Academic Sciences

International Journal of Current Pharmaceutical Research

ISSN- 0975-7066 Vol 4, Issue 3, 2012

Research Article

A STUDY ON SOLUBILITY ENHANCEMENT OF OXAPROZIN FOR DEVELOPMENT OF PARENTERAL DOSAGE FORMS

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Received: 23 May 2012, Revised and Accepted: 11 June 2012

ABSTRACT

Oxaprozin is chemically designated as 4,5-diphenyl-2-oxazole-propionic acid. It is practically insoluble in water which precludes its use in parenteral and oral solutions dosage forms. This study explores the solubility enhancement of celecoxib using hydrotropy and cosolvency solublization approaches.

The equilibrium solubility studies were performed using hydrotropes piperzine, sodium citrate, and urea and cosolvents PEG 200, PEG 400, PEG 600, DMA, Ethanol and Propylene glycol at various temperatures. Parenteral formulations using hydrotrope and cosolvents were developed and studied for accelerated stability study.

The solubility of oxaprozin was increased upto 1846 times in DMA at 25±2°C. The results of hydrotropic solubilization and combination of hydrotropic and cosolvent solubilization showed that the increase in solubility of oxaprozin is smaller in sodium citrate, sodium glutamate, sodium acetate and urea when used alone as compare to the increase in solubility which was found when these hydrotropes were used in combination with cosolvents. All the formulations stored were found to be stable for drug content, pH and change in physical appearance i.e. color, precipitation.

Keywords: Solubilization, Oxaprozin, Hydrotrope, Cosolvent, Parenteral formulation.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAID) are among the most frequently prescribed medications. 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 prostaglandins while Cox-2 is primarily associated with inflammation, pain, and fever[1-3]. The traditional NSAIDs are nonselective Cox inhibitors. 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 prodrugs have not had a significant impact. Many studies 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. The 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.

Formulation of lipophilic drugs is frequently hampered by their poor aqueous solubility which again can limit their therapeutic applications. Oxaprozin is a chemically designated as 4,5-diphenyl-2-oxazole-propionic acid[4,5]. Oxaprozin is an inhibitor of several steps along the arachidonic acid pathway of prostaglandin synthesis, and one of its modes of action is presumed to be due to the inhibition of prostaglandin synthesis at the site of inflammation[6,7]. It is supplied only in tablets and capsules for oral administration. Oxaprozin is practically insoluble in water which precludes its use in parenteral and oral solutions dosage forms. 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 drugs. Solubilization of insoluble drugs has been extensively studied to overcome difficulties which may be encountered during pharmaceutical formulation.

Attempts have been reported in the literature for improving the aqueous solubility of various drugs for parenteral formulation, through various solubilization approaches. The major approaches for increasing the solubility of drugs are alteration of properties of solute or solvent. According to Yalkowsky[8] buffers, hydrotropes, surfactants, cosolvents and complexing agents are the most commonly used excipients to improve the solubility of a non polar drug in aqueous media. These can be used either alone or in combination. Recently the synergism of two or three techniques has drawn particular interest[9-12].

The present work explores the utility of hydrotropes and cosolvents as solubilizing agents for Oxaprozin to enhance the solubility with an aim to formulate the aqueous injections of these drugs, which will be definitely more effective, economical, safe and with the least side effects as compared to their oral dosage forms i.e. tablet, capsules. Parenteral formulations may be useful in patients with rheumatic disorders, peptic ulcers etc. where the oral administration of these drugs is contraindicated.

MATERIALS AND METHODS

Materials

The gift sample of Oxaprozin was provided by M/S Gen Pharm Inc., Canada. Sodium citrate, sodium hydroxide, urea were procured from Loba Chemie, Mumbai, India and Sodium acetate, Sodium gluconate and sodium glutamate from BDH, Mumbai, India. All other chemicals used were of analytical grade.

Estimation of oxaprozin

In the present study, UV spectrophotometric method[13] was used for the estimation of oxaprozin. The calibration curve of oxaprozin was prepared using 0.1N sodium hydroxide at 284 nm using double-beam spectrophotometer (UV-1601, Shimadzu, Japan).

Solubility study

pH solubilization

The phosphate buffer of pH 2.5 to 10 and citrophosphate buffers of pH 5.0 to 8.0 (prepared in freshly boiled and cooled distilled water were used for solubilization study.

Hydrotropic solubilization

The solutions of various molar concentration of hydrotropes were prepared i.e. sodium citrate (0.2-1.2M), sodium glutamate (0.2-1.6 M), urea (0.8-4.8 M), sodium acetate (0.4-2.4 M) and sodium gluconate (0.2-1.4 M) by dissolving their required quantities in water for the solubilization study.

Cosolvent solubilization

The cosolvents such as Polyethylene glycol (PEG) 200, PEG 400, PEG 600, Dimethyl acetamide (DMA), Ethanol (Eth) and Propylene glycol (PG) were selected in this study. The solubility of oxaprozin was determined in different cosolvent:water blend of ratio i.e. 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2 and 9:1, respectively.

Solubilization Studies Using Combination of Cosolvents and Hydrotropes

The combination of hydrotropes and cosolvent solubilization was also explored to improve the solubility of oxaprozin[9-12]. The role of solvent in hydrotropic solubilization was observed by studying the effect of different hydrotropes sodium citrate, sodium glutamate, sodium acetate and urea in combination with cosolvents PEG 600, PEG 400, PEG 200 and Eth as shown in Table 4[14-18].

Aqueous solutions of the above mentioned hydrotropes in different concentrations (10%-30% w/v) were prepared by dissolving their required quantities in distilled water. The cosolvents were used in the 70-90% v/v concentration. An excess drug was added to a series of screw capped 15 ml glass vials containing cosolvents. The required amount of hydrotropic solution was added separately to each of the vials containing cosolvents to produce the effective combination of cosolvents and hydrotropic solution in the ratios 1:9, 3:7, 5:5, 7:3, 8:2 and 9:1.

Solubility Determination

Solubilization studies were performed according to the method of Higuchi and Conners[19]. An excess quantity of oxaprozin was added to screw capped 20 ml glass vials containing the different aqueous systems viz. distilled water, phosphate buffers of pH 2.5–10; hydrotropic solutions; cosolvent-water blends and combination of cosolvents with hydrotropes. These vials were shaken mechanically for 12 h at 25 ±2°C, 37 ±2°C and 45±2°C in a mechanical shaker (Elico Pvt. Ltd, Mumbai, India). These solutions were allowed to equilibrate for next 24 h and then centrifuged for 5 min at 2000 rpm. The supernatant of each vial was filtered through Whatman filter paper no. 1, filtrate diluted with suitable quantity of 0.1N NaOH and analyzed spectrophotometrically at 284 nm. The solubility was determined in triplicate.

Formulation of aqueous injection

On the basis of solubility data obtained, four formulations of aqueous injection of oxaprozin were prepared using sodium acetate and urea as hydrotropes[20-26] and PEG 400, PEG 600 and DMA as cosolvents. The quantity of different ingredients for the prepared aqueous injections was taken as given in the Table 1. In all the formulations, 0.1% w/v sodium bisulfite was added as an antioxidant. Other additives like chelating agent and buffering agent were not included in these formulations as they might lead to change in the solubility behavior and upset the basic solubility enhancement ratio

Selection, Washing and Sterilization of Packaging Materials and Preparation of Aseptic Area

Glass vials of 3 ml and 5 ml capacity were used for preparation and dispensing of final formulations. Glass vials were evaluated as per B.P., 1999a. Test for alkalinity was carried out using powdered glass test. The vials were first washed several times with distilled water, dipped in 5% v/v nitric acid for a period of 10 h to neutralize surface alkalinity. The vials were then rinsed with distilled water and immersed in 0.5% Teepol® solution for a period of 2 h. The vials were then scrubbed with a soft brush and rinsed with distilled water. The vials were then soaked in 5% v/v nitric acid for 30 min to remove the excess soap and then rinsed with distilled water. Finally vials were rinsed under a laminar air flow bench with filtered double distilled water. The vials were placed inverted in an enameled tray, covered with an aluminium foil and sterilized by dry heating in hot air oven at 160°C for 3 h.

Rubber stoppers used for plugging the vials were first washed several times with distilled water and then boiled in distilled water for 20 min and finally dried in vacuum oven.

The walls and floor of aseptic room were thoroughly washed with water and then disinfected with 5% w/v phenol solution. The laminar airflow bench was cleaned with 70% v/v ethanol and the UV light was switched on for 30 min prior to filling of injections into vials.

Preparation of Aqueous Injection

The weighed quantity of drug was taken in each of the glass vials and dissolved in the required amount of respective cosolvent. Then the weighed amount of hydrotropes were separately dissolved in measured quantity of water for injection and mixed with the above solution. In case of formulations without hydrotrope and only in co-solvents, the drug solution in cosolvent was mixed with the sufficient water for injection (WFI). In each of the vials 0.1% w/v sodium bisulfite was added. The pH of these preparations was recorded using digital pH meter. The solutions were filtered through 0.22 µ disposable membrane filter (Sartorius, Germany), under vacuum and transferred aseptically to the clean and sterile glass vials of 3 and 5 ml capacity stoppered with rubber stoppers. The solutions were analyzed spectrophotometrically at 284 nm for drug content after appropriate dilutions with 0.1N NaOH.

Table 1: Formulae designed for aqueous injections of oxaprozin

Ingredients	Formulation code			
	ODMAW	ODMAS	OPEG4S	OPEG6U
Oxaprozin	1.67 g	1.67 g	1.67 g	1.67 g
Urea	-	-	-	4.5 g
Sodium acetate	-	7.5 g	6.0 g	-
PEG 600	-	-	-	35 ml
PEG 400	-	-	30 ml	-
DMA	35 ml	25 ml	-	-
Sodium bisulfite	50 mg	50 mg	50 mg	50 mg
Water for injection (ml) q.s.	50	50	50	50
Final strength of formulation	100 mg/3 ml	100 mg/3 ml	100 mg/3 ml	100 mg/3 ml

Stability Study[27, 29]

The protocol of the stability studies was in conformity with the recommendations given in WHO document pertaining to stability testing of products intended for global market and ICH (International Conference on Harmonization) guidelines. To assess the accelerated stability, the sealed vials of the formulations were stored in ICH certified stability chambers (Forma Scientific Ltd., Mumbai, India)at 40±2°C and 75%±5% relative humidity (RH) for six months. The samples were withdrawn periodically and evaluated for change in physical appearance (color, precipitation) and percent drug content, if any[30-31]. The change in pH of each formulation was recorded using digital pH meter after 1, 3 and 6 months. The observations are reported in Table 6.

RESULTS AND DISCUSSION

pH solubilization

The results of solubility studies at different pH indicated that oxaprozin was more soluble at alkaline pH than acidic pH. This may

be due to the acidic nature of oxaprozin by virtue of its carboxylic group. The aqueous solubility of oxaprozin was increased upto 62 times at pH 10.0 (Table 1). One of the major factors responsible for dissolution of an organic compound is its ability to dissociate into ionic species, which depends on the pH of the media[18]. The percentage ionized and hence solubility may increase of oxaprozin was more with an increase in pH value of the buffers used for solubilization.

Table 2: pH dependent solubility of oxapprozin in phosphate buffers of pH 2.5 to 10 at different temperatures

Temp (^{0}C)	Solubility* (mg/ml) of drugs in water and phosphate buffer of pH								
	Water	2.5	4.0	5.5	7.0	7.5	8.0	9.0	10.0
25±1	0.0805	0.0012	0.0109	0.170	2.1873	2.1995	2.9327	4.8391	4.9205
37±1	0.0812	0.0015	0.0112	0.1951	2.1923	2.2012	2.9523	4.8871	4.9501
45±1	0.0852	0.0017	0.0115	0.2012	2.2011	2.2168	2.9920	4.9255	4.9913

*Average of three determinations

Hydrotropic solubilization

The solubility of oxaprozin was found to increase upto 9 times at 25±2°C in 1.2M sodium citrate solution. The elevation of the temperature from 25±1°C to 45±1°C was accompanied by a minor but detectable increase in the solubility of drug, which indicates that the solubilization process in endothermic. The solubility enhancement power of different hydrotropes for oxaprozin could be ranked in decreasing order- as sodium citrate>urea>sodium acetate>sodium glutamate>sodium gluconate as shown in Fig 2-6 and the solubility enhancement ratio as 9, 4, 3, 2 and 1, respectively (Table 2). The enhancement in solubility is not a linear function of hydrotrope concentration. The solubility of drugs increased slowly with increase in hydrotrope concentration.

To explain the mechanism of solubilization of oxaprozin in presence of structurally different hydrotropes, it is necessary to have the basic understanding of chemical structures of drugs and hydrotropes. The structures of drugs and hydrotropes with different centers of different electro negativity (denoted by 'a' in the structure) where the intermolecular hydrogen bonding and electrostatic attraction may be possible, have been shown in Fig. 1.

Table 3: Solubility enhancement ratio of hydrotropes for oxaprozin

Hydrotrope	Temp (°C)	Solubility factor* for oxaprozin in different concentrations of hydrotrope (%w/v)					
		5	10	15	20	25	30
	25±1	1.09	1.24	1.38	3.63	5.18	8.69
Sodium citrate	37±1	1.11	1.26	1.42	3.66	5.19	8.64
	45±1	1.07	1.27	1.42	3.55	5.00	8.31
	25±1	1.02	1.34	1.53	1.81	2.43	2.85
Sodium glutamate	37±1	1.08	1.38	1.59	1.86	2.47	2.89
	45±1	1.05	1.38	1.55	1.84	2.44	2.95
	25±1	1.86	2.42	2.84	3.23	3.37	4.32
Urea	37±1	1.93	2.44	2.85	3.27	3.42	4.31
	45±1	1.89	2.37	2.79	3.17	3.39	4.17
Sodium acetate	25±1	1.02	1.04	1.13	1.44	1.89	2.20
	37±1	1.04	1.06	1.17	1.51	1.94	2.22
	45±1	1.00	1.03	1.17	1.50	1.90	2.16
	25±1	1.00	1.00	1.00	1.22	1.44	1.59
Sodium gluconate	37±1	1.00	1.00	1.00	1.24	1.50	1.60
	45±1	1.00	1.00	1.00	1.25	1.51	1.61

*Solubility factor = solubility in hydrotropic solution (mg/ml)/solubility in water (mg/ml)

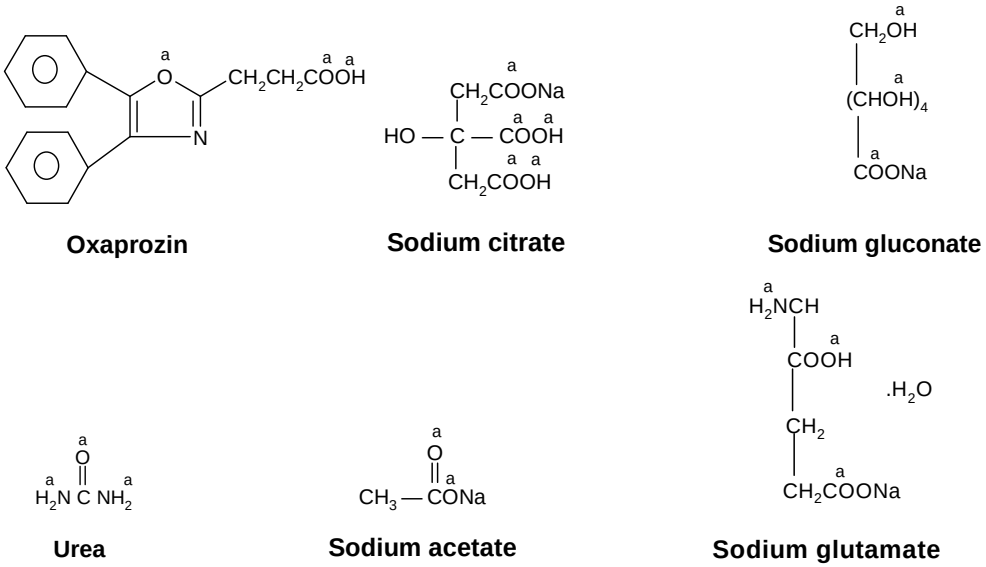

Fig. 1: Structures of drug and hydrotropes

The solubilization of oxaprozin in presence of sodium citrate can be explained on the basis that sodium citrate possess 3 carboxylate and 1 alcoholic group, which make it more acidic. Because of high acidity these acidic groups break the dimer of oxaprozin in water and solubilize it by intermolecular hydrogen bonding. Sodium acetate imparts polarity because of the presence of sodium ion, which converts free acid of oxaprozin into its salt form, which resulted in increased solubility. Urea increases the solubility of oxaprozin due to intermolecular hydrogen bonding between hydrogen of its amino group and oxygen of oxazole ring of oxaprozin and electrostatic attraction between electron rich nitrogen (because of lone pair of electrons) of urea and electron deficient oxygen of carboxylate ion of oxaprozin.

Sodium glutamate and sodium gluconate showed less increase in solubility of oxaprozin as compared to other hydrotropes, which may be attributed to the fact that these both hydrotropes are bigger molecules therefore the steric hindrance occurs because of phenyl group and propionic acid chain of oxaprozin as sodium glutamate and sodium gluconate are less stabilized by 6 and 4 carbon atoms, respectively.

The phase solubility diagrams (fig 2-4) indicated that initially the solubility was increased linearly with the increase in hydrotrope concentration, then a nonlinear increase in solubility was found on increasing the hydrotrope concentration. The positive deviation in the phase solubility diagrams, which is characterstic of hydrotropic solubilization, could be the result of aggregation of hydrotrope molecules at higher concentration. 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.

Water is a solvent in which the molecules of water join to form cluster together. For solubilization the ionized hydrotropes break this association and use the ion dipoles of water for solvation. The increasing hydrotrope concentrations result in unassociated form to make cluster around the hydrophobic sites by inter and/or intramolecular association such as hydrogen bonding and non-bonding interactions at the various centers of drug molecule. Therefore the planar structure of hydrotrope molecules allow a stacking type of association in which one hydrotrope molecule can lie flat on the top of another one. Drug planar molecules may be solubilized by inclusion within the hydrotrope aggregates and interaction of drug with these aggregates may have significant contribution to the increase in solubility by hydrotropes.

The increase in temperature of hydrotropic salt solution was accompanied by a detectable increase in drug solubility. The increased solubility by temperature could probably due to the expansion of hydrotrope aggregates leading to accommodation of a much higher number of drug molecules. Thus a higher concentration of drug gets entrapped in the stacks of the hydrotrope molecules to bring about greater solubilization.

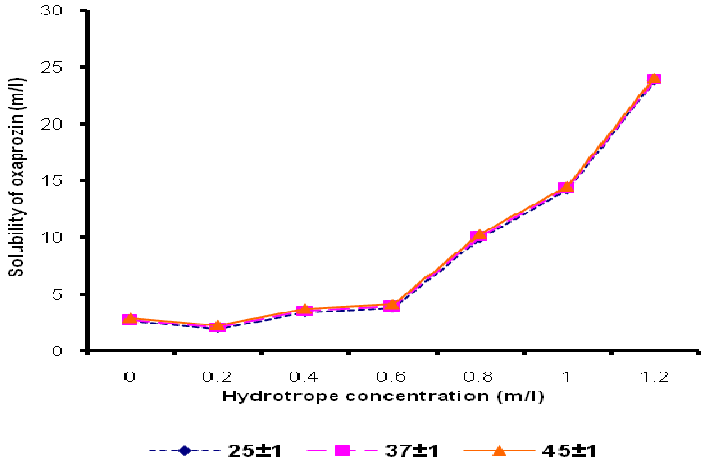

Fig. 2: Phase solubility curves of oxaprozin in sodium citrate at different temperature

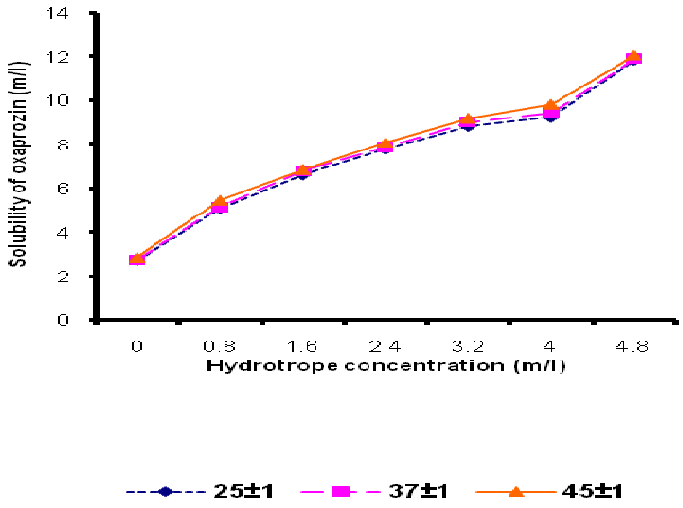

Fig. 3: Phase solubility curve of oxaprozin in urea at different temperatures

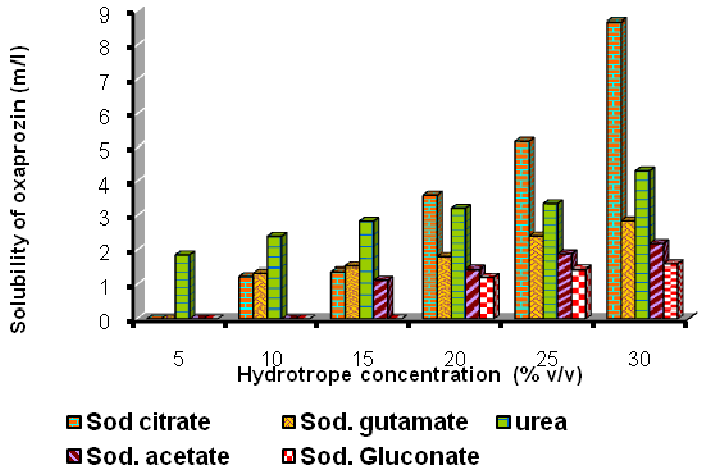

Fig. 4: Comparative phase solubility of oxaprozin in various hydrotropic solutions

Moreover the thermodynamics of drug solubility in the hydrotropic solution were calculated and the results are shown in Table 3. The free energy change (ΔG) associated with the solubility process indicating the type of reaction occurring between the drug and hydrotropes were calculated by using eq:

ΔG = -2 303 RT log K .... (I)

Where ΔG is free energy change during solubilization process; K is ratio of the molar solubilities of the drug in water and hydrotropic solutions and R gas constant (8.314 $JmoleK^{-1}$) and T is absolute temperature repectively. The results showed that in case of oxaprozin the negative values of ΔG can be arranged in the following order: sodium citrate>urea>sodium glutamate> sodium acetate>>sodium gluconate. These finding are in accordance with the order of solubilizing power of different hydrotropes used for oxaprozin. The free energy values showed that the increase in hydrotrope concentration provided a more thermodynamically suitable environment for the solubility of drug in all the cases (ΔG decreases). The negative free energy of solubilization process is indicative of spontaneity of the process; more negative the free energy of the complexation, the more will be the solubility. This possibility is determined by three factors, the change in 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 of the system.

$$\Delta S = \frac{\Delta H - \Delta G}{T} \quad \text{.... (II)}$$

Regression analysis of log K vs. 1/T (a Van't Hoff plot) yield ΔH (slope value). The enthalpy change ΔH is related to ΔS and ΔH.

Table 4: Thermodynamic parameters for drug-hydrotrope interaction of oxaprozin in aqueous solution

Hydrotrope	Temp (°C)	Δ G (JM^{-1})	Δ H (JM^{-1})	Δ S (JM^{-1})
	25±1	-6758.56		22.68
Sod. Citrate	37±1	-7042.93	1.0454	22.73
	45±1	-7314.10		23.00
	25±1	-11419.64		38.32
	37±1	-12045.67	1.6337	38.86
	45±1	-12589.30		39.59
	25±1	-7835.61		26.10
Sod. glutamate	37±1	-8279.18	1.4073	26.71
	45±1	-8574.39		26.96
	25±1	-9279.44		31.14
	37±1	-10132.91	1.6356	32.69
	45±1	-10425.58		32.79
	25±1	-5893.38		-19.77
Urea	37±1	-6159.59	0.459	-19.87
	45±1	-6318.27		-19.87
	25±1	-10766.60		36.13
	37±1	-11209.34	1.2565	36.16
	45±1	-11671.18		36.70
	25±1	-7729.57		25.95
Sod. acetate	37±1	-9519.15	4.0419	30.72
	45±1	-10813.65		34.04
	25±1	-10119.86		33.97
	37±1	-10591.10	4.6604	34.18
	45±1	-10885.07		34.24
	25±1	-7586.53		25.95
Sod. gluconate	37±1	-7975.46	0.4135	25.72
	45±1	-8360.52		26.29
	25±1	-9527.16		31.97
	37±1	-9966.86	0.9899	32.15
	45±1	-10226.56		32.16

The breaking up of water clusters surrounding the non polar portion requires heat (ΔH). The variation in the enthalpy of the systems may be due to the formation of intermolecular interaction between the hydrotropes and drug molecules. Moreover the solubilization process is endothermic one as ΔH is positive in this case. Therefore an increase in temperature from 25±1°C to 45±1°C caused an increase in solubility of oxaprozin. The hydrotropic solubilization was found primarily to be entropy driven process at high hydrotrope concentration that was accompanied by small free energy change, and large entropy change. The positive values of entropy change ΔS as shown in Table 4 suggest the involvement of weak hydrophobic interaction in solubilization process. Stripping the water molecules from the hydrotrope results in randomization of water molecules and drug molecules in the aqueous medium during the solubilization process. These cause a disordering and increase in the entropy associated with the system. The more positive the entropy change ΔS, the greater will be the randomness or disorder degree of the system and the environment is thermodynamically more favorable for solubilization[25,32].

On the basis of these data obtained (Table 4), the overall solubility enhancement can be differentiated in two categories: solubility at lower hydrotrope concentration and solubility at higher hydrotrope concentration. The solubility enhancement of drug in hydrotropic solution may be due to weak ionic interaction and hydrogen bonding. These interactions are small in magnitude and contributed solubility enhancement at lower hydrotrope concentration. The solubility at higher hydrotrope concentrations may be the result of hydrophobic effect and charge transfer phenomenon.

Further the probability of some kind of molecular interaction taking place between drug and hydrotrope was monitored by UV spectral studies. Oxaprozin in water and 0.1 N NaOH gives peaks at 222 and 284 nm. In case of oxaprozin-sodium citrate-water system, there is a slight shift of 2-3 nm for oxaprozin suggesting some complexation but the degree of complexation is very low. In case of oxaprozin-sodium-glutamate-water and oxaprozin-sodium gluconate-water system there is negligible effect in λ_{max} values of drug. In case of oxaprozin-urea-water and oxaprozin-sodium acetate-water, there is slight bathochromic shift of 4 nm and 3 nm for oxaprozin, respectively. This is expected because of the possible effect of hydrotrope molecule on the electronic configuration of oxaprozin molecule. It can be concluded that the minor shift in λ_{max} may be because of electronic changes in the structure of drug molecules. There is very weak possibility to assume any complex formation, as the complex formation can be evidenced by the formation of new chromophore, which is indicated by the appearance of a new peak or merging of two peaks to the hydrotrope self-association significantly plays a role in solubilization mechanism. In addition to this, high concentration of hydrotrope in conjunction with self-association changes the solvent behavior of water.

Cosolvent solubilization

The solubility of oxaprozin was increased upto 1846 times in DMA at 25±2°C (Fig 5). The cosolvent solubilizing power of different cosolvents i.e. ratio of solubility of drug in cosolvent-water blends to solubility of drug in water may be ranked in the order: DMA>PEG 600>PEG 400>PEG 200>Eth>PG and their cosolvent efficiency ratio as- 1829, 247, 224, 178, 169 and 62, respectively (Table 5).

Table 5: Solubility enhancement ratio of cosolvent-water system for oxaprozin

Cosolvent used	Temp (°C)	Solubility enhancement ratio* for oxaprozin of cosolvent-water blends of different ratios								
		10	20	30	40	50	60	70	80	90
	25±1	1.00	1.09	1.11	1.84	3.64	6.62	14.42	38.46	62.75
PG	37±1	1.03	1.11	1.18	1.89	3.79	6.75	14.35	38.05	61.99
	45±1	1.02	1.06	1.23	1.91	3.70	6.50	13.76	36.35	59.24
	25±1	1.01	1.10	1.77	5.19	14.21	26.56	38.72	123.31	169.94
Ethanol	37±1	1.08	1.11	1.86	5.21	14.10	26.26	38.47	122.36	168.50
	45±1	1.05	1.08	1.86	5.04	13.59	25.14	36.82	116.82	160.87
	25±1	1.55	2.901.77	3.17	8.03	16.42	28.25	47.82	127.27	178.78
PEG 200	37±1	1.68	1.90	3.24	8.02	16.28	27.90	47.18	125.55	177.34
	45±1	1.67	1.87	3.21	7.77	15.69	26.67	45.04	119.84	169.52
	25±1	1.86	2.11	3.80	8.59	20.36	44.14	106.44	221.65	224.82
PEG 400	37±1	1.89	2.18	3.86	8.55	20.13	43.60	104.92	218.45	221.61
	45±1	1.89	2.15	3.81	8.25	19.31	41.58	100.03	208.25	211.36
	25±1	1.96	2.46	4.66	9.21	21.98	67.46	118.42	236.08	250.50
PEG 600	37±1	2.00	2.48	4.73	9.18	21.75	66.56	116.87	232.66	246.89
	45±1	2.01	2.53	4.61	8.02	20.77	63.55	111.39	221.69	235.38
	25±1	1.13	1.43	4.06	9.68	28.63	160.85	439.27	989.04	1846.27
DMA	37±1	1.21	1.56	4.16	9.68	28.22	158.71	432.91	974.57	1828.99
	45±1	1.48	1.59	4.09	9.34	26.98	151.35	412.69	928.96	1743.27

*Average of three determinations

The solubility figures (Fig 5-9) showed the exponential increase in the solubility of drugs with increasing concentration of cosolvents[14-18]. 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 water's hydrogen bonding network, reducing the overall intermolecular attraction of water. By disrupting water's self-association, cosolvents reduce water's ability to squeeze out non-polar, hydrophobic compounds, thus increasing solubility. A different perspective is that by simply making the polar water environment more non-polar like the solute, cosolvents facilitate solubilization.

A simple and accurate one suitable for preformulation that requires little or no experimental data is the well-known log-linear model proposed by Yalkowsky and coworkers (Yalkowsky et al., 1976; Yalkowsky and Roseman, 1981). The log linear model (Millard, 2002) is commonly used to quantify the total solubility of drug in cosolvent system. The correlation between cosolvency and properties of drug, cosolvent and water can be established by applying log-linear model to the solubility data of drugs. The semilogarithmic relationship between total drug solubility (S_m) in a mixture and cosolvent fraction f can be described by the equation:

$$\log S_m = \log S_w + \sigma f$$

Where S_m is the solubility of drug in water-cosolvent mixture, volume fraction of the cosolvent is f; S_w are the solubility of drug in water and σ is cosolvent solubilization power. Values of solubility can be either in moles or mg/ml.

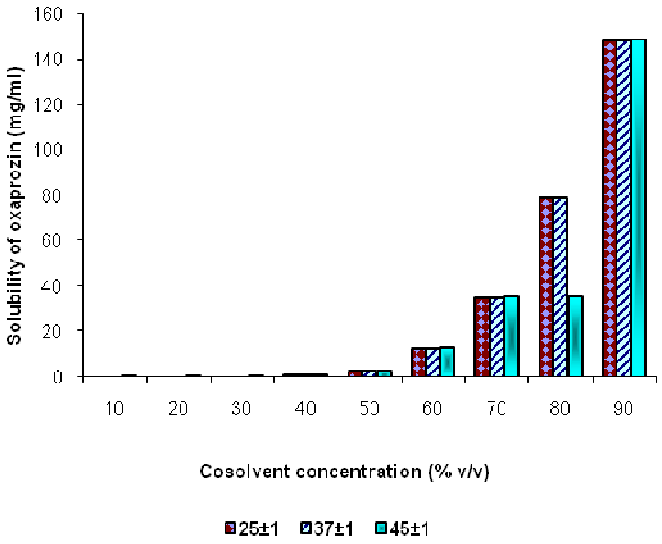

Fig. 5: Phase solubility curve of oxaprozin in DMA at different temperatures

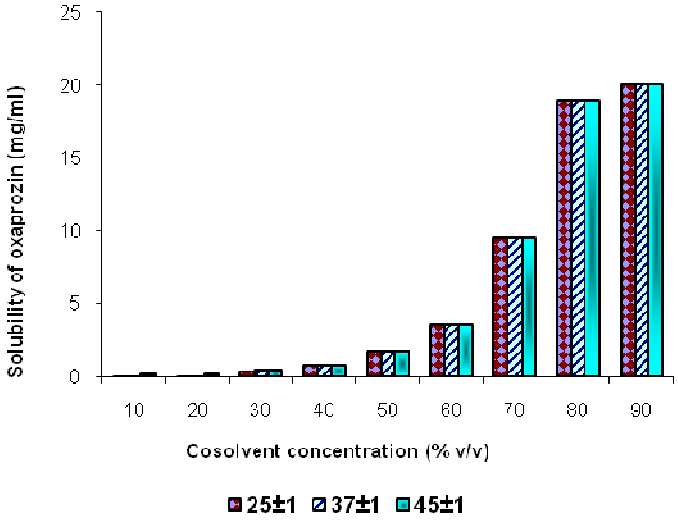

Fig. 6: Phase solubility curve of oxaprozin in PEG 600 at different temperatures

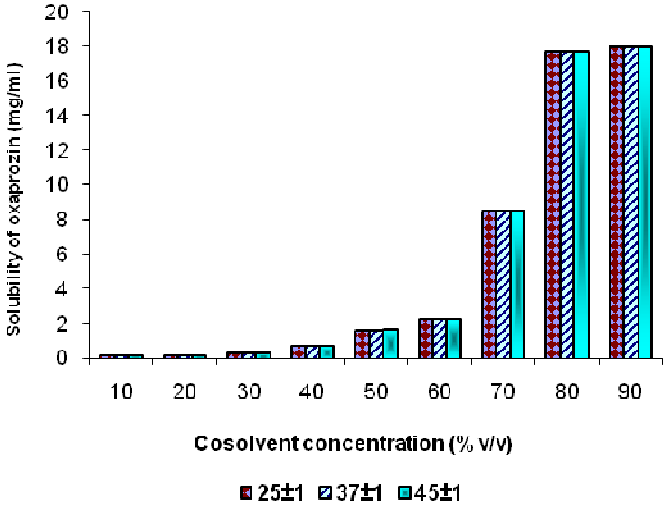

Fig. 7: Phase solubility curve of oxaprozin in PEG 400 at different temperatures

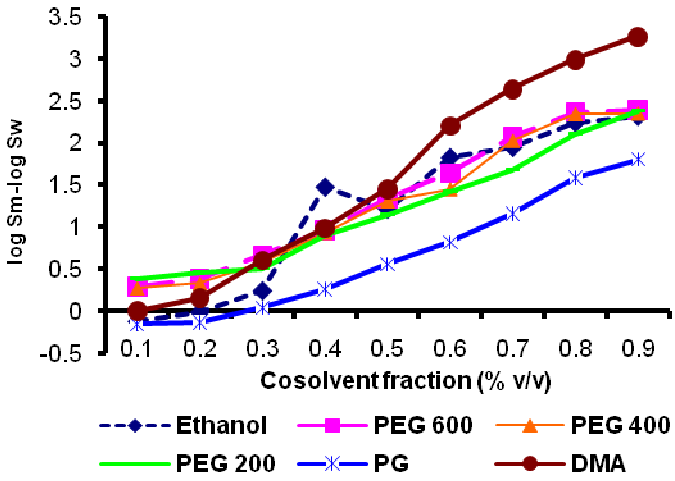

Fig. 8: Log linear plots of oxaprozin in different cosolvents

The solubility diagrams of drugs in water-cosolvent mixture as shown in Fig. 5-7 showed slight deviation from the ideal line which indicates non-ideality of solvent mixture or less interaction between hydrate cosolvent molecules. From the plots it was apparent that solubility of oxaprozin in water-cosolvent mixture confirms the semilogarithmic relationship between total drug solubility (S_m) in cosolvent-water mixture and cosolvent concentration. The solubilizing power σ of cosolvent for each drug was determined from slope of the curves plotted log S_m vs. cosolvent concentration (% v/v fraction in water) as shown in fig 8. The value of σ depends inversely on polarities of both the solute and the cosolvent. For a single nonpolar solute, the value of σ depends only on cosolvent polarity.

The values of solubilizing power of different cosolvents 'σ' were found in the order DMA (15.20)> PEG 600 (2.64)> PEG 400 (2.38)> PEG 200 (1.92)> Eth (1.71)> PG (0.50). The slope value suggests that DMA has high solubilization power for oxaprozin. The semilogarithmic relationship between total solubility of drug and cosolvent concentration in case of each drug suggest that the solubility of drug in mixed solvent to water (log S_m) is proportional to volume fraction of solvent (f). As the cosolvent concentration increases the solubility of drugs also increases.

The increase in solubility of oxaprozin in presence of different cosolvents can be explained on the basis that the molecule of oxaprozin stabilize through hydrogen bonding, although having a carboxyl group which is normally present as dimer, and N and O present in the oxazole ring are also not that much electron rich to make it solubilize through hydrogen bonding. Therefore the mechanism of solubilization may be attributed to the electrostatic attraction between electro rich nitrogen of DMA and electro deficient carboxylate ion of oxaprozin and hydrophobic bonding with the solvent. The higher the number of carbon atoms in the solvent, the better will be the solubility and hence more solubility in case of DMA was observed which was followed by PEGs and ethanol. PEGs form etheral linkage hence produced less increase in solubility of drug as compared to that of DMA.

Combined effect of cosolvent and hydrotropic solubilization

The study showed that the increase in solubility of oxaprozin is smaller in sodium citrate, sodium glutamate, sodium acetate and urea when used alone as compare to the increase in solubility which was found when these hydrotropes were used in combination with cosolvents PEG 600, PEG 400, DMA and Eth (Fig 9-10).

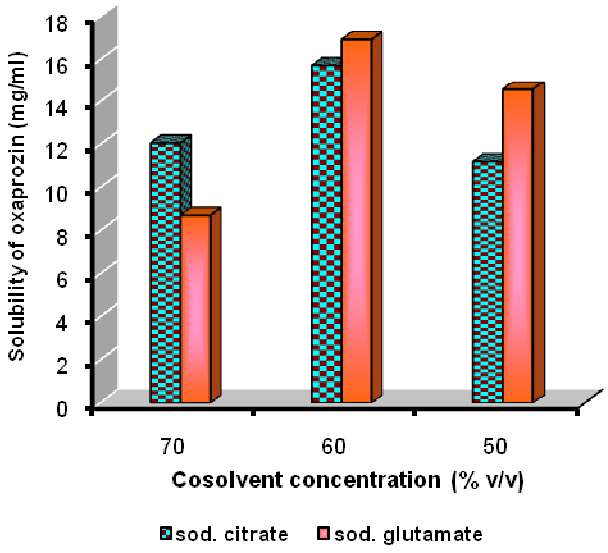

Fig. 9: Phase solubility diagramme of oxaprozin in PEG 400 with hydrotropes sodium citrate and sodium glutamate.

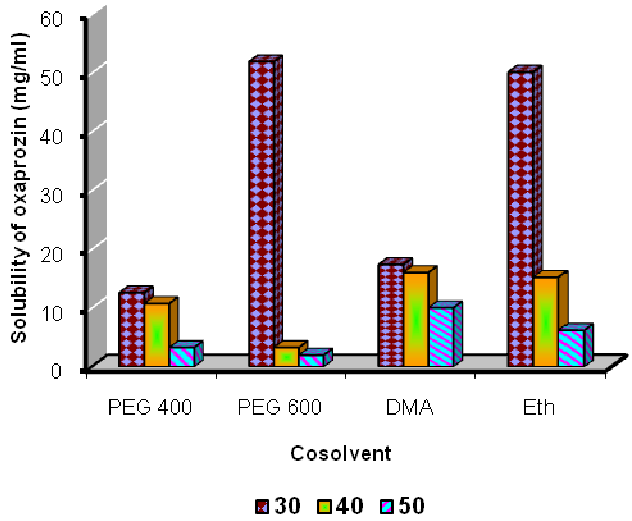

Fig. 10: Phase solubility diagramme of oxaprozin in cosolvents in urea solution of different cocentrations.

The nonaqueous solvents used were of different nature and polarity. The more increase in solubility of oxaprozin in combination of hydrotrope with cosolvent may be due to additive effect of both cosolvent and hydrotrope on solubility of drug. Solutropic behavior was observed in the case of all the solvents. The effect was found to be additive on solubilization of drugs. The solubility data suggest that there is no correlation between solvent polarity and solutropic solvent. However, some correlation with hydrogen bonding and electrostatic attraction may be possible. All the solvents selected are capable of forming hydrogen bond. This suggested that the ability of a solvent to be hydrogen donor must be a key factor in solutropic solubilization phenomenon and there is no correlation between solvent polarity and hydrotropic solubilization[9-12].

Stability Study

During accelerated stability studies at 40°C/75% RH all the formulations stored were found to be stable against precipitate formation. The pH value was also stable (4.6) and no change in color (absorbance) was observed. The oxaprozin content was also found to be within the pharmacopoeial limits (99.95 to 95.00) in all the formulations, indicated no degradation of drug in the formulations. The difference in drug content was statistically insignificant (P>0.05) as per ICH guidelines (Table 6). It may be concluded from the results of accelerated stability studies that the optimized formulations had a minimum shelf-life of two years.

Table 6: Drug content of selected formulations of oxaprozin during 6 months of storage at accelerated stability conditions (40°C and 75% RH).

Time (days)	Percent residual oxaprozin* in formulations			
	OPEG6U	ODMAW	ODMAS	OPEG4S
7	98.12±1.99	98.65±1.34	99.98±3.33	99.04±4.23
15	98.09±2.45	97.77±1.89	98.85±3.10	98.76±3.90
30	98.12±3.42	97.24±2.11	98.76±2.98	97.25±3.22
45	96.35±2.67	96.50±2.15	98.69±3.29	97.05±2.78
60	95.84±2.12	96.28±2.32	98.10±2.25	96.88±2.75
75	95.71±2.98	95.38±2.29	97.36±2.33	96.62±1.76
90	95.22±3.16	95.27±2.60	97.53±2.56	96.18±2.22
105	95.15±2.44	95.16±3.54	97.11±1.88	96.01±2.12
120	95.00±3.35	95.00±3.32	97.02±2.23	96.00±2.33

*Average of three determinations

CONCLUSION

In conclusion these results show that oxaprozin can be conveniently prepared in aqueous solution in cosolvents or in combination of cosolvents and hydrotropes. These combinations eliminate the need for including any surfactant in the parenteral dosage formulation with the potential advantage of fewer toxic reactions.

ACKNOWLEDGEMENT

One of the authors, Shikha Agrawal, expresses her thanks to Council of Scientific and Industrial Research, New Delhi, India, for awarding Senior Research Fellowship during Ph.D. The authors thank to Gen Pharm Inc., Canada, for providing the gift sample of drug and Head, Department of Pharmaceutical Sciences, Sagar, India, for providing necessary facilities to carry out these investigations.

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