RESEARCH PAPER

Accepted 10 August 2001
Revised 28 July 2001
Received 7 November 2000
Indian J. Pharm. Sci., 2001, 63(6) 459-467

Solubilization of Etodolac for Parenteral Administration

M. A. ETMAN*, R. O. SALAMA, M. A. SHAMSEDEEN AND A. EL-KAMEL
Department of Pharmaceutics, Faculty of Pharmacy
University of Alexandria, Alexandria, Egypt

Etodolac (ETO) is a nonsteroidal antiinflammatory drug (NSAID) that exhibits analgesic, antipyretic and antiinflammatory activities and is practically insoluble in water. The solubility of ETO in four different co-solvents; ethanol, propylene glycol, polyethylene glycol 400, and glycerol, three sugars; sucrose, sorbitol, and mannitol, two hydrotropic salts; sodium benzoate and sodium salicylate, and two enhancers; Tween 80 and Brij 58 was investigated. The solubility of ETO by the used co-solvents can be arranged in the following order: ethanol>PEG 400>PG>glycerol. Similar increase in solubility was observed with Tween 80 and Brij 58. The increase in temperature from 25 to 37° was accompanied by an increase in drug solubility at higher concentrations of co-solvents and hydrotropic solutions but the effect was insignificant with Tween 80 and Brij 58. The thermodynamic parameters calculated for some of these systems showed positive entropy and enthalpy in addition to negative free energy values suggesting high degree of randomness, endothermic dissolution and spontaneity of the solubility process. The used sugars and sodium salicylate showed no effect on ETO solubility. Based on the solubility data, a trial has been done to propose a formulation (100 mg/3 ml) for parenteral use in an aqueous solvent blend. The proposed formulation was tested physically for color, turbidity and precipitation upon storage for two months. In addition, the formulation didn't show any evidence of visible precipitation upon dilution with normal saline or 5% dextrose intravenous fluid except in low dilutions. Finally, in addition to parenteral formulation, the solubilized systems of ETO could be appreciable in the design of other liquid formulations intended for topical and oral administration of the drug.

Non-steroidal antiinflammatory drugs (NSAID) are among the most frequency prescribed medications[1]. Concerns about the overuse of NSAID stems from the potential toxicity of these agents, particularly with respect to GI complications. Attempts to reduce the GI effects of these drugs including enteric coating, non-acidic formulations and the use of pro-drugs have not had a significant impact[2]. Many studies[3-5] have shown that the newer NSAIDs are significantly better than traditional NSAIDs in terms of reduced micro-bleeding and endoscopically demonstrable GI lesions and ulcers. It could be pointed out that gastrointestinal irritation and ulceration occur to a lesser extent with etodolac[6]. Etodolac[7], (±) 1,8-diethyl-1,3,4,9-tetrahydropyrano-[3,4-b] indole-1-acetic acid, is a potent new NSAID that exhibits antiinflammatory, analgesic and antipyretic activity[8,9]. It is supplied only in the form of tablets and capsules for oral administration. Poorly soluble drugs usually possess hydrophilic-hydrophobic balance favorable to their permeation through GI membranes so that dissolution becomes the decisive factor in the bioavailability of these drugs[10]. Formulation of lipophilic drugs is frequently hampered by their poor aqueous solubility which again can limit their therapeutic applications. Etodolac is practically insoluble in water which precludes its use in parenteral and oral solutions and in topical dosage forms. Solubilization of insoluble drugs has been extensively studied to overcome difficulties which may be encountered during

*For correspondence

pharmaceutical formulation. The solubility of this poorly water soluble drug; ETO, can be improved by many approaches. These include the use of hydrotropic salts[11,12], co-solvents[13,14], surface active agents[15,16], sugars[17,18] and hydrophilic polymers[19]. The purpose of the present study was to investigate the effect of various techniques of solubilization on the solubility of etodolac. The study deals also with some aspects of thermodynamics in an attempt to interpret etodolac solubility in various co-solvent vehicles. Finally, a trial has been done to propose and preliminary assess the physical stability of a formulation for parenteral administration.

EXPERIMENTAL

Etodolac (Pharco Pharmaceuticals, Egypt), Tween 80 and ethyl alcohol (Prolabo, France), Brij 58 (Atlas Chemicals Industries Inc., Willington Delaware, USA) sucrose (B.P. grade), sorbitol (Wilkinson-Vickers, Wharfedal Labs., U.K.) polyethylene glycol 400; PEG (Winlab, U.K.), propylene glycol; PG (Jena Pharma-Laborchemie, Germany), glycerol (El-Nasr Pharmaceuticals, Egypt), sodium benzoate; SB (Bayer, Germany), D (-) mannitol and sodium salicylate (Riedel-de Haen, Germany) were used in the present study.

Solubility study:

Excess amounts of ETO were added to a 20 ml volume of distilled water, or mixtures of water and co-solvents, surfactants, hydrotropic salts or sugars in stoppered conical flasks. The flasks were then shaken (120 rpm) in a constant temperature water bath at 25 and 37 ±1° for 24 h and allowed to stand for another 24 h to attain equilibrium. Samples were then withdrawn, properly filtered (through a 0.45 µm membrane), suitably diluted and analyzed spectrophotometrically (Pharmacia LKB Biochem, Sweden) at 276 nm. A respective dilution of the solubilizing agent as a blank has been used. Three determinations were made for each sample. Preliminary experiments involving repetitive sampling and analysis were performed to ensure equilibrium of the saturated solutions.

Thin layer chromatographic study:

Plates of silica gel, activated at 105° for 1 h, were used. The alcoholic solution of ETO (50 µg/ml) alone, the aqueous solution of the solubilizer alone, as well as solubilized ETO we spotted on the base line with the aid of a microdropper. The plates were then left in air for 10 min to dry and transferred to a solvent jar saturated with a solvent system composed of toluene/absolute alcohol/glacial acetic acid (70:30:0.5 v/v). The solvent system was allowed to run to about 10 cm height of the plate for better separation. Finally, the plates were transferred to air ovens maintained at 80° for 5 min and spots are visualized under ultraviolet light (254 nm).

Formulation of aqueous injection:

On the basis of the solubility studies using co-solvents and hydrotropic salts, an aqueous injection of ETO was proposed (100 mg/3 ml). Fifty milliliters of the selected vehicle (50% v/v PG and 20% w/v S.B.) were placed in a screw capped bottle and the calculated amount of ETO was then added. Sodium bisulfate (0.1% w/v) was added to preclude the possibility of oxidation. The bottle was shaken for 24 h on a mechanical shaker to ensure complete solubilization followed by equilibration for the next 24 h. The solution was filtered through a 0.45 µm membrane filter and analyzed for drug content.

Evaluation of the injection:

Physical stability of the proposed formulation was inspected visually every day for 2 mo under fluorescent light against black and white background for any change in the physical appearance of the solution including turbidity, precipitation or discoloration. The proposed formulation was also evaluated by dilution with both normal saline (0.9% w/v NaCl) and 5% w/v glucose solutions. Several dilutions were prepared, including 1:1, 1:2, 1:5, 1:10, 1:25, 1:50 and 1:100. The various dilutions were monitored for their stability against precipitation at time intervals of 5, 10, 15, 30, 45, 60, 75 and 90 min.

RESULTS AND DISCUSSION

A solid drug will not be absorbed to any appreciable extent across the GI barriers unless it is in solution. Moreover, many pharmaceutical formulations intended for parenteral and topical use require the addition of a solubilizer to enhance the solubility of sparingly soluble components. Therefore, the effect of four co-solvents, two hydrotropic salts, two enhancers and three sugars on the solubility of etodolac has been investigated. The four co-solvents studied, ethanol, propylene glycol, polyethylene glycol 400 and glycerol resulted in variable degrees of improvement in etodalac solubility (figs. 1 and 2). However, the effect was dependent on both the concentration and the type of co-solvent used. It can be

generally observed that the solubility of the drug increases by increasing the co-solvent concentration. However, the effect is much significant at high co-solvent concentrations. This effect resulted in a positive deviation in the solubility phase diagram as shown in figs.1 and 2. This finding is in accordance with a previously reported data[13] regarding indomethacin solubility in some selected co-solvents. It can be also noted that the maximum solubilizing effect was observed with ethanol whereas, glycerol exhibited the minimum effect. Polyethylene glycol and propylene glycol showed intermediate effects. According to the obtained results, the four co-solvents

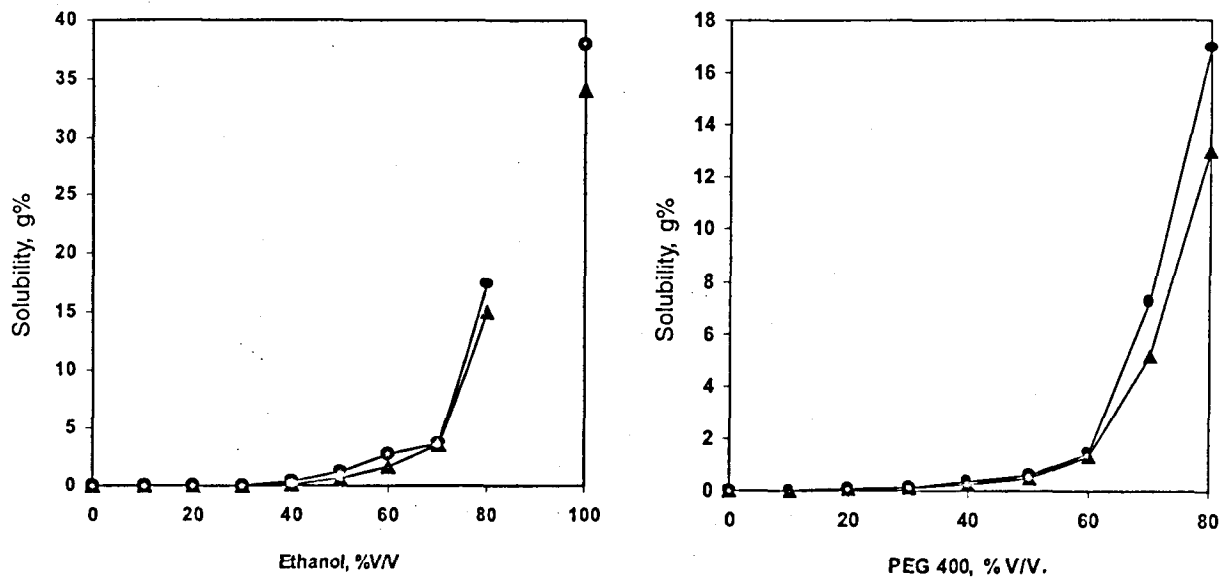

Fig. 1: Solubility of etodolac in ethanol and polyethylene glycol 400
Solubility of etodolac in ethanol and polyethylene glycol 400 at 25° (-▲-) and 37° (-O-).

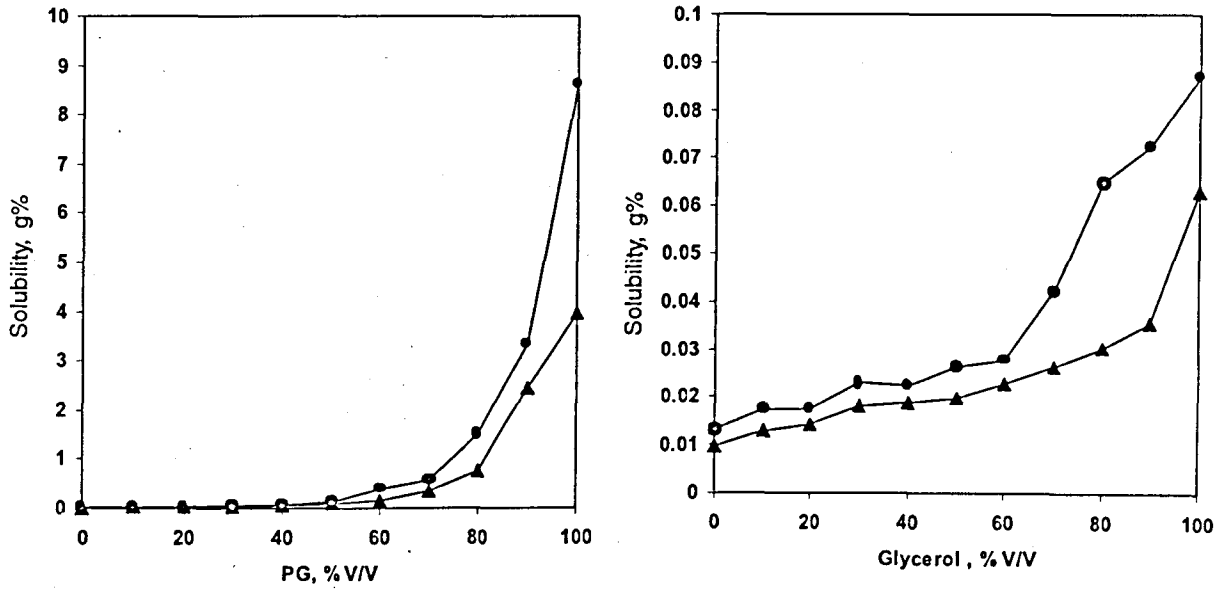

Fig. 2: Solubility of etodolac in propylene glycol and glycerol
Solubility of etodolac in propylene glycol and glycerol at 25° (-▲-) and 37° (-O-).

TABLE 1: SOLUBILIZING POWER OF DIFFERENT SOLULIZERS*

Conc.% v/v or %w/v	Ethanol (δ=12.8, ∈=24.3)		PEG 400		PG (δ=15, ∈=32.1)		Glycerol (δ=17.7, ∈=42.5)		Sodium Benzoate	
	Temperature°									
	25	37	25	37	25	37	25	37	25	37
5									16.91	6.26
10	1.45	1.37	2.23	1.52	2.02	1.22	1.31	1.02	18.27	15.65
15									22.66	33.82
20	2.89	2.89	5	3.5	2.31	1.37	1.42	1.025	27.25	106.74
25									53.76	144.37
30	5.2	3.35	9.34	6.55	2.6	3.04	1.81	1.21	78.61	160.82
35									144.74	501.66
40	13.58	19.33	21.71	19.18	5.2	3.65	1.88	1.18		
50	66.19	65.91	49.79	31.81	10.12	6.09	1.98	1.39		
60	163.01	142.77	133.35	76.26	15.61	20.39	2.27	1.46		
70	359.54	195.43	515.26	383.41	34.97	29.376	2.63	2.24		
80	1505.2	918.57	1308.18	894.98	77.17	80.67	3.03	3.44		
90					246.24	175.49	3.56	3.83		
100	3418.2	2008.22			397.11	455.56	6.36	4.61		

Conc. % v/v or w/v	Tween 80		Brij 58	
	Temperature°			
	25	37	25	37
0.0013	1.01	0.78	-	-
0.052	1.3	0.715	-	-
0.13	1.71	2.59	-	-
0.52	4.45	3.44	-	-
1	-	-	10.09	7.35
1.3	10.17	5.62	-	-
2	30.26	10.06	20.95	10.79
3	31.91	15.21	27.83	15.62
4	36.97	19.59	42.25	20.02
5	47.92	25.54	54.45	30.97
6	58.47	39.18	63.24	31.55
10	-	-	153.66	61
15	-	-	245.09	132.94
20	-	-	358.41	183.35

* Solubilizing power = solubility in solubilizer / solubility in water

PEG 400 = polyethylene glycol 400; PG = propylene glycol; δ = solubility parameter; ∈ = dielectric constant

can be arranged regarding their solubilizing power according to the following rank: ethanol>polyethylene glycol>propylene glycol>glycerol (Table 1). This order is in agreement with the ranking of the co-solvents with respect to their reported dielectric constant or solubility parameter[20] (Table 1). Co-solvents were reported[21] to decrease the dielectric constant of water, the effect increasing with co-solvent concentration. The solubility results obtained in the present study are in accordance with the dielectric constant concept which states that when the polarity of a solvent is decreased, it becomes a more favorable medium for the dissolution of non polar or relatively non-polar drugs[18].

To investigate the effect of temperature on the solubility of ETO by the four co-solvents, the solubility study was performed at two temperature levels i.e. 25 and 37°. Elevation of the temperature was accompanied by a minor but detectable increase in the solubility of the drug (figs.1 and 2). The solubility of ETO as in case of solids in general increased with temperature (endothermic) due to the lowered stability of the crystal lattice[22].

Moreover, the thermodynamics of (ETO) solubility in these co-solvents were calculated and the results are shown in Table 2. The free energy change (ΔG) associated with the solubility process may indicate the type of reaction occurring between the solutes and solvents:

$$\Delta G = - 2.303\ RT \log k \qquad (1)$$

Where, k is ratio of the molar solubilities of the drug in water and co-solvent solution, respectively[23]. The greater the negative value of ΔG the better would be the solubility. The negative values of ΔG can be arranged in the following rank: ethanol>PEG>PG>glycerol (Table 2). This finding is in accordance with the solubilizing power of the four co-solvents under investigation (Table 1). The free energy change values showed that the increase in co-solvent concentration provided a more thermodynamically suitable environment for the solubility of the drug (ΔG decrease). When non-polar molecules are dissolved in water, hydrophobic association may lead to a structuring of the aqueous environment and to a decrease in entropy[24]. The changes in any system are spontaneous when the free energy of the system decreases. This possibility is determined by three factors, the change of heat ΔH (bonding strength), temperature (T) and entropy change ΔS (disordering or bond breaking). At a constant temperature, the free energy will be determined by the change in the heat content and the entropy change, the equilibrium considered being between the same standard states.

$$\Delta G = \Delta H - T\,\Delta S \qquad (2)$$

ΔH can be determined using the integrated form of the van't Hoff equation

$$\Delta H = 2.303 \log (Ss/Sw)_2\ RT_2T_1/\ (Ss/Sw)_1 \quad T_2\text{-}T_1 \qquad (3)$$

Where Ss and Sw are the molar solubilities of the drug in co-solvent solutions and water; respectively, R is the gas constant, T is the absolute temperature and 1 and 2 refer to 25° and 37°, respectively. The different thermodynamic parameters are listed in Table 2. It is evident from Eq. 2 that the free energy change (ΔG), which accompanies dissolution is dependant on the value and sign of the change in enthalpy (ΔH).

The breaking up of water clusters surrounding the non-polar portion requires heat (+ΔH). Moreover, the dissolution process is endothermic one when ΔH is positive (Table 2). Therefore, an increase in temperature from 25° to 37° caused an increase in ETO solubility (figs.1 and 2). In addition, the solute molecules become randomly spread through the medium during the dissolution process. This causes a disordering and an increase in the entropy associated with the system. The more the positive the entropy change is the greater the randomness or disorder degree of the system and the environment is thermodynamically more favorable (ΔS increase, Table 2).

The effect of hydrotropic salts on the solubility of (ETO) can be illustrated by sodium benzoate (SB) as shown in fig. 3. It is evident that the increase in the concentration of the salt resulted in an increase in the aqueous solubility of etodolac. The positive deviation in the hydrotropic solubilization phase diagram which is characteristic to hydrotropic solubilization could be the result of aggregation of sodium benzoate molecules at critical concentration[25]. The tendency of aggregation lies in the fact that in aqueous media essentially all molecules containing the exposed organic groups are not protected by polar groups on more than one side and show some degree of hydrophobicity. This leads to an inter- and/or intramolecular association[26] which depends on the concentration of the hydrophobic moieties present in the

TABLE 2: THERMODYNAMIC PARAMETERS FOR THE SOLUBILITY OF ETODOLAC IN DIFFERENT COSOLVENT SYSTEMS

Conc. % v/v	ΔG (cal mol $^{-1}$)							
	Ethanol		PEG 400		PG		Glycerol	
	Temperature°							
	25	37	25	37	25	37	25	37
10	-217.99	-193.48	-473.59	-258.75	-417.23	-121.48	-160.87	-9.17
20	-628.45	-654.13	-953.07	-771.91	-496.32	-193.48	-206.08	-15.22
30	-976.52	-744.56	-1322.79	-1157.32	-566.06	-685.73	-352.09	-119.01
40	-1544.93	-1824.46	-1822.45	-1819.57	-976.52	-798.09	-373.42	-103.32
50	-2482.68	-2580.06	-2314.22	-2131.34	-1370.37	-1112.74	-405.34	-202.69
60	-3016.43	-3056.24	-2897.54	-2669.91	-1627.14	-1857.52	-485.96	-233.65
70	-3483.98	-3249.67	-3044.55	-3664.79	-2104.89	-2082.26	-573.33	-496.02
80	-4332.79	-4203.03	-4249.7	-4187.01	-2573.59	-2700.48	-657.45	-760.53
90	-	-	-	-	-3260.73	-3183.39	-751.16	-827.74
100	-4818.46	-4684.84	-	-	-3543.73	-3771.01	-1095.46	-941.76

Conc. % v/v	ΔH (cal mol $^{-1}$)			
	Ethanol	PEG 400	PG	Glycerol
10	9.58	9.26	9.13	9.38
20	9.64	9.28	9.11	9.31
30	9.19	9.28	9.79	9.24
40	9.99	9.51	9.28	9.17
50	9.63	9.19	9.13	9.28
60	9.5	9.08	9.9	9.19
70	9.03	9.34	9.46	9.47
80	9.14	9.26	9.68	9.76
90	-	-	9.29	9.71
100	9.11	-	9.77	9.32

Conc. % v/v	ΔG (cal mol^{-1} K^{-1})							
	Ethanol		PEG 400		PG		Glycerol	
	Temperature°							
	25	37	25	37	25	37	25	37
10	0.76	0.66	1.62	0.86	1.43	0.42	0.57	0.06
20	2.14	2.14	3.23	2.52	1.69	0.65	0.72	0.08
30	3.31	2.43	4.47	3.76	1.93	2.24	1.21	0.41
40	5.22	5.92	6.15	5.9	3.31	2.6	1.28	0.36
50	8.36	8.35	7.79	6.9	4.63	3.62	1.39	0.68
60	10.15	9.89	9.75	8.64	5.49	6.02	1.66	0.78
70	11.72	10.51	10.25	11.85	7.09	6.75	1.96	1.63
80	14.57	13.59	14.29	13.54	8.47	8.74	2.24	2.48
90	-	-	-	-	10.97	10.29	2.55	2.7
100	16.19	15.14	-	-	11.92	12.19	3.71	3.07

PEG 400 = polyethylen glycol 400, PG = propylene glycol, ΔG = free energy change, ΔH = enthalpy change and ΔS = entropy change.

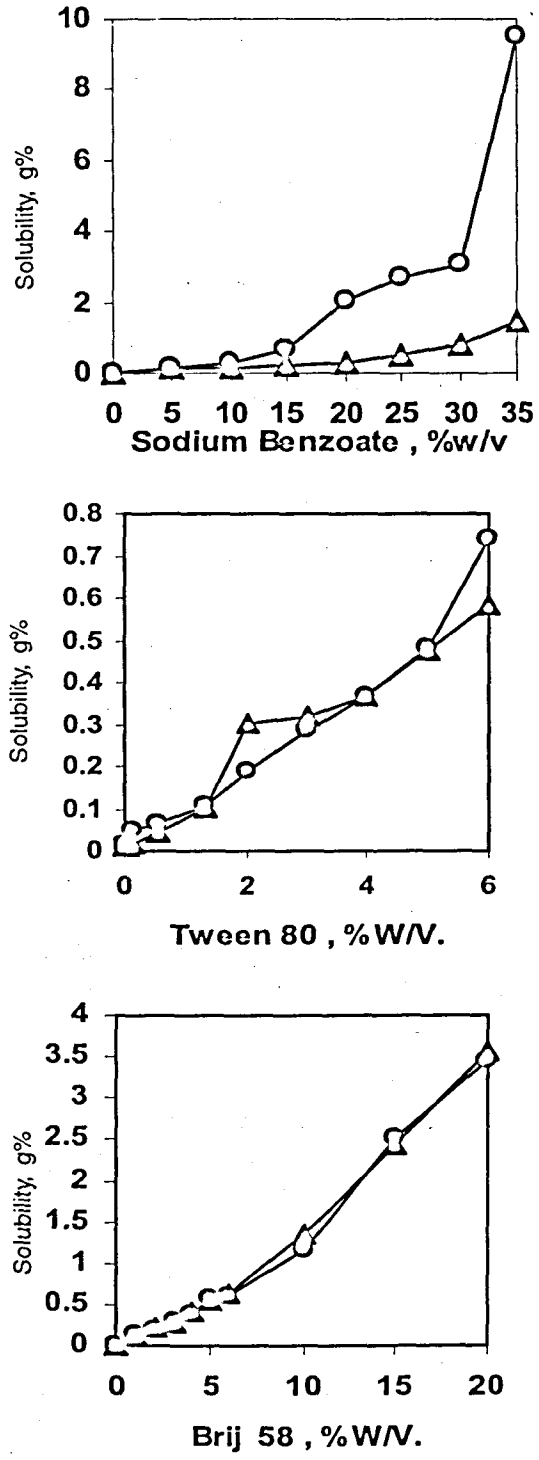

Fig. 3: Solubility of etodolac in sodium benzoate, Tween 80 and Brij 58.

Solubility of etodolac in sodium benzoate, Tween 80 and Brij 58 at 25° (-▲-) and 37° (-O-).

solution. Therefore, the planar structure of sodium benzoate molecules allows a stacking type of association, within which each molecule can lie flat on the top of another molecule. Etodolac plannar molecules may be solubilized by occlusion within the hydrotrope aggregates. Interaction of the hydrotrope aggregate with the solute molecules is probably a mechanism of hydrotropic solubilization beyond critical solute concentration[12]. The increase in temperature of hydrotropic salt solution was accompanied by a significant enhancement of etodolac dissolution. The increased solubility by temperature could probably be due to the expansion of hydrotrope aggregates leading to accomodation of a much higher number of the drug molecules. Thus, a higher concentration of (ETO) gets entrapped in the stacks of the hydrotrope molecules to bring about solubilization[11].

It is worth noting that the TLC results testing revealed that the spots of solubilized products were separated into two spots, one of the solubilizer and the other for the drug. Thus, molecular interaction or complex formation has been ruled out.

The polyoxyethylene containing surfactants, namely, polysorbate 80 (Tween 80) and polyoxyethylene 20 cetyl ether (Brij 58) were found to be effective as solubilizers for ETO (Table 1 and fig. 3). However, Brij was similar to Tween 80 in ETO solubilization. The process of transfer of drug from water to surfactant solution cannot be envisaged entirely as a simple solution mechanism but rather as an interaction between surfactant and cosolute, i.e., comicellization[27]. The drug may be associated with the ethyleneoxide portion of the surfactant. The aggregation number of a surfactant varies with temperature due to a change of monomer hydrophobicity as well as difference in configuration of polyoxyethelene chain at different temperatures[16]. These effects could influence the mode of packing of the monomers in the micelles[27], which would lead to form larger micelle of larger volumes, thus accomodating more drug[28]. The increase of temperature from 25 to 37° was, therefore, expected to be accompanied by an enhanced solubility as a result of increasing the inherent solubility of the drug in the aqueous phase in addition to the increased amount of the drug solubilized within the micelles[15]. This was not the situation in the surfactant systems under investigation. The amount of ETO solubilized by Tween 80 and Brij 58 was almost the same at both temperatures (fig. 3). However, in addition to enhancing the solubility of the drug, nonionic

TABLE 3: RESULTS OF THE DILUTION TEST OF THE PROPOSED FORMULA

	Glucose 5% w/v								
	Time, min.								
Dilution	0	5	10	15	30	45	60	75	90
1:1	-	-	-	-	-	-	-	-	-
1:2	-	+	+	+	+	+	+	+	+
1:5	-	+	+	+	+	+	+	+	+
1:10	-	-	-	-	-	-	-	-	-
1:25	-	-	-	-	-	-	-	-	-
1:50	-	-	-	-	-	-	-	-	-
1:100	-	-	-	-	-	-	-	-	-

	Normal Saline (NaCl 0.9% w/v)								
	Time, min.								
Dilution	0	5	10	15	30	45	60	75	90
1:1	-	-	-	-	-	-	-	-	-
1:2	-	+	+	+	+	+	+	+	+
1:5	-	+	+	+	+	+	+	+	+
1:10	-	-	-	-	+	+	+	+	+
1:25	-	-	-	-	-	-	-	-	-
1:50	-	-	-	-	-	-	-	-	-
1:100	-	-	-	-	-	-	-	-	-

(+) Visual precipitation, (-) no precipitation

surfactants would be expected to allow more drug to penetrate into viable tissues and systemic circulation[29,30]. It is worth mentioning that insignificant improvement in etodolac solubility could be observed with the tested sugars and sodium salicylate.

By increasing the solubility of ETO, it could be possible to formulate an aqueous injection, which would be useful in patients with rheumatic disorders, with peptic ulcers or gastrointestinal bleeding in which the oral administration of ETO is contraindicated. Additionally, it would be possible to reduce the dose and hence the drugs adverse effects.

Based on the results of solubility study, a trial has been done to formulate a solution for parenteral administration. The choice of an appropriate solubilization system can ensure the solubility of all formulation components and minimize tissue irritation at the site of administration[31]. Considering the pharmacokinetic data of the drug[32], the selected dose for parenteral formulation was 100 mg. Sodium bisulfate (0.1 % w/v) was added as antioxidant to preclude any oxidation. Other additives like preservatives, chelating agents or buffering agents were not used, as the inclusion of these agents might upset the basic solubility enhancement ratios[14]. The proposed formulation (100 mg/3 ml), in addition to etodolac, consisted of 50% PG, 20% SB, 0.1% sodium bisulfate and sterile water. Propylene glycol has been successfully used in our laboratory in the formulation of diazepam injection[33]. In this study, the proposed formulation has been investigated for color change, turbidity or precipitation upon storage for 2 mo in addition to the possible precipitation upon dilution with two intravenous infusion fluids namely; normal saline (0.9% w/v) and glucose 5% w/v. Monitoring the physical stability of the proposed formulation revealed that the product did not change its color, get turbid or precipitate upon storage for 2 mo. at room temperature (25±1°). Precipitation of injections during dilution with biological fluids may be associated with poor drug bioavailability and pain after injection[34]. The results of the dilution test are shown in Table 3. The dilution behavior of ETO formulation indicated good solubility in saline and glucose solutions as it shows low tendency for precipitation except in low dilutions.

Caution is required in assessing the complete successfulness of the formulation because of the possible local reactions that propylene glycol might induce in patients when used in increased amounts[35]. However, dilution in saline or glucose solutions would greatly reduce such possibility.

REFERENCES

1. Roth, S.H., **Ann. Intern. Med.**, 1988,109, 353.
2. Wallace, J., **Can. J. Physiol. Pharmacol.**, 1994,72, 1493.
3. Roth, S.H., Tindall, E.A. and Jain, A.K., **Arch. Intern. Med.**, 1993,153, 2565.
4. Lanza, F.L., **Amer. J. Gastroenterol.**, 1993, 88, 1318.
5. Lain, L., Sloane, R. and Ferretti, M., **Gastroentest. Endosc.**, 1995, 42, 428.
6. Craige, C.R., and Stitzel, R.E., In; Modern Pharmacology with Clinical Applications, 5th Edn., Little Brown and Company, USA, 1997, 328.
7. Jamali, F., Mehvar, R., Lemko, C. and Eradiri, O., **J. Pharm. Sci.**, 1988, 77, 963.
8. Martie, R. and Clictus, I., **Can. J. Physiol.**, 1976, 54, 245.
9. Martie, R. and Clictus, I., **Agent Actions**, 1982, 12, 295.
10. Fini, A., Zecchi, V. and Tartarini, A., **Pharm. Acta. Helv.**, 1985, 60, 58.
11. Jain, N.K., Khapra, P., Singkai, A.K. and Uppadhyay, R.K., **Pharmazie**, 1991, 46, 799.
12. Jain, N. K., Singhai, A.K. and Jain, S., **Pharmazie**, 1996, 51, 235.
13. Etman, M.A. and Nada, A.H., **Acta Pharmaceutica**, 1999, 49, 291.
14. Singhai, A.K., Jain, S. and Jain, A.K., **Pharmazie**, 1996, 51, 737.
15. Saket, M.M., **Alex. J. Pharm. Sci.**, 1996, 10, 13.
16. Naggar, V. and Ebian, A., **Die Pharmazeutische Ind.**, 1985, 47, 1098.
17. Etman, M.A. and Naggar, V., **Int. J. Pharm.**, 1990, 58, 17.
18. Paruta, A.N., **J. Pharm. Sci.**, 1964, 53, 1252.
19. Najib, N.M. and Sulieman, M.S., **Int. J. Pharm.**, 1985, 24, 165.
20. Yalkowsky, S.H., Amidon, G.L., Zografi, G. and Flynn, G.L., **J. Pharm. Sci.**, 1975, 64, 48.
21. Paruta, A.N., Sciarrone, B.J. and Lordi, N.G., **J. Pharm. Sci.**, 1964, 53, 1349.
22. Chen, L.K., Cadwallader, D.E. and Jun, H.W., **J. Pharm. Sci.**, 1976, 65, 868.
23. Shihab, F.A., Ezzedeen, F.W. and Stohs, S.J., **J. Pharm. Sci.** 1988, 77, 455.
24. Lund, W., In; The Pharmaceutical Codex, 12th Edn., The Pharmaceutical Press, London, 1994, 42.
25. Badwan, A.A., El-Khordagui, L.K., Saleh, A.M. and Khalil, S.A., **Int. J. Pharm.**, 1983, 13, 67.
26. Mukerjee, A.T., **J. Pharm. Sci.**, 1974, 63, 972.
27. Humphrey, K.J. and Rhodes, C.T, **J. Pharm. Sci.**, 1968, 57, 79.
28. Abdel-Rahman, A., Aboutaleb, A. and Samy, E., **Assiut Bull. Pharm. Sci.**, 1991, 14, 35.
29. Elgindy, N.A., **Pharmazie**, 1993, 48, 616.
30. Sasaki, H., Kojima, M., Makamura, J. and Shibasaki, J., **J. Pharm. Sci.**, 1991, 80, 533.
31. Yalkowesky, S., In; Techniques of solubilization of drugs, Marcel Dekker, Inc., NY, 1981, 82.
32. Ansel, P.A, In; The Pharmacological Basis of Therapeutics, 9th Edn., McGraw-Hill, NY, USA, 1996, 635.
33. Eshra, A.G., Etman, M.A., Ebian, A.R. and Saleh, A.M, **Alex. J. Pharm. Sci.**, 1991, 5, 202.
34. El-Khordagui, L.K., Saleh, A.M. and Khalil, S.A., **Int. J. Pharm.**, 1980, 7, 111.
35. Kortilla, K., Sothman, A. and Anderson, P., **Acta Pharmacol. Toxicol.**, 1976, 39, 104.