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Development and *in vivo* Evaluation Lovastatin by Self-Nanoemulsifying Drug Delivery System

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ABSTRACT

In the present investigation, self-nanoemulsifying drug delivery system (SNEDDS), of Lovastatin is being formulated to increase the solubility and bioavailability. The optimized Lovastatin SNEDDS formulation (F8) has a composition of Acrysol EL 135 as oil phase, Lauro glycol 90 and Capmul MCM as surfactant and co-surfactant respectively. Formulation F8 was found to be best formulation based on evaluation parameters. No drug precipitation or phase separation was observed in the optimized formulation. The particle size of the optimized formulation was found to be 4.9 nm & Z-Average of 71.5 nm indicating all the particles were in the nanometer range. The zeta potential of the optimized SNEDDS formulation was found to be -13.7 mV which comply with the requirement of the zeta potential for stability. Furthermore, pharmacokinetic studies in rats indicated that compared to the pure drug, the optimized SMEDDS formulation significantly improved the oral bioavailability of Lovastatin. Therefore, from our results the study suggests that the Lovastatin loaded self-nanoemulsifying formulation has a great potential for clinical application.

Keywords: Lovastatin, SNEDDS, Hypercholesterolemia, Bioavailability studies.

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INTRODUCTION

Self-nanoemulsifying drug delivery system (SNEDDS) is an isotropic mixture of natural or synthetic oil, surfactants and co-surfactants that have a unique ability of forming fine oil-in-water (O/W) nano-emulsions under mild Agitation followed aqueous media. [1] Self-Nano emulsifying Drug Delivery System having size range of globules is less than 100 nm under dispersion of water. Self-nanoemulsifying drug delivery systems (SNEDDS) are thermodynamically and kinetically stable formulations that are mainly mild O/W nano-emulsions. [2] Self-microemulsifying drug delivery system (SMEDDS) and self-emulsifying drug delivery systems (SEDDS) is used to improve the aqueous solubility of poorly water-soluble drugs. [3] A vital feature of a successful SNEDDS formulation is its

capability to hold the drug in solution, throughout the GIT, for sufficient time to allow for absorption. [4] SNEDDS are also important in providing a large interfacial area for partitioning of drug between the oil and aqueous phase, thus increasing the overall bioavailability of the drug. [5]

Lovastatin is a HMG-CoA reductase inhibitor used for lowering the increased cholesterol level in patients with hypercholesterolemia. Elevation of total blood cholesterol is considered as a primary risk factor for coronary artery disease. Statins are highly efficacious lowering blood plasma cholesterol. For the last few years, Nanotechnology is continuously developed to circumvent various formulation problems and one such approach is formulating SNEDDS with an optimum drug release profile. There are many pharmaceutical liquid excipients available like oils, biological lipids, hydrophobic and hydrophilic surfactants etc. that can form colloidal emulsions. Self-emulsification is specific to the nature and quantity of components, the ratio of oil/surfactant and the temperature at which self-emulsification begins. The final droplet size of formulation decides the rate and extent of drug release and its stability. Zeta potential is used to identify the charge on oil droplets that is negative due to the presence of free fatty acids. A high zeta potential confers stability and long shelf life. [6]

The aim of the present study is to preparation and in vivo evaluation of Lovastatin SNEDDS to increase solubility and bioavailability with novel carriers.

MATERIALS AND METHODS

Materials

Lovastatin was obtained from Aurobindo Pharma limited, Hyderabad. Acrysol EL 135, Labrasol, Lauro glycol 90, Macrogol 400 and Labrafil M 1944 are obtained from Corel Pharma Chem, Ahmedabad, Gujarat, India. Polysorbate, PEG 600, Oleic acid and Sunflower oil were obtained from SD Fine Chemical Limited, Mumbai. Caproic acid was obtained from Merck, Mumbai. Nillo; HCO-50 was obtained from Ajanta Pharma, Jalgaon. Cremophore EL was obtained from Astron Research Centre, Ahmedabad. Acconon, Capmul MCM and Captex 300 were procured from Gattefosse Ltd, Mumbai. Transcutol P was obtained from Gangwal chemicals, Mumbai.

Solubility Studies

The solubility study was used to find out the suitable oil, surfactant and co-surfactant that possess good solubilizing capacity for Lovastatin. An excess amount (10 mg) of Lovastatin was added into 2 ml of each excipient (Oils -Acrysol EL 135, Labrafil M 1944, Oleic acid, Sunflower oil. Surfactants –Cremophore EL, Nikkol HCO - 50, Caproic acid, Lauro glycol 90, Labrasol. Co-surfactants - Acconon, Captex 300, PEG 600, Capmul MCM, Macrogol 400, Polysorbate, Transcutol P and kept in mechanical shaker for 24hrs and centrifuged at 10,000 rpm for 20 min using a centrifuge. Supernatant was filtered through membrane filter using 0.45µm filter disk. [7] Filtered solution was appropriately diluted with methanol, and UV absorbance was measured at 237 nm. Concentration of dissolved drug was determined spectrophotometrically. [8]

Pseudo ternary Phase Diagram

To determine the concentration of components for the existing range of SNEDDS, pseudo ternary phase diagram was constructed using water titration method at ambient temperature (25°C). Surfactant and co-surfactant (Smix) in each group were mixed in different volume ratio (1:1, 2:1, 3:1). Oil and surfactant/co-surfactant mixture (Smix) were mixed thoroughly in different volume ratios 1:9 to 9:1 (1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2 and 9:1) w/w for all the three Smix ratios 1:1,2:1, 3:1. The mixture of oil, surfactant and co-surfactant at certain ratios were titrated with water by drop wise addition under gentle agitation. Deionized water was used as diluting medium and added into the formulation. The proper ratio of one excipient to another in the SNEDDS formulation was analyzed. Pseudo ternary plots were constructed using Chemix software. [9]

Visual Observation

A visual test to assess the self-emulsification properties was modified and used in the present study. With the use of this method, a predetermined volume of mixture (0.2 ml) was added to 300 ml of water in a glass beaker under stirring and temperature was maintained at 37^0C using a magnetic stirrer. The tendency of formation of emulsion was observed. If the droplet spreads easily in water was judged as 'good' and judged as 'bad' when there was milky or no emulsion or presence of oil droplets. [10]

Formulation trials of Lovastatin SNEDDS

A series of SNEDDS formulations for Lovastatin were prepared based on solubility studies, pseudo ternary phase diagram and visual observation. Here, Acrysol EL 135 was used as oil phase andLauro glycol 90 and Capmul MCM were used as surfactant and co-surfactant respectively. The compositions are given in the Table 1.

Lovastatin was added in accurately weighed amount of oil into screw-capped glass vial and heated in a water bath at 40^oC. The surfactant and co-surfactant were added to the oily mixture using positive displacement pipette and stirred with magnetic bar. The formulation was further sonicated for 15 minutes and stored at room temperature until its use in subsequent studies (Table 1).

Thermodynamic Stability Studies

The objective of thermodynamic stability is to evaluate the phase separation and effect of temperature variations on SNEDDS formulations.

Freeze Thawing

Formulations were subjected to freeze cycle (-20°c for 2 days followed by 40°C for 2 days). Only stable formulations were selected for further studies. [11]

Table 1: Formulation trials of liquid SNEDDS

Smix (Surfactant: Co-surfactant)	Oil: Smix	Formulation code	Drug (Lovastatin) (mg)	Oil (Acrysol EL 135) (ml)	Surfactant (Lauro glycol 90) (ml)	Co-surfactant (Capmul MCM) (ml)
	1:9	F1	10	0.15	0.675	0.675
	2:8	F2	10	0.3	0.6	0.6
1:1	3:7	F3	10	0.45	0.525	0.525
	4:6	F4	10	0.6	0.45	0.45
	5:5	F5	10	0.75	0.375	0.375
	3:7	F6	10	0.45	0.7	0.35
	4:6	F7	10	0.6	0.6	0.3
2:1	5:5	F8	10	0.75	0.5	0.25
	6:4	F9	10	0.9	0.4	0.2
	7:3	F10	10	1.05	0.3	0.15
	5:5	F11	10	0.75	0.562	0.187
	6:4	F12	10	0.9	0.45	0.15
3:1	7:3	F13	10	1.05	0.337	0.112
	8:2	F14	10	1.2	0.225	0.075
	9:1	F15	10	1.35	0.112	0.0375

Centrifugation

Centrifugation was performed at 3000 rpm for 5 minutes. The formulations were then observed for phase separation. Only formulations that were stable to phase separation were selected for further studies. [12]

% Transmittance Measurement

The percent transmittance of various SNEDDS formulations was measured at 237 nm using UV spectrophotometer keeping water as a blank. [13]

Determination of Drug Content

SNEDDS equivalent to 10 mg of Lovastatin was weighed accurately and dissolved in 100 ml of phosphate buffer pH 6.8. The solution was filtered, diluted with phosphate buffer and drug content was analyzed at λ_{max} 237 nm against blank by UV spectrometer. [14]

In vitro Dissolution Studies

The release of drug from liquid SNEDDS formulations and pure drug was determined using a US Pharmacopoeia Type II dissolution apparatus. SNEDDS of Lovastatin (equivalent to 10 mg of Lovastatin) was filled in size "0" hard gelatin capsules. The dissolution media is potassium di hydrogen phosphate buffer pH 6.8 and temperature of the dissolution medium was maintained at 37°C operated at 50 rpm. An aliquot of 5 ml was withdrawn at predetermined intervals 2, 5, 10, 15, 20, 25, 30, 45, and 60 mins and filtered through 0.45 µm pore size membrane filters. The removed volume was replaced each time with 5 ml of fresh medium. The concentrations were assayed spectrophotometrically at 237 nm.

Characterization of SNEDDS

Determination of Droplet Size

The average droplet size of Lovastatin SNEDDS formulations were determined by Photon correlation spectroscopy (Malvern Instrument, UK) able to measure sizes between 10 and 5000 nm. The selected formulations were diluted with deionized water and placed in an electrophoretic cell for measurement. [15]

Determination of Zeta Potential

The emulsion stability is directly related to the magnitude of the surface charge. In conventional SNEDDS, the charge on an oil droplet is negative because of the presence of free fatty acids. The zeta potential of the diluted SNEDDS formulation was measured using a zeta meter system. The SNEDDS were diluted with a ratio 1:2500 (v/v) with distilled water and mixed with magnetic stirrer. Zeta-potential of the resulting micro emulsion was determined using a Zetasizer. [16]

Scanning Electron Microscopy

Shape and surface morphology of microspheres was studied using scanning electron microscopy (SEM). The SNEDDS after converting to emulsion were mounted on metal stubs and the stub was then coated with conductive gold with sputter coater attached to the instrument HITACHI, S-3700N. [17]

Percent Entrapment Efficiency

The contents of free drug were separated from nanoemulsion by ultra filtration at 3500 Da with centrifugation at 3000 RPM for 5 to 10 minutes. [18]

Stability Studies

Stability testing was conducted at 40°C ± 2°C/75% RH ± 5% RH for 6 months using stability chamber (Thermo Lab, Mumbai). Samples were withdrawn at predetermined intervals 0, 30, 90 and 180 days period according to ICH guidelines. [19] Various *in vitro* parameters like % drug content and in vitro drug release studies were evaluated.

In vivo study

Animals

Healthy Wistar rats were (Weighing 150-180 g) selected for this study, all the animals were healthy during the period of the experiment. All efforts were made to maintain the animals under controlled environmental conditions (Temperature 25°C, Relative Humidity 45% and 12 h alternate light and dark cycle) with 100 % fresh air exchange in animal rooms, uninterrupted power and water supply. Rats were fed with standard diet and water *ad libitum*. The protocol of animal study was approved by the institutional animal ethics committee bearing No: IAEC/1657/CMRCP/T2/Ph D-16/76.

Study Design

Rats were divided in to two groups at random. The rats were fasted for 24 hours prior to the experiments. After 4 hours of dosing, foods were reoffered. First group was administered with pure Lovastatin (as such) made suspension with 0.5% methocel and second group was administered Prepared Lovastatin SNEDDS diluted in 0.5% methocel by oral route at a dose of 10 mg/kg. Then, 500µL blood samples were collected from the femoral artery at certain times 0, 0.50, 1, 1.50, 2, 2.50, 3, 4, 5, 6, 8, 12, 16, 20, 24 h post dose and transferred into Eppendorf tubes containing heparin in order to prevent blood clotting. Plasma was separated by centrifugation of the blood at 5000 rpm in cooling centrifuge for 5min to 10 minutes and stored frozen at −20°C until analysis. [20]

Determination of Lovastatin in Rat plasma by HPLC method

Determination of Lovastatin and internal standard niacin was carried out by using Symmetry C8 (4.6 × 250 mm, 5µm) column with the mobile phase containing acetonitrile: phosphate buffer (pH 4.0 ± 0.5) in the ratio of 65:35 v/v. The optimized flow rate was 0.7 ml/min and the UV detection was carried out at 240 nm. The retention time of lovastatin and niacin (internal standard) were found to be 3.093 min and 6.196 min respectively. [21]

Pharmacokinetic analysis

The pharmacokinetic parameters employed to evaluate were maximum plasma concentration (C_{max}), time to attain C_{max} i.e., T_{max} and $t_{½}$ values, area under plasma concentration–time curve from zero to the last sampling time (AUC_{0-t}), area under plasma concentration–time curve from zero to infinity ($AUC_{0-\infty}$). AUC_{0-t} was calculated by the linear trapezoidal rule and $AUC_{0-\infty}$ from the following formula.

$AUC_{0-\infty} = AUC_{0-t} + C_t / K_E$

RESULTS AND DISCUSSIONS

Solubility Studies

The drug solubility values of these polymers were found to be highest when compared with the pure drug (0.0004 mg/mL) and other polymers. The results are tabulated as graphical representation is shown in Fig. 1, 2 & 3.

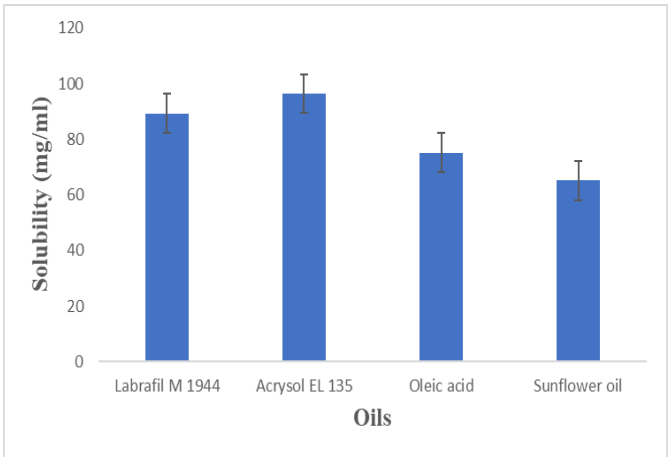

Fig. 1: Solubility studies of Lovastatin in oils

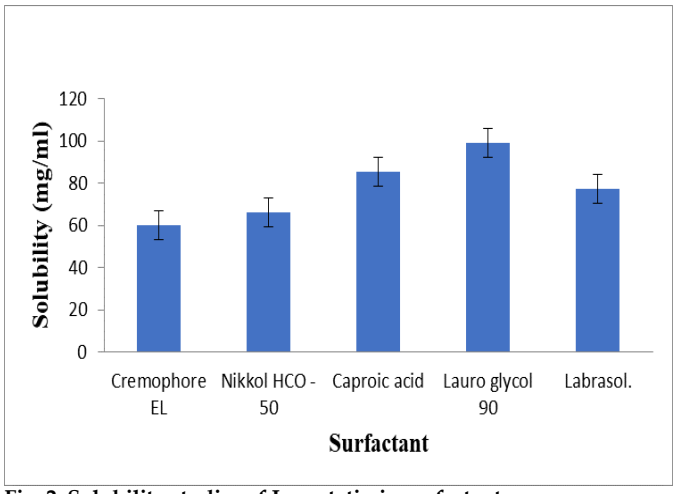

Fig. 2: Solubility studies of Lovastatin in surfactant

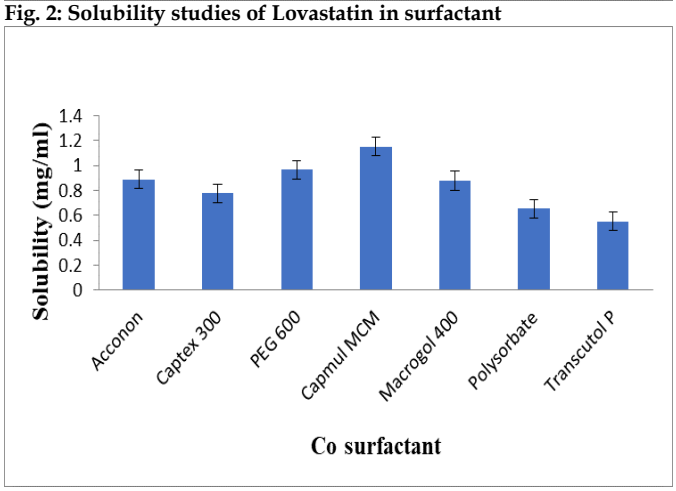

Fig. 3: Solubility studies of Lovastatin in co-surfactants

Pseudo Ternary Phase Diagram

From the solubility studies, Acrysol EL 135, Lauro glycol 90 and Capmul MCM were selected as oil, surfactant and co-surfactant respectively. From the phase diagram (Figure 4), it was observed that self-emulsifying region was enhanced with increasing concentrations of surfactant and co-surfactant with oil. Efficiency of self-emulsification was good when the surfactant concentration increased (Fig. 4).

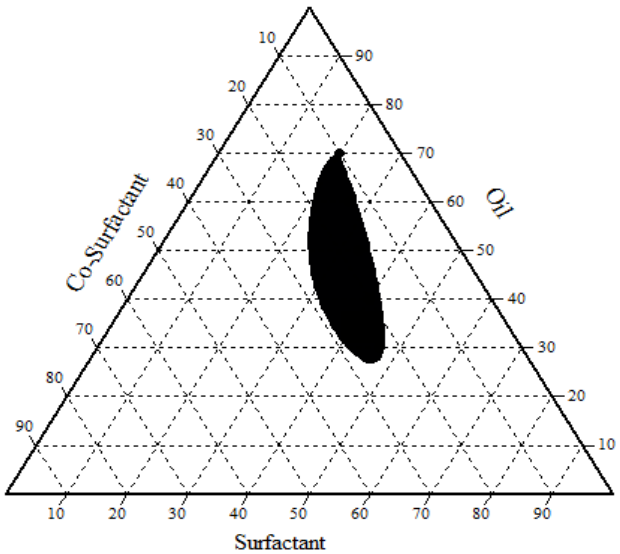

Fig. 4: Ternary phase diagram of Acrysol EL 135, Lauro glycol 90 and Capmul MCM

Visual Observation

By visual observation method, the tendency of formation of emulsion was observed. Visual observation test was performed for different ratios by keeping the surfactant and co-surfactant ratio (Smix) as 1:1, 2:1 and 3:1. Grades were given to the ratios based on the tendency of formation of micro-emulsion. Ratios 4:6, 5:5, 6:4 and 7:3 of Smix 1:1 and 1:9, 2:8, 3:7, 4:6, 5:5 of Smix 2:1 and 9:1, 2:8, 3:7, 4:6, 5:5 of Smix 3:1 showed rapid formation of micro emulsion within a minute having a clear appearance (Fig. 5). Therefore, these ratios were selected for the formulation of SNEDDS.

Fig. 5: Visual observation test

Preparation of Lovastatin SNEDDS

SNEDDS of Lovastatin were prepared by using Acrysol EL 135 (oil), Lauro glycol 90 (surfactant) and Capmul MCM (co-surfactant). In the present study, fifteen formulations were prepared and their complete composition. All the formulations prepared were found to be clear and transparent.

Thermodynamic Stability Studies

In thermodynamic stability study, no phase separation and effect of temperature variations on prepared formulations were observed. There was no change in the visual description of samples after centrifugation freeze-thaw cycles. Formulations which are thermodynamically stable only those were selected for further characterization.

% Transmittance Measurement

The clarity of microemulsion was checked by transparency, measured in terms of transmittance (%T). SNEDDS forms o/w microemulsion since water is external phase Formulation F8 has % transmittance value greater than (98.77%) other formulations. These results indicate the high clarity of microemulsion.

Drug Content of SNEDDS

Actual drug content of all 15 formulations are shown in Fig. 6-8. The drug content of the prepared SNEDDS was found to be in the range of 91.43-97.45%. Maximum % drug content i.e. 97.45% was found in the formulation F8.

In-vitro Dissolution Studies of SNEDDS

The results of *in vitro* dissolution comparisons of SNEDDS formulations are summarized in Fig. 6, 7 and 8. The faster dissolution from SNEDDS may be attributed to the fact that in this formulation, the drug is a solubilized form and upon exposure to dissolution medium results in small droplet that can dissolve rapidly in the dissolution medium. The release from liquid SNEDDS formulation F8 was faster and higher amount (i.e 98.25 ± 4.28 within 60 min) than other SNEDDS formulations and pure drug, indicating influence of droplet size on the rate of drug dissolution.

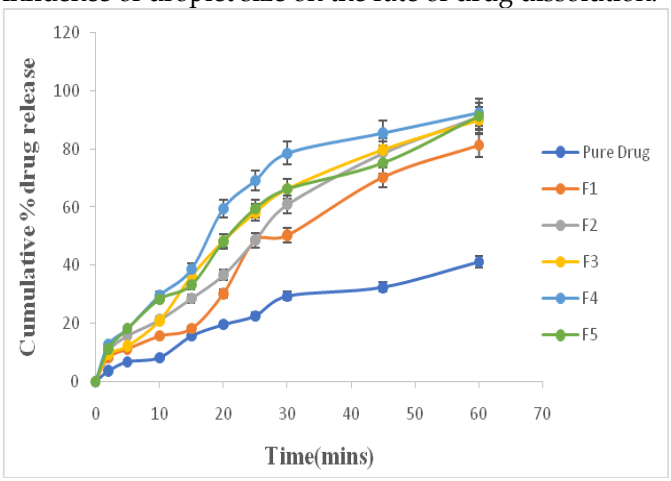

Fig. 6: Dissolution profiles ofLovastatin pure drug and formulations (F1 to F5)

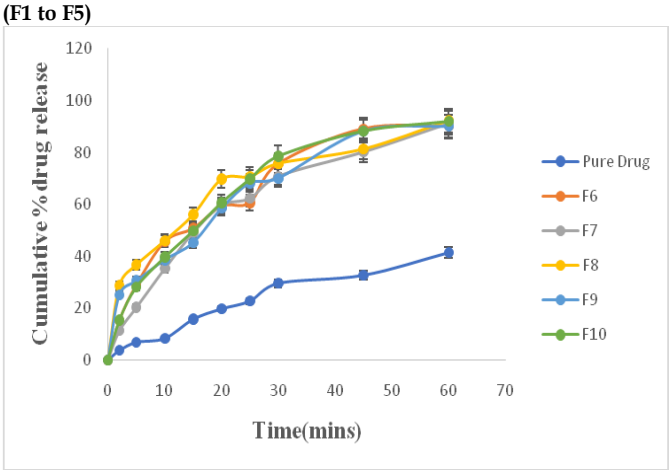

Fig. 7: Dissolution profiles ofLovastatin pure drug and formulations (F6 to F10)

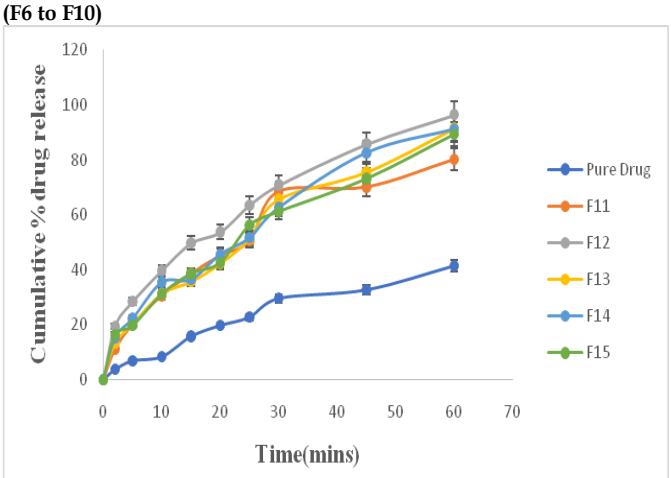

Fig. 8: Dissolution profiles ofLovastatin pure drug and formulations (F11 to F15)

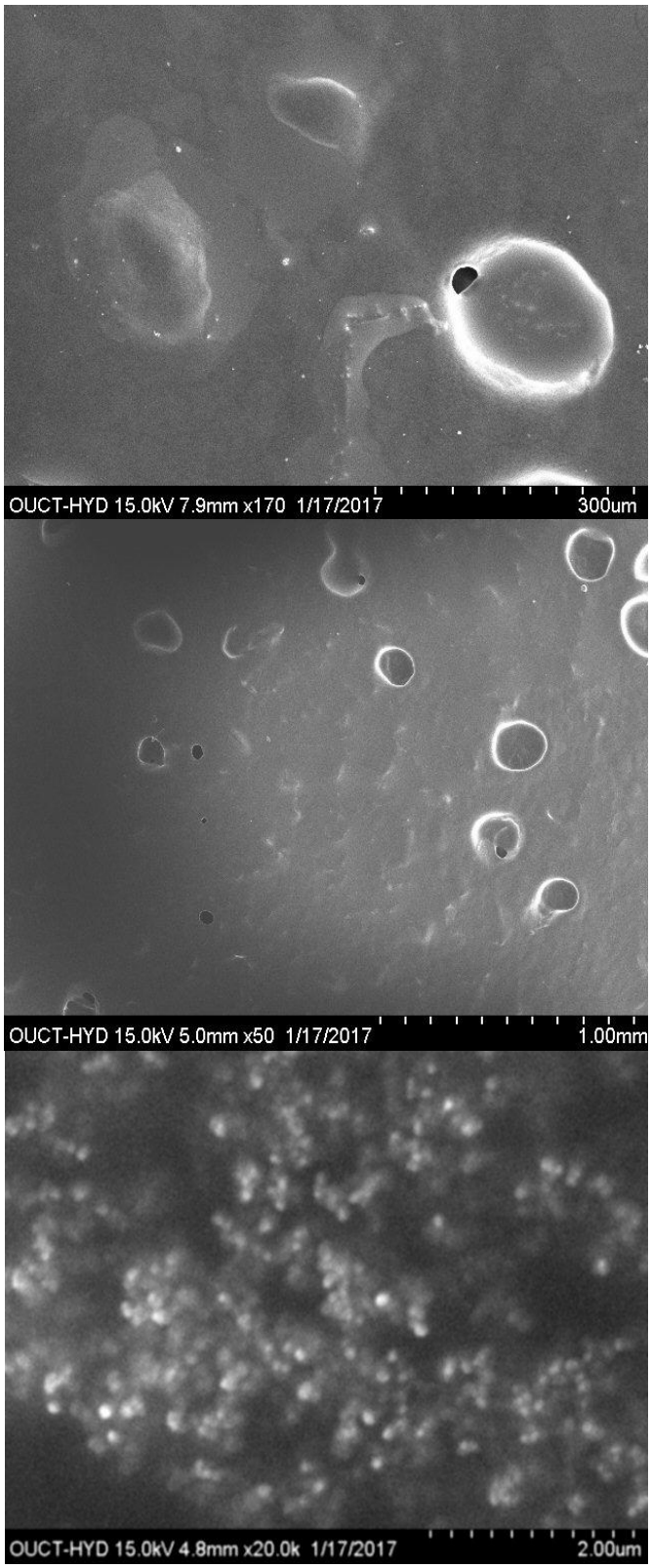

Fig. 9: SEM photographs of optimized formulation F8

Percent entrapment efficiency

The percent entrapment efficiency of the optimized formulation of Lovastatin F8 was found to be 96-97%, which is highly beneficial and indicates the right selection of ingredients.

Droplet size analysis of SNEDDS

The droplet size (or) particle size is the crucial factor in the SNEDDS performance because it determines the rate and extent of drug release as well as drug absorption. Moreover, the smaller the particle size, the larger the interfacial surface area which leads to more rapid absorption and improved bioavailability. Systems with a mean droplet size below 200 nm fulfill the criteria of SNEDDS. The particle size of the emulsion is a crucial factor in self-emulsification performance because it determines the rate and extent of drug release as well as absorption. The particle size of the optimized SNEDDS formulation was found to be 4.9 nm & Z-Average of 71.5 nm indicating all the particles were in the nanometer range. Fig. 9 represents the particle size analysis of optimized SNEDDS formulation.

Zeta potential of SNEDDS

Zeta potential has got practical application in the stability of emulsion since it governs the degree of repulsion between adjacent, similarly charged, and dispersed droplets. In general, the zeta potential value of ±30 mV is sufficient for the stability of a micro emulsion. The zeta potential of the optimized SNEDDS formulation was found to be -13.7 mV which comply with the requirement of the zeta potential for stability

Scanning electron microscopy (SEM) for Lovastatin SNEDDS

The surface morphology of SNEDDS as well as droplet size was predicted by using scanning electron microscopy. The droplets were spherical in shape, with a size smaller than 50 nm, which satisfies the criteria of nano size range required for micro emulsifying formulations (Fig. 9).

Stability studies

The Lovastatin SNEDDS were put into hard gelatin capsules as the final dosage form. The formulation (F8) was subjected to stability studies for 6 months. There was no significant change in the drug content, drug release. It was also seen that the formulation was compatible with the hard gelatin capsule shells, as there was no sign of capsule shell deformation. There was no significant change in the appearance or micro emulsifying property.

In vivo study

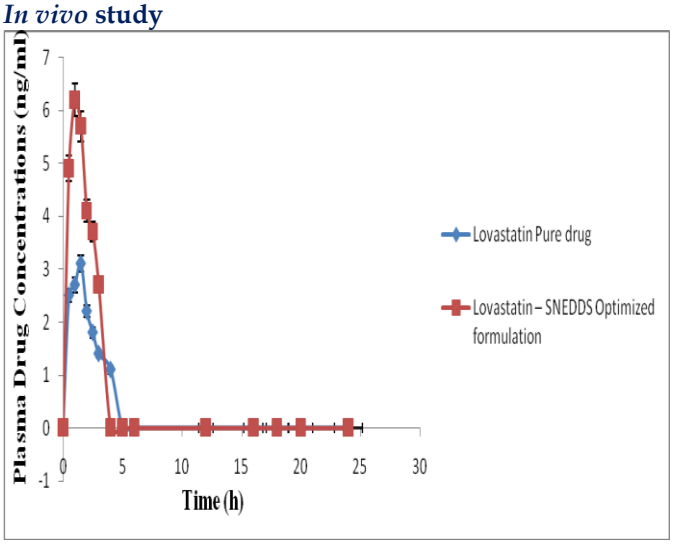

Fig. 10: Plasma concentration profiles of Lovastatin SNEDDS and pure drug

Table 2: Pharmacokinetic Parameters of Lovastatin SNEDDS formulation and pure drug

Pharmacokinetic parameters	Lovastatin Pure drug	Lovastatin SNEDDS
C_{max} (ng/ml)	3.1 ± 0.03	6.2 ± 0.04
AUC_{0-t} (ng. h/ml)	22.2 ± 0.02	74.4 ± 0.01
AUC_{0-inf} (ng. h/ml)	45.7 ± 0.02	90.5 ± 0.04
T_{max} (h)	1.50 ± 0.03	1.00 ± 0.01
$t_{1/2}$ (h)	3.50 ± 0.02	2.62 ± 0.02

Pharmacokinetic parameters comparison for pure drug suspension and SNEDDS

Figure 10 shows the plasma concentration–time curve in Wistar rats after a single oral dose of Lovastatin SNEDDS formulation as compared to Lovastatin pure suspension. At all the indicated time points, the Lovastatin plasma concentrations in rats treated with solid SNEDDS formulation was significantly higher than those treated with pure drug. Pharmacokinetic parameters of Lovastatin after oral administration of the two formulations in Wistar rats are shown in Table 2. C_{max} of the SNEDDS 6.2 ± 0.04 ng/ml was significant (p<0.05) as compared to the pure drug suspension formulation 3.1 ± 0.03 ng/ml. T_{max} of both SNEDDS formulation and pure drug suspension was 1.00 ± 0.01 and 1.50 ± 0.03 h, respectively. AUC is an important parameter in evaluating bioavailability of drug from dosage form, as it represents the total integrated area under the blood concentration time profile and represents the total amount of drug reaching the systemic circulation after oral administration. $AUC_{0-\infty}$ for SNEDDS formulation was higher (90.5 ± 0.04 ng. h/ml) than the pure drug suspension formulation 45.7 ± 0.02 ng. h/ml. Statistically, AUC_{0-t} of the SNEDDS formulation was significantly higher (p<0.05) as compared to pure drug suspension formulation.

The present study has undoubtedly proved the potential effectiveness of SNEDDS for formulating Lovastatin with improved solubility and dissolution. Different formulations of Lovastatin were developed by using different polymers. The solubility study was conducted to find out the suitable oil, surfactant and co-surfactant for Lovastatin and was shown good solubility in Acrysol EL 135, Lauro glycol 90 and Capmul MCM were selected as oil, surfactant and co-surfactant respectively. From Pseudo ternary phase diagram with Acrysol EL 135, Lauro glycol 90 and Capmul MCM as a surfactant and co-surfactant, it was observed that self-emulsifying region was enhanced with increasing concentrations of surfactant and co-surfactant with oil. The drug content of all the formulations was performed. Maximum drug content was found in the formulation F8. Formulation F8 was found to be best formulation based on evaluation parameters. The particle size of the optimized SNEDDS formulation was found to be 4.9 nm & Z-Average of 71.5 nm indicating all the particles were in the nanometer range. The zeta potential of the optimized SNEDDS formulation was found to be -13.7 mV which comply with the requirement of the zeta potential for stability. From *in vivo* studies pharmacokinetic parameters in rats indicated that compared to the pure drug, the optimized SMEDDS formulation significantly improved the oral bioavailability of Lovastatin. Therefore, from our results the study suggests that the Lovastatin loaded self-nanoemulsifying formulation has a great potential for clinical application. The current investigation of nano emulsion may serve as a promising approach for the formulation development of poorly soluble drug Lovastatin.

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