

## Solubility Enhancement of Cox-2 Inhibitors Using Various Solvent Systems

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### ABSTRACT

This study examined the solubility enhancement of 4 cox-2 inhibitors, celecoxib, rofecoxib, meloxicam, and nimesulide, using a series of pure solvents and solvent mixtures. Water, alcohols, glycols, glycerol, and polyethylene glycol 400 (PEG 400) were used as solvents and water-ethanol, glycerol-ethanol, and polyethylene glycol-ethanol were used as mixed-solvent systems. A pH-solubility profile of drugs was obtained in the pH range 7.0 to 10.9 using 0.05M glycine-sodium hydroxide buffer solutions. Lower alcohols, higher glycols, and PEG 400 were found to be good solvents for these drugs. The aqueous solubility of celecoxib, rofecoxib, and nimesulide could be enhanced significantly by using ethanol as the second solvent. Among the mixed-solvent systems, PEG 400- ethanol system had highest solubilization potential. In the case of meloxicam and nimesulide, solubility increased significantly with increase in pH value. Physico-chemical properties of the solvent such as polarity, intermolecular interactions, and the ability of the solvent to form a hydrogen bond with the drug molecules were found to be the major factors involved in the dissolution of drugs by pure solvents. The greater the difference in the polarity of the 2 solvents in a given mixed solvent, the greater was the solubilization power. However, in a given mixed-solvent system, the solubilization power could not be related to the polarity of the drugs. Significance of the solubility data in relation to the development of formulations has also been discussed in this study.

**KEYWORDS:** solubility enhancement, cox-2 inhibitors, solvent systems

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### INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most widely prescribed medications in the world. As a therapeutic class, NSAIDs exhibit analgesic, anti-inflammatory, antipyretic, and platelet inhibitory properties.<sup>1,2</sup> However, these drugs have serious side effects such as gastrointestinal (GI) toxicities, gastric mucosal ulcerations and hemorrhage due to inhibition of prostaglandin production.<sup>3,4</sup> The mechanism of action of NSAIDs has been attributed to their ability to inhibit the cyclooxygenase enzyme (cox). Out of the 2 isoforms of cyclooxygenase, cox-1 is responsible for mediating the production of prostaglandin while cox-2 is primarily associated with inflammation, pain, and fever.<sup>5,6</sup> The traditional NSAIDs are nonselective cox inhibitors. Cox-2 selective NSAIDs are, therefore, ideal anti-inflammatory drugs with minimum drug-related side effects, since they spare cox-1 activity.

The very poor aqueous solubility and wettability of cox-2 inhibitors, however, give rise to difficulties in the design of pharmaceutical formulations and lead to variable oral bioavailability. The use of cosolvents has been employed by a number of workers<sup>7-9</sup> to enhance the solubility of poorly soluble drugs. Some attempts have been made to increase the solubility of nimesulide and meloxicam<sup>10-13</sup> by using techniques other than the use of cosolvents. Enhancement of solubility of celecoxib and rofecoxib has not received much attention so far. In the present study, an attempt has been made to increase the solubility of 4 cox-2 inhibitors, celecoxib, rofecoxib, meloxicam, and nimesulide, using a series of solvents and solvent-cosolvent mixtures. The work is relevant in relation to the development of liquid and parenteral formulations of these drugs.

### MATERIALS AND METHODS

Rofecoxib and celecoxib were obtained as gift samples from Ranbaxy Research Laboratories, Gurgaon, India. Meloxicam and nimesulide were also gift samples from Sun Pharmaceutical Industries Ltd (Mumbai, India) and Panacea Biotec Ltd (Lalru, India), respectively. All solvents were of analytical grade and were purchased

**Table 1.** Solubility of Various Drugs in Different Solvents at 25°C\*

Solvent	Solubility (mg/mL)			
	Celecoxib	Rofecoxib	Meloxicam	Nimesulide
Water	0.007	0.009	0.012	0.014
Glycerol	-	0.108	0.138	0.218
Methanol	113.94	0.835	0.382	8.812
Ethanol	63.346	0.683	0.354	3.320
Butanol	29.030	0.189	0.285	2.120
Octanol	7.870	0.117	0.187	0.970
Ethylene Glycol	3.856	0.126	0.094	0.510
Propylene Glycol	30.023	1.152	0.307	1.760
Polyethylene Glycol (PEG) 400	414.804	11.234	3.763	63.120

\*Solubility of celecoxib in glycerol could not be determined due to the very high viscosity of the saturated solution.

from Merck, Ltd (Mumbai, India). Dimethylsulfoxide (DMSO) and dimethylformamide (DMF) were first dried by keeping in contact with Linde (Union Carbide Corporation, Linde Division, Terrytown, NY) type-4A molecular sieves overnight. DMSO was further purified by vacuum distillation (75.6°-75.8°C) at a pressure of 12 millimeters of mercury. DMF was also vacuum distilled (76°C) at a pressure of 39 millimeters of mercury. Acetonitrile (ACN) was refluxed with 1% (wt/vol) phosphorus pentoxide for one-half hour and then distilled (81.6°C). Water used was double distilled in all glass apparatus.

On the basis of preliminary experiments, the following solvents were selected for the analysis of drug solutions: 10% aqueous DMSO for rofecoxib, 10% aqueous DMF for meloxicam, and 20% aqueous ACN for celecoxib and nimesulide. Extinction coefficients of all the drugs in the selected solvents were determined at 252, 263, 363, and 302 nm for celecoxib, rofecoxib, meloxicam, and nimesulide, respectively. The drug concentration range for the validity of Beer-Lambert law was found to be 10 to 50 µg/mL in each case.

For the determination of solubility, excess of drug was placed in contact with 5 mL of solvent in sealed glass tubes. The tubes were shaken occasionally on a vortex mixer and were maintained at 25°C for 24 hours. The saturated solution was centrifuged and the supernatant was filtered through a sintered glass crucible (grade 4). The concentration of drug in the saturated solution was determined by ultraviolet absorption spectroscopy after appropriate dilution with the selected solvents.

A pH-solubility profile of drugs was obtained in the pH range 7.0 to 10.9 by determining the solubility of drugs in 0.05M glycine-sodium hydroxide buffer solutions of different pH values. The pH of the saturated drug solution, measured on a pH meter, was taken as the final pH in each case. To measure drug concentration, extinction coefficients of various drugs were also determined at each pH value.

## RESULTS AND DISCUSSION

### *Solubility in Pure Solvents*

The solubility of 4 cox-2 inhibitors, celecoxib, rofecoxib, meloxicam, and nimesulide in water and in some nonaqueous solvents at 25°C is provided in **Table 1**. All the drugs exhibit poor water solubility. This is because the studied drugs, being predominantly nonpolar molecules, cannot effectively break into the lattice structure of water; hence water solubility is low. High values of octanol-water partition coefficients (log *P*) of drugs (**Table 2**) also suggest good solubility in lipophilic solvents. Celecoxib, having the highest log *P* value, has exceptionally high solubility in all the nonaqueous solvents studied. Solubility of celecoxib was found to be particularly high in methanol and PEG 400. In general, alcohols were better solvents than water. Among alcohols, solubility decreased with increasing chain length in each case. Among glycols, solubility increased in moving from ethylene glycol to pro-

**Table 2.** Physico-Chemical Properties of Various Nonsteroidal Anti-inflammatory Drugs

Drug/Solvent	Property	
	Dielectric constant ( $\epsilon$ )	Partition Coefficient* ( $\log P$ )
Celecoxib	-	3.683
Rofecoxib	-	1.705
Meloxicam	-	1.904
Nimesulide	-	1.788
Water	78.36	-
Glycerol	42.5	-1.223
Methanol	32.63	-0.271
Ethanol	24.3	0.133
Butanol	17.1	1.001
Octanol	9.72	2.737
Ethylene Glycol	37.7	-0.897
Propylene Glycol	32.0	-0.193
Polyethylene Glycol (PEG) 400	12.4	-

\*Values calculated using Molinspiration software (Molinspiration Cheminformatics, Bratislava, Slovak Republic).

ylene glycol. For all the drugs, solubility was exceptionally high in polyethylene glycol.

Some physico-chemical parameters of the solvents and the drugs used in the present study are given in **Table 2**. Dielectric constants of the solvents show that the polarity of the solvents varies as water > glycerol > ethylene glycol > ethanol > polyethylene glycol 400. **Table 1** shows that the solubility of the drugs decreases with an increase in the polarity of solvents. Thus, polarity of the solvent is an important factor governing the solubility of the drugs. Hydrophobicity of the solvents, measured as octanol-water partition coefficients ( $\log P$ ), also showed that the solubility increases with the hydrophobicity of the solvent. However, polarity and hydrophobicity are not the only factors involved. Among alcohols, solubility does not increase with a decrease in the polarity or an increase in hydrophobicity of alcohol; solubility was maximum in methanol and decreased with an increase in the chain length of alcohol. This effect indicates that the ability of the solvent to form hydrogen bonds with the hetero-atoms in the drug molecule is another important factor governing the solubility of drugs in alcohols. As the alkyl chain length in alcohols increases, their ability to form

hydrogen bonds with the drug molecules decreases<sup>14</sup>; hence the solubility decreases. The greater solubility of drugs in ethanol than in ethylene glycol suggests that the solubility is also governed by the intermolecular interactions between the solvent molecules, which are expected to be stronger in glycols than in alcohols.<sup>14</sup> In the case of glycols, the increase in solubility in moving from ethylene glycol to propylene glycol suggests that the hydrophobic interactions are more important in governing the solubility of the studied drugs in glycols. The exceptionally high solubility of drugs in PEG 400 is probably because of extensive hydrophobic interactions with the solvent because PEG 400 has a long nonpolar part compared with other solvents.

### **Solubility in Mixed-Solvent Systems**

Cosolvent addition is a highly effective technique for enhancement of solubility of poorly soluble drugs.<sup>7, 8, 15</sup> The small nonpolar hydrocarbon region in the cosolvent can reduce the ability of the aqueous system to squeeze out nonpolar solutes. The mixed-solvent systems in the present study include ethanol-PEG 400,

**Table 3.** Solubility of Various Drugs in Glycerol-Ethanol Mixtures at 25°C\*

Weaker Solvent (%)	Stronger Solvent (%)	Dielectric Constant ( $\epsilon$ )	Solubility (mg/mL)			
			Celecoxib	Rofecoxib	Meloxicam	Nimesulide
100	0	42.50	-	0.108	0.138	0.218
90	10	40.68	-	0.124	0.298	0.416
80	20	38.86	-	0.203	0.392	0.691
60	40	35.22	28.850	0.544	0.403	1.693
40	60	31.58	37.690	0.685	0.484	2.749
20	80	27.94	58.850	0.759	0.407	3.420
10	90	26.12	61.540	0.739	0.372	4.040
0	100	24.30	63.346	0.683	0.354	3.320

\*Solubility of celecoxib above 60% glycerol in the solvent-cosolvent mixture could not be determined due to the very high viscosity of the saturated solution.

**Table 4.** Solubility of Various Drugs in Polyethylene Glycol-Ethanol Mixtures at 25°C\*

Weaker Solvent (%)	Stronger Solvent (%)	Dielectric Constant ( $\epsilon$ )	Solubility (mg/mL)			
			Celecoxib	Rofecoxib	Meloxicam	Nimesulide
Ethanol	PEG-400					
100	0	24.30	63.346	0.683	0.354	3.320
80	20	21.92	171.778	1.005	0.783	9.900
60	40	19.54	251.810	2.228	1.610	24.640
40	60	17.16	327.939	3.964	2.730	36.000
20	80	14.78	366.980	8.143	3.842	56.512
10	90	13.59	391.585	8.973	4.023	65.600
0	100	12.40	414.804	11.234	3.763	63.120

\*PEG indicates polyethylene glycol.

glycerol-ethanol, and water-ethanol. The solvent with higher drug solubility in the pure state is referred to as the stronger solvent and the other as the weaker solvent in each case. The data are provided in **Tables 3, 4, and 5**. Dielectric constants of the solvent mixtures were calculated from the relation  $\epsilon_{\text{mix}} = \epsilon_{\text{ws}}f_{\text{ws}} + \epsilon_{\text{ss}}f_{\text{ss}}$ , where  $\epsilon$  and  $f$  are the dielectric constant and volume fraction, respectively; and subscripts mix, ws, and ss represent values for the mixture, weaker solvent, and stronger solvent, respectively. These values are also provided in **Tables 3, 4, and 5**. As shown, in most cases solubility increased with a decrease in the dielectric constant of the mixture only up to a certain concentration of the

stronger solvent, 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 solvent are also involved.

The logarithmic relationship between total drug solubility in a mixed-solvent system and the volume fraction of the stronger solvent can be described by Equation 1.<sup>8,16</sup>

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

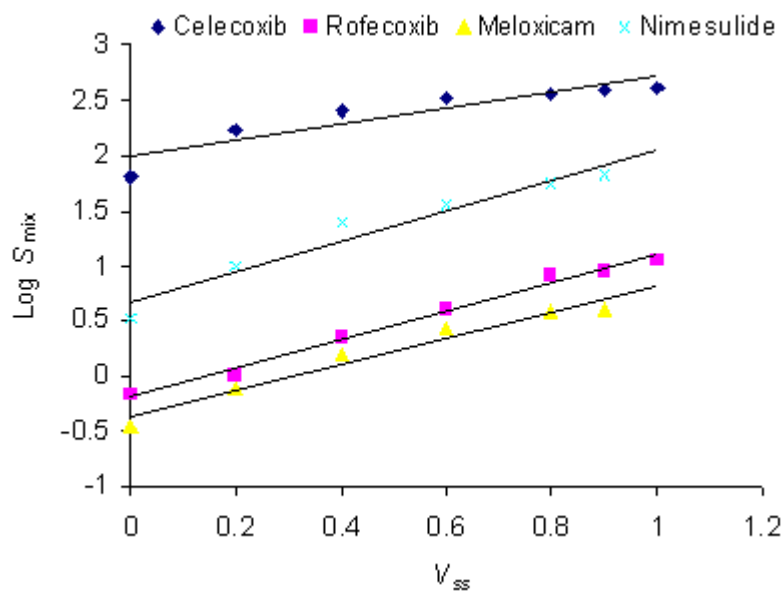
**Table 5.** Solubility of Various Drugs in Ethanol-Water Mixtures at 25°C

Weaker Solvent (%)	Stronger Solvent (%)	Dielectric Constant ( $\epsilon$ )	Solubility (mg/mL)			
			Celecoxib	Rofecoxib	Meloxicam	Nimesulide
Water	Ethanol					
100	0	78.36	0.007	0.009	0.012	0.014
90	10	72.95	0.010	0.016	0.042	0.062
80	20	67.55	0.015	0.032	0.051	0.101
60	40	56.74	0.294	0.168	0.061	0.125
40	60	45.92	5.062	0.548	0.134	0.642
20	80	35.11	31.904	1.018	0.255	2.628
10	90	29.71	48.654	1.041	0.298	3.560
0	100	24.30	63.346	0.683	0.354	3.320

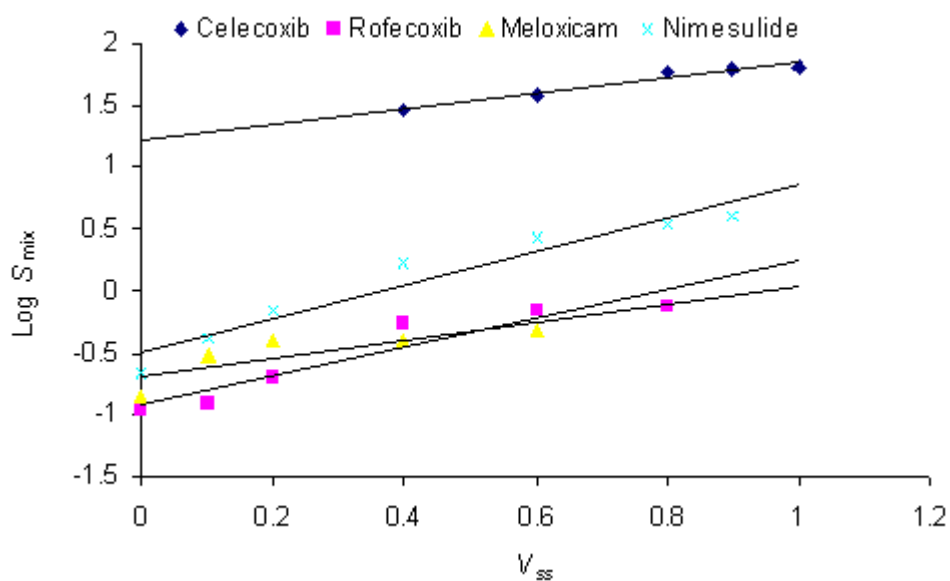
where  $S_{\text{mix}}$  and  $S$  are the solubilities of drug in solvent mixture and pure solvent, respectively.  $V_{\text{ss}}$  is the volume fraction of the stronger solvent and  $\Phi$  is the solubilization power of the stronger solvent. The  $\Phi$  value was obtained from the linear  $\log S_{\text{mix}}$  versus  $V_{\text{ss}}$  plots (Figures 1, 2, and 3). The solubilization parameters for various drugs are given in Table 6. For a given solvent system, the solubilization power ( $\Phi$ ) gave a quantitative estimate of the ability of the stronger solvent to increase the solubility of a drug in a given solvent. Some of the previous reports<sup>17,18</sup> have shown that the solubilization power can be correlated to the cosolvent polarity or octanol-water partition coefficient of solute. Our results show that the greater the difference is in the polarity of the 2 solvents in a given mixed-solvent, the greater the solubilization power is. However, in a given mixed-solvent system, the solubilization power does not bear a simple relationship to the polarity of the drugs, determined by their partition coefficients. Solubilization power data again shows that structural factors other than the polarity/hydrophobicity of drugs are also involved. The aqueous solubility of celecoxib, rofecoxib, and nimesulide were enhanced significantly by the use of ethanol as the second solvent. The increase was relatively smaller for meloxicam. Maximum drug solubility was observed in PEG-ethanol mixtures, in the case of all the drugs.

### *pH-Solubility Profile*

The solubility of all the drugs in aqueous solutions was very low in acidic medium. The pH-solubility profile was determined in the alkaline range between pH 7 to 10.9 using 0.05M glycine-NaOH buffer solution. The solubility data for various drugs at different pH values is given Table 7. Meloxicam and nimesulide showed significant increase in solubility with an increase in pH value. For celecoxib, the increase was much smaller, and for rofecoxib, pH change had negligible effect on solubility. One of the major factors responsible for dissolution of an organic compound is its ability to dissociate into ionic species, which in turn depends on the pH of the medium. Rofecoxib does not contain any ionizable group and therefore cannot ionize at any pH. Its solubility is therefore practically unaffected by pH. All other drugs used contain one or more ionizable groups and because they are acidic drugs, the percentage of drug ionized and thus the solubility increases with an increase in the pH value. When the pH of the drug solution was increased by about 3 units, the solubility increased about 2 times in the case of rofecoxib, about 8 times in the case of celecoxib, about 300 times in the case of meloxicam, and about 1000 times in the case of nimesulide. The pH-dependence of solubility can have useful application in the design of liquid and parenteral formulation of these drugs.



**Figure 1.** Log  $S_{mix}$  vs  $V_{ss}$  plots for ethanol-PEG 400 system.



**Figure 2.** Log  $S_{mix}$  vs  $V_{ss}$  for glycerol-ethanol system.

### Significance of Solubility Data

Although the drugs used in this study have poor aqueous solubility, solubility could be significantly enhanced by using a series of pure solvents and mixed-solvent systems. The aqueous solubility of celecoxib, rofecoxib, and nimesulide could be enhanced significantly by the use of ethanol as the second solvent. In general, ethanol, PEG, and ethanol-PEG mixtures are found to be good solvents for these drugs. In some cases, propylene glycol and glycerol-ethanol mixtures

also produced sufficient solubility. These solvents are generally considered safe for oral administration.<sup>19-21</sup> The commonly used doses of celecoxib, rofecoxib, meloxicam, and nimesulide, and the minimum solubility of the drug required for a 5-mL and a 2-mL dose are provided in **Table 8**. The solvents with drug solubility greater than that required for 5-mL and 2-mL doses are also given in **Table 8**. The data can be useful in the development of oral formulations of these drugs.

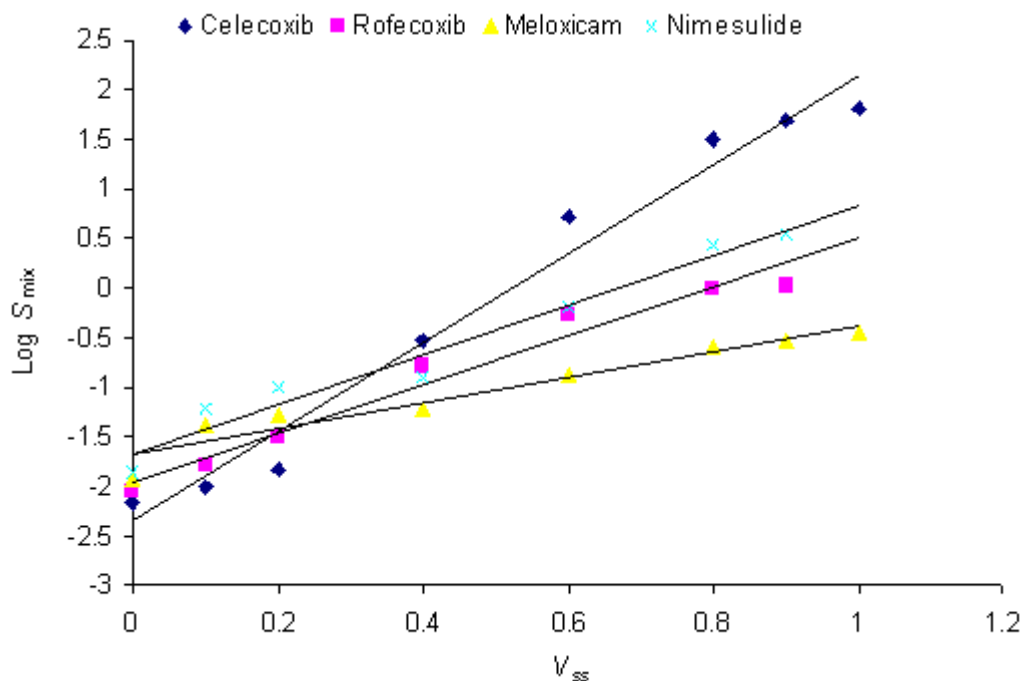


Figure 3.  $\text{Log } S_{mix}$  vs  $V_{ss}$  for water-ethanol system.

Table 6. Solubilization Parameters for Various Solvent-Cosolvent Systems

Weaker Solvent	Stronger Solvent	Drug	Concentration Range (Volume Fraction)	Stronger Solvent Solubilization Power ( $\Phi$ )
Ethanol	PEG 400	Celecoxib	0.0-1.0	0.716
Ethanol	PEG 400	Rofecoxib	0.0-1.0	1.285
Ethanol	PEG 400	Meloxicam	0.0-0.9	1.181
Ethanol	PEG 400	Nimesulide	0.0-0.9	1.386
Glycerol	Ethanol	Celecoxib	0.4-1.0	0.620
Glycerol	Ethanol	Rofecoxib	0.0-0.8	1.179
Glycerol	Ethanol	Meloxicam	0.0-0.6	0.732
Glycerol	Ethanol	Nimesulide	0.0-0.9	1.359
Water	Ethanol	Celecoxib	0.0-1.0	4.486
Water	Ethanol	Rofecoxib	0.0-0.9	2.395
Water	Ethanol	Meloxicam	0.0-1.0	1.293
Water	Ethanol	Nimesulide	0.0-0.9	2.489

**Table 7.** Solubility of Various Drugs in Glycine-NaOH Buffer Solution at Different pH Values\*

Celecoxib		Rofecoxib		Meloxicam		Nimesulide	
pH	Solubility (mg/mL)	pH	Solubility (mg/mL)	pH	Solubility (mg/mL)	pH	Solubility (mg/mL)
7.60	0.006	7.00	0.011	7.40	0.062	7.20	0.034
7.70	0.009	7.63	0.010	7.60	0.233	7.90	0.081
8.10	0.010	7.85	0.012	8.68	1.260	8.84	0.807
9.05	0.011	8.90	0.011	9.58	2.615	9.42	3.886
9.93	0.017	9.70	0.012	9.85	5.755	9.52	6.914
10.90	0.048	10.40	0.022	10.68	17.900 <sup>†</sup>	10.17	34.639 <sup>†</sup>

\*The pHs provided are the final pH values of the saturated solutions in each case.

<sup>†</sup>The reported solubility values are in 0.05N NaOH in the case of meloxicam and 0.10N NaOH in the case of nimesulide.

**Table 8.** Solvents With Drug Solubility Greater Than That Required for 5-mL and 2-mL Doses\*

Drug	Dose (mg)	Solvents With Drug Solubility	
Celecoxib	100	>20 mg/mL (5-mL dose)	>50 mg/ml (2-mL dose)
		ethanol, propylene glycol, PEG, glycerol-ethanol (40% ethanol & above), PEG-ethanol (all proportions), water-ethanol (80% ethanol and above)	ethanol, PEG, glycerol-ethanol (80% ethanol & above), PEG-ethanol (all proportions)
Rofecoxib	12.5	>2.5 mg/mL (5-mL dose)	>6.25 mg/mL(2-mL dose)
		PEG, PEG-ethanol (60% PEG & above)	PEG, PEG-ethanol (80% PEG & above)
Meloxicam	7.5	ethanol, propylene glycol, PEG, PEG-ethanol (40% PEG & above), pH 9.58 & above	PEG, PEG-ethanol (80% PEG & above), pH 9.85 & above
Nimesulide	100	>20 mg/mL (5-mL dose)	>50 mg/mL (2-mL dose)
		PEG, PEG-ethanol (40% PEG & above), pH 10.17 & above	PEG, PEG-ethanol (80% PEG & above)

\*PEG indicates polyethylene glycol.

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coxib, rofecoxib, meloxicam, and nimesulide, respectively.

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