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ORIGINAL RESEARCH

Development and Evaluation of Self-Emulsifying Drug-Delivery System–Based Tablets for Simvastatin, a BCS Class II Drug

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Background: Self-emulsifying drug-delivery systems (SEDDSs) are designed to improve the oral bioavailability of poorly water-soluble drugs. This study aimed at formulating and characterization of SEDDS-based tablets for simvastatin using castor and olive oils as solvents and Tween 60 as surfactant.

Methods: The liquids were adsorbed on microcrystalline cellulose, and all developed formulations were compressed using 10.5 mm shallow concave round punches.

Results: The resulting tablets were evaluated for different quality-control parameters at pre- and postcompression levels. Simvastatin showed better solubility in a mixture of oils and Tween 60 (10:1). All the developed formulations showed lower self-emulsification time (<200 seconds) and higher cloud point (>60°C). They were free of physical defects and had drug content within the acceptable range (98.5%–101%). The crushing strength of all formulations was in the range of 58–96 N, and the results of the friability test were within the range of USP (≤1). Disintegration time was within the official limits (NMT 15 min), and complete drug release was achieved within 30 min.

Conclusion: Using commonly available excipients and machinery, SEDDS-based tablets with better dissolution profile and bioavailability can be prepared by direct compression. These S-SEDDSs could be a better alternative to conventional tablets of simvastatin.

Keywords: simvastatin, self-emulsified drug-delivery system, castor oil, olive oil, Tween 60

Introduction

The oral route of drug administration is not only attractive but is preferred on account of its enhanced patient compliance, better stability, and self-administration, together with flexibility in dose.[1] Unlike sterile products, oral dosage forms need no sterile settings, so production costs are comparatively lower.[2] The major problem with the oral route of drug administration is the poor dissolution rate, especially of Biopharmaceutics Classification System (BCS) class II and IV drugs due to their poor solubility.[3] To cope with this issue, many strategies have been adopted to increase the dissolution and oral bioavailability of drugs, such as structural modification of drugs, development of different drug-delivery systems (DDSs)/drug carriers, reducing particle size, salt formation, and the use of different surfactants, as well as nanoparticles or liposomes.[4] Lipid-based formulations, such as lipid solution, emulsion, and emulsion preconcentrate, and lipid-based nanoparticles are gaining popularity because of their capability to encapsulate a wide range of poorly water-soluble drugs and enhance both dissolution rate and permeation through the gastrointestinal tract (GIT).[3,5] However, their use is limited because of stability issues and manufacturing problems.[6,7] A possible alternative to this is a self-emulsified DDS (SEDDS) in which active pharmaceutical ingredients, lipid (oil), and surfactant form an isotropic mixture, and when mixed with water form an oil-in-water emulsion.[8] Cosolvents and coemulsifiers can also be added to the formulation to increase drug solubility and emulsification. This enables

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oral administration of hydrophobic drugs in unit dosage form by dissolving in the oil phase and forms a fine emulsion in the presence of GIT fluids, resulting in enhanced dissolution rate and subsequent bioavailability.[9] Droplets of the resultant emulsions are usually in the nanometer to micrometer range.[10] The spontaneously formed emulsion should be stable to dilution with GIT fluids and the drug should remain solubilized for the time sufficient for its absorption. SEDDS technology has been used to increase the solubility and oral bioavailability of many poorly water-soluble drugs, including hydrocortisone, celastrol, indomethacin, and phyllanthin.[11,12]

According to Reiss et al, self-emulsification is possible when the energy required to increase the surface area of dispersion is less than the change in entropy.[13] In emulsions, there is a general tendency of phase separation with the passage of time, leading to their instability. Phase separation is prevented by emulsifying agents, which decreases interfacial tension and prevents coalescence. Silva et al reported that drug release from SEDDSs is controlled by the droplet size and its polarity.[14] Furthermore, waxy materials should be avoided for the preparation of SEDDSs, because polymorphic properties of the drug and the morphology of the material within the wax cannot be easily determined when a waxy mixture is formed. Therefore, the formulation should be kept simple, with a minimum number of excipients.[15] However, SEDDSs as liquid formulations possess several drawbacks, such as difficulty in drug loading, stability, leakage, and few choices of dosage forms. To overcome these, liquid SEDDSs (L-SEDDSs) can be converted to solid dosage form by using several techniques, including adsorption on solid carriers, filling capsules with liquid SEDDSs and nanoparticle formation.[12] Because of their anhydrous nature, SEDDSs can be encapsulated in hard or soft gelatin capsules. Solid SEDDSs (S-SEDDSs) combine the benefits of liquid lipid formulations with those of solid dosage forms, such as higher stability and longer storage time. In comparison with other drug carriers, such as polymeric carriers, liposomes, and micelles, S-SEDDSs can be easily scaled up for commercial manufacturing, as this only involves the preparation of solutions and their conversion to solid form. Production of S-SEDDSs at a commercial scale is also cost-effective and has higher interbatch uniformity.[16,17] Moreover, S-SEDDSs are gaining in importance, as some of the products based on SEDDSs, such as Neoral (cyclosporine A), Norvir (ritonavir), and Fortovase (saquinavir) have been successfully commercialized.[18]

Simvastatin (Figure 1) is a competitive inhibitor of the enzyme HMG CoA reductase and is used to decrease low–density lipoprotein cholesterol in the blood.[19] It has poor water solubility and has been classified as a class II drug based on BCS, with a pKa value of 4.68.[20,21] Being a BCS class II drug, its oral bioavailability depends upon its dissolution rate from the solid dosage form. Several strategies have been adopted to increase its dissolution rate and subsequent bioavailability. The present study aimed at the development of a formulation of a SEDDS for simvastatin with enhanced dissolution rate and subsequent bioavailability. Various formulations were developed using different oil phases. Liquid preparations were converted to solid form, compressed, and evaluated for different quality-control parameters as per US Pharmacopeia (USP) guidelines.[22]

Methods

Materials

The experimental drug (simvastatin, Maithri Laboratories, India; purity 99.73%) was obtained from Ferozsons Laboratories, Nowshera, Pakistan. The rest of the excipients — Tablettose 80 (Molkerei Meggle, Germany), micro-crystalline cellulose, cross-linked carboxymethyl cellulose sodium, colloidal silicon dioxide (FMC International, Ireland),

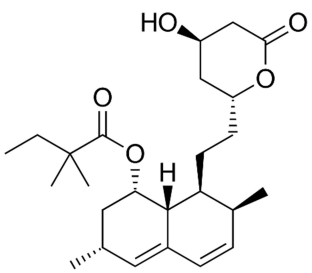

Figure 1 Chemical structure of simvastatin.

Tween 60, starch maize (I.C.I, Pakistan), and magnesium stearate (Coin Powder International, Taiwan) were purchased locally and used as such. All the solvents (ethanol and methanol) and reagents (HCl) were of analytical grade, and purified water was prepared using Milli-Q (Millipore, Milford, MA, USA).

Selection of Oil Phase

The criterion for selection of the oil phase was drug solubility. Drug solubility in oil was determined by the standard flask-shake method.[23,24] Oil was taken in a flask (capacity 50 mL) and excess drug mixed by water bath sonication for 10 min. The flask was continuously shaken for 8 h by a mechanical flask shaker at ambient temperature (26°±3°C). Following shaking, the drug solution was kept undisturbed for 1 h to reach equilibrium, filtered, and then simvastatin content was determined. The solubility of simvastatin was checked in castor and olive oils, alone and in combination with different concentrations of Tween 60. Equation 1 was used to determine the solubility.

$$\text{Solubility} = \frac{\text{Amount of drug (mg)}}{\text{Volume of solution (mL)}} \quad (1)$$

The compatibility of oil and surfactant with simvastatin was evaluated by FTIR. FTIR spectra of drug alone and its solution (prepared in mixture of oil and surfactant) were recorded and compared. An FTIR spectrophotometer (Shimadzu, Japan) was used for recording FTIR spectra, and the data were analyzed by IR Solutions version 1.10 software. Samples were prepared using KBr disk, which involved mixing the sample with KBr (2% w/w), its pulverization, and loading to sample holder. Spectra were recorded in the 400–4000 cm^{-1} region at a resolution of 8 cm^{-1} in transmittance mode.

Preparation of SEDDS Formulations

Several SEDDS formulations were developed using different ratios of the selected oils, keeping the ratio of drug to surfactant constant (Table 1). The surfactant was mixed with the oil by gentle heating in a water bath. A weighed quantity of drug was added to this mixture and subsequently mixed with the help of a high-speed homogenizer for 15 min.

Characterization of SEDDS Formulations

Centrifugation Tests

Centrifugation tests were performed to evaluate phase separation of the emulsion. Centrifugation of the developed formulations was carried out at 4000 *g* for 5 min and phase separation was checked.[25] The test was considered passed when there was no phase separation and vice versa.

Determination of Self-Emulsification Time

USP Dissolution Apparatus II (paddle method) was used for determination of the self-emulsification time of the developed formulations of SEDDS. Purified water (500 mL) was taken in a flask and equilibrated at 37°±2°C. SEDDS formulations (0.1 mL) were added to the flask and stirred with a paddle speed of 50 rpm. The time required to form a homogeneous dispersion was noted and considered the self-emulsification time. Determination of self-emulsification time was made in six flasks of dissolution apparatus under the same conditions and their mean was taken (n=6).[10]

Table 1 Composition of various formulations of SEDDSs for simvastatin

Ingredients (g)	F1	F2	F3	F4	F5
Simvastatin	10	10	10	10	10
Castor oil	19	0	9.5	0	0
Olive oil	0	18.4	0	9.2	23
Polysorbate 60 (Tween 60)	1.9	1.84	0.95	0.92	2.3
Total quantity	30.9	30.24	20.45	20.12	35.3

Robustness to Dilution

An aliquot of the developed SEDDS formulations was diluted with acid buffer pH 2.1 (10, 50 and 100 times). The formulations were visually observed for any breakage of emulsion.[10]

Determination of Cloud Point

Emulsion becomes cloudy by heating, and the temperature at which cloudiness is observed is called the cloud point.[25] For determination of the cloud point, an aliquot (1 mL) of each formulation was diluted with purified water (200 mL) and heated on a water bath. The temperature was gradually raised, and the point at which cloudiness was observed was recorded. Cloud points were determined in triplicate for each formulation and their mean value was taken (n=3).

Preparation of S-SEDDSs

The liquid SEDDS preparations were converted to S-SEDDSs by adsorption on microcrystalline cellulose (Avicel PH 112). Microcrystalline cellulose was taken in a benchtop cone mixer (Morgan Instruments, Lahore, Pakistan) and liquid SEDDS formulations added in portions with proper mixing. Colloidal silicon dioxide (1% w/w) was added to enhance adsorption and get a free-flowing powder. Table 2 shows the composition of various S-SEDDS formulations.

Preparation of Tablets Containing Self-Emulsifying Formulations

S-SEDDS preparations were blended with other excipients (Table 3) for 30 min in a laboratory scale double-cone mixer at 25 rpm. Compression of powder blend was carried out by a rotary compression machine (ZP-21, China). Round (10.5 mm), shallow, concave punches were used for tablet preparation. The compression weight of the tablets was set at 350 mg/tablet, and at least 300 tablets were compressed from each formulation.

Precompression Evaluation

Prior to compression, the flow of the powder blend was assessed using its angle of repose, Carr's index, and Hausner's ratio. The funnel method, as prescribed by the USP, was used for determination of angle of repose. For determination of bulk density, a weighed quantity of powder was taken in a graduated cylinder, its volume and the ratio of mass to occupied volume measured, and bulk density calculated. Sinilarly, a tapped volume of powder blend was determined by taking a weighed quantity of powder blend and tapping it manually until its volume became constant. The final volume was noted as tapped volume. Values of mass of powder blend and tapped volume were used for calculation of tapped

Table 2 Composition of different formulations of S-SEDDSs for simvastatin

Ingredients (g)	F1	F2	F3	F4	F5
L-SEDDS preparation	30.9	30.24	20.45	20.12	35.30
Avicel PH 112	110	110	110	110	120
Aerosil	2.39	2.39	2.89	2.19	4.39
Total*	143.29	140.24	133.34	132.31	159.69

Note: *Quantity of S-SEDDS for 500 tablets.

Table 3 Composition of different formulations of simvastatin self-emulsifying tablets

Ingredients (g)	F1	F2	F3	F4	F5
S-SEDDS preparation	143.29	140.24	133.34	132.31	159.69
Cross carmellose sodium	3.50	3.50	3.50	3.50	3.50
Magnesium stearate	1.75	1.75	1.75	1.75	1.75
Talcum	1.75	1.75	1.75	1.75	1.75
Tablettose 80	24.71	27.76	34.66	35.69	8.31
Total*	175	175	175	175	175

Note: *Quantity of powder blend for 500 tablets.

density. The tapped and bulk densities of the powder blend were used to calculate Carr's index and Hausner's ratio of the powder blend using the equations proposed by the USP.[22]

Postcompression Evaluation of Simvastatin Self-Emulsifying Tablets

Physical Parameters of Tablets

The thickness of randomly selected tablets (n=10) was measured with a digital hardness and thickness tester (Pharma Test, Germany), and results are presented as means ± SD. Weight-variation testing was performed as per official compendia[22] by randomly selecting tablets (n=20), weighing individually, and calculating their average weight. Weight variation was calculated based on the difference between individual and average weights.

Determination of Drug Content

Tablets from all the developed formulations of SEDDSs were analyzed for simvastatin content, as per an official monograph,[22] using HPLC. The HPLC system (PerkinElmer, USA) consisted of a pump, online degasser, Peltier column oven, and UV-visible detector (series 200). The chromatographic data were analyzed using PerkinElmer TotalChrom Workstation software (version 6.3.1) linked to the LC system through a network chromatography interface (NCI) 900. A stationary phase composed of a Hypersil BDS C_8 column (250×4.6 mm, 5 µm), while the mobile phase was composed of a mixture of phosphate buffer (pH 6.8) and acetonitrile (35:65, by volume). The flow rate of the mobile phase was set at 1.8 mL/min and elute was detected at 238 nm. Randomly selected tablets (n=10) were taken in a volumetric flask (250 mL), water added (10 mL), and swirled till disintegration of the tablets had completed. Dispersions were diluted to 250 mL by adding diluting solution, sonicating for 15 min, and cooling down. A portion of the mixture was centrifuged, and an aliquot of the clear supernatant was diluted with diluting solution to get a concentration of 0.1 mg/mL of simvastatin. Diluting solution was prepared according to the USP by adding glacial acetic acid (3 mL) to water (900 mL), adjusted its pH to 4 with NaOH solution (5 N) and increasing its volume to 1000 mL. To 200 mL of this solution, 800 mL of acetonitrile (800 mL) was added and mixed to get diluting solution. For preparation of standard solution, a weighed quantity of simvastatin was dissolved in diluting solution to get a concentration of 0.1 mg/mL. Equal volumes (≈10 µL) of both standard and test solutions were injected into the HPLC system, chromatograms recorded, and peak areas measured. Comparison of the peak area of standard and sample solutions was used for quantification of simvastatin (n=3).

Mechanical Strength of Tablets

The USP recommends determination of crushing strength, specific crushing strength, tensile strength, and friability testing for evaluation of the mechanical strength of tablets. Tablets (n=10) were randomly selected from each formulation and their crushing strength measured by a tablet hardness and thickness tester (PharmaTest, Hamburg, Germany). Average crushing strength of tablets and their SDs were calculated. Mean values of crushing strength and thickness of tablets were used for calculation of tensile strength and specific crushing strength using the equations proposed by the USP.[22]

$$\mathrm{Ts} = \frac{2\mathrm{F}}{\pi\,\mathrm{DH}} \tag{2}$$

$$\tau = \frac{\mathrm{F}}{\mathrm{DH}} \tag{3}$$

where Ts is tensile strength (N/mm^2), τ is specific crushing strength (N/mm^2), F is crushing strength (N), D is the diameter (mm), H is the thickness of tablets, and π is constant of proportionality and its value is 3.143. For determination of friability, tablets (≈6.5 g) were randomly taken from each formulation and dedusted. Dedusted tablets were loaded intoto the rotating drum of a friabilator and rotated at 25 rpm for 4 min.[22] After completion of rotations, tablets were checked for physical defects (breakage, chipping, capping, and lamination), reweighed, and weight loss calculated.

Determination of Disintegration Time

USP tablet-disintegration testing apparatus (Pharma Test, Germany) was used for determination of disintegration of tablets, as per official compendia,[22] using purified water as a media. Temperature of media was equilibrated at 37°±2°C and one tablet was taken in each cylinder of a basket and rack assembly. Time taken for disintegration of tablets was noted and average and standard deviation calculated (n=6).

In Vitro Drug Release

The release rate of simvastatin was determined according to the official monograph for conventional tablets of simvastatin using USP Apparatus II (paddle method) at 50 rpm.[22] Dissolution media (900 mL) consisted of buffer solution containing sodium dodecyl sulfate (0.5%) in sodium phosphate (0.01 M), with pH 7 adjusted with NaOH solution (50% w/v). Samples (5 mL) were taken after 0, 5, 15, 30, 45 and 60 min, filtered and analyzed for drug released using the HPLC system. A standard solution of the same concentration was prepared in dissolution media and analyzed by HPLC under the experimental conditions. The quantity of simvastatin in dissolution samples was determined by comparison of peak area of sample and standard solution.

Results

Solubility of Simvastatin

In the present study, the main formulation components of SEDDSs were oil and surfactant, these being selected based on drug solubility because solubility directly affects drug loading.[21] The objective of the study was to develop a simple, safe, and robust SEDDS formulation for simvastatin. Solubility of simvastatin was determined in different ratios of oils and surfactant (Table 4). Among these, better results were obtained at a ratio of 10:1 (v/v) for both the oils. Along with increasing drug solubility in oil, surfactants play a critical role in formulation of SEDDSs, as they stabilize dispersed droplets in an emulsion by decreasing interfacial tension between two phases and increase miscibility of the oil phase with GIT fluids during the process of self-emulsification. FTIR spectra of drug alone and in solution (prepared in mixture of oil and surfactant) were recorded and compared, as shown in Figure 2. The FTIR spectra of the pure drug and solution were similar (no change was observed in the peak position or relative intensities), indicating that there was no interaction or degradation of drug when dissolved in the oil or surfactant, meaning that these can be used in formulation without any stability issues.

Physical Characterization

Centrifugation Tests

Stability of emulsion was evaluated based on centrifugation tests. Phase separation was not observed in any formulation, and all of them remained stable after centrifugation at 4000 *g* for 5 min. There was no indication of phase separation, creaming, cracking, or coalescence, confirming their kinetic stability.

Table 4 Solubility of simvastatin in oils and their combination with Tween 60

Solvent	Solubility (mg/L)±SD
Castor oil	394±1.67
Olive oil	329.08±1.82
Castor oil + Tween 60 (1:1)	195±1.08
Castor oil + Tween 60 (2:1)	206±0.93
Castor oil + Tween 60 (5:1)	1501±1.06
Castor oil + Tween 60 (10:1)	1673±0.93
Olive oil + Tween 60 (1:1)	348±1.53
Olive oil + Tween 60 (2:1)	509±1.91
Olive oil + Tween 60 (5:1)	1698±1.38
Olive oil + Tween 60 (10:1)	1785±1.19

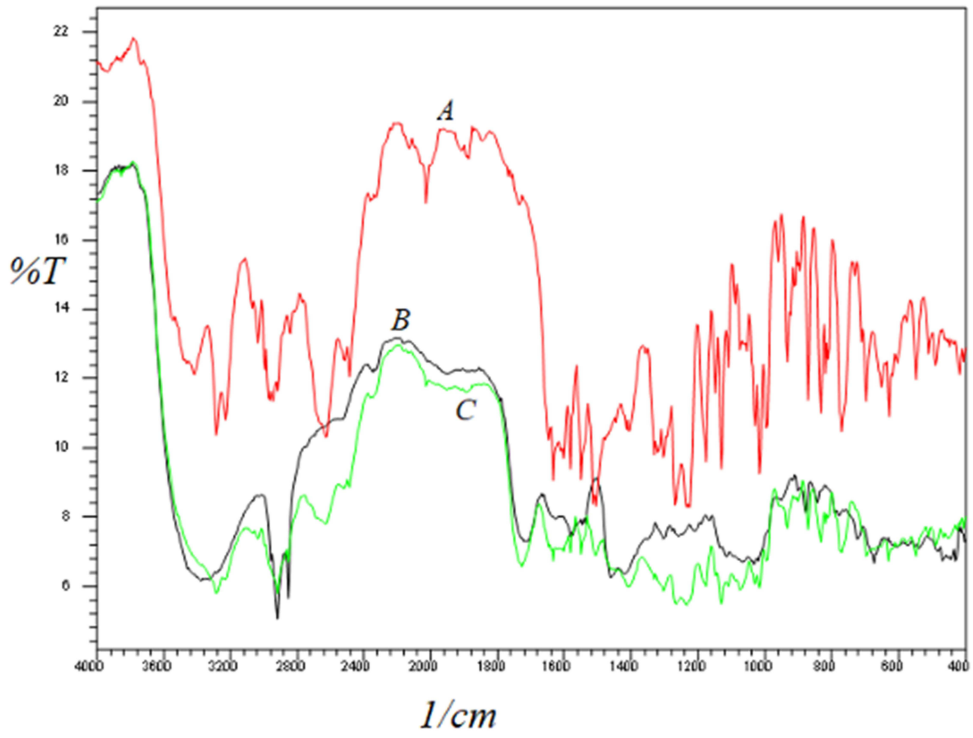

Figure 2 (**A**) FTIR spectra of pure simvastatin, (**B**) simvastatin solution prepared in a mixture of olive oil and Tween 60, and (**C**) simvastatin solution prepared in castor oil and Tween 60.

Determination of Self-Emulsification Time

Emulsification studies are a valuable tool for assessing the self-emulsifying properties of developed formulations. SEDDSs should completely and rapidly disperse when subjected to aqueous dilution with mild agitation. Surfactants in SEDDSs reduce interfacial tension between the oil and aqueous phases, facilitating dispersion and the formation of oil-in-water emulsions. In the present study, self-emulsification time was determined for all the developed formulation using USP Apparatus II. When exposed to aqueous media, an ideal SEDDS formulation should be able to disperse rapidly, with minimum agitation. In the present study, all the formulations had self-emulsification times <200 seconds (n=3, Table 5), indicating that they can form emulsions spontaneously upon exposure to gastric fluid. During determination of self-emulsification time, the speed of the USP Apparatus II was set to 50 rpm, which provided the lowest level of agitation. This indicates that normal GIT motility will be enough for self-emulsification. Self-emulsification time was dependent upon the concentration of surfactant and formulations. Aigher quantity of Tween showed shorter self-emulsification, time which may be due to increased water penetration at the oil-and-water interface.

Table 5 Emulsification time and cloud point of self-emulsified formulations

	SE time (seconds)	Cloud point (°C)
F1	179±0.93	56±1.64
F2	198±1.28	57±0.59
F3	156±1.96	54±1.08
F4	194±1.27	52±1.63
F5	148±1.39	58±0.98

Notes: Results are presented as means ± SD of three determinations. SE, self-emulsification.

Measurement of Cloud Point

Emulsions are unstable at higher temperatures, and the two phases tend to separate upon heating.[9] Surfactant plays a vital role in stabilization of emulsions, and solubility decreases with increasing temperature. Above certain temperatures, emulsions become cloudy, which indicates low solubility of surfactant and subsequent instability of the emulsion, hence measurement of the cloud point is an indicator of stability of emulsions at higher temperatures. The results presented in Table 5 showed that the cloud point was above 50°C for all the developed formulations, indicating their stability during processing, storage and in the GIT. It has been documented that the cloud point depends upon the nature and quantity of surfactant. In the present study, all formulations showed similar cloud points, which may be due to the addition of surfactants in equal concentrations (Table 5).

Robustness to Dilution

After oral administration, SEDDS preparations disperse and are diluted with GIT fluids, which may cause phase separation of the resultant emulsion. Dilution with GIT fluids can also cause drug precipitation, depending upon its solubility. To assess these problems, robustness to dilution was evaluated using acid buffer (pH 2.1). All the developed formulations remained stable upon dilution (10, 50, and 100 times) with acid buffer. Higher dilution capacity of the formulations showed that they will remain stable after dilution with GIT fluids.

Precompression Evaluation of SEDDS-Based Tablets

Because L-SEDDSs have some drawbacks,[12] an effort was made to obtain solid SEDDSs. Based on the obtained results, the optimal L-SEDDS formulation (F5) was used to prepare S-SEDDS. Prior to compression, the powder blend for all the formulations was evaluated for rheological characteristics, and better flow was observed with all formulations (Table 6). Values of angle of repose, Carr's index and Hausner's ratio indicated better flow of the powder blend, which may be due to a granulating effect of the oil phase.[9] Adsorption of the oil phase on MCC and subsequent coating with aerosol resulted in cohesion of powder particles and better flow. Furthermore, inclusion of excipients, such as Tablettose 80, also contributed to higher flow of the powder blend.

Postcompression Evaluation of SEDDS-Based Tablets

Physical Parameters

The theoretical weight of tablets was 350 mg/tablet, and weight variations were within the official acceptable limits of the USP (Table 7). All tablets, randomly selected from the developed formulations, showed that they were free of any physical defects, such as sticking and picking. The surface of the tablets was smooth and shiny, indication their proper lubrication. The thickness of the tablets was in a narrow range (3.5–3.7 mm), indicating that flow of the powder blend was uniform. The drug content of the tablets was >99% (Table 7), confirming appropriate mixing of the drug with additives.

Mechanical Strength

The mechanical strength of tablets was based on their crushing strength, specific crushing strength, tensile strength, and friability, determined according to the USP (Table 7).[22] The crushing strength of all the developed formulations was in the range of 58–96 N. Formulations containing a higher quantity of the oil tended to have low crushing strength

Table 6 Results of precompression evaluation of powder blends for different formulations of SEDDS-based tablets

	Angle of Repose (°)	Bulk density (g/mL)	Tapped density (g/mL)	Carr's index*	Hausner's ratio*
F1	26±0.91	0.56±0.03	0.68±0.09	17.65	1.21
F2	27±1.28	0.24±0.01	0.29±0.01	17.24	1.21
F3	24±1.70	0.36±0.03	0.4±0.04	10	1.11
F4	22±1.65	0.33±0.04	0.38±0.03	13.15	1.15
F5	24±1.29	0.32±0.06	0.37±0.01	13.51	1.16

Notes: Data rounded to two digits after decimal point. *Calculations were made on the basis of mean values of bulk density and tapped density.

Table 7 Physical parameters and mechanical strength of SEDDS-based tablets

	Quality-control parameters	F1	F2	F3	F4	F5
Physical parameters	Average tablet weight* (mg)	359±1.96	353±1.02	358±0.38	356±1.06	355±0.84
	Weight variation (%)	±1.47	±1.39	±2.73	±1.38	±1.21
	Thickness* (mm)	3.50±0.19	3.69±0.24	3.58±0.41	3.59±0.19	3.62±0.74
	Drug content** (%)	99.01±0.24	98.50±1.17	99.31±1.29	99.76±2.31	99.81±1.09
Mechanical strength	Crushing strength* (N)	71.81±1.91	75.9±1.46	91.37±1.05	95.28±1.39	58.79±1.61
	Specific crushing strength‡ (N/mm^2)	1.95	1.96	2.43	2.53	1.55
	Tensile strength‡ (N/mm^2)	1.24	1.25	1.55	1.61	0.98
	Friability* (%)	0.15	0.15	0.19	0.45	0.15

Notes: Data have been rounded to two digits after decimal point. *Data presented as means ± SD (n=10). **Data presented as means ± SD (n=3). ‡Calculations were made based on mean crushing strength and thickness of tablets.

(F5, 58.79±1.61) than those with lower oil content (F4, 95.28±1.39). Similarly, the values of specific crushing strength and tensile strength also indicated better mechanical strength. Friability testing was performed according to the USP, and all the formulations complied with the pharmacopeial requirements. After friability testing, tablets were free of edging, capping, lamination, and breakage, and their weight loss was within the permissible range (not more than 1%).

Disintegration Time

This was determined for six tablets (n=6) randomly selected from each formulation, and their average was taken. All the formulations showed disintegration time within the official limits (≤15 min, Figure 3). SEDDS formulations contained oil and were expected to have poor disintegration because of their hydrophobic nature. Disintegration of tablets was increased by disintegrants and further augmented by the presence of surfactant (Tween 60). Surfactants decreased surface tension and increased water penetration of the tablets, subsequently resulting in high disintegration.

In Vitro Drug Release

In vitro release of simvastatin from all tablets was tested as per official monograph. According to the USP, not less than 75% of the drug should release from simvastatin tablets within 30 min.[22] In the present study, drug release was evaluated for 1 hour to observe the time taken for 100% drug release. The dissolution rate of the market product of simvastatin was also checked and used as control for comparison. Quick and almost complete drug release was observed within 30 min

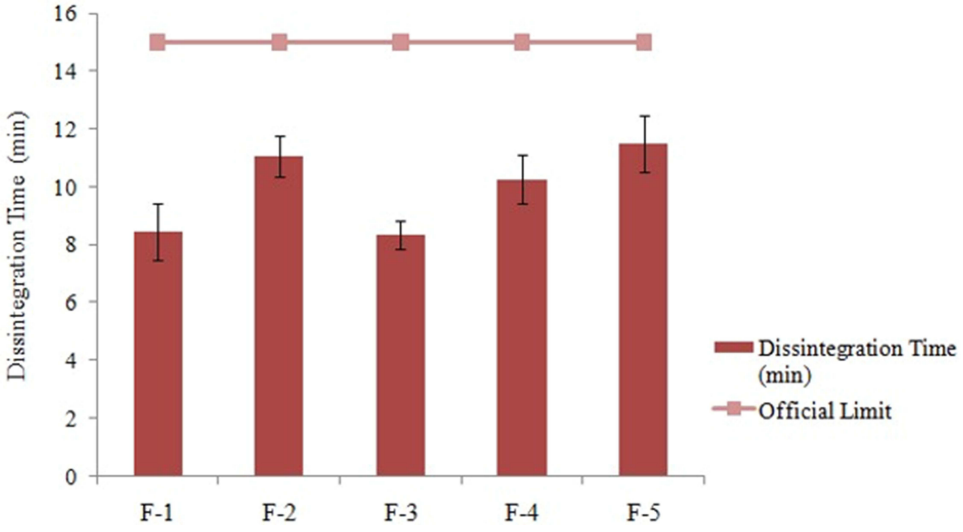

Figure 3 Disintegration time of different formulations of simvastatin self-emulsified tablets. Disintegration time was determined according to USP for six tablets (n=6), using purified water as media held at 37°±2°C.

from all the developed formulations (Figure 4). As all the formulations showed similar release characteristics, differences were determined based on burst release, ie, drug release within the first 15 min ($Q_{15\ min}$).

The dissolution rate of developed formulations and control (marketed conventional tablets of simvastatin) was assessed based on $Q_{15\ min}$ and $Q_{30\ min}$ (Figure 5). Results showed that all formulations had higher drug release at both

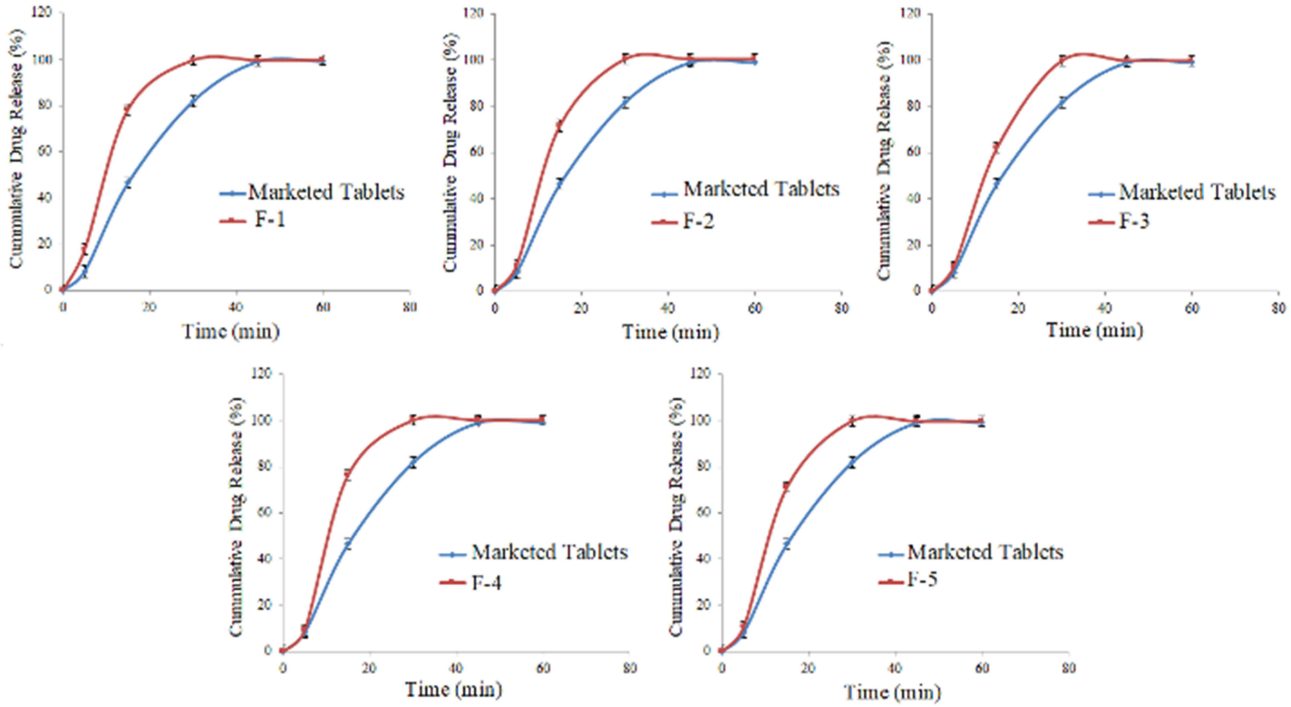

Figure 4 Dissolution rate from different formulations of simvastatin self-emulsified tablets.

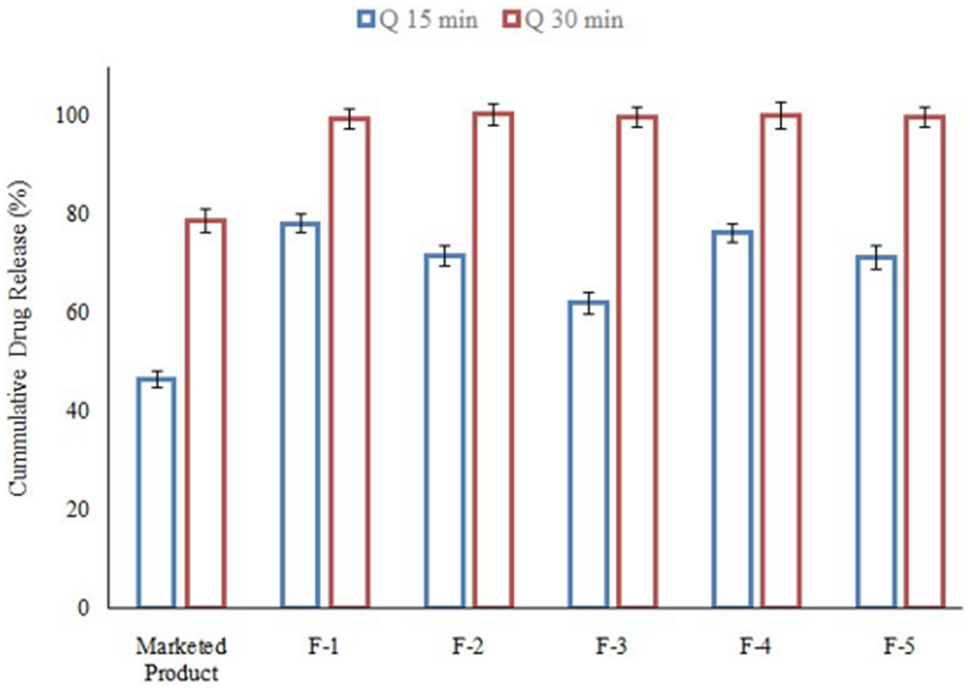

Figure 5 Comparison of cumulative drug release after 15 ($Q_{15\ min}$) and 30 min ($Q_{30\ min}$).

the test points. SEDDS formulations prepared with simvastatin showed higher drug release than conventional tablets, indicating that self-emulsification significantly enhanced the dissolution rate of poorly water-soluble drugs. SEDDSs, due to their unique solubilization properties, allow for the delivery of lipophilic drugs to the GIT in a dissolved state, avoiding the dissolution step, which is a limiting factor in the absorption rate of BCS class II drugs, including simvastatin.

Conclusion

This study aimed at formulating a SEDDS for simvastatin. Different formulations of simvastatin were prepared (n=5) using varying ratios of castor and olive oils. Drug solutions were adsorbed in MCC, and the formulations were compressed and tested at pre- and postcompression levels for different quality-control parameters. All the formulations, particularly F5, showed short emulsification time and high cloud point and dissolution rate. In conclusion, using commonly available excipients and machinery, self-emulsified tablets with better dissolution profiles can be prepared by direct compression. Enhanced dissolution rate, along with drug presence in emulsion form, will improve the bioavailability of simvastatin.

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Disclosure

The authors have no conflicts of interest to declare.

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