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RESEARCH PAPER

D-OPTIMAL MIXTURE DESIGN FOR OPTIMIZATION OF SELF MICRO-EMULSIFYING DRUG DELIVERY SYSTEM OF SIMVASTATIN: CHARACTERIZATION AND IN VITRO EVALUATION

Kalpana G. Patel*, Apeksha T. Patel, Jenee R. Christian, Asha S. Patel, Purvi A. Shah and Mukesh C. Gohel

Department of Quality Assurance; Department of Pharmaceutical Chemistry; Department of Pharmaceutics, Anand Pharmacy College, Anand, Gujarat 388001, India

**E-mail*: kalpanapatel.pharma@gmail.com
Tel.: +91 9825587547.

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The objective of present research work was to develop self-micro emulsifying drug delivery system to improve the in vitro dissolution of a Biopharmaceutical Classification System Class II lipid lowering agent, simvastatin. Solubility study was performed to identify the potent oil, surfactant and co-surfactant showing highest solubility of simvastatin. The ternary phase diagrams were constructed for selected components to identify the area of microemulsion formation. D-optimal mixture design was applied for optimization using three formulation variables namely, oleic acid, Tween 80 and Cremophore EL. The liquid self-micro emulsifying drug delivery systems (SMEDDS) were evaluated for droplet size, self-emulsification time, percent transmittance and drug solubility. The optimized batch showed self-emulsification time and solubility. The optimized liquid formulation was solidified using Aerosil 200 to prepare solid SMEDDS. Solid SMEDDS showed good flow property and uniform drug content. Solid state characterization was performed by differential scanning calorimetry, X-ray diffraction study and scanning electron microscopy. The zeta potential and globule size was -3.66mV and 755.3 nm, respectively. The rate and extent of drug dissolution from solid SMEDDS was significantly higher than tablet formulation. The optimized formulation was found to be stable. These results demonstrate the potential of SMEDDS as a means of improving solubility and dissolution.

Key words: Simvastatin, SMEDDS, D-Optimal design, Solubility, Dissolution.

INTRODUCTION

The statins are 3-hydroxy-3-methylglutaryl-coenzyme (HMG-CoA) reductase inhibitors, the most potent and most widely used cholesterol lowering drugs. They inhibit the conversion of HMG-CoA to mevalonic acid, leading to reduced biosynthesis of cholesterol. They have various pleiotropic properties; improvement of the endothelial function, stabilization of atheromatous plaque, an increase of nitric oxide (NO) synthesis, as well as the anti-inflammatory and antithrombotic effect that influences their therapeutic application (Słupski *et al* 2017). Simvastatin is lipophilic and being Biopharmaceutical Classification System II (BCS II) drug exhibits poor water solubility which results in low bioavailability, intra and inter subject variation and lack of dose proportionality. The recommended oral administration of solid dosage forms of simvastatin for primary hypercholesterolemia results in low bioavailability attributed to its low

solubility, pre-systemic clearance in the gastrointestinal (GI) mucosa, and extensive first-pass metabolism in the liver (Yeom *et al* 2016). Hence, it poses a challenge in developing an optimum oral solid dosage form with enhanced bioavailability.

Many techniques have been used to overcome or modify solubility and permeability issues including micronization, complexation, solid dispersion, cyclodextrin nanoparticles, co-precipitation (Janković *et al* 2016; Dahiya, 2017; Patel *et al* 2015; Prusty, 2014; Pabreja and Dua, 2011; Sachan and Pushkar, 2011; Pathak *et al* 2008; Dahiya *et al* 2008; 2015; Dahiya and Pathak, 2006; 2007). Lipid based drug delivery is an alternative and rational formulation strategy by selection of appropriate lipid vehicles. Moreover, many lipid excipients with acceptable regulatory and safety limits have been available. The availability of lipid excipient with acceptable regulatory and safety profiles coupled with their ability to improve solubility and permeability have gained much importance. An appropriate selection of lipid vehicle, formulation strategies and rational drug delivery system can lead to successful drug delivery system. Lipid based formulation approaches, particularly self-micro emulsifying drug delivery system (SMEDDS) is well established as a promising strategy for improvement of oral delivery of hydrophobic drug substances associated with limited solubility and low oral bioavailability (Silva *et al* 2015; Janković *et al* 2016).

According to the Lipid Formulation Classification System (LFCS), SMEDDS are type III B self-dispersing systems comprising a drug substance in a mixture of lipids (< 20%), hydrophilic surfactants (20-50%) and co-solvents (20-50%) (Djekic *et al* 2017). SMEDDS optimized to form oil-in-water micro-emulsion based formulation is a blend of oils and surfactants in suitable proportion that rapidly forms an oil in water micro-emulsion with moderate gastric motility when exposed to the aqueous media present in the gastrointestinal tract. It typically produces a transparent micro-emulsion having reduced globule size and high thermodynamic stability. Rapid emulsion formation helps to keep the drug in a dissolved form, however, small droplet size offers a considerably larger interfacial surface area which further accelerate the absorption rate of drug with limited solubility and the extent of drug absorption by different mechanism related with the micro-emulsion carrier itself, thereby causing disturbance of the cell membrane and tight junctions of the intestinal epithelium increasing the permeability of the intestinal barrier (Djekic *et al* 2017). Moreover, the lipoidal part of SMEDDS encourages the intestinal lymphatic uptake of drugs which further helps in avoiding the pre-systemic biotransformation of drug molecules (Qureshi *et al* 2015; Li *et al* 2017; Kalepu *et al* 2013). This feature makes SMEDDS a meaningful choice for oral delivery of lipophilic and low bioavailable simvastatin. Recently, numerous SMEDDS products such as Sandimmun Neoral®, Norvir®, and Fortovase® have been widely commercialized (Yeom *et al* 2016).

Further, a systematic and structured optimization study was employed to design the self-emulsifying drug delivery system of Simvastatin by using the Design of Experiments (DoE). With the application of DoE, drug products with high and reproducible quality can be anticipated. Among all experimental designs, D-optimal mixture design is particularly suited for micro-emulsion systems as microemulsions essentially consist of three components, namely oil, surfactant and co-surfactant phase. Moreover, D-optimal designs are model independent and hence a straight way of optimization based on a set of criterion chosen and the suitable model that can fit can be attained. This in turn, allow a systematic manipulation of critical process parameters to achieve better product and process understanding with the identification of the optimal values of the critical process parameters that would yield a product with the required properties and characteristics (Zhang and Mao, 2017; Kumar and Shishu, 2015).

Hence, the purpose of this study was to systematically investigate the influence of the type and concentration of the oil, surfactants and co-surfactant on the drug loading capacity, dispersibility in aqueous media, and in vitro potential for drug absorption enhancement of the SMEDDSs for oral delivery of simvastatin. Solidification was done by using suitable adsorbent so as to get advantage of unit dosage form and improved physical stability.

MATERIALS AND METHODS

Materials

Simvastatin was gifted by Zydus Cadila Pvt. Ltd., Ahmedabad, India. Cremophore EL and Cremophore RH 40 were gifted by BASF, Mumbai. Tween 80, Tween 20, PEG 200 and PEG 400 were purchased from S D Fine Chemicals,

Mumbai. Isopropyl myristate, isopropyl palmitate and oleic acid were purchased from Chemdyes Corporation, Rajkot. All other chemicals and reagents were of pharmaceutical grades.

Solubility studies

The solubility of simvastatin in various oils, surfactants and co- surfactant were determined by adding excess amount of drug in each vial containing 2 ml of vehicle. The prepared mixtures were then mixed using a vortex mixer to facilitate solubilization. Mixtures were shaken on shaker bath at 30°C for 48 h. After reaching equilibrium, the mixtures were centrifuged at 3000 rpm for 10 min, then 0.1 ml supernatant was taken and the drug content was quantified using UV visible spectrophotometer at 237.59 nm after dilution with methanol (Padia *et al* 2015).

Pseudo ternary phase study

Pseudoternary phase diagrams were constructed using water titration method in order to obtain the concentration range of components for identifying the region of microemulsion. Surfactant (Tween 80) and co-surfactant (Cremophore EL) were mixed in six different volume ratios [1:1(A), 1:2(B), 1:3(C), 2:1(D), 3:1(E) and 4:1(F)] to prepare six different Smix. These S_{mix} ratios were chosen to reflect the increasing concentration of co-surfactant with respect to surfactant and increasing concentration of surfactant with respect to co-surfactant for detailed study of the phase diagram in the microemulsion formation. Pseudo ternary phase diagrams were constructed using the aqueous titration method from 1:9 to 9:1 ratio of oil to Smix. Slow titration with the aqueous phase was performed for each combination of oil and S_{mix} separately. The amount of aqueous phase added was varied to produce a water concentration in the range of 5% and 95% of total volume at around 5% interval. After each 5% addition of the aqueous phase to the oil: S_{mix} mixture, visual observation was made and recorded. Through visual observations, the categories assigned were either transparent and easily flowable, oil/ water microemulsion or milky/cloudy emulsion. The physical state of the microemulsion was marked on pseudo three component phase diagram constructed using PROSIM software with one axis representing aqueous phase, the other representing oil and the third representing a mixture of surfactant and co-surfactant at fixed weight ratios. For each S_{mix} ratio, a separate phase diagram was constructed. Only microemulison points are plotted (shaded area), so that there is no overcrowding of the phases in the diagram, as for the formulation development viewpoint, only the microemulsion formation area is of interest (Dokania and Joshi, 2015; Andey *et al* 2016).

Optimization of SMEDDS using D-Optimal mixture design

Development of SMEDDS involves rational selection of excipients, like oil, surfactant, co-surfactant. One of the current requirements in dossier for ANDA submission is the development of product considering the concepts of quality by design (QbD). Hence, thorough understanding of influence of excipients on the performance of product is essential. D-optimal mixture design provides an efficient means of optimizing the process as well as determining the optimal formulation of a specific mixture of oil, surfactant, co-surfactant in self micro emulsifying drug delivery system. To explore simvastatin apparent solubility, a mixture (D-optimal) experimental design was set up within the restricted domain.

In this study, the restricted experimental region was selected on the basis of results obtained from ternary phase diagram. The experimental study was designed based on a three component system: the oil X1 (oleic acid), the surfactant X2 (tween 80) and the co-surfactant X3 (Cremophore EL). Based on the previous results obtained from phase diagram and preliminary screening, the range of X1 was selected as 1-10%, X2 was selected as 10-29% and X3 was selected as 5-15%. Values of independent variables were introduced into the Design-Expert version 7 software and batch matrix was derived. Sixteen batches were prepared within the restricted domain, which allowed fitting of a reduced cubic model, a check for lack-of-fit and an estimate for experimental error. The experiments were carried out randomly to minimize systematic errors and experimental results were analyzed with Design Expert 7.0. The self- emulsification time (Y1) and solubility (Y2) were chosen as the responses (Patil *et al* 2016; Chatterjee *et al* 2016).

Preparation of liquid SMEDDS

A series of SMEDDS were prepared by mixing accurately measured amount of oleic acid,

Tween 80 and Cremophore EL into glass vials. The components were mixed well by gentle stirring at 37°C in water bath. Then, weighed amount of simvastatin (20 mg per 0.5 ml) was added and the systems were stirred continuously until simvastatin was completely dissolved. The mixtures were stored at room temperature.

Characterization of liquid SMEDDS

Self-emulsification time, solubility study, percent transmittance determination, droplet size analysis and zeta potential were determined for characterization of liquid SMEDDS. The efficiency of self-emulsification of oral micro emulsion was assessed using a standard USP dissolution apparatus. One millilitre of each formulation was added to 500 ml of water at 37±0.5°C. A standard stainless steel dissolution paddle rotating at 50 rpm provided gentle agitation. Time required to form emulsion was assessed visually (Čerpnjak *et al* 2015; Chavan *et al* 2015).

For solubility study, drug was added to 2 ml of liquid SMEDDS till super saturation. The resultant solution was kept in orbital shaker for 48 h. Each vial was centrifuged at 3000 rpm for 10 min. The supernatant was diluted with methanol. The concentration of drug was quantified by measuring the absorbance at specific wave length (238.73 nm) using UV–visible spectrophotometer. The content of drug was calculated from the standard calibration curve (Jannin *et al* 2015). Percent transmission measurement can be used to reflect clarity and micron size of globules. The percent transmittance of the system was measured at 650 nm using UV-visible spectrophotometer by using distilled water as blank (Zhang and Mao, 2017). For droplet size analysis and zeta potential measurements, one ml of liquid SMEDDS of simvastatin was dissolved in 500 ml of distilled water. The droplet size of the emulsions was determined by using a zetasizer that is able to measure sizes between 10 and 5000 nm. Light scattering was monitored at 25°C at a 90° angle, after external standardization with spherical polystyrene beads. The micromeritic size range of the globules is retained even after 500 times dilution with water proves the system's compatibility with excess water (Zhang and Mao, 2017).

Preparation of solid SMEDDS of simvastatin

Adsorption on solid carrier is easy and reliable method to convert liquid SMEDDS into solid product (S-SMEDDS). Colloidal silicon dioxide (Aerosil 200) shows high adsorption capacity and so it was used. The liquid SMEDDS (0.5 ml) was added dropwise over solid absorbent in a broad petri dish. After each addition, the mixture was homogenized using glass rod to ensure uniform distribution of the components. The resultant S-SMEDDS were passed through 500 mesh to get uniform free flowing aggregates. The aggregates were stored over anhydrous calcium chloride in desiccator until further evaluation.

Evaluation of solid SMEDDS of simvastatin

DSC, XRD and SEM studies

Differential scanning calorimetry (DSC) thermo scans of the pure simvastatin and respective S-SMEDDS were recorded using thermal analyzer. The samples were heated from 50 to 180°C at a rate of 10°C/min in an open pan using alumina as a reference material.

X-ray diffraction pattern of drug alone and formulation were recorded using X-ray diffractometer. D8 advance of Bruker AXS instrument, with Vertical Theta-Theta Goniometer with -1100 < 2θ < 1680 goniometer control was used. New short ceramic Copper X-ray tube with fine long focus was used. Two exchangeable detectors of scattered X-rays: NaI scintillator type detector with low background (0.4 cps) and high dynamic range (up to 2 × 106) and Braun position-sensitive detector were employed.

Scanning Electron Microscopy was performed for morphological study, sample was fixed on an aluminium stub with conductive double sided adhesive tape and coated with gold/palladium in an argon atmosphere (50 Pa) at 50 mA for 50 s and micrograph was taken at an appropriate magnification for detailed visualization of the surface using a Nova nano SEM 450 (FEI Ltd., USA). The samples were scanned at a voltage of 5kV.

Drug content studies

Drug content was determined by accurately weighing powder equivalent to 10 mg drug dissolved in 10 ml methanol. It was stirred for 15 min and filtered. Appropriate dilutions were prepared subsequently and were analyzed by UV-VIS spectrophotometer (UV-1600, Shimadzu, Japan) at 238.73 nm. Flow property was evaluated in terms of Carr's index,

compressibility index, Hausner's ratio and angle of repose.

In-vitro drug release study

The in-vitro dissolution study of S-SMEDDS and marketed drug product were carried out using USP-Type II dissolution test apparatus in 900 ml 0.1 M hydrochloric acid at 37±0.5°C with 100 rpm rotating speed. Samples were withdrawn at 10, 20, 30, 40, 50 and 60 min time interval and filtered through whatman filter paper. An equal volume of dissolution medium was replenished after every sampling to maintain constant volume. Samples were analyzed using a double beam UV spectrophotometer at 238.73 nm. The cumulative percentage drug released was calculated and graph was plotted against time.

RESULTS AND DISCUSSION

Solubility study

In this study, different oils, surfactants and co-surfactants were explored for determining solubility of simvastatin. For each excipient, λmax of the drug in methanol, *i.e.* 237.59 nm was found to be retained. This information indicates that each of these oils, surfactant and co-surfactants were compatible with the drug at room temperature. Amongst the oils tested, the maximum solubility of simvastatin was found in the oleic acid.

The reason behind this result is that other oils are less polar than oleic acid. The hydrophilic lipophilic balance (HLB) value has been proven to be very useful in choosing the best type of surfactant for immediate formation of O/W droplets and/or rapid spreading of the formulation in the aqueous environment. An important criterion for selection of the surfactant is that the required HLB value to form O/W micro-emulsion is greater than 10. A proper surfactant HLB value is a key factor for the formation of emulsion with small droplets. Among surfactants tested, Tween 80 could solubilize highest amount of simvastatin. Therefore, Tween 80 was selected as the surfactant for SMEDDS formulation. Among co-surfactants tested, Cremophore EL showed highest drug solubility. Therefore, cremophore EL was selected as the co-surfactant for SMEDDS formulation. The average solubility of simvastatin in various oils, surfactant and co-surfactant is as depicted in **Figure 1**.

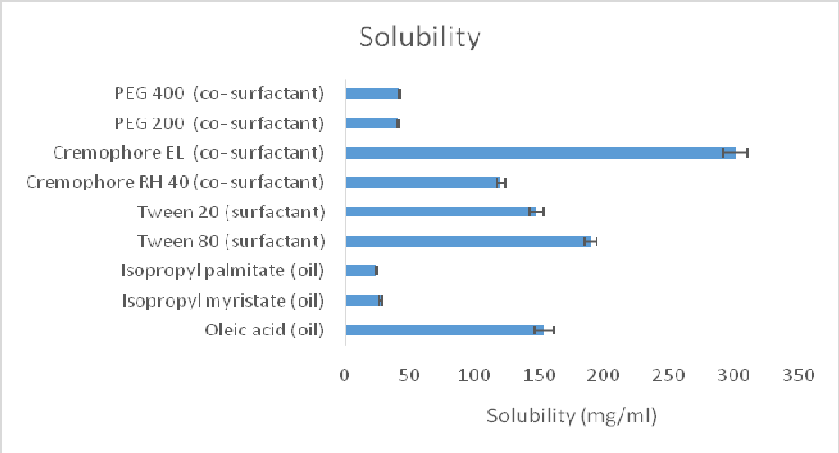


Figure 1. Solubility of simvastatin in various components, oil, surfactant and co-surfactant

Pseudo ternary phase diagram

The concentration of mixture components were recorded in order to complete the pseudoternary phase diagrams, and then the contents of oil, blend of surfactant and co-surfactant (Smix) and water at appropriate weight ratios were selected based on the results of ternary phase diagrams.

An *o/w* microemulsion region was found towards the water-rich apex of the phase diagram mixture. Only certain combinations of oil, surfactant and co-surfactant produced fine microemulsion upon dilution with water. The area bound by the points in the phase diagram displays the concentration range of SME mixture components that resulted in a clear microemulsion out of all the trial concentrations. All the combinations under test formed a microemulsion in certain concentrations, but the combination with wider SME region is

considered to be a better combination in terms of self-micro emulsification efficiency. In this study, ratio 2:1 was found to have wider SME region (**Figure 2**).

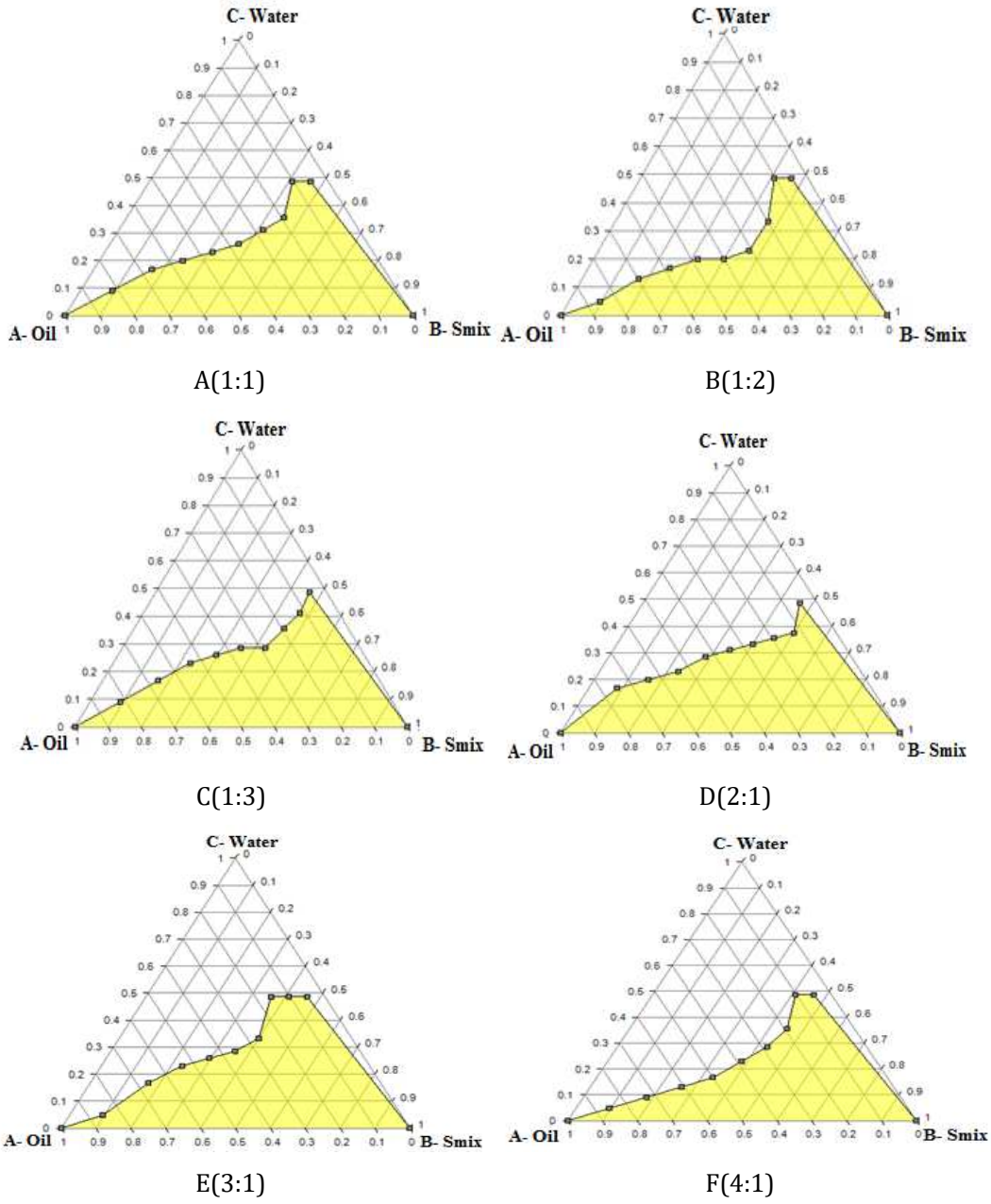


Fig. 2. Pseudo-ternary phase diagram formed by olive oil, Tween 80 and Cremophore EL surfactant blend and water; (A) 1:1; (B) 1:2; (C) 1:3; (D) 2:1; (E) 3:1; (F) 4:1

Optimization of SMEDDS using D-optimal mixture design

From pseudo ternary phase diagram study and preliminary experiments, the ranges of A (oleic acid in %), B (Tween 80 in %) and C (cremophore EL in %) were selected as 1-10%, 10-29% and 5-15% respectively. D-optimal mixture design was selected for the optimization. The mixture design includes a total of 16 experiments for three factors (amount of oleic acid, Tween 80 and Cremophore EL). The experimental runs with independent variables and the observed responses for the 16 SMEDDS formulations are shown in **Table 1**. The model incorporating main effect and interaction effects was selected based on the estimation of several statistical parameters, such as the multiple correlation coefficient (r^2), adjusted multiple

correlation coefficient (adjusted r^2) and the predicted residual sum of squares (PRESS), provided by the Design-Expert software (7.0) version.

Table 1. D-optimal mixture design with responses

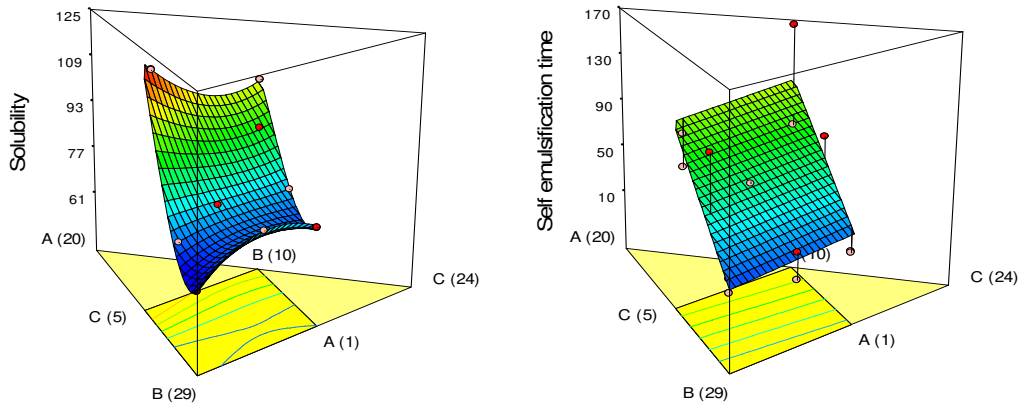
Run	Oleic acid (%)	Tween 80 (%)	Cremophore EL (%)	Solubility of simvastatin (mg/ml)	Self emulsification time (sec)
1	4.763	24.794	5.441	72.862	108
2	1.000	28.99	5.007	66.055	31
3	1.321	18.678	15.00	71.640	16
4	5.270	14.729	15.00	76.876	92
5	9.992	10.007	15.00	105.846	166
6	10.00	19.214	5.785	117.539	73
7	1.321	18.678	15.00	71.815	15
8	1.000	23.693	10.306	77.748	11
9	9.992	10.007	15.00	105.846	102
10	4.550	18.094	12.355	74.432	83
11	1.000	28.993	5.007	66.055	20
12	5.544	20.453	9.001	78.621	70
13	10.00	19.214	5.785	117.714	100
14	8.154	12.893	13.952	93.63	93
15	1.000	23.693	10.306	77.574	33
16	8.631	15.134	11.234	95.898	105

The statistical parameters of ANOVA analysis for each response is listed in the **Table 2**. The difference observed in the predicted and adjusted r2 is less depicting their close agreement. Adequate precision measures the signal to noise ratio. Adequacy of precision compares the range of predicted values of the design points to the average prediction error. Ratios greater than 4 indicate adequate model discrimination.

Table 2. Statistical parameters by ANOVA analysis for models and responses

Response	Std. Dev.	Mean	% CV	PRESS	r^2	Adjusted r^2	Predicted r^2	Adequate Precision	*p* value
Solubility	0.17	85.63	0.190	7.99	1	0.991	0.992	391.660	<0.0001
Self emulsification time	25.2	69.88	3.607	13.02	0.92	0.985	0.947	8.990	0.0002

The polynomial equation in terms of coded factors can be used to make predictions about the response for given levels of each factor. By default, the high levels of the factors are coded as +1 and the low levels of the factors are coded as -1. The model was cubic for response solubility and linear for self-emulsification time. The coded equation is useful for identifying the relative impact of the factors by comparing the factor coefficients; for response solubility, -20.25*A+ 1.008*B-1.99*C+1.87*A*B+1.59*A*C+0.28*B*C-0.09*A*B*C+0.04*A*B*(AB)-0.005*A*C*(A-C)+0. 0024*B*C*(B-C) and for self-emulsification time, +10.12*A+0.24*B+1.18*C. The model F value for both the responses further indicates that the model is significant. The three-dimensional graphs of RSM are generated by plotting the response model against three of the factors, in which the interaction between the variables and their mutual dependence is clearly observed as depicted in **Figure 3a-b**. A, B and C respectively represents percentage of oleic acid, Tween 80 and Cremophore EL. The **Figure 3a** shows that solubility of simvastatin increases with increase in amount of oil up to certain extent and decreases with increase in amount of surfactant and co- surfactant. The **Figure 3b** depicts linear relationship between factor A, B and C. It can be observed from the plot that self emulsification time increases with increase in amount of oil and decreases with increase in amount of surfactant and co-surfactant.



(a) (b)

Fig. 3. 3-D response surface plot for (a) solubility and (b) self emulsification time

The design offered many solutions to prepare an optimized batch, but the solutions were reduced by setting constraints for the response self emulsification time (less than 25s). The Design expert 7.0 suggested 5 solutions with desirability 1 and among these two were selected for optimization of formulation composition. Therefore, to validate the optimized model, the formulation composition 1 and 2 were prepared. Observed value of an optimized solution 2 was quite closer to the predicted value, resulting in less % error (**Table 3**). Hence, optimized formula (1:28.993:6.199) was selected for preparation of SMEDDS.

Table 3. Verification study: a comparison of predicted and experimentally observed responses of all components

Oil (%): Surfactant (%): Co-surfactant (%)	Response	Predicted	Observed	% Prediction error
Solution 1 : 1:27.801:5.007	Solubility (mg/ml)	66.03	65	2.96
	Self emulsification time (sec)	23.94	24.65	1.55
Solution 2 : 1:28.993:6.199	Solubility (mg/ml)	70.43	71.23	1.135
	Self emulsification time (sec)	24.06	23.78	1.16

Evaluation of optimized SMEDDS

In order to assess the optical clarity, UV-visible spectrophotometer was used to measure the amount of light of given wavelength transmitted by the SMEDDS. The % transmittance of optimized batch was found to be 99.1%. Droplet size is considered to be a decisive factor in self emulsification performance because it is related with the rate and extent of drug release and absorption.

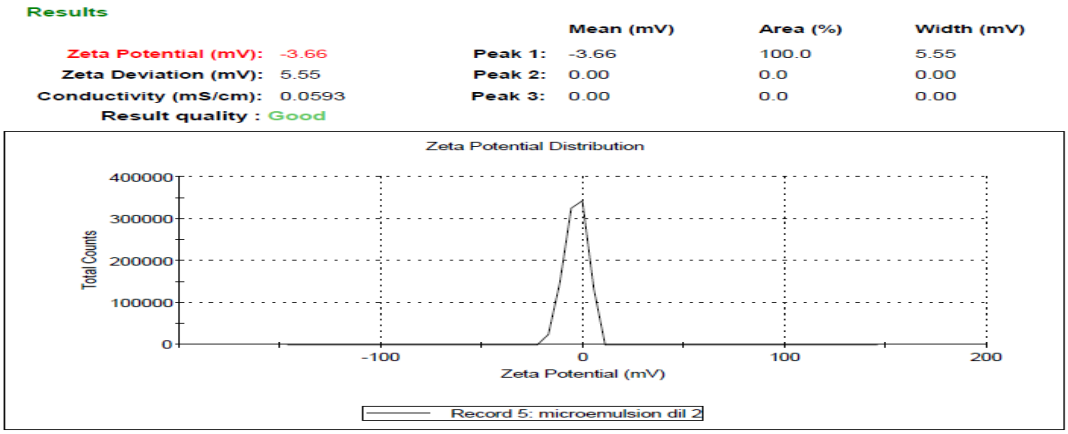
Non-ionic surfactants can effectively stabilize the oil-water interface and hence are more efficient. Furthermore, the decrease in the droplet size reflects the formation of a better closed packed film of the surfactant at the oil-water interface, thereby stabilizing the oil droplets. The droplet size of optimized SMEDDS was determined after dilution of 500 times in water. The mean droplet size was found to be 755.3 nm. Zeta potential of the optimized batch was found to be -3.66 mV. The low value of zeta potential indicate better physical stability (**Figure 4**).

Evaluation of solid SMEDDS of simvastatin

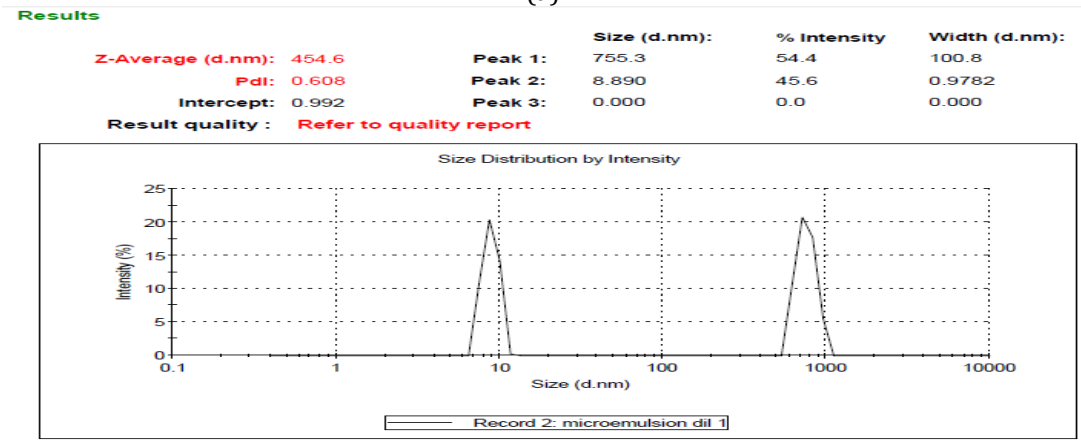
The physical state of the drug present in solid SMEDDS was confirmed from DSC studies. The DSC curves of simvastatin and S-SMEDDS formulations are shown in **Figure 5** and pure simvastatin showed sharp endothermic peak at temperature 138 °C, corresponding to its melting point and indicating its crystalline nature showing melting occurred at that temperature. However, result shows the disappearance of endothermic peak of the drug in the S-SMEDDS and supports the presence of simvastatin in an amorphous form in S-SMEDDS.

X-ray diffraction pattern of simvastatin and solid SMEDDS was recorded using X-ray diffractometer, XRD study was used to measure the crystallinity of the solid SMEDDS. The peak position (angle of diffraction) is an identification tool of a crystal structure, whereas the number

of peak measures sample crystallinity in a diffraction. The XRD pattern of simvastatin and solid SMEDDS are presented in **Figures 6a-b** respectively.

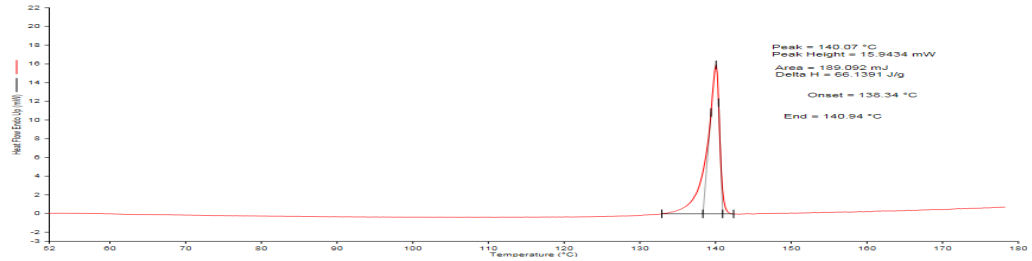


(a)

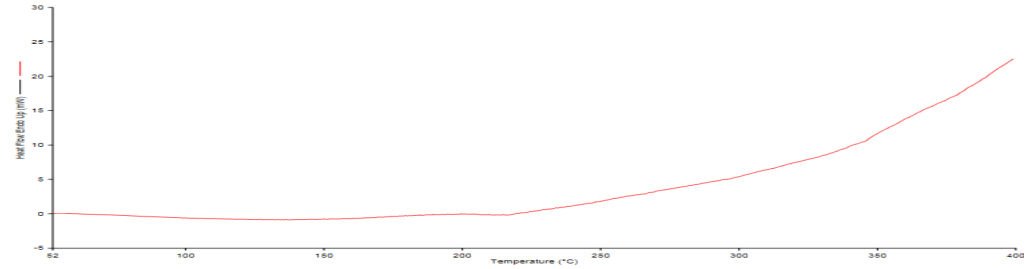


(b)

Fig. 4. SMEDDS: (a) zeta potential and (b) globule size



(a)



(b)

Fig. 5. DSC thermogram of (a) pure simvastatin and (b) solid SMEDDS of simvastatin

The XRD pattern of simvastatin indicated the presence of major peaks at 8.32°, 10.88°, 17.17°, 18.6°, 21.38°, 22.16°, 23.9°, 24.66°, 31.6° and 32.06°. The diffraction pattern of pure drug reflected the crystallinity of drug and above peaks were noticeably reduced in case of S-SMEDDS indicating the conversion of crystalline state to an amorphous state.

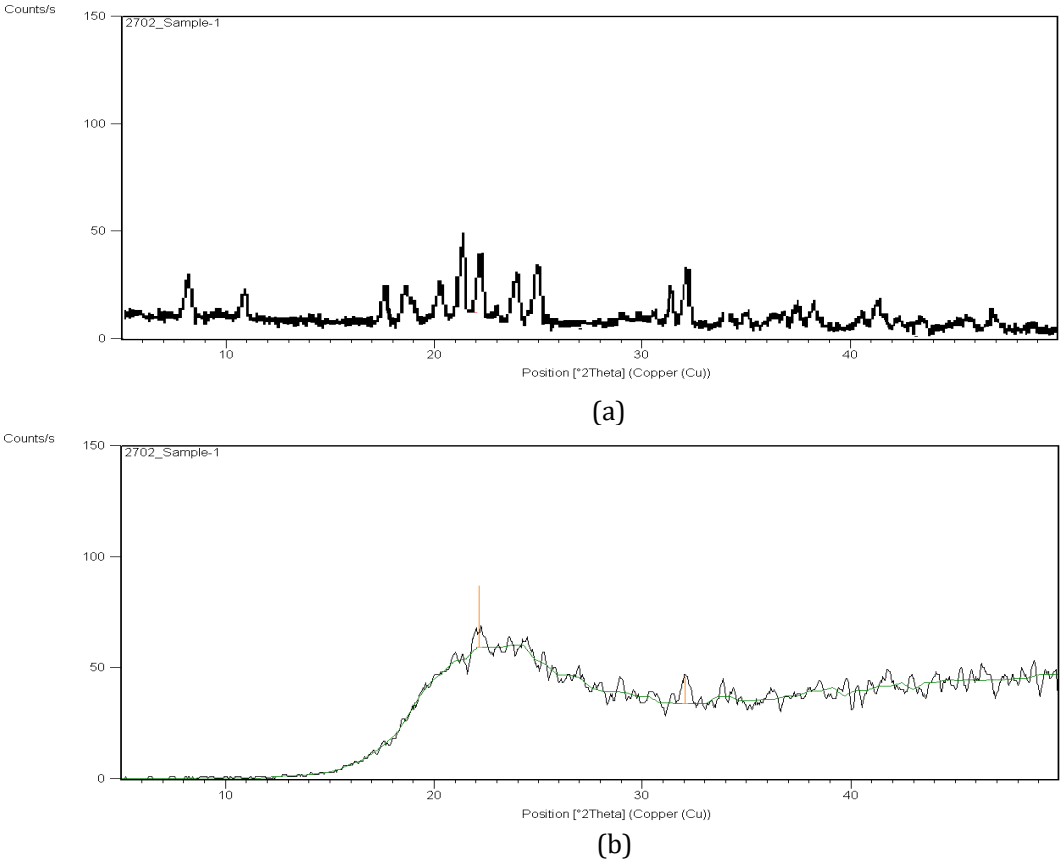


Fig. 6. X-ray diffraction pattern of (a) pure simvastatin and (b) solid SMEDDS of simvastatin

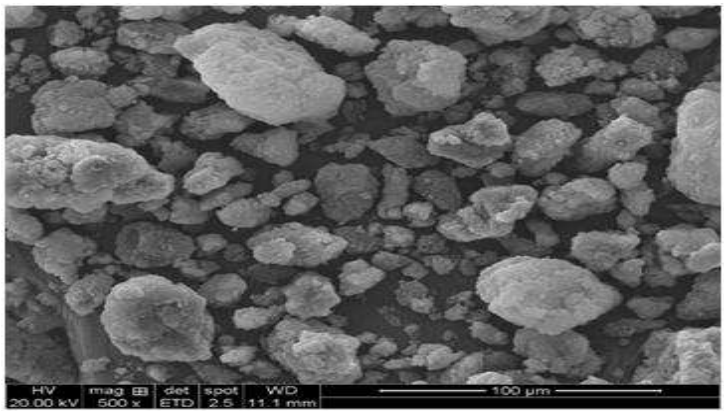


Fig. 7. SEM image of solid SMEDDS

The morphology of the optimized S-SMEDDS showed spherical particles without aggregation by scanning electron microscopy (**Figure 7**). The mean percent drug content of S-SMEDDS was found to be 96.931±0.236%. S-SMEDDS exhibited good flow property in terms of bulk volume (4.133 ± 0.152), tapped volume (3.7 ± 0.173), angle of repose (29.367 ± 0.416), bulk density (0.484 ± 0.017), tapped density (0.541 ± 0.025), compressibility index (10.499 ± 1.509) and hausner's ratio (1.118 ± 0.018). Dissolution profile of optimized batch of S-SMEDDS revealed

83.833% drug release within 20 min, whereas tablet showed 42.391% drug release after 20 min. So, it can be concluded that the optimized S-SMEDDS had better dissolution profile compared to marketed tablet, as shown in the **Figure 8**.

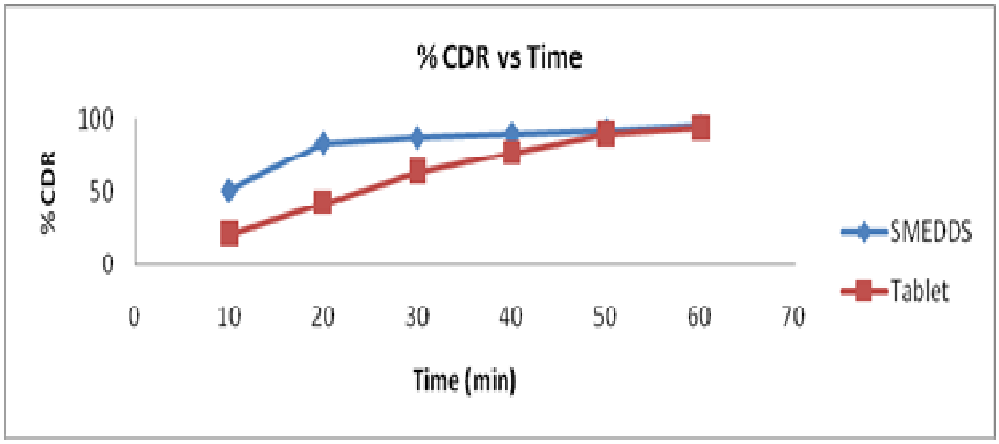


Fig. 8. Cumulative drug release profiles for S- SMEDDS and tablet formulation

CONCLUSION

Solid SMEDDS is one of the recent approaches for formulation of unit dosage form for drugs with low aqueous solubility. Selection of oil and surfactant, co surfactant blend is crucial and vary from drug to drug based on solubility study and hence optimization using experimental design allowed evaluating the selected factors simultaneously, including interactions between factors, by means of a rational approach in order to reach the optimum conditions.

The optimized batch showed good results in terms of self-emulsification time (<25 s) and solubility (>70 mg/ml). The optimized solid SMEDDS formulation of simvastatin showed significant increase in dissolution rate compared to marketed tablet indicates the potential of SMEDDS. In nutshell, solid SMEDDS formulation is capable to enhance solubility and dissolution of poorly water soluble drugs like simvastatin which may result in improved therapeutic performance.

CONFLICT OF INTEREST

There is no conflict of interest.

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