ASIAN JOURNAL OF BIOMEDICAL & PHARMACEUTICAL SCIENCES

e-ISSN: 2249-622X

RESEARCH ARTICLE

Formulation and Evaluation of Self microemulsifying drug delivery system of low solubility drug for enhanced solubility and dissolution

Divyakumar Bora, Priyanka Borude, Kiran Bhise*

M.C.E. Society's Allana College of Pharmacy, K.B. Hidayatullah Road, Azam campus, camp, Pune, Maharastra 411001, India

4th Dec 2012
Received in revised form:
18th Dec 2012
Accepted:
20th Dec 2012
Available online:
15th Jan 2013

OPEN ACCESS

Online ISSN 2249–622X
http://www.jbiopharm.com

ABSTRACT

Atorvastatin is a BCS class II lipid lowering agent. It is insoluble in aqueous solution of pH 4 and below; it is very slightly soluble in water and pH 7.4 phosphate buffer. In the present investigation an attempt has been made to enhance solubility and dissolution of poorly soluble drug by formulating self microemulsifying drug delivery system (SMEDDS). The solubility of atorvastatin in individual microemulsion components viz. oil and surfactants was determined. The surfactants were screened for emulsification ability. Based on the solubility determinations and emulsification properties sunflower oil and surfactants cremophor RH 40 and capmul MCM C8 were selected for further study. The solubility of atorvastatin in different ratios of selected oil and surfactants was determined. The composition of oil:surfactants with maximum solubility for atorvastatin was used for SMEDDS formulation. Pseudoternary phase diagrams were used to evaluate the microemulsification existence area. Formulation development and screening was done based on results obtained from phase diagrams and characteristics of resultant microemulsions. The microemulsions were evaluated for emulsion droplet size, self emulsification and phase separation, *In vitro* dissolution and stability. The SMEDDS formulation showed complete release in 30 min. as compared with the plain drug, which showed a limited dissolution rate.

KEY WORDS: Atorvastatin, Solubility enhancement, SMEDDS,

1. INTRODUCTION

The fundamental step in the solubilisation of drug compounds is the selection of an appropriate salt form, or for liquid dosage forms, adjustment of pH of the solution. This is an especially important selection process for polar compounds as the majority of newer solubilisation techniques such as nanosuspensions and microemulsions utilize co-solvents when applied to a polar compound (1). These technologies include both traditional methods of solubility enhancement, such as particle size reduction via comminution, spray drying, addition of surfactants, inclusion in cyclodextrin-drug complexes, and the use of more novel mechanisms such as self-emulsifying systems, micronisation via nanoparticles, pH adjustment and salting-in processes (2, 3). Microemulsions and self-emulsifying systems have emerged as potential solubility enhancing technologies, whose solubilising and absorption promoting effect is thought to lay in the reactivity of triglycerides and surfactants with the walls of the gastrointestinal tract. Traditionally, long and medium-chain triglycerides (LCTs and MCTs, respectively) have been employed with surfactants to incorporate drugs into self- emulsifying systems (4, 5). Non-ionic surfactants, such as Tweens (polysorbates) and Labrafil (polyoxyethylated oleic glycerides), with high hyrophile-lipophile balances (HLB) are often used to ensure immediate formation of oil-in-water (o/w) droplets during production.

Amphiphilic, non-ionic surfactants

*Corresponding author: Kiran Bhise | M.C.E. Society's Allana College of Pharmacy, K.B. Hidayatullah Road, Azam campus, camp, Pune, Maharastra 411001, India | Email: bhisekiran99@yahoo.com

allow higher degrees of drug solubilisation to occur and may prevent the precipitation of drug out of the microemulsion *in vivo*. Co-surfactants are frequently employed to increase the amount of drug capable of being dissolved into the lipid base, because the concentration of surfactant in most self-emulsifying systems is required to be in excess of 30 per cent w/w. These co-surfactants are often organic solvents suitable for oral administration, such as ethanol, propylene glycol and poly ethylene glycol. Similar to the impact of introducing organic solvents elsewhere in drug product manufacture, the use of co- solvents increases processing complexity while improving the potential drug load of the emulsion (6). Most self-emulsifying systems are limited to administration in lipid-filled soft or hard-shelled gelatin capsules due to the liquid nature of the product. Interaction between the capsule shell and the emulsion should be considered so as to prevent the hydroscopic contents from dehydrating or migrating into the capsule shell.

Atorvastatin, as a synthetic lipid-lowering agent, is an inhibitor of 3-hydroxy-3-methyl- glutaryl-coenzyme A (HMGCoA) reductase which catalyzes the conversion of HMG-Co A to mevalonate, an early rate-limiting step in cholesterol biosynthesis. Atorvastatin is currently used as calcium salt for the treatment of hypercholesterolemia. It is insoluble in aqueous solution of pH 4 and below; it is very slightly soluble in water and pH 7.4 phosphate buffer. The intestinal permeability of atorvastatin is high at the physiologically relevant intestinal pH. However, it is reported that the absolute bioavailability (*F*) of atorvastatin is 12% after a 40 mg oral dose (7). In present study SMEDDS of Atorvastatin was prepared for enhanced solubility and dissoloution of poorly soluble drug.

MATERIALS AND METHODS:

Materials:

Atorvastatin calcium and Cremophor RH 40 were procured as a gift sample from Ajanta Pharma Ltd., Mumbai, India. Capmul PG-8, Capmul MCM C-10 were gifted by Abitec Corp. Janesville, WI. Other chemicals and reagents used were of analytical grade.

Solubility Studies:

The solubility of Atorvastatin calcium in various oils, surfactants, co-surfactants and Oil; surfactant mixture was measured using shake flask method (8 - 12). An excess amount of Atorvastatin Calcium was added into each vehicle followed by vortex mixing for 30 sec (Remi mixer, Mumbai). Mixtures were shaken for 48 h at 30^0 C in a thermostatically controlled shaking water bath, followed by equilibrium for 24 hr. Mixtures were then centrifuged at 3000 rpm for 10 min and the supernatant was filtered through a Millipore membrane filter (0.45µ). Samples were suitably diluted with methanol and drug concentration was obtained via UV validated method at 246 nm using methanol as a blank. The experiment was repeated in triplicates. Results are represented as mean value (mg/ml) ± SEM.

Combinations of oil and surfactant, cosurfactant were as follows.

1. Sunflower oil + $Surfactant_{mix}$ (Cremophor RH 40: Capmul MCM C8 [1:1])
2. Sunflower oil + $Surfactant_{mix}$ (Cremophor RH 40: Capmul MCM C8 [1:2])
3. Sunflower oil + $Surfactant_{mix}$ (Cremophor RH 40: Capmul MCM C8 [1:3])

Preliminary screening of surfactants

Different surfactants for the peroral use were screened for emulsification ability. Briefly,

150 mg of each surfactant was added to 150 mg of the oily phase. The mixtures were gradually heated at 50^0C for homogenization of the components. Each mixture, 100 mg, was then diluted with distilled water to 100 ml in a stoppered conical flask. Ease of emulsification was judged by the number of flask inversions required to yield homogenous emulsion. Emulsions were allowed to stand for 2 h and their % transmittance was evaluated at 638 nm by UV-Visible spectrophotometer (Shimadzu,

Japan) using distilled water as a blank. Emulsions were furthermore observed visually for any turbidity or phase separation.

Preliminary screening of surfactants

The selected oily phase and surfactant were used for further screening of the different co-surfactants (Glycerol and Capmul MCM C8) for their emulsification ability. Mixtures of 200 mg of co-surfactant, 400 mg cremophor RH40, and 600 mg Sunflower oil were prepared and evaluated in a similar fashion as described in preliminary screening of surfactants.

Phase diagram Study:

In a pseudo-ternary phase diagram study, systems consisting of sunflower oil, Cremophor RH40 as surfactant, and Capmul MCM C8 as co-surfactant were titrated with water, and self-emulsifying formulations were selected observing regions of infinite dilution.

In Vitro Dissolution assessment of Atorvastatin:

Atorvastatin calcium 10 mg was filled in hard gelatin capsule shell. Dissolution study was carried out using USP Type II apparatus (TDT – 082 – Electrolab, Mumbai, India) a 50 rpm, 37 ± 5^0C, two dissolution medium were used for study viz. 0.1N HCl and 6.8 pH phosphate buffer. The particle size distribution of the Atorvastatin calcium as provided by the manufacturer is d (0.9) =43.2 µ, d (0.5) =19.7 µ, and d (0.1) =5.1 µ.

Formulation of SMEDDS:

A series of SMEDDS formulations were prepared using Cremophor RH40 and Capmul MCM C8 as the Surfactant/cosurfactant combination and Sunflower oil (Table I). Briefly, accurately weighed atorvastatin was placed in a glass vial, and oil, surfactant, and cosurfactant were added. Then the components were mixed by gentle stirring and vortex mixing on a magnetic stirrer, until atorvastatin was perfectly dissolved. The mixture was stored at room temperature until further use.

Evaluation of SMEDDS:

Self Emulsification and Phase Separation:

Different compositions were categorized on speed of emulsification, clarity, and apparent stability of the resultant emulsion (15, 16). Visual assessment was performed by drop wise addition of the preconcentrate (SMEDDS) into 100, 250 and 1000 mL of distilled water, 0.1N HCl and pH 6.8 phosphate buffer. This was done in a glass beaker at room temperature, and the contents were gently stirred with glass rod. Precipitation was evaluated by visual inspection of the resultant emulsion after 24 hours. The formulations were then categorized as clear (transparent or transparent with bluish tinge), nonclear (turbid), stable (no precipitation at the end of 24 hours), or unstable (showing precipitation within 24 hours).

Eulsion Droplet Size*:*

Particle size of emulsion was determined by Laser Diffractometer Mastersizer 2000 ver.2.00, Malvern Instruments, Malvern, UK (8, 14). Samples were diluted to 250 mL with the Distilled water for the measurement.

Drug Content:

SMEDDS containing Atorvastatin Calcium was added in volumetric flask containing methanol. The mixture was stirred vigorously for 2 hr. The sample was analysed for atorvastatin concentration after suitable dilution using UV –spectrophotometer at 246 nm (5, 8, 13).

***In Vitro Dissolution*:**

Based on the drug content determinations self microemulsifying formulations containing 10 mg atorvastatin were filled in hard gelatin capsule shells. The dissolution was carried out using dissolution test apparatus USP Type II, at 37±5^0C, 50 rpm paddle speed. Dissolution was performed in two different mediums viz. 0.1N HCl and 6.8 pH Phosphate buffer 900 ml. The samples were withdrawn at predetermined time intervals and were analyzed for drug concentration by UV-Visible spectrophotometer after filtration through 0.22 µ filter (9, 17, 19, 20).

Stability Studies:

In order to evaluate the stability of the optimized SMEDDS the formulation was added into sealed glass vials and the vials were subjected to stability studies at 40ºC±2^0C/75%±5% RH for a period of three months (2, 21, 22). Samples were charged in stability chambers (Thermolab, Mumbai, India) with humidity and temperature control. The samples were evaluated for clarity, phase separation, Drug content and in vitro drug release at predetermined intervals.

RESULTS AND DISCUSSION:

Solubility studies:

Selection of right component is important prerequisite for formulation of stable SMEDDS. The drug should have good solubility in components of microemulsion so as the precipitation of drug during shelf life of formulation and after dilution in GI lumen can be avoided. Therefore, the solubility of Atorvastatin calcium was determined in various oils, surfactants and cosurfactant mixtures. The solubility results are depicted in figure I. Among the various components studied sunflower oil, Cremophor RH40 and capmul MCM C8 showed maximum solubility 40.68 ± 1.79, 74.363 ± 1.73 and 53.83 ± 0.51 mg/ml respectively. The solubility results for oil: surfactant mixtures are showed in Table I. As the solubility of Atorvastatin was maximum in sunflower oil, cremophor RH40 and capmul MCM C8 these were selected as oil and surfactant component for further development of SMEDDS. Final selection among different components would secondly be confirmed according to emulsification properties with other ingredients. Regarding surfactants and co-surfactants selection, drug solubility would come second to the main selection perspective: emulsification efficiency.

Preliminary screening of surfactants:

The surfactants were compared for their emulsification efficiencies using different oily phases. It has been reported that well formulated SNEDDS is dispersed within seconds under gentle stirring conditions. Transmittance values of different mixtures are demonstrated in Table II.

Results inferred that among all the surfactants employed the oily phase Sunflower oil exhibited the highest emulsification efficiency with Cremophor RH40 ranking first, requiring only 7 flask inversions (7 s) for homogenous emulsion formation. On the other hand, Span 80 showed poor emulsification properties with all the surfactants

employed, requiring a minimum of 51 flask inversions (51 s).

Oil: Surfactant mix	Solubility (mg/ml)*		
	Surfactant mi x (1:1)	Surfactant mi x (1:2)	Surfactant mi x (1:3)
1:	73.9±0.10	77.55±0.44	79.70±0.61
2:	72.69±0.46	75.59±0.51	75.96±0.89
3:	71.72±0.59	72.72±1.10	74.21±0.41
4:	62.06±1.13	69.60±0.82	71.81±0.95
5:	57.75±0.66	67.48±0.57	68.29±0.39
6:	55.85±0.67	64.24±0.55	65.33±0.55
7:	54.30±0.60	61.26±1.11	63.06±0.68
8:	53.93±0.95	59.14±0.55	59.81±0.91
9:	51.96±0.94	53.66±0.58	55.29±0.45

Table 1: Solubility of Atorvastatin Calcium in various oil: surfactant mixtures.

	% Transmittance				
Surfactant	Castor Oil	Soybean Oil	Sunflower Oil	Isopropyl Myristate	Capmul PG8
Tween 20	39.1	45.7	60.0	55.1	40.1
Tween 40	45.0	51.2	52.1	41.3	35.1
Tween 60	43.0	43.0	45.8	35.2	43.2
Tween80	51.2	50.0	55.0	44.3	45.7
Cremophor RH40	77.1	60.3	92.1	66.1	55.9
Span 20	39.0	29.0	22.5	25.1	37.3
Span 80	21.2	27.3	11.0	20.1	20.0
Capmul MCM C8	-	-	98.6	-	-
Glycerol	-	-	76.3	-	-

Table 2: Preliminary Screening of Surfactants and Co-surfactants

It was observed that oils of medium carbon chain length and higher HLB values such as Sunflower oil (HLB 5-6) are better than longer chain length and higher HLB such as Castor oil (HLB 10), Soybean oil (HLB 7) and isopropyl myristate (HLB 9). Water-in-oil emulsions are formed generally from oil-soluble surfactants of low HLB number and oil- in-water emulsions from more hydrophilic surfactants of high HLB number. Amongst the surfactants studied Cremophor RH 40 has HLB number 14-15 whereas span 80 has HLB number 4.3. Therefore span exhibits poor emulsification property for sunflower oil as compared to cremophor RH40. The aforementioned results suggested the use of Sunflower oil as an oily phase with Cremophor RH40 as a surfactant for further study.

Preliminary screening of co-surfactants:

Addition of a co-surfactant to the surfactant-containing formulation improves dispensability and staility of formulation. In view of current investigation, two co-surfactants, namely glycerol and Capmul MCM C8 were compared. As depicted in Table II, Capmul MCM C8 exhibited good emulsification with Sunflower oil and Cremophor RH 40 mixture, showing maximum transmittance (98.6%) compared to Glycerol 76.3%. Herein, solubility of the drug in different co-surfactants may judge the final selection. Results of solubility study demonstrated in Fig. I inferred higher solubility in Capmul MCM C8.

Based on the results of preliminary screening, a distinct systems was selected consisting Sunflower oil as oily phase /Cremophor RH40 as surfactant /Capmul MCM C8 as cosurfactant and detailed study of the system was performed with pseudoternary phase diagram.

Pseudoternary phase diagrams:

The detailed composition of the SMEDDS formulations used to construct the phase diagram are depicted in Table III. Pseudoternary phase diagram is used to identify the microemulsion region is depicted in figure II. In the pseudoternary phase diagram DA1 formulation, the area of self-microemulsifying region was much bigger than that of MA1 and SA1 formulation. With the decreasing of co-emulsifier concentration, the area decreased slightly. Self-microemulsifying formulations could be obtained under the condition of surfactant: cosurfactant ratio from 1:1 to 1:3, and oil: (Surfactant: cosurfactant) ratio equal to 1:9, 2:8, 3:7. Sunflower oil was introduced to the system as its relatively good solubilizing efficiency. Self-microemulsifying systems form fine oil– water emulsions with only gentle agitations, upon their introduction into aqueous media. Surfactant and co-surfactant get preferentially absorbed at the interface, reducing the interfacial energy as well as providing a mechanical barrier to coalescence. The decrease in the free energy

Sunflower Oil (% w/w)	FC	$Surfactant_{mix}$ (1:1)		FC	$Surfactant_{mix}$ (1:2)		FC	$Surfactant_{mix}$ (1:3)	
		Cremophor RH40 (%w/w)	Capmul MCM C8 (% w/w)		Cremophor RH40 (%w/w)	Capmul MCM C8 (%w/w)		Cremophor RH40 (%w/w)	Capmul MCM C8 (%w/w)
9.90	SA1	44.55	44.55	MA1	29.7	59.4	DA1	22.2	66.8
19.80	SA2	39.60	39.60	MA2	26.4	52.8	DA2	19.8	59.4
29.70	SA3	34.65	34.65	MA3	23.1	46.2	DA3	17.3	51.9
39.60	SA4	29.70	29.70	MA4	19.8	39.6	DA4	14.8	44.5
49.50	SA5	24.75	24.75	MA5	16.5	33	DA5	12.3	37.1
59.40	SA6	19.80	19.80	MA6	13.2	26.4	DA6	9.9	29.7
69.30	SA7	14.85	14.85	MA7	9.9	19.8	DA7	7.4	22.2
79.20	SA8	9.90	9.90	MA8	6.6	13.2	DA8	4.9	14.8
89.10	SA9	4.95	4.95	MA9	3.3	6.6	DA9	2.4	7.4

Table III: Various SMEDDS formulations.
All Formulations contain 10mg (0.99 %w/w) of Atorvastatin calcium

FC	NTU		%Drug Content*	FC	NTU		%Drug Content*	FC	NTU		%Drug Content*
	with drug	without drug			with drug	without drug			with drug	without drug	
SA 1	96.3	41.3	99.52±0.90	MA1	87	38.6	99.79±0.77	DA 1	52	23	100.10±0.43
SA 2	134	64	98.97±0.77	MA 2	109.6	61	99.43±0.51	DA 2	87	39.2	99.85±0.51
SA 2	206.5	106.4	98.86±0.55	MA 3	187	95.4	98.91±0.75	DA 3	107	46	99.17±0.65
SA 4	287	147	97.41±0.41	MA 4	232	112	97.69±0.78	DA 4	198	63	98.41±0.95
SA 5	468.3	229.6	96.89±0.73	MA 5	432	202.2	96.91±0.45	DA 5	265	103	97.60±0.51
SA 6	592.4	318	95.13±0.15	MA 6	549.3	263	95.37±0.55	DA 6	432	173	97.14±0.44
SA 7	768	378.8	94.90±0.23	MA 7	675	298	94.84±0.23	DA 7	556	234	96.18±0.214
SA8	-	-	93.44±0.42	MA8	-	-	93.56±0.49	DA8	-	-	95.52±0.472
SA9	-	-	91.12±0.47	MA9	-	-	91.30±0.49	DA9	-	-	95.30±0.496

Table IV: Turbidimetric Evaluation and Drug content determination of SMEDDS formulations

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Formulation	Droplet size (μ)		
	D(0.1)	D(0.5)	D(0.9)
SA1	0.073	0.114	0.184
MA1	0.07	0.101	0.152
DA1	0.068	0.096	0.143

Table V: Emulsion droplet size

Sr. No.	tc h	Physical appearance				Drug content			
		T=0	T=30	T=60	T=90	T=0	T=30	T=60	T=90
1.	SA1	No change	No Change	No change	No change	99.52±0.90	99.68±0.13	99.75±43	99.84±0.22
2.	MA1	No Change	No Change	No Change	No Change	99.79±0.77	99.69±0.43	99.89±0.3	99.94±0.25
3.	DA1	No Change	No Change	No Change	No Change	100.10±0.4	100.02±0.3	99.96±0.8	99.87±0.55

Table VI: Stability study of SMEDDS formulations.

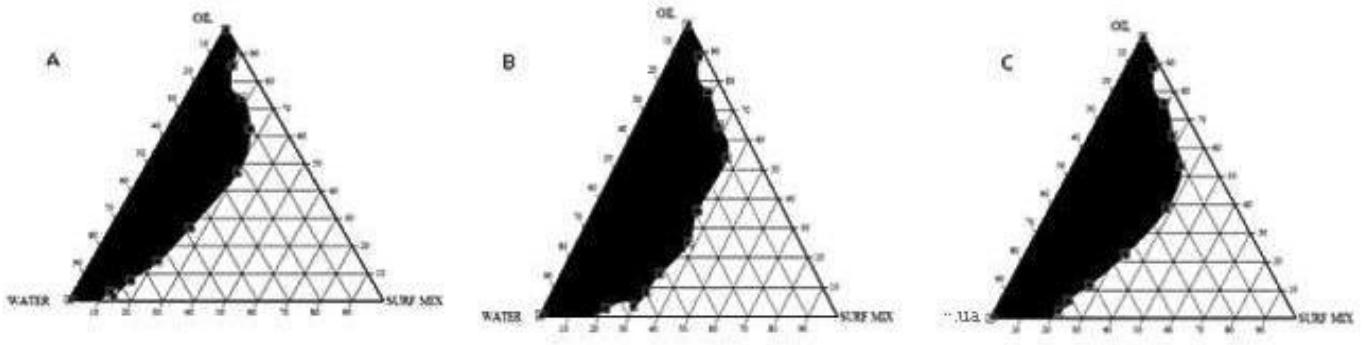


Figure 2: : Pseudoternary phase diagrams

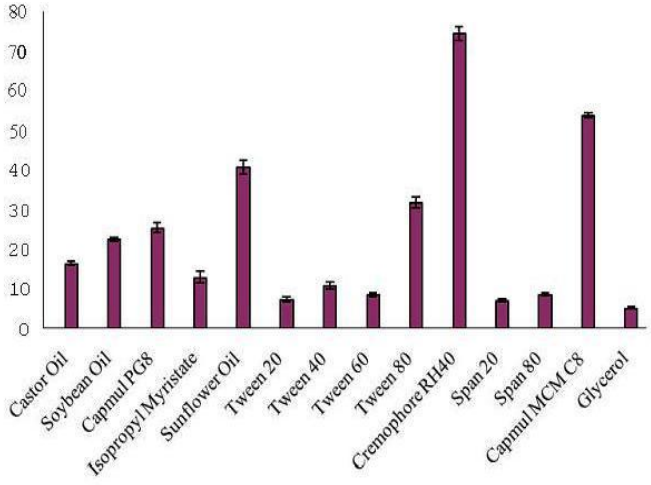
required for the emulsion formation consequently improves the thermodynamic stability of the microemulsion formulations. The efficiency of self emulsification of surfactant and co-surfactant is much related to their hydrophilic– lipophilic balance (HLB) value. Generally surfactants with HLB 12–15 are regarded as being of good efficiency for self emulsification. Considering the solubilizing efficiency and biocompatibility of the excipients, the selected system, known to produce SMEDDS consist of a nonionic surfactants (Cremophor RH40 and Capmul MCM C8), Sunflower oil was considered suitable for the development of SMEDDS.

EVALUATION OF SMEDDS

Self emulsification, phase separation study

The surfactant: cosurfactant ratio of 1:1 to 1:3 yields clear

dispersion when oil: (Surfactant: cosurfactant) ratio equal to 1:9, 2:8, 3:7. Thus, formulations SA1, SA2, SA3, MA1, MA2, MA3, DA1, DA2, and DA3 produced clear dispersion which was stable i.e. no precipitation observed after 24 hr. All the other formulations produced turbid emulsion upon addition into water except formulation SA4, MA4 and DA4 which produced clear emulsion but showed precipitation after 24 hr.



FigureI:Solubility of Atorvastatin Calcium

Drug content:

The results are depicted in Table IV.

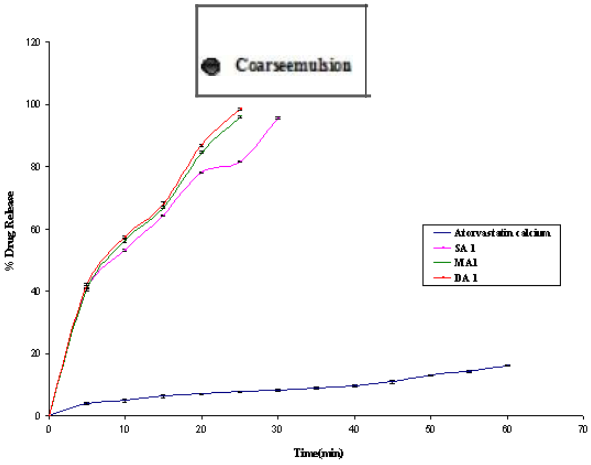


Figure III: Dissolution study in 0.1 N HCl.

Emulsion droplet size:

Only those formulations that exhibited good thermodynamic stability were subjected to droplet size analysis. The results are depicted in Table V. An increase in the ratio of the oil phase (Sunflower oil) resulted in a proportional increase in particle size, because of the simultaneous decrease in the Surfactant: cosurfactant proportion. The formulations with surfactant: cosurfactant ratio 1:3 (DA, DA2, DA3) exhibited least mean particle size. This could be attributed to an increased cosurfactant proportion relative to surfactant. It is well known that the addition of surfactants to the microemulsion systems causes the interfacial film to stabilize and condense, while the addition of cosurfactant causes the film to expand; thus, the relative proportion of surfactant to cosurfactant has varied effects on the droplet size. (15, 16, 23, 24)

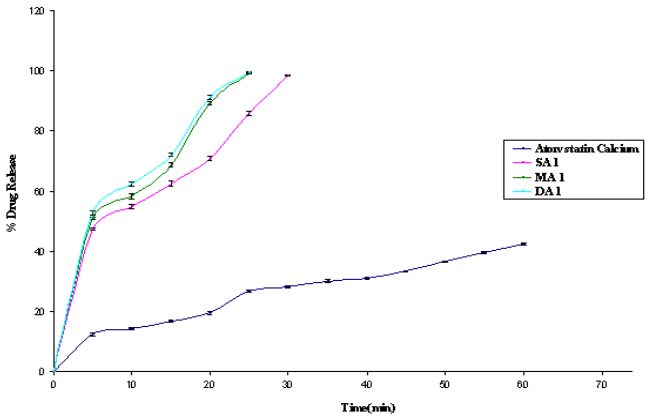


Figure IV: Dissolution study in 6.8 pH Phosphate buffer.

In Vitro dissolution:

The dissolution study was performed in two different mediums viz. 0.1N HCl and 6.8 pH phosphate buffer. The formulations that exhibited good thermodynamic stability were subjected to dissolution study. The results are depicted in figure III and IV. The SA1, MA1, and DA1 formulations depicted above 90 % drug release in 30 min. in both the medium showing pH independent release of atorvastatin from SMEDDS formulations. The rapid release of atorvastatin from SMEDDS formulations could be attributed to the spontaneous formation of microemulsion with a small droplet size, which permitted a faster rate of drug release into the aqueous phase, much faster than that of plain atorvastatin. Thus, this greater availability of dissolved atorvastatin from the SMEDDS formulation could lead to higher absorption and higher oral bioavailability. It was also seen that changes in the dissolution medium (0.1N HCl and 6.8 pH phosphate buffer) had no effect on the drug release SMEDDS formulation whereas with plain atorvastatin it was observed that the dissolution was faster in 6.8 pH Phosphate buffer as compaired to that in 0.1N HCl. This observation can be explained by the fact that Atorvastatin has pKa 4.46 i.e. ionizable at alkaline pH and its solubility and dissolution is pH dependent.

Stability Studies:

Samples of SMEDDS were charged on accelerated and long term stability conditions. Chemical and visual observations of samples were shown in Table VI. No significant change in the drug content in the formulations was observed over the period of 3 months at accelerated and long term stability conditions. The drug release in both the mediums for all three formulations studied remained unchanged.

CONCLUSION:

An optimized atorvastatin loaded formulation consisting of sunflower oil, Cremophor RH 40 and Capmul MCM C8 offers the advantage of good solubilization of Atorvastatin. Thus our studies confirmed that SMEDDS can be used as a possible alternative to conventional oral formulation of atorvastatin. Results further conclude that SMEDDS can be explored as a potential drug carrier for dissolution enhancement of atorvastatin and other insoluble drugs.

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Conflict of Interest: None Declared

