ORIGINAL ARTICLE

Formulation and Optimization of Fluvastatin Loaded Self-emulsifying Drug Delivery Systems

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Abstract

Introduction: The current research is aimed at formulating and evaluating fluvastatin self-nanoemulsifying drug delivery system (SNEDDS). **Materials and Methods:** Fluvastatin SNEDDS formulated using sefsol-218 (oil), Cremophor RH40 (surfactant), and propylene glycol (cosurfactant). The optimal concentration of excipients confirmed by self-emulsification region of pseudo-ternary phase diagram. Fluvastatin SNEDDS optimized by Box–Behnken design employing the study factors – the amount of sefsol-218 (a), Cremophor RH40 (b), and propylene glycol (c) and responses – droplet size (DS) (Y1), zeta potential (Y2), and cumulative percentage of drug release after 60 min (Y3). **Results:** The results revealed that FVT8 comprising 30% sefsol-218, 50% Cremophor RH40, and 35% propylene glycol have close agreement between predicted and observed values. The optimized formulation FVT8 exhibited enhanced drug release with minimum DS of 22.1 nm and zeta potential of –6.7 mV and maximum drug release 98.62%. The Fourier transform infrared studies indicated no significant interaction among the drug and formulation excipients used; SEM data revealed that particle size is in nanometer range with a Zeta potential indicating higher absorption and stability. **Conclusion:** Hence, the results revealed that the use of SNEDDS formulation for fluvastatin increased solubility, dissolution rate and has potential to enhance the bioavailability.

Key words: Box–Behnken design, fluvastatin, hypercholesterolemia, sefsol- 218, SNEDDS, solubility

INTRODUCTION

The majority of novel therapeutic moieties in recent years belong to BCS Classes II or IV that exhibit poor aqueous solubility which limit oral administration.[1,2] Incomplete drug dissolution and precipitation in the gastrointestinal fluids are major factors responsible for the lower bioavailability of the drug. Such drugs are potential candidates for the lipid-based drug delivery system that enhances their oral bioavailability.[3,4] Advancements in nanotechnology recommend the use of nano-based drug delivery systems to conquer these confines. These systems comprise polymeric nanoparticles, lipid-based systems, and noisome. Self-nanoemulsifying drug delivery system (SNEDDS) is one such approach that enhances the drug release and bioavailability. It is a lipid based system in which drug is carried in a lipid which is exclusively a medium chain triglyceride that spontaneously forms an emulsion on coming in contact with the body fluids, which is stabilized by surfactants that decrease the interfacial tension between the fluids and lipid enabling the drug to get disperse easily and more available for absorption, thus improving drug release and bioavailability.[5] SNEDDS also exhibits long-term stability, higher patient compliance, palatability, reduced drug dosage, ease of formulation, and ease of scale-up which make them superior to other formulation techniques.

Fluvastatin is used to treat hypercholesterolemia and prevents cardiovascular disease, which belongs to Class II drug in BCS classification which suffers with low aqueous solubility.[6] Fluvastatin belongs to statin class that reduces plasma cholesterol levels thus preventing from cardiovascular disease. It is synthetic HMG-CoA reductase inhibitors that catalyze the conversion of HMG-CoA to mevalonic acid which is rate-limiting step in cholesterol biosynthesis.[7]

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Recently, the response surface methodology (RSM), by proper experimental designs, has become widely used for formulation optimization. RSM is generally applied to experimental situations where several independent variables influence a response variable. The Box–Behnken design (BBD) is RSMs for understanding the effects of independent and dependent factors.[8,9]

The current research work is focused to formulate, evaluate, and optimize fluvastatin SNEDDS using BBD to improve solubility and dissolution rate.

MATERIALS AND METHODS

Materials

Fluvastatin is generously gifted by Aurobindo Pharma Limited, Hyderabad. Acrysol K140, acrysol EL135, acconon E, acconon CC400, acconon sorb20, Capmul GMO 50, Caprol PGE 860, Caprol ET, Cremophor EL, Cremophor RH40, Gelucire 44/14, Labrasol, Solutol HS15, tween 80, tween 20 and triton-9100, Capmul MCMC8, Lauroglycol 90, PEG 400, PG, EG, Plurol Oleique CC497, triacetin, Transcutol P, propylene Glycol, Capmul MCM, Captex 355, Capmul PG8, Capryol 90, Imwitor 742, IPM, Labrafil M2, Labrafac CC, Labrafac lipophile WL 1349, Maisine 35-1, Miglyol 812, Paceol, sefsol-218, olive oil, oleic acid, and castor oil procured from Gattefose France.

Methods

Selection of oil

The solubility of fluvastatin in each of the oils determined by mixing little excess of drug with the vehicles in sealed glass containers followed by vertexing for 5 min. The contents are later subjected to steady mixing over shaker bath for 72 h at 37°C at 300 rpm followed by centrifugation at 10,000 rpm for 10–12 min. Contents filtered and concentration of drug determined spectrophotometrically at 304 nm. The study executed in triplicate and mean value recorded.[10]

Selection of surfactant

0.03 g of various surfactants mixed with selected oil phase, vortexed for 60 s and 0.01 g of the mixture diluted with distilled water to obtain emulsion. The % transmittance (%T) of all samples analyzed at 304 nm. The study executed in triplicates and means values recorded.[11]

Selection of cosurfactant

A mixture of 300 ml of oil, 200 ml of optimized surfactant, and 100 ml of chosen cosurfactants were vortexed. Weighed amount of this mixture is diluted to form emulsion and evaluated for % transmittance at 304 nm .The study executed in triplicate and mean value recorded.[12]

Construction of pseudo-ternary phase diagram

From pseudo-ternary phase diagram the self-emulsify region under dilution and agitation can be identified by visual test method. Surfactant and cosurfactant (S_{mix}) mixed in diverse ratio (1:1, 1:2, 1:3, 2:1, 3:1, and 4:1). Further for each S_{mix}, oil, and specific S_{mix} of about 17 ratios ranging from 1:9 to 9:1. From the mixtures, 0.1 ml was taken in the beaker to which 100 ml water added, contents mixed using magnetic stirrer. The % transmittance of the formed emulsion was checked at 304 nm using UV visible spectrophotometer. The resultant emulsion was checked for clarity, phase separation and coalescence of oil droplets. Emulsions showing phase separation and coalescence were judged as unstable emulsions. Ternary phase plots drown by recognizing good self-emulsifying region with oil, S_{mix}, and water where each of them representing apices of triangle.[13]

Experimental design

Box–Behnken experiment design

A 3^3 BBD was used to explore and optimize the main effect, interaction effect, and quadratic effect of ingredients on the performance of SNEDDS. 17 randomized experimental runs for the selected independent variables, including five replicates at the center point (asterisk-marked) generated from a three factor, three-level BBD, and their corresponding responses. The variables that were chosen as dependent and independent are specified in Tables 1 and 2.

The BBD matrix was generated using Design Expert® software (Version7.0, Stat-Ease Inc., Silicon Valley, CA, USA), the second-order quadratic equation approximated using mathematical model:

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_4 X_1 X_2 + \beta_5 X_2 X_3 + \beta_6 X_1 X_3 + \beta_7 X_1^2 + \beta_8 X_2^2 + \beta_9 X_3^2$$

Where Y is the level of the measured response, β_0 is intercept, β_1 to β_9 are regression coefficients, X_1, X_2, and X_3 are main effects, X_1X_2, X_2X_3, and X_1X_3 represent the interaction among main effects, and X_1^2, X_2^2, and X_3^2 are the quadratic terms of the independent variables.[14]

Preparation of fluvastatin-loaded SNEDDS

Based on solubility study the oil phase (sefsol-218), surfactant (Cremophor RH40), and cosurfactant (propylene glycol) were chosen for formulation of fluvastatin SNEDDS. 40 mg of drug added to oil at 40 °C for complete dissolution followed by addition of surfactant and cosurfactant and sonicated for 60 min. Seventeen such formulations prepared and filled into size 0 gelatin capsule shells.[15]

Table 1: List of dependent and independent variables in in Box–Behnken design

Independent variable	Variables name	Units	Low(-1)	Middle (0)	High(+1)
A	Amount of sefsol-218	mg	10	20	30
B	Amount of Cremophor RH 40	mg	40	50	60
C	Amount of propylene glycol	mg	15	25	35
Dependent variable			**Goal**		
Y1	Droplet size	nm	Minimize		
Y2	Zeta potential	mV	Minimize		
Y3	% Cumulative drug released 60 min	%	Maximize		

Table 2: Box–Behnken design with observed responses

Run	Amount of Sefsol-218 (mg)	Amount of cremophor RH 40 (mg)	Amount of propylene glycol (mg)	Droplet size (nm)	Zeta potential (–mV)	% Cumulative drug released (%)
1	10	40	25	37.5	9.5	93.77
2	30	40	25	98.6	19.6	87.38
3	10	60	25	81.6	22.3	84.58
4	30	60	25	59.8	16.8	83.48
5	10	50	15	35.1	15.6	87.23
6	30	50	15	60.4	18.3	94.59
7	10	50	35	69.5	21.9	93.54
8	30	50	35	22.1	6.7	98.62
9	20	40	15	41.2	13.5	91.37
10	20	60	15	76.1	25.2	89.25
11	20	40	35	44.5	27.5	86.37
12	20	60	35	78.6	10.1	95.29
13	20	50	25	50.3	27.8	85.11
14	20	50	25	87.5	20.2	90.15
15	20	50	25	65.3	24.1	82.47
16	20	50	25	81.8	14.7	88.45
17	20	50	25	81.6	22.13	84.58

Physicochemical evaluation of fluvastatin SNEDDS

Developed fluvastatin SNEDDSs were physicochemically evaluated for droplet size (DS), Zeta potential (ZP), entrapment efficiency, drug content, and cumulative % drug release.

DS and zeta potential

The DS and ZP of all 17 formulations determined by Zetasizer Nano ZS90 dynamic light scattering particle size analyzer (Malvern, Worcestershire, UK) as per the method referred.[16]

Entrapment efficiency

A known quantity of SNEDDS mixed with 100 ml phosphate buffer (pH 7.4) and kept in dark for 24 h. The contents filtered, filtrate diluted, and analyzed for drug content at 304 nm.[17] Entrapment efficiency was calculated by formula

$$\text{Drug entrapment efficiency} = \frac{\text{Experimental drug content}}{\text{Theoretical drug content}} \times 100$$

Percentage drug content

All the 17 formulations of fluvastatin SNEDDS were analyzed for assay by dissolving accurately weighed samples in 10 ml carbinol and vortexed mixer for 10 min. Each of the samples filtered, and drug content of filtrate analyzed spectrophotometrically against blank at 304 nm.[18]

Cumulative percentage drug release (CDR) studies of fluvastatin SNEDDS

Drug release tests on each batch of the SNEDDS carried out using a USP I dissolution rate test apparatus at 50 rpm and temperature of 37 ± 0.5°C. An amount of the SNEDDS equal to 40 mg of drug filled into hard gelatin capsule (size no.0), placed in the dissolution medium containing 900 ml of phosphate buffer (pH 7.4). The analysis carried out as per referred method and samples analyzed using RP- HPLC UV detector at 304 nm.[19]

Characterization of fluvastatin SNEDDS

Fourier transform infrared (FTIR) spectroscopy

FTIR spectrophotometer (Shimadzu FTIR 8400S, Japan) was used to record the FTIR spectra of pure drug and drug loaded SNEDDS in 4000–400cm^{-1} range.[20]

Surface morphology

Scanning electron microscopy studies (JEOL JEM 2100 F, USA) were carried out by diluting the same with distilled water to 1000 times and then plunging on a 2% uranyl acetate solution stained carbon grid.[21]

Stability studies

Stability testing was conducted as per the ICH guidelines for 3 months in stability chamber (Thermo Lab, Mumbai). The samples were withdrawn at predetermined intervals 0, 30, 60, and 90 day's period. Various *in vitro* parameters such as drug content, entrapment efficiency, and *in vitro* release studies were evaluated.[22]

RESULTS AND DISCUSSION

Selection of formulation excipients

The solubility of fluvastatin studied in various excipients. Based on maximum solubility, the sefsol-218 as oil, Cremophor RH40 as surfactant and propylene glycol as cosurfactant were chosen [Figures 1-3]. Each value represents the mean ± SD (n = 3).

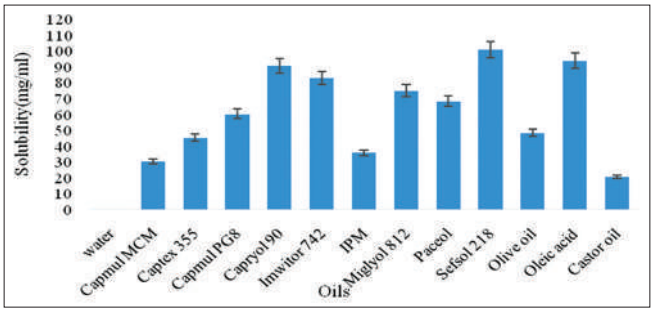

Figure 1: Solubility of fluvastatin (mg/ml) in various oils

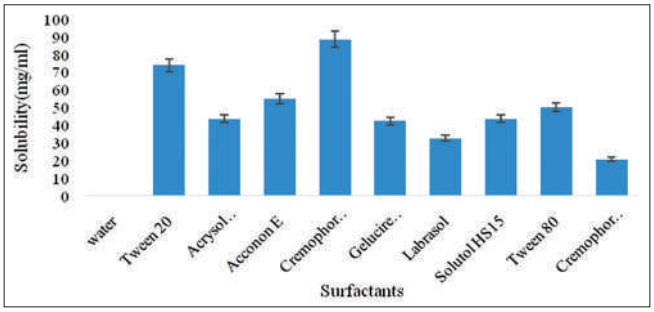

Figure 2: Solubility of fluvastatin (mg/ml) in various surfactants

Construction of pseudo-ternary phase diagram

Three component systems chosen for the fluvastatin SNEDDS preparation were sefsol-218 – Cremophor RH40 – propylene glycol [Figures 4-9]. The selection done based on preliminary trials performed. A pseudo-ternary phase diagram of the investigated quaternary system is plotted. Self-nanoemulsifying region that was termed efficient was shown as grey region of the diagram. Each component ranges on the basis of diagram selected as follows: 10% ≤ sefsol-218 ≤30%, 40% ≤ Cremophor RH40 ≤60%, and 15% ≤ propylene glycol ≤35%.

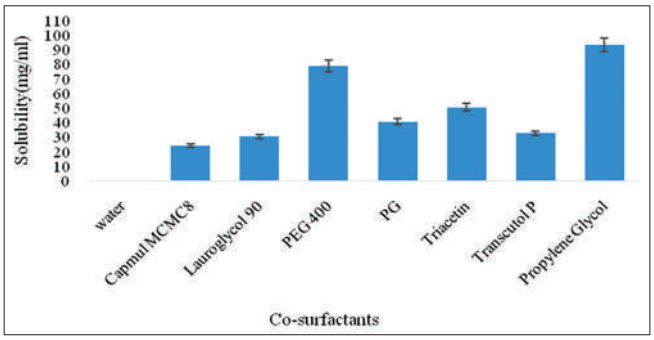

Figure 3: Solubility of fluvastatin (mg/ml) in various cosurfactants

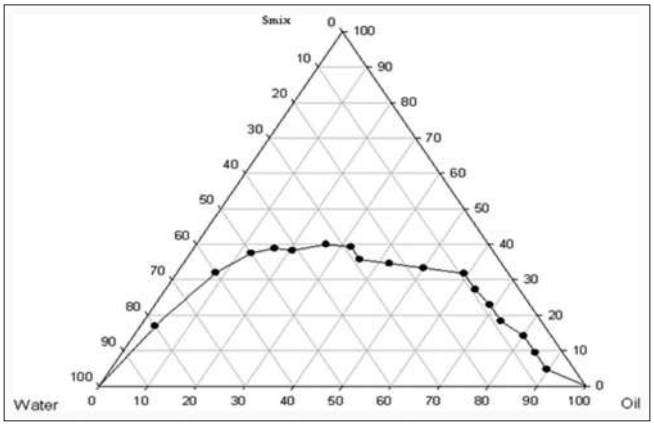

Figure 4: Pseudo-ternary graph of S_{mix} ratio1:1

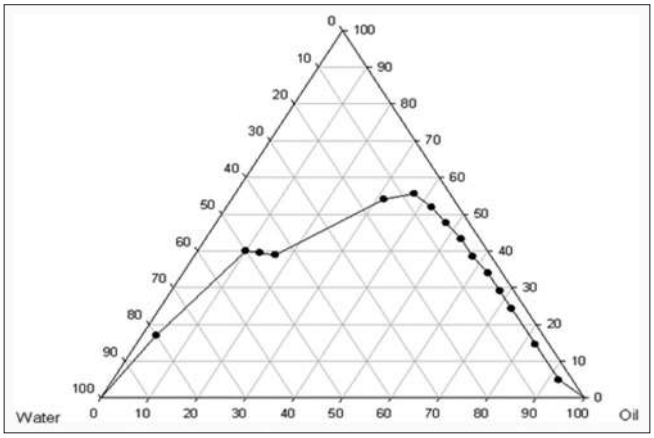

Figure 5: Pseudo-tertiary graph of S_{mix} ratio 1:2

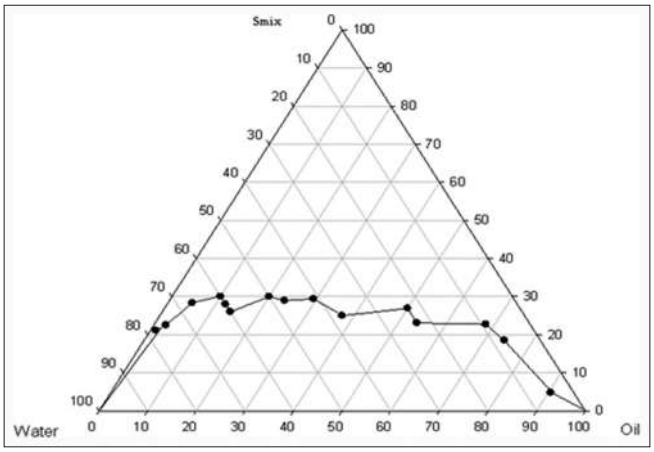

Figure 6: Pseudo-ternary graph of S_{mix} ratio1:3

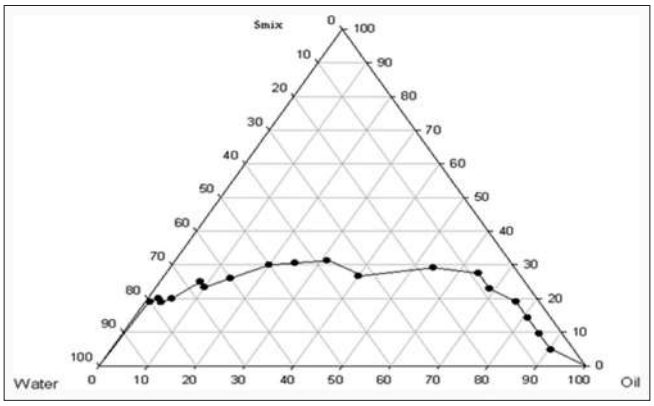

Figure 7: Pseudo-ternary graph of S_{mix} ratio2:1

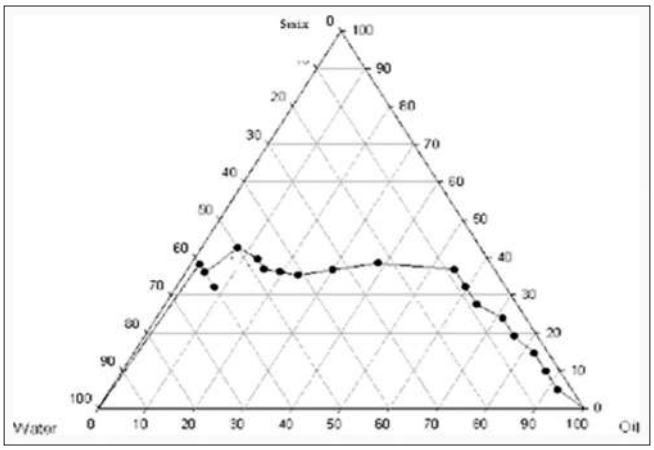

Figure 8: Pseudo-ternary graph of S_{mix} ratio 3:1

Physicochemical evaluation of fluvastatin SNEDDS

The drug loaded nanoparticles were sonicated before size and morphology determination. The DS of all fluvastatin SNEDDS ranged between 23.8 nm and 98.6 nm indicating nanoparticle range that facilitates rapid absorption as drug absorption by oral delivery is enhanced by decreasing the size of the particle to nanorange [Figure 10]. The ZP values of SNEDDS formulations ranged between –6.7 mV and –27.3mV indicating good stability [Table 2]. The ZP value >5 mV provides an excellent stability [Figure 11]. Figures 7 and 8 depict the optimized formulation's FVT8 DS and ZP of 23.8 and –6.7mV, respectively. The drug content of all formulations ranged between 96.19 ± 0.21 and 99.42 ± 0.15% with maximum value exhibited by FVT8. The entrapment efficiency of all 17 formulations varies between 93.18 ± 0.067 and 98.26 ± 0.079% with maximum value displayed by FVT8 [Table 3].

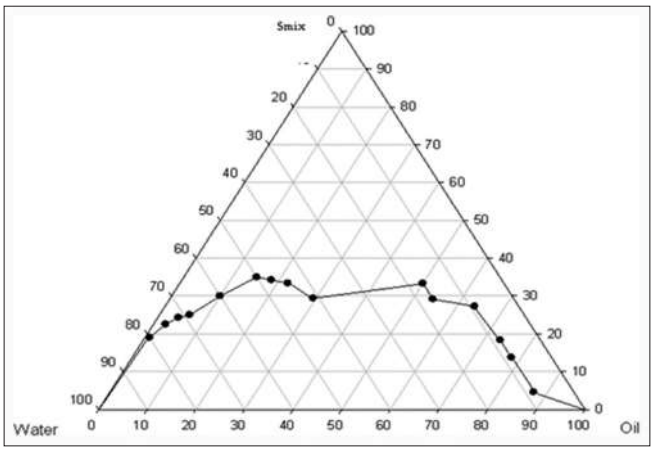

Figure 9: Pseudo-ternary graph of S_{mix} ratio 4:1

CDR results of fluvastatin SNEDDS

As shown in Figures 12 and 13, more than 85% of drug was dissolved from all fluvastatin SNEDDS formulations (FVT1-FVT17) after 60 min. This result suggested that the SNEDDS formulation significantly enhanced the dissolution of fluvastatin with the highest drug release for FVT8 (98.62 ± 1.47 %) compared to pure drug (13.76 ± 1.56 %). The enhanced dissolution is attributed to decline in crystallinity. The enhancement of drug release is due to immediate dispersion of drug in dissolution medium which aids rapid self-emulsification. Each value represents the mean ± SD (n = 3).

Design of experiment

A series of experiments performed based on experimental runs obtained from a three-factor, three-level BBD. All responses fitted into second quadratic model [Table 4] and the adequacy of this model was verified and validated by analysis of variance (ANOVA) tests provided by Design-Expert software. Stat-Ease Design Expert ® software V8.0 was utilized for analyzing data, to get regression equation, regression coefficient, and ANOVA.

DS

A smaller DS provides a larger surface area for facilitating drug absorption and permits a faster release rate in SNEDDS. The DS of the nanoparticles ranged between

23.8 and 98.6 nm [Table 2]. The mathematical model generated for DS (Y1) was found to be noteworthy with F-value of 3629.72 implies the model is significant [Table 4]. The results of the equation indicate that the effect of B is more significant than A and C. The quadratic model generated exposed that the amount of sefsol-218, amount of Cremophor RH40, and amount of propylene glycol have a considerable effect on the DS. The theoretical (predicted) values and the observed values were in rationally good agreement as shown in Table 5. The response surface plots show the main effects of A, B, and C on the DS (Y1). These figures clearly show that B has the main and the major effect on Y1 followed by A and C which have restrained effect on Y1 [Figures 14 and 15].

Table 3: Percentage drug content and entrapment efficiency of fluvastatin SNEDDS

F. Code	% Drug content	% Entrapment efficiency
FVT1	96.19±0.21	95.29±0.043
FVT2	98.23±0.19	96.35±0.051
FVT3	96.89±0.65	96.87±0.069
FVT4	97.67±1.59	94.12±0.043
FVT5	96.73±0.19	95.61±0.022
FVT6	96.27±0.49	93.18±0.067
FVT7	96.12±0.78	94.28±0.053
FVT8	99.42±0.15	98.26±0.079
FVT9	98.32±0.66	97.68±0.073
FVT10	95.38±0.45	95.53±0.035
FVT11	98.76±0.13	97.44±0.039
FVT12	97.51±0.62	96.57±0.095
FVT13	98.59±0.89	97.67±0.084
FVT14	98.51±0.39	94.59±0.070
FVT15	97.36±0.78	96.88±0.067
FVT16	97.13±0.98	95.42±0.069
FVT17	96.29±0.79	94.45±0.018

*Each value represents the mean±SD (*n*=3)

Zeta potential

The ZP of the nanoparticles ranged between –6.7 and –27.5 [Table 2]. The mathematical model generated for Zeta potential (Y2) was found to be significant with F-value of 0.038 implies that the model is significant [Table 4]. The quadratic model generated reveals that the amount of Cremophor RH40 and amount of propylene glycol have a noteworthy influence on Zeta potential. The response plots show that B has major effect on Y2 followed by C which has moderate effect on Y2 [Figures 16 and 17]. The theoretical (predicted) values and the observed values were in reasonably good agreement, as shown in Table 5.

Cumulative percent drug released (CDR)

The CDR in 60 min from the nanoformulations ranged between 82.47 and 98.62 % [Table 2]. The mathematical

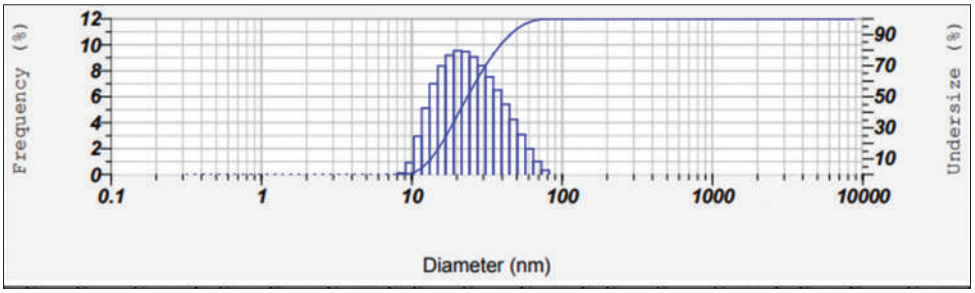

Figure 10: Droplet size of fluvastatin self-nanoemulsifying drug delivery system

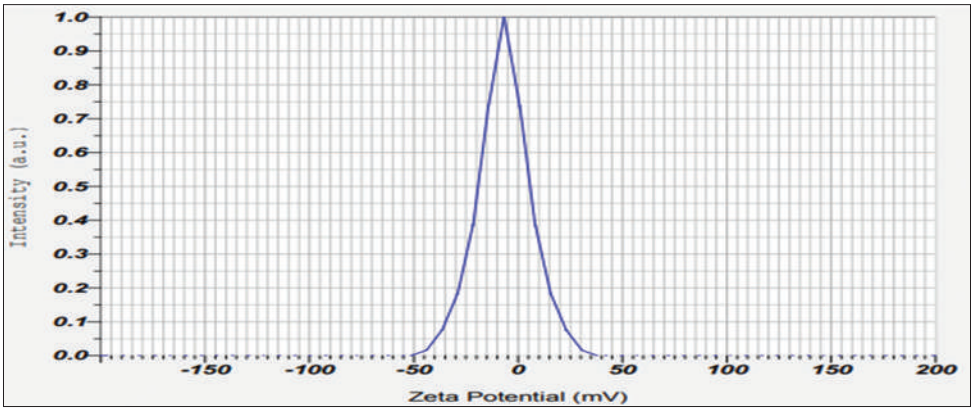

Figure 11: Zeta potential fluvastatin self-nanoemulsifying drug delivery system

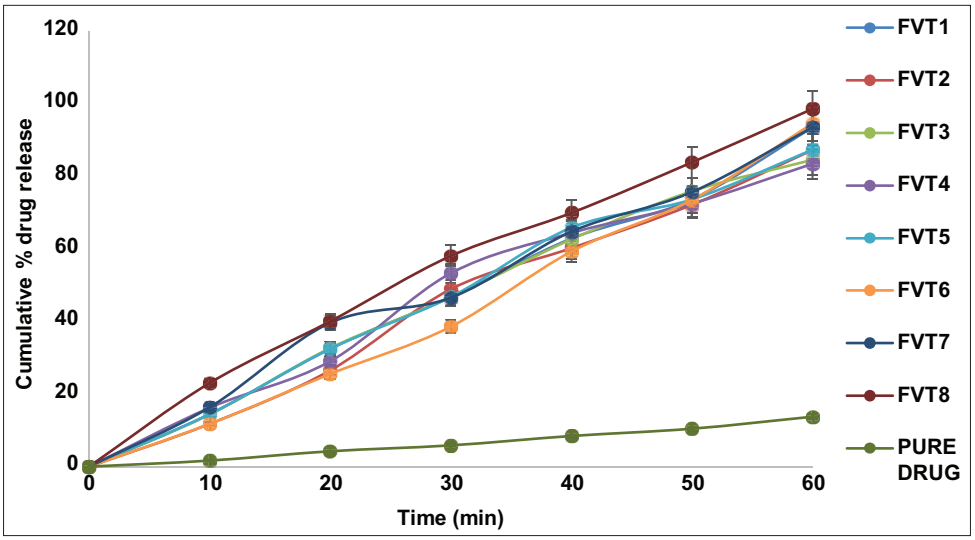

Figure 12: The CDR profile of fluvastatin self-nanoemulsifying drug delivery system (FVT1-FVT8) with pure drug

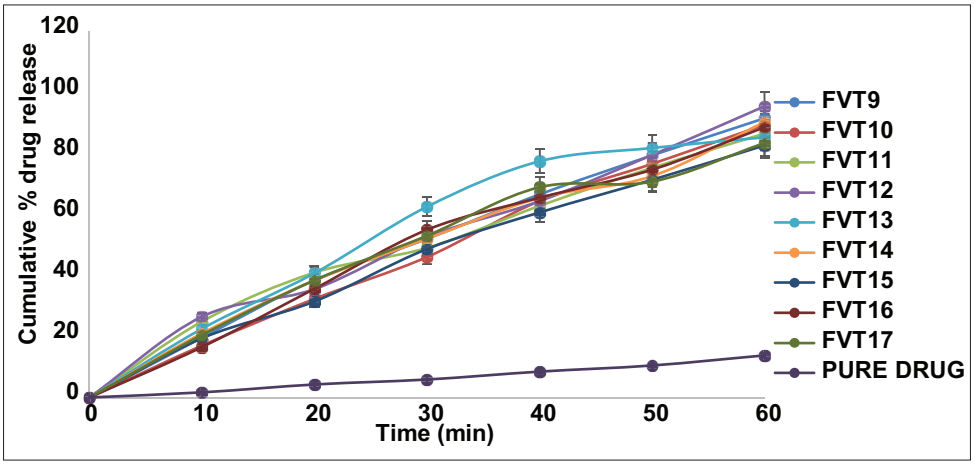

Figure 13: The CDR profile of fluvastatin self-nanoemulsifying drug delivery system (FVT9-FVT17) with pure drug

Table 4: Regression equations of the fitted models

Response	Equation
Droplet size (Y1)	$88.32+13.11X_1-17.69X_2-1.15X_3-0.19X^2_1+0.17X_1X_3+29.47X^2_2-1.56X_2X_3+1.05X^2_3$
Zeta potential (Y2)	$20.14+09.56X_1+11.38X_2+5.42X3+0.22X^2_1-0.13X_1X_3-14.35X^2_2-3.43X_2X_3-2.64X^2_3$
% Cumulative drug released (Y3)	$94.48-3.55X_1+79.14X_2-16.29X3+0.57X^2_1-18.64X_1X_3+05.31X^2_2-49.24X_2X_3+1.72X^2_3$

model generated for percent drug release in 60 min (Y3) was found to be significant with F-value of 0.0195 implies that the model is significant [Table 4]. The quadratic model generated revealed that the amount of sefsol-218, amount of Cremophor RH40, and amount of propylene glycol have a significant influence on the DS. The response surface plots indicate that amount of surfactant was primarily responsible for the augment in CDR from the formulation [Figures 18 and 19]. The theoretical (predicted) values and the observed values were in reasonably good agreement, as shown Table 5.

Optimization by desirability function and evaluation of SNEDDS

Based on optimization process the responses: DS (Y1), zeta potential (Y2), and CDR in 60 min (Y3) were transformed into the desirability scale where Y1 and Y2 are to be minimized, and Y3 has to be maximized. The results analyzed by Design-Expert software. The optimum formulation obtained at X1:30, X2:50, and X3:35. The factor level combination predicted the responses Y1 = 26.8 nm, Y2 = –6.7 mV, and Y3 = 98.62%. To confirm the model adequacy, three batches of fluvastatin SNEDDS under the optimum composition prepared, and responses evaluated. The results indicate fine agreement between the predicted and observed values demonstrating the success of BBD combined with a desirability function in optimization of fluvastatin SNEDDS formulations [Table 5].

Table 5: Optimized values obtained by the constraints applies on Y1, Y2, and Y3

Independent variable	Nominal values	Predicted values			Batch	Droplet size (Y1) (nm)	Zeta potential (Y2)	% Cumulative drug released (Y3)
		Droplet size (Y1) (nm)	Zeta potential (Y2) mV	% Cumulative drug released (Y3)				
Amount of sefsol-218 (A)	30	26.8	−6.7	98.62	1	27.1	−7.5	97.66
Amount of Cremophor RH 40 (B)	50				2	28.6	−6.9	98.23
Amount of propylene	35				3	26.9	−7.2	98.17

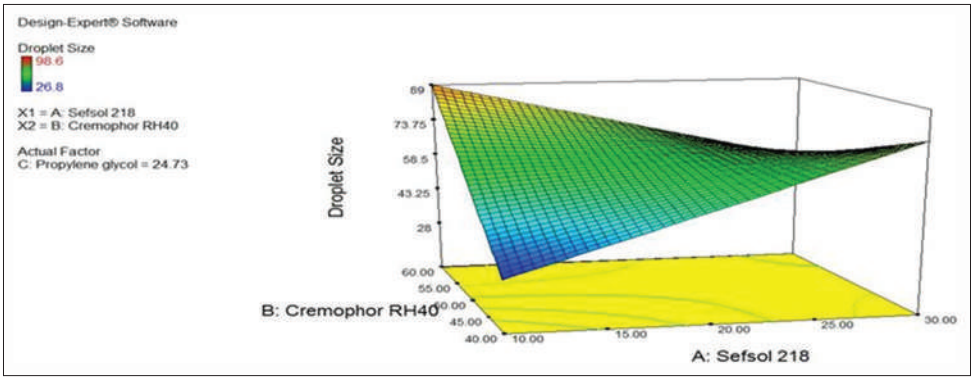

Figure 14: Response 3D surface plot indicating the influence of amount of sefsol-218 and amount of Cremophor RH40 on droplet size fixed level of C

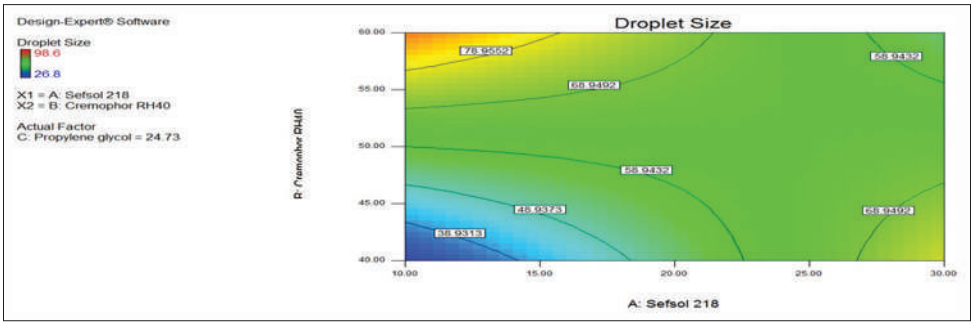

Figure 15: Contour plot indicating the influence of amount of sefsol-218 and amount of Cremophor RH40 on droplet size fixed level of C

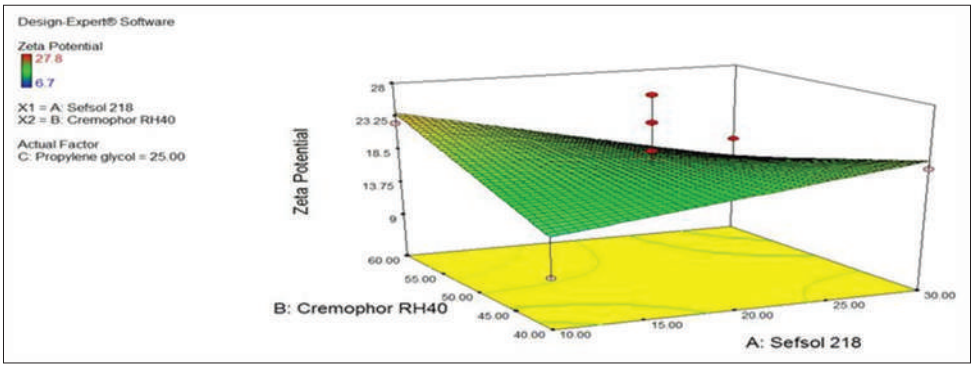

Figure 16: Response 3D surface plot showing the influence of amount of sefsol-218 and amount of Cremophor RH40 on zeta potential level of C

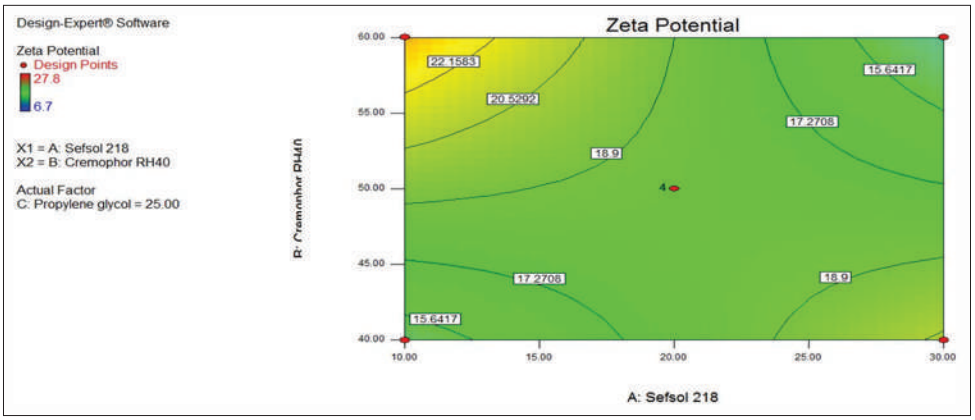

Figure 17: Contour plot showing the influence of amount of sefsol-218 and amount of Cremophor RH40 on zeta potential level of C

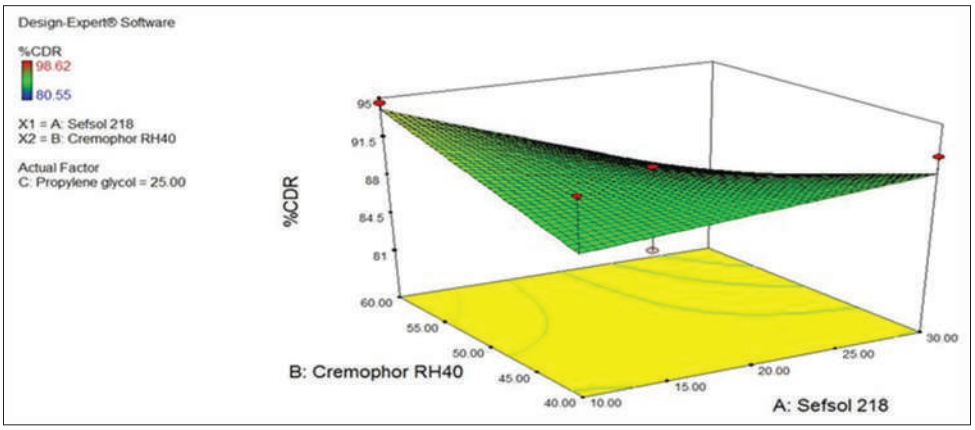

Figure 18: Response 3D surface plot showing the influence of amount of sefsol-218 and amount of Cremophor RH40 on % CDR level of C

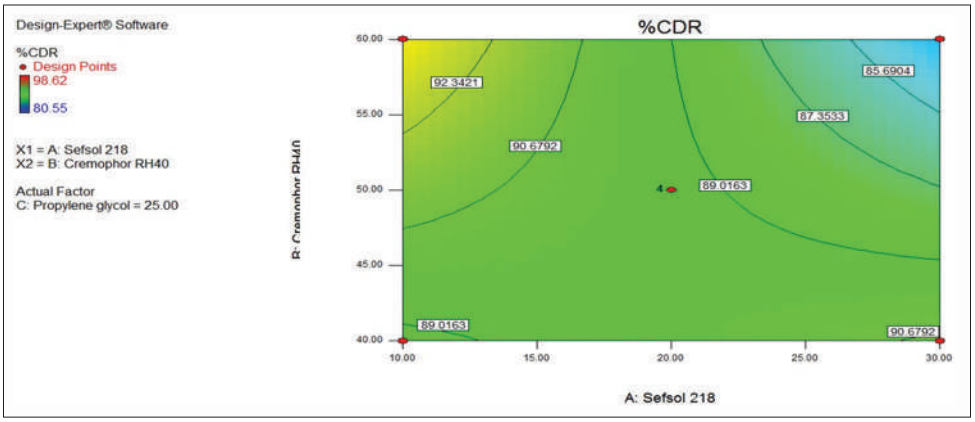

Figure 19: Contour plot showing the influence of amount of sefsol-218 and amount of Cremophor RH40 on % CDR of C

The FTIR spectra of pure fluvastatin showed peaks characteristic of all functional groups present in drug's chemical structure [Figure 20], which were also seen in the spectrum of optimized SNEDDS (FVT8) loaded with the drug indicating no interaction among the drug and excipients [Figure 21]. The SEM studies indicate that the results were in agreement to particle size analysis. The particles are relatively uniform in shape, existed as spherical particles and had a small size distribution [Figure 22].

Stability studies

The fluvastatin SNEDDS (FVT8) filled in hard gelatin capsules as the final dosage form and subjected to stability studies. There were no noteworthy alterations in the % entrapment efficiency, drug content, and CDR. It was also seen that the formulations were compatible with the hard gelatin capsule shells, as there was no sign of capsule shell deformation [Table 6].

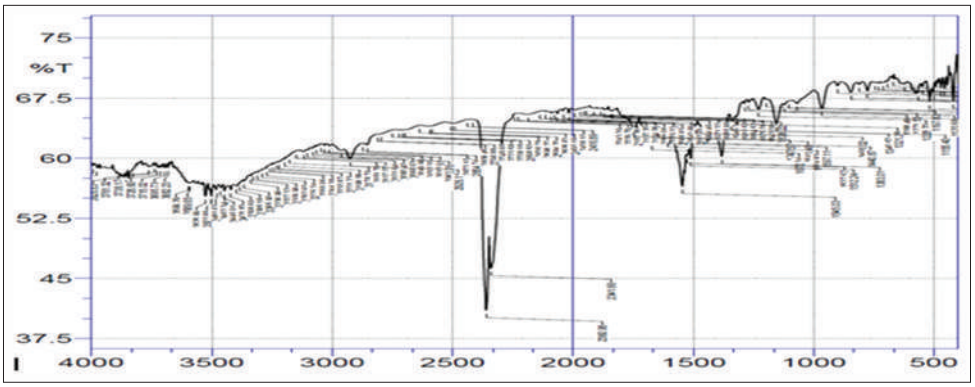

Figure 20: Fourier transform infrared of fluvastatin pure drug

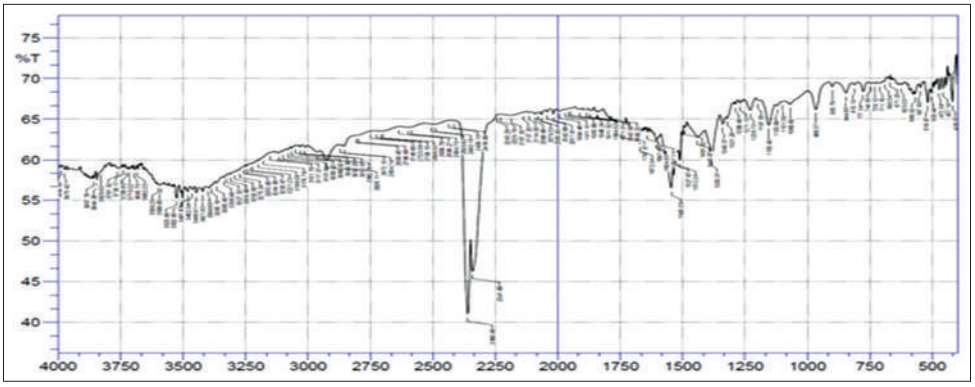

Figure 21: Fourier transform infrared of optimized fluvastatin self-nanoemulsifying drug delivery system FVT8

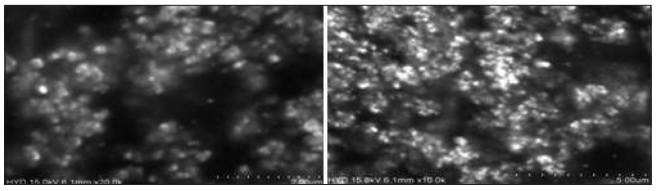

Figure 22: SEM of optimized fluvastatin self-nanoemulsifying drug delivery system

Table 6: Stability study of optimized formulation (FVT8)

Retest time for optimized formulation FVT8 (days)	%Entrapment efficiency	% Drug content	*In vitro* drug release (%)
0	98.26±0.079	99.42±0.15	98.62±1.47
30	98.06±0.043	99.10±0.45	98.02±1.73
60	97.75±0.092	98.82±0.82	97.60±1.54
90	97.20±0.034	98.30±0.18	97.25±1.50

*Each value represents the mean±SD (*n*=3)

CONCLUSION

An optimized SNEDDS formulation of fluvastatin consisting of sefsol-218 as oil, Cremophor RH40 as surfactant and propylene glycol as cosurfactant was successfully prepared by applying BBD. The optimized formulation FVT8 exhibited enhanced drug release with minimum DS of 22.1 nm and zeta potential of -6.7 mV and maximum drug release 98.62%. The characterization of SNEDDS carried out by FTIR and SEM studies indicating molecular dispersion state of drug. The optimized formulation found stable over a period of 3 months. Thus, our study confirmed that SNEDDS could be successful alternative to traditional oral formulations of FVT for enhanced solubility and dissolution rate.

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