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RESEARCH ARTICLE

Formulation and Pharmacokinetic Evaluation of Phosal Based Zaltoprofen Solid Self-Nanoemulsifying Drug Delivery System

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Abstract: ***Background*:** Phosal based excipients are liquid concentrates containing phospholipids. They are used to solubilize water-insoluble drug and also act as an emulsifier to get the smallest droplet size of the formed emulsion after administration.

***Objective*:** The aim is to prepare phosal based self nanoemulsifying drug delivery system (SNEDDS) for water insoluble drug zaltoprofen.

***Methods*:** The various parameters like solubility of drug in different vehicles, ternary phase diagram are considered to formulate the stable emulsion which is further characterized by Self emulsification time and globule size analysis to optimize liquid SNEDDS of Zaltoprofen. Optimized L-SNEDDS was converted into free-flowing powder Solid-SNEDDS (S-SNEDDS). S-SNEDDS was evaluated for Globule size analysis after reconstitution, *in vitro* dissolution study and *in vivo* pharmacokinetic study in rats.

***Results*:** Phosal 53 MCT with highest drug solubility was used as oil along with Tween 80 and PEG 400 as surfactant and cosurfactant respectively to prepare liquid SNEDDS. Neusilin us2 was used as an adsorbent to get free-flowing S-SNEDDS. S-SNEDDS showed improved dissolution profile of the drug as compared to pure drug. *In vivo* study demonstrated that there is a significant increase in C_{max} and AUC of S-SNEDDS compared to zaltoprofen powder.

***Conclusion*:** Phosal based SNEDDS formation can be successfully used to improve the dissolution and oral bioavailability of poorly soluble drug zaltoprofen.

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1. INTRODUCTION

Many newly developed drugs are having poor solubility which results in the poor oral bioavailability of such drugs [1]. The solubility of such drugs can be successfully enhanced by various methods like lipid-based system, complex formation, nanosization, *etc*. which result in an increase in dissolution rate and oral bioavailability of such drugs [2].

One such approach is Self-micro emulsifying drug delivery system (SMEDDS) or Self nano emulsifying drug delivery system (SNEDDS) which can be used to increase oral bioavailability of such drugs [3]. It forms the drug in a fine droplet of oil after oral administration and increases solubility and permeability through the intestinal wall and reduce first pass metabolism of drug [4-6].

Self nano emulsifying drug delivery system after dilation with gastric fluid forms thermodynam-

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ically and kinetically stable nanoemulsion. It is an isotropic mixture of suitable oil and a fixed ratio of surfactant to co-surfactant with drug [7, 8]. This nanoemulsion gives better drug release and absorption [9].

Phospholipids are the important excipient used for enhancing drug solubility, oral absorption and bioavailability of poorly water-soluble compounds. Phosal based excipients are liquid concentrates containing phospholipids. They are used to solubilize water-insoluble drug and also act as an emulsifier to get the smallest droplet size of the formed emulsion after administration [10].

Zaltoprofen (Fig. **1**) is a newly developed NSAID having selective COX2 inhibiting activity. Zaltoprofen is used to relieve pain and inflammation after surgery and used in arthritic conditions like osteoarthritis, rheumatoid arthritis, *etc*. Furthermore, use of zaltoprofen is limited by its poor aqueous solubility and poor oral bioavailability as it belongs to BCS Class II drug. Solubility enhancement of zaltoprofen will overcome this problem and bioavailability and therapeutic efficacy can be enhanced [11-14].

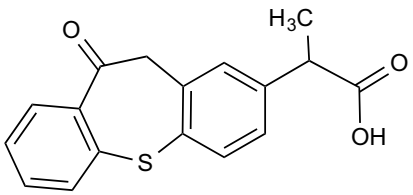


Fig. (1). Zaltoprofen.

In the present study, we have developed zaltoprofen loaded S-SNEDDS in order to increase its aqueous solubility and bioavailability. Solubility study was carried out in different vehicles based on which phase diagram was plotted. Zaltoprofen loaded L-SNEDDS was prepared which was further converted into S-SNEDDS. It was characterized by globule size analysis, *in vitro* drug release and *in vivo* animal studies.

2. MATERIALS AND METHODS

2.1. Materials

Zaltoprofen was obtained as a gift sample from IPCA Labs, Mumbai, Neusilin us2 was gifted by Gangwal chemicals Mumbai, Phosal 53 MCT (Phosphatidylcholine solubilized in a carrier system) by Lipoid, Germany, Polysorbate 80 (Tween 80) and PEG 400 were purchased from Research Lab. All other chemicals were of reagent grade and used as received.

2.2. Solubility Studies

An excess amount of zaltoprofen (about100 mg) was added in 2ml glass vial containing 1ml each of different vehicles like oil, surfactant and cosurfactant. The mixture was then vortex mixed and kept in orbital shaker incubator (Labline india) for equilibration for 72hr at 25°C [15]. Then, the equilibrated samples were centrifuged ((Bioera) for 15 min at 8000RPM. The supernatant was filtered and diluted with methanol for determination of zaltoprofen.

2.3. Construction of Ternary Phase Diagram

The ternary phase diagram is constructed to identify the best suitable composition of Oil, surfactant and cosurfactant to form microemulsions which are selected through solubility and preliminary study. Phosal 53 MCT, Tween 80 and PEG 400 were selected as oil, surfactant and as co-surfactant respectively to construct a ternary phase diagram. A series of self-microemulsifying systems were prepared with varying ratios of Phosal 53 MCT, Tween 80 and PEG 400. 100mg of each formulation was introduced into 100mL of volumetric flask maintained at 37°C and was mixed gently. The tendency to form microemulsion spontaneously and easy spread of emulsion droplets forming a fine milky or slightly bluish emulsion in short time indicated good emulsion [16].

2.4. Preparation of Liquid SNEDDS Formulations

The L-SNEDDS were prepared by dissolving the specific dose of zaltoprofen in the mixture of oil, surfactant and co-surfactant at 35°C in the concentration mentioned in Table **1**. The final mixture was kept in the orbital shaker to get a clear solution. The formulations were examined for any signs of turbidity or phase separation or gelling effect before to self emulsification and globule size analysis [17].

Table 1. Composition of L-SNEDDS.

Drug	Oil	Surfactant	Cosurfactant
Zaltoprofen (1.33g)	Phosal 53 MCT (1.5)	Tween 80 (2.5g)	PEG 400 (1g)

2.5. Evaluation of L-SNEDDS Formulations

2.5.1. Relative Turbidity & % Transmittance

Relative turbidity and percent transmittance of zaltoprofen loaded SNEDDS was measured by using nephaloturbidimeter and UV-Visible spectrophotometer respectively by diluting the formulation with purified water. % Transmittance was measured at λ_{max} 638.2 nm.

2.5.2. Self-emulsification Time

USP dissolution Type II apparatus was used to measure the self emulsifying ability of developed formulation. Developed L-SNEDDS formulation was added slowly to 500 mL of purified water in the vessel maintained at 37 ± 0.5°C at 50 RPM. Self emulsification time was recorded based on visual observation as the time required to form transparent emulsion [18].

2.5.3. Globule Size and Zeta Potential

The smaller the globule size the better the emulsifying ability of formulation. Zetasizer was used to measure globule size and zeta potential of developed L-SNEDDS using a photon correlation spectroscopy. An L-SNEDDS sample was diluted 100 times with purified water to determine globule size.

2.6. Preparation of Solid SNEDDS Formulation

Developed liquid SNEDDS was adsorbed on neusilin us2 to convert it into solid SNEDDS (S-SNEDDS). Neusilin us2 was added slowly in a Petri plate containing L-SNEDDS in small quantities to get a free-flowing powdered S-SNEDDS. The quantity of Neusilin us2 required to adsorb L-SNEDDS completely was calculated [19].

2.7. Solid State Characterization of Zaltoprofen Solid SNEDDS

Developed S- SNEDDS is characterized for its Solid State stability and morphology by Fourier transformed infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), powder X-Ray diffraction (XRD), and scanning electron microscopy (SEM). The FTIR spectra were recorded using FTIR spectrophotometer (Schimadzhu Infinity), DSC thermogram was recorded using SII Nanotechnology (SEIKO) DSC (DSC 6220) and SEM was performed using JEOL Model JSM - 6390LV.

2.8. Droplet Size of Reconstituted S-SNEDDS

Zetasizer, Malvern Instruments, UK was used to measure the globule size of reconstituted S-SNEDDS using a photon correlation spectroscopy.

2.9. Drug Dissolution Studies

In-vitro drug dissolution studies from Developed SNEDDS were performed using USP type II dissolution apparatus using 900 ml of 0.1M HCl and phosphate buffer pH 6.8 as a dissolution medium at 37 ± 0.5°C [20]. The rotation speed of the paddle was adjusted to 75 RPM. Zaltoprofen loaded L-SNEDDS, S-SNEDDS (equivalent to 80 mg of zaltoprofen) and 80 mg of powder zaltoprofen were placed in a dissolution tester (Labindia). Aliquot of 5ml was withdrawn at a particular time interval and replaced with an equivalent volume of fresh dissolution medium. The aliquot was filtered, diluted and analyzed for the content of zaltoprofen by UV spectrophotometry method.

2.10. *In vivo* Study

2.10.1. Bioavailability Study

The *in vivo* Bioavailability study Protocol was approved by Institutional Animal Ethics Committee (Reg. No. 535/02/a/CPCSEA/Jan.2002, Protocol No. IPER/IAEC/2015-16/07). The study was carried out in male Wistar rats weighted approximately 200-250 g each. The animals were grouped each having six rats into three groups and were kept on fasting overnight with continuous access

to water during the study period. One group was administered with the suspension of zaltoprofen S-SNEDDS, one with 0.3% sodium carboxy methyl-cellulose suspension of zaltoprofen at a dose of 5 mg/kg by oral gavage and another group served as the control without any treatment. Blood samples (0.25 ml) were collected at a time interval of 0, 0.5, 1, 2, 4, 8, 12, and 24 h through Retro orbital plexus into microcentrifuge tubes containing 2.6 mmol sodium edetate. Collected blood samples were centrifuged at 5000 RPM for 15 min and separated plasma samples were stored in a deep freezer till analysis for zaltoprofen concentration.

2.10.2. HPLC Analysis of Zaltoprofen in Rat Plasma

HPLC method developed and reported by Hwa Jeong Lee with slight modification was used to determine the concentrations of zaltoprofen. HPLC system (Jasco) with UV/Visible detector, Manual sample injector and C18 column was used. The wavelength of the UV detector was set at 340 nm and column C18 was eluted with a mobile phase of 35:65 v/v mixture of acetonitrile and 10 M phosphate buffer pH 6.8 at a flow rate of 1 mL/min [21-23].

2.10.3. Preparation of Standard Solutions

About 10 mg of zaltoprofen was dissolved in methanol in a volumetric flask and made up to 10 ml to get a stock solution of the drug. From the above solution, various concentrations of zaltoprofen solutions were prepared using a mobile phase. The standard drug solutions were spiked in the plasma sample and appropriate plasma standard concentrations of 1, 5, 10, 20, 30, 40, 50, and 100 mcg/ml were prepared.

2.10.4. Pharmacokinetic Analysis

PK solver 2.0 was used to calculate various Pharmacokinetic parameters after oral administration of zaltoprofen S-SNEDDS formulation and zaltoprofen drug suspension in rats [24]. The plasma drug concentration-time plot from 0 to 24 Hours was plotted and Area under the curve (AUC) was determined by the linear trapezoidal rule. The maximum zaltoprofen concentration in plasma (C_{max}) and time taken to reach the maximum zaltoprofen concentration in plasma (T_{max}) was obtained from the plasma drug concentration-time plot. Other parameters like Volume of distribution, half-life, *etc*. were calculated with the use of software. The relative bioavailability (F) of zaltoprofen formulations was calculated by taking the ratio of AUC of S-SNEDDS and AUC of drug suspension.

3. RESULTS AND DISCUSSION

3.1. Solubility Study

In SNEDDS oil, surfactant and co-surfactant selected should have the ability to dissolve the maximum amount of drug to get thermodynamically stable emulsion when introduced to aqueous phase [25]. The solubility of the drug in the various oils and surfactant, cosurfactant is presented in Fig. (**2**).

Zaltoprofen showed highest solubility in Phosal 53 MCT (333.1 ± 1.23 mg/mL) in Oils, Tween 80 (455.17 ± 2.42 mg/ mL) in Surfactants and PEG 400 (407.26 ± 2.63 mg/mL) in co-surfactants. Considering the capability of meeting needs of a dose of zaltoprofen, they were screened for further formulation of zaltoprofen SNEDDS.

3.2. Construction of Ternary Phase Diagram

Based on the solubility study, screened oil, surfactant and cosurfactant were used to plot the ternary phase diagram. Ternary phase diagram is plotted by taking phosal 53 MCT as oil phase, tween 80 as a surfactant and PEG 400 as co-surfactant (Fig. **3**). The optimal ratios of components in the areas forming microemulsion are studied by varying their concentration using water as a blank. The blue-shaded region in the diagram represents the efficient self-emulsifying region where there is spontaneity of the emulsion formation, clarity of the solution and no phase separation. It can be concluded from the study that formulation with less than 40% of oil forms a grayish transparent emulsion. It was also observed that Surfactant concentration should be more than cosurfactant concentration. From the self microemulsifying domain in the ternary diagram (Fig. **3**), the range and level for each component were selected for optimization and optimized concentration was used for the preparation of L-SNEDDS [26, 27].

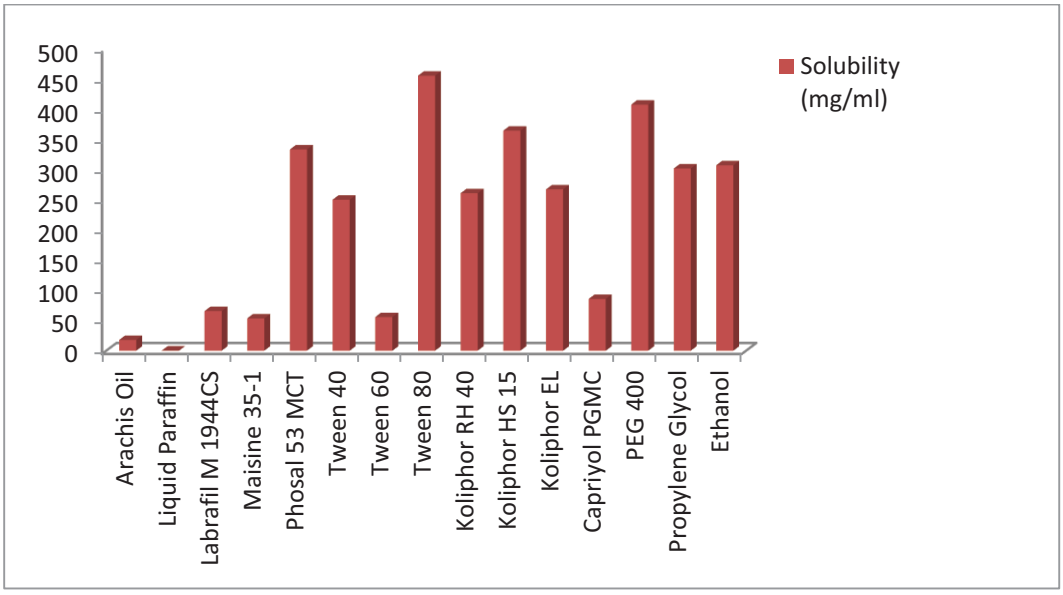


Fig. (2). Solubility of Drug in different vehicles.

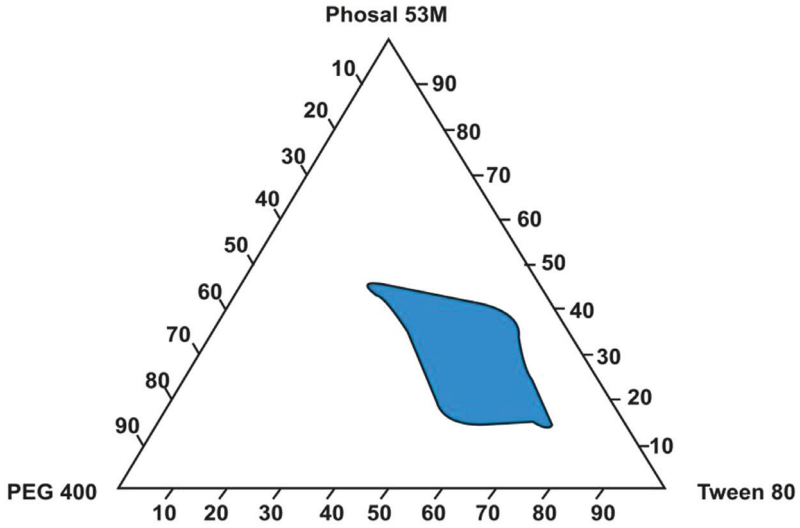


Fig. (3). Ternary phase diagram for zaltoprofen SNEDDS.

3.3. Evaluation of L-SNEDDS Formulations

3.3.1. Relative Turbidity and % Transmittance

SNEDDS having low relative turbidity and high transmittance value is desirable. It indicates good optical clarity. Optimized SNEDDS formulations showed relative turbidity less than 10NTU and 99.3% transmittance values confirming the optical clarity of developed SNEDDS.

3.3.2. Determination of Self-emulsification Time

The spontaneity of SNEDDS for nanoemulsion depends on its Self emulsification time. Developed SNEDDS formulations showed emulsification in 100sec indicating good emulsification efficiency.

3.3.3. Globule Size and Zeta Potential

Globule size of developed L-SNEDDS formulation was found to be 93.42 nm and zeta potential as -16.1 mV.

3.4. Preparation of S-SNEDDS

Neusilin us2 with high adsorption capacity and large surface area was selected as an adsorbent. 2.04 g of Neusilin us2 was required for converting 4 g of liquid SNEDDS into free-flowing S-SNEDDS.

3.5. Solid State Characterization of S-SNEDDS

FTIR spectra of pure zaltoprofen showed bands at 1278.81 (C-O group), 2998 (Carboxylic acid

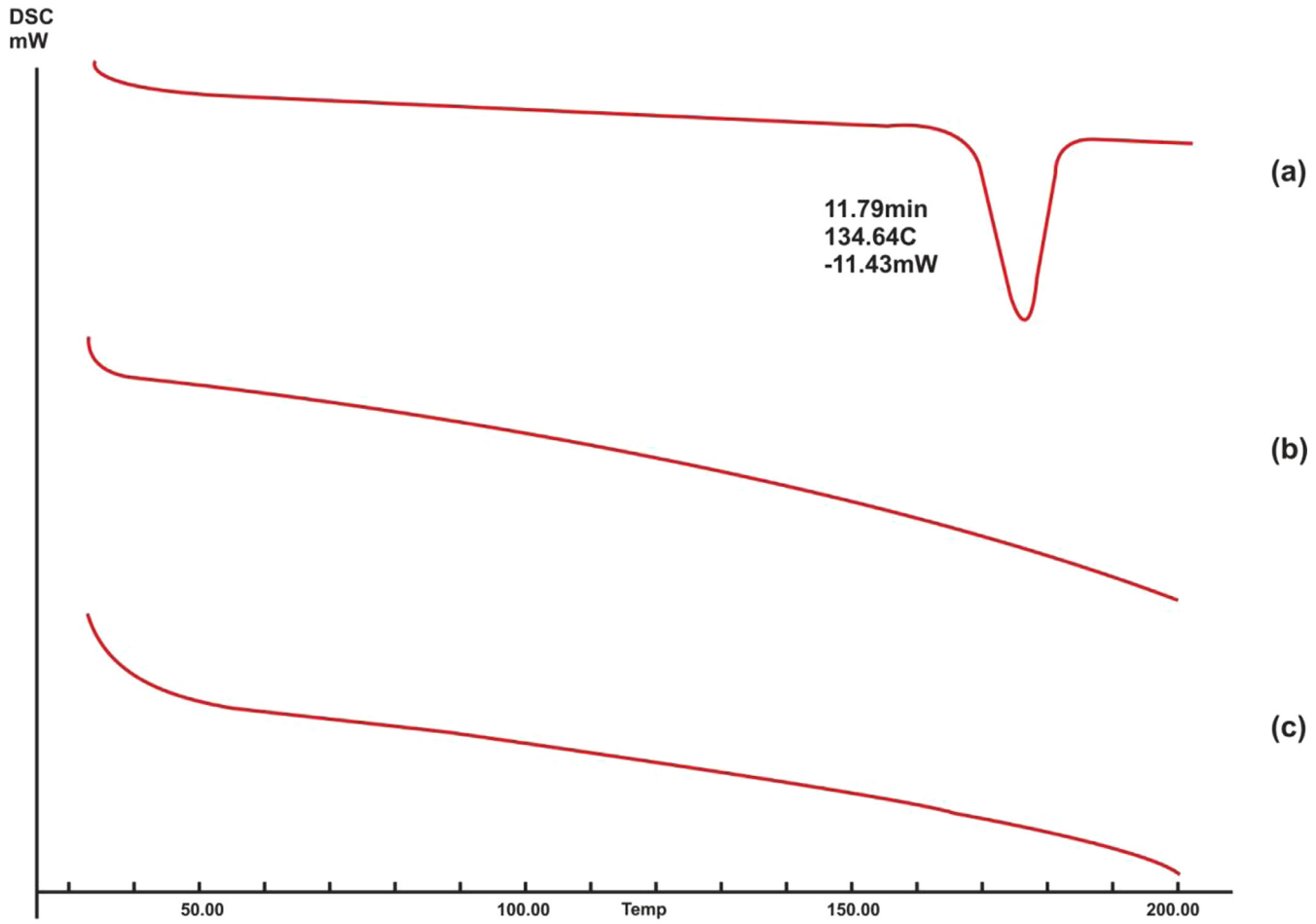


Fig. (4). DSC (**a**) Zaltoprofen (**b**) Neusilin us2 (**c**) S-SNEDDS of Zaltoprofen.

functional group), 1697.3 (C=O stretching region of functional carbonyl group). In the FTIR spectra of zaltoprofen, S-SNEDDS system showed the characteristic absorption peaks of the Zaltoprofen with broad neusilin us2 peaks. However, a slight shift and broadening of the peak were observed because of the formation of dispersion. The FTIR spectrum of S-SNEDDS with no new additional peaks signified the presence of only physical interaction between the drug and other components [28, 29].

DSC thermogram of pure zaltoprofen (Fig. **4**) showed sharp endothermic peak at 134.64°C, corresponding to the melting point of zaltoprofen confirming the crystalline nature of the drug used, whereas DSC thermogram of S-SNEDDS didn't show any endothermic peak confirming solubilize state of drug.

The Powder XRD spectra of zaltoprofen confirm its crystalline nature. It showed sharp peaks at 10.48°, 15.60°, 16.07°, 23.39°, and 23.32°. XRD spectra of S-SNEDDS showed no such peaks indicating conversion to amorphous form.

SEM of zaltoprofen showed irregular shaped crystalline particles as shown in Fig. (**5**). SEM of S-SNEDDS did not show such crystalline particles or precipitation of the drug on the surface after adsorbing the L-SNEDDS onto Neusilin us2. This confirms the conversion of the drug in its micronized/solubilized state [30].

3.6. Globule Size of Reconstituted Solid SEDDS

The globule size and polydispersity index of the solid SNEDDS after reconstitution was found to be 176.6nm and 0.132, respectively (Fig. **6**). Lower droplet size of less than 250 nm confirms the Self emulsification efficiency of formulation and formation of nanoemulsion after reconstitution.

3.7. *In vitro* Dissolution Study

The dissolution study of zaltoprofen from S-SNEDDS and L-SNEDDS was performed in com-

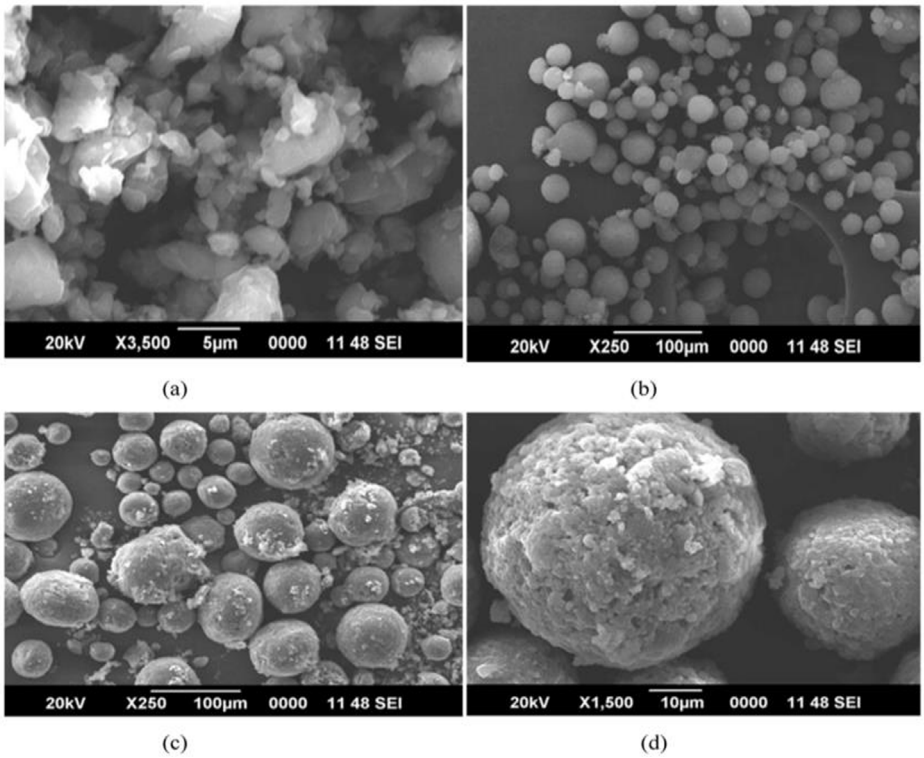


Fig. (5). SEM (**a**) Zaltoprofen (**b**) Neusilin us2 (**c**) and (**d**) S-SNEDDS of Zaltoprofen.

Sample Name: f 7 1
SOP Name: mansettings.nano
File Name: dnyaneshwar.dts
Record Number: 39
Material RI: 1.59
Material Absorbtion: 0.010

Dispersant Name: Water
Dispersant RI: 1.330
Viscosity (cP): 0.8872
Measurement Date and Time: Tuesday, January 10, 2017 10:3:

Temperature (°C): 25.0
Count Rate (kcps): 357.7
Cell Description: Glass cuvette with square aperture

Duration Used (s): 60
Measurement Position (mm): 4.65
Attenuator: 6

		Size (d.nm):	% Intensity:	St Dev (d.nm):
Z-Average (d.nm): 176.6	**Peak 1:**	196.5	100.0	71.25
PdI: 0.132	**Peak 2:**	0.000	0.0	0.000
Intercept: 0.957	**Peak 3:**	0.000	0.0	0.000
Result quaility: Good				

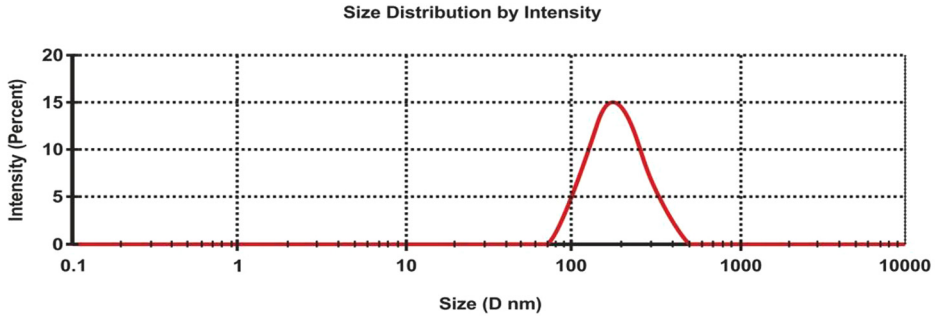
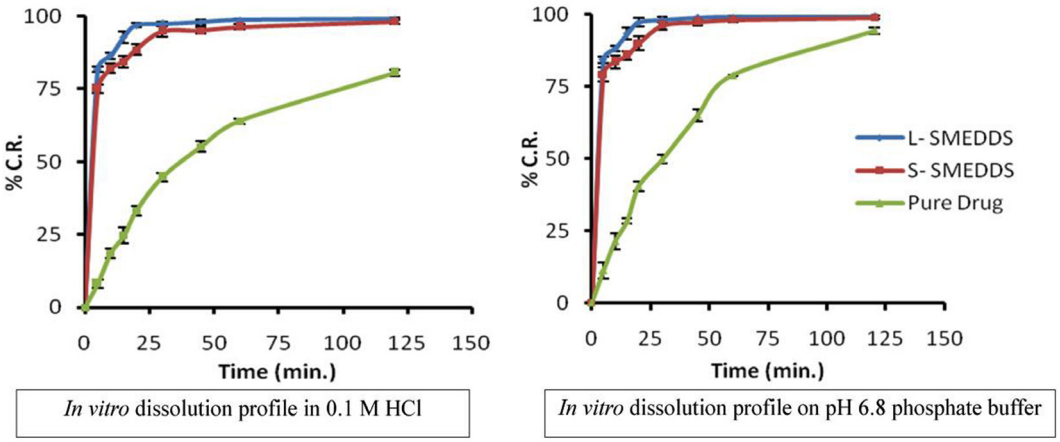


Fig. (6). Globule size of reconstituted S- SNEDDS.



In vitro dissolution profile in 0.1 M HCl

In vitro dissolution profile on pH 6.8 phosphate buffer

Fig. (7). *In-vitro* dissolution profile.

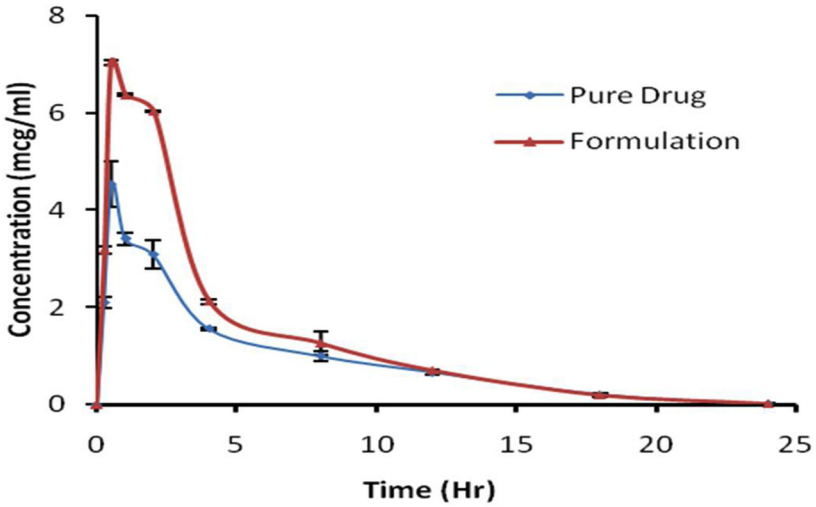


Fig. (8). Plasma concentration *vs*. time profile of Zaltoprofen after single-dose oral administration.

parison with the pure drug. The dissolution was carried out in two different media 0.1M HCl and phosphate buffer pH 6.8. S-SNEDDS showed more than 90% of drug release in 20 min in both 0.1 M HCl and phosphate buffer pH 6.8 media, whereas pure drug showed drug release of 15.36% and 36.98%, respectively as shown in Fig. (**7**). S-SNEDDS showed significantly higher dissolution rate than pure drug without any influence of pH suggesting S-SNEDDS could be absorbed more rapidly and completely than the pure drug. Thus, S-SNEDDS was useful for improving the dissolution rate of the poorly water-soluble zaltoprofen.

3.8. *In vivo* Study

The pharmacokinetic parameters after oral administration of zaltoprofen powder and S-SNEDDS of zaltoprofen in rats were determined (Table **2**). The mean plasma drug concentration time plot was plotted as shown in Fig. (**8**).

The maximum plasma drug concentration of zaltoprofen in zaltoprofen S-SNEDDS was significantly more than drug powder. The total plasma concentrations of drug in S-SNEDDS were higher than those in zaltoprofen powder. In particular, the initial plasma concentrations of zaltoprofen in S-SNEDDS were more than those in zaltoprofen powder. The solid SNEDDS gave significantly higher AUC and C_{max} of zaltoprofen than did zaltoprofen powder ($P < 0.05$).

The maximum peak plasma concentrations of zaltoprofen from solid SNEDDS and zaltoprofen pure drug powder were found to be 7.04 ± 0.06 and 4.53 ± 0.49 µg/mL, respectively. The time required to reach peak plasma concentration from solid SNEDDS and zaltoprofen powder was found to be 0.5 hr. The elimination rate constants were found to be 0.252 and 0.244 hr^{-1} and the corresponding half life was found to be 2.746 ± 0.627 hr and 2.83 ± 0.627 hrs after oral administration of

Table 2. Pharmacokinetic parameters of solid SNEDDS and Zaltoprofen powder.

Parameter	S-SNEDDS	Zaltoprofen Powder
C_{max} (mcg/ml)	7.04 ± 0.06	4.536 ± 0.479
t_{max} (h)	0.5	0.5
$t_{½}$ (h)	2.746 ± 0.17	2.83 ± 0.627
Ke (h^{-1})	0.252	0.244
$AUC_{(0-t)}$ (mcg h/ml)	33.42 ± 0.949	22.68 ± 0.409
$AUMC_{(0-\infty)}$	156.58 ± 4.58	127.73 ± 7.82
MRT (Hr)	4.67 ± 0.008	5.61 ± 0.241
CL_T (Lit/Kg.Hr)	0.149 ± 0.004	0.219 ± 0.004
V_d (Lit)	0.592 ± 0.052	0.897 ± 0.195

solid SNEDDS and zaltoprofen powder, respectively. The $t_{1/2}$ values are almost similar to the reported values. The values of $AUC_{(0-24)}$ of solid SNEDDS and zaltoprofen powder were 33.42 ± 0.94 and 22.68 ± 0.409, respectively.

The 1.5 fold higher AUC value of zaltoprofen from S-SNEDDS than that of zaltoprofen powder showed that it is possible to improve the bioavailability of zaltoprofen if given in the solid SNEDDS.

CONCLUSION

Zaltoprofen SNEDDS formulation containing Phosal 53 MCT, Tween 80 and PEG 400 as oil, surfactant and cosurfactant, respectively was successfully developed. The developed L-SNEDDS was converted into S-SNEDDS by use of Neusilin us2 as an adsorbent to overcome the limitations of L-SNEDDS. Solid-state characterization confirmed the stability and compatibility of drug and excipients. *In vitro* dissolution study reveals efficient dissolution rate of S-SNEDDS as compared to pure drug. *In vivo* pharmacokinetic study in rats showed a significant increase in AUC of solid S-SNEDDS than drug powder and showed an increase in the bioavailability of Zaltoprofen compared to the pure drug. Phosal based SNEDDS formation can be successfully used to improve the dissolution and oral bioavailability of poorly soluble drug zaltoprofen.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study is approved by Institutional Animal Ethics Committee of Institute of Pharmaceutical Education & Research, India (Reg. No. 535/02/a/ CPCSEA/Jan.2002).

HUMAN AND ANIMAL RIGHTS

No human was used in this research. All animal study protocols used in this study were in accordance with the guidelines of IAEC, IPER Wardha, India.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The authors confirm that the data supporting the findings of this research are available within the article.

FUNDING

None.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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