

# Design and Optimization of Simvastatin Self-Microemulsifying Drug Delivery System for Enhanced Therapeutic Potential

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## Abstract

**Aim:** In present study, a self-microemulsifying drug delivery system (SMEDDS) has been developed and optimized to enhance solubility and bioavailability of poorly water soluble drug simvastatin. **Material and Methods:** Phase solubility studies and emulsification tests were performed for selection of a suitable oil, surfactant, and co-solvent. A three factor, two level, mixture design of experiments was used to optimize the concentration of components for SMEDDS formulation for achieving excellent physicochemical properties such as small globule size (<150 nm) and high dissolution (more than 85% of drug released within 15 min). Lipolysis of optimized simvastatin loaded SMEDDS formulation by pancreatic lipase was done to investigate effect on solubilizing capacity of dispersed colloid in aqueous phase. Pharmacodynamic study on hyperlipidaemic rats models was done to investigate bioavailability of optimized simvastatin loaded SMEDDS formulation in comparison to pure drug. **Result and Discussion:** The optimized Simvastatin loaded SMEDDS formulation containing 10.0% w/w Capmul PG8(oil), 30.0% w/w Koliphore EL(surfactant) and 60.0% w/w Transcutol (co-solvent) shows smallest globule size (22.02nm) and maximum drug release (98.9% in 15 minutes). Lipolysis of optimized simvastatin loaded SMEDDS formulation showed that nature of colloidal species changed during lipolysis process does not affect solubilizing capacity of dispersed colloid in aqueous phase. Pharmacodynamic investigation on hyperlipidaemic rats models reveals that optimized simvastatin loaded SMEDDS formulation significantly reduced serum lipid levels when compared with Simvastatin drug and hence indicating improved bioavailability. **Conclusion:** These results suggest that the Mixture response surface design could be a suitable approach for optimizing Simvastatin SMEDDS formulation variables. **Key words:** Bioavailability, design of experiment, dissolution, globule size, lipolysis

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## INTRODUCTION

Simvastatin is used for the treatment of hypercholesterolemia and the reduction in the risk of cardiac heart disease mortality and cardiovascular events. Simvastatin is a specific inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme that catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in the biosynthetic pathway for cholesterol (CH). In addition, simvastatin reduces triglyceride (TG) and increases high-density lipoprotein (HDL). Simvastatin is BCS Class II drug having low water solubility. The bioavailability of simvastatin after oral administration is 5%.<sup>[1]</sup> Many approaches are available for enhancing the solubility of poorly water-soluble drugs to improve their bioavailability resulting in increase clinical efficacy. Out of these approaches self-microemulsifying drug delivery system (SMEDDS) is the most promising.

SMEDDS is a mixture of drug, oil, and surfactant usually with one or more of hydrophilic cosolvents. SMEDDS rapidly emulsify in the gastrointestinal fluid under gentle agitation given by gastrointestinal motion and form o/w microemulsion. In such a system lipophilic drug is solubilized in oil globules. The larger interfacial area promotes drug to diffuse into gastrointestinal fluid quickly and thereby to increase drug solubility.<sup>[2]</sup> In this study SMEDDS was prepared using Capmul PG8 (Oil), Kolliphor EL (Surfactant), and Transcutol (Co-solvent). Effect of simvastatin SMEDDS formulation variable on *in vitro* drug

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release and globule size was studied using response surface mixture design of the experiment. *In vitro* lipolysis study was done to study the effect of lipid digestion by pancreatic lipase on diffusion of the drug in aqueous phase from SMEDDS Formulation. *In vivo* pharmacodynamic study was done to study the effect of SMEDDS formulation on the bioavailability of simvastatin, in rats.

## MATERIALS AND METHODS

### Materials

Simvastatin was provided by Ranbaxy Laboratories Limited, India. Capmul PG8 was supplied by Abitec Corporation, USA. Kolliphor EL was supplied by BASF, Germany. Transcutol was supplied by Gattefosse, France. Pancreatin was purchased from Loba Chemie, India. Analytical grade solvents and reagents are used in the study.

### Animals

Animal experiments were performed in accordance with the committee for the purpose of control and supervision of experiments on animals, India, and were approved by the Institutional Animal Ethical Committee, Maharshi Dayan and University, India. Wistar Albino rat having weight 100–150 g and age 4–6 weeks were purchased from Lala Lajpat Rai University of Veterinary and Animal Science, Hisar.

### Phase solubility study

Phase solubility study of simvastatin in various excipients (oils, surfactants, and cosolvents) was carried out to identify suitable excipients that could solubilize a maximum quantity of the simvastatin drug. An excess amount of simvastatin was added to 5 mL of various excipients with continuous shaking for 48 h to achieve equilibrium.<sup>[3]</sup> Each mixture was filtered through 0.45  $\mu$  Nylon filter. Validated ultraviolet (UV) spectroscopy method was used to determine the concentration of simvastatin in the aliquot by measuring absorbance at wavelength ( $\lambda_{\max}$ ) of 239 nm. Oils, surfactants, and cosolvents having high drug solubility were taken for emulsification study.

### Emulsification study

The emulsification capacity of surfactants with oils was evaluated to select the best possible combination of surfactant and oil. 10% w/v aqueous solution of each surfactant prepared. 10 ml of each surfactant solution was titrated with each oil. The volume of oil where emulsion was turbid was noted. Surfactant and oil combination where the highest amount of oil emulsified was selected.

For a selection of cosolvent, each cosolvent has been mixed with a selected surfactant in a ratio of 1:1 ( $S_{\text{mix}}$ ) and various

formulations have been prepared with selected oil and  $S_{\text{mix}}$  where the concentration of oil ranges from 10% to 90%. 0.5 g of each formulation was mixed separately with 500 ml of purified water. Transparency of resultant emulsion was observed. Transparent/bluish appearance confirm microemulsion region and turbid appearance confirms macroemulsion region. Cosolvent which shows greater microemulsion region was selected.

### Construction of ternary phase diagram

Ternary phase diagram was constructed to find out range of oil, surfactant, and cosolvent required for microemulsion formation. The boundaries of the microemulsion domains were determined using a ternary phase diagram. Basis solubility and emulsification study, Capmul PG8, Kolliphor EL, and Transcutol were selected as oil, surfactant, and cosolvent, respectively. Kolliphore EL and Transcutol were mixed in the ratio of 1:0, 4:1, 3:1, 2:1, 1:1, and 1:2 to prepare  $S_{\text{mix}}$ . Various formulations have been prepared with Capmul PG8 and each  $S_{\text{mix}}$  where the concentration of Capmul PG8 ranges from 10% to 90%. Simvastatin (16% w/w) was added to each formulation. Efficiency of microemulsion formation was assessed by adding one unit dose of each formulation (equivalent to 80mg of simvastatin) to 500 ml of purified water and gently stirring with a magnetic stirrer. Transparency of resultant emulsion was determined by visual observation. Transparent/bluish Appearance confirm microemulsion region and turbid appearance confirms macroemulsion region.<sup>[4]</sup> Range of Capmul PG8, Kolliphor EL, and Transcutol where microemulsion region was observed were selected for further optimization.

### Formulation optimization

Out of various response surface methodologies, mixture design was selected as it considers the total system of SMEDDS as 100%. A three-factor, two-level mixture design was used to study the effect of formulation variables on responses based on the solubility study, and ternary phase diagram, concentrations of Capmul PG8 (oil; X1), Kolliphore EL (surfactant; X2), and Transcutol (co-solvent; X3) were set within ranges of 10–40% w/w, 20–70% w/w, and 15–60% w/w, respectively. Globule size (Y1) and percentage of drug released in 15 min (Y2) were evaluated to determine the optimal SMEDDS formulation with excellent physicochemical characteristics. JMP Software was used for developing and evaluating the experimental design. This design requires 14 experimental runs including two replicate center points for uniform estimation of the prediction variance for the required design space. Statistical data analysis was done to optimize and find out the formulation design space where globule size (Y1) will be below 150nm and percentage of drug released in 15 min (Y2) will be above 85.0%.

### Preparation of SMEDDS formulation

Placebo SMEDDS formulation was prepared by mixing oil, surfactant, and cosolvent under continuous stirring to obtain a clear solution. The simvastatin loaded SMEDDS formulation

was prepared by adding 16.0%w/w of simvastatin to the placebo SMEDDS formulation under continuous stirring to obtain a clear solution. SMEDDS formulation equivalent to 80.0 mg of simvastatin was filled into hard gelatin capsule shell.

### ***In vitro* dissolution studies**

For *in vitro* dissolution test, USP apparatus II (paddle) method was used. 0.5% sodium dodecyl sulfate in 0.01 M sodium phosphate buffer, pH 7.0 at  $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$  was used as the dissolution media. Paddle speed and volume of the dissolution medium were set at 50 rpm and 900 ml, respectively.<sup>[5]</sup> Samples were obtained after 15 min and filtered through 0.45  $\mu$  Nylon filter. Samples were analyzed by validated UV spectroscopy method.

### **Globule size analysis**

Determination of globule size of the emulsion was carried out by dynamic light scattering with Zetasizer (Malvern Instruments Ltd., UK). The globule size of the SMEDDS was assessed by diluting each SMEDDS formulation 100 times with distilled water and gently stirring the mixture to obtain a uniform clear dispersion. The samples were loaded into a cuvette and placed in a thermostatic chamber. Light scattering was evaluated at  $90^{\circ}$  angle.<sup>[6]</sup>

### ***In vitro* lipolysis studies**

The experimental medium which simulates fasting state gastrointestinal tract, composed of 36 ml of digestion buffer (2 mM Tris-maleate, 150 mM sodium chloride, 1.4 mM calcium chloride, and pH 6.5) containing 3 mM sodium deoxycholic acid and 0.75 mM phosphatidylcholine. The medium was continuously stirred at  $37^{\circ}\text{C}$ . Simvastatin SMEDDS formulation was dispersed in the medium. Afterward, 4 ml of pancreatic extract was added to maintain 600 USPU/ml of lipase activity and to initiate digestion. The digestion experiments were maintained at pH 6.5 with 0.1 M NaOH solution. Digestion experiments were run separately for 5 min, 15 min, 30 min, and 45 min when there is no further change in pH and digestion process completed. After each experimental run, 4-bromophenylboronic acid was immediately added to stop lipolysis and centrifuged to achieve separation of the aqueous phase.<sup>[7-9]</sup> Each sample was filtered through 0.45  $\mu$  Nylon filter. Samples were analyzed by validated UV spectroscopy method.

### **Pharmacodynamic study in rats**

Simvastatin causes a reduction in elevated total CH and TG levels in blood. Further, it causes elevation of plasma HDL level, which promotes removal of CH from peripheral cells and facilitates its delivery back to the liver. The pharmacodynamic effect of simvastatin is dose-dependent and hence was used basis for comparison of *in vivo* performance.

The effect of simvastatin loaded SMEDDS (test formulation) on lipid profile was determined by comparison with simvastatin drug (reference formulation) and SMEDDS without simvastatin (placebo formulation). Test, reference and placebo formulation was diluted with 2.0% acacia solution. Wistar rats were randomly divided into four treatment groups, i.e., control treatment group (CTG) ( $n = 3$ ), placebo treatment group (PTG) ( $n = 5$ ), reference treatment group (RTG) ( $n = 5$ ), and test treatment group (TTG) ( $n = 5$ ). Each treatment group received high-fat diet (Mixture of Dalda and coconut oil [3:2]) at the dose of 10 ml/kg body weight daily for a period of 4 weeks. TTGs, RTGs, and PTGs additionally receive test formulation, reference formulation, and placebo formulation, respectively, for a period of 4 weeks. The administered oral dose of the test product and reference product was equivalent to 10 mg/kg/day of simvastatin. Blood sample was collected under light ether anesthesia by a retro-orbital puncture at predetermined time interval, namely, before treatment and after 28 days in polo plain clot activator glass tubes.<sup>[10]</sup> Serum was separated by centrifugation for 10 min at 3000 RPM (Make-REMI) and used as a test sample for biochemical analysis. Samples were analyzed for total CH, HDL, and TGs using *in vitro* diagnostic kits.

For determination of total CH modified Roeschlau's method was used.<sup>[11]</sup> Method of Wako and the modification by McGowan and Fossati was used for determination of TG.<sup>[12]</sup> Method of Burstein was used for determination of HDL.<sup>[13]</sup> Total CH, TG and HDL (0 day and after 28 days) for each treatment group, i.e., CTGs, PTGs, TTGs, and RTGs are expressed as the mean  $\pm$  standard deviation. Statistical significance was determined with  $P \leq 0.05$  considered to be statistically significant.

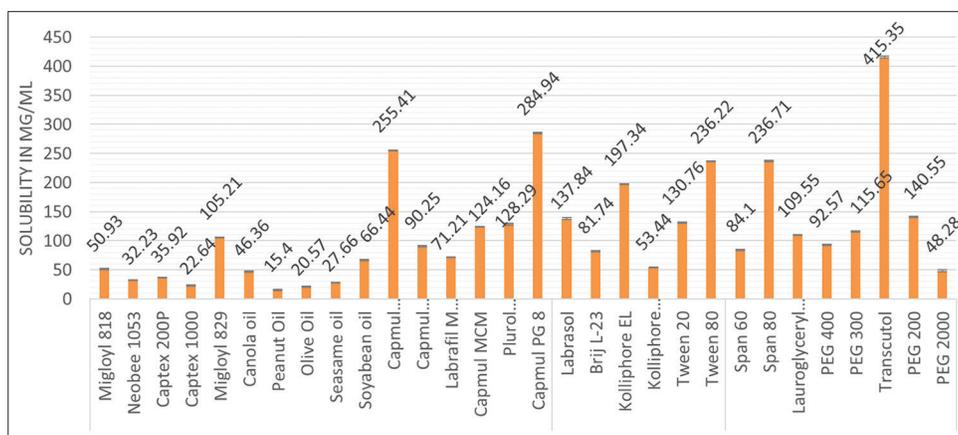
## **RESULTS AND DISCUSSION**

### **Phase solubility study**

Solubility of simvastatin in various oils, surfactants, and cosolvents has been given in Figure 1. On the basis phase solubility studies oils, surfactants, and cosolvents having high drug solubility were taken for selection of best possible combination for simvastatin loaded SMEDDS. Capmul PG8, Capmul MCM C8, Plurol Oleique CC 497, and Capmul MCM having simvastatin solubility of 284.94 mg/ml, 255.41 mg/ml, 128.29 mg/ml, and 124.16 mg/ml, respectively, have been selected as oils. Tween 80 and Kolliphor EL having simvastatin solubility of 236.22 mg/ml and 197.34 mg/ml, respectively, have been selected as surfactants. Transcutol and span 80 having simvastatin solubility of 415.35 mg/ml and 236.71 mg/ml have been selected as cosolvents.

### **Emulsification study**

The volume of each oil emulsified with 10 ml of 10% w/v solution of each surfactant has been given in Table 1.



**Figure 1:** Solubility of simvastatin in various excipients

The emulsification study showed that with Kolliphor EL highest amount of Capmul PG8 has been emulsified and hence Kolliphor EL as a surfactant and Capmul PG 8 as oil were selected for SMEDDS formulation. Greater microemulsion region has been observed with Transcutol and hence has been selected as cosolvents for SMEDDS formulation.

### Construction of ternary phase diagram

The phase diagram was constructed using CapmulPG8 as the oil, Kolliphor EL as surfactant, and Transcutol as cosolvent with 16% w/w simvastatin drug loading to determine an appropriate range of each component required for microemulsion formulation. As shown in Figure 2, the microemulsion region (white area) was developed using CapmulPG8, Kolliphor EL, and Transcutol in ranges of 10–40%, 20–70%, and 15–60%, respectively.

### Formulation optimization

The experimental matrix from the randomized runs for the independent variables and responses observed is shown in Table 2.

All responses were simultaneously fitted to regression models by using the JMP software. Actual versus Predicted profile for globule size and percentage drug release has been given in Figure 3.

By comparing statistical parameters, such as  $P$ -value and squared correlation coefficient ( $R^2$ ) it was found that regression model was fitting in the mathematical model for both responses.  $P$ -values for Y1 and Y2 were 0.0004 and 0.0056, respectively.  $P < 0.05$  indicates that model is statistically significant.  $R^2$  values define the total variation shown by the model.  $R^2$  values should be close to 1 for a good model fit.  $R^2$  values for the responses Y1 and Y2 were approximately 0.99 and 0.98, respectively.

### Response surface analysis

From the parameter estimates shown in Table 3, it was deduced that Capmul PG8 (X1) and its interaction with Kolliphor EL (X2) contributed to the regression model more than others

Figure 4a and b illustrate the relationship between the response studied and the three factors, amounts of CapmulPG8 (oil), Kolliphor EL (surfactant), and Transcutol (cosolvent).

Globule size is important for assessing the performance of SMEDDS. A smaller globule size provides a greater surface area, permits a faster release rate and increased drug absorption. From parameter estimates and prediction profiler for globule size, it can be concluded that Capmul PG8 and interaction of Capmul PG8 with Kolliphor EL has significant positive and negative effect, respectively, on globule size.

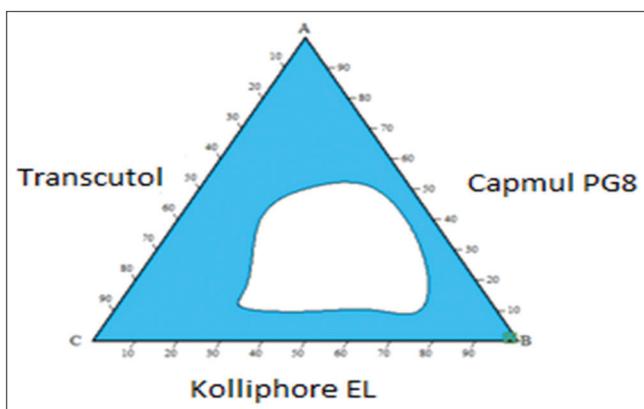
Rapid self-emulsification of the formulations in the dissolution medium results in the spontaneous formation of an oil-water interface. This increases the water penetration of oil globules, resulting in disruption of the interface, decreased globule size and thereby eventually increasing the release rate. From parameter estimates and prediction profiler for percentage drug release, it can be concluded that Capmul PG8 and interaction of Campul PG8 with Kolliphor EL has significant negative and positive effect, respectively, on percentage cumulative drug release.

An optimization process was done with desirability function to optimize the two responses simultaneously. Among them, Y1 (globule size) had to be minimized, while Y2 (% drug released in 15 min) had to be maximized. White area in contour profile as given in Figure 5 shows design space where *in vitro* drug release profile will be always >85% and globule size will always be <150nm.

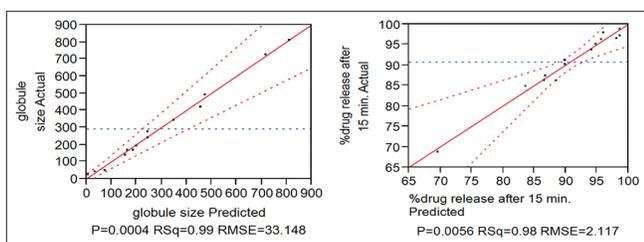
Hence from this optimization studies, it can be concluded that desired target for *in vitro* drug release profile >85% and globule size for <150 nm can be achieved with Capmul PG

**Table 1:** Emulsification of oils with different surfactant

Surfactant (10%w/v aqueous solution)	Oil	Amount of oil emulsified
Kolliphor EL	Capmul PG8	0.50 ml
Kolliphor EL	Capmul MCM C8	0.30 ml
Kolliphor EL	Plurol Oleique CC 497	0.40 ml
Kolliphor EL	Capmul MCM	0.45 ml
Tween 80	Capmul PG8	0.40 ml
Tween 80	Capmul MCM C8	0.35ml
Tween 80	Plurol Oleique CC 497	0.25 ml
Tween 80	Capmul MCM	0.40 ml



**Figure 2:** Ternary phase diagram of the self-microemulsifying drug delivery system formulation

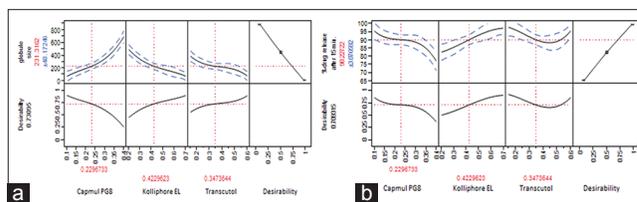


**Figure 3:** Actual versus predicted profile for globule size (Y1) and percentage drug release (Y2)

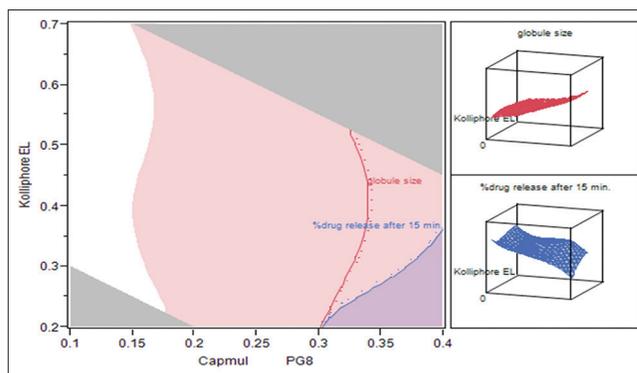
8 (0.10–0.15%), Kolliphor EL (0.30–0.70%), and Transcutol (0.15–0.60%).

**In vitro lipolysis studies**

When SMEDDS mixed with GI fluids, lipolysis increases dispersion of emulsified globules and nature of colloidal species will change during lipolysis process, which might affect the solubilizing capacity of dispersed colloids in the aqueous phase. Hence, an *in vitro* study was conducted to understand the effect of lipolysis on drug diffusion in the aqueous phase.



**Figure 4:** (a) Prediction profiler for Globule size (Y1). (b) Prediction profiler for percentage drug release (Y2)



**Figure 5:** Contour profile

Lipolysis study was carried out on optimized simvastatin loaded SMEDDS formulation (F9). After 5 min, 15 min, 30 min, and 45 min (end of lipolysis) of lipolysis of optimized SMEDDS formulation, percentage drug release in aqueous phase found to be 78%, 94%, 98%, and 99%, respectively. As more than 85% of the drug gets diffused in aqueous phase within 15 min of lipolysis; hence, it can be concluded that nature of colloidal species changed during lipolysis process does not affect the solubilizing capacity of dispersed colloids in the aqueous phase.

**Pharmacodynamic study in rats**

Pharmacodynamic study was carried out on optimized simvastatin loaded SMEDDS formulation (F9). Pharmacodynamics study results for total CH, TG, and HDL for each group has been given in Table 4 and Figure 6.

After 28 days of treatment with high-fat diet, CTG showed a significant marked increase ( $P < 0.05$ ) in total CH (228.3%) and TG (212.3%) and an insignificant change ( $P > 0.05$ ) in HDL indicating the inducement of hyperlipidemia due to the administration of high-fat diet.

After 28 days of treatment with high-fat diet, PTG showed a significant marked increase ( $P < 0.05$ ) in total CH (238.5%) and TG (234.9%) and an insignificant change ( $P > 0.05$ ) in HDL indicating that placebo has no appreciable effect on the lipid profiles of experimental animals.

After the 28-day treatment with high-fat diet, comparison of CTG against TTG and RTG confirmed the lipid-lowering effect of simvastatin. Plasma CH and TG levels

**Table 2: Experimental matrix and observed responses**

Formulation	Independent variable (% ratio)			Responses	
	Capmul PG8 (X1)	Kolliphor EL (X2)	Transcutol (X3)	Globule size (in nm) (Y1)	% Drug release in 15 min (Y2) (Mean±SD)
F1	0.275	0.575	0.15	342.4	96.4±1.5
F2	0.15	0.7	0.15	137.7	97.8±1.1
F3	0.1	0.7	0.2	43.22	97.2±1.7
F4	0.1768	0.558	0.2652	169.1	95.1±1.0
F5	0.236813	0.41373	0.34945	277	91.2±0.9
F6	0.34	0.37	0.29	419.6	86.3±1.0
F7	0.2	0.2	0.6	167.3	93.8±1.4
F8	0.4	0.2	0.4	810.2	68.7±1.1
F9	0.1	0.3	0.6	22.02	98.9±0.8
F10	0.31	0.2	0.49	489.3	84.9±1.0
F11	0.19	0.341	0.469	189.6	86.3±1.1
F12	0.236813	0.41373	0.34945	241.5	90.1±1.2
F13	0.4	0.45	0.15	724.2	87.4±0.9
F14	0.1	0.5	0.4	49.55	96.2±0.6

SD: Standard deviation

**Table 3: Parameter estimates for globule size and % drug release**

Term	Globule size				% drug release			
	Estimate	Standard error	t ratio	Prob> t	Estimate	Standard error	t ratio	P> t
X1	3493.3	783.4	4.4	0.0112*	-189.5	50.6	-3.7	0.0200*
X2	35.7	48.3	0.7	0.5005	-13.9	7.8	-1.7	0.1487
X3	-154.1	101.5	-1.5	0.2038	0	0		
X1*X2	-4626.2	1579.5	-2.9	0.0429*	328.1	100.8	3.2	0.0313*
X1*X3	-3885.1	1592.2	-2.4	0.0712	232.9	101.6	2.2	0.0838
X2*X3	536.3	274.0	1.9	0.1219	-35.8	17.5	-2.0	0.1097
X1*X2*X3	2123.1	2394.2	0.8	0.4253	-344.6	152.9	-2.2	0.0873
X1*X2*(X1-X2)	-2710.0	1147.3	-2.3	0.0775	180.9	73.2	2.4	0.0690
X1*X3*(X1-X3)	-2682.9	1164.1	-2.3	0.0825	180.8	74.3	2.4	0.0718
X2*X3*(X2-X3)	-490.4	444.5	-1.1	0.3318	48.8	28.3	1.7	0.1603

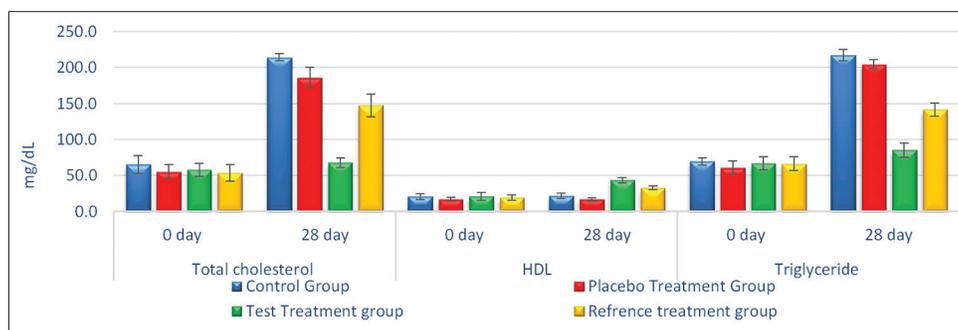
**Table 4: Lipid profile for each treatment group**

Group	Total CH (mg/dl) Mean±SD		HDL (mg/dl) Mean±SD		TG (mg/dl) Mean±SD	
	0 day	28 day	0 day	28 day	0 day	28 day
CTG	65.30±12.6	214.40±5.3	20.60±4.3	21.80±3.8	69.60±5.0	217.40±7.6
PTG	55.08±10.0	186.48±14.2	17.20±2.7	16.86±2.0	61.08±9.0	204.56±6.2
TTG	57.90±8.9	67.78±6.8	20.84±5.1	43.46±3.8	67.00±9.0	85.16±9.8
RTG	53.62±11.8	147.16±15.7	19.30±3.9	32.62±2.5	66.32±9.3	141.74±9.0

CTG: Control treatment group, PTG: Placebo treatment group, RTG: Reference treatment group, TTG: Test treatment group, SD: Standard deviation, CH: Cholesterol, HDL: High-density lipoprotein, TG: Triglyceride

were significantly lower ( $P < 0.05$ ) and HDL levels were significantly higher ( $P < 0.05$ ) in TTG and RTG compared to CTG.

After 28 days of treatment with high fat diet, TTG showed insignificant increase ( $P > 0.05$ ) in total CH (17.0%) and TG (27.1%) and a significant increase ( $P < 0.05$ ) in HDL



**Figure 6:** Comparative lipid profile of each treatment group

(108.5%). After 28 days of treatment with high fat diet, RTG showed significant increase ( $P < 0.05$ ) in total CH (174.4%) and TG (113.7%) and a significant increase ( $P < 0.05$ ) in HDL (69.0%). After the 28 days of treatment with high-fat diet, comparison of TTG against RTG inferred the plasma CH and TG levels were significantly lower ( $P < 0.05$ ) and HDL levels were significantly higher ( $P < 0.05$ ) in TTG compared to RTG. This clearly indicates the varying lipid-lowering effects of simvastatin obtained by administering test formulation and reference formulation. Test formulation has an appreciable effect on the lipid profiles of experimental animals in comparison to reference formulation. Thus, test formulation showed a significantly better *in vivo* performance than reference formulation in terms of pharmacodynamic parameters.

## CONCLUSIONS

The present study successfully demonstrated the use of the mixture design for the optimization of simvastatin SMEDDS. Effects of formulation variables on the responses were studied using variance profiler and contour plots. Furthermore, *in vitro* lipolysis studies showed that there is no significant effect of lipolysis on drug release. *In vivo* pharmacodynamic studies of the optimized SMEDDS using hypercholesterolemia model in rats significantly reduced serum lipid levels, as compared with plain simvastatin indicating improve bioavailability. These results suggest that the mixture response surface design could be a suitable approach for optimizing simvastatin SMEDDS formulation variables.

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