

Design and *in Vitro* Evaluation of Eudragit® S100/Lipid Based Simvastatin Chronotherapeutic Drug Delivery System

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Abstract

The present study was undertaken to 1) formulate a pulsatile colonic delivery of simvastatin (SIM) as chronotherapy for treatment of hypercholesterolemia, and 2) enhance the dissolution profile of the prepared SIM chronotherapeutic system. Lipid based formulations were utilized to formulate SIM in capsule dosage form coated with Eudragit® S100. SIM was formulated using different percentages of Cremophor EL40, Capmul MCM EP and PEG 400. SIM coated capsules (SIMcc) were evaluated for drug release in different pH media. The results showed that SIMcc were able to withstand the acidic pH for 2 hours. Drug release rate was higher (88%) from SIMcc containing 10% polyethylene glycol (PEG) 400. In conclusion, Eudragit® S100 as time-dependent and site specific polymer retards SIM release from coated capsules; hence SIMcc could be considered as successful pulsatile treatment of hypercholesterolemia. Also, dissolution profile of lipid based SIMcc was enhanced in comparison with that of SIM filled capsules.

Keywords

Chronotherapy, Circadian Rhythms, Colon Delivery, Dissolution Profile, Lipid Based Formulation

1. Introduction

Chronopharmaceutics is aimed to deliver drugs at a rhythm that ideally matches the biological requirement of a given disease therapy or prevention [1]. Circadian rhythms have been recognized in several diseases such as asthma, arthritis, duodenal ulcer, cancer, cardiovascular diseases, diabetes, neurological disorders, and hypercholesterolemia [2]. Cholesterol biosynthesis follows a circadian rhythm in which maximal production occurs

early in the morning and in the fasting state [3]. This is due to the higher activity of hepatic 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase at midnight [3]. Therefore, cholesterol level is generally higher during night time than day.

HMG-CoA reductase inhibitors, statins, reduce cholesterol levels, increased expression of LDL receptors and decrease triacylglycerol (TAG) rich lipoproteins [4]. Chronotherapy with HMG-CoA reductase inhibitors have suggested that evening dosing could be more effective than morning dosing [5]. Chronotherapeutic treatment with immediate-release dosage forms may be unfeasible if the symptoms of the disease are pronounced during the night or early morning [6]. Therefore, therapy with modified-release dosage forms with controlled higher drug plasma levels during the time of diseases attack or incidence could be more effective treatment than with immediate release dosage forms [7].

Colonic delivery system refers to targeting drugs into the colon for direct treatment of local diseases, delay drug release or time specific drug release as in case of chronotherapy. Colonic drug delivery systems have focused on four approaches: pH-dependent systems, time-dependent system, bacterially degradable systems, and intestinal luminal pressure-dependent systems [7] [8]. Therefore, colonic drug delivery systems are the important approach for the treatment of diseases that have peak symptoms in the early morning and that exhibit a circadian rhythm [9]. Colonic drug delivery systems in capsule dosage form may contain drug molecules either in liquid, semi-solid or solid state [10]. Eudragit[®] S100 is anionic copolymers based on methacrylic acid and methyl methacrylate. It is a pH-dependent polymer insoluble in the gastric fluid, and widely used for oral delivery systems. Eudragit[®] S100 provides enteric coat to the encapsulated drug and serves as a colon drug-targeting device. Eventually, these systems disintegrate and release the active ingredient in the duodenum or jejunum for absorption [11]. These properties suggested that Eudragit[®] S100 could be used as successful coating agent for pulsatile drug delivery system.

Simvastatin (SIM) is one of the statins groups which inhibit HMG-CoA reductase and hence it is effective in treatment of hypercholesterolemia [12]. SIM is a class II molecule according to Biopharmaceutical Classification System so its solubility is the rate limiting step in the dissolution process and hence its bioavailability [13]. Several strategies were used to overcome this problem, such as prodrug, particle size reduction [14], inclusion complex with cyclodextrins [15], or utilizing lipid-based formulations [16]. Lipid-based formulations have been widely used to enhance the dissolution and bioavailability of this class of drugs [16]. These formulations may contain surfactants and co-solvents such as Cremophor EL40, Capmul MCM EP and PEG 400. Such formulations can be used to orally administer lipophilic drugs and accelerate the dissolution step in the gastrointestinal tract (GIT) [17].

The present study was attempted to formulate SIM chronotherapeutic drug delivery system for treatment of hypercholesterolemia by utilized pH-dependent solubility behavior of Eudragit[®] S100, and also to improve the dissolution properties of SIM using lipid based formulation ingredients such as Cremophor EL40, Capmul MCM EP and PEG 400 in capsules dosage form. *In vitro* SIM release rate from the prepared coated capsules was evaluated at different pH and compared with that of SIM filled capsules.

2. Materials and Methods

2.1. Materials

Simvastatin (SIM) was a gift from Riyadh Pharm pharmaceutical company Saudi Arabia. Capmul MCM EP (Glyceryl Caprylate) was from Abitec Corporation, WI., USA. Cremophor RH 40 (polyoxyl 40 hydrogenated castor oil) was from BASF Ludwigshafen, Germany. Eudragit[®] S100 powder was form Rohm Pharma, Weiertadt, Germany. Polyethylene glycol (PEG) 400 was from Winlab England. Ethanol, Triethyl citrate, Ethyl cellulose, Hydroxypropyl methylcellulose (HPMC) and Tween 80 were from Sigma Chemical Company, USA. All other chemicals were of analytical grades and used as received.

2.2. Methods

2.2.1. Preparation of SIM Lipid Based Formulations

SIM lipid based formulations were prepared according to the design shown in **Table 1**. The exact amount of Cremophor RH 40 (Cr-RH40) as surfactant, Capmul MCM EP (Ca-MCM) as co-surfactant and PEG 400 as hydrophilic co-solvent was weighed and melted at 40°C. Then the amount of SIM was added with continues

Table 1. Composition of SIM lipid based formulations each containing (40 mg SIM).

Formulation No.	Cremophor EL 40 (mg)	Capmul MCM EP (mg)	PEG 400 (mg)
F1	100	100	0
F2	100	80	20
F3	100	60	40
F4	100	40	60
F5	100	20	80
F6	100	0	100

stirring. The mixture was sonicated using probe sonicator for 30 minutes then filled in hard gelatin capsules. Each capsule was containing 40 mg of SIM. All SIM capsules were sealed with 5% alcoholic solution of ethyl cellulose (w/v). Ordinary capsules filled with 40 mg SIM were prepared for comparison.

2.2.2. Coating Procedures

Aqueous Eudragit[®] S100 solution was partially neutralized by drop wise addition of ammonium solution with continuous stirring to form milky latex solution. Triethyl citrate, a non-toxic plasticizer with a melting point of 150°C, was added along with Tween 80 solution, which acts as emulsifying and dispersing agent, with continuous stirring for 10 minutes [7]. **Table 2** shows the exact composition of the coating dispersion liquid. SIM capsules were coated using Caliva Mini Coater/Drier 2. The dispersion liquid was fed to the top spray head with the aid of a peristaltic pump. The operating conditions were shown in **Table 2**. SIM capsules were coated, first, with an intermediate layer of 10% aqueous solution of HPMC till 3% weight gain and then, with Eudragit[®] S100 coating dispersion until 20% weight gain were obtained [7]. Coating process was interrupted every 15 min, 10 capsules were withdrawn, dried for 2 min at the same temperature and weighed. The coating process was continued till the target weight was achieved. Coating level was calculated as the percent weight gain between coated and uncoated capsules.

2.2.3. In Vitro Release of the Prepared SIMcc

Dissolution test of SIMcc was carried out using a USP dissolution apparatus type II (ERWEKA, DT-700, Germany) at a rotation speed of 50 rpm in 900 ml dissolution medium at 37°C ± 0.5°C. The dissolution media were simulated gastric fluid (0.1 N HCl of pH 1.2 for 2 h) and simulated intestinal fluid (phosphate buffer solution of pH 6.8 for 3 h and pH 7.4 till the end of the test). Dissolution medium was adjusted to the required pH values (6.8 and 7.4) by the addition of specific amount of tri-basic sodium phosphate. Each coated capsule was held to the bottom of the vessel using copper sinkers. Five mL aliquots of the dissolution fluid were removed at specified time intervals (replaced with another 5 ml of the dissolution medium), filtered and replaced with fresh dissolution medium and assayed for the amount of SIM by spectrophotometer (Spectro UV-Vis Double PC 8 Auto Cell Scanning Spectrophotometer UV-VIS Double Beam Model UVD-3000 Labomed INC., CA, USA) at wavelength 238 nm against a blank [18]. The samples were analyzed to calculate the percent cumulative SIM released at different time intervals. The dissolution profile of SIM filled capsules was performed as standard for comparison purpose. This test was done in triplicates.

3. Statistical Analysis

The data were expressed as the mean ± SD. The data were evaluated by one-way ANOVA followed by the Tukey-Kramer test for multiple comparisons. A probability value of ≤0.05 was used as the criterion for significance.

4. Results and Discussion

Chronopharmaceutical drug delivery systems should embody time-controlled and site-specific drug delivery systems [1]. Colon drug delivery is one of several approaches for chronotherapy. Due to the low amount of colon fluid, colon targeting formulations must allow better dissolution of drug substances [7]. Type IV lipid based

Table 2. Coat liquid dispersion composition and coating conditions.

Compound	Parts by weight (%)
Eudragit® S100	10
Ammonia solution (1 M)	5
Triethyl citrate	6
Tween 80 (33% aqueous solution)	2
Water	77
Coating conditions	
Agitation frequency (Hz)	15.2
Air temperature (°C)	40
Airflow (m/s)	11
Atomizing air pressure (bar)	1
Height of spray head (mm)	150
Peristaltic pump speed (rpm)	4

formulations which contain surfactants and co-solvent may provide a good approach to enhance the solubility and hence the dissolution of lipophilic drugs particularly at low fluid content of the colon [19]. These formulations facilitate the solubilization of drug by micellar formation which reduces drug particle size and hence enhance its dissolution rate [20]. Cr-RH40 (HLB < 16), Ca-MCM (HLB < 6) and PEG 400 have been widely used to enhance the dissolution rate of poorly-water soluble drugs [21].

Cr-RH40 is a nonionic water soluble surfactant used as emulsifying and solubilizing agent in topical, oral and parenteral formulations [16]. The pH value of Cr-RH40 is about 6-7 which enhance SIM solubility in the formulations.

Presence of Ca-MCM EP, a water insoluble surfactant, improves the dissolution rate and provides stabilization and solubilization to SIM, which could be attributed to its crystallization inhibition property [22].

PEG 400 has the ability to form complexes with large number of water insoluble drugs. Hence it is widely used as solvent and solubilizing agent mostly in liquid and semisolid formulations [23]. However, lipid based formulations which contain large quantities of PEG 400 may results in drug precipitation upon dispersion in dissolution medium, which is obvious in the low dissolution profiles of formulations F3-F6. Increasing the concentrations of PEG 400 in the expense of Ca-MCM resulted in lowering SIM release rate. That is due to that, PEG 400 has limited “on going” solubilization capacity after diluting the formulations with the dissolution media [24].

In the current work, SIM forms a homogenous mixture when blend with Cr-RH 40, Ca-MCM and PEG 400. In order to simulate the pH changes along the GIT, three dissolution media with pH 1.2, 6.8 and 7.4 were used. At pH 1.2 (simulating gastric fluid) all SIMcc succeeded to withstand up to 2 hours. As shown in **Figure 1**, dissolution profiles of SIMcc, F2 has the higher drug release rate (88%) followed by F1 (72%). Lipid based formulations which contain large quantities of PEG 400 results in low dissolution profiles as in case of formulations F3, F4, F5 and F6 (30%, 26%, 21% and 14% respectively).

The polymeric coat of Eudragit® S100 is insoluble in acidic pH medium, thus this layer may act as a barrier to any early SIM release in upper GIT prior to reach to the targeted site and provide an appropriate lag phase. Many workers have been reported this coat as effective colon delivery for several drugs based on chronopharmaceutical considerations [25].

In this study Eudragit® S100 coat at 20% level has the ability to retard water uptake and thus prolongs drug release time which is suitable approach to chronotherapy. These finding are in agreement with several studies which reported that pulsatile drug delivery systems are effective as chronotherapy [26]. The present results have concluded that, F2 could be suitable formulation for the time-dependent and site specific delivery of SIM as chronotherapeutic treatment.

In our pervious study, the bioavailability of SIMcc (F2) has been compared with that of Zocor® tablets in human volunteers [27]. The results revealed that SIMcc showed 29% increase in SIM bioavailability over that of Zocor® tablets. Also a significant higher T_{max} was observed for SIMcc (4 hr) compared to Zocor® tablets (1.5 hr).

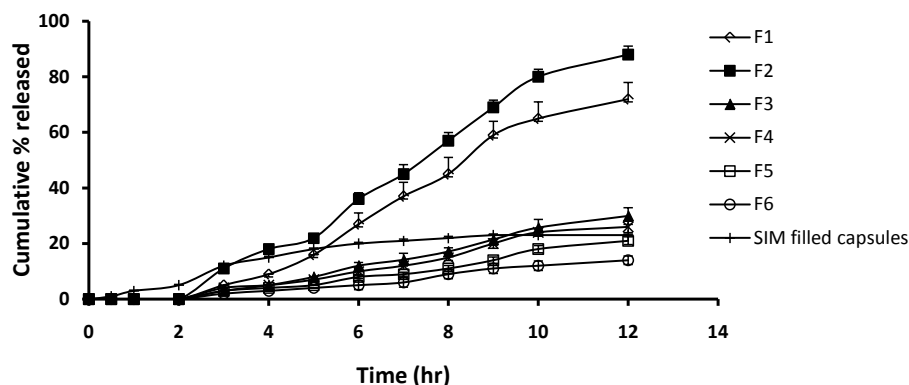


Figure 1. Dissolution profile of the prepared SIMcc and SIM filled capsules.

Moreover, SIMcc has the ability to significantly provide higher SIM plasma concentrations from 3 to 8 hr after oral administration compared to Zocor[®] tablets. These results suggested the suitability of SIMcc as chronotherapy for treatment of hypercholesterolemia over Zocor[®] tablets [27].

5. Conclusion

The present study concludes that SIMcc are the successful option for ileo-cecal targeting by achieving the desired lag time and drug release pattern. This was accomplished by proper selection of lipid formulation system and level of Eudragit[®] S100 coat. These findings suggest that SIMcc are successful system in chronotherapeutic treatment of hypercholesterolemia.

Declaration of Interests

The author declares that there are no conflicts of interest.

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