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Original Article

Self-Nanomicellar Dispersion of Rosuvastatin for Improved Bioavailability: Formulation, Optimization and Pharmacokinetic Studies

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ABSTRACT

Introduction: Rosuvastatin is a statin drug used to lower cholesterol, but it has poor water solubility and low bioavailability, limiting how effective it can be. The objective of the present study was to formulate and evaluate a SNEDDS "self-nano emulsifying drug delivery systems" of Rosuvastatin and to optimize its formulation. **Materials and Methods:** The SNEDDS was produced using Egg lecithin, Capmul MCM, and Tween 20 as co-surfactant, oil, and surfactant, respectively. The formulation was optimized by Design Expert 12 and was characterized by various techniques such as globule size, zeta potential, % transmittance, refractive index, drug release studies etc. The optimized SNEDDS was loaded with different adsorbents by adsorption using technique and characterized for *in vitro* release studies, *in vivo* drug release studies and comparison studies with pure drug. **Results:** The SNEDDS were optimized which shows a negative zeta potential of -4.32, a globule size of 42.21 nm, and a faster release compared to other formulations. Drug release studies (*in vitro*) showed that the optimized SNEDDS-loaded tablet had more rapid rate of drug release (99.9% at 40 min) when compared with the pure drug (36.73% at 40 min). The *in vivo* study in healthy rabbits showed a highest release rate of drug from the SNEDDS loaded tablet (RRSV1) when compared with the pure drug resulting in an enhanced bioavailability of Rosuvastatin. **Conclusion:** The study concludes that the SNEDDS of Rosuvastatin is a promising approach for increasing solubility, rate of dissolution and bioavailability.

Keywords: Rosuvastatin, SNEDDS, Statistical optimization, Solubility, Dissolution rate, Bioavailability.

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INTRODUCTION

Hyperlipidemia, or high blood lipid levels, is a serious and growing health concern linked to various chronic diseases.[1] Rosuvastatin is a highly effective drug for managing hyperlipidemia, but its poor water solubility limits its dissolving rate and bioavailability.[2] Improving Rosuvastatin's solubility could help optimize its therapeutic potential to treat hyperlipidemia. The objective of this study was to formulate a Self-Nanoemulsifying Drug Delivery System (SNEDDS) in order to increase the solubility, dissolution, and bioavailability of Rosuvastatin. Nanotechnology has enabled innovative advances in diagnostics, food, and drug delivery. SNEDDS are one such innovation that combines the benefits of lipid-based delivery and nanotechnology. SNEDDS is a novel drug delivery approach that overcomes the limitations of delivering Biopharmaceutics Classification System (BCS) class II drugs like Rosuvastatin, which have poor water solubility.[3,4]

This work examined whether a SNEDDS could enhance the effectiveness of Rosuvastatin for treating high cholesterol. SNEDDS formulations contain oils, surfactants, and co-surfactants that spontaneously form nano-sized emulsions when dispersed in water. The nanoemulsion can increase the concentration of a drug in the oil phase, thereby enhancing its solubility. The study hypothesized that a Rosuvastatin SNEDDS would increase its solubility and bioavailability, improving its effectiveness against hyperlipidemia.

MATERIALS AND METHODS

Materials

The study obtained Rosuvastatin from Glenmark Pharmaceuticals. It acquired the oils Capmul and Captex 200 from MCM Abitec group, and obtained the surfactants Span 20, Tween 20, Tween 80, as well as the co-surfactants Poly Ethylene Glycol (PEG) 400 and propylene glycol and the co-surfactant egg lecithin from Merck.

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It also procured the oils Labrafac Lipophilic WL 1349, Labrasol, and Cremophor EL and the oil Labrafil from Gattefosse.

Selection of oils, surfactants, and co-surfactants for Rosuvastatin

The components for the SNEDDS formulation are selected based on their effectiveness at solubilizing Rosuvastatin. Among the oils and surfactants tested, Rosuvastatin showed the highest solubility in Capmul MCM (oil), egg lecithin (co-surfactant), and Tween 80 (surfactant). These three components were therefore chosen for the SNEDDS formulation. Tween 80, a non-ionic surfactant with an HLB of 15, was selected because surfactants with HLB values greater than 10 are better able to produce small nanoemulsion droplets. Although natural lipids could solubilize Rosuvastatin, they were not used due to challenges with stability, solubility, and biocompatibility. The goal was to create a compact SNEDDS formulation that could deliver a therapeutic dose of Rosuvastatin in a minimal volume when encapsulated.[5-7]

Preparation of SNEDDS

The oils, surfactants, and co-surfactants used for the SNEDDS formulation were chosen based on Rosuvastatin solubility. 2 mL samples of various oils (soybean oil, olive oil, corn oil, peanut oil, sesame oil, ethyl oleate, Capmul MCM), surfactants (Tween 80, Span 80, Tween 20, Span 20, Cremophor EL, Labrasol, Labrafil), and co-surfactants (egg lecithin, PEG 400, propylene glycol, PEG 200) were evaluated for their ability to dissolve Rosuvastatin. The drug and vehicles were manually stirred for 30 min and then subjected to sonication for 2 hr and a 48 hr water bath to achieve equilibrium. The results of solubility are shown in Table 1. The mixtures were centrifuged for 20 min, filtered, and the concentration of dissolved Rosuvastatin in each vehicle was analyzed using a UV-spectrophotometer. The results showed Rosuvastatin had the highest solubility in Capmul MCM, egg lecithin, and Tween 80, which were selected for the SNEDDS formulation.[8]

Selection of SNEDDS Ingredients and Proportions: Pseudo-ternary phase diagram guided approach

Pseudo-ternary phase diagrams were developed to evaluate nanoemulsion formation using four components: oil, surfactant, co-surfactant, and aqueous system. The Chemix software was employed to generate the phase diagrams. Based on the Rosuvastatin solubility study, the selected components were Capmul MCM oil, Tween 80 surfactant, egg lecithin co-surfactant, and distilled water. Different surfactant to co-surfactant ratios (1:0, 1:1, 1:2, 1:3, 1:4, 2:1, 3:1, 4:1) and oil to Smix ratios (1:1 to 2:1) were mixed and titrated with water to determine optimal ingredient proportions for nanoemulsion development. Water was titrated into each mixture cautiously while monitoring for signs of nanoemulsion formation at different surfactant-co-surfactant and oil-Smix ratios. The ratios yielding nanoemulsions were mapped onto the pseudo-ternary phase diagrams. The aqueous titration method was applied to systematically evaluate how the surfactant-co-surfactant and oil-Smix ratios impacted nanoemulsion development in order to construct the phase diagrams and select the S-NEDDS composition. Only the nanoemulsion regions of the phase diagrams were shown by shading, as those areas are relevant for formulation development. The results identified appropriate ratios of the four components to produce Rosuvastatin Nanoemulsion.[9-11]

Selection of formulations from phase diagrams

The study selected formulations from the Nanoemulsion (NE) regions of the phase diagrams to incorporate Rosuvastatin. For each 5% increment of oil (e.g., 10%, 15%, 20%, 25%), the formulation that required the least amount of surfactant-co-surfactant mixture (Smix) to form a nanoemulsion was chosen. 20 mg of Rosuvastatin was dissolved in the selected oil phase. The goal was to identify the formulation that required the smallest amount of Smix to deliver the target dose of Rosuvastatin in a nanoemulsion. Particle sizes, Polydispersity Index (PDI), zeta potential, and Scanning Electron Microscopy (SEM) were measured for the selected SNEDDS compositions to analyze their characteristics. Analysis of particle size, PDI, zeta potential, and SEM images provided insights into the nano-droplet size, distribution, stability, and morphology of the nanoemulsions within the selected SNEDDS formulations.[12,13]

Evaluation studies for SNEDDS

The physico-chemical properties of the Rosuvastatin SNEDDS formulation were evaluated to assess its efficacy and stability. The analyses included:

- Measurement of particle size and polydispersity index.
- Determination of zeta potential.
- Measurement of refractive index and percent transmittance.
- Estimation of Rosuvastatin content in the SNEDDS.

Drug release studies of SNEDDS

A dissolution apparatus II containing 900 mL of pH 6.8 buffer kept at 37°C with paddle agitation of 50 rpm was employed to analyze Rosuvastatin release from the SNEDDS. At time points of 0, 5, 10, 15, 20, 30, 40, and 60 min, samples were taken and diluted with pH 6.8 buffers. The amount of released Rosuvastatin was analyzed using spectrophotometry at 252 nm. To compensate for volume loss from sampling, an equivalent amount of fresh dissolution medium at 37°C was added.[14-16]

Preparations of solid SNEDDS (S-SNEDDS)

Solid SNEDDS (S-SNEDDS) were produced using an adsorption technique. The SNEDDS was loaded with the adsorbents

Aerosil 200, porous polystyrene beads (TULSION® ADS-600), or Fujicalin (anhydrous dicalcium phosphate). The adsorbent was gradually blended with the SNEDDS until a non-flowing cohesive mass formed. The mass was passed through a 250 μm mesh to standardize particle size. The S-SNEDDS was kept in a desiccator before further analysis. The tablets were obtained by direct compression using microcrystalline cellulose (MCC) as super disintegrating agent was, while the directly compressible diluent was Cross Carmellose Sodium (CCS).[17,18]

Experimental design for the preparation of SNEDDS loaded tablets

A central composite design is employed to develop and optimize the SNEDDS-loaded tablets. Two factors, the amounts of microcrystalline cellulose and Cross carmellose sodium, were each tested at three levels. The experimental design comprised 9 combinations of the factor levels by Design-Expert 12.0 software. The factors and levels were selected to be practical and have a significant effect on the responses. The dependent variables or responses were tablet hardness, disintegration time, and percentage of Rosuvastatin release at 40 min. The optimal levels of the factors were identified to achieve the target responses. A polynomial equation was used to analyze the effect of the factors on the responses.

$$Y = \beta_0+\beta_1X_1+\beta_2X_2+\beta_{12}X_1X_2+\beta_{11}X_1\ X_1+\ \beta_{22}X_2\ X_2\ (1)$$

Where, Y is the dependent variable, β0 represents the average output of the 9 trials, and β1, and β2 designate the calculated coefficients for factors X1, and X2 correspondingly. The preliminary trials and previous experience determined the upper, middle, and lower levels of the factors. The design identified the optimal levels of the factors to achieve the target responses (composition of tablets is shown in Table 2).[19]

Table 1: Solubility of Rosuvastatin in various oils/surfactants.

Oils/Surfactants	Solubility of Rosuvastatin in mg/mL Mean±S.D.*
Oils	
Olive oil	7.2±0.33
Soyabean Oil	10.3±0.12
Peanut oil	11.5±0.77
Sesame oil	17.3±0.41
Capmul MCM	44.5±2.6
Arachis oil	22.4±0.32
Castor oil	19.2±1.1
Linseed oil	17.6±1.5
Captex 200	31.5±0.14
Labrafac LipophileWL1349	39.6±0.67
Surfactants	
Tween 20	76.3±0.34
Span 20	78.2±0.63
Labrasol	80.1±0.47
Cremophor EL	91.4±0.91
Labrafil	93.5±1.2
Tween 80	95.9±0.37
Co surfactants	
Egg lecithin	85.2±0.31
PEG 200	59.3±0.65
PEG 400	55.2±0.51
Propylene glycol	49.7±1.5
Capmul MCM+ Tween 80	120.5±0.33
Capmul MCM+ Tween 80+Egg L	230.5±0.98

*Standard deviation; *n*=3

Table 2: Formulae of Rosuvastatin SNEDDS tablet.

Ingredients	RSV1	RSV2	RSV3	RSV4	RSV5	RSV6	RSV7	RSV8	RSV9
Rosuvastatin Loaded SNEDDS (mg) Consists of 20 mg of drug	500	500	500	500	500	500	500	500	500
Microcrystalline Cellulose (mg)	250	225	200	225	250	225	200	200	250
Cross Carmellose Sodium (mg)	15	20	15	10	10	15	10	20	20
Lactose (mg)	25	45	75	55	30	50	80	70	20
Magnesium Stearate (mg)	5	5	5	5	5	5	5	5	5
Talc (mg)	5	5	5	5	5	5	5	5	5
Total(mg)	800	800	800	800	800	800	800	800	800

Table 3: Globule size, zetapotential, Polydispersibility index, viscosity, Refractive index and Percentage transmission.

Formulation Code	Globule Size (nm)	Zeta (mV)	Polydispersibility index	Viscosity (cps)	Refractive index (R.I)*	% Transmission*
B25	80.57	-6.78	0.184	28.4±0.4	1.457±0.02	98.4±1.8
C15	42.21	-4.32	0.124	25.7±0.5	1.457±0.03	97.2±0.2
D15	60.78	-4.89	0.269	19.8±0.2	1.458±0.03	97.7±0.9
E20	70.92	-6.71	0.327	26.2±0.4	1.456±0.01	95.6±1.6
F30	110.43	-7.19	0.256	23.1±0.6	1.456±0.02	96.8±1.8

* Mean±Standard deviation, *n*=3.

Evaluation studies on SNEDDS loaded tablets

Twenty prepared tablets from each formulation were chosen at random, weighed separately, and the average weight was estimated to determine the weight variation. With the Roche Friabilator, the fragility of tablets was evaluated. 10 tablets had been weighed at first and then loaded through the equipment, revolved for up to 100 revolutions. 5 tablets had been powdered after being separately weighed. The powder equal to a single dose was measured and drug had been isolated using ethanol and filtered. Utilizing a UV-spectrophotometer, the filtrate had been diluted using ethanol to measure the drug concentration.

In vivo evaluation

Animals

The bioavailability of Rosuvastatin from the optimized SNEDDS tablet formulation is evaluated using healthy New Zealand White rabbits. The rabbits were obtained from Sainath Agencies and housed in an animal facility that was authorized by the Institutional Animal Ethics Committee at Aditya Pharmacy College, Aditya Nagar, ADB Road, Surampalem, 533437, Gandepalli (Post and Mandal) (REG.No.1176/PO/Re/S/08/CPCSEA). The rabbits had free movement and access to standard food and water.[20]

Study design

The bioavailability study used a parallel design with two groups of rabbits. One group received pure Rosuvastatin suspension, while the other received the optimized S-SNEDDS tablet. Each group contained 6 rabbits of either sex. The Rosuvastatin suspension or S-SNEDDS tablet was administered to the rabbits by oral gavage. Blood samples were collected at time points over 12 hr and analyzed for Rosuvastatin concentration. The pharmacokinetic parameters were calculated and compared between the two groups to assess the enhancement in Rosuvastatin bioavailability from the S-SNEDDS tablet.[21]

Oral administration of the drug

Rosuvastatin is administered to rabbits using a feeding tube to ensure delivery to the stomach. For 12 hr prior to receiving the drug, the rabbits abstained from food while continuing to have access to water. To administer the drug, the rabbit's head was held in place using a rabbit holder and mouth gag. A glycerine-coated infant feeding tube was inserted into the mouth and down the oesophagus into the stomach.[22] The Rosuvastatin suspension or S-SNEDDS tablet was placed into the feeding tube and flushed with 3 mL of water. This method ensured delivery of the full dose to the stomach. Blood samples were then collected at time points over 12 hr to measure Rosuvastatin plasma concentrations.

Collection of blood samples

The marginal ear vein of the rabbits was accessed to draw blood samples for analysis. The vein was dilated by rubbing, and a 22-gauge needle was used to pierce the vein against the direction of blood flow. Samples of blood were collected at 0 (pre-dose), 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, and 12 hr subsequent to Rosuvastatin administration for analysis. Plasma was segregated from the blood through centrifugation at 2500-3500 rpm for 10 min. The plasma samples were refrigerated until Rosuvastatin analysis. The plasma concentration-time data were used to calculate pharmacokinetic parameters and compare Rosuvastatin bioavailability from the S-SNEDDS tablet and suspension.[23]

Data analysis

The study used non-compartmental analysis to estimate Rosuvastatin pharmacokinetic parameters from the data. The parameters included maximum plasma drug concentration (C_{max}), time to reach Cmax (t_{max}), Area under the curve (AUC), which represents extent of bioavailability, Apparent terminal elimination rate constant (K_e), half-life ($t_{1/2}$). The pharmacokinetic parameters were calculated using KineticaTM 2000 software. The parameters were compared between the S-SNEDDS tablet and suspension to assess the enhancement in Rosuvastatin bioavailability from the S-SNEDDS tablet.[24,25]

RESULTS

Selection of formulations from phase diagrams

SNEDDS formulations with optimal properties were identified from the phase diagrams. Up to 43% of the oil phase could be solubilized, allowing for a range of formulations to be selected from the nanoemulsion region in increments of 10-40%. The formulations requiring the minimum amount of surfactant-co-surfactant mixture (S_{mix}) were chosen for further study. The selected formulations had the smallest amount of surfactant, fastest self-nanoemulsification, and smallest droplet sizes were shown in Figure 1.

Evaluation studies

Globule size determination: Among the five optimized SNEDDS formulations, C15 had the smallest particle size i.e., 42.21 nm compared to the other formulations was displayed in Table 3.

Zeta potential: The zeta potential of C15 was the most negative among the SNEDDS formulations i.e., -4.32 was displayed in Table 3.

Viscosity: The SNEDDS formulations were ranked in order of decreasing viscosity as: D15<F30<C15<E20<B25. The viscosities of the formulations ranged from 19.8 to 28.4 cps were displayed in Table 3.

Refractive index and % transmittance: The refractive index and percent transmittance values were 1.456±0.02 to 1.458±0.03

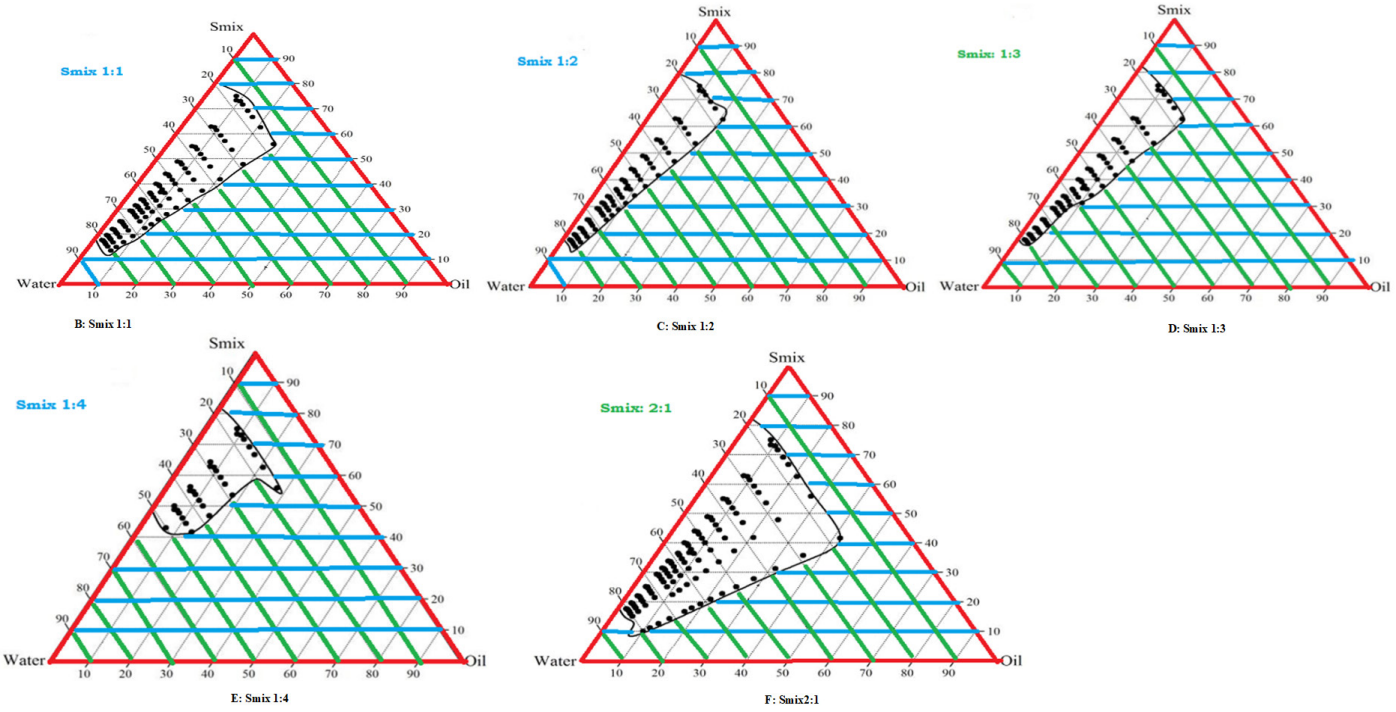

Figure 1: Phase diagrams for different oil-Smix-water systems.

Table 4: Composition of Rosuvastatin loaded SNEDDS Tablets.

Ingredient	Quantity (mg)
Rosuvastatin loaded SNEDDS	500
MCC	200-250
Cross Carmellose Sodium	10-20
Lactose	q. s
Magnesium stearate	5
Talc	5

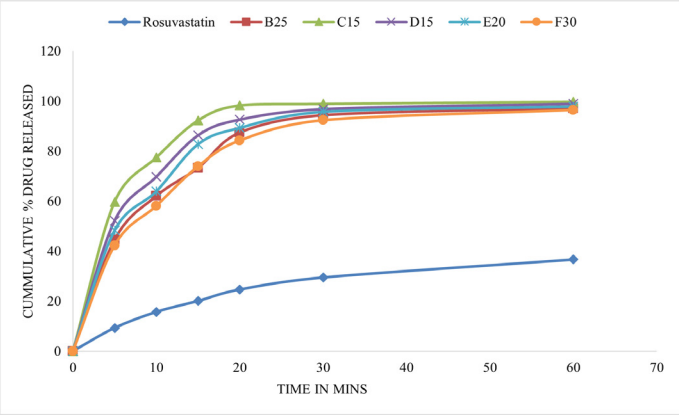

Figure 2: Comparative *in vitro* release data of Rosuvastatin and optimized formulations.

and 95.6±1.6% to 98.4±1.8% were indicated in Table 3 of the optimized SNEDDS formulations.

Drug release studies: *In vitro* Rosuvastatin release from the optimized SNEDDS formulations and pure Rosuvastatin is evaluated. In pH 6.8 buffer, the pure drug showed 29.54% release at 30 min due to its poor aqueous solubility. Among five SNEDDS formulations, C15 shows 98.9±2.61 at 30 min displayed in Figure 2.

Compounding of Solid SNEDDS (S-SNEDDS): Among these three the adsorbents, Aerosil 200 were achieved the highest loading and best stability due to its high surface area and adsorption capacity.

Preparation of Rosuvastatin loaded SNEDDS tablets: The compositions of the Rosuvastatin-loaded S-SNEDDS tablets are shown in Table 4 of the study. The S-SNEDDS was designed to provide the benefits of the liquid SNEDDS in a solid dosage form.

Design of experiments

The goodness of fit of the model was linear and significant with R^2 values for Hardness (Y_1), Disintegration time (Y2) and Cumulative % drug release (Y3) responses of Rosuvastatin SNEDDS tablets was found to be 0.9904, 0.9896 and 0.8681 respectively and F-values were found to be 308.25, 285.86 and 19.75 respectively.

Data analysis, optimization, and evaluation of the model: The application of response surface methodology yielded the following regression equations:

$$\text{Hardness}=4.86+0.5500*X_1+0.2000*X_2$$

$$\text{Disintegration time}=105.17+12.17\ X_1-4.25X_2$$

$$\text{Cumulative \% drug release}=97.13-1.70X_1+1.93X_2$$

Where, X_1 and $X_2$are the coded values of the test variables.

Contour plots and response surface plots showed the effects of the factors on the responses

were displayed in Figure 3a, 3b, 3c and 3d, 3e, and 3f.

Figures 3: A Contour plot showing the influence of amount of MCC (X_1) and super disintegrant (CCS) (X_2) on a Hardness (Kg/cm^2), BCumulative % drug release, C Disintegration time (Sec) D Response surface plot showing the influence of amount of MCC (X_1) and super disintegrant (CCS) (X_2) on d Hardness (Kg/cm^2), E Cumulative % drug release in 40 mins and F Disintegration time (Sec) and G Overlay Plot showing the influence of amount of MCC (X_1) and super disintegrant (CCS) (X_2) on Hardness (Kg/cm^2),Cumulative % drug release in 40 mins, Disintegration time (Sec).Optimization: The desirability value found to be 1 indicates a more suitable formulation that Showed in response surface and overlay plots in Figure 3g. The optimized formulation was expected to have the desired hardness value was 4.74 kg/cm^2, disintegration time value was 84.11 sec, and percentage Rosuvastatin release value was 98.3%.

Evaluation of tablets

The friability, drug content and thickness of all SNEDDS tablet formulations ranges from 0.81±0.19 to 0.95±0.059%, 98.33±0.62 to 102.32±0.57% and 4.2±0.033 to 4.4±0.183 mm.

Relative *in vitro* drug release studies

The dissolution profiles of the optimized Rosuvastatin SNEDDS tablet formulation and pure Rosuvastatin were contrasted. The dissolution curves demonstrate the optimized SNEDDS tablet releasing Rosuvastatin more rapidly (99.9% released at 40 min) than pure Rosuvastatin (36.73% released at 40 min) was displayed in Figure 4.

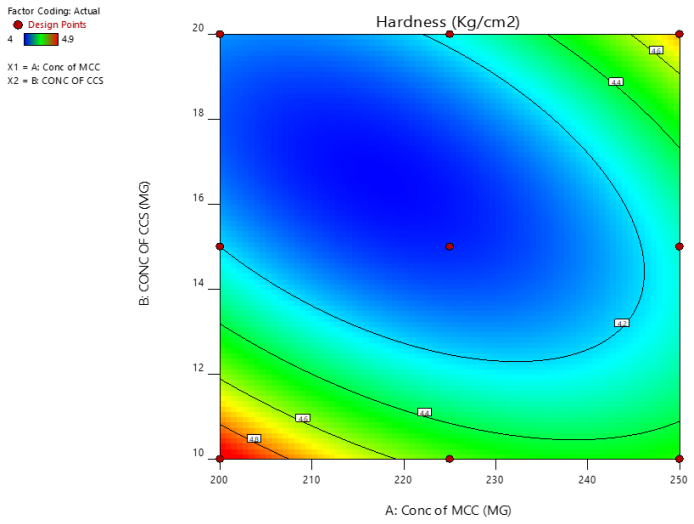

Figure 3A: Contour plot showing the influence of amount of MCC (X1) and super disintegrant (CCS) (X2) on a Hardness (Kg/cm^2).

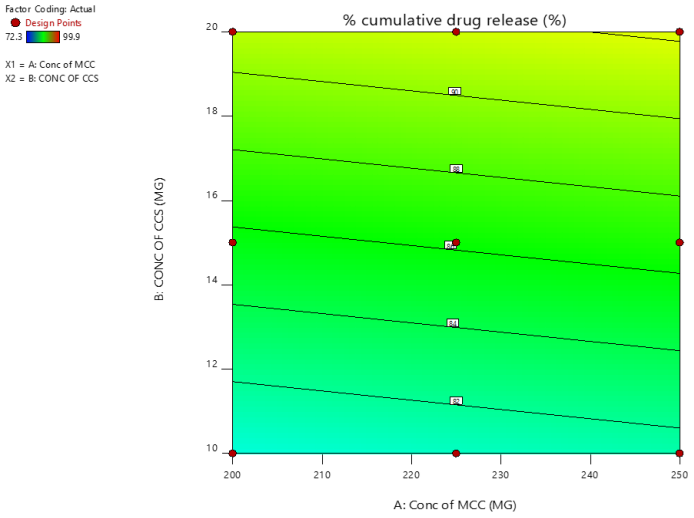

Figure 3B: Contour plot showing the influence of amount of MCC (X1) and super disintegrant (CCS) (X2) on a Cumulative % drug release.

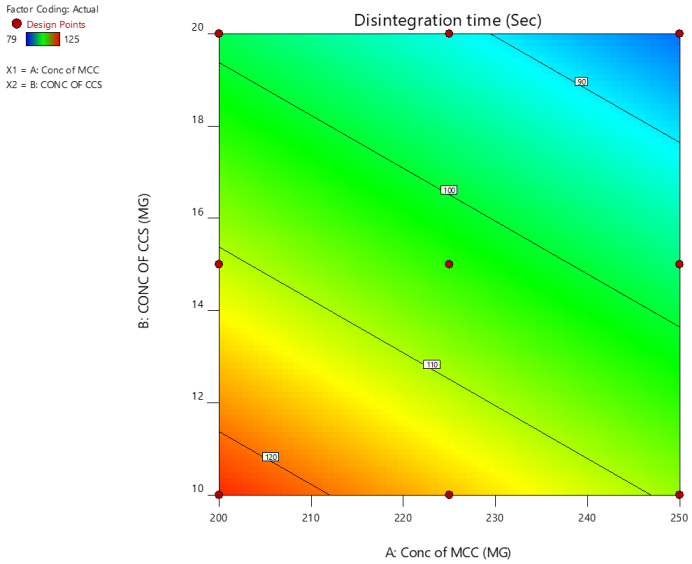

Figure 3C: Contour plot showing the influence of amount of MCC (X1) and super disintegrant (CCS) (X2) on a Disintegration time (Sec).

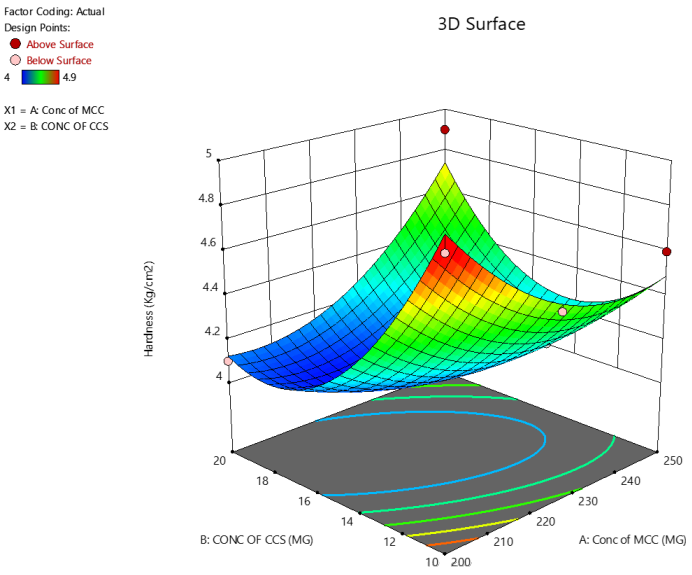

Figure 3D: Response surface plot showing the influence of amount of MCC (X1) and super disintegrant (CCS) (X2) on d Hardness (Kg/cm^2).

Cross validation

The model predicted that a formulation with a hardness of 4.7 kg/cm^2, a disintegration time of 84.1 sec, and 98.3% of the drug released within 40 min could be achieved using the optimal concentrations identified.

In vivo studies

Pharmacokinetic assessment of Rosuvastatin: The optimized RSV1 formulation was administered after reducing it to the rabbit dose as RRSV1. Pharmacokinetic parameters were calculated using a non-compartmental model. The comparative mean plasma concentration-time profiles are shown in Figure 5. The peak plasma concentration (C_{max}) was 524.0±6.96 ng/mL for pure Rosuvastatin and 1069.9 ± 10.57 ng/mL for RRSV1. The time to reach maximum concentration (T_{max}) was 4.0 hr for pure Rosuvastatin and 0.5 hr for the RRSV1 formulation. The Area Under the Curve (AUC) was 912.93 ± 1.77 ng·hr/mL for pure Rosuvastatin and 2982.5±0.83 ng·hr/mL for the RRSV1 formulation. The elimination rate constant was 0.041±0.001 hr^{-1} for pure Rosuvastatin and 0.41±0.001 hr^{-1} for RRSV1. The half-life ($t_{1/2}$) was 16.7± 0.24 hr for pure Rosuvastatin and 16.6±0.61 hr for RRSV1.

DISCUSSION

This research aimed to improve the solubility and bioavailability of Rosuvastatin, a poorly soluble drug, using a Self-Nanoemulsifying Drug Delivery System (SNEDDS). Smix concentrations for C15 observed that increased dispersion entropy,

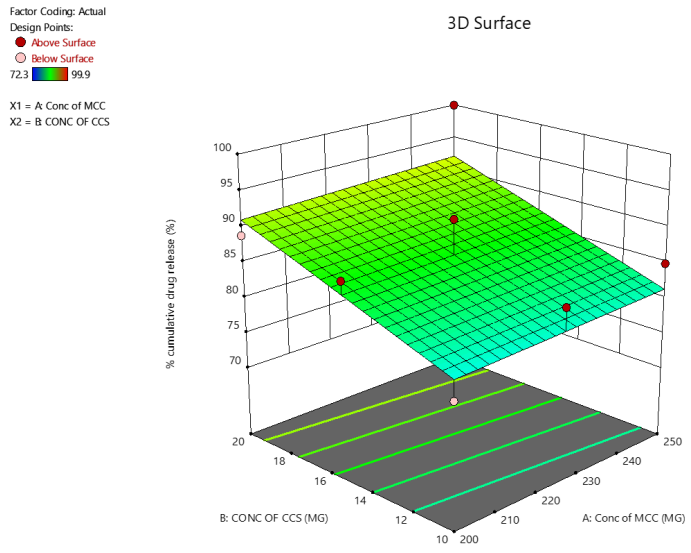

Figure 3E: Response surface plot showing the influence of amount of MCC (X1) and super disintegrant (CCS) (X2) on a Cumulative % drug release in 40 mins.

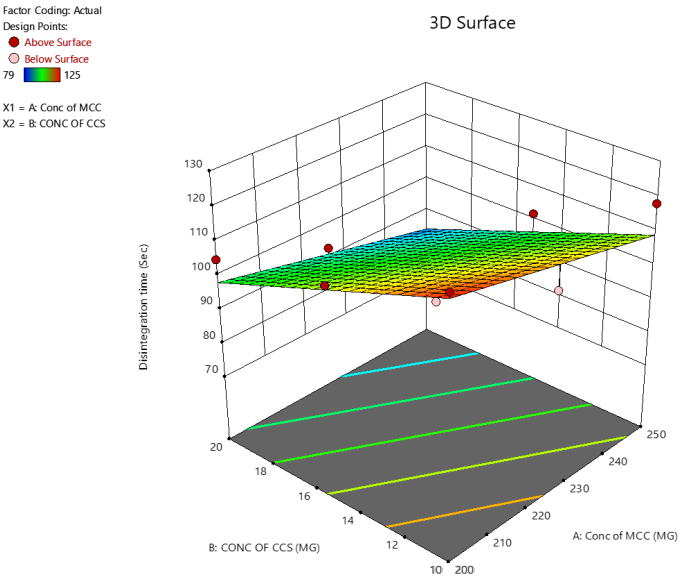

Figure 3F: Response surface plot showing the influence of amount of MCC (X1) and super disintegrant (CCS) (X2) on a Disintegration time (Sec).

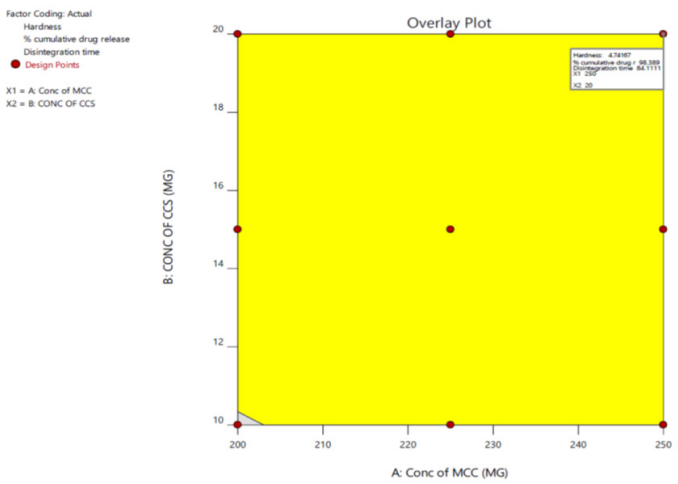

Figure 3G: Overlay Plot showing the influence of amount of MCC (X1) and super disintegrant (CCS) (X2) on Hardness (Kg/cm2),Cumulative % drug release in 40 mins , Disintegration time (Sec).

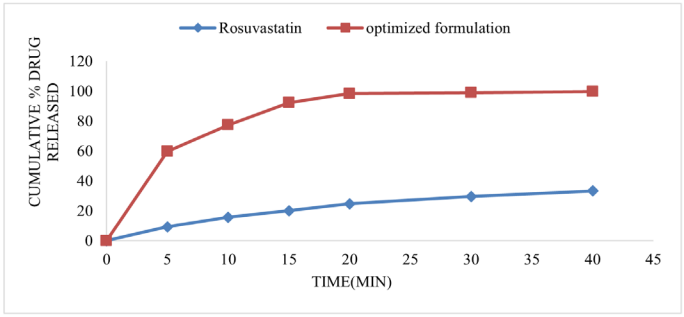

Figure 4: Comparative dissolution profile of optimized Rosuvastatin SNEDDS loaded tablet formulation and pure drug.

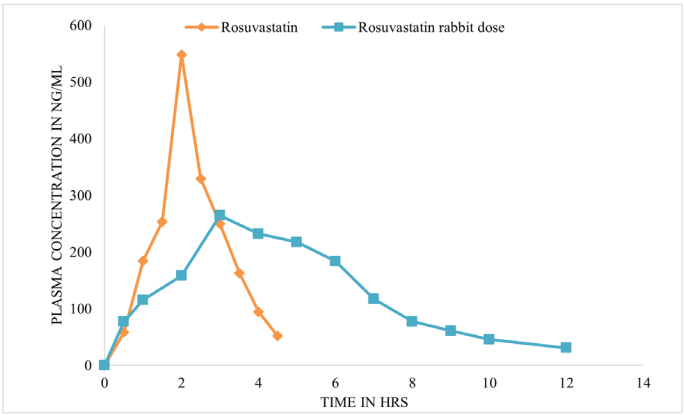

Figure 5: Comparative mean plasma concentration vs. time profiles of Rosuvastatin.

reduced interfacial tension, increased interfacial area, lowered the free energy of the system and formed thermodynamically stable spontaneous dispersion. More it was observed that incorporation of co-surfactant egg lecithin within the self-emulsifying region increased the spontaneity of the self-emulsifying process. The higher surfactant and co-surfactant levels in C15 therefore resulted in the smallest particle size. The higher surfactant and co-surfactant levels in C15 led to greater charge on the oil droplets and more stable nanoemulsion, as indicated by the most negative zeta potential. A polydispersity index under 0.4 indicated uniform droplet size distribution. Viscosity studies showed that lower-viscosity SNEDDS formed o/w nanoemulsions with Newtonian flow. Drug release studies showed faster release from SNEDDS than pure Rosuvastatin due to the drug's dissolved state in SNEDDS. Formulation C15 showed the fastest release due to lower oil and higher surfactant concentrations, enabling rapid emulsification into finer droplets. Drug release correlated with droplet size. The larger surface area of nano-sized droplets enabled faster diffusion of solubilized Rosuvastatin from SNEDDS to the

dissolution medium. Statistical optimization is advantageous in developing of S-SNEDDS is satisfactory and efficient. It provided the information regarding the relationship between controllable (independent variables) and dependent variables quality of the formulation. Based on goodness of fit model, indicated a good correlation between the independent and dependent variables. The values of Prob>F (less than 0.05) for all the responses indicated the significance of the models. The *in vivo* studies showed that pure Rosuvastatin achieved maximum plasma concentration, while the RRSV1 formulation achieved maximum AUC. The lower AUC for pure Rosuvastatin may be due to rapid absorption and elimination from the body. T_{max} increased for the formulation. Absorption was more rapid for the pure drug than the formulation. The $t_{1/2}$ for RRSV1 remained within acceptable limits. All of these parameters indicate that the optimized RRSV1 formulation exhibited better release even in rabbits.

CONCLUSION

The research established that the SNEDDS approach facilitates greater solubilization and bioavailability of Rosuvastatin. The optimized RRSV1 SNEDDS formulation demonstrated improved stability, dispersion, and drug release compared to pure Rosuvastatin. Pharmacokinetic studies in rabbits confirmed that RRSV1 had higher bioavailability than pure Rosuvastatin. While further studies are required to assess the safety and efficacy of RRSV1 in humans, the results suggest that the SNEDDS approach could enable effective Rosuvastatin treatments for hyperlipidemia.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

SNEDDS: Self nano emulsifying drug delivery systems; **Capmul MCM:** Capmul Mono- diglyceride of medium chain fatty acids; **HLB:** Hydrophilic lipophilic balance; **PEG 400, 200:** Polyethylene glycol 400, 200; **UV:** Ultra violet; **NE:** Nano emulsion; **S_{mix}:** Surfactant-co-surfactant mixture; **PDI:** Polydispersity index; **SEM:** Scanning electron microscopy; **S-SNEDDS:** Solid-Self nano emulsifying drug delivery systems; **MCC:** Microcrystalline cellulose; **CCS:** Cross Carmellose sodium; **AUC:** Area under the curve; **C_{max}:** Maximum plasma drug Concentration; **$t_{1/2}$:** half-life; **RSV1:** Rosuvastatin; **RRSV1:** Rabbit dose of Rosuvastatin.

SUMMARY

In vitro drug release studies of the optimized formulation (RSV1) reveals that the drug release obeys first order kinetics followed by non-Fickian mechanism. For *in vivo* studies the tablets size was reduced to rabbit's dose. Drug release from the tablets (RRSV1) were higher when compared with the pure drug in healthy rabbits indicated by maintaining drug-plasma levels up to 12 h. There was difference in AUC values for optimized formulations and pure drug indicating significant difference in absorption. Thus, indicating the increased bioavailability for Rosuvastatin.

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