4000	poly(vinyl-pyrrolidone) K30	urea
0	11.3 ± 0.3	11.3 ± 0.3	11.3 ± 0.3	11.3 ± 0.3	11.3 ± 0.3
1	14.5 ± 0.2	17.5 ± 0.3	19.1 ± 0.2	20.7 ± 0.1	28.6 ± 0.2
2	14.6 ± 0.1	18.9 ± 0.4	23.2 ± 0.3	28.5 ± 0.4	58.6 ± 0.3
5	14.7 ± 0.1	22.3 ± 0.2	29.6 ± 0.6	84.3 ± 2.3	115.7 ± 4.4
10	14.8 ± 0.2	25.3 ± 1.3	67.2 ± 5.5	126.2 ± 6.6	155.8 ± 5.1

[a] Mean ± SE, $n = 6$.

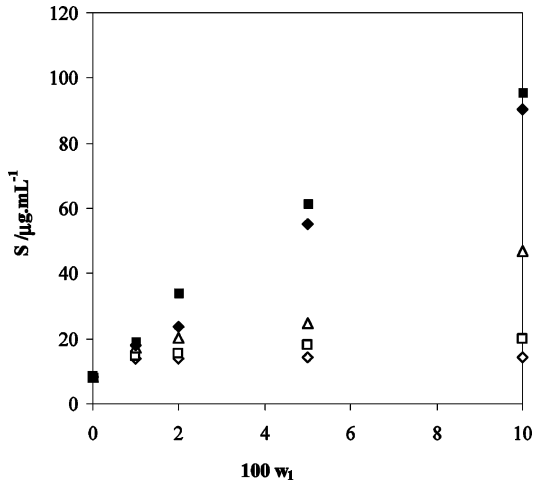

Figure 2. Solubility *S* of rofecoxib in hydrophilic carriers (1) + water (2) mixtures at 298.15 K: ◇, mannitol; □, poly(ethylene glycol) 6000; △, poly(ethylene glycol) 4000; ◆, poly(vinylpyrrolidone) K30; ■, urea.

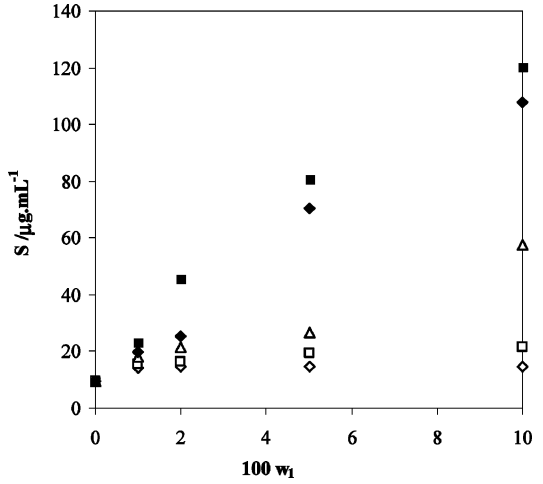

Figure 3. Solubility *S* of rofecoxib in hydrophilic carriers (1) + water (2) mixtures at 303.15 K: ◇, mannitol; □, poly(ethylene glycol) 6000; △, poly(ethylene glycol) 4000; ◆, poly(vinylpyrrolidone) K30; ■, urea.

In the present solubilization system, the enhanced solubility of rofecoxib could be attributed to the improved wetting of the hydrophobic surface of rofecoxib in water by these hydrophilic carriers. The solubility of rofecoxib increased with increasing mass fraction of all of the hydrophilic carriers except mannitol as well as by increasing the temperature of the dissolution medium. However, the extent of solubilization varied depending upon the type and mass fraction of the carrier. For instance, urea exhibited a higher solubilization potential at all of the mass fractions and temperatures studied than mannitol, poly-

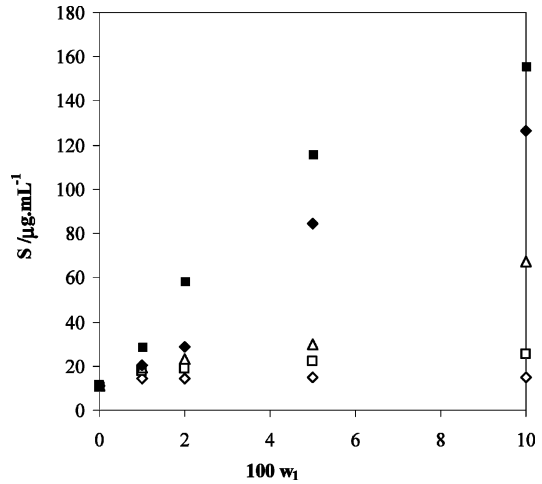

Figure 4. Solubility *S* of rofecoxib in hydrophilic carriers (1) + water (2) mixtures at 308.15 K: ◇, mannitol; □, poly(ethylene glycol) 6000; △, poly(ethylene glycol) 4000; ◆, poly(vinylpyrrolidone) K30; ■, urea.

(vinylpyrrolidone) K30, poly(ethylene glycol) 4000, and poly(ethylene glycol) 6000. At 10% mass fraction, the solubility of rofecoxib was enhanced up to 11.7-, 12.7-, and 13.8-fold by urea when compared to mannitol (1.7-, 1.8-, 1.9-fold), poly(ethylene glycol) 6000 (2.4-, 2.3-, 2.5-fold), poly(ethylene glycol) 4000 (5.7-, 6.0-, and 6.0-fold), and poly-(vinylpyrrolidone) K30 (11-, 11.3-, 11.3-fold) at (298.15, 303.15, and 308.15) K, respectively. Urea is regarded to be nontoxic and an effective carrier drug solubilizer. Its solubility in water is greater than 1 in 1, and it also exhibits good solubility in many organic solvents. In one of the first bioavailability studies of solid dispersions, it was shown that sulfathiazole was better absorbed in rabbits when given as a eutectic with urea.[1]

Polymerization of vinylpyrrolidone leads to poly(vinylpyrrolidone) of molecular weight ranging from 2500 to 3 000 000. These can be classified according to the *K* value, which is calculated using Fikentscher's equation.[1,3] Among the different poly(vinylpyrrolidone)s, poly(vinylpyrrolidone) K30 is commonly used for the enhancement of solubility/dissolution rate of poorly water soluble drugs.[1,3] In the present study, poly(vinylpyrrolidone) K30 was found to be the second most effective carrier for the solubilization of rofecoxib. For instance, it exhibited higher solubilization potential at all mass fractions and temperatures studied than mannitol, poly(ethylene glycol) 4000, and poly-(ethylene glycol) 6000. The solubility of rofecoxib was enhanced up to 1.8-, 2.5-, 7.5-, and 11.3-fold ($K = 308.15$) at 1, 2, 5, and 10% mass fraction, respectively.

Poly(ethylene glycol)s vary in their molecular weight in the range of (200 to 300 000). As the molecular weight increases, so does the viscosity of poly(ethylene glycol).[1] In

Table 4. Thermodynamic Parameters of the Solubility Process of Rofecoxib in Mannitol, Poly(vinylpyrrolidone) K30, Urea, Polyethylene Glycol 4000, and Polyethylene Glycol 6000 (1) + Water (2) Mixtures at 298.15 K

	$\Delta_{tr}G°$/kJ·mol^{-1}[a]				
	carrier				
$100w_1$	mannitol	poly(ethylene glycol) 6000	poly(ethylene glycol) 4000	poly(vinyl-pyrrolidone) K30	urea
1	−12.8 ± 0.2	−14.2 ± 0.3	−18.4 ± 0.2	−19.8 ± 0.3	−21.3 ± 0.2
2	−13.4 ± 0.1	−15.6 ± 0.2	−22.5 ± 0.3	−26.6 ± 0.4	−35.7 ± 0.1
5	−13.7 ± 0.3	−19.8 ± 0.1	−27.5 ± 1.4	−47.6 ± 1.3	−50.4 ± 0.5
10	−13.9 ± 0.4	−22.3 ± 0.5	−43.6 ± 1.5	−60.0 ± 2.3	−61.4 ± 3.2

[a] Mean ± SE, $n = 6$.

Table 5. Thermodynamic Parameters of the Solubility Process of Rofecoxib in Mannitol, Poly(vinylpyrrolidone) K30, Urea, Polyethylene Glycol 4000, and Polyethylene Glycol 6000 (1) + Water (2) Mixtures at 303.15 K

	$\Delta_{tr}G°$/kJ·mol^{-1}[a]				
	carrier				
$100w_1$	mannitol	poly(ethylene glycol) 6000	poly(ethylene glycol) 4000	poly(vinyl-pyrrolidone) K30	urea
1	−12.27 ± 0.2	−14.7 ± 0.2	−19.5 ± 0.3	−21.7 ± 0.4	−22.5 ± 0.2
2	−12.48 ± 0.3	−16.4 ± 0.4	−24.6 ± 0.4	−29.4 ± 0.2	−39.2 ± 0.4
5	−12.68 ± 0.4	−21.1 ± 0.5	−31.1 ± 0.8	−60.0 ± 0.7	−53.5 ± 1.1
10	−13.0 ± 1.1	−24.2 ± 1.3	−54.0 ± 2.1	−72.9 ± 1.4	−63.6 ± 1.2

[a] Mean ± SE, $n = 6$.

Table 6. Thermodynamic Parameters of the Solubility Process of Rofecoxib in Mannitol, Poly(vinylpyrrolidone) K30, Urea, Polyethylene Glycol 4000, and Polyethylene Glycol 6000 (1) + Water (2) Mixtures at 308.15 K

	$\Delta_{tr}G°$/kJ·mol^{-1}[a]				
	carrier				
$100w_1$	mannitol	poly(ethylene glycol) 6000	poly(ethylene glycol) 4000	poly(vinyl-pyrrolidone) K30	urea
1	−8.7 ± 0.3	−15.3 ± 0.6	−18.4 ± 0.4	−21.2 ± 0.2	−23.2 ± 0.1
2	−8.9 ± 0.2	−18.0 ± 0.5	−25.2 ± 0.3	−32.4 ± 0.1	−41.2 ±0.3
5	−9.2 ± 0.2	−23.8 ± 0.7	−33.7 ± 1.0	−70.4 ± 1.7	−58.2 ± 1.4
10	−9.4 ± 0.4	−28.2 ± 1.0	−62.4 ± 1.9	−84.5 ± 2.4	−65.8 ± 1.1

[a] Mean ± SE, $n = 6$.

the present study, poly(ethylene glycol)s with a molecular weight of (4000 to 6000) are studied because these are widely used as carriers while developing oral solid formulations. The results of the present study indicated that the solubility of rofecoxib decreases with increasing molecular weight of the poly(ethylene glycol)s studied. For instance, poly(ethylene glycol) 4000 exhibited higher solubilization potential at all mass fractions and temperatures when compared to poly(ethylene glycol) 6000. As the molecular weight of the poly(ethylene glycol)s increases, the viscosity of the aqueous medium also increases, which might have retarded the dissolution of drug particles into the aqueous medium. In the case of mannitol + water mixtures, the solubility of rofecoxib did not improve much with increasing mass fraction of mannitol in water at (298.15, 303.15, and 308.15) K (Figures 2, 3, and 4). This indicates that mannitol is a poor solubilizing agent for rofecoxib.

To understand the reaction conditions in all of the hydrophilic carriers (mannitol, poly(vinylpyrrolidone) K30, urea, poly(ethylene glycol) 4000, and poly(ethylene glycol) 6000) + water mixtures, the solubility data of rofecoxib at (298.15, 303.15, 308.15) K was fit with following equation:[12]

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

An indication of the process of transfer of rofecoxib from pure water to the hydrophilic carriers + 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 molar solubility of rofecoxib in hydrophilic carriers + water mixtures to that in pure water. The obtained values of the Gibbs free energy of hydrophilic carriers (mannitol, poly(vinylpyrrolidone) K30, urea, poly(ethylene glycol) 4000, and poly(ethylene glycol) 6000) + 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 rofecoxib in the presence of hydrophilic carriers in water. Gibbs free energy values were all negative for all hydrophilic carriers (mannitol, poly(vinylpyrrolidone) K30, urea, poly(ethylene glycol) 4000, and poly(ethylene glycol) 6000) + water mixtures tested, indicating the spontaneous nature of rofecoxib solubilization, and they decreased with increasing carrier mass fraction. The $\Delta_{tr}G°$ values for all of the hydrophilic carriers + water mixtures tested decreased further when the temperature of the dissolution media increased from (298.15 to 308.15) K. However, $\Delta_{tr}G°$ decreases to a greater extent in the case of urea + water mixtures when compared to mannitol + water, poly(vinylpyrrolidone) K30 + water, poly(ethylene glycol) 4000 + water, and poly(ethylene glycol) 6000 + water mixtures. The results of the solubility studies indicated that urea or poly(vinylpyrrolidone) K30 is an effective and appropriate carrier for preparing rofecoxib-urea or rofecoxib-poly(vinylpyrrolidone) K30 oral solid dispersions as well as for drug solubilization in liquid oral formulations.

Conclusions

It has been shown that the solubility of rofecoxib in water can be enhanced by the addition of various mass fractions of urea, poly(vinylpyrrolidone) K30, poly(ethylene glycol) 4000, and poly(ethylene glycol) 6000 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 rofecoxib in water. The values of the Gibb's free energy indicated that reaction conditions were more favorable in urea + water or poly(vinylpyrrolidone) + water mixtures than in the other carriers + water mixtures tested. On the basis of the results of the present study, it can be emphasized that urea and poly(vinylpyrrolidone) K30 are effective solubilizing carriers for preparing oral solid formulations containing rofecoxib.

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