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Research Article

Solubility Enhancement of Etoricoxib by Cosolvency Approach

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The purpose of the present study was to examine and compare the cosolvency using three different cosolvents, namely PEG 400, PG, and glycerin on the aqueous solubility enhancement of a poorly aqueous soluble drug, etoricoxib, since solubilization of nonpolar drugs constitutes one of the important tasks in the formulation design of liquid dosage forms. The aqueous solubility of etoricoxib was 0.0767 ± 0.0018 mg/mL, which was significantly improved by the addition of PEG 400, PG, and glycerin as cosolvents. It was scrutinized that the less-polar solvents were found to increase the aqueous solubility by greater extent, thus accentuating hydrophobic interaction mechanism. Among various solvent-cosolvent blends investigated, water-PEG 400 showed highest solubilization potential. Thus, the study generated an important array of data to compare the effect of these cosolvents on the aqueous solubility of etoricoxib.

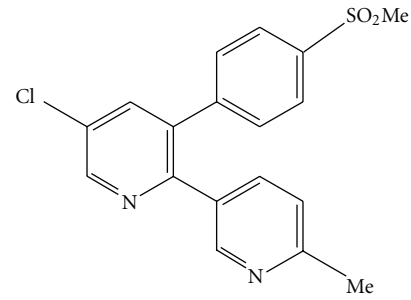
1. Introduction

Solubility is defined in quantitative terms as the concentration of the solute in a saturated solution at a certain temperature. In qualitative terms, solubility may be defined as the spontaneous interaction of two or more substances to form a homogeneous molecular dispersion [1, 2]. The solubility of drug molecules plays a key role in its bioavailability. The aqueous solubility of poorly aqueous soluble drug molecules in the gastrointestinal fluid often causes unsatisfactory bioavailability. Poorly aqueous soluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration of any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption [1]. However, various leading pharmaceutical companies have been able to triumph over technical hitches with very slightly aqueous soluble drugs, those with aqueous solubility of less than 0.1 mg/mL present some unique challenges. These drugs are particularly good candidates for advanced solubilisation technologies developed by companies specializing in drug delivery. Solubilisation of poorly aqueous soluble drugs is a frequently encountered challenge in screening studies of new chemical entities as well as in formulation design and development [3].

Cosolvency, pH adjustment, surfactant addition, and complexation are the most commonly encountered pharmaceutical approaches for solubilising drug candidates with low aqueous solubility [4]. Among them, use of cosolvent (i.e., cosolvency) is one of the most popular approaches for improving the solubility of poorly aqueous soluble drugs in pharmaceutical liquid formulations [5]. Cosolvents are the mixtures of miscible solvents often used to water which can dramatically change the solubility of poorly aqueous soluble drugs [6]. Weakly electrolytes and nonpolar molecules frequently have poor water solubility. Their solubility usually can be increased by the addition of water miscible solvent in which the drug has good solubility. This process is known as cosolvency, and the solvents used to increase solubility are known as cosolvent. Cosolvent system works by reducing the interfacial tension between the aqueous solution and hydrophobic solute. It is also commonly referred to as solvent blending [6]. Most cosolvents have hydrogen bond donor and/or acceptor groups as well as small hydrocarbon regions. Their hydrophilic hydrogen-bonding groups ensure water miscibility, while their hydrophobic hydrocarbon regions interfere with waters hydrogen bonding network, reducing the overall intermolecular attraction of water. By disrupting waters self-association, cosolvents reduce waters ability to squeeze out nonpolar, hydrophobic compounds, thus

increasing solubility [7]. The advantage of cosolvent technology enhancing drug solubility in a liquid-based formulation includes [8] convenience, removing the need for mixing solvent before administration; safety, avoiding contamination in the dispensing process; inexpensive, no need for expensive pharmaceutical technology for formulation of dosage form. The most frequently used low-toxicity cosolvents for parenteral use are propylene glycol, ethanol, glycerin, polyethylene glycol (PEG), dimethylsulfoxide (DMSO), and dimethylacetoamide (DMA) [9–13].

Etoricoxib, 5-chloro- 6′-methyl- 3[4-(methyl sulfonyl) phenyl] - 2, 3′–bypyridine, is a highly selective second generation cyclooxygenage-2 (COX-II) inhibitor administered orally as an analgesic and nonsteroidal anti-inflammatory drug [14]. It is used in the treatment of rheumatoid arthritis, osteoarthritis, postoperative dental pain, chronic back pain, and acute gout [15, 16]. Its chemical structure is shown in Scheme 1. Since very low aqueous solubility of etoricoxib can cause formulation problems and limit its therapeutic applications by delaying rate of absorption and onset of action, it is essential to improve the solubility of etoricoxib. Although there have been enormous amount of research work performed using different techniques of solubilisation for the solubility improvement of etoricoxib, cosolvency technique needs to be explored. Nevertheless, in previous literature, no attempt has been taken to investigate the aqueous solubility enhancement of etoricoxib by cosolvency approach. The aim of present study is to investigate the effect of various pharmaceutically accepted cosolvents like polyethylene glycol 400 (PEG 400), polypropylene glycol (PG), and glycerin on the aqueous solubility of etoricoxib.



Scheme 1: Chemical structure of etoricoxib.

Table 1: Solubility profile of etoricoxib in water, PEG 400, PG, and glycerin at room temperature.

Solvent	Dielectric constant	Solubility of etoricoxib (mg/mL) (Mean ± S.D., $n = 3$)
Water	78.36	0.0767 ± 0.0018
PEG 400	12.40	2.1918 ± 0.0828
PG	32.00	1.6657 ± 0.0482
Glycerin	42.50	0.8488 ± 0.0196

2. Experimental

2.1. Materials. Etoricoxib was gift samples by Zydus Health Care Ltd. India. PEG 400, PG, and glycerin were purchased from Qualigen Fine Chemicals, India. All other chemicals were of analytical reagent grade, and freshly prepared distilled water was used throughout the study.

2.2. Estimation of Etoricoxib. Estimation of etoricoxib was made in distilled water at λ_{max} of 284 nm by UV-VIS spectrophotometry method using a UV-VIS spectrophotometer (U. V. 2440 Double beam spectrophotometer, SHIMADZU Corporation, Japan). The drug content was estimated from the calibration curve, which was constructed between 2 and 10 μg/mL concentration ranges. The method was validated for linearity, accuracy, and precision. The regression equation for the calibration curve was $y = 0.0519x + 0.0171$, $R^2 = 0.9912$.

2.3. Solubility Studies. Distilled water and cosolvents (PEG 400, PG, and glycerin) will be mixed volumetrically to form mixtures containing 0, 10, 20, 30, 40, 50, 60, 70, 80, 90, and 100% various cosolvents in screw cap amber color bottles. Excess drug will be added directly into the pure and cosolvant mixed solvents. These bottles will be shaken using a shaker at 50 rpm and room temperature (25 ± 1°C) for 24 h in order to obtain equilibrium. After 24 h of equilibrium, aliquots will be withdrawn, filtered (0.22 μm pore size), and diluted suitably. These samples will be analyzed using UV-VIS spectrophotometer (U. V. 2440 double beam spectrophotometer, SHIMADZU Corporation, Japan) at 284.0 nm wavelength, and solubility of etoricoxib (mg/mL) in each sample were calculated.

3. Results and Discussion

3.1. Solubility of Etoricoxib in Pure Solvents. The solubility of etoricoxib in water, PEG 400, PG, and glycerin at room temperature is given in Table 1. Etoricoxib exhibited poor aqueous solubility in water. This is because of the drug, being predominantly nonpolar molecules, cannot effectively break the lattice structure of water; hence, the aqueous solubility of the etoricoxib is low. The solubility of etoricoxib was found higher in PEG 400 than other solvents investigated in the study. Dielectric constants (ε) of these pure solvents were collected from the literature [4] and presented in Table 1, which indicates that the solubility of etoricoxib decreases with an increase in the polarity of these solvents. Thus, the polarity of solvents is an important factor governing the solubility of drugs. Hydrophobicity of solvents also showed that the solubility increases with the solvent's hydrophobicity. However, polarity and hydrophobicity are not only the factors involved. In the case of glycols (PEG 400 and PG), the increase in solubility suggests that the hydrophobic interactions are more important in governing the solubility of the drugs in glycols. The high solubility of drugs in PEG 400 is probably because of extensive hydrophobic interactions. With the solubility data obtained in the pure solvents, the enhancement of solubility was attempted using cosolvency approach, which is outlined in the further discussion.

Table 2: Solubility profile of etoricoxib in water-PEG 400 mixture at room temperature.

Water (% v/v)	Polyethylene glycol 400 (% v/v)	Dielectric constant	Solubility of etoricoxib (S_m, mg/mL) (Mean ± S.D., $n = 3$)
0	100	12.50	2.1918 ± 0.0828
10	90	19.00	2.0840 ± 0.0607
20	80	25.59	1.7664 ± 0.0552
30	70	32.19	1.4311 ± 0.0417
40	60	38.78	1.1682 ± 0.0312
50	50	45.38	0.8329 ± 0.0210
60	40	51.98	0.6044 ± 0.0098
70	30	58.57	0.3757 ± 0.0066
80	20	65.17	0.2708 ± 0.0043
90	10	71.76	0.1590 ± 0.0037
100	0	78.36	0.0767 ± 0.0018

Table 3: Solubility profile of etoricoxib in water-PG mixture at room temperature.

Water (% v/v)	PG (% v/v)	Dielectric constant	Solubility of etoricoxib (S_m, mg/mL) (Mean ± S.D., $n = 3$)
0	100	32.00	1.6657 ± 0.0448
10	90	36.64	1.5431 ± 0.0427
20	80	41.27	1.3487 ± 0.0383
30	70	45.91	1.0899 ± 0.0216
40	60	50.54	0.7581 ± 0.0175
50	50	55.18	0.6122 ± 0.0093
60	40	59.82	0.4486 ± 0.0072
70	30	64.45	0.3187 ± 0.0050
80	20	69.09	0.2250 ± 0.0032
90	10	73.72	0.1479 ± 0.0026
100	0	78.36	0.0767 ± 0.0018

3.2. Solubility of Etoricoxib in Water-Cosolvent Systems. Cosolvent addition is a highly effective technique for enhancement of solubility of poorly soluble drugs [10, 17]. The small nonpolar hydrocarbon region in the cosolvent can reduce the ability of the aqueous system to squeeze out nonpolar solutes. The cosolvents are water miscible solvents, widely used in pharmaceutical field for drug solubilization. Three commonly used pharmaceutical cosolvents, PEG 400, PG, and glycerin were investigated in the present study as cosolvents for the aqueous solubility of etoricoxib. The solvent with higher drug solubility (cosolvent) in the pure state is referred to as the stronger solvent and the other as the weaker solvent (here water). All these cosolvents formed a homogeneous mixture with water. The solubility of etoricoxib in various water-cosolvent blend with their respective dielectric constants collected from the literature [4] are given in Tables 2, 3, and 4.

Dielectric constants of the solvent mixtures were calculated from the relation

$$\varepsilon_{\text{mix}} = \varepsilon_{\text{ws}} f_{\text{ws}} + \varepsilon_{\text{ss}} f_{\text{ss}}, \quad (1)$$

where ε and f are the dielectric constant and volume fraction, respectively; subscripts mix, ws, and ss represent values for the mixture, weaker solvent, and stronger solvent, respectively. In most of the cases, solubility increased with a decrease in the dielectric constant of the mixture. This effect occurs because the drug, etoricoxib, has 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 solubilization of hydrophobic solutes in water-cosolvent mixtures can be described by the log-linear model [18]. Accordingly, the solubility in a water-cosolvent mixture (S_m) can be estimated from the solubility values in pure water (S_w) and in the neat cosolvent (S_c) and the volume fraction concentrations of water and the cosolvent, f_w and f_c respectively, in the solvent mixture

$$\log S_m = f_c \log S_c + f_w \log S_w. \quad (2)$$

The above expression predicts a straight line for log S_m as a function of cosolvent concentration, corresponding to an exponential increase in solubility by the addition of an organic cosolvent. The log-linear model accounts for the effect of solute-solvent interactions in the mixture as the (volume fraction) weighted average of the solute-solvent

Table 4: Solubility profile of etoricoxib in water-glycerin mixture at room temperature.

Water (% v/v)	PG (% v/v)	Dielectric constant	Solubility of etoricoxib (S_m, mg/mL) (Mean ± S.D., $n = 3$)
0	100	42.50	0.8488 ± 0.0196
10	90	46.09	0.8310 ± 0.160
20	80	49.67	0.7099 ± 0.0153
30	70	53.26	0.5893 ± 0.0088
40	60	56.84	0.5314 ± 0.0072
50	50	60.43	0.3400 ± 0.0056
60	40	64.02	0.2961 ± 0.0048
70	30	67.60	0.2291 ± 0.0034
80	20	71.19	0.1978 ± 0.0032
90	10	74.77	0.1309 ± 0.0018
100	0	78.36	0.0767 ± 0.0018

Table 5: Solubilization powers of PEG 400, PG, and glycerin calculated from the log-linear solubilization plot by regression analysis.

Solvent	Solubilization power (σ)	R^2
PEG 400	1.4358	0.9466
PG	1.3080	0.9622
Glycerin	1.0154	0.9582

interactions present when the solute is dissolved in each of the individual solvents [18].

The log-linear model is frequently expressed in the alternative form

$$\log S_m = \log S_w + \sigma f_c, \tag{3}$$

where $\sigma = \log(S_c/S_w)$, the slope of the solubilization line, is often referred to as the solubilization power of the cosolvent.

Using the solubility of etoricoxib in water-cosolvent mixture data, we have drawn log-linear solubilization plot ($\log S_m$ versus Volume fraction of cosolvent used) for all the cosolvents investigated (Figure 1). In the log-linear solubilization plot, it was evidenced that PEG 400 produced higher solubility as a cosolvent with water than the two other cosolvents that is, PG and glycerin investigated in this study. Solubilization powers of these cosolvents were calculated from the log-linear solubilization plot by regression analysis and presented in Table 5.

The cosolvents usually reduce chemical potential of solution by decreasing hydrogen bond density of water, thus create a less-polar environment in the balk, resulting in more drug molecules going into solution. As expected, PEG 400 being less-polar exhibited better solubilization power (1.4358) in comparison with PG (1.3080) and glycerin (1.0154). These results indicate that the drug molecules preferably solubilize in nonpolar environment rather than polar environment.

The structure of PEG 400 is H-(O-CH_2-CH_2)$_n$-OH, where n is approximately 8 to 9. Hydrogen bonding makes this peculiar structure of PEG 400 miscible with water, which has some unique properties as a solvent: large surface

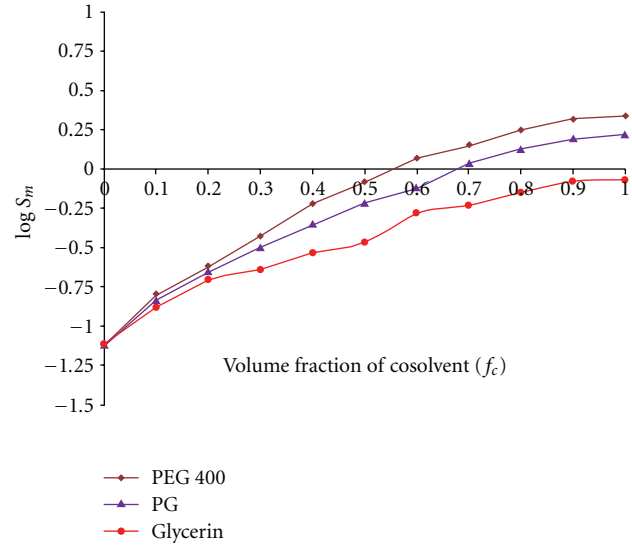


Figure 1: Comparative solubility profile of etoricoxib in various water-cosolvent mixtures by log-linear solubilization plot. Cosolvents used were PEG 400, PG, and glycerin.

tension (71.8 dyne/cm), a high level of hydrogen bonding, and sizable dielectric constant (80 at 20°C). Hydrogen bonding between water molecules is broken with the help of hydrophobic hydrocarbon region of insoluble drugs, thus reducing intermolecular interaction [7, 19]. In addition, it can be stated that PEG may assist to reduce the dipole moment of water and allow hydrophobic compounds to fit in [19].

4. Conclusion

The present study evaluated and compared aqueous solubility enhancement of etoricoxib using three different cosolvents, namely, PEG 400, PG, and glycerin. PEG 400 has been an acceptable cosolvent in terms of side-effect profile and most efficient solubilizing cosolvent. The study may also generate an array of data for solubilisation of etoricoxib

using various pharmaceutically accepted cosolvents like PEG 400, PG, and glycerine, which will be useful in formulation design and development of liquid dosage forms containing etoricoxib.

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References

[1] V. R. Vemula, V. Lagishetty, and S. Lingala, "Solubility enhancement techniques," *International Journal of Pharmaceutical Sciences Review and Research*, vol. 5, no. 1, pp. 41–51, 2010.

[2] V. R. Babu, S. H. Areefulla, V. Mallikarjun et al., "Solubility and dissolution enhancement: an overview," *Journal of Pharmacy Research*, vol. 3, no. 1, pp. 141–145, 2010.

[3] B. Bittner and R. J. Mountfield, "Intravenous administration of poorly soluble new drug entities in early drug discovery: the potential impact of formulation on pharmacokinetic parameters," *Current Opinion in Drug Discovery and Development*, vol. 5, no. 1, pp. 59–71, 2002.

[4] P. R. Sathesh Babu, C. V. S. Subrahmanyam, J. Thimmasetty, R. Manavalan, and K. Valliappan, "Solubility of meloxicum in mixed solvent systems," *Ethiopian Pharmacutical Journal*, vol. 25, no. 1, pp. 23–28, 2007.

[5] K. Amin, R. M. Dannenfelser, J. Zielinski, and B. Wang, "Lyophilization of polyethylene glycol mixtures," *Journal of Pharmaceutical Sciences*, vol. 93, no. 9, pp. 2244–2249, 2004.

[6] S. H. Yalkowsky and T. J. Roseman, "Solubilization of drugs by cosolvents," in *Techniques of Soluhilization of Drugs*, S. H. Yalkowsky, Ed., p. 91, Dekker, New York, NY, USA, 1981.

[7] J. W. Millard, F. A. Alvarez-Núñez, and S. H. Yalkowsky, "Solubilization by cosolvents: establishing useful constants for the log-linear model," *International Journal of Pharmaceutics*, vol. 245, no. 1-2, pp. 153–166, 2002.

[8] M.-K. Yeh, L.-C. Chang, and A. H.-J. Chiou, "Improving tenoxicam solubility and bioavailability by cosolvent system," *AAPS PharmSciTech*, vol. 10, no. 1, pp. 166–171, 2009.

[9] P. R. Babu, C. V. Subrahmanyam, J. Thimmasetty, R. Manavalan, K. Valliappan, and S. A. Kedarnath, "Solubility enhancement of cox-II inhibitors by cosolvency approach," *Dhaka University Journal of Pharmaceutical Sciences*, vol. 7, no. 2, pp. 119–126, 2008.

[10] S. H. Yalkowsky and J. T. Rubino, "Solubilization by cosolvents I: organic solutes in propylene glycol-water mixtures," *Journal of Pharmaceutical Sciences*, vol. 74, no. 4, pp. 416–421, 1985.

[11] L. Pan, K. Tsutsui, L. Takahashi et al., "Comparison of chromatographic and spectroscopic methods used to rank compounds for aqueous solubility," *Journal of Pharmaceutical Sciences*, vol. 90, no. 4, pp. 521–529, 2001.

[12] S. Nema, R. J. Washkuhn, and R. J. Brendel, "Excipients and their use in injectable products," *PDA Journal of Pharmaceutical Science and Technology*, vol. 51, no. 4, pp. 166–171, 1997.

[13] J. T. Rubino and S. H. Yalkowsky, "Co-solvency and deviations from log-linear solubilization," *Pharmaceutical Research*, vol. 4, no. 3, pp. 231–236, 1987.

[14] A. Das, A. K. Nayak, B. Mohatny, and S. Panda, "Solubility and dissolution enhancement of etoricoxib by solid dispersion technique using sugars," *ISRN Pharmaceutics*, vol. 2011, Article ID 819765, 8 pages, 2011.

[15] D. J. Cochrane, B. Jarvis, and G. M. Keating, "Etoricoxib," *Drugs*, vol. 62, no. 18, pp. 2637–2651, 2002.

[16] D. M. Patel and M. M. Patel, "Optimization of fast dissolving etoricoxib tablets prepared by sublimation technique," *Indian Journal of Pharmaceutical Sciences*, vol. 70, no. 1, pp. 71–76, 2008.

[17] N. Seedher and S. Bhatia, "Solubility enhancement of Cox-2 inhibitors using various solvent systems," *AAPS PharmSciTech*, vol. 4, no. 3, article 33, 2003.

[18] Y. Miyako, Y. Zhao, K. Takeshima, T. Kataoka, T. Handa, and R. Pinal, "Solubility of hydrophobic compounds in water-cosolvent mixtures: relation of solubility with water-cosolvent interactions," *Journal of Pharmaceutical Sciences*, vol. 99, no. 1, pp. 293–302, 2010.

[19] P. Chaudhari, P. Sharma, N. Barhate, P. Kulkarni, and C. Mistry, "Solubility enhancement of hydrophobic drugs using synergistically interacting cyclodextrins and cosolvent," *Current Science*, vol. 92, no. 11, pp. 1586–1591, 2007.