

## Original Article

# Formulation Development and Evaluation of Self-Emulsifying Drug Delivery System of Atorvastatin.

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## Abstract

The aim of the present study was to formulate a Self-emulsifying drug delivery system (SEDDS) of Atorvastatin calcium (ATR). Various technological strategies are reported in the literature including solid dispersions, cyclodextrins complex formation, or micronization. Including these approaches self-emulsifying drug delivery system. (SEDDS) has gained more attention for enhancement of oral bio-availability and Solubility enhancement with reduction in dose and its characterization including *in vitro*, particle size distribution, zeta potential, stability study. The solubility of ATR was determined in various vehicles such as Olice acid, Tween 20, and PEG 400. Pseudoternary phase diagrams were plotted on the basis of solubility data of drug in various components to evaluate the micro emulsification region. Formulation development and screening was done based on result obtained from phase diagrams and characteristics of resultant microemulsions. Prepared SEDDS formulations were tested for microemulsifying properties and the resultant microemulsions were evaluated for clarity, precipitation, viscosity, drug content and *in vitro* dissolution. The optimized SEDDS formulation further evaluated for particle size distribution, zeta potential, stability studies and *in vitro* dissolution.

**Keywords:** Atorvastatin Calcium, Self-Emulsifying Drug Delivery System, Bioavailability enhancement, Solubility enhancement.

## Introduction

In recent years, the oral route is the most preferred route of drug delivery for treatment of a number of diseases. Up to 40% of new chemical entities discovered by the pharmaceutical industry are poorly soluble or lipophilic compounds, which lead to poor oral bioavailability, high intra and inter subject variability and lack of dose proportionality. Currently a number of technologies are available to deal with the poor solubility, dissolution rate and bioavailability of insoluble drugs.

Various formulation strategies reported in the literature includes, incorporation of drug in oils, solid dispersions, emulsions, liposomes, use of cyclodextrins, coprecipitates, micronization, nanoparticles, permeation enhancers and lipid solutions. Recently a new technique, Self-Emulsifying Drug Delivery System (SEDDS) has been developed to enhance the solubility of drug. SEDDS are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants or alternatively, one or more hydrophilic solvents & co-solvents/co-surfactants. Self-Emulsifying Drug Delivery Systems (SEDDS) formed using surfactants of HLB < 12 and Self-Micro Emulsifying Drug Delivery Systems (SMEDDS) formed with surfactants of HLB > 12. Both SEDDS and SMEDDS are stable preparations and improve the dissolution of the drug due to increased

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surface area on dispersion. Therefore, they are not dependent on bile secretion for absorption. The emulsified form itself is readily absorbable. This ensures a rapid transport of poorly soluble drugs into the blood. Potential advantages of these systems include enhanced oral bioavailability (enabling dose reduction), more consistent temporal profiles of drug absorption, selective drug targeting toward a specific absorption window in the GI tract, and drug protection from the hostile environment in the gut.<sup>1</sup> Atorvastatin, a 3-hydroxy 3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitor (a statin), is a lipid regulating drug with actions on plasma lipids similar to those of simvastatin. It is used to reduce LDL cholesterol, apolipoprotein B, and triglycerides, and to increase HDL cholesterol in the treatment of hyperlipidaemias, including hypercholesterolaemias and combined (mixed) hyperlipidaemia (type IIa or IIb hyperlipoproteinaemias), hypertriglyceridaemia (type IV), dysbetalipoproteinaemia (type III). Atorvastatin lowers plasma cholesterol and lipoprotein levels by inhibiting HMG CoA reductase and cholesterol synthesis in the liver and by increasing the number of hepatic LDL receptors on the cell surface to enhance uptake and catabolism of LDL, it also reduces LDL production and the number of LDL particles. The absolute bioavailability of atorvastatin (parent drug) is approximately 14% and the systemic availability of HMG CoA reductase inhibitory activity is approximately 30% this low systemic availability is ascribed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. The food decreases the rate and extent of drug absorption by approximately 25% and also responsible for reduction in C<sub>max</sub> and AUC, LDL-C level. A blood/plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells. Based on observations in rats, atorvastatin calcium is likely to be secreted in human milk. So it is aimed to formulate a SEDDS containing a lipophilic drug, atorvastatin and to explore the potential of this carrier for improvement of the oral bioavailability of Atrovastatin.<sup>2</sup>

## Materials & Methods

Atorvastatin calcium taken as gift sample from Wockhardt Pharmaceutical Pvt. Ltd, Aurangabad. Olice acid, Tween 20, PEG 400 procured from Belie Drugs, Surat, Gujarat.

### Preformulation study

#### a) Melting point

Melting point of Atorvastatin Calcium was determined by using Melting point apparatus (VEEGO Model-Vmp-0).<sup>8,9</sup>

#### b) Infrared spectroscopy:

IR spectroscopy study of Atorvastatin Calcium was done by using FT-IR spectrophotometer (S). The spectra were scanned over the wavelength region of 400 cm<sup>-1</sup>. The procedure consisted of dispersing a sample of KBr and compressing into the disc by applying of pressure consisted of 5 tons for 5 minutes in a hydraulic press. The pellets were placed in the light path and the spectrum was obtained.<sup>8,9</sup>

#### c) Differential Scanning Calorimetry:

Differential Scanning Calorimetric studies of pure Atorvastatin Calcium samples were carried out at the 10<sup>0</sup>C/min between the temperature range 30<sup>0</sup>C-300<sup>0</sup>C under a nitrogen flow of 2-bar pressure.<sup>9</sup>

#### d) UV Spectrophotometer:

UV spectrum of Atorvastatin Calcium solution in distilled water was scanned at 400 to 200 nm. The wavelength of maximum absorption ( $\lambda$  max) was determined.<sup>9</sup>

#### e) Calibration Curve of Atorvastatin Calcium:

##### Preparation of standard stock solution:

Accurately weighed 10 mg of Atorvastatin Calcium was transferred to 100 ml of volumetric flask and volume was made up to the mark with Methanol, pH 1.2 and pH 6.8 phosphate buffers separately to obtained strength of 100 mc/ml. This was further diluted to give the solutions of concentration 2-20 mcg/ml. these solutions were measured for absorbance on UV spectrophotometer at 242nm plotted against the concentration to give the standard calibration curve.<sup>9</sup>

### **Solubility Determination of Atorvastatin, Oil, Surfactants and Co-Surfactants.**

2ml of different oil was taken in small vials separately and excess amount of the drug was added to each vial. The vials were tightly stopper and were continuously stirred for 72 hrs in mechanical stirrer at 25°C and after that, oils were centrifuged. The supernatant was separated and dissolved in methanol and solubility was quantified by UV-spectroscopy method at 247nm after appropriate dilution with methanol.<sup>1</sup>

### **Construction of Pseudo-Ternary Phase Diagram**

Pseudo ternary phase diagrams of oil, surfactant / co-surfactant ( $S_{mix}$ ), and water were constructed using the water titration method; each of them represents a side of triangle. Ternary mixtures with varying composition of surfactant, co-surfactant and oil were prepared.<sup>60</sup> Surfactant and co-surfactant were mixed in different ratios (1:1,1:2, 2:1, 3:1, 1:3). For each phase diagram, oil and specific surfactant to co-surfactant ratio were mixed thoroughly in different ratios from 1:9 to 9:1 in different conical Flask. Nine different combinations of oil and  $S_{mix}$ , 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, 9:1, were prepared so that maximum ratios were covered for the study to delineate the boundaries of phase precisely formed in the phase diagrams. A transparent and homogeneous mixture of oil /  $S_{mix}$  was formed by stirring for five min, and then each mixture was titrated with water and observed for phase clarity and flowability. The point at which system become bluish or turbid, titration was discontinued and at this point quantity of oil, surfactant and co-surfactant was calculated. These results were then used to determine the boundaries of the self-emulsion domain. To determine the effect of drug addition on the self-emulsion boundary, phase diagram was also constructed in the presence of the drug using drug enriched oil. Phase diagram were then constructed using Chemix School software version 3.5. The following studies were carried out by constructing a pseudo-ternary phase diagram.

- The influence of various surfactants on the self-emulsion formation with the various co-surfactants as PEG 400.

- Influence of various co-surfactants on the self-emulsion formation with various surfactant as Tween 80, Tween 20 and their mixture.
- Influence of surfactant / co-surfactant ratio on the formulation of self-emulsion. The self-emulsion regions in the diagrams were plotted and the red colored region indicates the better self-emulsification capacity.<sup>10,11</sup>

### **Formulation of SEDDS Batches**

A series of 1- SEDDS formulation were prepared using Olice acid as oil, Tween 20 as a surfactant and PEG 400 as a co-surfactant. Proportion of oil, surfactant and co-surfactant was determined by pseudoternary phase diagram. In the formulation batch 1-5, the level of Atorvastatin was kept constant as (1%) and in formulation batch 6-9, the level of Atorvastatin was kept constant as (2%). Accurately weighed Atorvastatin was placed in glass vial and oil, surfactant and co-surfactant were added. The ingredients were further mixed by gentle stirring and were heated at 25°C until Atorvastatin was perfectly dissolved. The mixture was stored at room temperature until further use.<sup>12</sup>

### **Characterization and Evaluation Of The Formulation**

#### **Dilution Study**

Dilution study plays a very important role in the development and optimization of final formulation. For the development of SMEDDS formulation, right blend of emulsifier is necessary to form stable microemulsion. SEDDS formulations containing 10 mg of ATR (1 part) were diluted with 10 parts of distilled water, 0.1 N HCl and Phosphate buffer of pH 6.8.<sup>1,2,10</sup>

#### **Drug Content:**

ATR from pre weighed SEDDS formulations was extracted by dissolving the formulations in 25 ml of methanol. ATR content in the methanolic extract was analyzed spectrophotometrically (Lab, India Ltd. UV-3000+) at 241 nm, against the standard methanolic solution of ATR.<sup>10,11</sup>

#### **Disintegration Test:**

The test was performed according to procedure and specification mention in official compendia of standards. Placed one capsule in each of six tubes of the basket and added a

disk. Operated the apparatus using pH 6.8 buffers as immersion fluid maintained at  $37 \pm 2$  °C. All the capsules have disintegrated except the fragments from capsule shells. If one or two capsules fail to disintegrate completely repeat the test for 12 additional capsules. Not less than 16 of total 18 capsules tested disintegrate completely.

#### **Self-Emulsification and Precipitation Assessment**

A 'self-emulsifying' system is a mixture of oil and surfactant which emulsifies in water under conditions of gentle agitation. Such mixtures may be spontaneously emulsifying if the entropy change favoring dispersion is larger than the energy required to increase the surface area of the dispersion. In practice the rate of spontaneous emulsification is difficult to establish because when mechanical agitation is absent gravitational force provides a small quantity of energy for emulsification. For the purpose of pharmaceutical formulation it is not essential to identify those systems which are spontaneously emulsifying; it is more important to distinguish between self-emulsifying systems and conventional emulsion systems which will be finely dispersed only after exposure to strong shearing forces. Assessment of the self-emulsifying properties of SEDDS formulations were performed by visual assessment. Different formulations were categorized on the basis of speed of emulsification, clarity, and apparent stability of the resultant emulsion. Visual assessment was performed by drop wise addition of the SEDDS into 250 ml of distilled water at room temperature, and the contents were gently stirred magnetically at 100 rpm. Precipitation was evaluated by visual assessment of the resultant emulsion after 24 h. The formulations were then categorized as clear (transparent or transparent with bluish tinge), nonclear (turbid), stable (no precipitation at the end of 24 h), or unstable (showing precipitation within 24 h).<sup>12</sup>

#### **Percentage Transmittance**

A total of 1 ml of SEDDS formulation was diluted with 100 ml distilled water. Percentage transmittance was then measured spectrophotometrically at 680 nm using distilled water as a blank.

#### **Viscosity Determination**

SEDDS (1 ml) was diluted 10 and 100 times with the distilled water in beaker with constant stirring on magnetic stirrer. Viscosity of the resultant microemulsion and undiluted SEDDS was measured using viscometer (Brookfield Engineering Laboratories, LV-DV-E, 8542327).<sup>10,14</sup>

#### **Droplet Size Analysis**

Droplet size of SEDDS diluted with water was determined using a photon correlation spectrometer (Zetasizer Ver.6.20, MAL1051945) based on the laser light scattering phenomenon. The system inherently measures the integral light scattering from all particles present in the beam. As material flows through the beam, the measured light scattering is continuously changing to give the instantaneous integral of the material illuminated by the analyzer beam. Approximately 0.002 % of emulsion concentration in water was incorporated into a 15 ml volume cell, under slow agitation, the scattered light intensity was measured. Optimized formulation was diluted 200 times with purified water. Diluted samples were directly placed into the module and measurements were made in triplicate after 2-min stirring<sup>13</sup>.

#### **Zeta-Potential Determination**

The charge of the oil droplets of SEDDS is an additional property that should be assessed. The charge of the oil droplets in conventional SEDDS is negative due to the presence of free fatty acids; however, incorporation of a cationic lipid, such as oleylamine at a concentration range of 1–3%, will yield cationic SEDDS. SEDDS (1 ml) was diluted 10 times and 100 times with distilled water in beaker with constant stirring on a magnetic stirrer. Zeta-potential of the resulting microemulsion was determined using the Zetasizer (Ver.6.20 MAL1051945)<sup>10</sup>

#### **In Vitro Dissolution Studies**

The quantitative in vitro release test was performed in 900 mL of phosphate buffer pH 6.8 maintained at  $37 \pm 0.5$  °C using type II dissolution apparatus (TDT-08L Electrolab). The paddles were rotated at 100 rpm. The SEDDS formulations were filled into hard gelatin capsules (0 sizes) and used for drug

release studies; results were compared with marketed ATR tablet (ZIVAST, 10 mg, FDC Ltd.). 5 ml aliquots were collected periodically and replaced with fresh dissolution medium.

Aliquots, after filtration through Whatmann filter paper were analyzed spectrophotometrically at 241 nm for ATR content.<sup>13</sup>

## Results & Discussion

### Solubility Studies

Solubility is the most important criteria for selecting the vehicle for formulating a self emulsifying formulation. Therefore, the components used in the system should have high solubilization capacity for the drug, ensuring the solubilization of the drug in the resultant dispersion. As seen from the results of solubility study, PEG 400, Olice acid, and Tween 20 showed the highest solubilization capacity for ATR, as compared to other components. Thus, for present study Olice acid selected as oil, Tween 20 as surfactants and PEG 400 as co-surfactant.

### Construction of Pseudo-Ternary Phase Diagram

Pseudo ternary phase diagrams of oil, surfactant / co-surfactant ( $S_{mix}$ ), and water were constructed using the water titration method; each of them represents a side of triangle. Ternary mixtures with varying composition of surfactant, co-surfactant and oil were prepared.<sup>60</sup> Surfactant and co-surfactant were mixed in different ratios (1:1, 2:1, 3:1, 1:3). For each phase diagram, oil and specific surfactant to co-surfactant ratio were mixed thoroughly in different ratios from 1:9 to 9:1 in different conical Flask. Nine different combinations of oil and  $S_{mix}$ , 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, 9:1, were prepared so that maximum ratios were covered for the study to delineate the boundaries of phase precisely formed in the phase diagrams.

For the determination of existence zone of microemulsion, pseudoternary phase diagrams were constructed using water titration method. To construct pseudoternary phase diagrams, the oil phase (oleic acid) was mixed with different ratio of surfactant and cosurfactant (Tween 20 and PEG 400 respectively) and mixture was titrated with distilled water until it turned turbid. Examine each and every point I detailed and note it down. Pseudo ternary

phase diagrams were drawn by using data obtained in aqueous titration method as shown in figure. The amount of water added to give water concentration in the range of 5-95% of total volume at 5% intervals. After every 5% addition of the water to the oil and Smix mixture, visual observations were made as shown in figure. The ratio of surfactant and co surfactant (Tween 20 and PEG 400) were used for the titration.

### Dilution Study

Accurate mixture of emulsifier is necessary to form stable microemulsion for the development of SEDDS formulation. When 1 part of each SEDDS formulation was diluted with 10 parts of distilled water, 0.1 N HCl and phosphate buffer 6.8 pH (Table 6). It implies that the formulation F1 was more stable because there was no precipitation or crystallization of drug.

### Drug Content

Drug content of the SEDDS formulations were shown in (Table 7)

### Disintegration Test

The disintegration time of SEDDS formulation was shown in (Table7).

### Self-Emulsification and Precipitation Assessment

It was found that self-emulsification time (SET) was decreases with increase in concentration of surfactants up to 49 %, beyond and below which there was turbid and unstable dispersion. The decrease in self-emulsification time can be assumed due to the relative increase in surfactants concentration. Hence combinations of high and low HLB value surfactants were used because low HLB surfactants were behaving as coupling agent for high HLB surfactants. Furthermore, using a blend of low and high HLB surfactants may also lead to more rapid dispersion and finer emulsion droplet size on addition to an aqueous phase (Table 7). The ratio of Smix of 2:1 and S/CoS of 4:1 was kept constant for the preparation of formulations.

### Viscosity Determination

Viscosity of SEDDS without dilution was found to be in between 151 – 161 cPs, which was suitable for filling in hard gelatin capsule without risk of leaking problem. As SEDDS was diluted 10 and 100 times with water, viscosity of the system was decreased, which indicates that oral administration of SEDDS

formulation will be diluted with the stomach fluid and viscosity will be decreased and therefore absorption from the stomach will be fast (Table 7).

#### **Droplet size determination**

The average size of droplets formed after emulsification was measured by using Malvern Zetasizer at room temperature. Which was found to be 518.4 nm with poly dispersity index of 0.7 showing that the particles generated were mono disperse.

#### **Zeta potential measurement**

The zeta potential of optimized batch was found to be -26.8 mV. (Figure 15) A high zeta potential above 25 (Either positive or negative) indicates that the droplets/particles generated after emulsification, shall repel each other and remain deflocculated and imparts physical stability to the system. Therefore Self emulsifying system of meloxicam appears to be physically stable.

#### **In Vitro Dissolution Studies**

Atorvastatin is poorly soluble in water and showed pH dependent solubility. As shown in Figure, pure drug showed very less release 43%, 38% and 42% even after 60 min. in HCL buffer pH 1.2, and phosphate buffer PH 6.8 respectively. Marketed formulation (ZIVAST 10 mg, FDC Ltd. India) showed only 30%, 29% and 30 % release after 15 min in HCL buffer pH 1.2, and Phosphate buffer PH 6.8 respectively. Whereas SEDDS showed rapid release of drug in both solutions. At 20 min about 85% of Atorvastatin from SEDDS was released and more than 96% was released after 30 min. HCL buffer pH 1.2 and phosphate buffer. In other words, SEDDS could form quickly clear and transparent solution under the condition of dissolution. It was also evident that release of atorvastatin from SEDDS was independent of dissolution medium pH.

#### **Comparative study with marketed formulation**

The formulation (F1) was compared with the marketed tablet it was found that evaluation parameters of formulation (F1) were found to be better that of marketed tablet and pure drug. The optimized formulation (F1) percent drug release study compared with the marketed formulation and pure drug.

#### **Stability Studies**

Optimized formulation (F1) filled into hard gelatin capsules '0' size as the final dosage form. However liquid-filled hard gelatin capsules are prone to leakage, and the entire system has a very limited shelf life owing to its liquid characteristics and the possibility of precipitation of the drug from the system. Thus, the optimized formulation (F1) was subjected to stability studies to evaluate its stability and the integrity of the dosage form. No any changes were found in the physical parameters such as homogeneity and clarity was observed during the stability studies. There were no major change in the drug content, disintegration time, and in vitro dissolution profile. It was also observed that the formulation was compatible with the hard gelatin capsule shells. Also, there was no phase separation, and drug precipitation was found at the end of 1 month's stability studies indicating that ATR remained chemically stable in SEDDS (Table.10).

#### **Conclusion**

ATR was formulated as a SEDDS in an attempt to increase its solubility and bioavailability. An optimized formulation of SEDDS containing ATR was developed through the construction of pseudo-ternary phase diagram, particle size analysis and zeta potential. SEDDS appeared to be an interesting approach to improve problems associated with oral delivery of ATR. ATR SEDDS formulation was superior to marketed Tablet formulation with respect to in vitro dissolution profile. Thus, SEDDS can be regarded as novel and commercially feasible alternative to current ATR formulations.

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**Table 1:** Developed formulation with their composition.

Formulation	Ingredients( % w/w )				Sur. / Co-sur. ratio
	Surfactant	Co-surfactant	Oil	Drug	
	Tween 20	PEG400	Oilce acid	Atorvastatin	
<b>F1</b>	59.40	29.70	9.90	1.00	2:1
<b>F2</b>	52.80	26.40	19.80	1.00	2:1
<b>F3</b>	46.20	23.10	29.70	1.00	2:1
<b>F4</b>	39.60	19.80	39.60	1.00	2:1
<b>F5</b>	33.00	16.50	49.50	1.00	2:1
<b>F6</b>	58.80	29.40	9.80	2.00	2:1
<b>F7</b>	52.28	26.14	19.60	2.00	2:1
<b>F8</b>	45.75	22.87	29.41	2.00	2:1
<b>F9</b>	39.21	19.60	39.21	2.00	2:1

**Table 2:** Characterization & UV absorbance of Atorvastatin Calcium.

Sr. No.	Conc. (ppm)	Absorbances (242nm)
1	2	0.162
2	4	0.298
3	6	0.442
4	8	0.576
5	10	0.712

Sr. No	Test	Specification	Test Result
1	Description	White powder	White powder
2	Melting point	152-159 <sup>0</sup> C	159-160 <sup>0</sup> C

**Table 3:** Solubility of oil.

Sr.No.	Oil	Solubility(mg/ml)
1	Arachise oil	8.8
2	Soyabean oil	8.9
3	Castor oil	9.2
4	Olice acid	49.23
5	Seasam oil	7.8

**Table 4: Solubility of surfactant.**

Sr.No.	Surfactant	Solubility(mg/ml)
1	Tween 20	32
2	Span 20	38
3	Tween 80	28
4	Campul PG8	18.32

**Table 5:** Solubility of co-surfactant.

Sr.No.	Co-Surfactant	Solubility(mg/ml)
1	PEG400	44
2	Ethanol	28
3	Iopylene Glycol	32
4	PEG200	30

**Table 6:** Dilution Study.

Vehicles	F1	F2	F3	F4	F5	F6
Distilled Water	Stable up to 5 h	Unclear within 30 min	Stable up to 3 h	Unclear within 30 min	Stable up to 1 h	Unclear within 30 min
0.1 N HCl	Stable up to 5 h	Unclear within 30 min	Stable up to 3 h	Unclear within 30 min	Stable up to 1 h	Unclear within 30 min
Phosphate buffer 6.8	Stable up to 5 h	Unclear within 30 min	Stable up to 3 h	Unclear within 30 min	Stable up to 1 h	Unclear within 30 min



**Table 7: Characterization of SEDDS formulations.**

Parameters		F1	F2	F3	F4	F5	F6
Drug Content (%)		97.60±2.15	87.78±2.83	92.50±1.9	90.7±1.15	89.68±2.78	73.3±2.43
Disintegration Time (Sec.)		1.23±1.1	2.23±1.2	1.49±0.9	3.5±0.35	2.13±1.2	3.23±1.44
S.E.T.(Sec.)		61±2	50±3	62±5	40±6	50±7	51±1.8
Precipitation		Stable	Stable	Unstable	Stable	Unstable	Unstable
Clarity		Turbid	Bluish	Turbid	Bluish	Bluish	Bluish
Viscosity (cps)	0 Times dilution	165	150	155	153	149	151
	10 Times dilution	1.24	1.10	1.12	1.22	1.20	1.18
	100 Times dilution	0.851	0.884	0.820	0.871	0.80	0.845

**Table 8: % Drug release for Pure drug, Marketed formulation and Optimized SEDDS in HCL Buffer pH 1.2.**

Sr. No.	Time	% Drug Released with S.D. (n=3)		
		Pure Drug	Marketed Formulation	SEDDS Formulation
1	0	0	0	0
2	5	19.93 ± 2.17	18.3 ± 0.81	50.74 ± 0.88
3	10	15.07 ± 0.81	22.89 ± 1.03	80.68 ± 1.05
4	20	25.23 ± 2.57	29.47 ± 0.67	88.53 ± 1.51
5	30	30.35 ± 2.52	37.62 ± 3.32	94.00 ± 1.30
6	45	38.54 ± 4.39	45.12 ± 2.02	96.52 ± 0.43
7	60	45.78 ± 3.91	57.96 ± 2.53	97.38 ± 0.26

**Table 9: % Drug release for Pure drug, Marketed Formulation and optimized SEDDS in Phosphate Buffer pH 6.8.**

Sr. No.	Time	% Drug Released with S.D. (n=3)		
		Pure Drug	Marketed Formulation	SEDDS Formulation
1	0	0	0	0
2	5	6.00 ± 1.22	15.59 ± 2.71	61.17 ± 3.61
3	10	11.50 ± 2.69	20.84 ± 2.39	75.53 ± 1.40
4	20	20.04 ± 2.79	28.18 ± 0.83	85.88 ± 1.84
5	30	27.24 ± 2.20	38.00 ± 3.40	91.38 ± 1.34
6	45	36.13 ± 3.27	53.54 ± 0.31	95.00 ± 2.83
7	60	45.03 ± 4.33	61.34 ± 4.77	99.79 ± 2.34

**Table 10: Stability Studies.**

Sampling Points	Disintegration time	% Drug Content	% Drug Release
0 day	1.33±1.1	95.1±1.83	96.98±2.78
15 days	1.49±0.9	94.7±2.15	95.31±3.35
30 days	2.33±1.2	93.3±2.43	93.7±2.85

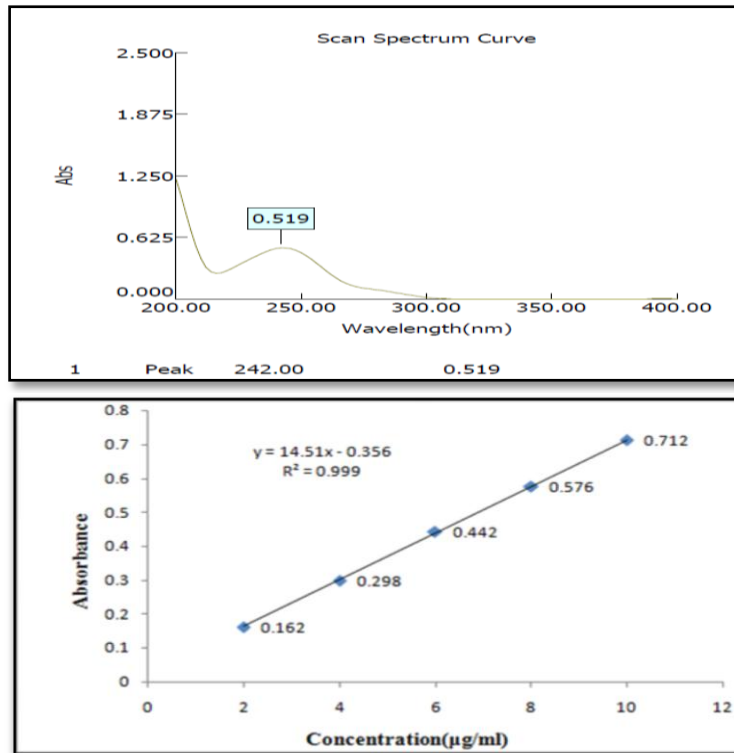


Fig. 1. UV absorbance & Calibration curve of Atorvastatin Calcium in pH 6.8 phosphate buffer

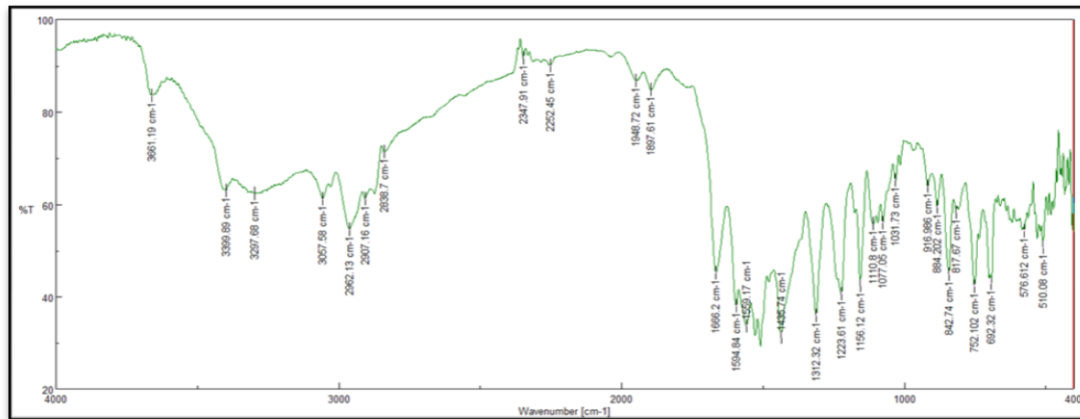


Fig. 2. FTIR Spectrum of Atorvastatin Calcium.

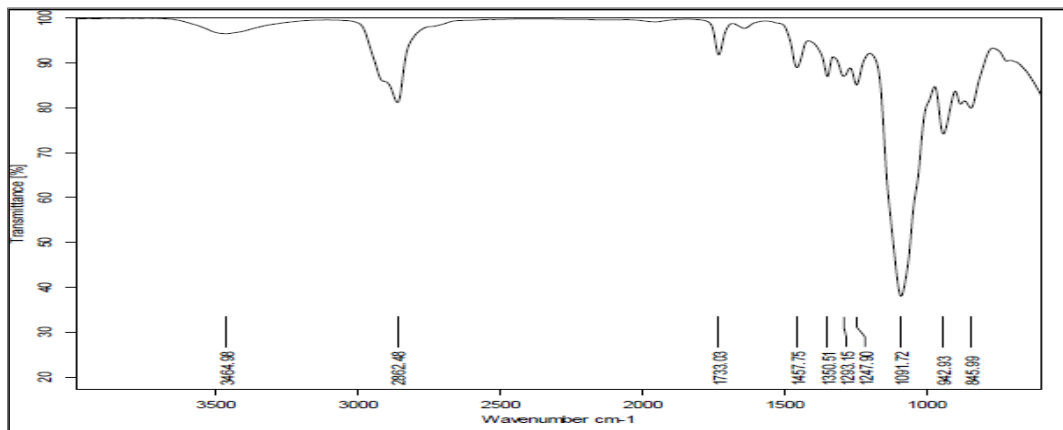


Fig. 3. FTIR of the formulation

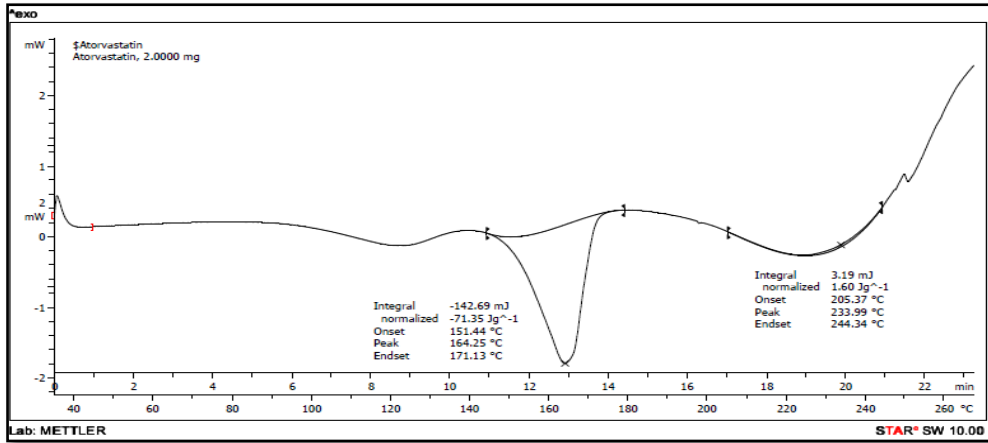


Figure 4: DSC of Atorvastatin

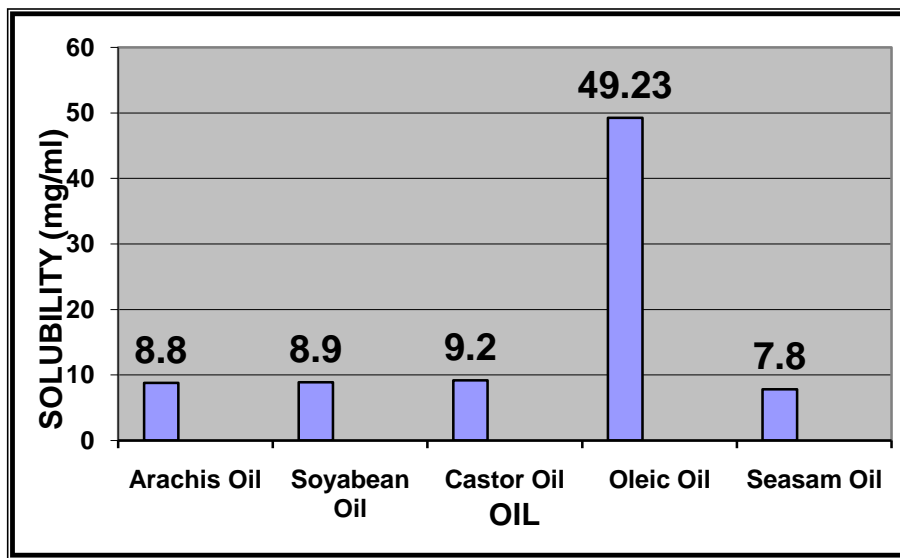


Figure 5: Solubility of Oil

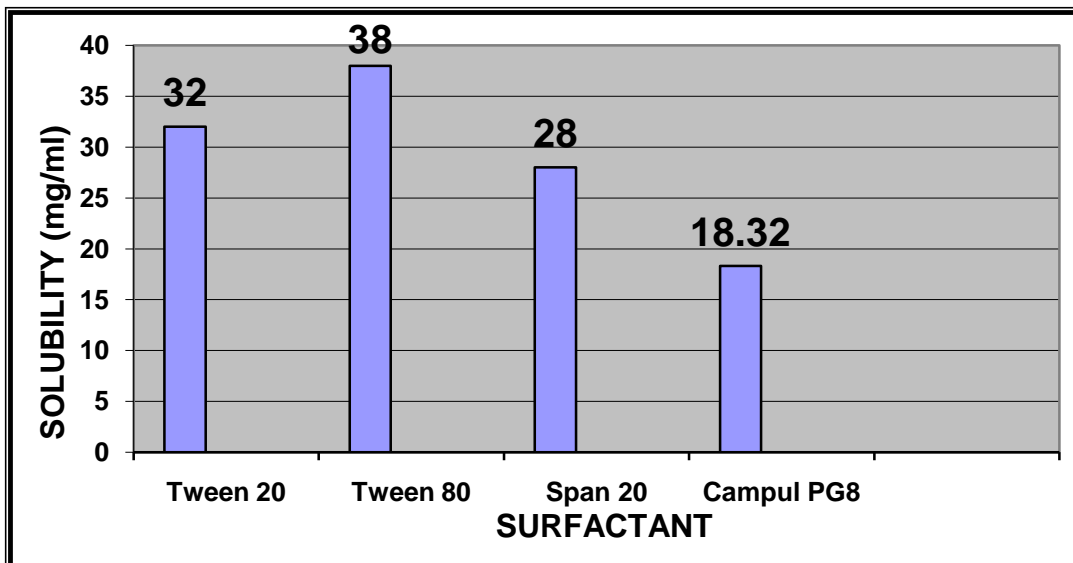


Figure 6: Solubility of Surfactant

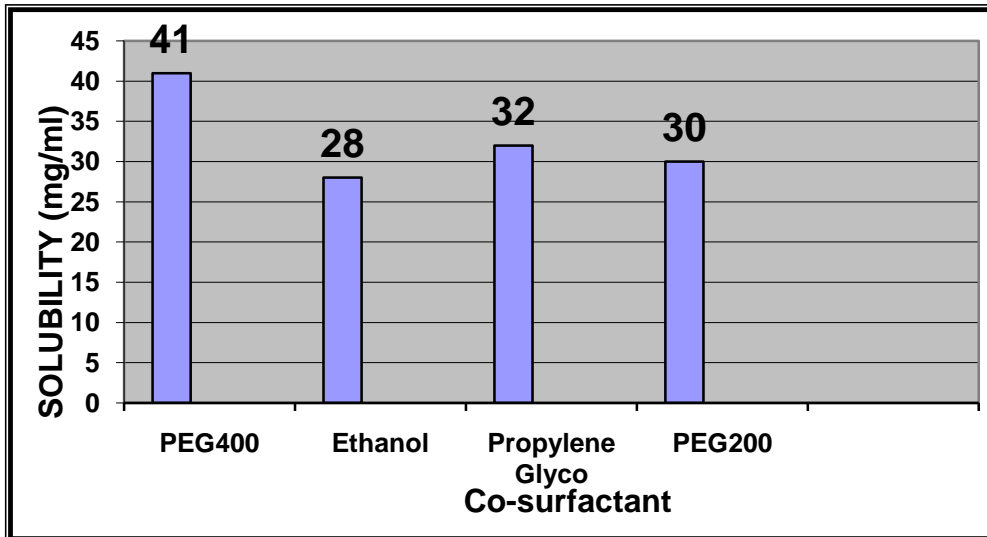


Figure 7: Solubility of Co-Surfactant.

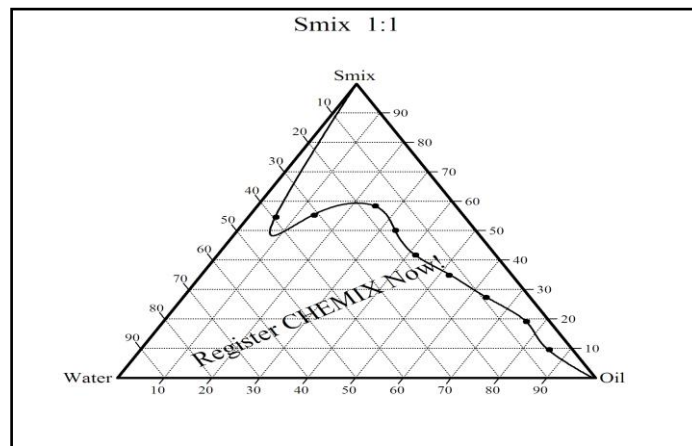


Figure 9: Pseudo ternary phase diagram, Smix 1:1

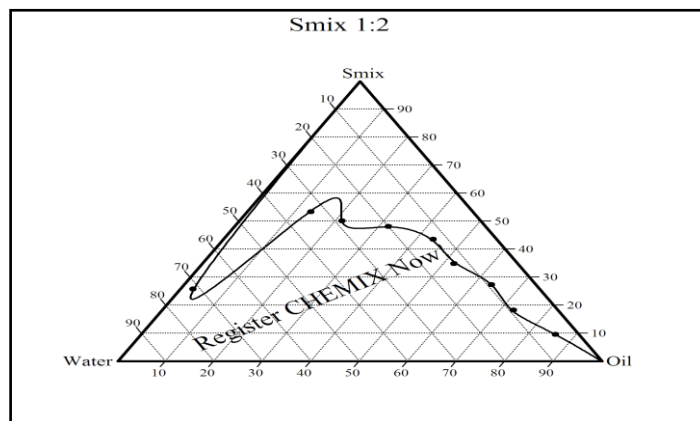


Figure 10: .Pseudo ternary phase diagram, Smix 1:2

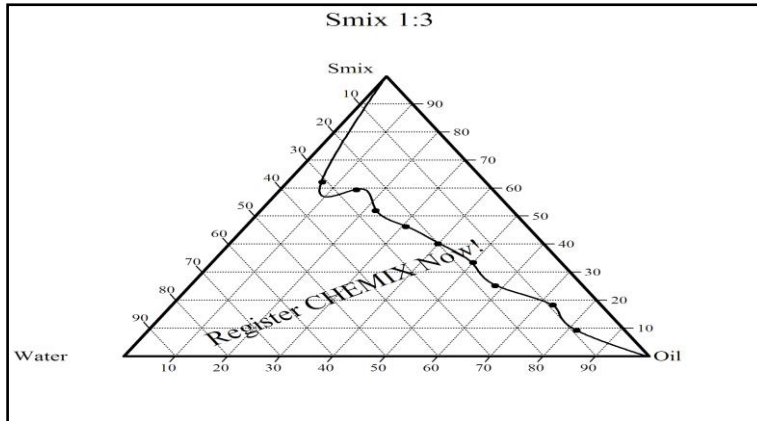


Figure 11: Pseudo ternary phase diagram, Smix 1:3

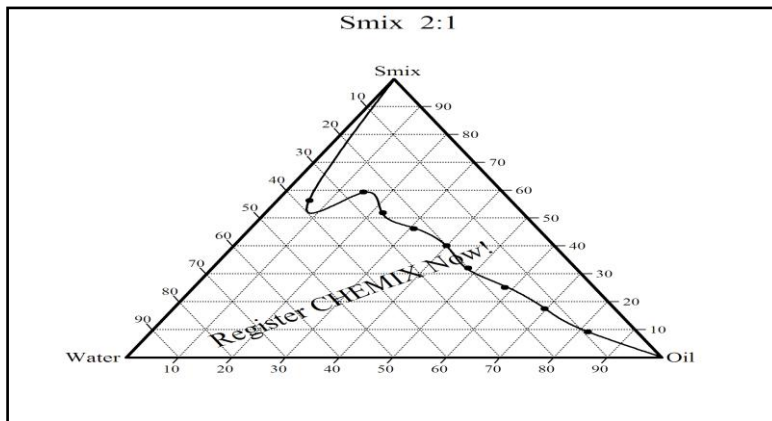


Figure 12: Pseudo ternary phase diagram, Smix 2:1

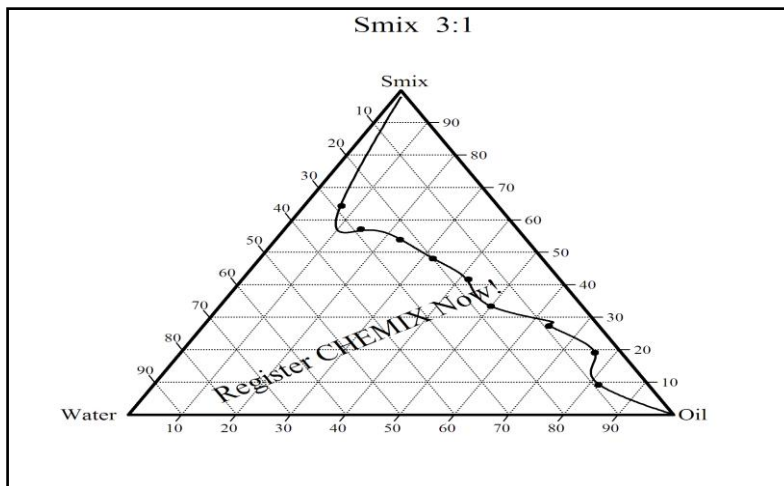
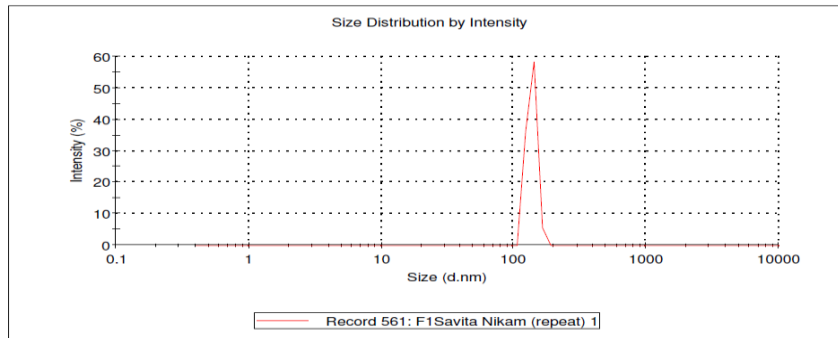


Figure 13: Pseudo ternary phase diagram, Smix 3:1

**Results**

<b>Z-Average (d.nm):</b> 518.4	<b>Peak 1:</b> 136.0	<b>Size (d.nm):</b>	<b>% Intensity</b>	<b>Width (d.nm):</b>
<b>Pdl:</b> 0.789	<b>Peak 2:</b> 0.000		100.0	11.44
<b>Intercept:</b> 1.13	<b>Peak 3:</b> 0.000		0.0	0.000
			0.0	0.000

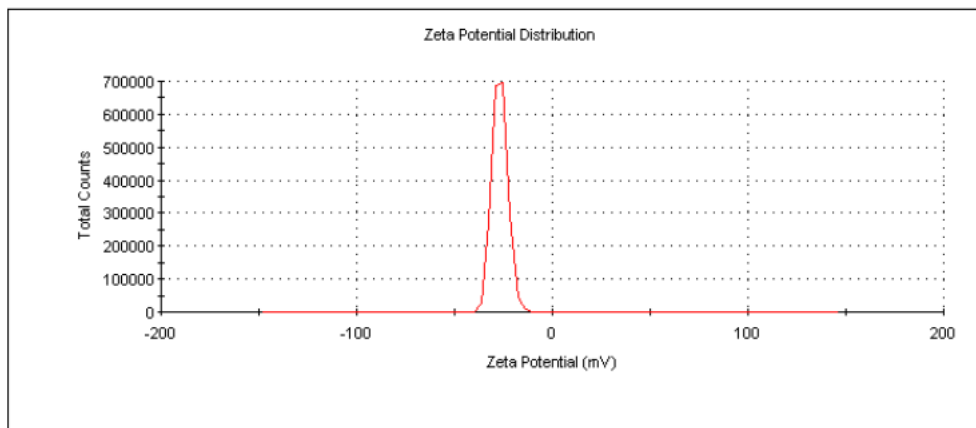
**Result quality :** Refer to quality report



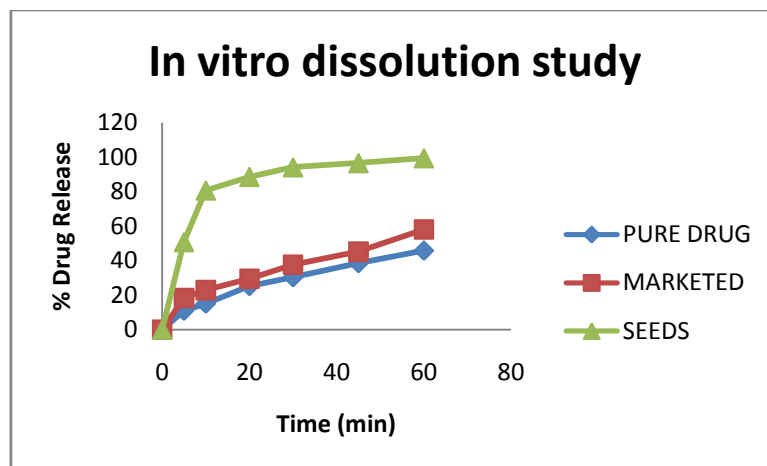
**Figure 14:** Droplet size for F1 formulation.

	<b>Mean (mV)</b>	<b>Area (%)</b>	<b>Width (mV)</b>
<b>Zeta Potential (mV):</b> -26.8	<b>Peak 1:</b> -26.8	100.0	3.86
<b>Zeta Deviation (mV):</b> 3.86	<b>Peak 2:</b> 0.00	0.0	0.00
<b>Conductivity (mS/cm):</b> 0.0309	<b>Peak 3:</b> 0.00	0.0	0.00

**Result quality :** Good



**Figure 15:** Zeta potential for F1 formulation



**Figure 16:** In Vitro release study of pure drug, Marketed Tablet and SEDDS formulation in HCL Buffer pH 1.2.

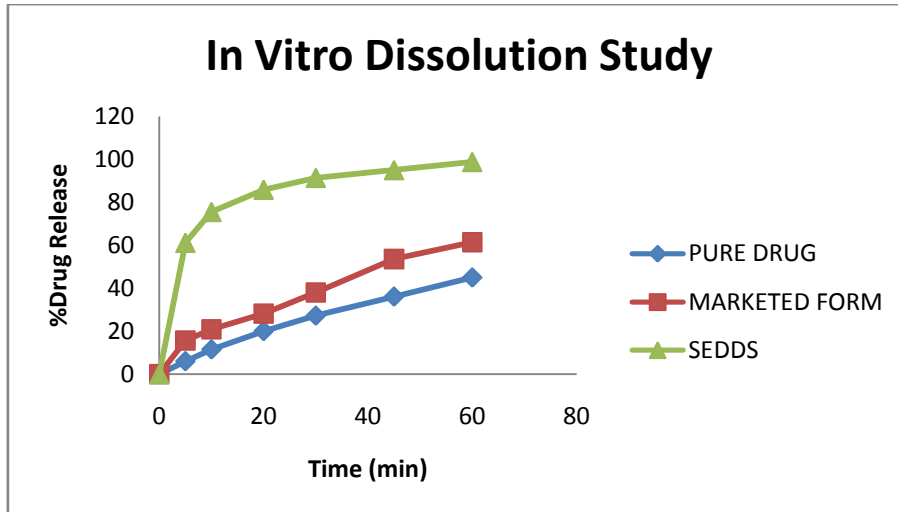


Figure 17: *In Vitro* release study of pure drug, Marketed Tablet and SEDDS formulation in Phosphate Buffer pH 6.8

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