ORIGINAL ARTICLE

SNEDDS in Shell: A Novel Approach to Enhance the Solubility of Rosuvastatin Calcium

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Abstract

Aim: The objective of this study was to develop a novel self-nanoemulsifying drug delivery system which produced very small and uniform emulsion droplets, resulting in enhanced solubility, dissolution, and oral bioavailability of poorly water-soluble rosuvastatin calcium. **Material and Methods:** The effects of oil, surfactant, and cosurfactant on the drug solubility were assessed, and pseudoternary phase diagrams were plotted. Among the liquid SNEDDS formulations tested, the liquid SNEDDS composed of cinnamon oil (oil), Cremophor RH 40 (surfactant), and Transcutol P (cosurfactant) at a ratio of 1:5 (o/S_{mix}), produced the smallest emulsion droplet size. The rosuvastatin-loaded liquid SNEDDS formulation was assessed for the emulsion droplet size, solubility, and dissolution of the emulsified SNEDDS and compared to the pure drug. Different SNEDDS formulations of rosuvastatin calcium were prepared by aqueous phase titration method. Prepared SNEDDS was filled in capsule shells as drugs with high solubility or low dose can be filled in capsule shell. Prepared SNEDDS was subjected to different thermodynamic stability tests. Thermodynamically stable SNEDDS was selected for self-nanoemulsification efficiency test. Selected formulations were characterized in terms of droplet size distribution, viscosity. Finally, selected SNEDDS (F1–F8) was subjected to *in vitro* dissolution/drug release studies. **Results and Discussion:** Droplet size and viscosity of formulation F6 were found to be lowest as compared to other formulations. The results of zeta potential indicated the formation of stable SNEDDS. *In vitro* drug release studies showed 97.7% release of drug from optimized formulation F6, where initial drug release profile of rosuvastatin calcium from optimized formulation F6 was found to be much faster than marketed rosuvastatin calcium capsule. **Conclusion:** Thus, this novel SNEDDS developed represents a potentially powerful oral delivery system for rosuvastatin calcium to enhance solubility and thereby bioavailability.

Key words: Cinnamon oil, Pseudoternary phase diagrams, Rosuvastatin calcium, Self-emulsifying drug delivery systems, Solubility

INTRODUCTION

Rosuvastatin calcium (RST) is an most effective statin, antihyperlipidemic drug commonly used to treat hypercholesterolemia that produces a considerable dose-dependent reduction in low-density lipoprotein cholesterol[1] and raising high-density lipoprotein cholesterol levels thereby. It is the latest synthetic drug in the statin group, which acts as an inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A reductase (the rate-limiting enzyme in cholesterol biosynthesis).[2] It was also reported to treat benign prostatic hyperplasia, osteoporosis, and Alzheimer's disease. It is a Class II drug in the Biopharmaceutics Classification System that shows low dissolution because of its crystalline nature and thus poor oral bioavailability of 20%. Food reduces rosuvastatin bioavailability by approximately 20%, but the extent of absorption is unchanged. It occurs at approximately 3 h after multiple dosing. Rosuvastatin calcium is strongly and reversibly bound to plasma protein (90%). It has a prolonged effect on hepatic cholesterol synthesis in animal models. It extensively metabolized by the liver[3] through oxidation, lactonization, and glucuronidation. The major

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factor in tailoring oral pharmaceutical delivery systems is enhancing the solubility and bypassing the hepatic metabolism is a desirable approach for improving rosuvastatin calcium therapeutic performance.

Hence, self-emulsifying drug delivery system (SNEDDS) was proposed to simultaneously improve solubility, avoid the first pass metabolism, and facilitate the lymphatic absorption. It also improves the bioavailability of the drug through improving its solubility and increasing the membrane permeability of the gastrointestinal tract.[4,5] SNEDDS is able to emulsify rapidly and spontaneously in the gastrointestinal fluids and create fine oil/water emulsions under the gentle agitation provided by gastrointestinal motion.[6,7] These fine droplets lead to improve the drug solubility capacity in the stomach and its dissolution through providing a large interfacing surface area for partitioning the drug between the oil and gastrointestinal tract (GIT) fluid as a lipid-based drug delivery system.[8] Small droplets of oil created by SNEDDS also increase the drug diffusion into intestinal fluids (because of large surface area). Moreover, the emulsion droplets lead to faster and more uniform distribution of drug in the GIT. They also minimize the mucosal irritation due to the contact between the drug and the gut wall.[9] SNEDDS is normally prepared as liquid dosage forms then incorporated in capsule shells. This combination offers the sum of the benefits of both SEDDS and solid dosage forms. This combination offers the sum of the benefits of both SEDDS and solid dosage forms which includes rapid onset of action (there were no time for dispersion) and stability of drug molecules. In SNEDDS, isotropic mixtures of drug, lipid phase (oil), surfactant, and/or cosurfactant, forming very tiny emulsion lipid droplets, ranging in size between 20 and 300 nm.[10,11] The aim of this study is to develop and characterize SNEDDS formulations containing rosuvastatin calcium using different oils, surfactants, and cosurfactants. The main objective was to increase the therapeutic efficacy of rosuvastatin calcium.

MATERIALS AND METHODS

Materials

Rosuvastatin calcium was obtained as gift sample from Dr. Reddy's Laboratories (Hyderabad). All other chemicals, Tween 80 (polyoxyethylene sorbitan monooleate), Tween 20 (polyoxyethylene sorbitan monolaurate), and PEG 400 (polyethylene glycol), were obtained from Merck, Mumbai. Cremophor RH 40, propylene glycol, Transcutol P, Span 80, and oils (Capmul MCM oil, orange oil, coconut oil, cinnamon oil, flax seed oil, and oleic acid) were obtained from Sigma (St. Louis, MO), Fine-Chemicals Limited, Mumbai. Madhuca oil was obtained from KS Essentials, New Delhi. Other chemicals were in analytical grade.

Methods

The solubility of rosuvastatin calcium was determined in various carriers oils, namely, Capmul MCM oil, orange oil, cinnamon oil, flax seed oil, Madhuca oil, coconut oil, and oleic acid, and surfactants, namely, Cremophor RH 40, polyethylene glycol, Tween 80, Tween 20, Caprol 3GO, and Miglyol 812 and cosurfactants, namely, Transcutol P, Span 80, and PEG 400 were screened by placing an excess amount of rosuvastatin calcium into 2 ml of each vehicle. Then, the mixture was vortexed and kept for 48 h at 37 ± 1°C in a shaking water bath to facilitate the solubilization. The samples were centrifuged at 3000 rpm for 10 min to remove the undissolved rosuvastatin calcium. The supernatant was collected, and concentration was calculated employing ultraviolet (UV)–visible spectrophotometer (Shimadzu UV 1800, Japan) at a wavelength of 248 nm, the test was repeated in triplicate.[12,13]

Pre-formulation studies

The pre-formulation studies like Fourier transform infrared (FTIR) studies were performed for selected excipients, drug, and physical mixture. Partition coefficient determination was done by shaking flask method. The phase diagrams were constructed with oil, surfactant, and cosurfactant as three apexes of the triangle. The water titration method was used for the construction of the phase diagrams. Various weight ratios of pre-concentrates of oil to surfactant-cosurfactant mix were prepared from 1:9 to 9:1. The surfactant and cosurfactant mixtures were prepared at various ratios of 1:9–9:1, which were then used in the preparation of SEDDs pre-concentrates. The pre-concentrates were mixed by vortex mixing, and the system was allowed to stand overnight to avoid non-isotropic mixtures if any. To identify the emulsification region of choice, water titration was carried for the isotropic mixtures. Accurately weighed quantity (100 mg) of the pre-concentrate was taken and titrated with distilled water (20 ml). All samples were visually inspected over a period of 24 h at ambient temperature to verify the miscibility of the components and to further clarify the compositions which resulted in monophasic dispersions. Samples exhibiting phase separation or blur dispersions were excluded from further studies.

Continuous shaking was done while titrating with water. The formed emulsions were evaluated for particle size using Malvern Zetasizer. The phase diagrams were constructed using Chemix software for the identification of self-emulsifying microemulsion region. Each apex of the phase diagram represents 100% of each component, that is, oil, surfactant, and cosurfactant. Area of microemulsification[14] was determined. The phase diagrams were plotted for self-emulsifying systems of various ratios of oil, surfactant, and cosurfactant with drug. The system with more area of microemulsification was optimized.[15]

Design of self-nanoemulsifying lipid formulations (SNEDDs)

Once the self-emulsifying region was identified, different SEDDS formulations (F1–F8 compositions) were prepared.

The drug-loaded self-emulsifying formulations were prepared using different oils, lipophilic/hydrophilic surfactants, and water-soluble cosolvents which are presented in Tables 1 and 2. The oil and Smix were mixed at various ratios. To prepare L-SEDDS, surfactant and cosurfactant were mixed through magnetic stirring at 25°C, and then, the oil phase was added to the mixture. Afterward, drug was added with continuous stirring until the mixture became clear and transparent. A whole range of formulations and alternative formulations was prepared and then subjected to characterization.[16]

Characterization of SNEDDS

Infrared spectroscopy

Drug-excipient compatibility was studied by utilizing ATR-FTIR spectroscopy[17] (PerkinElmer). The FTIR overlay of rosuvastatin calcium and SEDDS formulation (F6), samples were scanned for IR spectra from 4000 to 400 cm^{-1}.

Stability study

The stability of the optimized SNEDDS sealed in a 10 mL centrifugal tube was assessed through centrifugation and temperature tests, wherein samples were stored at 4°C, 25°C, and 60°C for 1 month. In the centrifugation test, the samples were exposed to a centrifuge for 10 min after day 1, day 15, and day 30. This was followed by the observation of their physical appearance. In addition, the particle size and drug content were monitored to assess the comprehensive stability of SEDDS.

Table 1: Solubility of rosuvastatin calcium in various vehicles (oils)

Oils	Solubility (mg/ml)
Cinnamon oil	97.30±0.91
Orange oil	66.78±0.98
Capmul MCM oil	79.37±0.85
Flax seed oil	15.43±0.45
Coconut oil	12.87±0.58
Oleic acid	1.87±0.11
Madhuca oil	1.54±0.43

Table 2: Solubility of rosuvastatin calcium in various vehicles (surfactants and cosurfactants)

Surfactant/cosurfactant	Solubility (mg/ml)
Tween 80	20.07±1.20
Tween 20	17.20±0.25
Cremophor RH40	38.9±0.86
Caprol 3GO	14.28±2.15
Miglyol 812	0.13±0.83
PEG 400	18.34±0.95
Transcutol P	89.56±0.67
Span 80	60.45±0.46

Percentage transmittance

The percentage transmittance of the SNEDDS gave an idea about the formulation features including uniformity and size of the droplets. Percentage transmittance was measured by taking 1 mL of each formulation and diluting it 10 times with distilled water. A UV spectrophotometer was used to measure the percentage transmittance at 248 nm by taking distilled water as a blank

Dispersibility test

Each formulation (0.1 ml) is added to 500 ml of distilled water at 37°C ± 0.5°C. A standard stainless steel dissolution paddle rotating at 50 rpm provided gentle agitation. By visual assessment, the formulations are graded as follows:

- Grade A: Rapidly forming (and lt;1 min) nanoemulsion having a clear (or) bluish appearance
- Grade B: Rapidly forming, slightly less clear emulsion, having bluish appearance
- Grade C: Fine milky emulsion that formed within 2 min
- Grade D: Dull grayish-white emulsion and slow to emulsify.

Determination of globule size, zeta potential, and drug loading

The globule size and zeta potential of diluted rosuvastatin calcium SNEDDS were determined using dynamic light scattering technique (Malvern, UK). The mean droplet size of the formulations was determined using scanning electron microscope (SEM).[18] Drug loading was determined by dissolving 1 ml of rosuvastatin calcium-SNEDDS in 10 ml of methanol. The solution was filtered and analyzed at 248 nm using UV–visible spectrophotometer.

Self-emulsification time

Self-emulsification time is the time required by the pre-concentrate to form a homogeneous mixture on dilution, when disappearance of SNEDDS is observed visually. The efficiency of self-emulsification of SNEDDS was assessed using a standard USP XXII dissolution apparatus. One milliliter of each formulation was added dropwise to the medium (250 ml of purified water and pH 6.8 phosphate buffer with a paddle speed of 60 rpm at 37.0 ± 0.5°C) by a dropping pipette and the time required for the disappearance of the SNEDDS was recorded.[19] The efficiency of self-emulsification was visually assessed.

Zeta potential analysis

The nanoemulsion stability is directly related to the magnitude of the surface charge. The zeta potential of the selected

formulations was determined by laser diffraction analysis using particle size analyzer (Malvern Zetasizer Nano Series ZS 90). The samples were diluted with a ratio of 1:100 (v/v) with distilled water and mixed for 1 min using a magnetic stirrer. All studies were repeated in triplicate.

Surface topology studies

Surface topology studies were performed for optimized formulations utilizing scanning electron microscopy (Shimadzu, S-3700 N, Japan) to observe morphology as well as shape.[20] The analysis was performed by mounting each sample on sterilized brass metal stub consists of dual-sided adherent carbon tape. The particles were then coated with gold to make them electroconductive in ion vacuum using an ion sputter (E-1010). The SEM images of each sample were taken and formulation was then characterized.

Dissolution studies

Dissolution studies were carried out for plain drug rosuvastatin calcium and for optimized formulations in phosphate buffer media pH 6.8 to compare release pattern employing USP paddle type apparatus (DS 8000, LABINDIA, Mumbai, India) at a stirring rate of 75 rpm and at constant temperature (37 ± 0.5°C). At prefixed time points, 5 mL aliquots were taken and replenished with fresh media. Samples were filtered (0.45 μm) and analyzed spectrophotometrically at 248 nm.

RESULTS AND DISCUSSION

Screening of oil, surfactant, and cosurfactant

Rosuvastatin calcium solubility was done in different vehicles. Among the selected lipids, rosuvastatin calcium depicted higher solubility in cinnamon oil (97.3 ± 0.91 mg/ml) followed by Capmul MCM oil (79.37 ± 0.85 mg/ml) and orange oil (66.78 ± 0.98 mg/ml). Cremophor RH 40 (38.9 ± 0.86 mg/mL) and Tween 80 (20.07 ± 1.20 mg/mL) among surfactants and Transcutol P (89.56 ± 0.67 mg/mL) and Span 80 (60.45 ± 0.46) among cosurfactants showed comparatively high solubility. To choose an ideal mixture of various vehicles used in the study, miscibility and percentage transmittance were checked. The studied vehicles have more than 90% of transmittance; hence, cinnamon oil, Cremophor RH 40, and Transcutol P were chosen as oil phase, surfactant, and cosurfactant for preparing SNEDDS as they have showed maximum solubility of rosuvastatin calcium and the values are shown in Tables 1 and 2.

The highest solubility of rosuvastatin calcium was obtained in cinnamon oil. This was advantageous as it has been reported that unsaturated fatty acids aid in lymphatic transport as compared to saturated fatty acids after oral administration.[21] Therefore, cinnamon oil was selected as oil phase to get maximum drug loading and to avoid precipitation of the drug on dilution in the gut lumen for formulation development. It has been reported that SNEDDS should readily disperse (within seconds) after administration under gentle agitation.[22] Therefore, emulsification study was conducted which clearly distinguished the ability of various surfactants to emulsify the selected oil. The results showed that Cremophor RH 40 had highest ability to emulsify oil cinnamon oil as compared to other surfactants. Moreover, Cremophor RH 40 is P-gp and CYP 450 enzyme inhibitor and hence would aid in bioavailability enhancement. The cosurfactant increases the fluidity of interfacial film which aids in the formation of emulsion. In the current investigation, Transcutol P (hydrophilic lipophilic balance [HLB] 4) showed good emulsification ability with highest transmittance. As Transcutol P has shorter chain length (C6), it is considered more efficient and can easily promote water penetration at interface.[23] In general, the longer the length of the hydrophobic alkyl chain, the higher the molecular volume of the oil phase affecting the emulsification ability of surfactant mixtures. In this view, cinnamon oil is a C9 medium chain fatty acid that can be easily emulsified. The addition of suitable cosurfactant lowers the interfacial tension, fluidizes the hydrocarbon region of the interfacial film, and decreases the bending stress of the interface which results in improvement in spontaneity of emulsification and reduction in emulsion droplet size and polydispersity.[24]

Establishment of pseudoternary phase diagram

To develop a stable SNEDDS, pseudoternary phase plot has been plotted to identify the self-nanoemulsifying zone and also to determine the amount of various vehicles concentration (oil, surfactant, and cosurfactant) used for the preparation of L-SNEDDS. The phase diagrams were plotted using CHEMIX software[25] and region shaded in black color in Figure 1 shows the actual emulsification zone with nanosized droplets. Cremophor RH 40 (HLB-14) decreases the tension at the interface thus leading to a stable emulsion. Transcutol P (HLB-4), being the cosurfactant, acts as an amphiphilic moiety to ameliorate the interfacial wetting of external phase improving the emulsification process on dilution. In general, surfactant and cosurfactant having large and small HLB values cause entrapment of later

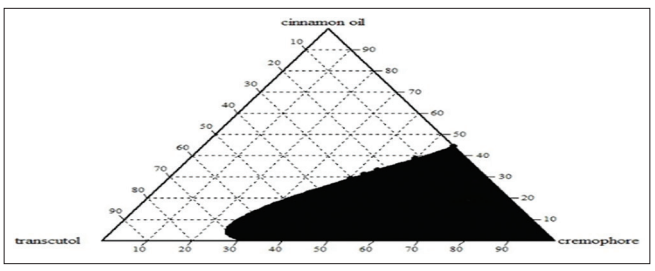

Figure 1: Ternary phase diagram of F6 formulation

surfactant in former surfactant thereby help in the formation of fine droplet-sized stable emulsion. Further, cinnamon oil penetrates through surfactant film creating void spaces hereby increasing the interfacial fluidity. The effectiveness of self-microemulsification system is more correlated with the HLB values of the surfactants. The surfactants with HLB value greater than 10 are significantly superior in providing small and uniform microemulsion droplets with less particle size. Smaller microemulsion region was obtained at 1:1 ratio of S/Cos, as surfactant alone was insufficient to minimize the o/w interfacial tension. The maximum region was obtained at 1:5 ratio of S/Cos. Further increase in a surfactant from 1:1 to 1:5 showed an increase in the formation of microemulsion region indicating that optimum emulsification was achieved at 1:5 ratio of S/Cos. This can be because more amount of Transcutol P will increase the aqueous solubility of oil which will increase the globule size as a result of expansion of interfacial film.[26] Hence, 1:5 ratio was considered as optimum surfactant/cosurfactant ratio.

Preparation of rosuvastatin SNEDDs

Once the self-emulsifying region was identified, the desired component ratios of SNEDDs were selected for drug incorporation and further optimization. Ten milligrams of drug and mixed surfactant and cosurfactant were incorporated in their determined ratios into oil phase containing drug. Finally, homogeneous mixture was obtained by vortex mixing. The prepared rosuvastatin calcium SNEDDS whose composition is shown in Table 3 was filled in capsule shells, as drugs with high solubility or low dose can be filled in capsule shell which was kept in a tightly closed bottle at 25°C and from these the stable formulations were subjected to further studies, that is, dilution studies, droplet size analysis, self-emulsification time, particle size analysis, and zeta potential analysis.

ATR-FTIR spectroscopy

To determine the interactions between constituents, spectra of pure drug, excipients employed, and formulated batches were measured and the same is depicted in Figures 2 and 3. Drug peaks remained unchanged in SNEDDS. No additional peaks were observed endorsing the existence of only physical interactions between the drug molecule and various components used. No significant chemical incompatibility was present between drug, carrier, and other constituents, thereby suggesting the compatibility of excipients.

Table 3: Composition of SNEDDS formulation

Formulation code	Oil (%)	Surfactant (%)	Cosurfactant (%)
F1	33.33 (A)	13..33	53.28
F2	33.33 (A)	9.52	57.13
F3	20.0 (A)	40.0	40.0
F4	16.66 (B)	41.66	41.66
F5	16.66 (B)	8.33	75
F6	16.66 (B)	13.88	69.44
F7	50 (A+B)	25	25
F8	50 (A+B)	10	40

Where A: Capmul oil., B: cinnamon oil

Spectroscopic characterization of optical clarity

The percentage transmittance is an important parameter to determine the isotropic nature of the system. A value of percentage transmittance closer to 100% signified that all selected formulae were clear, transparent, and globules size in the nanometric range, which, in turn, indicates that the formula has a large surface area for drug release, high capacity to undergo enhanced absorption in biological matrix and thus have ability for increased oral bioavailability. Higher transmittance should be obtained with optically clear solutions, since cloudier solutions will scatter more of the incident radiation, resulting in lower transmittance. On 100-fold dilution, the percentage transmittance of SNEDDs formulae was found to be in the range of 98.70–99.90% which confirms good transparent nature of all rosuvastatin calcium-loaded SNEDDS formulae. These results found that the percentage transmittance of the prepared SNEDDS formulae was close to 100%.

Droplet size, Polydispersity index (PDI), and zeta potential

In general, droplet size, PDI, and zeta potential are most important considerations as they impact solubility and bioavailability of any drug. These parameters directly influence stability of the emulsion formed and also play a vital part in the drug release and absorption. Smaller particles possess greater surface area for rapid drug dissolution. An optimized mixture of oil, surfactant, and cosurfactant gives SNEDDS that undergoes impulsive emulsion generation due to its reduced droplet dimension. The stability of the nanoemulsion is highly affected by oil and surfactant fatty acid chain length and also its unsaturation. Particles of <300 nm are more likely to cross the enterocytes without any difficulty and also play a key role in drug absorption and distribution. Droplet size [Figure 4] was in the range of 81.8–110 nm which is in nanometric size range. A lower droplet size of the nanoemulsion results in less emulsification time attributed to greater surface is resulting in enhanced absorption by lymphatic uptake and helps in intensifying efficacy of the drug. Cinnamon oil being a good solubilizer for poorly soluble molecules aids in dispersion, thus leading to good emulsification when subjected to hydration. Further, the application of surfactants with greater HLB values has an additional benefit in ameliorating the interfacial wetting of poorly wettable constituents and quick emulsification

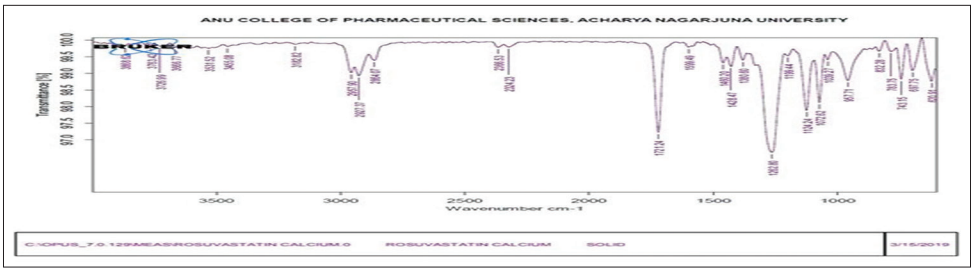

Figure 2: Fourier transform infrared spectra of pure drug

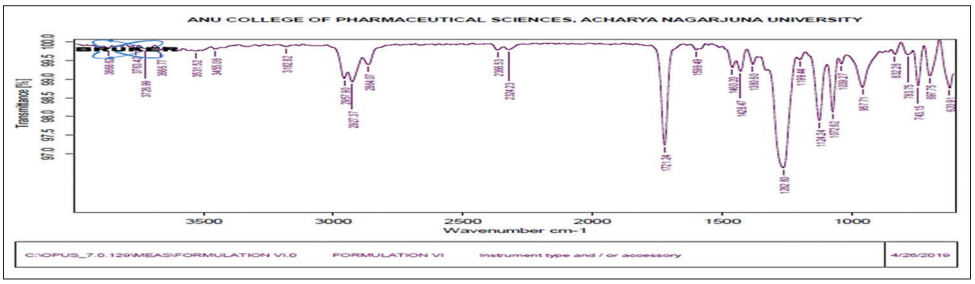

Figure 3: Fourier transform infrared spectra of optimized formulation F6

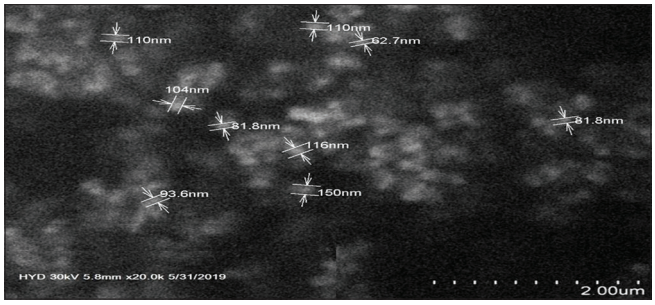

Figure 4: Scanning electronic microscopic image of F6 formulation

of nanoemulsion when diluted with aqueous vehicle. Cremophor RH 40 (HLB 14), a non-ionic surfactant and Transcutol P (HLB 4), is accountable toward the arrangement of reduced droplet size. The presence of fatty acid chain and combination of Cremophor RH 40 being the surfactant (HLB 14) as well as Transcutol P, a low HLB coemulsifier, were required for reduced droplet size as well as lesser PDI. Among the various prepared batches, F6 possessed smallest size of 81.8 ± 0.9 nm, a PDI of 0.209, and a zeta potential of 1.53 mV. Although optimized SNEDD formulation shows a slightly low zeta potential value, it is still within the expected range and there is no phase separation, agglomeration and sedimentation observed. The closer to zero the PDI value, the more homogenous are the particles. The small values of PDI shown by SNEDDS formulae (0.209) indicate homogenous droplet population and narrow globule size distribution. This, in turn, indicates more uniform emulsions with higher physical stability, while samples with larger particle size usually produce in a higher PDI values more than 0.7, indicating the poor stability. Even though all the formulations are within the range of particle size and PDI, F6 was selected for further studies based on the % transmission at 635 nm.

Self-emulsification time

The rate of emulsification was a major index for the assessment of the efficiency of self-emulsification. The SNEDDS should disperse completely and quickly when subjected to dilution under mild agitation.[27] Formulations F1, F3, F6, and F8 showed very less emulsification time.

Robustness to dilution

Uniform emulsion formation from SNEDDS is very important at different dilutions because drugs may precipitate at higher dilution *in vivo* which affects the drug absorption significantly.[28] Different fold dilutions of selected formulations were exposed to different media to mimic the *in vivo* conditions where the formulation would encounter gradual dilution. Hence, each formulation was subjected to 50, 100, and 1000 times dilution in water, pH 1.2, pH 3, and pH 6.6. The resulting emulsions (F1–F8) were found to be in the acceptable nanoemulsion region, proving their robustness to dilution. This result will ensure the prospect of uniform drug release profile *in vivo*. Even after 24 h, formulation showed no signs of precipitation, cloudiness, or separation which ensured the stability of the reconstituted emulsion.

In vitro drug release study

The *in vitro* drug release study of the optimized formulations was performed in 900 ml, pH 6.8 of phosphate buffer. The release pattern of SNEDDS reveals that the maximum drug release was observed with F6 formulation [Figure 5]. This could be due to proper composition of oil and surfactant in the system. The formulation of F3 showed less drug release of around 91.05 ± 0.15%. The data indicate that the release

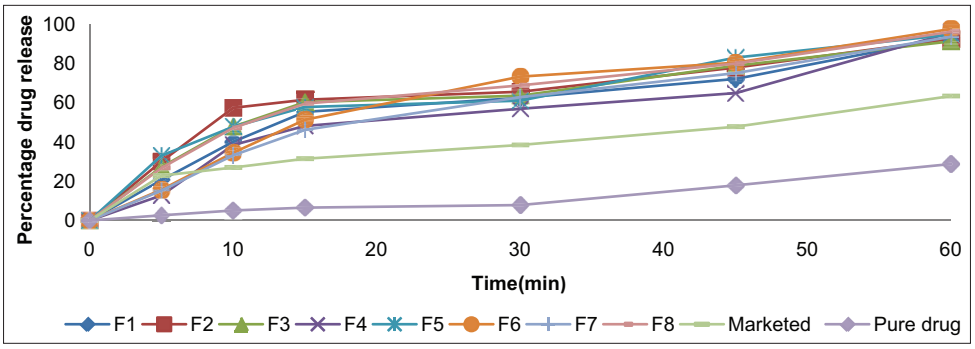

Figure 5: Drug release pattern of SNEDDS formulations and comparison with pure drug, marketed formulation

rate of rosuvastatin calcium from SNEDDS formulations was considerably faster than the marketed drug formulation. The cumulative percentage drug release from F6 was found to be 97.70 ± 0.25%, which was significantly higher than the marketed formulation (63.5 ± 0.28%). Thus, *in vitro* results reveal that the prepared SNEDDS formulations showed improved solubility of rosuvastatin calcium.

CONCLUSION

In this study, SNEDDS for oral delivery of highly lipophilic drug rosuvastatin calcium was successfully designed with the significantly superior features based on different component ratios. Among these, F6 showed greater potential in terms of reduced particle size (81.8 ± 0.9) and increased oral bioavailability. The formulation was stable over a 3-month storage period at 25°C and 4°C in terms of particle size, physical appearance, and drug loading. Hence, the present approach demonstrated the substantial increase in oral bioavailability of highly lipophilic drugs through the use of SNEDDS.

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