Nigerian Journal of Pharmaceutical and Applied Science Research,
Vol.14 (1): 23-29; March 2025 ISSN: 2971-737X (Print); ISSN: 2971-7388.
Available at www.nijophasr.net https://doi.org/10.60787/nijophasr-v14-i1-580

Encapsulated Self-Emulsifying Drug Delivery System of Simvastatin: A Novel Approach for Enhanced Dissolution

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ABSTRACT

***Background*:** The solid form of a self-emulsifying drug delivery system (SEDDS) enhances formulation stability and dissolution. This study aimed to develop an encapsulated self-emulsifying drug delivery system of simvastatin utilizing Tween 80/ethanol mixture as the surfactant/co-surfactant system.

Methods: Two separate 10 mL Tween 80/ethanol mixes (ratios 5:5 and 1:9) were used in formulating Liquid SEDDSs containing 0.1 g simvastatin. Compatibility studies using FTIR spectroscopy and particle size analysis using zeta sizer were carried out. The liquid SEDDSs were adsorbed on microcrystalline cellulose and later encapsulated. *In vitro* dissolution of the capsules in comparison with a marketed product was carried out.

***Results*:** The observed peaks in the fingerprint region in the spectrum of simvastatin were superimposed in the spectrum of the SEDDS. There was no significant difference in the particle size of simvastatin and the SEDDS. The marketed product released less than 5% of the drug after 120 minutes, whereas the formulated SEDDSs showed a drug release of 32–40% (an increase of over 600%).

***Conclusion*:** The solid SEDDS formulation of simvastatin improves drug delivery compared to the conventional formulation. Additionally, a 5:5 Tween 80/ethanol ratio is superior to a 1:9 ratio for SEDDS formulation.

Keywords: drug delivery, encapsulation, self-emulsification, Simvastatin

1. INTRODUCTION

The low commercial availability of liquid SEDDSs is primarily due to stability and portability issues, the potential for drug precipitation upon dilution, and the lack of predictive in vitro protocols. The best approach to mitigate some of these challenges is to make solid dosage form of the liquid SEDDS [1,2]. In addition to the enhanced stability and improved absorption of drugs with low aqueous solubility, solid SEDDS (S-SEDDS) has tremendous advantages like controlled drug release, prolonged gastric residence time and improved permeability [3].
Solidification can be achieved by formulating super-saturated SEDDS (su-SEDDS) that is adsorbed onto porous carriers or by encapsulation of the liquid SEDDS [4]. Most commercial products that are based on self-emulsifying drug delivery systems (SEDDSs) are liquids which are encapsulated either in hard gelatine capsule (Gengraf®, Lipirex®) or soft gelatine capsule (Sandimmune®, Neoral®, Norvir®, Fortovase®, Agenerase®, Depakene®, Rocaltrol®, Targretin®, Vesanoid®, Accutane®, Aptivus®) [5]. Simvastatin is characterized by low solubility and low bioavailability. Several studies have reported the successful development of S-SEDDS of the drug using various oil, surfactant, and co-surfactant combinations. For instance, Ahmed [6] developed a ternary solid dispersion of simvastatin with nanoemulsion, which in rats showed significantly enhanced bioavailability compared to the pure drug. Similarly, Arora [7] prepared a solid SEDDS of simvastatin using a mixture of Capryol 90, Cremophor EL, and Transcutol HP, which in rabbits showed improved pharmacokinetic parameters compared to the pure drug. Elshamy [8] also developed a solid SEDDS of simvastatin using Capmul MCM, Tween 80, and PEG 400, which exhibited prolonged hypolipidemic activity and cardiovascular protection in rats. Our preliminary investigation showed that the Tween 80/ethanol combination was superior to Tween 80/PEG 400, oleic acid/ethanol, and oleic acid/PEG 400 combinations for the formulation of liquid SEDDSs of simvastatin. Hence, this work aims to prepare a solid SEDDS of simvastatin by the encapsulation of the liquid SEDDS containing Tween 80/ethanol as surfactant/co-surfactant system.

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2. MATERIALS AND METHODS

2.1. Materials

Simvastatin (with 98% purity) was obtained from Liansi Chemical Technology (Shangai) Co., Ltd. Other materials used include: cod-liver oil (Merck, England), Tween 80 (BDH Chemicals, England), ethanol (Millipore, USA), HCl (Fischer Scientific U.K. Ltd) and microcrystalline cellulose (Suffolk, England). A marketed simvastatin tablet formulation registered by National Agency for Food and Drug Administration and Control was used as a reference conventional formulation.

2.2. Methods

2.2.1. Formulation of Liquid SEDDS

Simvastatin (0.1 g) was dissolved in 20 mL of cod-liver oil in duplicate. One of the solutions was mixed with 10 mL 1:9 Tween 80/ethanol mix earlier produced while the second solution was mixed with 10 mL 5:5 Tween 80/ethanol mix. Each mixture was sealed in a vial, vortex-mixed, and heated at 40 °C in a water-bath to facilitate the formation of the emulsion. After complete dissolution, the mixture was stored at room temperature until used [9].

2.2.2. Compatibility Studies

Fourier transform infrared (FTIR) spectra of simvastatin, cod liver oil, ethanol, Tween 80 and the self-emulsifying drug delivery system containing 5:5 Tween 80/ethanol were obtained using a spectrophotometer (model 8400S, Shimadzu Corporation, Kyoto-Japan) [10]. The reading was taken at 500 to 4000 cm^{-1} wavenumbers.

2.2.3. Particle Size Analysis

A charged colloidal dispersion of simvastatin and that of liquid SEDDS containing 5:5 Tween 80 and ethanol were placed separately in a zeta cell. After applying an external electric field, particle sizes were recorded using a Zetasizer (Nano ZS Malvern Panalytical, United Kingdom).

2.2.4. Determination of Self-Emulsification Time

A 2 mL sample of the SEDDS formulation was introduced into 100 mL of 0.1 N HCl (to mimic Gastrointestinal fluid concentration) under constant stirring at room temperature. A timer (Smart stopwatch) was started immediately after the formulation contacted the solvent. The time taken for self-emulsification, characterized by the formation of a clear microemulsion, was taken in quadruplicates [11].

2.2.5. Granulation and Encapsulation

Each liquid SEDDS was converted to Solid SEDDS using microcrystalline cellulose (MCC) as the granulating agent. Microcrystalline cellulose was first heated to 30°C before being added to load the liquid SEDDS in a 3:1 proportion following the works of Salawi [4] and Lavra *et al.* [12]. Residual moisture was removed by lyophilization at -4°C with a freeze drier (Gore® PharmBIO) for a duration of 5 h. Amounts of liquid SEDDS equivalent to 20 mg simvastatin were filled into Size 5 empty capsule shells and sealed by a manually-operated capsule filling machines.

2.2.6. In Vitro Drug Dissolution Studies

One capsule of 20 mg simvastatin was inserted in each dissolution basket and placed in a dissolution vessel containing 900 mL 0.1 N HCl maintained at 37.0 ± 0.5 ^{O}C. The dissolution machine was set at 50 revolutions per minute (rpm). Ten millilitre samples were withdrawn at 10 minutes intervals and the same volume of fresh dissolution medium was replaced after each withdrawal [7]. Each withdrawn sample was filtered through a No. 2 Whatman filter paper and the filtered sample was analyzed through a UV-Visible spectrophotometer at 238 nm. A graph of percent drug released was plotted against time for the two test formulations and the marketed product.

2.3. Statistical Analysis

Data obtained from self-emulsification time test were subjected to Student's t-test and presented as mean ± standard deviation (p-value < 0.05 being taken as indicating a significant difference) while those obtained from the release studies were analyzed using Microsoft Excel.

3. RESULTS

3.1 Fourier Transform Infrared Spectra

The FTIR spectra of simvastatin, cod liver oil, ethanol, Tween 80 and the SEDDS containing 5:5 Tween 80/ethanol are shown in Figure 1. Many peaks were found at the fingerprint region (600 – 1,400 cm^{-1}) in the spectrum of simvastatin (Figure 1a). All the major absorption peaks in the various individual ingredients (Figure 1a--d) were

found in the spectrum of the SEDDS containing Tween 80/ethanol (Figure 1e). The observed peaks in the fingerprint region in the spectrum of simvastatin were superimposed in the spectrum of the SEDDS containing 5:5 Tween 80/ethanol.

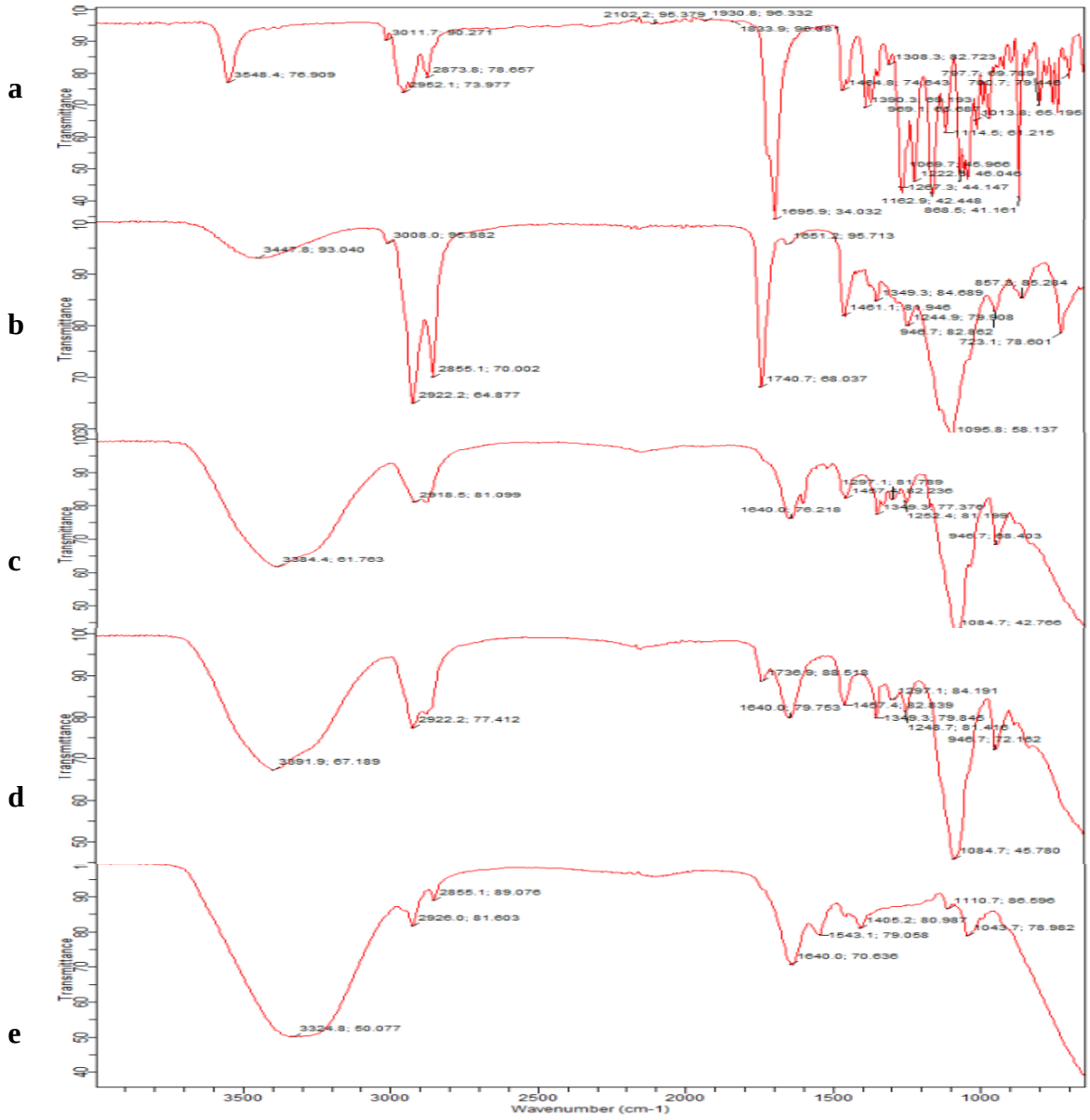

Figure 1: Fourier transform infrared spectra of simvastatin, formulation components and the formulation (a = simvastatin, b = cod liver oil, c = ethanol, d = Tween 80, e = SEDDS containing 5:5 Tween 80/ethanol)

3.2. Particle Size Distribution

The particle size of simvastatin ranged from 0.5 to 5,000 nm, with most particles falling between 10 and 1,000 nm (Figure 2a). The particle size of the SEDDS equally ranged from 0.5 to 5,000 and majority of the particles were in the range of 10 and 1,000 nm (Figure 2b).

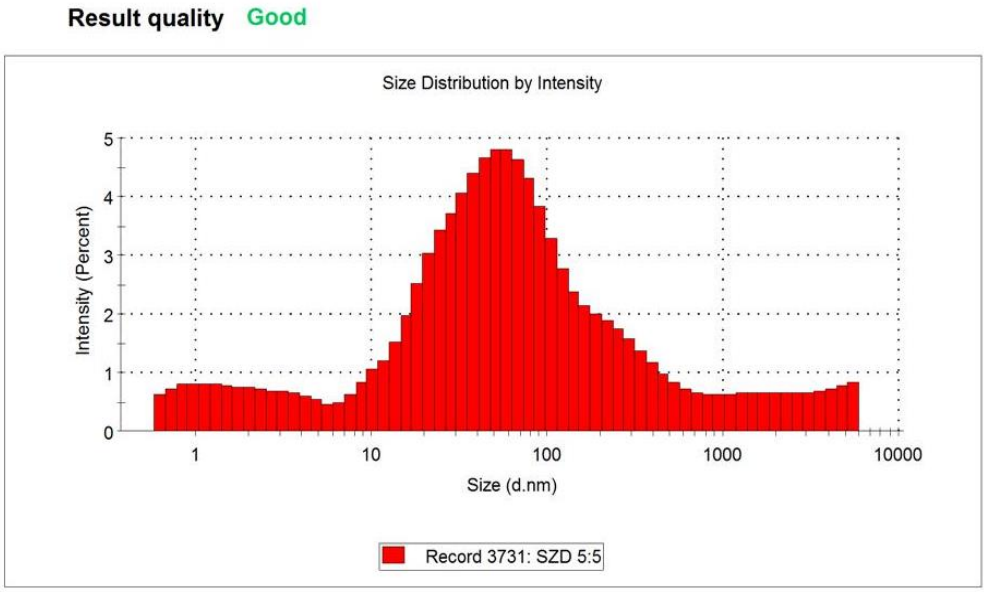

Figure 2a: Particle size distribution of simvastatin

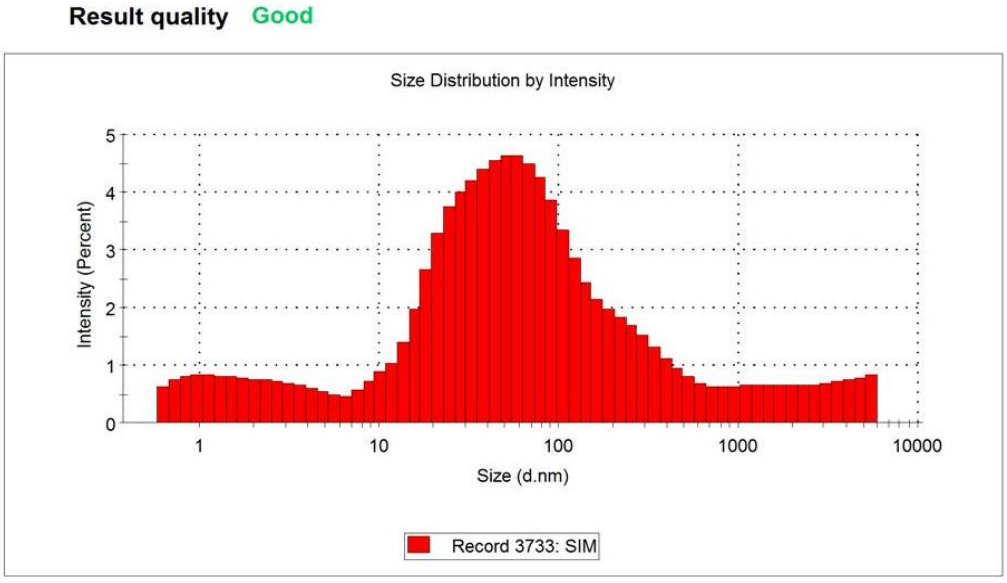

Figure 2b: Particle size distribution of SEDDS containing 5:5 Tween 80/ethanol

3.3. Self-Emulsification Time

The mean self-emulsification times of the SEDDSs are shown in Table 1. A significant difference was observed with the two values, the SEDDS containing 5:5 Tween 80/ethanol having lower emulsification time (P= 0.014).

Table 1: Emulsification times of formulations

Formulation	Self-emulsification time (seconds)
SEDDS with 1:9 Tween 80/ethanol	135.25 ± 1.60
SEDDS with 5:5 Tween 80/ethanol	121.00 ± 1.23
Marketed formulation	Not applicable

3.4. In Vitro Drug Release

The drug release profiles of the SEDDSs containing 1:9 Tween 80/ethanol and 5:5 Tween 80/ethanol as well as that of the conventional formulation are shown in Figure 3.

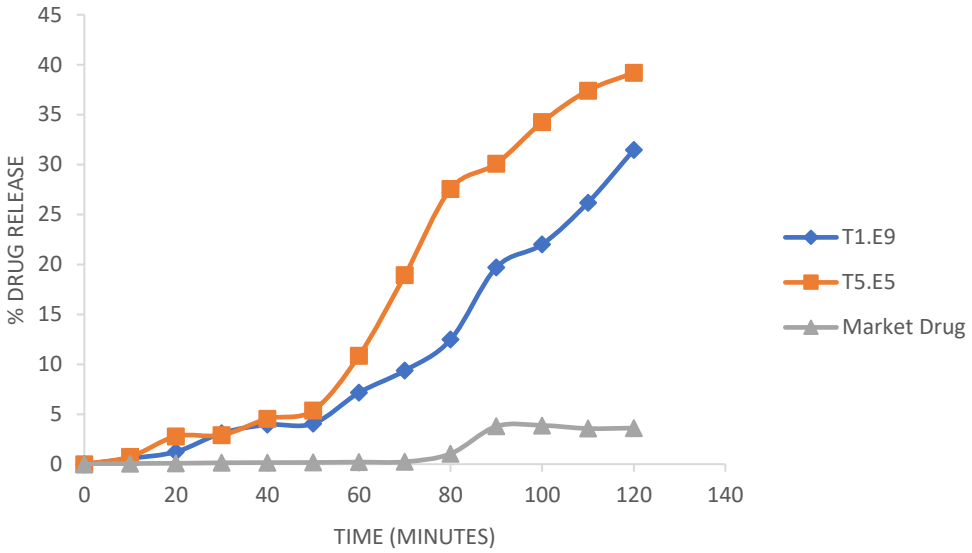

Figure 3: Release profiles for SEDDS and marketed simvastatin (T1:E9 = SEDDS containing 1:9 Tween 80/ethanol; T5:E5 = SEDDS containing 5:5 Tween 80/ethanol; Market Drug = Conventional formulation)

4. DISCUSSION

Simvastatin is compatible with the other ingredients. However, there was an observed superimposition of the absorption band in the fingerprint region of simvastatin when the drug was formulated as a self-emulsifying drug delivery system (Figure 1). Both simvastatin powder and the SEDDS exhibit a broad size distribution. Despite the formulation as SEDDS, the particle sizes of the drug remain similar as the formulation (Figures 2a and 2b). This suggests that the formulation is a microsystem rather than a nanosystem. However, majority of the particles are within 10 and 1000 nm. Emulsification is required for the enhancement of both dissolution and absorption. The SEDDS containing 5:5 Tween 80/ethanol had a shorter emulsification time. Hence, this formulation which contains equal proportions of the surfactant and co-surfactant is likely to be characterized by faster dissolution and be more readily available for absorption. Microcrystalline cellulose was added during the granulation process so as to create powder agglomeration before encapsulation. This procedure has significant advantages over the traditional wet granulation because it is a single-step process that eliminates the incorporation of liquid components and subsequent drying phases. [4]. The granulates were packed inside the capsule shells to achieve the desired solid formulation. The dissolution test results showed that the two SEDDS formulations had higher drug release compared to the conventional simvastatin tablets (Figure 3). This shows that the self-emulsification significantly enhanced the dissolution rate of the poorly water-soluble simvastatin [11]. The findings are in agreement with the report of Saleem *et al.* [13] which showed that microemulsion formulation enhances drug dissolution. Drug release from the conventional formulation was < 5% after 120 minutes while the formulated SEDDSs after the same period showed drug release of 32 and 40% from formulations containing 1:9 Tween 80/ethanol and 5:5 Tween 80/ethanol respectively. Therefore, up to 600% increase in drug release can be achieved with SEDDS formulation. With the SEDDS formulation, the dose of the drug may be reduced up to sixfold and this could still achieve the desired result. There is a potential for reduced side effects due to increased bioavailability and the possibility of reducing the dose. The formulation containing 5:5 Tween 80/ethanol with shorter emulsification time exhibited faster drug release while the formulation containing 1:9 Tween 80/ethanol

with longer emulsification time exhibited slower drug release. Hence, the study reflects an inverse relationship between emulsification time and drug delivery. Furthermore, the formulation containing 5:5 Tween 80/ethanol resulted in higher drug release suggesting that increasing the proportion of Tween 80 in the SEDDS formulation enhances drug release. The observation is in agreement with the work of Essien *et al*. [14] which involved the formulation of encapsulated SEDDS of hydrochlorothiazide. Encapsulation of a SEDDS harnesses the benefits of good drug delivery of a liquid formulation and high stability of a solid formulation. Therefore, filling the SEDDS into the gelatin capsule shells enhances the stability of the formulation. This is an indication of long-term storage potential. *In-vivo* evaluation of the formulation not carried out is the limitation of the study. Such assessment will be required to establish the performance of the formulation in an animal model. It is therefore recommended that future work be carried out as an *in-vivo* study on the SEDDS formulation.

5. CONCLUSION

The SEDDS formulation is suitable for optimizing the delivery of simvastatin by up to sixfold. This approach can be utilized to achieve a reduction in the dose of simvastatin to be administered for the purpose of reducing the side effect of the drug while still maintaining the therapeutic effect. There is potential for animal studies and human pharmacokinetic evaluation.

Declarations

Acknowledgements

The authors are grateful to Mr Ema Uduk for the technical assistance.

Conflict of Interest

There is no conflict of interest associated with this publication.

Funding Information

This work was not funded by any organization

Authors' Contributions

This study was conceptualized and designed by Emmanuel Olorunsola. Data collection and analysis was done by Ntiido Aniekan. The manuscript was written by Ntiido Aniekan while the critical revision was done by Tenderwealth Jackson and Emmanuel Olorunsola. All the authors gave the final approval for the submission of the manuscript.

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