

## Original Research Article

# Development and Evaluation of Solid Self Nano-Emulsifying Formulation of Rosuvastatin Calcium for Improved Bioavailability

Nilesh S Kulkarni<sup>1\*</sup>, Nisharani S Ranpise<sup>2</sup> and Govind Mohan<sup>1</sup>

<sup>1</sup>Institute of Pharmacy, NIMS University, Jaipur, Rajasthan, <sup>2</sup>Department of Pharmaceutics, Sinhgad College of Pharmacy, Vadgaon (Bk.), Pune, Maharashtra, India

\*For correspondence: **Email:** [nileshpcist@gmail.com](mailto:nileshpcist@gmail.com)

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### Abstract

**Purpose:** To develop rosuvastatin calcium-loaded self-nanoemulsifying powder for improved oral delivery of the drug.

**Methods:** Solubility study was carried out in different oils, surfactants and co-surfactants. Based on the solubility study, liquid formulations were prepared using LAS/Capryol 90: Maisine 35-1 as oil phase and Tween 20 with Lutrol E400 as surfactant mixture (Smix). The liquid formulations were adsorbed onto Aerosil 200 in a ratio of 1: 0.25 % w/w to convert them into a solid form. The formulations were evaluated for globule size, zeta potential, and emulsion properties. Transmittance study, scanning electron microscopy, and in-vitro dissolution studies were carried out. Biochemical studies were carried out using a triton-induced hyperlipidemia model in Wistar rats.

**Results:** The developed formulations exhibited some desirable characteristics of self-emulsifying systems with nano-sized globules in the range 119.8 to 228.9 nm, rapid emulsification in approximately 60 s and transmittance of close to 100 %. In-vitro dissolution studies on the developed formulations indicate a 4-fold increase in drug release in 10 min, compared to the pure drug (ROC) while pharmacodynamic data showed significant improvement in oral bioavailability compared to the pure drug.

**Conclusion:** The developed formulation containing the oils, LAS and combination of capryol 90 with Maisine 35-1, has the capability to improve the solubility and bioavailability of rosuvastatin calcium when formulated as a self-nanoemulsifying product.

**Keywords:** Rosuvastatin, Particle size, Zeta potential, Nanoemulsion, Oral bioavailability, Hyperlipidemia, Pharmacodynamics, Surfactants, Co-surfactants

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## INTRODUCTION

Rosuvastatin calcium (ROC) is a synthetic lipid-lowering agent used for oral administration. The IUPAC name of ROC is his [(E)-7-4(4-fluorophenyl)-6-isopropyl-2 [methyl (methyl sulfonyl) amino] pyrimidin-5-yl] (3 R, 5 S)-3-5-duhydroxyhept-6-enoic acid] calcium salt], which is slightly soluble in water. The available statins

have extensive first-pass metabolism [1]. First pass hepatic metabolism is responsible for the poor bioavailability of ROC. Various approaches, includes solid dispersion [2], complexation [3], have been reported to overcome solubility and bioavailability problems. There is increased interest in the development of emulsion type of dosage forms; lipid-based self-micro emulsifying drug delivery system (SMEDDS) is considered to

be promising technology to improve rate and extent of absorption of poorly or slightly water soluble drugs to improve bioavailability [4,5].

SMEDDS is defined as isotropic mixtures of natural or synthetic oils, surfactants, one or more hydrophilic solvents and co-solvents/surfactants that have a unique ability of forming fine oil-in-water (o/w) micro emulsions upon mild agitation followed by dilution in aqueous medium and formed emulsion have particle size in the range of 1 to 200 nm [6,7]. Thus, for drugs with solubility and bioavailability issues, these systems may offer the advantages of improvement of rate and extent of absorption, and thus result in improved bioavailability. Since liquid SMEDDS are thermodynamically unstable, to achieve improved stability, self-emulsifying preparations are generally prepared as a solid form [8].

The objective of the study was to prepare a solid self-nanoemulsifying dosage form of ROC to improve its bioavailability using novel, less costly technique, i.e., adsorption to a solid carrier technique

## EXPERIMENTAL

### Materials

Sefsol 228 (propylene glycol dicaprylate) and HCO 40 (PEG 40 hydrogenated castor oil) were received as gifts from Barnet Product Corporation, NJ. Maisine 35-1 (glycerol monolinoleate), Capryol 90 (propylene glycol monocapryl), Cremophore RH 40 (polyoxyl 40 hydrogenated castor oil), Gelucire 44/14 (saturated polyglycolized glycerides) and Lutrol E400 (polyethylene glycol 8) were gifts from BASF, India, LAS (PEG-8-caprylic glycerides), Transcutol, Lauroglycol 90 (propylene glycol monolaurate) were gift samples from Gattefosse India P. Ltd. Captex 200, Captex 355 (triglycerides of caprylic/capric acids) was a gift from Abitech WI. Rosuvastatin calcium was purchased from Balaji Drugs, Surat, India. Olive oil, tween 20, ethyl oleate, propylene glycol and castor oil were analytical grade.

### Determination of solubility of rosuvastatin calcium

Excess amount of ROC was added to 20 ml of distilled water. The suspension was equilibrated on a mechanical shaker for 24 h at 25 °C and resulting suspensions were filtered through 0.5 µm Whatman filter paper no. 1. The filtrate (0.1 ml) was diluted with 10 ml of distilled water to

determine the dissolved amount of ROC using UV visible spectrophotometer (Jasco V-505, Japan) at 241 nm.

### Determination of rosuvastatin calcium solubility

Excess amount of ROC was added to 3 ml of different oils (Sefsol 228, HCO 40, Maisine 35-1, LAS, ethyl oleate, olive oil, castor oil, Capryol 90, Gelucire 44/14), surfactants (Tween 20, Lauroglycol and Cremophore RH 40) and co-surfactants (Lutrol E-400, propylene glycol and Transcutol). In each case, the suspension was sonicated for 15 min and heated on a water bath maintained at 40 °C to allow solubilization of ROC. The resulting suspension was agitated on a rotary shaker for 24 h to achieve equilibration. Thereafter, the suspension was centrifuged at 4000 rpm for 15 min. The supernatant suitably diluted with methanol and the dissolved concentration of ROC was determined spectrophotometrically at 241 nm.

### Identification of micro-emulsion region

From the solubility study, oil, surfactant and co-surfactant were selected to construct a pseudo ternary phase diagram. Maisine 35-1, Capryol 90, LAS were selected as oil phase; Tween 20 and Lutrol E 400 were selected as surfactant and co-surfactants respectively. From pseudo-ternary phase diagram, a stable micro-emulsion zone was identified. For the identification of a micro emulsion zone, surfactant to co-surfactant ratio (Smix) was kept at 1:1. The Smix concentration was increased from 1 to 9 by keeping oil phase as constant. Oil and surfactant mixture were mixed at a ratio of 1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:8 and 1:9, respectively.

Furthermore, study was carried out by keeping Smix as constant 1:1. Oil and surfactant mixture was mixed at a ratio of 1:1, 2:1, 3:1, 4:1, respectively [9]. To each of the mixture distilled water was added drop wise until the first sign of turbidity occurred; the solution was allowed to equilibrate and if turbidity changed to a clear solution again, excess amount of water was added to the observed turbidity.

### Preparation of liquid L-SMEDDS and S-SMEDDS

Based on the phase diagram, oil and Smix ratio were selected as vehicle at which wide micro emulsion region is observed were selected as the vehicle for the formulation of L-SMEDDS. ROC was added to the oil phase and sonicated for 10 min. To it, surfactant and co-surfactant

were added in the proportions shown in Table 1. The resultant mixtures were heated over a water bath maintained at 40°C for 10 min to facilitate solubilization of ROC, and vortexed for 15 min until ROC was completely dissolved.

### Conversion of Liquid-SMEDDS to Solid-SMEDDS

Based on the preliminary evaluation, liquid formulations containing LAS/ Capryol 90: Maisine 35-1 with Tween 20: Lutrol E 400 was selected for conversion into solid formulation.

S-SMEDD system was prepared by addition of L-SMEDD to aerosil-200 in 1:0.25 % w/w proportion. L-SMEDDS was added drop wise onto aerosil-200 in a porcelain dish to get uniform distribution of drug and dried at room temperature.

### Evaluation of L-SMEDDS and S-SMEDDS

#### Drug content

L-SMEDDS ( L 1 to L 4) and S-SMEDDS ( S 1 and S 2) equivalent to 10 mg were dissolved in 10 ml of methanol in 10 ml volumetric flask separately and suitably diluted with methanol to determine ROC content at 241 nm spectrophotometrically.

#### Assessment of transmittance and reconstitution

L-SMEDDS (L 1 to L 4) and S-SMEDDS (S 1 and S 2) formulations (equivalent to 10 mg of ROC) were diluted with 100 ml of distilled water maintained at 37 ± 2 °C and content was mixed gently using magnetic stirrer, and emulsion droplet size was observed with respect to time. Reconstitution property was evaluated qualitatively as good when clear microemulsion formed, or bad, if turbid or milky emulsion formed after cessation of stirring. For the resultant solutions, percent transmittance was determined

spectrophotometrically at 638.2 nm using distilled water as blank.

#### Assessment of self-emulsification and precipitation

It was performed by drop wise addition of pre-concentrate (L-SMEDDS), One ml of formulation was added to 250 ml of distilled water maintained at 37 ± 0.5 °C with stirring of 50 rpm. Precipitation was evaluated by visual inspection of resulting emulsion after 24 h. Based on precipitation study; formulations were categorized as Grade A Clear (transparent or transparent with bluish tinge), Grade B not clear (turbid), Grade C Stable (no precipitation at the end of 24 h), Grade D Unstable (showing precipitation within 24 h).

#### Robustness to dilution

L-SMEDDS (L 1 to L 4) and S-SMEDDS (S 1 and S 2) formulations (equivalent to 10 mg of ROC) were added to 100 ml of distilled water. The resulting solutions were observed for phase separation for 12 h and 24 h.

#### In vitro dissolution studies of L-SMEDDS and S-SMEDDS

*In-vitro* dissolution study was carried out using USP type II apparatus operated at 50 rpm. L-SMEDDS and S-SMEDDS containing 10 mg equivalent of ROC and plain ROC were filled in size 0 capsule shells. The capsule was added to 900 ml of distilled water as dissolution medium maintained at 37± 0.5 °C. Aliquots (10 ml) were withdrawn at predetermined time intervals for 60 min and analyzed for dissolved ROC content spectrophotometrically at 241 nm.

#### Particle size and zeta potential measurement

One ml (Equivalent to 10 mg) of L-SMEDDS containing LAS, Capryol 90: Maisine 35-1 and 10 mg equivalent of S-SMEDDS containing LAS, Capryol 90: Maisine 35-1 were diluted/reconstituted with 100 ml of distilled water.

**Table 1:** Composition of L-SMEDDS and S-SMEDDS

Formulation	Rosuvastatin calcium (mg)	Maisine 35-1 (%)	Capryol 90 (%)	Maisine:35-1: Capryol 90 (%)	LAS (%)	Tween 20 (%)	Lutrol E 400 (%)
L 1	1000	15	-	-	-	21	21
L 2	1000	-	15	-	-	25	25
L 3	1000	-	-	15	-	21	21
L 4	1000	-	-	-	48	11	11
S 1	1000	-	-	-	48	11	11
S 2	1000	-	-	15	-	21	21

The resulting emulsions were subjected to determination of globule size and zeta potential respectively using malvern zetasizer.

### Scanning electron microscopy

The surface morphology of S-SMEDDS containing LAS as well as plain ROC powder were investigated by S-4100 scanning electron microscope (S-4100 Hitachi, Japan) at 500 X at 5 kv.

### Biochemical studies

The protocol of the animal study was approved by the institutional animal ethical committee (IAEC Protocol Approval no. 1036/a/07/CPCESA/IAEC/12-13/E-4). The animals were handled and maintained as per the guidelines provided by Committee for the Purpose of Control and Supervision on Experiments on Animals, and also Organization for Economic Co-operation and Development (OECD) guidelines were adhered to the study [10].

The test sought to compare the lipid lowering potential of ROC in L-SMEDDS and S-SMEDDS formulations. Triton-induced hyperlipidemia model in Wistar rats was used. The lipid lowering potential of plain ROC was compared with L-SMEDDS and S-SMEDDS formulations.

The animals were divided into seven groups of six animals each as follows: Group I - normal, Group II - control, Group III - L-SMEDDS containing Maisine 35-1: Capryol 90 as oil (L 3), Group IV - L-SMEDDS containing LAS as oil (L 4), Group V - plain ROC, and Group VI - S-SMEDDS containing Maisine 35-1: Capryol 90 (S 2), and Group VII - S-SMEDDS containing LAS (S 1).

Triton X 100 (100 mg/kg) was administered intraperitoneally to each animal. Blood samples were withdrawn after 72 h after triton injection by retro orbital route under light ether anesthesia and analyzed for total cholesterol (TC), total triglycerides (TG), high density lipoprotein (HDL), low density lipoprotein (LDL) and very low density lipoprotein (V-LDL) using a diagnostic kit provided by Accozyne (India).

After that dose equivalent to 10 mg/kg were administered to groups I, II to VII respectively. The blood samples were withdrawn after 24 h and analyzed for TC, TG, HDL and V-LDL concentration. The comparison was carried out between the control and test groups [11].

### Statistical analysis

All values were expressed as a mean  $\pm$  standard deviation (SD, n = 3). Comparison between the groups was made by one-way analysis of variance (ANOVA) followed by Turkey's test using Graph Pad InStat version 2008. Differences between groups were considered significant at  $p < 0.05$ .

## RESULTS

### Solubility of rosuvastatin calcium

The solubility of ROC was 0.32 mg/ml in distilled water.

### Solubility of rosuvastatin calcium in various liquids

Maisine 35-1, Capryol 90 and LAS showed highest solubilizing capacity for rosuvastatin calcium (Table 2).

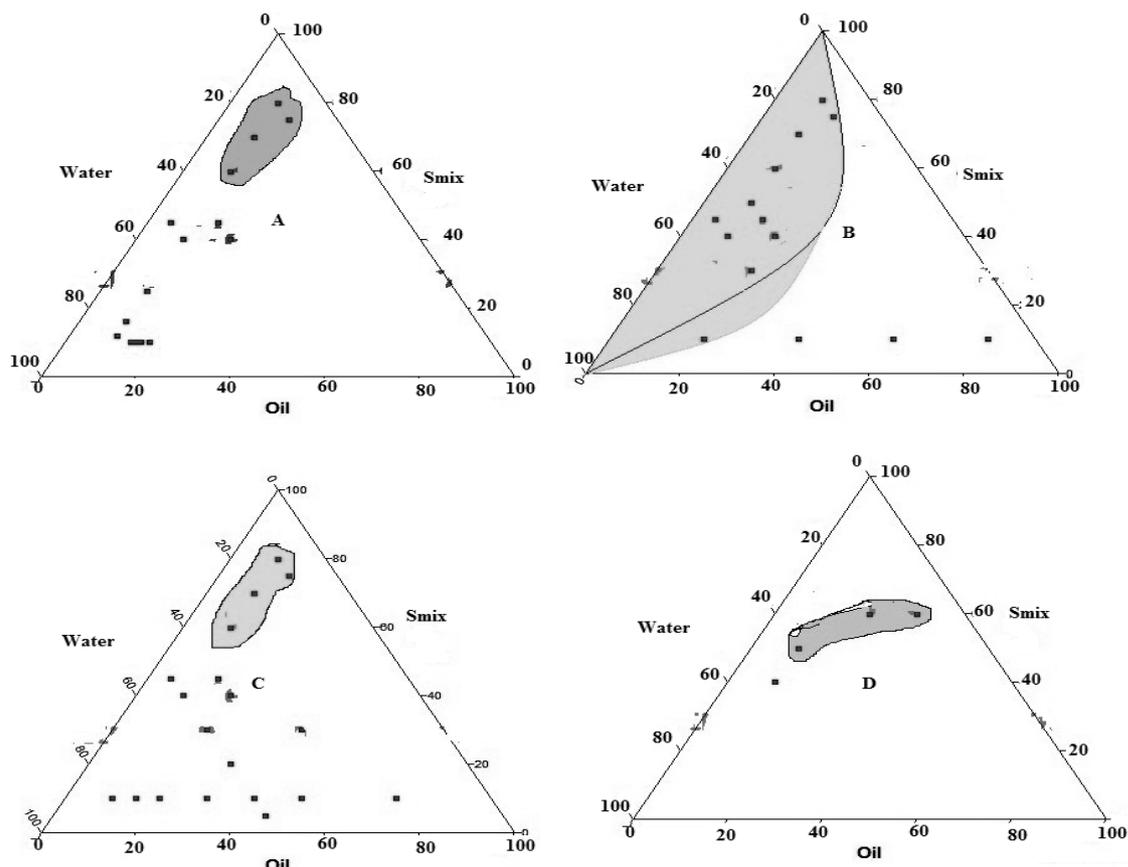
**Table 2:** Solubility of rosuvastatin calcium in different oils (mean, n = 3)

Oils	Solubility (mg/ml)
Maisine 35-1	57.43
Capryol 90	27.33
LAS	44.22
Gelucire 44/14	18.34
Sefsol 228	0.40
HCO 40	8.56
Castor oil	0.78
Olive oil	7.08
Ethyl oleate	1.30
Captex 200	0.049
Captex 355	0.21

Among surfactants, Tween 20 showed highest solubility (32.15 mg/ml) whereas solubility in lauroglycol (11.72 mg/ml) and Cremophore RH 40 (6.16 mg/ml) was found to be insignificant. Among co-surfactants, Lutrol E-400 showed highest solubility of 75.59 mg/ml whereas solubility in transcitol and propylene glycol was found to be 68.65 mg/ml and 23.72 mg/ml respectively.

### Identification of micro-emulsion zone

Self-microemulsifying system form fine oil in water emulsion upon gentle agitation when added to aqueous medium. Surfactant and co-surfactant gets preferentially adsorbed at interface, reducing the interfacial energy as well as providing mechanical barrier for coalescence.



**Figure 1:** Pseudo-ternary phase diagrams. A = Maisine 35-1, B = LAS, C = Capryol 90, D = Capryol 90: Maisine 35-1 as oil phase with Tween 20 and Lutrol E 400 as surfactant and co-surfactant at Smix ratio of 1:1 (mean n = 3)

As seen from the ternary plot (Figure 1), LAS gave a wider microemulsion region as compared to Capryol 90 and Maisine 35-1. Combinations of Capryol 90 and Maisine 35-1 resulted into increased oil concentration as that of individual oil. Thus LAS and Capryol 90: Maisine 35-1 were preferred vehicle with Tween 20 and Lutrol E 400 as surfactant and co-surfactant, respectively, for development of formulation. Based on the pseudo ternary phase diagram formulation were selected which has less % w/w concentration of Smix and greater % w/w of oil phase.

#### L-SMEDDS and S-SMEDDS characteristics

##### Drug content

The drug content of all the formulation was in the range of 95 to 105 %.

**Table 3:** Drug content and transmittance of L-SMEDDS and S-SMEDDS (Mean, n = 3)

Test Parameters	SMEDDS					
	L1	L2	L3	L4	S1	S2
Drug Content*	98.24	99.26	99.38	100.23	100.13	99.23
Percentage of Transmittance*	86.29	87.12	90.34	99.12	98.23	96.29

#### Transmittance of L-SMEDDS and S-SMEDDS, and reconstitution of S-SMEDDS

The transmittance values of L3, L4, S1 and S2 formulation above 90 % confirming the self-nanoemulsifying efficiency of SMEDDS (Table 3). The reconstitution of solid formulations was found to be spontaneous micro emulsification upon stirring and it was observed within 60 sec upon reconstitution and no sign of precipitation and milky appearance for the formed emulsion.

#### Self-emulsification and precipitation assessment

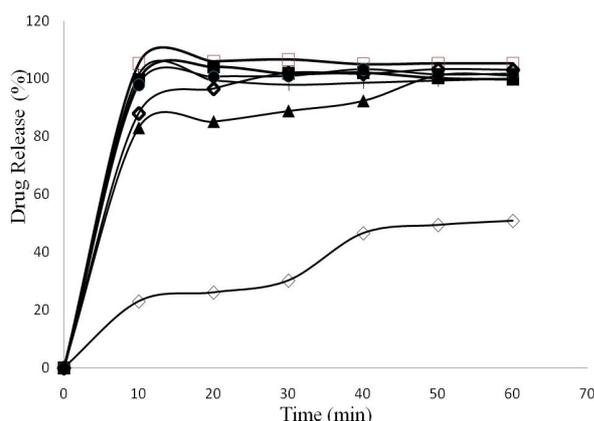
Among the liquid formulations L 1 to L 4, formulations L 3 and L 4 exhibited grade A type

of emulsion with self-emulsification time less than 1 min, whereas L 1 and L 2 formulation were categorized as grade D.

### Robustness to dilution

No phase separation was observed for preparations L 3, L 4, S 1, S 2 at the end of 24 h in distilled water whereas L 1 and L 2 formulations showed precipitation after 12 h.

### In-vitro dissolution profile



**Figure 2:** In-vitro dissolution profile. ◇ = plain ROC, ● = L 1 Formulation, + = L 2 formulation, ■ = L 3 formulation, □ = L 4 formulation, ◇ = s 1 formulation, ▲ = s 2 formulation (mean ± SD, n = 3)

The dissolution study showed that plain ROC showed poor release profile when compared to L-SMEDDS and S-SMEDDS. At the end of 60 min, 40 % of the drug was dissolved whereas more than 90 % drug was dissolved in distilled water from L-SMEDDS and S-SMEDDS formulations containing LAS and Capryol 90: Maisine 35-1 as oil (Figure 2).

### Globule size and zeta potential

For L3, L 4, S 1 and S 2 had z-average globule size diameter of 146.1, 119.8, 213.2 and 228.9 nm, respectively. Zeta potential of the formulations was found to be -4.93, -9.14, - 8.06 and -11.8 respectively. As L 1 and L 2 were categorized as unstable formulation and categorized as grade D formulation so they are excluded from the study.

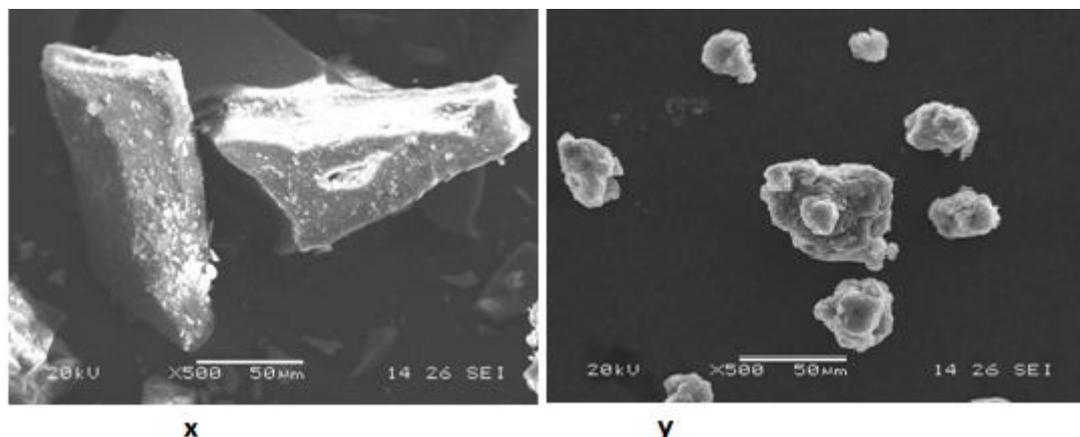
### Morphology of ROC and S-SMEDDS

The SEM micrograph of ROC and S-SMEDDS containing LAS were shown in Figure 3. The micrograph of Plain Rosuvastatin calcium appeared as crystalline (Figure 3, Part X). The SEM images of solid SMEDDS showed well-separated particles with no agglomeration (Figure 3, Part Y).

### Lipid profile

Triton is a non-ionic detergent that inhibits lipoprotein lipase; therefore it raises levels of serum lipids in experimental animals. A single injection of triton (100 mg/kg, i.p.) elevated TC, TG, LDL and V-LDL levels 2-fold, respectively, compared with the untreated group, whereas high density lipoprotein level decreased by up to 50 % in all groups, compared to an untreated control group ( $p > 0.05$ , Table 4).

At the end of 24 h of dosing, reduction in TC, TG, LDL and V-LDL levels was observed in all groups except normal group. Formulations containing LAS as oil showed greater reduction in elevated level of TC, TG, LDL and VLDL ( $p > 0.05$ , Table 4) compared to the formulations containing Maisine 35-1: Capryol 90 as oil.



**Figure 3:** Scanning electron micrograph of ROC (X) and S-SMEDDS containing LAS (Y)

**Table 4:** Blood TC, TG, HDL, LDL, V- LDL levels of groups after 72 h of Triton injection

Group	Treatment	TC	TG	HDL	LDL	VLDL
I	Normal	69.79±3.31	126.75±4.2	34.39±1.14	82.84±2.83	28.66±1.91
II	Control	131.77±2.6	184.41±8.8	17.34±2.26	139.68±2.31	75.16±4.92
III	L 3	129.46±3.02	188.69±4.92	17.87±2.01	138.29±2.54	70.32±4.68
IV	L 4	132.04±3.62	196.15±4.49	16.8±2.4	142.66±3.17	73.43±3.86
V	ROC	132.47±2.45	193.19±3.15	17.54±5.45	138.7±0.89	74.97±0.48
VI	S 2	133.18±6.28	187.59±4.79	18.72±1.99	139.1±2.72	74.46±3.87
VII	S 1	130.72±3.7	193.63±5.67	19.19±2.94	137.76±4.79	74.97±4.62

**Table 5:** Blood TC, TG, HDL, LDL, V- LDL levels of groups after 24 h of administration of ROC dose

Group	Treatment	TC	TG	HDL	LDL	VLDL
I	Normal	77.81±2.86	120.86±3.48	35.64±2.78	75.31±4.93	25.87±2.41
II	Control	131.51±2.47 <sup>c</sup>	174.3±8.21 <sup>c</sup>	16.24±1.9 <sup>c</sup>	153.72±4.77 <sup>c</sup>	64.47±2.01 <sup>c</sup>
III	L 3	75.86±3.82 <sup>t, l</sup>	120.8±2.92 <sup>t, l</sup>	39.01±1.3s5 <sup>t</sup>	92.81±6.09 <sup>t, k</sup>	25.76±2.18 <sup>t, k</sup>
IV	L 4	62.57±3.06 <sup>t, l</sup>	114.53±2.82 <sup>t, l</sup>	39.44±5.02 <sup>t</sup>	77.72±7.71 <sup>t, l</sup>	22.72±1.04 <sup>t, k</sup>
V	ROC	108.69±5.5 <sup>e</sup>	144.32±3.9 <sup>e</sup>	36.03±2.85 <sup>e</sup>	120.72±2.83 <sup>e</sup>	45.45±6.13 <sup>e</sup>
VI	S 2	80.56±2.62 <sup>t, l</sup>	122.2±2.9 <sup>t, l, l</sup>	38.5±4.16 <sup>t</sup>	93.14±6.00 <sup>t, l</sup>	26.45±2.89 <sup>t, k</sup>
VII	S 1	65.78±2.85 <sup>t, l</sup>	117.42±4.51 <sup>t, l</sup>	38.38±3.24 <sup>t</sup>	80.69±4.74 <sup>t, l</sup>	22.45±2.04 <sup>t, l</sup>

## DISCUSSION

All formulations of liquid and solid nano-emulsifying system with ROC gave stable clear micro emulsion region.

Drug content, which was in the range of 95 to 105 %, indicates good drug distribution in the selected vehicle. Transmittance values, being 90 to 100 %, indicate the micro emulsion was virtually transparent. With regard to emulsification, precipitation and robustness to dilution, precipitation was observed within 24 h for L 1 and L 2 formulations, and this may be attributed to the high concentration of surfactants in the formulations, indicates formulations are not stable. On the contrary, for L 3, L 4, S 1 and S 2 formulations, no precipitation was observed for 24 h. It indicates developed formulations were stable. Rapid reconstitution is required for the rapid absorption of drug from gastrointestinal environment. The solid formulations S 1 and S 2 showed rapid emulsification time of < 90 sec, which may lead to improved absorption of ROC from gastrointestinal tract since the drug is available in submicron size.

*In-vitro* dissolution data showed improvement in ROC solubility for all formulations compared with plain ROC. This may be attributed to increase in effective surface area through reduction in the mean diameter of globule size.

Globule sizes of formulations were in nano-meter range for formulations L 3, L 4, S 1 and S 2. The globule size of the emulsion is an important factor in self-emulsification process because it

determines rate and extent of drug dissolution and absorption of drug. The charge on the droplet is the property determined for assessment of absorption. The zeta potential for the L 3, L 4, S 1 and S 2 is negative; it is because of presence of fatty acids, it confirms formed emulsion is nano emulsion and was stable. The reported value of formulations was in negative between -4.93 to -11.8. The absolute value of zeta potential was lower than those values reported in the literature. This might be attributed to tween 20 and lutrol E 400, non-ionic surfactants which decreases the electrostatic repulsion between the particles and sterically stabilizes the system by forming a coat around their surface [12]. The SEM micrograph showed crystalline nature of ROC. It is not observed in solid SMEDDS micrograph suggesting that the drug is completely solubilized in a solid SMEDDS.

Clinical studies have demonstrated that ROC is the most effective drug in reducing low-density lipoprotein cholesterol [13].

Statins also have beneficial effects on other lipid parameters, including increase in high-density lipoprotein cholesterol levels and decrease in triglyceride levels, and are predominantly metabolized by cytochrome P450 [14]. Mixture of Capryol 90: Maisine 35-1 and LAS as oil phase respectively has the capability to minimize variability in absorption as well as to avoid first pass metabolism of ROC as it could produce more uniform drug concentration in the systemic circulation and avoids first pass metabolism,

which leads to improvement in bioavailability [15].

## CONCLUSION

An optimized self-nanoemulsifying formulation consisting of a mixture of Capryol 90: Maisine 35-1/ LAS as the oil phase with Tween 20: Lutrol 400 as surfactant exhibits spontaneous emulsification properties. The formulation shows better in-vitro release profile as well as superior lipid-lowering potential than plain ROC. Furthermore, Aerosil 200 is an effective carrier with high drug loading capacity for the administration of liquid drugs in solid dosage form.

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