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(RESEARCH ARTICLE)

Development and characterization of self micro emulsifying drug delivery system of rosavastatin

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Abstract

The present study was undertaken to enhance solubility and dissolution rate of rosuvastatin by formulating it as a self -micro emulsifying drug delivery system (SMEDDS). The SMEDDS were prepared by using castor oil and sesame oil as oils, Tween 80 as surfactant and PEG 200 as co-surfactant. The prepared SMEDDS were further evaluated for drug content, thermodynamic stability and *in vitro* drug release. Among all the formulations the drug release for F2 formulation was 99.70% in 120 min. So it was considered as the optimized formulation. The selected optimized F2 formulation was characterized by drug excipient compatibility using FTIR spectroscopy, scanning electron microscopy and globule size. The stability studies indicate that the formulated SMEDDS was stable for 60 days.

Keywords: Rosuvastatin; FTIR; SMEDDS; Tween80; PEG- 200; Ternary phase diagram; Globule size analysis

1. Introduction

In recent years, the formulation of poorly aqueous soluble drugs is a challenging job to scientist. Oral delivery of poorly aqueous soluble drugs is frequently associated with low bioavailability, high inter and intra–subject variability lack of dose proportionality. These class of Biopharmaceutical classification (BCS-II) II drugs. Here drug dissolution is the rate limiting step is the absorption process. To overcome this problem, different formulation approaches have been exploited including the use of surfactant, lipids, permeation enhancers and formation of salt, solid dispersion and colloidal vesicles like liposome. The most popular and commercially viable lipid based formulation approach for solving this problem is self-micro-emulsifying drug delivery system (SMEDDS) [1].

In modern drug discovery, various techniques are used to improve the bioavailability of those drugs like salt formation, pH change, β-cyclodextrines complex, micro-emulsion etc. Self-micro-emulsifying drug delivery (SMEDDS) is one of the methods for the improvement of oral bioavailability. SMEDDS are a class of emulsion that has received particular attention as a means of enhancing oral bioavailability of poorly absorbed drugs. These systems are essentially mixes of oil and surfactant (sometimes with added co-surfactant) that form emulsion on mixing with water with little or no energy input [2].

The main objective of the investigation is to formulate, optimize and stabilize SMEDDS containing rosavastatin with surfactants and co-surfactants. Rosavastatin is poorly soluble drug, SMEDDS are prepared to increase their solubility in gastric fluid and improve bioavailability.

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2. Material and methods

2.1. Materials

2.1.1. Chemicals

Rosuvastatin was gifted from Sun pharmaceutical Ltd, Mumbai, Castor oil (Color cone Asia Ltd., Verna, Goa), Sesame oil (MJ Biopharmaceuticals, Mumbai), PEG-200(MJ Biopharmaceuticals, Mumbai), Tween 80(MJ Biopharmaceuticals, Mumbai).

2.1.2. Instruments Used

UV-Visible Spectrophotometer obtained from (PG Instruments, T60), Weighing Balance (XB120A) (Essae-Teraoka ltd, DS-852j), Over Head Stirrer (Techno Scientific products, Bangalore), Over Head Stirrer (Techno Scientific products, Bangalore), Rheometer (DV-E) (Brooke Field Viscometer), Magnetic Stirrer (MB instruments, MB575, Delhi), Mechanical Stirrer (MB instruments, MB575, Delhi), Dissolution apparatus (DS 8000 Lab, India).

2.2. Methods

2.2.1. Solubility studies

Solubility of rosuvastatin was determined in various modified oils, surfactants, and co-surfactants. Two mL of each component was taken in screw cap vials with known quantity of excess drug. A vortex mixer (Spinix, India) was used to facilitate the solubilization. Sealed vials were kept on isothermal mechanical shaker at 40±2 °C for 72 hours. After equilibrium, each test tube was centrifuged at 6000 rpm for 20 min using a centrifuge (R-8C, Remi, India). The supernatant was filtered through membrane filter using 0.45 µm filter disk. The filtered solution was appropriately diluted with methanol, and UV absorbance was measured at 243 nm [10].

2.2.2. UV spectroscopy

The 10 mg of rosuvastatin was dissolved in 10 mL of 0.1 N HCl by slight shaking to get the concentration of (1000 µg/mL). 1 mL of this solution was taken and made up to 10 mL with 0.1 N HCl which gives 100 µg/mL concentration (stock solution). From the stock solution take 2.5 mL of the solution and make up to the mark with 0.1 N HCl to get the concentration of 25 µg/mL, this solution was analyzed in UV spectrophotometer of (model No. T60), in order to determine the absorption maxima.

For construction of calibration curve using 0.1 N HCl buffer, 10 mg of Rosuvastatin was dissolved in 10 mL of 0.1 N HCl by slight shaking (1000 µg/mL). 1 mL of this solution was taken and made up to 10 ml with 0.1 N HCl, which gives 100 µg/mL concentration (stock solution). From the stock solution, concentrations of 5, 10, 15, 20, 25 and 30 µg/mL in 0.1 N HCl were prepared. The absorbance of diluted solutions was measured at 292 nm and a standard plot was drawn using the data obtained. The correlation coefficient was calculated [4].

2.2.3. Emulsification studies

Emulsification studies were conducted to select the best surfactant and co-solvent from a range of co-solvents and surfactants that are used for oral drug delivery. The surfactant and co-solvent were mixed at a fixed ratio of 2:1. The oil to S–Co mixture ratio was 1:3, and the mixture was homogenized with the aid of gentle heat (30–40 °C) and vortexed for 2 min in a vortex mixer. 0.2 mL of the mixture was diluted with 200 mL of distilled water with gentle stirring on a magnetic stirrer. The ease of formation of emulsions was noted by noting the time required to give uniform emulsion. The resulting emulsions were observed visually for the relative turbidity [11].

2.2.4. Construction of pseudo ternary phase diagrams

Pseudo ternary phase diagrams were constructed using the water titration method. The surfactant and co-surfactant were mixed in different volume ratios (1:1, 2:1 and 3:1). Oil and S-mixture (S/Co-S) were mixed thoroughly in different volume ratios (9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8 and 1:9) in different test tubes. The mixture in each tube was mixed homogeneously using a vortex mixer until the oily liquid mixture was obtained at room temperature. Water was then added drop-by-drop at 0.05-mL increments using a pipette into each oily mixture. During the titration, samples were stirred vigorously for a sufficient length of time for homogenization and visually monitored against a dark background by illuminating the samples with white light. The concentrations of water at which the solutions became clear were noted down. A pseudo ternary phase diagram was prepared using Triplot free version [12- 13].

2.2.5. Preparation of SMEDDS

Rosuvastatin was added in the accurately weighed amount of oil into a screw-capped glass vial and heated in a water bath at 40°C. The surfactant and co-surfactant were added to the oily mix using positive displacement pipette and stirred with magnetic bar. The formulation was further sonicated (Ultrasonic Cleaner EN-30-US, Electroquip, India) for 15 min and stored at room temperature until its use in subsequent studies. Six SMEDDS formulations were prepared, and their self-emulsifying performance was compared. The composition of six formulations is shown in Table 1.

Table 1 Formulation of Rosuvastatin SMEDDS [14]

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Rosuvastatin(mg)	50	50	50	50	50	50
Castor oil(ml)	45	45	45	-	-	-
Sesame oil(ml)	-	-	-	45	45	45
Tween 80(ml)	175	125	75	175	125	75
PEG 200(ml)	75	125	175	75	125	175

2.2.6. Drug content

The total amount of the drug in the formulation was analyzed by dissolving the formulation in 10 mL ACN. This solution was vortexed for 10 min in a vortex mixture. The mixture was centrifuged at 5000 rpm for 5 min. Then, the supernatant was filtered through a Whatman filter paper. The filtrate was analyzed by UV after suitable dilution at 292 nm [15].

2.2.7. Thermodynamic stability studies

The objective of the thermodynamic stability was to evaluate the effect of temperature variation on the SMEDDS formulations. Rosuvastatin SMEDDS were centrifuged at 15,000 rpm for 15 min and the formulations were observed visually for phase separation. The formulations were subjected to freeze–thaw cycles (-5°C for 2 days followed by +40°C for 2 days). The samples were observed visually after the freeze–thaw cycles. Thermodynamically stable formulations were selected for further characterization [5].

2.2.8. Cloud point measurement

The formulations were compared for cloud point value. Each formulation was diluted with water in the ratio of 1:100 and placed in a water bath with a gradual increase in temperature. At the cloud point, drop in sample % transmittance was measured spectrophotometrically [6].

2.2.9. In vitro dissolution

Rosuvastatin SMEDDS was filled in a capsule shell and the in vitro release profile was taken in a USP apparatus I at 37 ± 0.5 °C, at 100 rpm, in 0.1 N HCl. At predetermined intervals, 5 mL of the medium was sampled and filtered through a Whatman filter paper. The resulting solution (1 mL) was mixed with 1 mL of acetonitrile, vortexed for 2 min and centrifuged at 10,000 rpm for 10 min. Then, 2ml of the supernatant layer was analyzed by UV spectrophotometer at 243 nm [15].

2.2.10. Characterization of SMEDDS

Drug –excipient compatibility study using FTIR spectroscopy

The physical compatibility between the pure drug and e used in the research was tested by Infra-Red (IR) spectroscopy. FTIR absorption spectra of pure drug and physical mixture were recorded in the range of 400-4000cm-1 by KBr disc method using FTIR spectrophotometer.

Scanning electron microscopy (SEM)

The samples were mounted on a specimen studies using double sided adhesive tape, and gold-palladium alloy of 120 Å Kness was coated on the sample using spatter coating unit (Model E5100 Polaron, UK) in an argon ambient of 8-10 pascal with plasma voltage about 2 Kv and discharge current about 20 mA. The sputtering was done for nearly 3 minutes to obtain uniform coating on the samples to enable good quality SEM images. The SEM operated at the low accelerating

voltage of about 15 Kv with the load current of about 80 mA. The condenser lens position was maintained between 4.4 – 5.1. The objective lens aperture has a diameter of 240 microns and the working distance WD = 39 mm.

Globule size analysis

The globule size, size distribution and zeta potential were analyzed by dynamic light scattering with a globule size apparatus (Malvern Zeta sizer version 6.11, United Kingdom). Liquid SMEDDS were diluted 250-times with 0.1 N HCL at 25 °C under gentle shaking. After equilibrium, the emulsions were filtered through a Whatman filter paper. The filtrates were analyzed by Zeta sizer [16].

2.2.11. Determination of the stability of the optimized formulation

Accelerated stability studies were also performed for determination of the shelf-life of the optimized formulations. The SMEDDS formulations were kept at three different temperatures and ambient humidity conditions (30±0.5, 40±0.5 and 50±0.5 °C) for 2 months. The samples were withdrawn at specified time intervals (0, 30, and 60 days) [18-19].

3. Results and discussion

3.1. Solubility

The results of solubility studies showed that, 0.1 N HCL solutions has more solubility when compared to water and 6.8 pH buffer solutions**.**

Table 2 Solubility studies of rosuvastatin

Sr. No.	Medium	Solubility (mg/ml)
1	Water	0.046±0.08
2	0.1 N HCl	0.225±0.29
3	6.8 pH buffer	0.174±0.12

Table 3 Emulsification studies

Oil	Surfactant	Co-surfactant	D.T.	%T
Castor oil	Tween 80(40:60)	PEG 200	20-45	71.09
Castor oil	Tween 80(30:70)	PEG 200	20-45	75.11
Castor oil	Tween 80(20:80)	PEG 200	0-20	87.50
Castor oil	Tween 80(10:90)	PEG 200	0-20	93.16
Sesame oil	Tween 80(40:60)	PEG 200	20-45	68.60
Sesame oil	Tween 80(30:70)	PEG 200	20-45	70.71
Sesame oil	Tween 80(20:80)	PEG 200	0-20	82.09
Sesame oil	Tween 80(10:90)	PEG 200	0-20	91.10

3.2. UV Spectroscopy

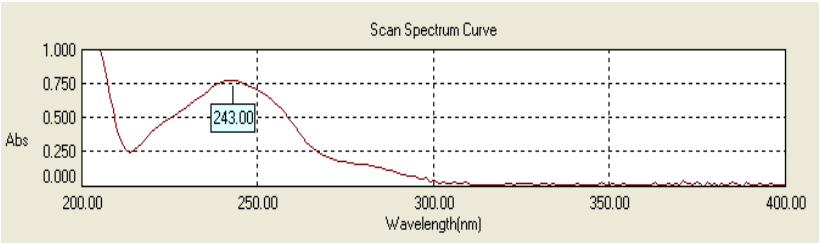

Figure 1 UV spectrum of rosuvastatin in 0.1N HCl buffer

The absorption maxima of rosuvasatin (λ-max) in 0.1 N HCl buffer is 243 nm.

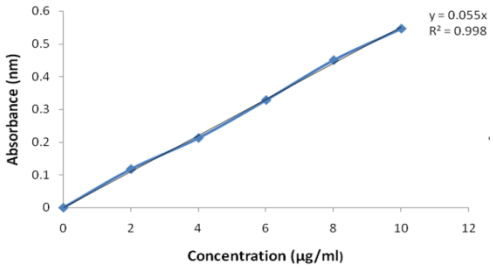

Figure 2 Calibration curve in 0.1N HCl Buffer

The linearity was found to be in the range of 2-10 µg/ml in 0.1 N HCL buffer and the method obeys Beer-lambert's law.

3.3. Construction of ternary phase diagram

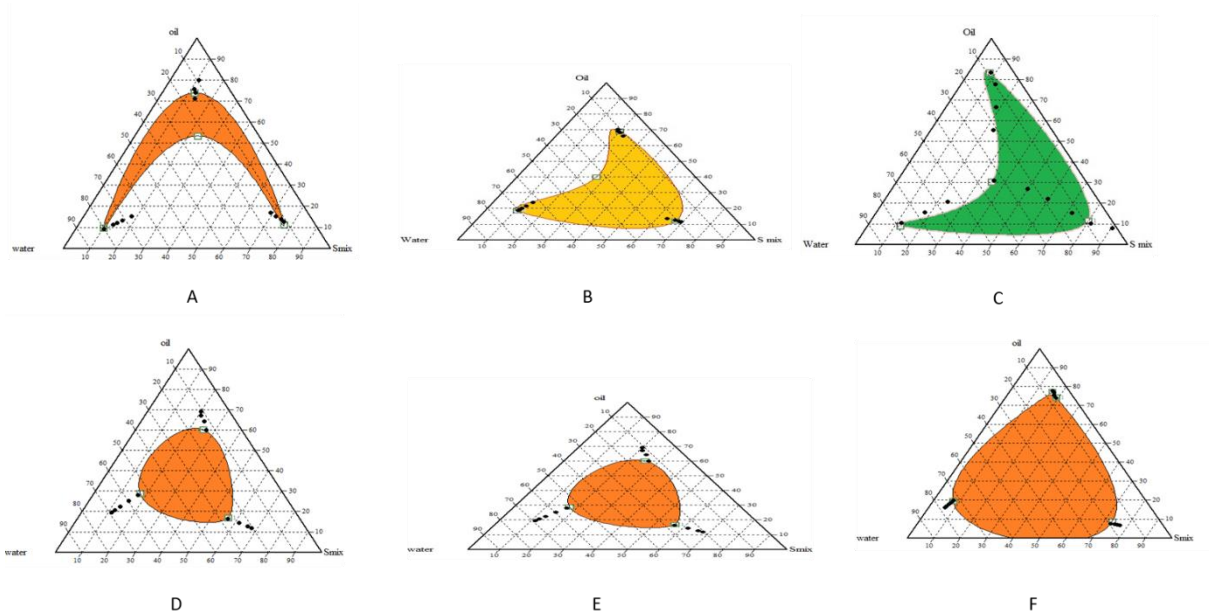

Figure 3 Pseudoternary phase diagrams of oil, S_{mix} and water
Ratio of (Oil: Surfactant) and S_{mix}[A- 1:1(9:1-1:9), B-1:1(1:9-9:1), C-2:1(1:9-9:1), D-2:1(9:1-1:9), E- 3:1(1:9-9:1) and F-3:1(9:1-1:9)].

The above mentioned figure 3 F in ternary phase diagram has got highest miscibility concentration compared to all other and found to be more stable concentration.

3.4. Drug content

The drug content of the formulations was found to be 96.28-98.78%.

Table 4 Drug content of SMEDDS formulations

Formulation code	Drug content
F1	96.21±0.28
F2	98.78±0.38
F3	97.68±0.12
F4	96.92±0.34
F5	98.52±0.02
F6	97.92±0.18

The drug content of the formulations was found to be 96.28-98.78%.

Table 5 Thermodynamic stability and cloud point of SMEDDS formulations

Formulation	Centrifugation test	Freeze thaw cycle	Cloud point (°c)
F1	No Phase Separation	No Phase Separation	71
F2	No Phase Separation	No Phase Separation	65
F3	No Phase Separation	No Phase Separation	69
F4	No Phase Separation	No Phase Separation	65
F5	No Phase Separation	No Phase Separation	76
F6	No Phase Separation	No Phase Separation	98

3.5. *In vitro* drug release

Among all the formulations the drug release for F2 formulation [rosuvastatin (5 mg), castor oil (45 ml), Tween 80 (125 ml), PEG200 (125 ml)] the drug release was 99.70% in 120 min. So it was considered as the optimized formulation.

Table 6 *In vitro* drug release of the formulated SMEDDS

Time (Min)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
5	83.87±0.12	93.81±0. 46	75.11±0.24	79.18±0.12	89.98±0.02	71.15±0.32
10	85.51±0.36	94.50±0.54	78.80±0.18	82.21±0.26	91.56±0.24	77.89±0.41
20	97.70±0.22	95.08±0.12	82.16±0.06	85.53±0.12	92.23±0.16	80.13±0.22
30	88.16±0.18	95.72±0.36	85.53±0.01	87.06±0.34	93.31±0.28	82.25±0.16
45	90.02±0.06	96.11±0.22	87.70±0.12	88.11±0.58	93.89±0.42	85.57±0.01
60	91.13±0.18	97.32±0.16	90.16±0.36	90.57±0.02	94.47±0.18	87.77±0.82
90	96.40±0.02	98.16±0.24	93.33±0.48	93.37±0.16	96.30±0.52	88.80±0.16
120	98.71±0.24	99.70±0.04	95.58±0.08	94.48±0.01	96.88±0.36	92.27±0.08

3.6. Drug excipient compatibility

Drug and excipients compatibility was confirmed by comparing spectra of FTIR analysis of pure drug with that of various excipients used in formulation.

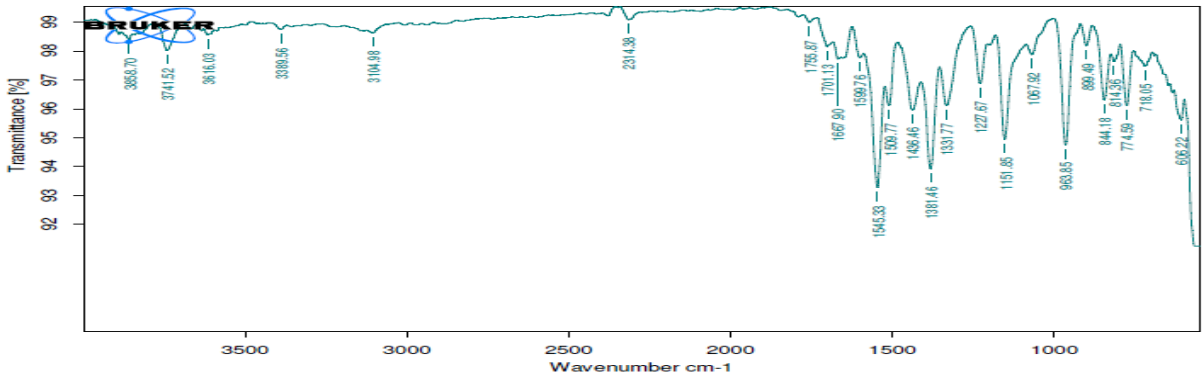

Figure 4 FTIR spectrum of pure rosuvastatin

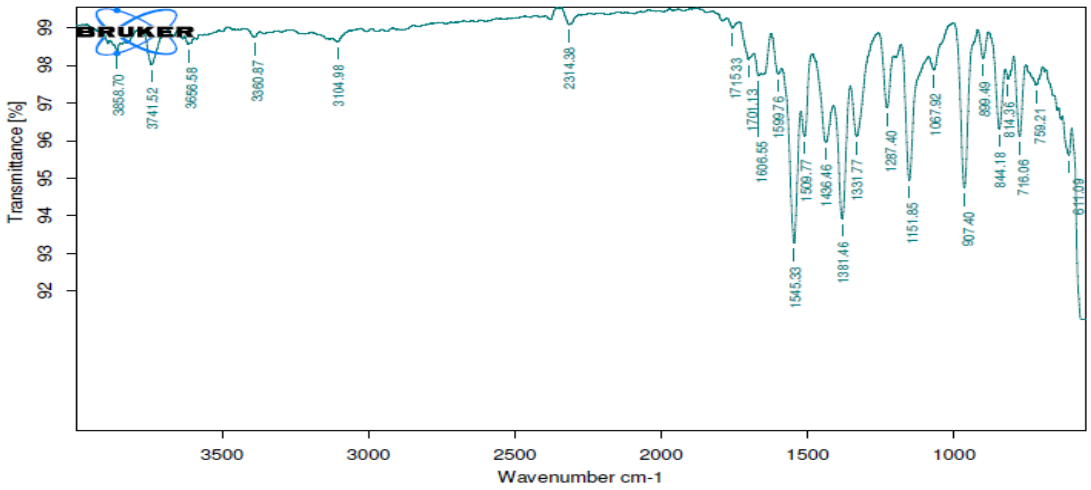

Figure 5 FTIR spectrum of rosuvastatin optimized formulation

FTIR Spectra of Rosuvastatin shows OH stretching at 3741.52 cm^{-1}, C=O stretching at 1151.85 1381.46 cm^{-1} shows s=o stretching. 907.41 cm^{-1} indicates C=C bending, 716.05 cm^{-1} indicates C-H bending. The FTIR Spectra of optimized formulation Shows OH stretching at 3741.52 cm^{-1}, C=O stretching at 1151.85 1381.46 cm^{-1} shows S=O stretching. 907.41 cm^{-1} indicates C=C bending, 716.05 cm^{-1} Indicates C-H bending.

Compatibility studies were performed using IR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and excipients were studied. The characteristic absorption peaks of were obtained as above and the drug is compatible with excipients.

3.7. Scanning Electron Microscopy (SEM)

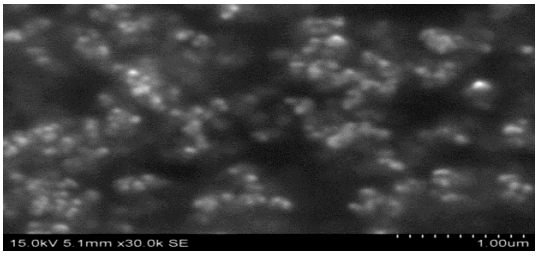

Figure 6 SEM globule size of optimized rosuvastatin formulation

Table 7 Globule size analysis of the SMEDDS Formulation (F1-F6)

Formulation	Goluble size (nm)
F1	121
F2	116
F3	118
F4	126
F5	122
F6	124

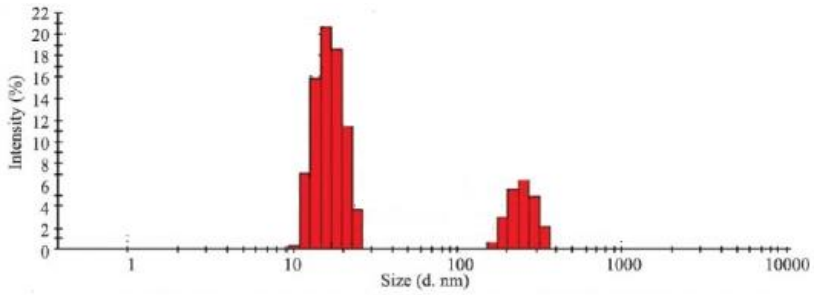

Figure 7 Globule size of optimized F2 formulation

3.8. Stability Studies

Table 8 *In vitro* drug release of the optimized formulation (F2)

Time (min)	Cumulative drug released (%± SD)		
	1st day	30th day	60th day
0	0	0	0
5	93.81±0. 46	92.96±0.52	93.02±0.42
10	94.50±0.54	93.51±0.65	94.86±0.51
20	95.08±0.12	94.26±0.18	95.28±0.08
30	95.72±0.36	94.89±0.42	95.12±0.34
45	96.11±0.22	95.82±0.29	96.08±0.16
60	97.32±0.16	96.28±0.20	97.52±0.02
90	98.16±0.24	97.92±0.27	98.29±0.21
120	99.70±0.04	98.86±0.06	99.20±0.01

From the above conducted stability studies of optimized formulation for about 60 days by comparing the results we can say that there is no change in the optimized formula on storage which indicates that it passes the stability studies.

4. Conclusion

In the present study, SMEDDS of rosuvastatin were prepared by using oils, surfactants and co-surfactants like Castor oil, Sesame oil, PEG-200 and Tween 80. Among various six formulations (F1 to F6), F2 was found to be the best formulation with castor oil. The FTIR study of pure drug and physical mixture of drug and excipients revealed that there was no interaction between drug and polymers. The globule size of the SMEDDS formulations was found to be in the range of 113-128nm.The stability studies indicates the optimized formulation has stability for time period of 60days. Further studies are also conducted for *in vivo* determination studies.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors have declared that no conflict of interest exists among them.

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