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Formulation and Evaluation of Self-Emulsifying Drug-Delivery System Tablets for Enhanced Oral Bioavailability of Simvastatin

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ABSTRACT

Oral absorption of poorly water-soluble drugs like simvastatin is often limited. Self-emulsifying drug-delivery systems (SEDDSs) offer a strategy to enhance solubility and bioavailability. This study aimed to develop and evaluate SEDDS-based tablets of simvastatin using castor and olive oils as the lipid phase and Tween 60 as the surfactant.Liquid SEDDS formulations were adsorbed onto microcrystalline cellulose and compressed into tablets using 10.5 mm shallow concave punches. The tablets were then assessed for key quality attributes, including drug content, mechanical strength, disintegration, and dissolution.Simvastatin showed high solubility in a 10:1 mixture of oils and Tween 60. The tablets exhibited rapid self-emulsification (<200 seconds) and high thermal stability (cloud point >60°C). All formulations met content uniformity requirements (98.5–101%) and passed mechanical tests, including crushing strength (58–96 N) and friability (≤1%). Tablets disintegrated within 15 minutes and released the drug completely within 30 minutes.Direct compression of SEDDS formulations using common excipients produced simvastatin tablets with improved dissolution and potential bioavailability. These SEDDS-based tablets represent a promising alternative to conventional simvastatin tablets.

Keywords: Simvastatin, SEDDS, Self-emulsifying tablets, Castor oil, Olive oil, Tween 60

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Introduction

Oral drug administration is widely preferred due to its convenience, patient compliance, dosing flexibility, and suitability for self-administration, in addition to generally lower production costs compared with sterile formulations [1, 2]. However, a major limitation is the poor dissolution of certain drugs, particularly those classified as Biopharmaceutics Classification System (BCS) class II and IV, which have low aqueous solubility [3]. Various strategies have been explored to enhance dissolution and oral bioavailability, including chemical modification, particle size reduction, salt formation, use of surfactants, incorporation into novel drug-delivery systems (DDSs), nanoparticles, or liposomes [4].

Lipid-based formulations, including lipid solutions, emulsions, self-emulsifying systems, and lipid nanoparticles, have gained attention for their ability to improve solubility and absorption of poorly water-soluble compounds [3, 5]. Despite these advantages, challenges such as stability and manufacturing complexity remain [6, 7]. Self-emulsifying drug-delivery systems (SEDDSs) offer an alternative, forming isotropic mixtures of drug, oil, and surfactant that spontaneously emulsify upon contact with gastrointestinal fluids [8]. Co-solvents and co-emulsifiers can further enhance drug solubility and emulsification, enabling hydrophobic drugs to be administered in unit dosage forms and forming fine emulsions that improve dissolution and bioavailability [9]. Droplet sizes in these emulsions generally range from nanometers to micrometers [10], and the emulsion must remain stable in gastrointestinal fluids long enough for absorption. SEDDSs have been successfully applied to poorly soluble drugs such as hydrocortisone, celastrol, indomethacin, and phyllanthin [11, 12].

Self-emulsification occurs when the energy required to increase the surface area of the system is less than the entropy gain, allowing spontaneous formation of stable emulsions [13]. Emulsifying agents prevent phase separation by reducing interfacial tension and limiting droplet coalescence, while droplet size and polarity influence drug release from SEDDS formulations [14]. Waxy excipients are typically avoided in SEDDS preparation due to unpredictable polymorphic behavior and morphology, highlighting the importance of simple formulations with minimal excipients [15].

Liquid SEDDS (L-SEDDS) face challenges such as limited drug loading, stability issues, and formulation constraints. Converting L-SEDDS to solid dosage forms—via adsorption onto solid carriers, capsule filling, or nanoparticle formation—overcomes these limitations [12]. Solid SEDDS (S-SEDDS) retain the benefits of liquid lipid formulations while offering enhanced stability, longer shelf life, and easier handling. Compared with other delivery systems such as polymeric carriers, liposomes, and micelles, S-SEDDS are easier to scale up commercially, cost-effective, and show high batch-to-batch uniformity [16, 17]. Several SEDDS-based products, including Neoral® (cyclosporine A), Norvir® (ritonavir), and Fortovase® (saquinavir), demonstrate successful clinical translation [18].

Simvastatin **(Figure 1)**, a competitive inhibitor of HMG CoA reductase, is widely used to lower low-density lipoprotein cholesterol [19]. It is a BCS class II drug with poor water solubility (pKa 4.68), meaning its oral bioavailability is limited by its dissolution rate [20, 21]. Various strategies have been explored to improve dissolution and subsequent absorption. This study aimed to develop a SEDDS formulation of simvastatin to enhance dissolution and oral bioavailability. Various oil-based formulations were prepared, converted to solid dosage forms, and evaluated for quality attributes according to US Pharmacopeia guidelines [22].

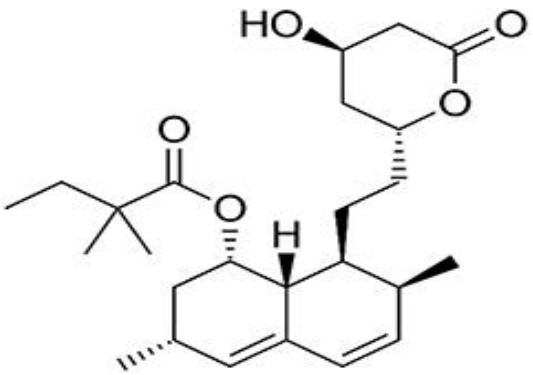

Figure 1. Chemical structure of simvastatin.

Materials and Methods

Simvastatin (purity 99.73%) was procured from Maithri Laboratories, India, through Ferozsons Laboratories, Nowshera, Pakistan. Additional excipients used included Tablettose 80 (Molkerei Meggle, Germany), microcrystalline cellulose, cross-linked carboxymethyl cellulose sodium, colloidal silicon dioxide (FMC International, Ireland), Tween 60, maize starch (I.C.I, Pakistan), and magnesium stearate (Coin Powder International, Taiwan), all of which were utilized without further purification. Analytical-grade solvents such as ethanol and methanol, along with HCl reagent, were used, while purified water was generated using a Milli-Q system (Millipore, Milford, MA, USA).

Oil phase selection

The choice of oil was guided by its capacity to dissolve simvastatin effectively. Solubility assessments were conducted following the flask-shake procedure [23, 24]. Briefly, an excess amount of simvastatin was added to a 50 mL flask containing the selected oil, and the mixture was sonicated in a water bath for 10 minutes. The flask was then agitated continuously for 8 hours at room temperature (26 ± 3°C) using a mechanical shaker. After equilibration for 1 hour, the mixture was filtered to remove undissolved drug, and the concentration of solubilized simvastatin was determined. Solubility testing was carried out for castor oil, olive oil, and their blends with various concentrations of Tween 60. Drug solubility was calculated according to Eq. 1.

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

Compatibility Studies

The compatibility between simvastatin and the selected oil-surfactant system was assessed using Fourier-transform infrared spectroscopy (FTIR). Spectra of the pure drug and its solution prepared in the oil-surfactant mixture were recorded and compared. A Shimadzu FTIR spectrophotometer (Japan) was employed for spectral acquisition, and data analysis was performed using IR Solutions version 1.10 software. Samples were prepared as KBr disks by blending the sample with potassium bromide (2% w/w), grinding the mixture into a fine powder, and loading it into the sample holder. Spectra were captured in the range of 400–4000 cm^{-1} at a resolution of 8 cm^{-1} in transmittance mode.

Formulation of SEDDS

Multiple SEDDS formulations were prepared using varying proportions of the selected oils, while maintaining a constant drug-to-surfactant ratio **(Table 1)**. The surfactant was first combined with the oil phase through gentle heating in a water bath. The accurately weighed drug was then incorporated into the oil-surfactant mixture and homogenized at high speed for 15 minutes to ensure uniform dispersion.

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

Characterization of SEDDS formulations

Centrifugation test

Phase stability of the emulsions was assessed using centrifugation. The prepared formulations were subjected to centrifugation at 4000 g for 5 minutes, and any phase separation was visually inspected. Formulations showing no separation were considered stable, while those with phase separation were deemed unstable [25].

Self-Emulsification time

The self-emulsification time of SEDDS formulations was determined using USP Dissolution Apparatus II (paddle method). Purified water (500 mL) was equilibrated at 37°±2°C, and 0.1 mL of each SEDDS formulation was added with stirring at 50 rpm. The time required for the formation of a homogeneous dispersion was recorded. Measurements were performed in six replicates, and the mean value was reported (n=6) [10].

Robustness to dilution

To evaluate the stability of the formulations upon dilution, aliquots were diluted with acid buffer (pH 2.1) at ratios of 10, 50, and 100 times. The diluted formulations were visually inspected for any signs of emulsion breakdown [10].

Cloud point determination

The cloud point, defined as the temperature at which the emulsion becomes turbid, was determined by diluting 1 mL of each formulation in 200 mL of purified water and gradually heating in a water bath. The temperature at which cloudiness appeared was recorded. All measurements were performed in triplicate, and the mean values were reported (n=3) [25].

Preparation of solid SEDDS (S-SEDDS)

Liquid SEDDS formulations were transformed into solid SEDDS by adsorption onto microcrystalline cellulose (Avicel PH 112). The cellulose was placed in a benchtop cone mixer (Morgan Instruments, Lahore, Pakistan), and the liquid SEDDS was added gradually with thorough mixing. To improve adsorption and achieve a free-flowing

powder, 1% w/w colloidal silicon dioxide was incorporated. The composition of the resulting S-SEDDS formulations is summarized in **Table 2.**

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.

Preparation of tablets containing self-emulsifying formulations

The prepared S-SEDDS powders were mixed with additional excipients **(Table 3)** for 30 minutes using a laboratory-scale double-cone mixer operated at 25 rpm. The resulting powder blends were then compressed into tablets using a rotary tablet compression machine (ZP-21, China). Tablets were formed with round, shallow concave punches (10.5 mm diameter) and a target weight of 350 mg per tablet. A minimum of 300 tablets were produced from each formulation for subsequent evaluation.

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.

Precompression evaluation

Before tablet compression, the flow properties of the powder blends were assessed by measuring the angle of repose, Carr's index, and Hausner's ratio. The angle of repose was determined using the funnel method as described in the USP. Bulk density was calculated by weighing a known quantity of powder in a graduated cylinder and dividing the mass by the occupied volume. Tapped density was determined by manually tapping the powder until the volume remained constant. Carr's index and Hausner's ratio were then calculated from the bulk and tapped densities using USP-recommended equations [22].

Postcompression evaluation of simvastatin S-SEDDS tablets

Physical parameters of tablets

Tablet thickness was measured for ten randomly selected tablets using a digital hardness and thickness tester (Pharma Test, Germany), with results expressed as mean ± SD. Weight variation was assessed according to USP guidelines by individually weighing twenty tablets, calculating the average weight, and comparing individual weights against the mean [22].

Determination of drug content

The simvastatin content of tablets from all SEDDS formulations was determined using HPLC as described in the official monograph [22]. The HPLC system (PerkinElmer, USA) included a pump, online degasser, Peltier column oven, and UV-visible detector (series 200), with data analyzed via PerkinElmer TotalChrom Workstation software (version 6.3.1). A Hypersil BDS C8 column (250 × 4.6 mm, 5 µm) was used as the stationary phase, and a mixture of phosphate buffer (pH 6.8) and acetonitrile (35:65, v/v) served as the mobile phase at a flow rate of 1.8 mL/min, with detection at 238 nm.

For sample preparation, ten randomly selected tablets were placed in a 250 mL volumetric flask, 10 mL of water was added, and the mixture was swirled until complete disintegration. The solution was diluted to 250 mL, sonicated for 15 min, and cooled. After centrifugation, an aliquot of the supernatant was further diluted to 0.1 mg/mL of simvastatin using a USP-prepared diluting solution. The diluting solution was prepared by adding 3

mL glacial acetic acid to 900 mL water, adjusting pH to 4 with 5 N NaOH, and making up the volume to 1000 mL, followed by mixing 200 mL of this solution with 800 mL acetonitrile. A standard solution of simvastatin (0.1 mg/mL) was prepared similarly. Approximately 10 µL of both standard and sample solutions were injected into the HPLC, and simvastatin content was quantified by comparing peak areas (n=3).

Mechanical strength of tablets

The mechanical strength of tablets was evaluated according to USP guidelines, which recommend assessing crushing strength, specific crushing strength, tensile strength, and friability. Ten tablets from each formulation were randomly selected, and their crushing strength was measured using a tablet hardness and thickness tester (PharmaTest, Hamburg, Germany). The mean crushing strength and standard deviations were calculated. Subsequently, tensile strength and specific crushing strength were determined using the mean values of tablet thickness and crushing strength, following USP-recommended equations [22].

$$TS = \frac{2F}{\pi DH} \quad (2)$$

$$\tau = \frac{F}{DH} \quad (3)$$

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.

Disintegration assessment

Tablet disintegration was measured using a USP disintegration apparatus (Pharma Test, Germany) in accordance with standard compendial procedures [22]. Purified water, maintained at 37°±2°C, served as the medium. Each tablet was placed individually in the basket of the apparatus, and the time until complete breakdown was recorded. The average disintegration time and standard deviation were calculated from six tablets (n=6).

In vitro dissolution study

The release of simvastatin from the tablets was studied using the USP paddle apparatus (Apparatus II) at 50 rpm, following the official simvastatin monograph [22]. Dissolution medium consisted of 900 mL phosphate buffer (0.01 M, pH 7) containing 0.5% sodium dodecyl sulfate. Samples (5 mL) were withdrawn at 0, 5, 15, 30, 45, and 60 minutes, filtered, and analyzed via HPLC. Drug content was determined by comparing the peak areas of the samples against a standard solution prepared in the same medium.

Simvastatin solubility in formulation components

For SEDDS formulation, oils and surfactant were chosen primarily based on their ability to dissolve simvastatin, as solubility directly affects drug loading [21]. Various ratios were tested **(Table 4)**, and the combination of oils with surfactant at 10:1 (v/v) showed the best solubilization. Surfactants also improved emulsification by lowering interfacial tension and enhancing miscibility with gastrointestinal fluids. FTIR analysis of simvastatin in the oil-surfactant mixture showed no significant changes in peak positions or intensities compared to the pure drug **(Figure 2)**, indicating chemical stability and no interaction, confirming the compatibility of the chosen excipients for SEDDS preparation.

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

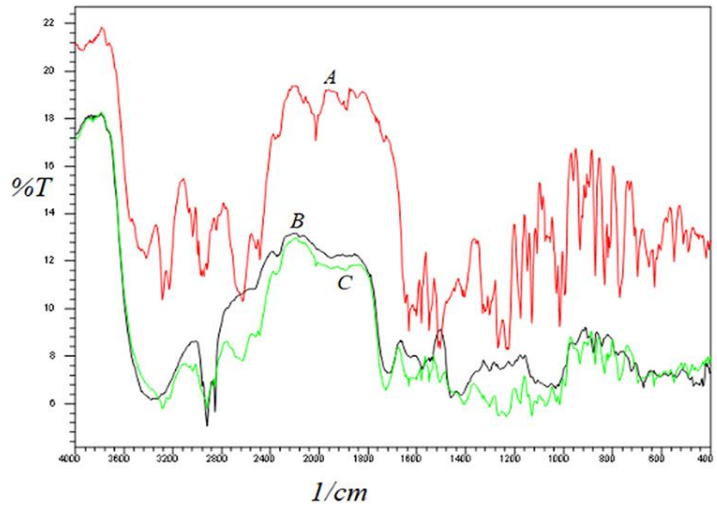

Figure 2. shows the FTIR spectra of (A) pure simvastatin, (B) simvastatin dissolved in a mixture of olive oil and Tween 60, and (C) simvastatin dissolved in castor oil and Tween 60.

Physical characterization

Centrifugation stability

The physical stability of the SEDDS formulations was assessed via centrifugation. Samples were spun at 4000 g for 5 min, and none of the formulations exhibited phase separation, creaming, cracking, or coalescence. These observations confirm the kinetic stability of the prepared emulsions.

Self-Emulsification time

Self-emulsification time is a critical parameter for evaluating the performance of SEDDS, as it reflects how quickly the formulation disperses in aqueous media. The presence of surfactants in SEDDS reduces interfacial tension between oil and water, allowing rapid formation of an oil-in-water emulsion. In this study, the self-emulsification time of all formulations was measured using USP Apparatus II at a paddle speed of 50 rpm, simulating minimal agitation comparable to gastrointestinal motility. All formulations achieved complete dispersion in under 200 seconds (n=3, **Table 5**), indicating their ability to spontaneously emulsify in the stomach. Notably, formulations containing higher Tween 60 content demonstrated shorter self-emulsification times, likely due to enhanced water penetration at the oil–water interface.

Table 5. summarizes the self-emulsification times and cloud points of the prepared 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.

Cloud point determination

Emulsions can lose stability at elevated temperatures, leading to phase separation. Surfactants play a key role in maintaining emulsion stability, but their solubility decreases as temperature rises. When the emulsion turns

cloudy, it indicates reduced surfactant solubility and potential instability. Therefore, cloud point measurement serves as an important indicator of thermal stability. In this study, all SEDDS formulations exhibited cloud points above 50°C **(Table 5)**, suggesting they are stable during processing, storage, and passage through the gastrointestinal tract. The observed similarity in cloud points across formulations is likely due to the uniform surfactant concentrations used in all samples.

Robustness to dilution

Upon oral administration, SEDDS are exposed to gastrointestinal fluids, which can dilute the formulation and potentially induce phase separation or drug precipitation. To assess this, formulations were diluted with acid buffer (pH 2.1) at 10-, 50-, and 100-fold ratios. All formulations maintained homogeneity without precipitation or phase separation, indicating their robustness and predicting stable behavior in vivo upon dilution with gastrointestinal fluids.

Precompression evaluation of S-SEDDS

To overcome the limitations of liquid SEDDS, the optimized formulation (F5) was converted to a solid dosage form. Before compression, the powder blends were evaluated for flow properties. All formulations demonstrated satisfactory flow, as indicated by favorable values of angle of repose, Carr's index, and Hausner's ratio **(Table 6)**. Improved flowability is attributed to the granulating effect of the adsorbed oil phase on microcrystalline cellulose, which, when combined with colloidal silicon dioxide, reduced cohesion between particles. The inclusion of excipients such as Tablettose 80 further enhanced powder flow, facilitating uniform tablet compression.

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

	Angle of Repose (⁰)	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.

Postcompression evaluation of SEDDS-Based tablets

Physical parameters

The prepared tablets were designed with a target weight of 350 mg each, and the observed weight variations fell within the official limits specified by the USP **(Table 7)**. Randomly selected tablets from all formulations showed no visible physical defects, including sticking or picking. The tablet surfaces were smooth and glossy, reflecting adequate lubrication during compression. Tablet thickness ranged narrowly from 3.5 to 3.7 mm, indicating uniform flow and consistent die filling of the powder blend. Analysis of drug content revealed values exceeding 99% **(Table 7)**, confirming homogeneous distribution of simvastatin within the formulations.

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.

Mechanical strength

Tablet mechanical properties were evaluated in terms of crushing strength, specific crushing strength, tensile strength, and friability according to USP guidelines **(Table 7)**. The crushing strength of the formulations ranged from 58 to 96 N. Formulations with higher oil content, such as F5 (58.79±1.61 N), exhibited lower crushing strength compared to those with reduced oil content, such as F4 (95.28±1.39 N). Similar trends were observed for specific crushing strength and tensile strength, reflecting overall robust mechanical characteristics. Friability tests confirmed that all tablets met pharmacopeial standards, showing no signs of capping, lamination, edging, or breakage, and weight loss did not exceed 1%, as required.

Disintegration time

Disintegration was measured for six tablets (n=6) randomly selected from each formulation, and mean values were calculated. All tablets disintegrated within the USP-specified limit of 15 minutes **(Figure 3)**. Although the hydrophobic nature of oils in SEDDS formulations could reduce disintegration, the inclusion of disintegrants and surfactants, such as Tween 60, enhanced water penetration and lowered surface tension, thereby promoting rapid tablet disintegration.

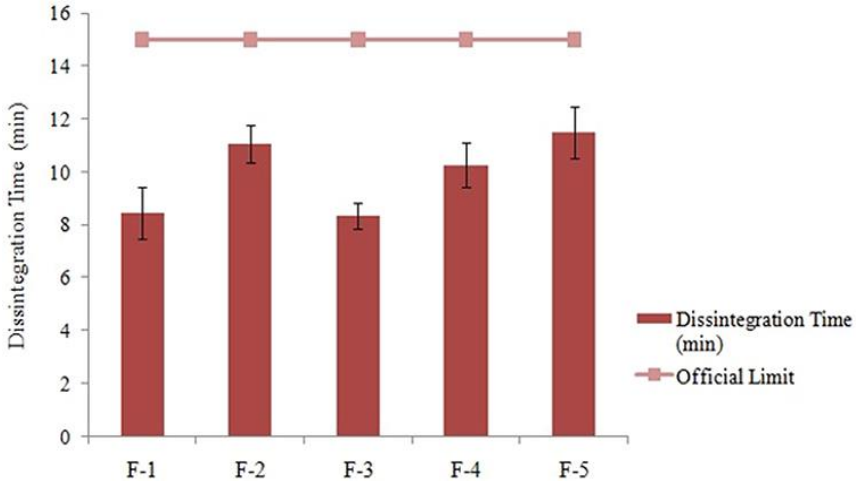

Figure 3. Disintegration times of the various simvastatin S-SEDDS tablet formulations were measured according to USP specifications. Six tablets from each formulation (n=6) were tested using purified water maintained at 37°±2°C as the disintegration medium.

In vitro drug release

The in vitro release profiles of simvastatin from the developed tablets were evaluated following the USP monograph guidelines. According to USP, at least 75% of simvastatin should be released within 30 minutes. In this study, dissolution was monitored for 1 hour to determine the time required for complete drug release. The market reference product of simvastatin was also tested for comparison. All S-SEDDS formulations demonstrated rapid and nearly complete drug release within 30 minutes **(Figure 4)**. Since the overall release profiles were similar, the formulations were further compared based on burst release, defined as the fraction of drug released within the first 15 minutes (Q15 min).

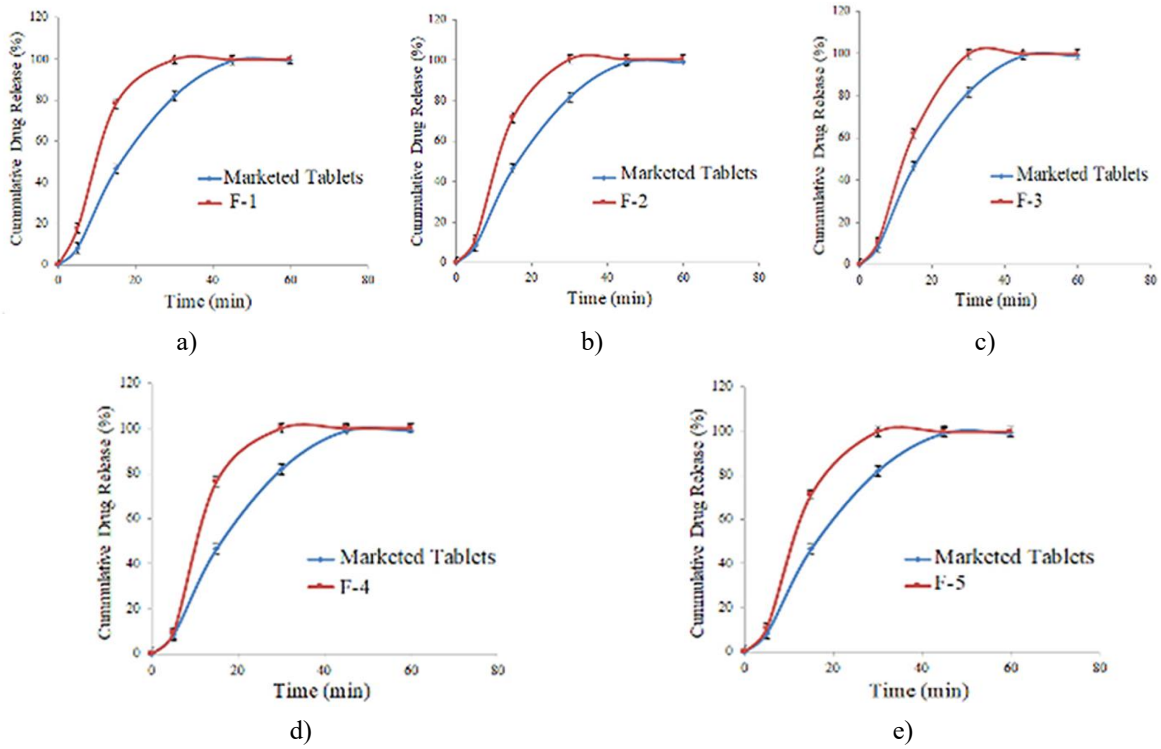

Figure 4. Dissolution profiles of various simvastatin S-SEDDS formulations are shown.

The release of simvastatin from the developed S-SEDDS tablets and the control (marketed conventional tablets) was evaluated at 15 min (Q15) and 30 min (Q30) time points **(Figure 5)**. The results demonstrated that all S-SEDDS formulations released a higher amount of drug compared to the conventional tablets at both time points. This indicates that the self-emulsifying system substantially improved the dissolution of simvastatin, a poorly water-soluble drug. The enhanced release can be attributed to the ability of SEDDS to maintain the drug in a solubilized state in the gastrointestinal tract, bypassing the dissolution step that typically limits the absorption of BCS class II compounds like simvastatin.

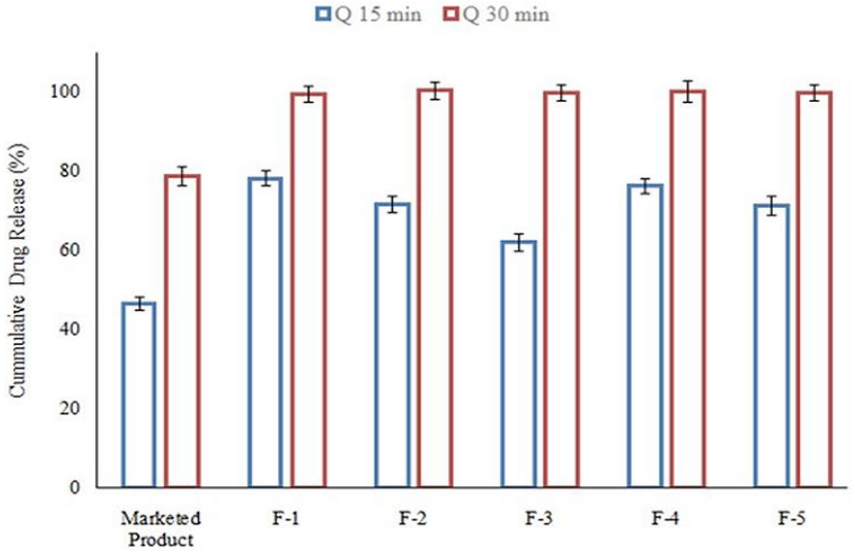

Figure 5. Comparison of cumulative drug release after 15 ($Q_{15\ min}$) and 30 min ($Q_{30\ min}$).

Conclusion

This study successfully developed self-emulsifying drug-delivery system (SEDDS) formulations for simvastatin. Five different formulations were prepared using varying proportions of castor and olive oils, followed by adsorption onto microcrystalline cellulose and compression into tablets. All formulations, especially F5,

demonstrated rapid emulsification, high cloud points, and enhanced dissolution rates. These results indicate that self-emulsified tablets of simvastatin can be efficiently produced using standard excipients and conventional tablet-compression techniques. By maintaining the drug in a solubilized emulsion form, these S-SEDDS tablets are expected to improve the oral bioavailability of simvastatin compared to conventional dosage forms.

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Ethics Statement: None

References

1. Amjad K. Optimization of the process variables of roller compaction, on the basis of granules characteristics (flow, mechanical strength and disintegration behavior): an application of SeDeMODT expert system. Drug Dev Ind Pharm. 2019;45(9):1537–46. doi:10.1080/03639045.2019.1634094
2. Hazal EG, Serdar T, Fatmanur TD, Füsun A. 3D printed extended release tablets for once daily use: an in vitro and in vivo evaluation study for a personalized solid dosage form. Int J Pharm. 2021;596:120222. doi:10.1016/j.ijpharm.2021.120222
3. Amjad K, Zafar I, Yasar S, Lateef A, Ismail Z, Aman U. Enhancement of dissolution rate of class II drugs (Hydrochlorothiazide); a comparative study of the two novel approaches; solid dispersion and liqui-solid techniques. Saudi Pharm J. 2015;23:650–7. doi:10.1016/j.jsps.2015.01.025
4. Hassan M, Shanbaz N, Khan SI, Khan I. Formulation and evaluation of taste masked orally disintegrating tablets of itopride HCl using hydrophillic polymers as drug carrier. Lat Am J Pharm. 2015;34(7):1364-72.
5. Batista P, Castro PM, Madureira AR, Sarmento B, Pintado M. Recent insights in the use of nanocarriers for the oral delivery of bioactive proteins and peptides. Peptides. 2018;101:112–23. doi:10.1016/j.peptides.2018.01.002
6. Arshad R, Tabish TA, Kiani MH, Ibrahim IM, Shahnaz G, Rahdar A, et al. A hyaluronic acid functionalized Self-Nano-Emulsifying Drug Delivery System (SNEDDS) for enhancement in ciprofloxacin targeted delivery against intracellular infection. Nanomaterials (Basel). 2021;11(5):1086. doi:10.3390/nano11051086. PMID: 33922241; PMCID: PMC8146397.
7. Ioele G, Tavano L, Muzzalupo R, De-Luca M, Ragno G. Stability-indicating methods for NSAIDs in topical formulations and photoprotection in host-guest matrices. Mini Rev Med Chem. 2016;16:676–82. doi:10.2174/1389557515666150709111744
8. Mahmood A, Schnürch AB. SEDDS: a game changing approach for the oral administration of hydrophilic macromolecular drugs. Adv Drug Deliv. 2019;142:91–101. doi:10.1016/j.addr.2018.07.001
9. Bhattacharya SA. Self-Emulsifying Drug Delivery System (SEDDS) and its pharmaceutical applications. Appl Clin Res Clin Trials Regul Aff. 2020;7:206–24. doi:10.2174/2213476X07666200827102951
10. Gayathri T, Venkata MR, Rama RN. Formulation and evaluation of self nano emulsifying drug delivery system of raloxifene hydrochloride. JDDT. 2021;11:16–9.
11. Benish A, Amjad K, Hamad SA, Majeedullah W, Munair B, Attiqa N. Evaluation of the effect of carrier material on modification of release characteristics of poor water soluble drug from liquisolid compacts. PLoS One. 2021;16(8):1–18.
12. Anna CK, Marta S, Aleksandra A, Emilia S, Katarzyna W. Development and evaluation of liquid and solid self-emulsifying drug delivery systems for atorvastatin. Molecules. 2015;20:21010–22. doi:10.3390/molecules201219745

13. Bruno FBS, Eduardo FM, Ulf O, Per L. Size, shape, and charge of salt-free catanionic microemulsion droplets: a small-angle neutron scattering and modeling study. J Phys Chem B. 2009;113:10230–9. doi:10.1021/jp901752s
14. Singh D. Self-nanoemulsifying drug delivery system: a versatile carrier for lipophilic drugs. Pharm Nanotechnol. 2021;9(3):166-76. doi:10.2174/2211738509666210422124023. PMID: 33888054.
15. Qiang W, Rui S, Juan H, Qiang X. Development and characterization of a new non-aqueous self-double-emulsifying drug delivery system for topical application of rutin. J Drug Deliv Sci Technol. 2021;61:101243. doi:10.1016/j.jddst.2019.101243
16. Sandra ME, Diana R, Ivonne H, Valderrama BVA, Diana MA. Development of a self-emulsifying drug delivery system (SEDDS) to improve the hypoglycemic activity of Passiflora ligularis leaves extract. J Drug Deliv Sci Tec. 2021;64:102604. doi:10.1016/j.jddst.2021.102604
17. Kanghee J, Khadka P, Taejun J, Soo-Jin K, Seong-Ha H, Jaehwi L. Enhanced intestinal lymphatic absorption of saquinavir through supersaturated self-microemulsifying drug delivery systems. Asian J Pharm Sci. 2020;15:336–46. doi:10.1016/j.ajps.2018.11.009
18. Nazzal S, Smalyukh I, Lavrentovich O, Mansoor AH. Preparation and in vitro characterization of a eutectic based semisolid self nanoemulsified drug delivery system (SNEDDS) of ubiquinone: mechanism and progress of emulsion formation. Int J Pharm. 2002;235:247–65. doi:10.1016/S0378-5173(02)00003-0
19. Rao AK, Del FC, Janapati HZ, Voelker H, Lu X, Criner G. Effects of simvastatin on tissue factor pathway of blood coagulation in STATCOPE (Simvastatin in the prevention of COPD exacerbations) trial. J Thromb Haemost. 2021;19:1709–17. doi:10.1111/jth.15282
20. Singh P. Preparation, characterization and dissolution of solvent evaporated simvastatin solid dispersions. J Med Pharm Allied Sci. 2021;10:2813–18. doi:10.22270/jmpas.V10I3.1179
21. Bravo-Alfaro DA, Muñoz-Correa MO, Santos-Luna D, Toro-Vazquez JF, Cano-Sarmiento C, García-Varela R, et al. Encapsulation of an insulin-modified phosphatidylcholine complex in a self-nanoemulsifying drug delivery system (SNEDDS) for oral insulin delivery. J Drug Deliv Sci Technol. 2020;57:101622
22. The United States Pharmacopeial Convention, Inc. The United States Pharmacopeia and National Formulary USP 41 –NF 36. Rockville, MD: The United States Pharmacopeial Convention, Inc.; 2018.
23. Khan A. Development and validation of discriminatory dissolution testing method for orally disintegrating tablets (ODTs) of Domperidone. Dissolution Technol. 2017;24:28–36. doi:10.14227/DT240217P28
24. Pagano C, Latterini L, Di Michele A, Luzi F, Puglia D, Ricci M, et al. Polymeric bioadhesive patch based on ketoprofen-hydrotalcite hybrid for local treatments. pharmaceutics. 2020;12(8):733. doi:10.3390/pharmaceutics12080733. PMID: 32759858; PMCID: PMC7464538.
25. Ravinder V, Deepak K. Design and optimization of candesartan loaded self-nanoemulsifying drug delivery system for improving its dissolution rate and pharmacodynamic potential. Drug Deliv. 2020;27:756–71. doi:10.1080/10717544.2020.1760961