ORIGINAL ARTICLE

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JOURNAL OF PHARMACOLOGY AND BIOMEDICINE

Published by RB Science Home Page: www.rbscience.co.in

Development of self microemulsifying drug delivery system for simvastatin using essential oil as a carrier

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Article History

Received on: 26/05/2022

Revised on: 13/06/2022

Accepted on: 18/06/2022

Published on: 28/07/2022

Keywords

Simvastatin,

Essential Oil,

SMEDDS,

Ternary phase,

Surfactant,

Solubility

ABSTRACT

The present investigation was undertaken with an objective to prepare the SMEDDS of simvastatin in order to improve its bioavailability. Among the tested oils, simvastatin exhibited significantly higher solubility in lemon oil compared to all other oils. Emulsification studies showed that Span 60 was able to produce clear microemulsion with lemon oil upon dilution, and hence, it was employed as the surfactant in further studies. PEG 400 was used as the cosurfactant for the formulation of SMEDDS. The results revealed that span 60 and PEG 400 used in ratios of 2:1 (F15-16) and 3:1 (F23-24) exhibited largest microemulsion area and shortest emulsification time (less than 1 min). A fixed simvastatin concentration of 5% w/w was selected to be loaded in all self-emulsifying formulations. The *in vitro* dissolution studies revealed the drug release profiles for the L-SMEDDS. All the formulations exhibited quick drug release characteristics and almost complete drug release in 15-20 minutes.

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JOURNAL OF PHARMACOLOGY AND BIOMEDICINE

ISSN No. 2456-8244

Publication Hosted by
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Introduction

According to World Health organization (WHO), one-third of ischemic heart disease is attributable to high cholesterol which has caused 2.6 million deaths and 29.7 million disability adjusted life years (DALYS), globally. In 2008, the global prevalence of raised total cholesterol among adults was 39% (WHO, 2021). In a survey conducted in United States in the year 2009-2012, 13.4% adults aged 20 years and above had high serum total cholesterol. The mean serum total cholesterol levels for the same group of people were 196 mg/dL (CDC, 2021).

In India, 28% of the entire population is attributable to cardiovascular diseases of which Ischemic heart disease is the most leading cause for the deaths among people accounting for about 12.4% (1215.4 thousand people) in 2012 (WHO, 2014; WHO, 2015). According to a study carried out by ICMR, about 7.7% of the adult population had three lipid abnormalities (hypercholesterolemia + hypertriglyceridemia + low HDL-C) and 4.8% of the population had all four lipid abnormalities (hypercholesterolemia + hypertriglyceridemia + low HDL-C + high LDL-C) (Joshi et al., 2014).

Initial therapy for any lipoprotein disorder is dietary restriction of total saturated fat and cholesterol and an increase in polyunsaturated fat intake along with regular exercise (Grundy, 1984). Several different classes of drugs are used to treat hyperlipidemia which differ not only in their mechanism of action but also in the type and magnitude of lipid reduction (Mckenney, 2003). Majority of the traditionally used anti-hyperlipidemic drugs like Atorvastatin, Fluvastatin, Pravastatin, Simvastatin, Lovastatin and Rosuvastatin are well absorbed but undergo extensive hepatic first pass metabolism, which leads to very low absolute bioavailability (Srinivasa Rao et al., 2004).

As most of the antihyperlipidemic drugs approved for clinical use are known to be possessing poor aqueous solubility and poor bioavailability, newer delivery systems are the need of the hour for these drugs. SEDDS provide an alternate to overcome the problems related to the solubility and bioavailability of these antihyperlipidemic drugs.

The overall goal of the present postulation was to improve the dissolvability, dissolution pace, conceivably the intestinal penetratability and bioabavailability of lipophilic medications by using self-microemulsifying drug delivery systems (SMEDDS) for oral administration.

Material and Methods

Simvastatin was procured from Yarrow Pharmaceuticals; all other chemicals, excipients and oil were procured from various chemical suppliers and were used without puirification.

Solublility Study

The solubility of simvastatin in different oils, surfactants and co-surfactants was determined according to the method of Date and Nagarsenker (2007). Briefly, an excess amount of the drug was mixed with fixed amounts of the oil, surfactants and cosurfactants and the mixtures were shaken for 48 hours at 25°C to attain equilibrium. The samples were then centrifuged to remove the undissolved drug, filtered through a 0.45 μm membrane filter, and the supernatant was

suitably diluted before spectrophotometric analysis at 238 nm using UV-visible spectrophotometer to determine the amount of the drug dissolved in each excipient.

Surfactant and oil miscibility

The oil and surfactant in the ratio of 1:1 were shaken at 40°C in 3 ml transparent glass vials. The miscibility was monitored optically and considered to be good when the mixture was transparent.

Screening of surfactants for emulsifying ability

The emulsification ability of different surfactants was evaluated by mixing the surfactant with the selected oily phase in a 1:1 weight ratio. The mixtures were vortex mixed and diluted up to 200 fold dilution. The ease of formation of an emulsion was assessed by observing the number of inversion of the volumetric flask required to obtain a uniform emulsion. The resulting emulsion was also examined visually for relative turbidity according to different grading systems (Grades A – E) described by Khoo et al (1998) that depict the spontaneity and appearance of the nanoemulsion formed upon dilution. Mixtures that showed grades A and B upon dilution were assigned for further evaluation.

The ability of co-surfactants (or co-solvents) to improve the emulsification ability of surfactants was also evaluated. Mixtures of the selected oily phase, surfactants and co-surfactants (or co-solvents) were mixed at a ratio of 3:2:1, respectively, and then diluted with distilled water for 200 fold dilution. The appearance and the ease of formation of microemulsion were assessed.

Construction of ternary phase diagrams

Based on the solubility of simvastatin, lemon oil was chosen as the oil phase. Span 60 was used as the surfactant and PEG 400 was employed as the cosurfactant. Distilled water was used as the aqueous phase for development of these phase diagrams. The surfactant and co-surfactant (Smix) in were mixed in different weight ratios (1:1, 2:1, 3:1) so that the concentration of surfactant increases with respect to co-surfactant. The ternary phase diagram was constructed to identify the microemulsifying region, using oil and Smix ratios which form 'good' emulsions upon dilution with purified water.

Preparation of simvastatin -loaded self-microemulsifying formulations (L-SMEDDs)

Simvastatin was added to the optimized blank ternary systems at a drug loading concentration of 5% w/w. Final mixtures were mixed and shaken for 24 hours at 25°C in a shaking water bath to ensure complete solubilization.

Evaluation of Thermodynamic stability studies and cloud point

Stability of the optimized L-SMEDDS formulation was evaluated at different stress conditions such as heating cooling cycles (4°C and 40°C) and freeze thaw cycles (-21°C and +25°C) along with storage at specified temperature for 48 h.

Determination of particle size and zeta potential

The particle size and polydispersity index of the L-SMEDDS was obtained using calibrated ocular micrometer using a microscope. The particle size, polydispersity index and zeta potential of the best formulation was also determined using a dynamic light scattering particle

size analyzer.

Drug Content Determination

An accurately weighed amount of the resulting drug-loaded SMEDDS formulation was dispersed in a suitable quantity of methanol and shaken thoroughly to ensure release and dissolution of the drug in methanol. The samples were centrifuged at 3000 rpm for 15 minutes and the supernatant was filtered through a 0.45 µm membrane filter and the filtrate was assayed spectrophotometrically for the drug at 238 nm. The drug content was calculated using the following equation:

$$drug\ content = \frac{drug\ content\ in\ the\ weight\ taken\ from\ solid\ \ SNEDDS}{weight\ of\ the\ solid\ SNEDDS\ taken}$$

***In vitro* dissolution study**

The *in vitro* dissolution studies of different simvastatin SMEDDS formulations were carried out in dissolution apparatus II using 900 ml phosphate buffer pH 7.2 as the dissolution medium. An amount of SMEDDS formulation equivalent to 25 mg of simvastatin was filled in dialysis membrane and used for dissolution studies.

Results and Discussion

Among the tested oils, simvastatin exhibited significantly higher solubility in lemon oil compared to all other oils. In order to form clear microemulsion judicious selection of oil, surfactant, co-surfactant and oil to surfactant/ co-surfactant ratio is very important. In order to achieve this, it is recommended that a surfactant should have hydrophilic-lipophilic balance (HLB) value more than 10 to form an o/w emulsion. Lemon oil was considered as the oil phase form formulation of the microemulsion. The highest solubility was exhibited by Span 60 and it has an HLB value of 4.7 while PEG 400 has HLB value of 13.1 (Figure 1).

Emulsification studies showed that Span 60 was able to produce clear microemulsion with lemon oil upon dilution, and hence, it was employed as the surfactant in further studies. PEG 400 (used as cosurfactant) was helpful in improving emulsification ability of surfactant.

Ternary phase diagram

In order to identify the self-emulsifying regions and to optimize the percentages of different liquid SMEDDS components, a ternary phase diagram was constructed in the absence gure 2).

The results revealed that span 60 and PEG 400 used in ratios of 2:1 (F15-16) and 3:1 (F23-24) exhibited largest microemulsion area and shortest emulsification time (less than 1 min). It was observed that with increase in the ratio of the PEG 400, spontaneity of the self-emulsification process got increased.

Thermodynamic stability and cloud point determination

All the formulations passed the thermodynamic stability studies without any signs of phase separation and precipitation during alternative temperature cycles (4°C and 40°C), freeze thaw cycles (-21°C and +25°C) and centrifugation at 10,000 g indicating good stability of formulations and their emulsions. The cloud point temperature of the tested L-SMEDDS was found to be in the range of 89-94°C (Table 2).

Droplet Size, Polydispersity and zeta potential

It was observed from the results that decreasing the oil content of the formulations resulted in a decrease in the size of formulation droplets (Table 2). Self-emulsifying formulations

possess a negative charge on the oil droplets due to the presence of anionic groups of free fatty acids contained in their composition; the oil, surfactant and co-surfactant. The obtained high negative values of zeta potential indicate that the tested formulations are less likely to flocculate or aggregate during storage or in biological environment.

In vitro dissolution

The *in vitro* dissolution studies revealed the drug release profiles for the L-SMEDDS. All the formulations exhibited quick drug release characteristics and almost complete drug release in 15-20 minutes (Figure 3). In contrast, the pure drug exhibited only a maximum of 41.3% release in 60 min duration.

Conclusion

The bioavailability of the lipophilic drugs can be enhanced by formulating them as SMEDDS. From the release behavior witnessed through the present investigation it could be proven that the bioavailability of the lipophilic drug (simvastatin) could be almost doubled by formulating it as SMEDDS.

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Table 1. Composition of optimized ternary systems for L-SMEDDs

Formulation	Oil %w/w	Surfactant % w/w	Cosurfactant %w/w	Smix ratio
F15	70	20	10	2:1
F16	60	26.6	13.3	2:1
F23	40	45	15	3:1
F24	30	52.5	17.5	3:1

Table 2. Stability and characterization of L-SMEDDS

Formulation	Thermodynamic Stability				Surface characterization		
	Cloud point (° C)	Centrifugation	Cooling/ Heating	Freeze/ Thawing	Mean droplet size (μm)	PDI	Zeta potential
F15	89.26	No phase separa-	No Phase inversion	No Phase inversion	481.15 ± 7.09	0.318 ± 0.002	-25.4
F16	92.45	No phase separa-	No Phase inversion	No Phase inversion	336.31 ± 0.63	0.392 ± 0.004	-26.5
F23	90.84	No phase separa-	No Phase inversion	No Phase inversion	334.03 ± 1.08	0.291 ± 0.003	-31.3
F24	93.66	No phase separa-	No Phase inversion	No Phase inversion	314.15 ± 0.75	0.431 ± 0.008	-29.6

Figure 1. Ternary Phase diagrams (A) Smix(1:1)-water-lemon oil; (B) Smix(2:1)-water-lemon oil; (C) Smix(3:1)-water-lemon oil

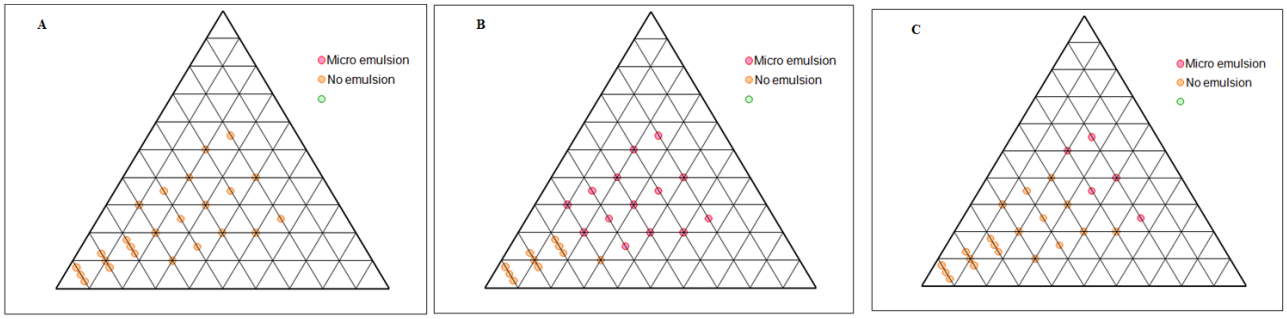
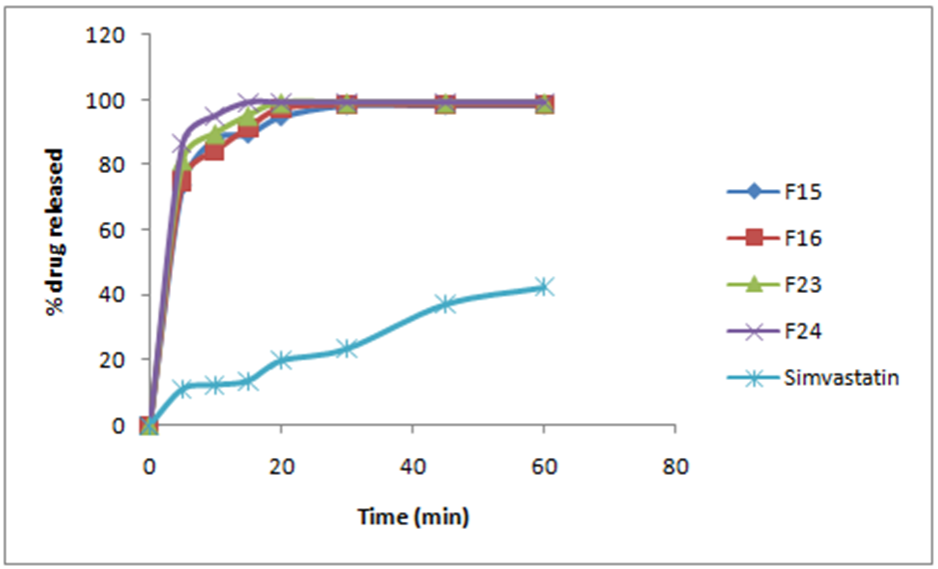


Figure 2. In vitro dissolution profile of L-SMEDDS of simvastatin



Cite this article as

Tiwari A, Shende R, Dubey A, Dangi S. Development of self microemulsifying drug delivery system for simvastatin using essential oil as a carrier. J Pharmacol Biomed. 2022; 6(3): 507-513