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FORMULATION AND DEVELOPMENT OF SELF-MICROEMULSIFYING DRUG DELIVERY SYSTEM OF SIMVASTATIN

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ABSTRACT

Self-micro emulsifying drug delivery system (SMEDDS) is a promising system for the Biopharmaceutics Classification System (BCS) class II drugs. The current research aimed to improve the dissolution of poorly water-soluble anti-diabetic drug simvastatin by formulating it in SMEDDS. Liquid SMEDDS of simvastatin were formulated with Capmul MCM C8 and oleic acid as oil phase, Cremophor RH 40 and Tween 80 as surfactant phase, and Transcutol P as cosurfactant phase after screening various vehicles. The prepared formulations were evaluated for self-emulsifying ability and phase diagram was constructed to optimize the system. These systems were further characterized for globule size, effect of pH and robustness, zeta potential, drug content, viscosity, self-emulsification time, poly dispersity index, % transmittance, thermodynamic stability, surface morphology, and drug release. The system was robust to different pH media and dilution volumes. The optimized system possessed a mean globule size of 122.2 nm, zeta potential around -22.9 mV, drug content 99.66 ± 0.47%, viscosity 0.8874 ± 0.026 cP, emulsification time 38 s, poly dispersity index value of 0.5, and transmittance value of 99.3 ± 0.6%. Drug release in hydrochloric acid buffer pH 2 was found to be 99.35 ± 0.38%. More than three-fold increase in dissolution characteristics of simvastatin in SMEDDS was observed as compared to pure and marketed formulation. Liquid SMEDDS filled in hard gelatin capsule (HGC) shell was found to be compatible. Stability studies show there was no sign of phase separation or precipitation and no change in drug content was observed.

KEY WORDS: Pseudoternary phase diagram, self-microemulsifying drug delivery system, surfactant/cosurfactant ratio.

INTRODUCTION

Diabetes mellitus (Type I and II) is a progressive disease characterized by hyperglycemia, due to inadequate control of levels of blood glucose by the pancreatic hormone insulin and/or abnormal resistance to insulin. Initial treatment includes modifications to diet and exercise, followed by prescription of an oral antidiabeticagent. Simvastatin (thiazolidinediones) is classified under Biopharmaceutics Classification System (BCS) classification II, that is, highly permeable and low soluble and is a potent antidiabetic drug. Though simvastatin has good bioavailability, but the poor aqueous solubility and slow dissolution rate of drug may have negative impact on its bioavailability and subtherapeutic plasma drug levels may lead to therapeutic failure. Also presence of foods affect theabsorption and delays peak plasma concentration up to 5-6 h.[1] Recently, much attention has been focused on lipid-based formulations like self-microemulsifying drug delivery system (SMEDDS) and has been an attractive option due to its potential for delivery of hydrophobic drugs and the outstanding advantages includingspontaneity of formation, high solubilization capacity, thermodynamic stability, self-preserving nature, low cost, etc. Self-microemulsifying systems are isotropic mixtures of oil, surfactants, and cosurfactants that form fine oil in water (O/W) microemulsion upon mildagitation followed by dilution in aqueous media, suchas gastrointestinal tract (GIT) fluids. These formulationsspread readily in the GIT, and the digestive motility of the stomach and the intestine provide the agitation necessary for self-emulsification. [1, 2]

MATERIALS AND METHODS

Simvastatin was gifted by Microlabs Pharma, Bangalore. Capmul MCM C8 obtained as gift sample from AbitechCorporation. Transcutol P and LabrafacLipophile WL 1349 were gifted by Gattefosse India Ltd; Cremophor

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RH 40 was gifted by BASF, Mumbai. Tween 80 and oleic acid were purchased from Research Lab Fine Chem Industries, Mumbai.

EXPERIMENTAL

Solubility studies

Screening of excipients was done by determining the equilibrium solubility of simvastatin in different oils and surfactants. Two milliliter of each of selected oil, surfactant sample was added in glass vial containing excess amount of simvastatin (200-300 mg), the drug was mixed in oil and surfactant by means of magnetic stirrer for 30 min and the vials were kept in sonicator for 1 h. Further mixing was carried out by keeping the vials on the mechanical shaker for 72 h for reaching the equilibrium. These vials were centrifuged at 7,000-10,000 rpm for 10 min. After centrifugation, undissolved drug was removed by filtering through 0.44 μm Whatman filter paper. The amount of dissolved drug was determined by diluting the supernatant with methanol and analyzing by ultraviolet (UV)-spectrophotometer (Jasco V 630, Japan) at 267 nm.[3-5]

Selection of surfactant

The selection of best surfactant from a large pool of surfactants was done on the basis of emulsification study, solubility study, and % transmittance study. For emulsification study, oil and surfactant were mixed in 1:1 ratio by weight, heated at 40-50°C and stirred to form homogeneous mixture, ratio of oil to surfactant was decided on the basis of requirement as stated in literature for spontaneously emulsification formation, oil surfactant mixture was added in distilled water in 1:100 ratio, and then visually assessed using the grading system. From the solubility study, best surfactant of choice for SMEDDS formulation was screened. For % transmittance study, oil-surfactant mixture (1 ml) was added in 100 ml distilled water in drop-wise manner and % transmittance was measured using UV-visible (VIS) spectrophotometer.[6-8]

Selection of cosurfactant

Cosurfactant was selected on the basis of enhancement of emulsification in the emulsifying study, solubility study, and % transmittance study. Various cosurfactants were screened by mixing surfactant with selected cosurfactants in 1:1 ratio by weight. Oily phase was added to this mixture in 1:3 ratio by weight, heated, and stirred gently to form homogeneous mixture.[7,9,10]

Formulation and development of simvastatin SMEDDS

A series of SMEDDS formulation [Table 2] were prepared using Capmul MCM and oleic acid in ratio of 2:1 as oil, CremophorRH 40 and Tween 80 combination in ratio of 3:1 as a surfactant.

Table 1: Formulation of trial batches

Ingredients (mg)	F1	F2	F3	F4
Pioglitazone HCl	15	15	15	15
Capmul MCM+Oleic acid (2:1)	180	420	600	200
Cremophor RH 40+Tween 80 (3:1)	740	480	330	740
Transcutol P	80	100	70	60
Total Weight (mg)	1,000	1,000	1,000	1,000

Table 2: Pioglitazone HCL SMEDDS formulation with their composition

Formulation (oil:SmixAB)	Oil (mg) (Capmul MCM+oleid-2:1)	SmixAB (3:1) (mg)	Drug (mg)
F1 (2:8)	105	480	15
F2 (3:7)	165	420	15
F3 (4:6)	225	360	15
F4 (5:5)	285	300	15
F5 (6:4)	345	240	15
F6 (7:3)	405	180	15
F7 (8:2)	465	120	15

Total weight: 600gm

Phase (SmixA), and Transcutol P as a cosurfactant. The mixture of surfactant phase and cosurfactant phase in the ratio of 3:1 is called SmixAB. Proportion of oil, surfactant, and cosurfactant was determined by pseudoternary phase diagram. In all the formulations, the level of simvastatin was kept constant (15 mg). Briefly accurately weighed simvastatinwas placed in glass vial, and oil, surfactant, and cosurfactant were added. The ingredients were further mixed by gentle stirring and were heated at 40-50°C (30 min) until simvastatin was perfectly dissolved. The mixture was stored at room temperature until further use. The formulation batches were selected to cover low concentration of oil to high concentration as to get optimum oil and surfactant concentration, and hence,oil concentration from 20 to 80% and surfactant concentration 80 to 20% were selected for formulation (oil:SmixAB = 2:8:8:2).

Filling of SMEDDS in hard gelatin capsule

The liquid SMEDDS of the selected batch was filled in the Hard Gelatin Capsule (HGC) shell (Qualicaps, Japan). The size of the capsule shell selected according to the final volume of the formulation. The leakage problem of the liquid filled in the HGC was solved by the band sealing process (5% gelatinsolution was prepared and in this solution approximately 10 empty HGC shells were soaked for about 10-12 h, this solution was used for band sealing).[14,15]

EVALUATION OF SMEDDS

Robustness

Robustness to dilution was studied by diluting the final liquid SMEDDS 100 and 1,000 times with various dissolution media viz. 0.1N HCl and Phosphate buffer pH 6.8. The diluted microemulsions were stored for 12 h and observed for any signs of phase separation or drug precipitation.[10,16]

Self-emulsification and dispersibility test

Evaluation of the self-emulsifying properties of SMEDDS formulations was performed by visual assessment. The formulations were subjected to test for speed of emulsification, clarity, and apparent stability of the resultant emulsion and further categorized as per grading system (A-bluish clear microemulsion and B-milky white microemulsion, both these type emulsify within 1 min.). Visual assessment was performed by drop-wise addition of the preconcentrates (SMEDDS) into250 ml of distilled water. This was done in a glass beaker at room temperature, and the contents were gently stirred magnetically at ~100 rpm. [14, 16, 17]

Droplet size measurement

SMEDDS formulation (1 ml) was diluted with 100 ml deionized water in a beaker with constant stirring using a glass rod. The resultant emulsion was then subjected to particle size analysis. The droplet size distribution, polydispersity index of the resultant microemulsion was determined by dynamic light scattering with particle size apparatus (Malvern Zetasizer, UK). After equilibrium, the particle (droplet) size was recorded. The reduction of the droplet size to values below 200 nm lead to the formation of SMEDDS; which are stable, isotropic, and clear oil/water (o/w) dispersions. All studies were repeated in triplicate. This is a crucial factor in self-emulsification performance because it determines the rate and extent of drug release as well as the stability of the emulsion. [11, 12, 18]

Percentage transmittance

A total of 1 ml of SMEDDS formulation was diluted with 100 ml distilled water. Percentage transmittance was then measured spectrophotometrically at 638.2 nm using distilled water as a blank by UV-spectrophotometer. [17]

Thermodynamic stability studies

SMEDDS was diluted with deionized water and then centrifuged at 10,000 rpm for 10 min and formulation was observed visually for phase separation. The formulations that did not show any sign of phase separation after centrifugation were subjected to three to four freeze-thaw cycles, which included freezing at −4°C for 24 h followed by thawing at 40°C for 24 h. Centrifugation was performed at 3,000 rpm for 5 min. The formulations were then observed for phaseseparation. Only formulations that were stable to phaseseparation were selected for further studies.[19]

Drug content determination

SMEDDS (100 mg) was dissolved in 10 ml of methanol in a 10 ml volumetric flask separately and then 0.1 ml of stock solution measured accurately and then transferred to 10 ml volumetric flask to which 10 ml methanol was added and filtered through Whatman filter paper. The above solution was analyzed by UV spectrophotometer at 267 nm. The amount of drug present in the formulation was determined using the prepared standard calibration curves of drug in methanol.[16]

Viscosity determination of SMEDDS

Ten to twenty grams of each formulation was weighed and transferred to beaker, and the viscosity of formulation was determined with the help of Brookfield Viscometer DV-E model, spindle no. 6, at 10 rpm for 5 min.

Zeta potential

Zeta potential is used to identify the charge of the droplets. In conventional SMEDDS, the charge on an oil droplet isnegative due to presence of free fatty acids. Zeta potential determined by Zetameter was monitored at 25°C at a scattering angle 173° (Zetasizer Nano-ZS, Malvern, UK).[16]

Scanning electron microscopy

The liquid Scanning electron microscopy (SEM) analysis was done to assess SMEDDS morphology, microemulsionappearance, and droplet size range.

In vitro dissolution studies

The quantitative in vitro release test was performed in hydrochloric acid buffer pH 2 as per United States Food and Drug Administration (USFDA) Guideline, using US Pharmacopoeia XXIV dissolution apparatus, Paddle apparatus at 50 rpm speed and temperature 37 ± 0.5°C. The SMEDDS formulations were filled into HGCs (00 size) followed by band sealing and used for drug release studies. During dissolution study, the HGC was tied to paddle with wire to avoid floating of capsule, results were compared with those of plain drug in HGC and marketed formulation. During the release studies, sample of medium was withdrawn at various time intervals and subjected to drug

analysis using UV spectrophotometer (JascoV-630, Japan) at 267 nm. The removed volume was replaced each time with 10 ml of fresh medium.[16,19,20]

Stability study

The SMEDDS formulations were filled into empty HGCs (size 00) and subjected to stability studies at 4°C, 25 ± 2°C/65 ± 5% (relative humidity (RH)), and 40 ± 2°C/75 ± 5% RH. Samples were charged in stability chambers with humidity and temperature control. They were withdrawn at specified intervals for analysis over a period of 3 months. The SMEDDS was evaluated by visual inspection for physical changes such as color and drug precipitation andalso for drug content.[21-23]

RESULT AND DISCUSSION

Solubility studies

One important consideration when formulating a self-emulsifying drug delivery formulation is to avoid precipitation of the drug on dilution in the gut lumen in vivo. Therefore, the components used in the system should have high solubilization capacity for the selected drug. Solubility of simvastatin in various oils, surfactants, and cosurfactantsis shown in the Table 3. Simvastatin exhibited good solubility in the Capmul MCM C8 and oleic acid among the oils. Data suggest that drug has more solubility in medium chain triglycerides (MCT) rather than long chain triglycerides (LCT) because MCT possess higher ester content per gram than LCT, so drug has higher solubility in MCT than LCT. Thus, for further studies Capmul MCM and oleic acid as oils were selected. In case of surfactants, the drug exhibited good solubility in Cremophor RH 40 and Tween 80. In case of cosurfactants, Transcutol P shows good solubility.

Robustness

The influence of dilution (i.e., 100 and 1000 times) with various diluents (i.e., acid buffer pH 2 and buffer pH 6.8) was evaluated. Larger dilutions may mimic conditions better in the stomach following oral administration of SMEDDS (preconcentrate). On dilution with all the diluents there was no change in the visual clarity even after 8 h at room temperature for all formulations. Observation of the dilution studies showed that none of the formulation show phase separation or drug precipitation, because the selected oils and surfactants show high water uptake capacity. It was also observed that pH of dilution media does not affect SMEDDS stability.

Self-emulsification and dispersibility test

The result of self-emulsification and dispersibility studies is given in Table 5. It was observed that as the oil component increases in the formulation beyond a certain limit there was generation of nonclear dispersion. Among seven formulation, F1-F5 show grade A, while F6 and F7 exhibited grade B. Also self-emulsification time for F6 and F7 were more (57 s and 1.05 min, respectively). Therefore, these two batches were not taken for further study.

Droplet size measurement

The mean droplet size of the diluted SMEDDS preconcentrateswas very low and all were found to be in the nanometricrange (<200 nm). The mean droplet size of the formulation is shown in the Table 5. F4 was found to have the mean droplet size of 122.2 nm as indicated in Figure 2 with optimum concentration of oils and surfactants, therefore it was considered to be the best formulation. In all five formulations tested, the droplet size increased upon decreasing weight of Smix. All the polydispersity values were below 0.6, suggesting good uniformity in the droplet size distribution after dilution with water. Table 5 confirms the average size of simvastatin SMEDDS formulations to be in the range of 98.84-168.3 nm.

Percentage transmittance

Percentage transmittance of optimized F4 SMEDDS after diluting 100 times with deionized water was 99.30%. Transmittance value [Table 5] of SMEDDS formulation was in proximity to 100%; it indicated that clear microemulsion was obtained when SMEDDS was diluted 100 times with deionized water.

Tabble 3: Viscosity, % Transmittance, droplet size, ploydispersity index (PDI), drug content, % drug release dispersibility grade, self-emilsification time, and zeta potential of various SMEDDS

Batch	Viscosity (cP)	% Transmittance	Droplet size (nm)	PDI	Drug content(%)	Drug release(%)	Dispersibility grade	Emulsification time (min:s)	Zeta Potential (mV)
F1	0.8873±0.43	98.4±0.5	98.84	0.332	98.68±0.18	100.85±0.65	A	00:29	
F2	0.8869±0.012	98.8±0.4	122.69	0.312	99.09±0.102	100.18±0.97	A	00:32	
F3	0.8871±0.077	99.1±0.1	152.8	0.551	99.91±0.38	98.41±0.25	A	00:35	
F4	0.887±0.026	99.3±0.6	122.2	0.5	99.66±0.47	99.35±0.38	A	00:38	-22.9
F5	0.8877±0.042	99.7±0.2	168.3	0.263	98.43±0.24	98.03±0.77	A	00:44	
F6	-	-	-	-	-	-	B	00:57	
F7	-	-	-	-	-	-	B	1:05	

SMEDDS: Self-microemulsifying drug delivery system

Thermodynamic stability studies

The objective of thermodynamic stability is to evaluate the phase separation and effect of temperature variation on SMEDDS formulations. The SMEDDS formulation is found to be stable in these conditions; metastable formulation is thus avoided and frequent test need not to be performed during storage. All the formulations were stable to centrifugation and did not show any phase separation. No changes in visual description of samples after freeze thaw cycles were observed. Transmittance study observations showed % transmittance after freeze thaw cycle in the range of 99.18-99.35% for all formulations.

Drug content determination

The percentage drug content of formulations was determined spectrophotometrically at 267 nm by preparing the calibration curve of pure simvastatin in methanol. The drug content of various batches is given in Table 5. The F4 formulation shows drug content of 99.66 ± 0.47%.

Viscosity determination of SMEDDS

The viscosity of microemulsion systems can be monitored by standard rheological techniques (Brookfield Viscometer DV-E). It depends on oils and surfactants used. It was observed that the viscosity of all the formulations is less than 0.8877 cP [Table 5]. Formulation; F4 has the minimum viscosity0.8874 cP, which is highly similar to that of water, that is, 1.0. Thus, it shows that SMEDDS forms o/w microemulsion, water remains as external phase and viscosity of SMEDDS is near to that of water. This reveals that formulation F4 is very clear, transparent, and low viscous liquid.

Zeta potential

The magnitude of the zeta potential gives an indication of thepotential stability of the colloidal system. If all the particles have a large negative or positive zeta potential they will repel each other and there is dispersion stability. Zeta potential of the system negative (−) mV, which indicates the droplets of microemulsion have negative charge. The zeta potential of optimized F4 formulation was found to be −22.9 and Figure 3 confirms the zeta potential of F4 simvastatin SMEDDS.

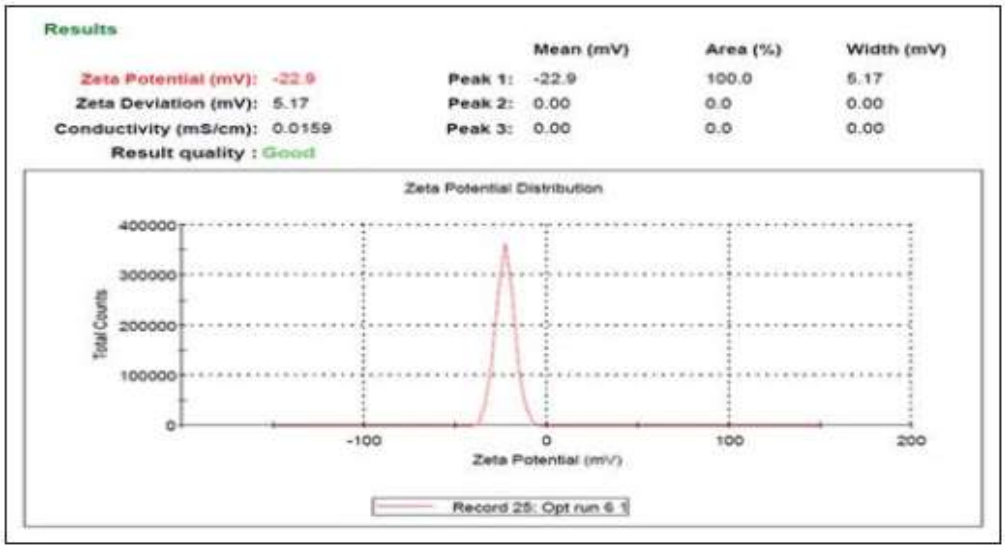

Figure 1: Zeta potential of pioglitazone HCI SMEDDS F4 formulation

In vitro dissolution studies

Simvastatin is insoluble in water and showed pH-dependent solubility. As shown in Figure 4, plain drug showed very less release 26% even after 40 min in pH 2 buffer. Marketed (Actos Tablet, 15 mg) formulation showed about 38% release after 40 min in pH 2. Whereas, SMEDDS showed rapid release of drug in buffer pH 2. At 20 min about 45% of simvastatin from SMEDDS (F4) was released and more than 86% was released after 35 min, complete release was observed in 40 min. In other words, SMEDDS could quicklyform clear and transparent solution under the condition of dissolution. It was also evident that release of simvastatin from SMEDDS was independent of pH dissolution medium.

SEM

Liquid SMEDDS micrographs suggesting that the drug is present in a completely dissolved state in the SMEDDS. From Figure 5, it was concluded that, the particle are globular, uniform in size, and well-separated. There was no agglomeration and globule size is in the nanometer scale.

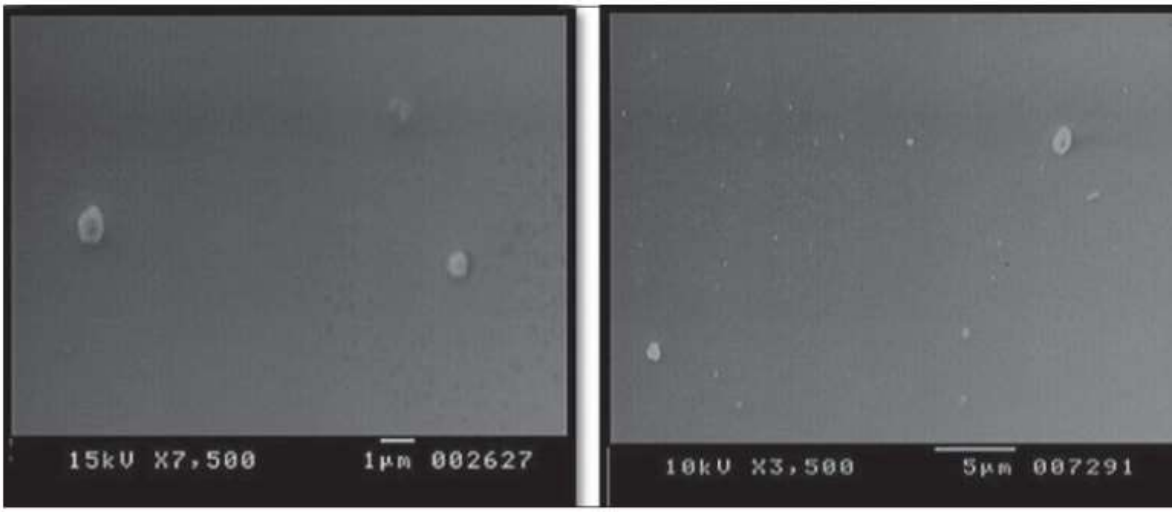

Figure 2: Scanning electron microscopy (SEM) Images of pioglitazone F4 SMEDDS formulation

Stability study

At the end of stability study, no phase separation and drug precipitation was observed in SMEDDS formulations. The drug content at the end of stability study for various SMEDDS formulation ranges from 99.04 to 99.58%.

CONCLUSION

SMEDDS preparations of simvastatin were successfully prepared using Capmul MCM C8 and oleic acid (2:1) as oil phase, Cremophor RH 40 and Tween 80 (3:1) as surfactant phase, and Transcutol P as cosurfactant phase. Liquid SMEDDS were filled in the HGC shell and it was found to be compatible. Based on in vitro dissolution studies, it was concluded that the simvastatin SMEDDS with optimum concentrationof oil and surfactant showed complete and faster dissolution profile as compared to marketed formulation of simvastatin (ACTOS 15 mg tablet). pH independent dissolution profile of SMEDDS compared to ACTOS tablet may definitely improve the oral bioavailability of simvastatin with reduced dose and variability.

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