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Release kinetic modeling of atorvastatin calcium loaded self microemulsifying drug delvery system

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ABSTRACT

The aim of the present study was to design and develop a self microemulsion drug delivery system (SMEDD) of Atorvastatin Calcium and evaluate its release kinetics by using mathematical models. Suitable oil, surfactant and cosurfactant were selected based on the solubility, HLB value and biocompatibility. Pseudo-ternary phase diagrams were constructed to identify the microemulsion existing zone and to get a tentative surfactant to cosurfactant ratio. Atorvastatin Calcium loaded SMEDD was developed and characterized for particle size, zeta potential, surface morphology, drug entrapment and comparative *in vitro* drug release study. Different dissolution models were applied to drug release data in order to evaluate release mechanisms and kinetics and the criterion for selecting the most appropriate model was based on linearity (coefficient of correlation). % Transmittance, Particle size and zeta potential of the formulation containing Labrafac PG as oil, Accenon CC as surfactant and Transcutol P as cosurfactant were found to be 99.87%±1.2, 31.82 nm± 1.15 and -15.8 mV± 1.13 respectively. The drug release data fit well to Koresmayer Peppas equation plot (r^2 =0.981) indicating the dissolution rate limited drug release from a SMEDD formulation. Drug release mechanism was found as a Super case-II transport, (i.e., n value-1.229).

Introduction

Oral route is still the most preferred route for the delivery of drugs, though several factors like pH and enzyme variation of GIT, and residence time can affect drug absorption or availability and hence the pharmacodynamics of the drug. Atorvastatin calcium is an antihyperlipidemic drug with Cmax, Tmax and plasma half life of 30%, 2hr and 2-3 hr. It is a BCS class-II drug having poor oral bioavailability (<4%) due to the first pass metabolism [1]. But Now-a-days much attention has been paid to the lipid based formulations. Marketed lipid based formulations are Sandimmune Neoral (Cyclosporine A), Novartis Pvt. Ltd. and Fortovase (Saquinavir), Roche Laboratories Inc. with much attention focused on SMEDDs [2].

SMEDDs are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants, or alternatively, one or more hydrophilic solvents and co-solvents/surfactants that have a unique ability of forming fine oil-in-water (o/w) microemulsions upon mild agitation followed by dilution in aqueous media, such as GI fluids [3]. SMEDDS spread readily in the GI tract, and the digestive motility of the stomach and the intestine provide the agitation necessary for self-emulsification. For lipophilic drugs SMEEDs exhibit dissolution rate-limited absorption, these systems may offer an improvement in the rate and extent of absorption and result in more reproducible blood-time profiles [4]. Hence, the objective of this study was to design a novel dosage form of Atorvastatin Calcium and to evaluate the kinetic modelling.

Materials & Methods

Materials

Atorvastatin Calcium was received as a gift sample from Torrent Pharmaceutical Ltd. (Gujarat, India). Labrafil M 1944CS, Capmul CMC, Accenon CC, Cremophor EL, Cremophor RH 40 and Transcutol P were received from Abitec Corporation (USA) as gift sample. Iso-propyl myristate, Labrafac PG, Soya bean oil, Tween-60, Tween-80, was purchased from Ozone internationals (Mumbai, India). Isopropyl alcohol, Isobutyl Alcohol, PEG 400 and PEG 600 were purchased from S.D. Fine Chemicals (Mumbai, India). All the other chemicals and solvents were of analytical reagent grade and used without further purification.

Methods

Selection of components of SMEDDs

Selection criteria for oil phase are drug solubility and biocompatibility and for surfactant are drug solubility, biocompatibility and HLB value [5]. Different oils i.e., Iso-propyl myristate, Labrafac PG, Soya bean oil, Labrafil M 1944CS, Capmul CMC, Oleic acid and surfactants like tween-60, tween-80, Accenon CC, Cremophor EL, Cremophor RH 40 were screened. Co-surfactants like Isopropyl alcohol, Isobutyl Alcohol, PEG 400, PEG 600, Transcutol P, glycerol and ethanol were screened based on their capability to form stable SMEDD with relevant surfactants at a minimum concentration [6].

Pseudo-ternary phase diagram

Pseudo-ternary phase diagrams were constructed to obtain the appropriate components, and their concentration ranges that resulted in a large existence area of SMEDD were chosen. In order to optimize the concentration of oil phase, surfactant and co-surfactant, different batches of varied concentration were prepared and titrated with distilled water till transparency persists. Ternary phase diagram was prepared by using a constant ratio of surfactant to co-surfactant [7]. Three ratios of surfactant and co-surfactant were selected (2.5:1, 3:1 and 3.5:1).

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Preparation of SMEDD

Atorvastatin Calcium was added and dissolved in the oil phase. To the mixture, surfactant and cosurfactant at the definite ratio was added with constant but mild stirring. Store the clear transparent oily liquid mixture at room temperature until further use [8].

Characterization of SMEDD

Transmittance Test: % Transmittance of the developed SMEDD and its diluted formulations was measured at 650 nm with a UV-VIS spectrophotometer (UV-1601-220X, Shimadzu).

Globule size and Zeta potential: Globule size and zeta potential of the SMEDD was determined by dynamic light scattering, using a Zetasizer HSA 3000 (Malvern Instruments Ltd., Malvern, UK)

Morphological study: A drop of the diluted SMEDD was directly deposited on the holey film grid and observed the morphology of formulation by Transmission electron Microscopy.

Drug solubility: Drug was added in excess to the optimized SMEDD formulation as well as each individual ingredient of the formulation. After continuous stirring for 24 hr at room temperature, samples were withdrawn and centrifuged at 6000 rpm for 10 min. The amount of soluble drug in the formulation as well as each individual ingredient of the formulation was calculated by subtracting the drug present in the sediment from the total amount of drug added. The solubility of drug in SMEDD was compared with respect to its individual ingredients [9].

% Assay: The developed SMEDD was suitably diluted with methanol and was stored for 2 hrs. Then both the samples were analysed by UV spectrophotometer at 247 nm [10].

Dilution study: Developed SMEDD and its diluted formulations (25, 50 and 100 times) were evaluated for % transmittance, globule size, phase separation and % assay.

Stability study: The drug loaded SMEDDs were kept for 3 months under cold condition (4-8^{0}C), room temperature and at elevated temperature (50 ± 2^{0}C) separately. After every 1 month, individual samples of the formulation were analyzed for phase separation, % transmittance, globule size and % assay [11].

Drug release studies

In-vitro drug release: *In-vitro* drug release study was carried out using rat ileum in a modified dissolution apparatus. The modified dissolution apparatus was filled with 500ml of phosphate buffer (pH=6.8) equilibrated at 37±2°C. Developed formulation, plain drug solution and marketed formulation with same drug concentration (500µg/ml) was put into the lumen of rat ileum and both ends were tied ileum was put in the dissolution medium stirred at 50 rpm. 5 ml aliquots were withdrawn at the interval of 1 hr and were analysed spectrophotometrically at 247 nm [12].

Release Kinetic Modelling: To analyze the *in vitro* release data, various kinetic models were used to describe the release kinetics. Zero order rate equation (Equation-1) describes drug release rate is independent of its concentration in the systems. The first order equation (Equation-2) describes the release from system where release rate is concentration dependent. Higuchi (1963) described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion (Equation-3). The Hixson-Crowell cube root law (Eqution-4) describes the drug release from systems where there is a change in surface area and diameter of particles or tablets (Hixson and Crowell, 1931). Korsmeyer *et al* (1983) derived a simple relationship which described drug release from a polymeric system (Eqution-5). To find out the mechanism of drug release, first 60% drug release data was fitted in Korsmeyer–Peppas model [13].

$C = k_o t$ ---------- (1)

Where, K_0 is zero-order rate constant expressed in units of concentration/time and t is the time.

$LogC = LogC_o - kt / 2.303$---------- (2)

Where, C_0 is the initial concentration of drug and K is first order constant.

$Q = Kt^{1/2}$ ---------- (3)

Where, K is the constant reflecting the design variables of the system.

$Q_0^{1/3} - Q_t^{1/3} = K_{HC} t$ ---------- (4)

Where, Q_t is the amount of drug released in time t, Q_0 is the initial amount of the drug in tablet and K_{HC} is the rate constant for Hixson-Crowell rate equation.

$M_t / M_\infty = Kt^n$ ----------(5)

Where M_t / M_∞ is fraction of drug released at time t, k is the rate constant and n is the release exponent. The n value is used to characterize different release mechanisms as given in Table 1, for cylindrical shaped matrices.

Table 1: Diffusion exponent and solute release mechanism

Diffusional Exponent, *n*	Type of Transport (release)	Time Dependence
n=0.5	Fickian diffusion	$t^{1/2}$
0.5<n<1	Anomalous transport	t^{n-1}
n = 1	Case II transport	time independent
n>1	Super case II transport	t^{n-1}

Plots were made *cumulative % drug release vs. Time* for zero order kinetic model, *log cumulative of % drug remaining vs. time* for first order kinetic model, cumulative *% drug release vs. square root of time* for *H*iguchi model, *log cumulative % drug release vs. log time* for korsmeyer model and *cube root of cumulative % drug release vs. time H*ixson-crowell cube root law.

Results and Discussion:

Preparation of SMEDD: Maximum drug solubility i.e., 54.0 ± 1.27 mg/ml was found in biocompatible Labrafac PG for oral delivery and hence was selected as oil phase for SMEDD preparation. Similarly Accenon CC showing minimum drug solubility (1.8 mg/ml) with required HLB value to form o/w microemulsion was selected as surfactant. Transcutol P was selected as cosurfactant due to its ability to form stable microemulsion and its drug solubility was minimal i.e., 5.6 mg/ml. From the data of the ternary phase diagrams, it was found that highest microemulsion zone was observed for SMEDD containing Accenon CC / Transcutol P at a ratio of 2.5:1.

Characterization of SMEDD:

Transmittance test: % transmittance of 50 and 100 times diluted drug loaded SMEDD were found to be 99.48 ± 1.5 and 99.87 ± 1.2, respectively indicates that dilution doesn't effect the formulation.

Globule size and Zeta potential measurement: Globule size of 50 and 100 times diluted SMEDD showed nanorange i.e., 31.82 nm± 1.15 and 32.1 nm± 1.07 after 3 hr of storage. Polydispersity index (PDI) of both samples were found to be well below 1.0 (i.e., 0.029 and 0.028), suggesting that dilution with gastric fluid and gastric emptying time don't effect in the stability of the system (14). Results of globule size have been shown in Figure 1. Zeta potential results at above same condition, as shown in Figure 1, were found to be -15.8

mV±1.13 and -16.5 mV±1.61 respectively. Aggregation was not observed which is due to negative charge of the droplet indicating the stability of the formulation.

Figure 1(a): Globule size of SMEDD

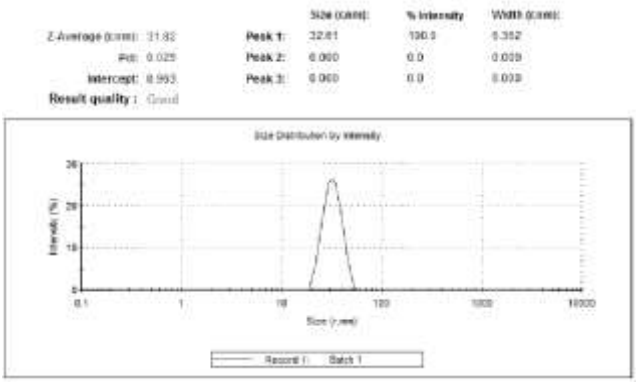
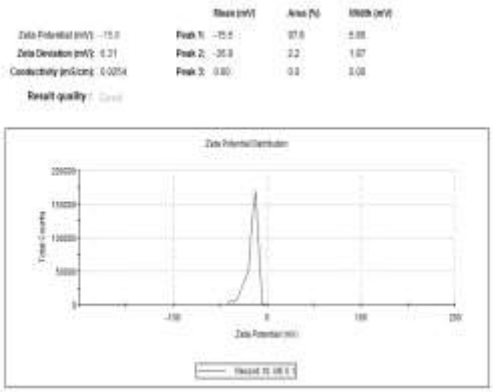


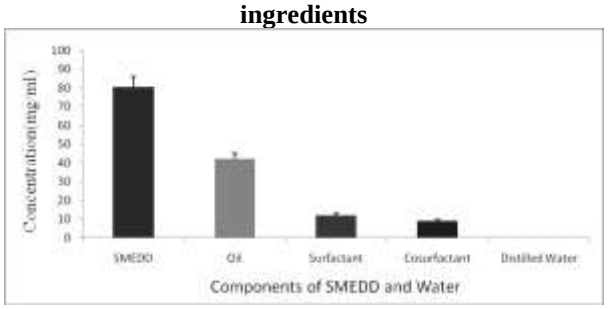
Figure 1(b): Zeta Potential of SMEDD



Transmission electron Microscopy study revealed that the size of the developed formulation was in nano range and with smooth surface.

Drug solubility: Result of drug solubility study as shown in Figure 2, revealed that developed SMEDD can enhance the solubility of Atorvastatin Calcium which accommodate the dose in little amount of the system.

Figure 2: Drug solubility study of SMEDD and its individual ingredients



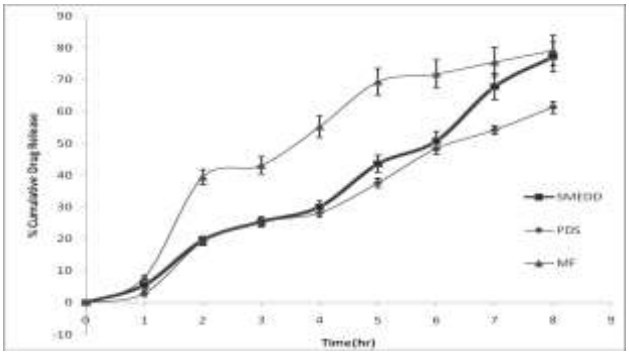
% Assay: Drug content of SMEED was measured by U.V. Spectrophotometer at 247 nm and was found to be 99.23±0.89 %.

Drug Stability: A result of stability studies on the optimized SMEDD has been recorded in Table 2. The optimized microemulsion was also subjected to centrifugal stability studies. Results obtained from both the stability studies indicated that the optimized Labrafac PG based SMEDD was stable up to 3 months

In-vitro drug release studies: *In-vitro* drug release profile of Atorvastatin Calcium was carried out for developed formulation, plain drug solution and marketed formulation. After 8 hr, the amount of drug released from the plain solution, marketed formulation and SMEDD was 59.90±0.97%, 69.13±0.68% and 75.40±0.76% respectively as shown in Figure 3.

More extent but sustained release of Atorvastatin Calcium from the SMEDD may be due to penetration enhancing effect of surfactant and co-surfactant present within formulation, small globule size and the partitioning of drug within the oil phase [15].

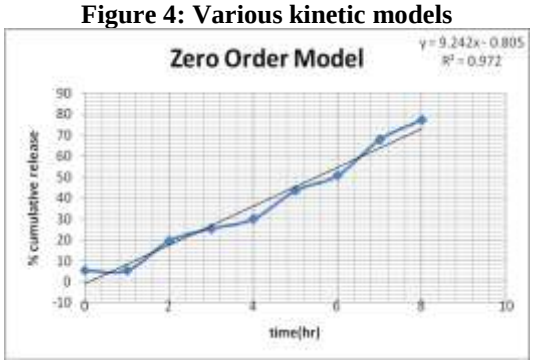
Figure 3: Comparative drug release study of Atorvastatin Calcium

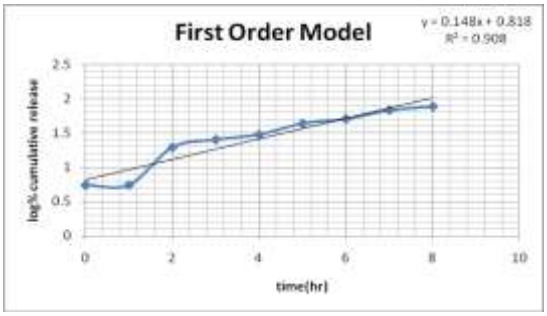


Release Kinetic Modelling

The best linearity was found in Koresmayer Peppas equation plot (r^2 =0.981) indicating the dissolution rate limited drug release from a SMEDD formulation. The n value (1.229) indicate the mechanism of drug release i.e., Super case-II transport. Various kinetic models are shown in Figure 4. The results of kinetic models are noted in Table 3.

Figure 4: Various kinetic models





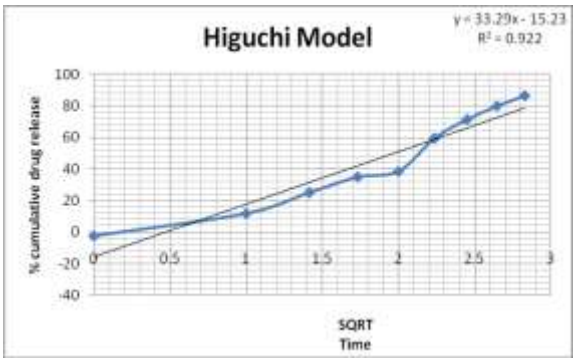
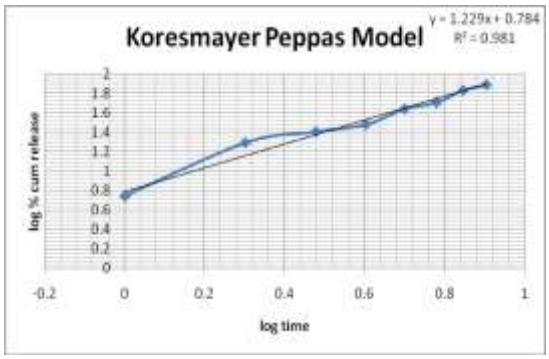


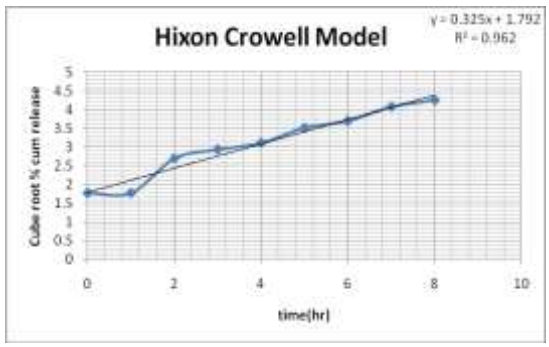
Table 2: Effect of temperature on stability of SMEDD

Temp (°C)	% Transmittance			Globule size (nm)			% of Assay		
	After 1 month	After 2 month	After 3 month	After 1 month	After 2 month	After 3 month	After 1 month	After 2 month	After 3 month
Cold temp	97.4±1.2	95.3± 1.3	92.4± 1.5	39.2 ± 1.6	48.5± 1.3	55.2 ± 1.2	91.2 ± 1.3	87.4 ± 1.2	84.7 ± 1.6
Room temp	99.5±1.4	99.1± 1.6	98.9± 1.8	36.6 ± 1.4	38.9 ± 1.5	42.5 ± 1.4	98.9 ± 1.7	95.5 ± 1.6	92.6 ± 1.4
Elevated Temp	98.7±1.5	94.3± 1.7	91.5± 1.3	40.6 ± 1.9	49.3 ± 1.2	57.8 ± 1.8	88.5 ± 1.9	82.3 ± 1.4	77.9± 1.9

Table 3. Results of kinetic models

Zero order release		First order release		Higuchi Model		Koresmayer Peppas		Hixson-crowell model		Release mechanism
K_0	R^2	K_1	R^2	K_H	R^2	N	R^2	K_{HC}	R^2	
9.242	0.972	0.148	0.908	33.29	0.922	1.229	0.981	0.325	0.962	Super case-II transport





Conclusion:

This study demonstrates that optimized SMEDD can be used to form release kinetic modelling. SMEDD containing Labrafac PG, Accenon CC, Transcutol P is a transparent and low viscosity system, with a particle size of 31.82 nm± 1.15. The stability studies confirmed that the optimized SMEDD was stable for three months. Results from the in-vitro studies revealed that the developed SMEDD possessed a higher rate and extent of absorption, compared to the plain drug solution and marketed formulation. Release kinetic modelling of SMEDD indicate that drug release data fit well to Koresmayer Peppas equation plot (r^2 =0.981) indicating the dissolution rate limited drug release from the formulation. Drug release mechanism was found as a Super case-II transport, (i.e., n value-1.229).

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