Design and Characterization of Self-Nanoemulsifying Drug Delivery System of Lovastatin

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ABSTRACT

Lovastatin belongs to the class of cholesterol lowering drugs and is the first clinically used statin. It is available as conventional and extended release tablets, but its low aqueous solubility finally escorts it to low oral bioavailability (less than 5%). Therefore, improvement in aqueous solubility of Lovastatin is the foremost aim. In the present work Self-nanoemulsifying drug delivery systems (SNEDDS) of Lovastatin is being formulated to increase the water solubility. Lovastatin SNEDDS was formulated with various oils, surfactants and co-surfactants and tested for its maximum solubility and drug release. 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. The current investigation of nano emulsion may serve as a promising approach for the formulation development of poorly soluble drug Lovastatin, which has undoubtedly proved the potential effectiveness of SNEDDS for formulating Lovastatin with improved solubility and dissolution.

Key words: Lovastatin, SNEDDS, Statin, Lauro Glycol 90, Solubility

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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. The SNEDDS have a size range of globules less than 100 nm in the dispersion of water. SNEDDS are thermodynamically and kinetically stable formulations that are mainly mild o/w nano-emulsions. Self-micro emulsifying drug delivery system (SMEDDS) and SNEDDS are used to improve the aqueous solubility of poorly water-soluble drugs. 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. The 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.

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.

MATERIALS AND METHOD

Materials

Lovastatin was obtained as gift sample from M/s Aurobindo Pharma limited, Hyderabad. Acrysol EL 135, Labrasol, Lauro glycol 90, Macrogol 400 and Labralfil M 1944 are obtained from M/s 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. Nikkol 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.
Methods

Solubility Studies - Selection of Phases

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. Filtered solution was appropriately diluted with methanol, and UV absorbance was measured at 237 nm. Concentration of dissolved drug was determined spectrophotometrically.

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.

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°C 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.

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 and Lauro 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°C. 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 min and stored at room temperature until its use in subsequent studies.

Table 1: Formulation of lovastatin liquid SNEDDS

| Smix (Surfactant: Co-surfactant) | Oil: Smix code | Drug (Lovastatin) (mg) | Oil (Acrysol EL 135) (ml) | Surfactant (Lauro glycol 90) (ml) | Co-surfactant (Capmul MCM) (ml) |
|----------------------------------|----------------|------------------------|---------------------------|----------------------------------|---------------------------------|
| 1:1                              | 1:9 F1         | 10                     | 0.15                      | 0.675                             | 0.675                           |
| 2:1                              | 2:8 F2         | 10                     | 0.30                      | 0.600                             | 0.600                           |
| 3:1                              | 3:7 F3         | 10                     | 0.45                      | 0.525                             | 0.525                           |
| 4:1                              | 4:6 F4         | 10                     | 0.6                       | 0.450                             | 0.450                           |
| 5:5                              | 5:5 F5         | 10                     | 0.75                      | 0.375                             | 0.375                           |
| 2:1                              | 3:7 F6         | 10                     | 0.45                      | 0.700                             | 0.35                            |
| 4:1                              | 4:6 F7         | 10                     | 0.60                      | 0.600                             | 0.300                           |
| 5:5                              | 5:5 F8         | 10                     | 0.75                      | 0.500                             | 0.250                           |
| 6:4                              | 6:4 F9         | 10                     | 0.90                      | 0.400                             | 0.200                           |
| 7:3                              | 7:3 F10        | 10                     | 1.05                      | 0.300                             | 0.150                           |
| 3:1                              | 5:5 F11        | 10                     | 0.75                      | 0.562                             | 0.187                           |
| 6:4                              | 6:4 F12        | 10                     | 0.90                      | 0.450                             | 0.150                           |
| 7:3                              | 7:3 F13        | 10                     | 1.05                      | 0.337                             | 0.112                           |
| 8:2                              | 8:2 F14        | 10                     | 1.20                      | 0.225                             | 0.075                           |
| 9:1                              | 9:1 F15        | 10                     | 1.35                      | 0.112                             | 0.0375                           |

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 2days followed by 40°C for 2days). Only stable formulations were selected for further studies\(^{11}\).

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 $\lambda_{\text{max}}$ 237 nm against blank by using UV spectrophotometer\textsuperscript{14}. The actual drug content was calculated using standard calibration curve of the drug.

**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 dihydrogen 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\textsuperscript{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\textsuperscript{16}. Zeta-potential of the resulting micro emulsion was determined using a Zeta sizer.

**Scanning Electron Microscopy**

Shape and surface morphology of microspheres was studied using scanning electron microscopy\textsuperscript{17} (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.

**Stability Studies**

Stability testing was conducted at 40°C ± 2°C/ and 75 ± 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. Various *in vitro* parameters like % drug content and in vitro drug release studies were evaluated.

**Statement of Human and Animal Rights:**
This article does not contain any studies with human or animal subjects performed by any of the authors.

**RESULTS AND DISCUSSIONS**

**Solubility Studies**

Initially, preliminary solubility analysis was carried out to select the appropriate excipient from various 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-Aconon, Captex 300, PEG 600, Capmul MCM, Macrogol 400, Polysorbate, Transcutol P. The solubility of pure drug was found to be 0.0004 mg/ml. Among all the oils, the drug has highest solubility (96.4±0.17 mg/ml) in Acrysol EL 135 (Table 2). Similarly, Lauro glycol 90 (Table 3) and Capmul MCM (Table 4) were selected as surfactant and co-surfactant respectively due to the maximum solubility of the drug. The drug solubility values of these excipients were found to be highest when compared with the pure drug and other excipients used in the study.

**Table 2: Solubility studies of Lovastatin in various oils**

| Oils                | Solubility (mg/ml) |
|---------------------|--------------------|
| Labrafil M 1944     | 89.3±0.13          |
| Acrysol EL 135      | 96.4±0.17          |
| Oleic acid          | 75.2±0.11          |
| Sunflower oil       | 65.1±0.09          |

**Table 3: Solubility studies of Lovastatin in various surfactants**

| Surfactants        | Solubility (mg/ml) |
|--------------------|--------------------|
| Cremophore EL      | 60.13±0.10         |
| Nikkol HCO -50     | 66.24±0.13         |
| Caproic acid       | 85.23±0.18         |
| Lauro glycol 90    | 99.1±0.22          |
| Labrasol.          | 77.21±0.15         |

**Table 4: Solubility studies of Lovastatin in various co-surfactants**

| Co-surfactants    | Solubility (mg/ml) |
|-------------------|--------------------|
| Aconon            | 0.891              |
| Captex 300        | 0.777              |
| PEG 600           | 0.968              |
| Capmul MCM        | 1.154              |
| Macrogol 400      | 0.879              |
| Polysorbate       | 0.654              |
| Transcutol P      | 0.553              |

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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 1), 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.

![Pseudo ternary phase diagram](image)

**Figure. 1: 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. Therefore, these ratios were selected for the formulation of SNEDDS.

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 was shown in Table 1. All the formulations prepared were found to be clear and transparent.

**Thermodynamic Stability Studies**

In thermodynamic stability studies, no phase separation and temperature effect on prepared formulations were observed. There was no change in the visual description of samples after centrifugation and freeze-thaw cycles (Table 5).

**Table 5: Thermodynamic stability studies of all the formulations lovastatin SNEDDS**

| Formulation code | Centrifugation | Freeze thaw method | -20°C for 2 days | +40°C for 2 days |
|------------------|----------------|---------------------|-------------------|-------------------|
| F1               | No phase separation | No change     | No change        | No change        |
| F2               | No phase separation | No change     | No change        | No change        |
| F3               | No phase separation | No change     | No change        | No change        |
| F4               | No phase separation | No change     | No change        | No change        |
| F5               | No phase separation | No change     | No change        | No change        |
| F6               | No phase separation | No change     | No change        | No change        |
| F7               | No phase separation | No change     | No change        | No change        |
| F8               | No phase separation | No change     | No change        | No change        |
| F9               | No phase separation | No change     | No change        | No change        |
| F10              | No phase separation | No change     | No change        | No change        |
| F11              | No phase separation | No change     | No change        | No change        |
| F12              | No phase separation | No change     | No change        | No change        |
| F13              | No phase separation | No change     | No change        | No change        |
| F14              | No phase separation | No change     | No change        | No change        |
| F15              | No phase separation | No change     | No change        | No change        |

**Transmittance Measurement**

The results of % T values of all the prepared formulations were shown in Table 6. The clarity of SNEDDS was checked by transparency, measured in terms of transmittance (% T). SNEDDS forms o/w microemulsion since water is external phase. Formulation F6-F9, F14 and F15 have % transmittance value greater than 95%. These results indicate the high clarity of microemulsion. In case of other formulations, the %T values were less than 90% suggesting less clarity of microemulsion. This may be due to greater particle size of the formulation. Due to higher particle size, oil globules may reduce the transparency of microemulsion and thereby values of % T.

**Table 6: Transmittance of different formulations of lovastatin SNEDDS**

| S.No. | Formulation Code | Visual observation | % Transmittance |
|-------|------------------|--------------------|-----------------|
| 1     | F1               | Turbid             | 76.36           |
| 2     | F2               | Slightly clear     | 87.55           |
| 3     | F3               | Slightly clear     | 84.97           |
| 4     | F4               | Slightly clear     | 78.30           |
Drug content of SNEDDS

The drug content of all 15 formulations was shown in Table 7. The drug content of the prepared SNEDDS was found to be in the range of 91.43±1.75 (F1) – 98.45±1.72 % (F8). The drug content of optimized formulation F8 was found to be 98.45±1.72 %.

| S. No. | Formulation code | % Drug content |
|-------|------------------|----------------|
| 1     | F1               | 91.43±1.75     |
| 2     | F2               | 92.16±2.14     |
| 3     | F3               | 92.50±1.76     |
| 4     | F4               | 94.11±2.23     |
| 5     | F5               | 94.84±1.25     |
| 6     | F6               | 96.76±1.79     |
| 7     | F7               | 95.98±2.26     |
| 8     | F8               | 98.45±1.72     |
| 9     | F9               | 95.31±1.89     |
| 10    | F10              | 94.22±1.44     |
| 11    | F11              | 95.27±2.29     |
| 12    | F12              | 93.12±1.55     |
| 13    | F13              | 94.22±1.74     |
| 14    | F14              | 94.04±1.88     |
| 15    | F15              | 95.00±1.94     |

In-vitro dissolution studies of SNEDDS

The in vitro dissolution profiles of formulations F1-F5 prepared with 1:1 ratio of Lauro glycol 90 Capmul CMC were shown in Figure 2. The release of drug from these formulations ranged from 85.25±4.06 (F1) to 92.60±4.88% (F4). The results of in vitro dissolution of SNEDDS formulations F6-F10 prepared with 2:1 ratio of Lauro glycol 90 Capmul CMC was shown in Figure 3. The release of drug from these formulations was ranged from 90.02±4.08 (F6) to 98.25±4.28 % (F8). The optimized formulation (F8) released about 98.25±4.28 % of drug in 60 min. Formulations F11-F15
prepared with 3:1 ratio of Lauro glycol 90 Capmul CMC and was shown in Figure 4. The release of drug from these formulations ranged from 87.29±4.08 (F11) to 94.35±4.55% (F12). The faster dissolution from SNEDDS may be attributed to the fact that 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 than other SNEDDS formulations and pure drug substance indicating influence of droplet size on the rate of drug dissolution.

Table 8: Stability studies of optimized formulation (F8) of lovastatin SNEDDS

| Parameters               | Temperature maintained at 40±2°C | Relative humidity (RH) Maintained at 75%±5% RH |
|--------------------------|----------------------------------|-----------------------------------------------|
|                          | Initially | 30th day | 90th day | 180th day |
| Drug content (%)         | 98.45±0.12 | 97.80±0.68 | 97.24±0.73 | 98.01±0.22 |
| In Vitro drug release (%)| 98.25±1.11 | 97.86±0.35 | 97.11±0.02 | 96.55±2.55 |

Figure 2: In vitro dissolution profiles of lovastatin SNEDDS prepared with 1:1 ratio of Lauro glycol 90 Capmul CMC (Mean±SD, n=3).
Figure 3: *In vitro* dissolution profiles of lovastatin SNEDDS prepared with 1:1 ratio of Lauroglycol 90 Capmul CMC (Mean±SD, n=3).

Figure 4: *In vitro* dissolution profiles of lovastatin SNEDDS prepared with 1:1 ratio of Lauroglycol 90 Capmul CMC (Mean±SD, n=3)
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 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 analysis of optimized formulation (F8) was shown in Figure 5 and was found to be 4.9 nm & Z-Average of 71.5 nm indicating all the particles were in the nanometer range.

Zeta potential of SNEDDS

Zeta potential has got practical application in the stability of dispersion system 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 optimized SNEDDS formulation (F8) was shown in Figure 6. The zeta potential of formulation F8 was found to be -13.7 mV which comply with the requirement of the zeta potential for stability. Due to the negative charge of the droplet, aggregations would not take place. Zeta potential, which can produce repulsive electrical forces among approaching oil
droplets and this prevents coalescence. The more the negative zeta potential, greater the net charge of droplets and more the stability of dispersion system\(^2\).

**Figure. 6:** Zeta potential of the optimized formulation (F8) of lovastatin SNEDDS.

**Scanning electron microscopy for Lovastatin SNEDDS**

The surface morphology of SNEDDS as well as droplet size was predicted by using scanning electron microscopy (SEM). 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 (Figure 7).

**Figure. 7:** SEM photographs of optimized formulation (F8) of lovastatin SNEDDS.
Stability studies:
The stability study of optimized lovastatin SNEDDS formulation (F8) was carried out 6 months as per the ICH guidelines and the results were shown in table 8. There was no significant change in the drug content and drug release for at least for 6 months. 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 nano-emulsifying property of the formulation.

CONCLUSION
The present study has undoubtedly proved the potential effectiveness of SNEDDS for formulating Lovastatin with improved solubility and dissolution. 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, 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 to 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. 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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Conflict of interest:
The authors declare that they have no conflict of interest

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