

# Solubility Enhancement of Poorly Water Soluble Drug Zaltoprofen by Mixed Hydrotropy Approach

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## Research Article

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### ABSTRACT :

The present study is probably the earliest attempt to enhance Solubility of Zaltoprofen by using mixed hydrotropy and mixed solvency approaches. Zaltoprofen is selected as model drug because it is practically insoluble in water hence there is need to increase the solubility for better absorption and improved therapeutic efficacy.

In the preformulation study physical compatibility of the drug-excipient was screened and compatibility was observed between Zaltoprofen and selected solubilizers. In the drug solubilizers interference study no interference was observed in UV spectrophotometric analysis of Zaltoprofen in presence of employed solubilizers. Aqueous solubility of Zaltoprofen was found 0.028 mg/ml. The solubilizers sodium acetate, sodium benzoate and sodium salicylate, ethanol, PEG 600, piperazine anhydrous, were selected for solubilization studies on the basis of solubility enhancement ratio. The solubility enhancement ratio in sodium citrate, citric acid, urea, PEG 6000, PEG 4000, PEG 200, PEG 400, propylene glycol and glycerin were found to be less as compare to selected solubilizers. The solubility determination of drug in hydrotropic solutions was carried out at room temperature and solubilizing power of different hydrotropes could be ranked as: Piperazine anhydrous > sodium salicylate > sodium benzoate > sodium acetate > PEG 600. From the equilibrium solubility curves of Zaltoprofen in solubilisers it was concluded that increase in the solubility was nonlinear function with respect to the hydrotrope concentration.

**Key words:** Mixed hydrotropy, Zaltoprofen, solubility, selective COX2 inhibitor.

## INTRODUCTION:

More than one-third of the drugs listed in the U.S. Pharmacopoeia fall into the poorly water-soluble or water-insoluble categories. It is commonly recognized in the pharmaceutical industry that on an average more than 40% of newly discovered drug candidates are poorly water-soluble. Poor "drug like" properties of lead compounds led to ineffective absorption from the site of administration, which has been designated as an important part of the high clinical failure due to poor pharmacokinetics.

In the pharmaceutical analysis and formulation development fields, it is most often required to increase the aqueous solubility of poorly water-soluble drugs. Most of the newly developed drug molecules are lipophilic in nature and poor solubility is one of the most difficult problems of these drugs.

It is well known that drug efficacy can be severely limited by poor aqueous solubility. It is also known that the side effects of some drugs are the result of their poor solubility. The ability to increase aqueous solubility can thus be a valuable aid to increasing efficiency and/or reducing side effects of drugs. This is true for parenterally, topically, and orally administered solutions.<sup>1</sup>

In pharmaceutical field, it is often required to prepare aqueous solutions of a variety of insoluble drugs. The ability to increase the aqueous solubility can be a valuable aid for increasing the efficacy and/or reducing adverse effects for certain drugs. Following approaches can be employed to enhance the aqueous solubility of poorly soluble drugs.<sup>2,3,4</sup>

- Complexation
- Use of cosolvents
- Alteration of pH
- Use of surfactants
- Supercritical fluid recrystallization
- Micronization
- Solid dispersion
- Eutectic mixture
- Hydrotropic solubilisation
- Mixed hydrotropic solubilisation
- Mixed solvency

The above mentioned methods have been used widely in various fields of pharmacy. However, applications of 'Mixed Hydrotropic Solubilization' and 'Mixed Solvency' have not been explored to appreciable extent in various fields of pharmacy.

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Hydrotropic agents are ionic organic salts. Additives may either increase or decrease the solubility of a solute in a given solvent. The salts that increase solubility are said to 'salt in' the solute and those salts that decrease the solubility 'salt out' the solute. The effect of an additive depends very much on the influence; it has on the structure of water or its ability to compete with the solvent water molecules.<sup>5,6</sup> A convenient quantitation of the effect of a solute additive on the solubility of another solute may be obtained by the Setschenow equation.

$\log S_0/S = KCa$  where

S = solubility in the presence of the additive

Ca = concentration of the additive

S<sub>0</sub> = solubility in the absence of the additive

K = salting coefficient, which is a measure of the sensitivity of the activity coefficient of the solute towards the salt.

Several salts with large anions or cations which are themselves very soluble in water result in a salting in of non electrolytes and are called 'Hydrotropic Salts' and the phenomenon is known as 'HYDROTROPISM'.<sup>7</sup>

The term hydrotropic agent was first introduced by **Neuberg (1916)**, to designate anionic organic salts. According to **Neuberg**, hydrotropic agents are metal salts of organic acids which at fairly high concentration considerably increase the aqueous solubility of organic substances normally slightly soluble in water. According to **Salehand El-Khordagui**, hydrotropic agents are freely soluble organic compounds which at a concentration sufficient to induce a stack-type aggregation considerably enhance the aqueous solubility of organic substances, practically insoluble under normal conditions. These compounds may be anionic, cationic or neutral molecules. However, the term has been used in the literature to designate non-micelle forming substances either liquids or solids, organic or inorganic capable of solubilizing insoluble compounds.

#### Mixed hydrotropy

It is the increase in solubility of poorly soluble drugs by the addition of more than one hydrotropic agent. Hydrotropic agents used in combination may enhance the solubility of poorly soluble drugs by miraculous synergistic effect in addition to the additive effect.<sup>8</sup>

The present study is probably the earliest attempt to enhance Solubility of Zaltoprofen by using mixed hydrotropy and mixed solvency approaches. Moreover, all the solubilizers used in the study are GRAS (Generally regarded as safe) listed.

Zaltoprofen is selected as model drug because it is practically insoluble in water hence there is need to increase the solubility for better absorption and improved therapeutic efficacy.

#### Materials and methods:

Zaltoprofen was obtained as gift sample from Lupin Ltd. Aurangabad, India. All other chemicals were of analytical grade. Deionized water was used during study and solutions were analyzed using Shimadzu 1700 double beam UV spectrophotometer.

#### Drug-solubilizers interference study

Interference of solubilizers in the spectrophotometric es-

timination of Zaltoprofen was determined by taking 10 mg of drug and 100 mg of various solubilizers dissolved in 1- 2 ml of distilled water. After complete dissolution Zaltoprofen was added in flask and flask was shaken vigorously to dissolve the drug. The volume was made up to the mark with distilled water. The absorbance were recorded against respective reagent blanks at appropriate wavelength.

#### Selection of solubilizers for Zaltoprofen

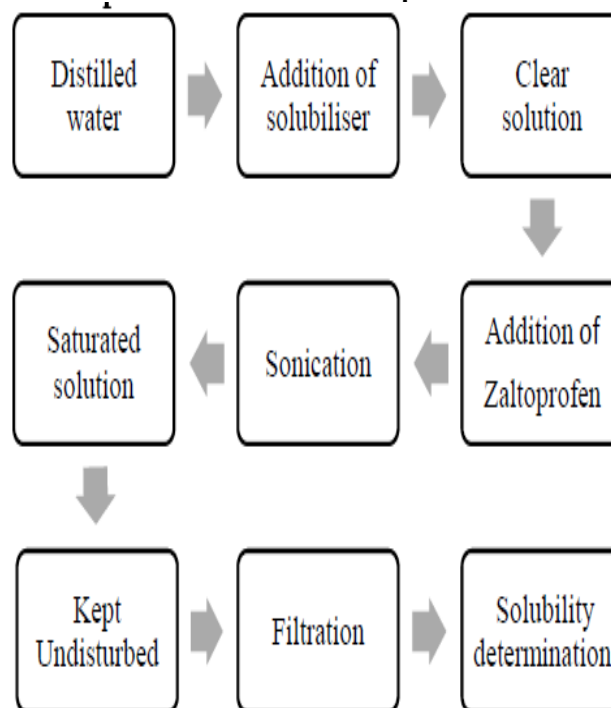


Figure 1: General procedure for solubility determination

Since, the present investigation is the beginning of the mixed solvency solubilization phenomenon. The widely used solubilizers, sodium benzoate, urea, sodium citrate, sodium acetate and cosolvents such as PEG 200, PEG 400, PEG 600, PEG 4000, PEG 6000, propylene glycol, glycerin, and ethanol were tried. Depending on the ease of availability, they were selected as model solubilizing agents to solubilize the model drug Zaltoprofen, which is poorly water-soluble. Therefore, in all the solutions of various solubilizers, the total concentration of dissolved solubilizers was kept 40% w/w (constant).

Aqueous solutions of hydrotropes and solvents having 40% concentration were prepared in distilled water. Sufficient excess amount of Zaltoprofen was added to amber coloured glass vials containing fixed volumes (10 ml) of the hydrotropic solutions separately. The vials were sonicated for 1 to 2 hours at room temperature. The solutions were allowed to equilibrate for next 24 hours and then centrifuged for 5 minutes. The supernatants of each vial were filtered through Whatman filter paper. An aliquot of each filtrate was diluted suitably with distilled water and the resulting solutions were analyzed on UV spectrophotometer at 339 nm against blank solutions.

#### Determination of equilibrium solubility of zaltoprofen:

Aqueous solutions of hydrotropic agents (sodium benzoate, sodium salicylate, Piperazine anhydrous, sodium acetate etc.) and solvent (PEG 600) of known concentrations (10%, 20%, 30%, and 40%) were prepared in distilled water.

Sufficient excess amount of Zaltoprofen was added to amber coloured glass vials containing fixed volumes (10 ml) of the hydrotropic solutions separately. The vials were sonicated for 1 to 2 hours at room temperature. The solutions were allowed to equilibrate for next 24 hours and then centrifuged for 5 minutes. The supernatants of each vial were filtered through Whatman filter paper. An aliquot of each filtrate was diluted suitably with distilled water and the resulting solutions were analyzed by UV spectrophotometer at 339 nm against blank solutions.

#### Determination of equilibrium solubility of Zaltoprofen in blends containing different solubilizers

Sufficient excess amount of Zaltoprofen was added to amber coloured glass vials containing fixed volumes (10 ml) of the solutions of solubilizers blend having three or more than three solubilizers (10% concentration) separately. The vials were sonicated for 1 to 2 hr at room temperature. The solutions were allowed to equilibrate for next 24 hours and then centrifuged for 5 minutes. The supernatants of each vial were filtered through Whatman filter paper. An aliquot

of each filtrate was diluted suitably with distilled water and the resulting solutions were analyzed by UV at 339 nm against blank solutions.

#### Determination of pH of solution containing solubilizers

The pH of solution containing solubilizers was determined by calibrated digital pH meter.

#### Determination of pH solubility of Zaltoprofen

The various phosphate buffers having pH 1.9, 3, 4, 4.8, 5.8, 6.8, 7.2, 7.8, 9.2, and 9.8 were prepared according to the Indian pharmacopoeia. Sufficient excess amount of Zaltoprofen was added to amber coloured glass vials containing fixed volumes (10 ml each) of the respective buffers. The vials were sonicated for 1 to 2 hr at room temperature. The solutions were allowed to equilibrate for next 24 hours and then centrifuged for 5 minutes. The supernatants of each vial were filtered through Whatman filter paper, filtrate was diluted suitably with distilled water and the resulting solutions were analyzed by UV at 339 nm against blank solutions.

## Results

### Drug-solubilizers interference study

Table 1: Drug solubilizers interference study

Drug	Solubilizers	Drug conc. (µg/ml)	Solubilizer conc. (µg/ml)	Wavelength (nm)	Absorbance against respective blank
Zaltoprofen	SB	30	3000	339.0	0.612
Zaltoprofen	SS	30	3000	339.0	0.697
Zaltoprofen	SA	30	3000	339.0	0.325
Zaltoprofen	Urea	30	3000	339.0	0.184
Zaltoprofen	PC	30	3000	339.0	0.242
Zaltoprofen	PG	30	3000	339.0	0.142
Zaltoprofen	SC	30	3000	339.0	0.205
Zaltoprofen	PEG 200	30	3000	339.0	0.225
Zaltoprofen	PEG 400	30	3000	339.0	0.245
Zaltoprofen	PEG 600	30	3000	339.0	0.289
Zaltoprofen	PEG 4000	30	3000	339.0	0.236
Zaltoprofen	PEG 6000	30	3000	339.0	0.232
Zaltoprofen	PA	30	3000	339.0	0.242
Zaltoprofen	G	30	3000	339.0	0.182

\*SB = sodium benzoate, UR = urea, SC = sodium citrate, SA = sodium acetate, PA = Piperazine anhydrous, PC = Piperazine citrate, sodium citrate, citric acid, PG = propylene glycol, ET = ethanol, GL = glycerin.

### Selection of solubilizers:

The solubility was determined using the corresponding regression equations given in Table 2. The equilibrium solubility of Zaltoprofen in 40% concentration of various solubilizers was determined and result indicates that maximum solubility of  $3.8 \pm 0.47$  gm/100 ml was obtained with sodium salicylate with enhancement ratio of 1357.14 and least solubility of  $0.0036 \pm 8.3 \times 10^{-03}$  was observed with sodium citrate. Moreover, significant improvement in solubility was found with piperazine anhydrous, sodium benzoate, sodium acetate and PEG 600 respectively. On the basis of results obtained sodium salicylate, piperazine anhydrous; sodium benzoate, sodium acetate and PEG 600 were selected for further study.

Table 2 :Regression equations of Zaltoprofen in presence of various solubilizers

Sr. no.	Blends	Equation	Linearity
1	Water	$Y = 0.013x - 0.001$	0.999
2	SB	$Y = 0.0173x - 0.1113$	0.9994
3	SA	$Y = 0.015x - 0.059$	0.9968
4	SS	$Y = 0.0132x - 0.003$	0.9994
5	PA	$Y = 0.016x - 0.0776$	0.9979
6	PEG 600	$Y = 0.0142x - 0.0314$	0.9980
7	AA	$Y = 0.0183x - 0.138$	0.9991
8	AB	$Y = 0.015x - 0.117$	0.9997
9	AC	$Y = 0.0175x - 0.138$	0.9955
10	AD	$Y = 0.016x - 0.073$	0.9988
11	AE	$Y = 0.017x - 0.106$	0.999
12	AF	$Y = 0.0157x - 0.064$	0.9996
13	BA	$Y = 0.0148x - 0.049$	0.9977
14	BB	$Y = 0.0159x - 0.069$	0.9955
15	BC	$Y = 0.018x - 0.0132$	0.9976
16	BD	$Y = 0.016x - 0.079$	0.9986
17	BE	$Y = 0.014x - 0.019$	0.9992
18	BF	$Y = 0.0148x - 0.045$	0.9992
19	BG	$Y = 0.02x - 0.177$	0.9984

\*SB = sodium benzoate, SA = sodium acetate, SS = sodium salicylate, PA = Piperazine anhydrous.

**Effect of concentration of selected solubilizers on equilibrium solubility of Zaltoprofen**

The effect of concentration of selected solubilizers was investigated on zaltoprofen equilibrium solubility.

Table 3: Equilibrium solubility of Zaltoprofen in sodium acetate solution

Sr. No	Solution in various concentrations (%)	Solubility gm/100ml± SD	Solubility enhancement ratio
1	10	$0.132 \pm 9.16 \times 10^{-03}$	4.64
2	20	$2.22 \pm 0.173$	73.92
3	30	$3.11 \pm 0.11$	107.14
4	40	$6.01 \pm 0.083$	217.86

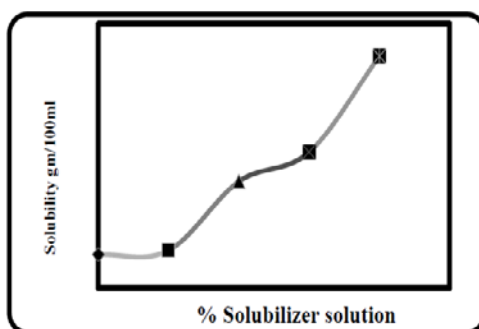


Figure 2: Equilibrium solubility of Zaltoprofen in sodium acetate solution

Table 4: Equilibrium solubility of Zaltoprofen in sodium salicylate solution

Sr. No	Solution in various concentrations (%)	Solubility gm/100ml± SD	Solubility enhancement ratio
1	10	$2.57 \pm 0.02$	71.43
2	20	$6.76 \pm 0.025$	235.71
3	30	$11.73 \pm 0.21$	401.07
4	40	$31.79 \pm 0.47$	1357.14

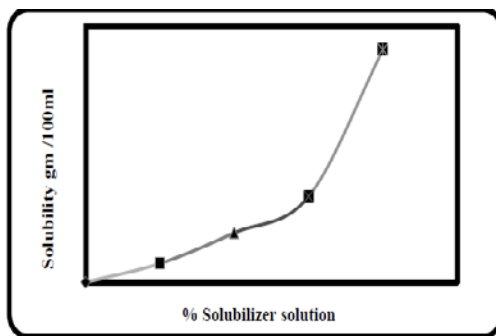


Figure3: Equilibrium solubility curve of Zaltoprofen in sodium salicylate solution

Table 5: Equilibrium solubility of Zaltoprofen in sodium benzoate solution

Sr. No	Solution in various concentrations (%)	Solubility gm/100ml± SD	Solubility enhancement ratio
1	10	0.305 ± 0.039	108.92
2	15	0.476 ± 0.084	170
3	20	0.728 ± 0.079	260.35

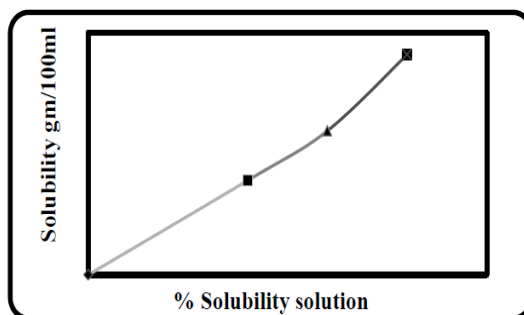


Figure4: Equilibrium solubility curve of Zaltoprofen in sodium salicylate solution

Table 6: Equilibrium solubility of Zaltoprofen in piperazine anhydrous solution

Sr. No	Solution in various concentrations (%)	Solubility gm/100ml± SD	Solubility enhancement ratio
1	10	1.062 ± 0.080	379.28
2	15	2.27 ± 0.05	810.71
3	20	3.46 ± 1.02 × 10 <sup>-03</sup>	1235.71

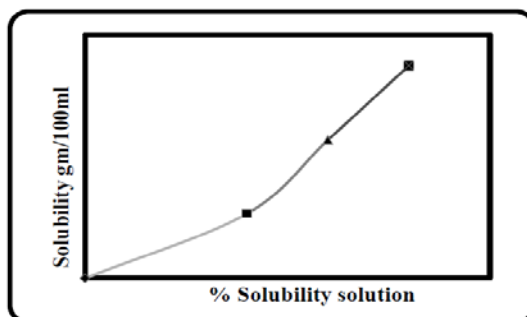


Figure 5: Equilibrium solubility curve of Zaltoprofen in piperazine anhydrous solution

Table 7: Equilibrium solubility of Zaltoprofen in PEG 600 solution

Sr. No	Solution in various concentrations (%)	Solubility gm/100ml± SD	Solubility enhancement ratio
1	10	0.0127 ± 5 × 10 <sup>-03</sup>	4.54
2	20	0.067 ± 0.07	23.79
3	30	0.182 ± 0.08	65
4	40	0.375 ± 0.064	133.93

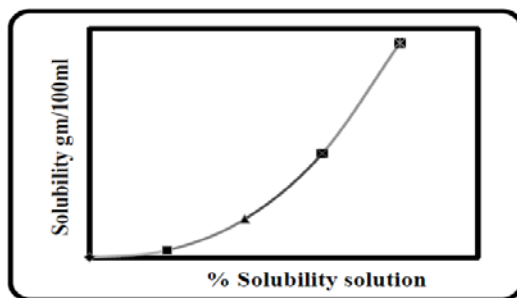


Figure 6: Equilibrium solubility curve of Zaltoprofen in PEG 600 solution

According to the Table 19, 20, 21, 22, 23 and Figure 9, 10, 11, 12, 13 the solubility of Zaltoprofen was increased with increasing concentration of hydrotropic agents in a non linear fashion. The solubilizing power of different solubilizing agent was in the order of **Piperazine anhydrous > sodium salicylate > sodium benzoate > sodium acetate > PEG 600**. The piperazine anhydrous and sodium benzoate were used in maximum concentration of 20% because large amount of drug was solubilized during preparation of saturated solution of drug in 40% concentration and lead to precipitation. However, significant improvement in solubility was obtained and toxic effects of these agents could be minimized by reducing concentration of these solubilizers. The utmost solubility enhancement ratio was obtained in maximum concentration of each hydrotropic agents but such a high concentration of individual hydrotropic agents is not acceptable hence the combinations of these agents were used systematically taking overall 10 % strength of hydrotropic solution to enhance the solubility of Zaltoprofen.

Table 8: Equilibrium solubility data of Zaltoprofen in blend containing more than three solubilizers

Blend codes	Solubilizers (% w/v)						Equilibrium solubility gm/100ml	SER
	S.B.	S.S	S.A	ET	PEG 600	PA		
BA	2.5	2.5	2.5	–	–	2.5	3.538	1236.57
BB	2.5	2.5	2.5	2.5	–	–	0.282	100.71
BC	2.5	2.5	–	–	2.5	2.5	5.251	1875.35
BD	2.5	–	–	2.5	2.5	2.5	3.325	1187.5
BE	–	–	2.5	2.5	2.5	2.5	5.102	1822.14
BF	–	2.5	2.5	2.5	2.5	–	0.2521	90.035
BG	1.75	1.75	1.75	1.25	1.75	1.75	4.856	1734.29

\*SB = sodium benzoate, SA = sodium acetate, PA = Piperazine anhydrous, ET = ethanol, sodium salicylate

The results showed in Table 25 that the solubility of Zaltoprofen in blend containing BC was maximum (5.2 gm/100ml) and raised up to 1875.35 fold, However blend BF shows minimum solubility of 0.2521 (90 fold) in 10% blend solution. Such observed effect showed that the employed hydrotropic agents provide synergistic enhancement in solubility when used in combination. The synergistic power of the above combination of agents could be ranked as: **BC > BE > BG > BA > BD**

But solubility was significantly increased in combination with blend of three solubilizers and pure drug (Table 16). In Figure 14. Shows the graphical representation of all blends determined equilibrium solubility.

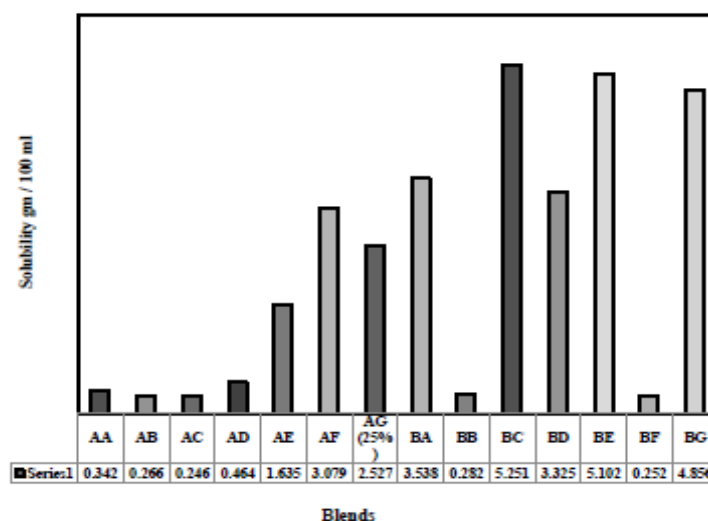


Figure 7: Zaltoprofen equilibrium solubility in different blends

**Determination of the pH of solution containing solubilizers**

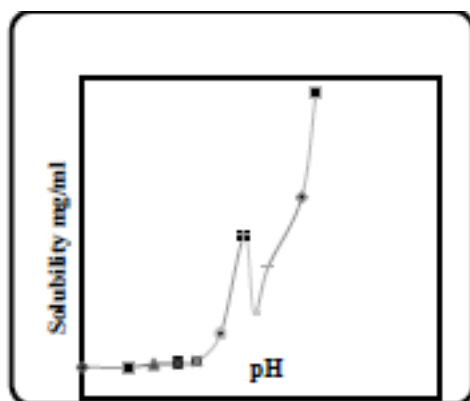
The pH of various blends was determined using digital pH meter. The results are shown in the Table 9.

**Table 9: Determination of pH of solution containing solubilizers**

Sr. no	Blends	pH
1	ET	8.26
2	SB	7.62
3	SA	8.12
4	SS	7.07
5	PA	12.4
6	PEG 600	7.71
7	AA	7.84
8	AB	8.39
9	AC	8.47
10	AD	11.64
11	AE	11.81
12	AF	11.92
13	BA	11.26
14	BB	11.62
15	BC	9.94
16	BD	10.91
17	BE	10.73
18	BF	11.25
19	BG	11.26

**Determination of the pH solubility of Zaltoprofen drug****Table 10: Determined pH solubility of Zaltoprofen**

Sr. no	pH	Solubility mg/ml $\pm$ SD
1	1.9	$0.00038 \pm 5.13 \times 10^{-03}$
2	3	$0.02 \pm 5.86 \times 10^{-03}$
3	4	$0.0246 \pm 2.12 \times 10^{-03}$
4	4.8	$0.037 \pm 5.77 \times 10^{-03}$
5	5.8	$0.209 \pm 5.47 \times 10^{-03}$
6	6.8	$0.819 \pm 0.011$
7	7.2	$0.338 \pm 3.15 \times 10^{-03}$
8	7.8	$0.627 \pm 0.015$
9	9.2	$1.057 \pm 7.21 \times 10^{-03}$
10	9.8	$1.704 \pm 0.03$

**Figure 8: Effect of pH on Zaltoprofen solubility**

pH study of zaltoprofen indicated that the solubility of zaltoprofen was increased with respective pH, but solubility enhancement ratio was very less as compare to solubilizers, and blend's solubility enhancement ratio. Result shown in Table 10.

At neutralized point pH solubility is decreased which indicate that the solubility in sodium benzoate (7.62), sodium acetate (8.12), sodium salicylate (7.07), PEG 600 (7.71) solution is not dependant on pH, It may be concluded that there is nearly negligible effect of pH on solubility enhancement of Zaltoprofen. The pH solubility of Zaltoprofen is presented in Figure 9.

#### Summary and conclusion:

Zaltoprofen is a novel NSAID, selective COX2 inhibiting new class of non-propionate steroidal anti-inflammatory for the treatment of chronic rheumatic arthritis, deformation of arthritis. However, it has low aqueous solubility, therefore higher solubility required to achieve the desired therapeutic efficacy.

The aim of the present research study was to explore the possibility of employing mixed solvency, mixed hydrotrophy techniques in the formulation and evaluation of aqueous oral liquid formulation of a poorly water soluble drug Zaltoprofen.

In the present study, Zaltoprofen was selected as model drug and attempt was made to solubilize by employing the combination of physiologically compatible hydrotropes and solubilizing agents and formulated its oral liquid syrup.

The melting point determination and spectrophotometric analysis showed purity of drug sample. The drug complied with the tests prescribed in the monograph. The Infrared spectra of the drug showed major peaks at wave numbers that are characteristic of Zaltoprofen.

In the preformulation study physical compatibility of the drug-excipient was carried out and compatibility was observed between Zaltoprofen and selected solubilizers. In the drug solubilizers interference study no interference was observed in UV spectrophotometric analysis of Zaltoprofen in presence of employed solubilizers. Partition coefficient was determined by using octanol/water system and was found near to the actual value.

The linearity of calibration curve showed that the Beer Lambert's law was obeyed in the concentration range of 15-75 µg/ml at the  $\lambda_{max}$  of 339 nm. Aqueous solubility of Zaltoprofen was found 0.028 mg/ml.

The solubilizers sodium acetate, sodium benzoate and sodium salicylate, ethanol, PEG 600, piperazine anhydrous, were selected for solubilization studies on the basis of solubility enhancement ratio. The solubility enhancement ratio in sodium citrate, citric acid, urea, PEG 6000, PEG 4000, PEG 200, PEG 400, propylene glycol and glycerin were found to be less as compare to selected solubilizers. Therefore, they were excluded from the study. The solu-

bility determination of drug in hydrotropic solutions was carried out at room temperature and solubilizing power of different hydrotropes could be ranked as:

Piperazine anhydrous > sodium salicylate > sodium benzoate > sodium acetate > PEG 600

From the equilibrium solubility curves of Zaltoprofen in solubilizers it was concluded that increase in the solubility was non linear function with respect to the hydrotrope concentration.

In order to minimize the probable toxic effects of individual hydrotrope at high concentration, the blends of the hydrotropes were tried to give the expected solubility. The hydrotropic blends of total strength 10% except AG (25%) were used for the solubility studies as this concentration gave maximum enhancement in solubility. The maximum synergistic effect was observed in the blends AF, AE, AG, BC, BE, BG, BA and BD.

This shows that mixed hydrotrophy and mixed solvency plays significant role in improving the solubility of practically insoluble drug, Zaltoprofen by employing the combination of solubilizers at lower concentration.

The pH solubility study indicates that solubility of drug increased with respect to pH but at the neutralized point (7.2). Solubility decreased and above 7.2 solubility again increased but it is less as compared to the solubility of solubilizers, thus the drug solubility is independent of pH effect.

#### Conclusion:

- Zaltoprofen, a poorly water soluble drug, having water solubility 0.028 mg/ml.
- The solubility of Zaltoprofen was increased by applying mixed solvency and mixed hydrotrophy approach using different solubilizers.

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