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Formulation Development of Aqueous Injection of Zaltoprofen

Harin Patel*, Shailendra Singh Solanki, Gajanan Darwhekar, Dinesh Kumar Jain
College of Pharmacy, IPS Academy, Rajendra Nagar, A.B. Road, Indore - 452012 (M.P.) India.

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ABSTRACT

Zaltoprofen, a non-steroidal anti-inflammatory drug (NSAID) exhibits strong analgesic, antipyretic and anti-inflammatory activities. It is practically insoluble in water, which limits its use in parenteral formulations. The present study was aimed to find the optimum aqueous solubility of zaltoprofen using minimum amount of solubilizing agents along with different hydrotropic agents to ease the formulation of stable aqueous injection, thereby reducing the concentration dependent toxicity of individual excipients. Selection of optimum blend of cosolvents was done by 2^3 factorial designs. Solubility of zaltoprofen in selected mixture of hydrotropic agent (2M sodium benzoate) and co-solvents blend (Propylene glycol, Glycerin and PEG 400) was increased by more than 1000 folds as compared to its aqueous solubility. The prepared aqueous injection was found to be effective as analgesic and anti inflammatory activity which was comparable to the indomethacin without major changes in hematological parameters in mice having the shelf life of about 15 months. Hence, the aqueous injection of poorly water soluble drugs is possible using combination of various solubilizers and hydrotropic agents which acts synergistically at very low individual concentrations. The proposed techniques would be safe, effective, economical, convenient and reproducible excluding the use of organic solvent in formulation development.

Keywords: *Zaltoprofen; Solubility; Aqueous injection; Shelf life.*

INTRODUCTION

Zaltoprofen, (2RS)-2-(10-oxo-10,11-dihydrodibenzo [b,f]thiepin-2-yl)propanoic acid [1], is nonsteroidal anti-inflammatory drug (NSAIDs) with powerful analgesic and anti inflammatory action. Zaltoprofen has a unique action in inhibiting bradykinin (BK) induced nociceptive responses more potently than other NSAIDs [2]. Zaltoprofen obtained as white, crystals or crystalline powder is freely soluble in acetone, soluble in methanol and ethanol and practically insoluble in water, which precludes its use in parenteral formulations. It is gradually decomposed by light [1], Parenteral products are administered to the body by injection. Since this route of administration bypasses the normal body defense mechanisms, it is essential that these products are prepared with a highest degree of care and skills than utilized in preparing conventional products. The finished product must be sterile and free from extraneous insoluble materials [3]. The various techniques for solubilization of poorly soluble drugs into aqueous injections are by hydrotropic agents reported [4-7]. Solubilization of drugs by these techniques required very high amount of solubilizing agents which are not devoid of toxic effects. Therefore, the purpose of present research was to investigate application of mixed solvents solubilization technique in the formulation of aqueous injection of insoluble drugs and to reduce concentration of individual hydrotropes and co-solvent to minimize the side effects.

MATERIALS AND METHODS

Materials:

The gift sample of zaltoprofen was provided by IPCA Laboratories, Ratlam, India. Sodium benzoate, Urea, Sodium citrate, Glycerin, PEG 600, PEG 400, PEG 200 and PEG 6000 were obtained from Merck Chemicals Limited, Mumbai, India. Nicotinamide and Propylene glycol were obtained from Loba Chemie Ltd. Mumbai, India. All other chemicals and reagents used were of analytical grade.

***Corresponding author:**
Harin Patel
College of Pharmacy, IPS Academy,
Rajendra Nagar, A.B. Road, Indore - 452012 (M.P.) India.
**E-Mail: harinpatel.13@gmail.com*

Methods:

Estimation of Zaltoprofen:

In the present study, UV spectrophotometric method was used for the estimation of zaltoprofen. The calibration curve of zaltoprofen was prepared in distilled water, in solvent system of hydrotropic agents and in co-solvents at 340 nm using double beam spectrophotometer (UV-1800, Shimadzu, Japan) [1, 9].

Determination of Solubility at Different pH:

All the samples of saturated solution of drug at different pH were kept for 30 days at 25± 2°C and analyzed for the drug content to obtain the % of degradation.

Solubility Determination:

Solubility of zaltoprofen in various solutions was determined by equilibrium solubility method. Sufficient excess amount of Zaltoprofen was added to 5 ml glass vials containing buffers of pH (1.2-10.0), aqueous solution of hydrotropic agents and different concentration of solubilizers (**Table 1 & 2**). The vials were shaken mechanically for 12 h on mechanical shaker (Lab Hosp, Mumbai, India) at 37 ± 2°C. The solutions were allowed to equilibrate for next 24 h. The solution was transferred into eppendorf tubes and centrifuged for 5 min at 2000 rpm. The supernatants of each vial were filtered through 0.45µ membrane filter (Pall Corporation, USA) and analyzed for drug content by UV visible spectrophotometer (UV 1800, Shimadzu, Japan) at 340nm after appropriate dilutions [7].

Optimization of Co-solvent Blends by Factorial Design Method:

Based on the preliminary solubility data the optimum blend of co-solvent was determined by factorial design [10]. Three factors, two levels (2^3) factorial design were introduced in which propylene glycol; glycerin and PEG 400 were the three factors at two levels i.e. 20% and 30% are two levels of experiments. Solubility of zaltoprofen in all the experimental blends having different concentration of co-solvents (**Table 3**) was determined.

Aggregation of best hydrotropic and optimized co-solvent blends solution:

The hydrotropic solution showing highest solubility and optimized blends of co-solvents were mixed together in 1:1 ratio to obtain the final strength of these solution as shown in **Table 4**. The solubility of zaltoprofen was determined in these systems [11].

Properties of hydrotropes and Co-Solvents solutions:

The various solution properties of hydrotropes and Co-Solvents such as pH, viscosity, specific gravity and surface tension were also studied in an attempt to reason out the increase in solubility of zaltoprofen with increase in concentration of hydrotropes and Co-Solvents [6,7].

Drug Excipeint Compatibility Studies:

UV spectral studies:

UV spectral studies of zaltoprofen were performed in different hydrotropic and Co-Solvents solutions to study the possible spectroscopic changes in the structure of zaltoprofen in presence of different hydrotropes and Co-Solvents [7].

Fourier transform infrared (FTIR) spectral studies:

FTIR spectra were obtained by means of a FTIR spectrophotometer (FTIR – 8300 s, Shimadzu, Japan). The samples were prepared by mixing of drug and potassium bromide and measurements were attempted with the accumulation of 20 scans and a resolution of 4 cm^{-1} over the range of 600–4000 cm^{-1} [6].

Thermal analysis:

Differential scanning calorimeter (DSC) curves were obtained with a Pyris-6 DSC (Jade DSC).The samples were prepared by placing 3.7 mg sample into an aluminum pan. Samples were kept with Indium calcium prior to estimation. Thermographs were analyzed qualitatively by examining both the peak temperature and the endothermic transition contour. The nitrogen flow rate was 20 ml/min and the heating rate was 10°C/min over the range of 30–300°C [6].

Formulation of Aqueous Injection:

Preparation of Aseptic Area:

The walls and floor of aseptic room were thoroughly washed with water and then disinfected by mopping with 2.5% v/v Dettol solution [6]. The bench was cleaned with 70% v/v isopropyl alcohol as well as sprayed in the atmosphere. The aseptic room was fumigated using a mixture of formaldehyde and potassium permanganate and the UV lights were switched on for 30 min prior to formulation of injections and the filling of injections into vials [12].

Treatment of Packing Material:

Amber color glass vials of 2 ml capacity were washed several times with water then finally rinsed with distilled water. All these vials were sterilized by dry heat in an oven at 180°C for 2 h. Rubber stoppers used for plugging the vials were first shaken in 0.2% liquid detergent solution for 2 h, then washed several times with water to remove any detergent residue and finally rinsed with distilled water. These stoppers were sterilized by autoclaving at 121°C temperature at 15 lbs pressure for 20 min. Finally, the stoppers were rinsed with freshly prepared sterile distilled water and dried in vacuum oven under aseptic condition [7, 12].

Preparation of Aqueous Injection:

On the basis of solubility data obtained from the final aggregation of blends, formulation of aqueous injection of zaltoprofen was prepared using solvent system 'C'. This formulation contained 40 mg/ml zaltoprofen in solvent system 'C' (1M sodium benzoate, 15% w/v propylene glycol, 15% w/v glycerin and 10% w/v PEG 400) solution [6, 7]. 0.1% w/v sodium metabisulfite 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.

For the preparation of aqueous injection of zaltoprofen, 45 ml of solvent system 'C' solution was placed in 50 ml glass beaker in the aseptic area and weighed amount of zaltoprofen and 0.1% w/v sodium metabisulfite were added as an antioxidant to the beaker and placed on magnetic stirrer after ensuring the complete dissolution of the former. pH of the solution was adjusted to 6-7.8 with 0.1 N HCl and 0.1 N NaOH solution then the volume was made up to 50 ml with water for injection. The contents of these beakers were stirred for additional 1 h on the magnetic stirrer for complete solubilization. These solutions were filtered through 0.45 µm membrane filter (Pall Corporation, USA). The solutions were analyzed spectrophotometrically at 340 nm for drug content after appropriate dilutions with distilled water using the same vehicle as blank after appropriate dilution [7].

Aseptic Filtration and Packaging:

The aqueous injection of zaltoprofen was sterilized by filtration through 0.2 µm disposable membrane filter fitted in a holder of 5 ml glass syringe and the pressure on the piston was adjusted. After filtration the preparation was packed by the sterilized air tight rubber closure and labeled [6]. The final packed vials were sterilized by autoclaving at 121°C temperature at 15 lbs pressure for 15 min [8].

Stability Studies:

Physical Stability studies:

The sealed or packed vials of the aqueous injections were visually inspected every day for 30 days against black and white backgrounds to see the changes occurring, if any, in physical appearance of aqueous injection like color, turbidity, pH etc., on storage at 4 ± 2°C in a refrigerator, 25 ± 2°C and 60 ± 2°C in thermostatically controlled ovens (Lab Hosp, Mumbai, India).

Chemical Stability studies:

The injection formulations were subjected to exhaustive chemical stability at 4 ± 2°C in a refrigerator, 25 ± 2° C and 60 ± 2°C in thermostatically controlled ovens for a period of 30 days. The formulations were analyzed spectrophotometrically initially and at particular intervals to calculate the drug content. The percent residual drug for each injection formulation at different time intervals as well as at different temperatures was calculated considering the initial drug content for each formulation to be 100% [7]. From the chemical stability data, the K values at 25± 2°C were determined. The time period required for 10% degradation of drug ($t_{10\%}$) or shelf life of formulation was calculated.

Animal Study:

All in-vivo investigations were performed as per the protocol approved by the Institutional Animal Ethical committee of College of Pharmacy, IPS Academy, Indore, India.

Analgesic Activity by Hot Plate Method:

The 3 groups of mice (n=3) of either sex with an initial weight of 18 to 22 g were used for each dose. The temperature of a metal surface in the hot-plate test was set at 55±1ºC. The time taken by the animals to lick the fore or hind paw or jump out of the place was taken as the reaction time. Latency to the licking paws or jumping from plate was determined before and after treatment. The latency was recorded at 30, 60, 90 and 120 min after intraperitoneal (IP) administration of injection formulation or standard drug.

Injection formulation, with doses of 15 mg/kg were injected IP in treated groups. Indomethacin 10 mg/kg was injected IP as reference drug used as gold standard (equipotent dose) [14, 15].

Anti Inflammatory Activity by Carrageenan Induced Paw Edema:

Mice were divided into three groups (n=3). Acute inflammation was produced by sub planter administration of 0.1 ml of 1% w/v carrageenan in normal saline in the right hand paw. The paw volume was measured at zero hours and 3 hours after carrageenan injection by using digital vernier caliper. Animals of group I received normal saline (10 ml/kg IP) and served as control. The groups II received Indomethacin gold standard (10 mg/kg IP) and group III received injection formulation (15mg/kg IP). Animals of all groups were treated with the saline and drug 1 hour before the administration of carrageenan. The percentage inhibition of edema was calculated for each group with respect to control group [16, 17].

$$\% \text{ inhibition of paw edema} = [1 - (Vt / Vc)] \times 100$$

Where Vc represent average increase in paw volume of the control group of rats at a given time; and Vt was the average inflammation of the drug treated (i.e. standard or test drug) rats at the same time.

Hematological Count:

The 3 groups of mice (n=3) of either sex with an initial weight of 18 to 22 g are used for this study. Group I administrated normal saline (10 ml/kg IP) and served as control. The groups II received Indomethacin standard (10 mg/kg IP) and group III received injection formulation (15mg/kg IP). After completion 1 h blood was collected from retro-orbital route of mice into the tubes containing anticoagulant [18]. The anticoagulated tubes were prepared from the disodium EDTA. For the 2 ml of blood sample 0.2 ml of 1% solution of anticoagulant was added in the tubes and it allows for evaporated. Blood samples of individual mice were analyzed on automatic haematology analyzer (Hema 2062, Gujarat, India).

RESULTS AND DISCUSSION

The results of solubility studies at different pH indicated that zaltoprofen was more soluble at alkaline pH than acidic pH. The aqueous solubility of zaltoprofen was increased up to fourteen times at pH 10.0 (**Table 1**). Storage of zaltoprofen solution at different pH for 30 days showed maximum stability of drug at basic pH.

The solubility of zaltoprofen in different hydrotropic agents and co-solvents is showed in **Table 2**. The solubility enhancement power of different hydrotropes was ranked in decreasing order as Sodium Benzoate > Nicotinamide > Urea > Sodium Citrate and in different co-solvents could be ranked in decreasing order as PEG 600 > PEG 6000 > PEG 400 > PEG 200 > Glycerin > Propylene Glycol. The solubilizers selected for the present study possess a hydrophobic centre which can interact due to a large surface area and a mobile electron cloud known as a sextet. Thus these sites are available for non-bonded and vander Wall's interaction with water and zaltoprofen. For solubilization the ionized solubilizers break this association and use the ion dipoles of water for salvation [6].

Increasing the solubilizer's concentration increases the solubility of zaltoprofen but on the other hand also increases the chances of toxicity level of formulation. Therefore, for achieving the highest solubility at the minimum concentration level of solubilizers optimization through factorial design study was performed. The study designs along with results are shown in table 3. The regression analysis [20] generated the following equation.

$$Y = -10.4 + 0.188\,X_1 + 0.185\,X_2 + 0.185\,X_3 \ldots\ldots\ldots\ldots\ldots 01$$

Where Y is the solubility of zaltoprofen (mg/ml) and X_1, X_2, X_3 are the three factors. r^2=82.4%.

The effects of each factor [20] on solubility of zaltoprofen was found to be 2.1, 1.85 and 1.84 for X_1, X_2, X_3 respectively, suggesting that all the three factors are equally important in modifying the solubility of zaltoprofen. The solubility enhancement in different experimental blends could be ranked in decreasing order as 'abc' > 'ab' > 'ac' > 'bc' > 'c' > 'b' > 'a' > '(1)'.

Aggregation of hydrotropic agent with the optimized experimental co-solvent blends could be ranked in decreasing order as solvent system code 'D' > 'C' > 'A' > 'B' shown in **Table 4**.

The UV absorption spectra of zaltoprofen in various solubilizers solutions showed a slight shift in λ_{max} (340 ± 1 nm), which can be due to minor electronic changes in the structure of drug molecules. There is no complex formed between drug and solubilizers, because the complex formation can be evidenced by formation of new chromophores. No evidence of strong complex formation was obtained from FTIR spectral analysis (**Fig. 1a & 1b**). Patterns of solubilized form of zaltoprofen and solubilizers molecules show approximately superimposition of spectra of solubilizers and drug. However, there is slight shift in the peaks and peak intensity of zaltoprofen. These changes may be due to weak interactions between zaltoprofen and solubilizers molecules.

The DSC curve of pure zaltoprofen showed a sharp endothermic peak at 134.99°C (**Fig. 2a**), attributed to melting point, indicating that the bulk powder is high quality crystalline powder. The curves of solubilized form of zaltoprofen and solubilizers molecules showed two peaks at 120.0°C and 160.0°C (**Fig. 2b**). Thus, in the solubilized forms no endothermic peak attributed to melting point of zaltoprofen was observed in DSC curve, which indicates alteration of crystalline nature of zaltoprofen.

The various solution properties of combination of solubilizers were found (**Table 5 & 6**). The specific gravity of all the solutions was slightly deviated due to little changes in total concentration of solutions. The viscosity of all the solutions was increased with increasing the slight changes in the concentration while the surface tension of solutions was constantly decreasing with increasing the viscosity of solutions.

The physical stability study showed that all formulations remain unchanged in respect of color stability and no turbidity or precipitate formation was observed at different storage conditions. The data on chemical stability at different temperatures and time intervals are shown in **Table 7**. The calculated K values, i.e. decomposition rate constant of formulations are reported in **Table 8**. The results show that the prepared formulations had a shelf life of 1.249 year.

The analgesic activity was performed by the hot plate method using the three groups having control, standard and test. Zaltoprofen injection significantly increased the hot splate reaction time of mice up to 60 min at a dose of 15 mg/kg. However, there was a decline in the reaction time beyond 90 min (**Table 9**).

Intraperitoneal injection of 1% solution of carrageenan in the hind paw increased in the paw edema volume in the control group. Zaltoprofen injection formulation, with most effective dose in 15 mg/kg, inhibited inflammation induced by carrageenan after 1 hour was 27.67%, after 3 hours formulation inhibited inflammation induced by carrageenan was 52.63% (**Table 10**). Therefore, the zaltoprofen injection formulation was well effective in the case of inflammation.

The hematological study of all the mice of three groups was analyzed by automatic haematology analyzer (Hema 2062, Gujarat, India). There were no significant changes in RBC, WBC, and Hemoglobin (Hb) in the control standard and test formulation shown in **Table 11**. Therefore, the zaltoprofen injection formulation was safe and did not showed interference in the basic blood count.

Table No. 1: Solubility and % Degradation of drug at different pH

Buffer Solutions	Solubility (mg/ml) of Zaltoprofen in Buffer Solutions		Degradation
	1st Day	30th Day	
Distilled Water	0.0718	0.0680	5.3 %
Hydrochloric acid buffer pH 1.2	0.0153	0.0137	10.5 %
Hydrochloric acid buffer pH 2.2	0.0286	0.0275	3.9 %
Acid phthalate buffer pH 4.0	0.0335	0.0314	6.3 %
Phosphate buffer pH 5.8	0.0358	0.0347	3.1 %
Phosphate buffer pH 8.0	0.1044	0.1021	2.2 %
Alkaline borate buffer pH 9.0	0.8041	0.7906	1.7 %
Alkaline borate buffer pH 10.0	1.0911	1.0754	1.4 %

Table No. 2: Solubility enhancement ratio of drug in Different solubilizers at 25± 2°C

Solvents	Solubility (mg/ml)	Enhancement Ratio
Distilled water	0.0750 ± 0.004	1.00
2M Sodium Benzoate	19.438 ± 0.12	259.17
2M Urea	1.455 ± 0.08	19.4
2M Nicotinamide	15.566 ± 0.06	207.54
2M Sodium Citrate	0.609 ± 0.09	8.12
20 % w/v Propylene Glycol	0.318 ± 0.11	4.24
30 % w/v Propylene Glycol	0.516 ± 0.13	6.88
40 % w/v Propylene Glycol	0.624 ± 0.11	8.32
20 % w/v Glycerine	0.577 ± 0.15	7.69
30 % w/v Glycerine	0.832 ± 0.14	11.09
40 % w/v Glycerine	0.908 ± 0.15	12.01
20 % w/v PEG 6000	0.468 ± 0.11	6.24
30 % w/v PEG 6000	0.842 ± 0.10	10.98
40 % w/v PEG 6000	1.321 ± 0.13	17.61
20 % w/v PEG 600	0.773 ± 0.09	10.31
30 % w/v PEG 600	0.932 ± 0.14	12.42
40 % w/v PEG 600	1.332 ± 0.13	17.76
20 % w/v PEG 400	0.972 ± 0.08	12.96
30 % w/v PEG 400	0.806 ± 0.09	10.74
40 % w/v PEG 400	1.256 ± 0.08	16.74
20 % w/v PEG 200	0.762 ± 0.15	10.16
30 % w/v PEG 200	0.822 ± 0.13	10.96
40 % w/v PEG 200	0.955 ± 0.12	12.73

Table No. 3: Three factors and two levels factorial design for investigation of saturated solubility

Experiment Blends	Factor X_1 Propylene Glycol (%w/v)	Factor X_2 Glycerin (%w/v)	Factor X_3 PEG 400 (%w/v)	Zaltoprofen Solubility (Y) (mg/ml)
(1)	20	20	20	1.405 ± 0.045
A	30	20	20	1.961 ± 0.048
B	20	30	20	2.950 ± 0.059
Ab	30	30	20	4.292 ± 0.074
C	20	20	30	3.016 ± 0.069
Ac	30	20	30	4.229 ± 0.077
Bc	20	30	30	3.185 ± 0.094
Abc	30	30	30	7.578 ± 0.103

Table No. 4: Combination of the hydrotropic solution and co-solvent solutions for saturated solubility determination

Solvent System Code	A	B	C	D
Solvent System	1M Nicotinamide	1M Nicotinamide	1M Sodium Benzoate	1M Sodium Benzoate
	15% Propylene Glycol	15% Propylene Glycol	15% Propylene Glycol	15% Propylene Glycol
	15% Glycerin	10% Glycerin	15% Glycerin	10% Glycerin
	10% PEG 400	15% PEG 400	10% PEG 400	15% PEG 400
Zaltoprofen Solubility (mg/ml)	20.637 ± 0.15	19.798 ± 0.21	87.592 ± 0.45	90.737 ± 0.68

Table No. 5: Properties of the optimized blends

Experiment Blends	pH	Viscosity (cps)	Surface tension (dynes/cm)	Specific gravity
(1)	7.08	7.36	52.35	1.082
A	7.12	7.62	50.46	1.091
B	7.15	7.84	48.96	1.098
Ab	7.26	7.92	48.11	1.109
C	7.14	7.74	49.15	1.094
Ac	7.28	7.86	48.72	1.105
Bc	7.29	8.08	47.24	1.112
Abc	7.36	8.36	45.82	1.124

Table No. 6: Properties of the final formulation blends

Solvent System Code	pH	Viscosity (cps)	Surface tension (dynes/cm)	Specific gravity
A	6.08	6.92	56.96	1.0708
B	6.02	6.84	57.45	1.0686
C	7.43	7.98	56.88	1.0726
D	7.96	9.94	56.91	1.0714

Table No. 7: Chemical Stability Data of Formulation

Formulation Code	Temperature	Concentration (mg per vials)				Degradation
		0 Day	7 Day	15 Day	30 Day	
C	4± 2°C	80.07 ± 0.016	79.88 ± 0.011	79.69 ± 0.015	79.69 ± 0.021	0.47%
	25± 2°C	80.07 ± 0.16	79.79 ± 0.015	79.60 ± 0.018	79.50 ± 0.022	0.71 %
	60± 2°C	80.07 ± 0.16	79.79 ± 0.024	79.41± 0.029	79.22 ± 0.028	1.06%

Table No. 8: Degradation rate constant and shelf life of formulated products

Formulation	Degradation rate constant K ($days^{-1}$) x 10^4 at 25± 2°C	Shelf life at 25± 2°C
Zaltoprofen injection	2.303	1.249 year

Table No. 9: Analgesic activity of zaltoprofen injection by hot plate method

Drug	Dose	Pre drug reaction time in seconds	Post drug reaction time in seconds			
			30 min	60 min	90 min	120 min
Control (Saline)	10 ml/kg	5.12 ± 0.64	6.28 ± 0.26	5.38 ± 0.30	5.16 ± 0.61	5.08 ±0.75
Indomethacin	10 mg/kg	6.24 ± 0.45	7.92 ± 0.23	11.56 ± 0.31	9.06 ± 0.28	8.79 ± 0.16
Zaltoprofen injection	15 mg/kg	5.78 ± 0.52	7.79 ± 0.59	12.21 ± 0.44	11.24 ± 0.20	9.46 ± 0.15

Table No. 10: Anti inflammatory activity of Zaltoprofen injection by carrageenan-induced paw edema

Drug	Dose	Increase in paw volume (% inhibition of paw edema)			
		Before	1 hour	2 hour	3 hour
Control (Saline)	10 ml/kg	1.28±0.024	2.24±0.026	2.48±0.035	2.85±0.082
Indomethacin	10 mg/kg	1.31±0.014	1.76±0.012 (21.42)	1.61±0.042 (35.11)	1.41±0.017 (50.52)
Zaltoprofen injection	15 mg/kg	1.32±0.042	1.62±0.018 (27.67)	1.50±0.011 (39.51)	1.35±0.028 (52.63)

Table No. 11: Hematological blood count in mice

Drug	Dose	RBC count (10^{12}/L)	WBC count (10^9/L)	Hb (g/dL)
Control (Saline)	10 ml/kg	8.74 ± 0.63	6.43 ± 0.73	13.6 ± 0.62
Indomethacin	10 mg/kg	8.95 ± 0.54	5.9 ± 0.31	14.21 ± 0.49
Zaltoprofen injection	15 mg/kg	9.1 ± 0.65	5.4 ± 0.24	14.73 ± 0.36

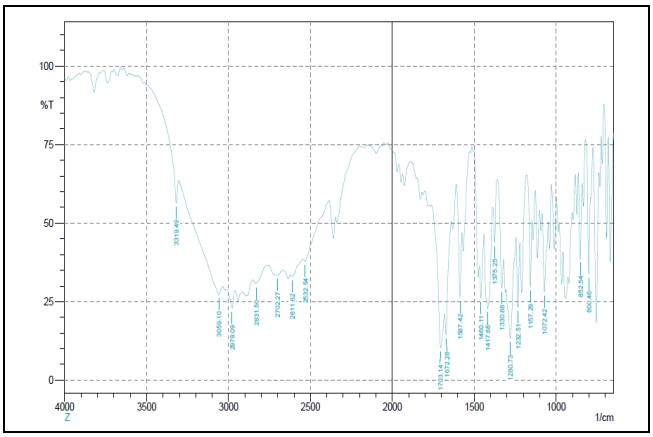

Fig. 1a: FTIR Spectrum of Zaltoprofen

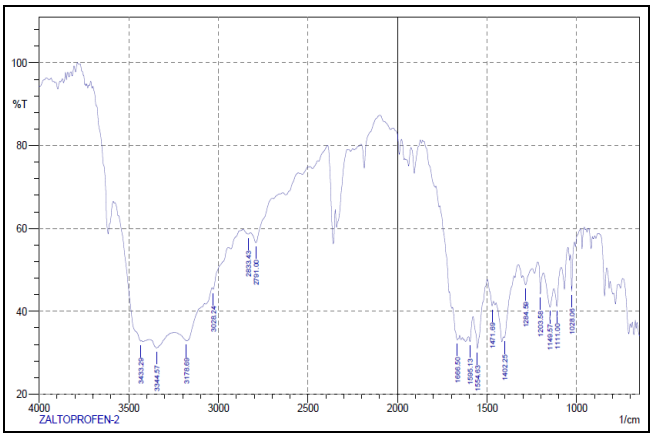

Fig. 1b: FTIR Spectrum of Zaltoprofen and all the Solubilizers

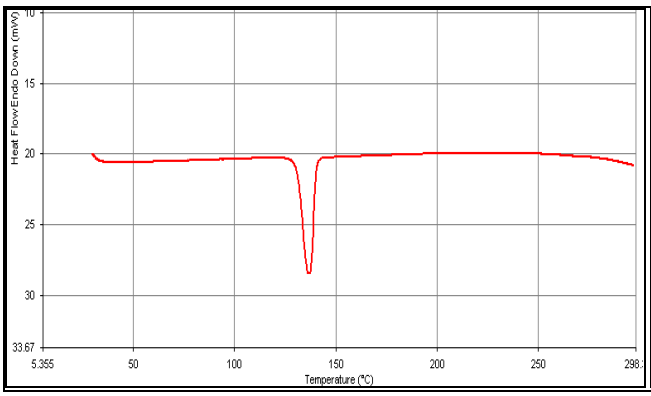

Fig. 2a: DSC Thermograph of Zaltoprofen

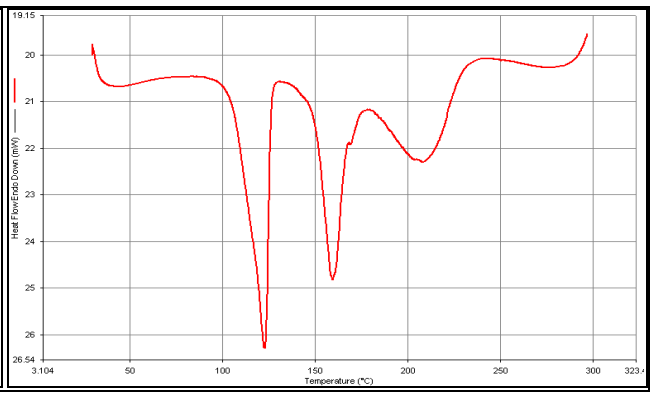

Fig. 2b: DSC Thermograph of Zaltoprofen and all Solubilizers

CONCLUSIONS

Solubilizers and the hydrotropic agents have been used for improvement of the solubility of poorly water soluble drugs. The amount of individual solubilizer required to increase the measurable solubility shall be very high which sometimes shows the toxicity. Therefore, the use of blends of solubilizers often acts synergistically to improve the solubility and reduces the risk of toxicity.

The results of present investigations showed the possibility of aqueous injection of poorly water soluble drugs using combination of various solubilizers and hydrotropic agents which acts synergistically at very low individual concentrations. Hence, the proposed techniques would be safe, effective, economical, convenient and reproducible excluding the use of organic solvent in formulation development.

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