ISSN 2063-5346

SIMVASTATIN SELF MICRO-EMULSIFYING DRUG DELIVERY SYSTEM: FORMULATION AND EVALUATION

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Article History: Received: 01.02.2023 **Revised:** 07.03.2023 **Accepted:** 10.04.2023

Abstract

The purpose of the current work was to create a solid dosage form tablet of self-micro emulsifying drug delivery system (SMEDDS) by adsorption liquid self-micro emulsifying drug delivery system with an inert solid carrier aerosil 200 and avicel PH 102 to increase the oral bioavailability of the medication Simvastatin, which is poorly water-soluble. Simvastatin, capryol 90, tween 80, and polyethylene glycol 400 were the ingredients of the self-micro emulsifying drug delivery system. The self-micro emulsifying drug delivery system examination revealed that the particle size was in the micro emulsion region. Magnesium stearate, polyvinylpyrrolidone, and avicel PH 102 were used in the direct compression method to turn the solid self-microemulsifying drug delivery system into a tablet. Tablets, self-micro emulsifying drug delivery systems, solid self-micro emulsifying drug delivery systems, and plane drug. Simvastatin's release rate was much lower than that of self-micro emulsifying drug delivery systems, solid self-micro emulsifying drug delivery systems, and tablet formulations. The findings of this study suggested that prepared tablets might be utilised as an efficient oral solid dosage form to increase the solubility and bioavailability of Simvastatin, a medication that is poorly soluble in water.

Keywords— *Simvastatin*, SMEDDS, *SEDDS, Pharmacodynamics, Tween 80, PEG 400, Avicel PH102, Tablet.*

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DOI: 10.31838/ecb/2023.12.s1.123

INTRODUCTION

An antihyperlipidemic drug called simvastatin is a chemical descendant of lovastatin. Simvastatin has two times the strength of lovastatin. It belongs to the class of medications known as HMG-CoA reductase inhibitors, or "statins." By blocking the liver enzyme HMG-CoA reductase, which is required for the creation of cholesterol, statins lower cholesterol. Statins reduce triglycerides, low density lipoprotein (LDL), or "bad" cholesterol, and total cholesterol in the blood. Coronary artery disease is thought to have a significant role in LDL cholesterol. Reversing coronary artery disease through lowering LDL cholesterol levels is possible. The "good" cholesterol known as high density lipoprotein (HDL) is likewise increased by statins. As with lowering LDL cholesterol, increasing HDL cholesterol levels may decrease coronary artery disease. Simvastatin is an active pharmacological medication that is extremely permeable and belongs to BCS class II. Self-micro emulsifying drug delivery systems (SMEDDS) have effectively arisen in recent years to increase the solubility, chemical stability, and oral bioavailability of a number of poorly water-soluble drugs. The SMEEDS are drug-infused isotropic mixes of oils, surfactants, and co-surfactants. They primarily create oil-in-water micro-emulsions, whose size should be between 100 and 10 nm. The small droplet size of the micro-emulsion provides a large interfacial surface area, which is beneficial for drug release and absorption. The current work's goal was to create a tablet formulation for simvastatin that would increase its oral solubility using SMEDDS. Simvastatin's solubility behaviour in various vehicles was studied, and an improved SMEDDS formulation including Simvastatin was created. Different criteria, including emulsification time, dispersibility test, optical clarity, thermodynamic stability, drug precipitation, drug content, and drug dissolution, were assessed for the SMEDDS formulation. Following evaluation, SMEDDS formulations were optimized, and the improved formulations were then turned into solid SMEDDS. (S-SMEDDS). Drug content, release, and flow characteristics of this formulation were assessed. S-SMEDDS was compressed into tablets and tested for drug content, drug release, hardness, thickness, weight variation, and friability.

Lipid-based formulations are attracting an increasing amount of attention for the therapeutic delivery of lipophilic active moieties (Class II drugs). One of the most widely used methods among a variety of such delivery alternatives is the use of self-emulsifying drug delivery systems. Other choices include the integration of drugs in oils, surfactant dispersions, emulsions, and liposomes. (SEDDS). SEDDS are mixes of oils and surfactants that are ideally isotropic and occasionally contain cosolvents. When put into an aqueous phase while being gently stirred, SEDDS spontaneously emulsify to generate fine oil-in-water emulsions. These systems work by administering them orally, which causes minor gastric movement and the formation of fine oil-in-water emulsions (or microemulsions) in the gastro-intestinal (GI) tract. These systems provide the drug in an advantageously dissolved form, and the small droplet size offers a significant interfacial area for drug absorption. Many researchers have reported using SEDDS in logical ways to deliver and target lipophilic medications like cyclosporin A, halofantrine, vitamin E, and coenzyme Q10. Improved oral bioavailability (enabling dose reduction), more consistent temporal profiles of drug absorption, selective drug targeting to a particular absorption window in the GI tract, and drug protection from the hostile environment in the gut are potential benefits of these systems. Simvastatin is a crystalline substance that almost has no water solubility and is therefore mostly absorbed from the GI tract. It is a strong and targeted inhibitor of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase, which is responsible for reducing HMG CoA to mevalonate. Thus, simvastatin arrests a key step for cholesterol biosynthesis in liver, and is hence widely used in the treatment of hypercholesterolemia and dyslipidemia, as an adjunct to diet. Simvastatin is metabolised from simvastatin by the cytochrome-3A system in the liver to its b-dihydroxy acid form (simvastatin acid), where it inhibits the rate-limiting step in cholesterol production. Low-density lipoprotein (LDL) receptors are upregulated as a result, and LDL cholesterol is catabolized

more frequently. Inhibition of the hepatic production of the precursor to LDL, very low-density lipoprotein (VLDL), may also result in a slight decrease in LDL production. Being a Class II medication, it frequently exhibits oral absorption that is dissolution rate-limited and has a wide range of pharmacological effects. Solubility and/or dissolution rate improvements could result in increased bioavailability. There have been numerous attempts to increase simvastatin's bioavailability and rate of dissolution.

MATERIALS AND PROCEDURES

(i) Materials- Alkem Pvt Ltd, Mumbai, generously donated simvastatin. Gattefosse India Pvt. Ltd. offered a generous gift of Capryol 90. Mumbai, Abitec Corp. US sent Capmul MCM, Captex 355, and Captex 200 as gifts. From Hi Media Laboratories Pvt. Ltd. in Mumbai, we bought Transcutol P, tween 20, span 80, propylene glycol, olive oil, and aerosil 200. From Mumbai's Loba Chemie Pvt Ltd., PEG 400, oleic acid, tween 80, magnesium sterate, and polyvinylpyrrolidone were bought. From Mumbai's Research Labs Finchem Industries, Avicel PH 102 was bought. Abitec Corp. provided diesters of caprylic/capric acids (Captex® 355) and C8/C10 mono-/diglycerides (Capmul® MCM) as a kind gift. (USA). Gattefosse gave away a sample of polyglycolyzed glyceride (Lauroglycol ® 90) as a present. (France). BASF supplied the polyoxyl 35 castor oil (Cremophore ® EL, Cr-EL). (Germany).

(ii) Excipient Inspection- Simvastatin's saturation solubility in different oils, surfactants, and co-surfactants was assessed. Each glass vial holding 2 ml of oil, surfactant, or co-surfactant had too much simvastatin added to it. For a half-hour, the medication was manually blended. To achieve equilibrium, the vials were then maintained in an orbital shaker for 48 hours. These vials are centrifuged at 5000 rpm for 20 minutes after 48 hours, and the amount of drug dissolved was assessed after dilution in methanol and measurement using a UV-spectrophotometer set to 238 nm maximum. By titrating mixes of oil and Smix with water at room temperature, pseudoternary phase diagrams were created in order to determine the concentration range of components necessary for the occurrence of the micro-emulsion zone. Tween 80, the chosen surfactant, and PEG-400, the co-surfactant, were mixed together (Smix) in various ratios, including 1:1, 1:2, and 2:1. Using a magnetic stirrer, each Smix was combined with a chosen oil, Capryol-90, to produce weight ratios of 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, and 1:9 (w/w). To attain equilibrium, these mixtures were titrated with distilled water while taking care to properly agitate the liquid phases. Using Chemix School software, the pseudoternary phase diagrams for each system were created by plotting the concentrations of water, oil, and Smix on various ordinates.

(iii) Preliminary Research- These findings led to the selection of the oils, which were then mixed in sealed glass vials to create SEDDS formulations utilising several surfactant systems (with variable ratios of surfactant to cosurfactant). Water was added to these systems to titrate them, and the phase clarity and emulsion quality produced were visually assessed.

(iv) SEDDS- it was used in a variety of formulations for SEDDS, with different ratios of surfactant to cosurfactant. (Table 1&2). In stoppered glass vials, simvastatin was dissolved in a 1:1 (V/V) mixture of Captex and Lauroglycol (used as the oil phase). Cr-EL and/or Capmul were added as needed and well combined with the mixture. For 30 minutes, these systems were warmed in a water bath at 40 °C while being shaken periodically to achieve thorough mixing. The prepared formulations were kept at room temperature until they were used.

Composition	Formulation				
	A	B	C[a]	D	E
Simvastatin (mg)	200	200	200	200	200
Captex 355 (mL)	0.5	0.5	0.5	0.5	0.5
Lauroglycol 90 (mL)	0.5	0.5	0.5	0.5	0.5
Cremophor EL (mL)	1.0	0.75	0.5	0.25	–
Capmul MCM (mL)	–	0.25	0.5	0.75	1.0

[a] Test formulation

Table 1- Compositions of SEDDS formulations

Evaluation parameter	Formulation			
	A	B	C	D
Turbidity (NTU)	14.21 ± 2.15	12.95 ± 2.06	BLD[b]	96.3 ± 15.24
Mean droplet size (nm)[d]	414.42 ± 35.24	258.43 ± 26.51	124.86 ± 17.83	ND[c]
Drug found (mg mL^{-1})	98.7 ± 10.3	102.1 ± 8.9	101.2 ± 9.7	ND[c]

[a] Mean ± SD, $n = 3$.
[b] BLD – below limit of detection.
[c] ND – not done.
[d] PI – polydispersity index was less than 0.35 in all experiments.

Table 2- Evaluation of SEDDS formulations[a]

(v) Turbidimetric Assessment- 0.1 mol L-1 hydrochloric acid (150 mL) was mixed continuously at 50 rpm with self-emulsifying system (0.2 mL) on a magnetic plate (Ika-Werke, Germany) at room temperature. The increase in turbidity was then recorded with a turbidimeter until equilibrium was reached. (Type 131, Systronics, India). It was not possible to observe the rate of change of turbidity, however, because the time required for complete emulsification was too short. (rate of emulsification).

(vi) Creation of the SMEDDS- By determining, solubility in different oils, surfactants, and co-surfactants, as well as by creating a pseudo-ternary phase diagram to identify the micro-emulsion region, authors have already successfully created and assessed liquid SMEDDS of TEL. A suitable mixture was chosen from it to create liquid SMEDDS. TEL (20 mg/10gm) was briefly put in a glass container. This was mixed with Acrysol EL 135 (10% w/w) and reheated in a water bath. Tween 80 (30% w/w) and PEG 400 (40% w/w) were added to this oily concoction. Once TEL was fully dissolved, the components were then gently stirred and vortex-mixed at 37°C. The combination was then put into a glass vial, sealed, and kept there until it was needed (Tang et al., 2008; Bhagwat et al., 2012). A glass vial was filled with precisely weighed oils, surfactants, and co-surfactants, and then the mixture was vortexed. Simvastatin was added to the formulation mentioned above. For later usage, the mixture was kept at room temperature. The SMEDDS formulation is shown in Table 3.

Components	Ratio 1:1		Ratio 1:2		Ratio 2:1	
	F-1	F-2	F-3	F-4	F-5	F-6
Simvastatin (mg)	5.0	5.0	5.0	5.0	5.0	5.0
Capryol 90 (mg)	10.5	21	10.5	21	10.5	21
Tween 80 (mg)	47.25	42	31.5	28	63	56
PEG 400 (mg)	47.25	42	63	56	31.5	28

Table 3- Formulation of SMEDDS

(vii) Assessment of SMEDDS- The self-emulsification time, dispersibility test, optical clarity, percent drug content, thermodynamic stability research, drug precipitation study, drug release studies, and globule size analysis of the SMEDDS formulations were all assessed. Oil, surfactant, and cosolvent were combined while being continuously stirred to create the placebo SMEDDS mixture. Simvastatin was added to the placebo SMEDDS formulation while being continuously stirred to create a transparent solution to create the simvastatin loaded SMEDDS formulation. Simvastatin equal to 80.0 mg of SMEDDS formulation was placed inside a hard gelatin capsule. The results of the emulsification study indicated that the greatest quantity of this surfactant and Capmul PG 8 oil were chosen for the SMEDDS formulation. Transcutol has been chosen as a cosolvent for the SMEDDS formulation because it has a greater microemulsion area. When SMEDDS are combined with GI fluids, the process increases the dispersion of emulsified globules and changes the character of the colloidal species, which may have an impact on the ability of dispersed colloids to dissolve in water. To ascertain the impact of lipolysis on drug diffusion in the aqueous phase, an in vitro research was carried out. Simvastatin loaded SMEDDS formulation with improved simvastatin underwent a lipolysis trial. (F9). The percentage of drug release in the aqueous phase of the optimised SMEDDS formulation was determined to be 78%, 94%, 98%, and 99%, respectively, after 5, 15, 30, and 45 minutes of lipolysis.

SOLID SMEDDS ARE CREATED USING THE ADSORPTION PROCESS

Simvastatin's liquid formulation (SMEDDS-F-5) was introduced dropwise to powder carriers such Aerosil 200 and Avicel PH 102, which have strong adsorption qualities, in a porcelain dish in various ratios like 0.5:1, 1:1, 2:1, 3:1, and 4:1. The mixture was physically stirred until it was well combined. Micromeritic characteristics of S-SMEDDS were assessed, including bulk density, tapped density, hausner ratio, carr's index, and angle of repose of the medication. 100 mg weighed Volume makeup was done up to 100 ml after the solid SMEDDS formulation was dissolved in 25 ml of methanol. Whatman filter paper number 41 was used to filter this stock solution, and the requisite dilutions were made. Methanol was used as a blank for the UV spectrophotometric analysis of the simvastatin content in methanol (UV Shimadzu-1700) at 238 nm.

Utilizing the USP XXIII, dissolving apparatus 2 (Veego Instruments VDA-8D4) and 500 cc of potassium phosphate buffer pH 7.0 as the medium at 37°C, drug release experiments from the S-SMEDDS were carried out. The paddle's speed was changed to 50 rpm. S-SMEDDS (10 mg of Simvastatin) were knotted in muslin and added to the dissolution media. At intervals of 10 minutes for one hour, an aliquot of volume 5 ml was taken for UV-spectrophotometer analysis at 238 nm. The new dissolving medium was added in an equal volume. The thermogram analysis performed using differential scanning calorimetry (DSC) was used to describe the physical state of simvastatin in S-SMEDDS. The Mettler Toledo DSC Star system was used to record the DSC patterns. Scanning electron microscopy (SEM) (JEOL JSM- 6360, Japan)

was used to examine the exterior morphology of the S-SMEDDS.

By adsorption to solid carriers, liquid SE formulas can be transformed into free-flowing powders. The only step in the straightforward adsorption process is the addition of the liquid formulation onto carriers by blending in a mixer. The resulting powder can then be compressed into tablets or, alternatively, combined with appropriate excipients before filling straight into capsules. Good material uniformity is one of the technique's key advantages. High amounts of SEDDS (up to 70% (w/w)) can be adsorbed onto suitable carriers. Avicel pH 101 or Aerosil 200 are examples of solid transporters. It was created by combining liquid SEDDS containing in 1:2, 1:1, as, or 2:1 ratios with Aerosil 200 or Avicel pH 101. SMEDDS liquid was quickly added progressively over the mortar's carriers. To ensure that the formulation was distributed evenly, the mixture was thoroughly mixed and homogenised after each addition. The resulting damp bulk was put through sieve number 120, dried at room temperature, and kept for later use.

CREATING TABLETS USING S-SMEDDS

The weights of all the components and S-SMEDDS were precise. Binders known as S-SMEDDS were mixed and sieved through sieve number 20#; glidants and lubricants were then added, mixed, and sieved.

Formulations	S-SMEDDS (mg)	Avicel PH 102 (mg)	PVP (mg)	Magnesium stearate (mg)	Total (mg)
TA-1	157.5	135	-	7.5	300
TA-2	210	180	-	10	400
TA-3	315	170	-	15	500
TA-4	210	180	-	10	400
TA-5	315	170	-	15	500
TA-6	420	60	-	20	500
TA-7	525	50	-	25	600
TP-1	157.5	-	15	7.5	180
TP-2	210	-	20	10	240
TP-3	315	-	30	15	360
TP-4	210	-	20	10	240
TP-5	315	-	30	15	360
TP-6	420	-	40	20	480
TP-7	525	-	50	25	600

Table 4- Formula for tablet compression

Using die numbers 10 and 12, this mixture was crushed using a Rotari tablet press (Karnavati-Remake). S-SMEDDS formulations with Aerosil as an adsorbent were used in tablet formulations TA-1 through TA-3, whereas S-SMEDDS formulations with Avicel PH 102 as an adsorbent were used in tablet formulations TA-4 through TA-7. Similar to how pill formulations TP-1 through TP-3 used Aerosil as an adsorbent, formulations TP-4 through TP-7 used Avicel PH 102 as an adsorbent for S-SMEDDS. Different tablet formulations with various binders, including PVP and Avicel PH 102, are shown in Table 4.

ASSESSMENT OF THE TABLET

The Vernier calliper, weight variation, Monsanto hardness tester, friability, percent drug content, and drug release were all used. The tablet formulation TP-7 was chosen for further investigation based on the findings of the aforementioned assessment parameters and observation of tablet formulations TA-1 to TA-7 and TP-1 to TP-7. Three tablets of the formulation TP-7 were crushed in a mortar and pestle to the equivalent of 5 mg of the medication, which was then weighed, dissolved in 100 ml of methanol, and sonicated for 20 minutes. The resulting solution was then further diluted with methanol before being filtered through

Whatman Filter Paper No. 41. At 238 nm, drug content was measured spectrophotometrically using a UV Shimadzu 1701 model. Three determinations were computed, and the mean was found. Utilizing USP XXIII equipment, drug release experiments of manufactured tablets were carried out. The dissolution media was first exposed to the tablet formulation TP-7. A Shimadzu-1701 UV spectrophotometer was used to measure the amount of simvastatin in an aliquot (5 ml) of the medium every 10 minutes for 1 hour. To offset the loss from sampling, an equivalent volume (5 ml) of fresh dissolving medium was added.

(i) Percent Drug Content- The tablet formulation TP-7 was chosen for further investigation based on the results of the aforementioned assessment criteria and observations of the tablet formulations TA-1 to TA-7 and TP-1 to TP-7. Three tablets of the formulation TP-7 were crushed in a mortar and pestle to the equivalent of 5 mg of the medication, which was then weighed, dissolved in 100 ml of methanol, and sonicated for 20 minutes. At 238 nm, drug content was measured spectrophotometrically using a UV Shimadzu 1701 model. Three determinations were computed, and the mean was found.

(ii) Drug Release Studies- Using USP XXIII equipment, drug release tests on manufactured tablets were carried out. At a temperature of 37.50°C, 900 cc of potassium phosphate buffer with a pH of 7.0 was utilised as the dissolution medium in Dissolution Apparatus 2 (DT 60, Veego Instrument).The paddle's speed was changed to 50 rpm. The dissolution media was first exposed to the tablet formulation TP-7. A Shimadzu-1701 UV spectrophotometer was used to measure the amount of simvastatin in an aliquot (5 ml) of the medium every 10 minutes for 1 hour. To offset the loss from sampling, an equivalent volume (5 ml) of fresh dissolving medium was added.

RESULTS AND DISCUSSION

(i) Construction of pseudoternary phase diagrams- Using the Chemix school program, pseudoternary phase diagrams were built using the oil Capryl-90, the surfactant Tween-80, and the co-surfactant PEG-400 at various Smix ratios (surfactant: co-surfactant ratios) of 1:1, 1:2, and 2:1. The micro-emulsion range in the 1:9 and 2:8 region of all pseudoternary phase diagrams plotted was evident; therefore, all formulations in all ratios were examined for evaluation. Diagrams of the pseudoternary phases were plotted.

(ii) Selection of SMEDDS- The formulations were made using various systems, namely Capryol 90: Tween 80: PEG 400 in different Smix ratios such as 1:1, 1:2, and 2:1. The formulations were chosen from the ternary phase diagram for the study based on preliminary studies and had varying concentrations of oil, surfactant, and co-surfactant.

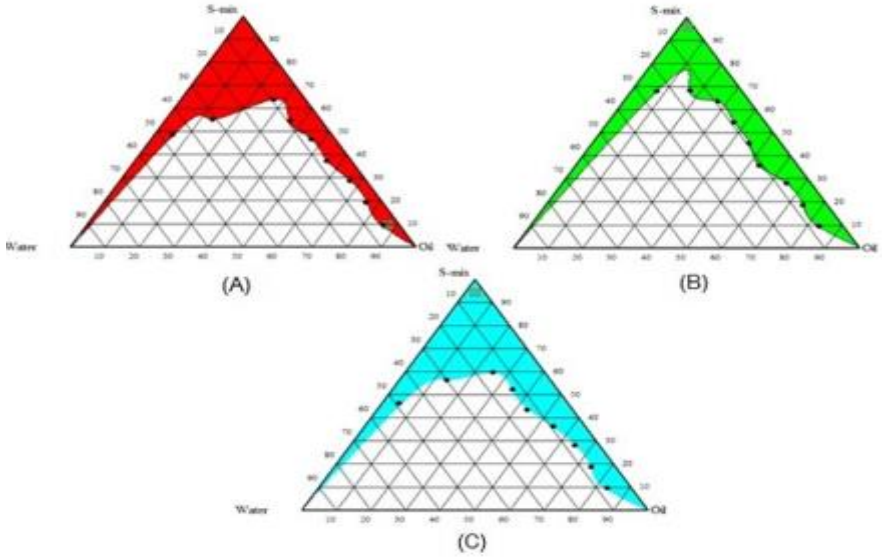

Figure 1- Pseudoternary phase diagram

CONCLUSION

By creating tablets using the solid SMEDDS formulation, Simvastatin's dissolution could be improved. This is probably going to increase the drug's bioavailability. The idea has the potential to be expanded industrially. The potential of simvastatin SEDDS for oral delivery was demonstrated in this study. To determine a relationship between the pharmacokinetics and pharmacodynamic effects of simvastatin when given as SEDDS, more research is necessary. Tablet TP-7's drug release profile was determined to be somewhat lower (84.71% at 60 min) than that of S-SMEDDSM-5's (84.80% at 60 min). There was only a 0.09% difference between the dissolution profiles of the tablet formulations TP-7 and S- SMEDDS. The tablet formulation's positive release rate demonstrated the formulations' great self-emulsion efficiency. Thus, it could be said that the solubilizing property of the formulation had been intact during the conversion of S-SMEDDS into tablets.

By creating tablets using the solid SMEDDS formulation, Simvastatin's dissolution could be improved. This is probably going to increase the drug's bioavailability. The idea has the potential to be expanded industrially.

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