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FORMULATION AND IN-VITRO EVALUATON OF PITAVASTATIN SELF MICRO EMULSIFIED DRUG DELIVERY SYSTEMS (SMEDDS) TO ENHANCE THE SOLUBILITY USING DIFFERENT OILS, SURFACTANTS AND COSURFACTANTS

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ABSTRACT: The current work aimed to formulate and evaluate (*In-vitro*) self-micro emulsified drug delivery (SMEDDS) of Pitavastatin using different oils, surfactants and co-surfactants to enhance the solubility of Pitavastatin which poorly water-soluble drug. Solubility studies were conducted in different oils, surfactants and co-surfactants to select oil, surfactant a co-surfactant for additional studies. L-SMEDDS have been converted into S-SMEDDS using silica gel at 1:1 ratio in China dish. Both L-SMEDDS and S-SMEDDS were characterized to assess the optimized formulations. Particle size analyzer, scanning electron microscopy (SEM), differential scanning calorimetry (DSC) and FTIR studies were performed to evaluate the physicochemical properties of S-SMEDDS and to assess the compatibility between drug with excipients which used in the formulations. Labrafil 1944 CS, Captex 200 have been selected as oils; Labrasol, Capmul MCM selected a surfactant and Peceol selected as co-surfactants for the studies based on their solubility studies. Ternary phase diagrams have been plotted using oil and Smix ratio selected as 1:1, 2:1, 3:1. Results revealed that both Labrasol 1944 CS and Captex 200 formulations shown highest emulsification ratio at 2:1 compared to 1:1, 3:1. In-vitro evaluation studies have revealed that PSF5 and TF5 have been selected as optimized formulations. In-vitro drug release study have been conducted for S-SMEDDS and revealed that PSF5 and PTF5 released 96.45±0.11 and 96.79±0.27 respectively and considered as optimized formulations.

KEYWORDS: **L-**SMEDDS, S-SMEDDS, solubility, surfactants, co-surfactants, oil

INTRODUCTION:

Most of the active pharmaceutical ingredients have grave problems of poor aqueous solubility which leads to low bioavailability upon administration (1,2). Low solubility of the drug may lead to limited dissolution rate of drug molecules and may leads to low bioavailability for administered drugs and molecules orally and may leads to limited absorption of the drug. Various techniques have been used to enhance the oral bioavailability of drugs which are poorly soluble in water (3-5).

The major, popular route of administering drug from time immemorial is the oral route for both chronic and acute dosage regimen. Unfortunately, more than 50 % of drug compounds have unfavorable physicochemical property of which high lipophilicity is the major one. Almost 40% of the new drug candidates exhibit low solubility in water which leads to poor bioavailability, high intra and inter -subject variability, and lack of dose proportionality (6). Thus, for such compounds, among numerous factors limiting bioavailability is the absorption rate from gastrointestinal lumen, this is in turn related to dissolution.

Oral route is one of the major routes of delivery of drugs for chronic treatment of most of the diseases. Oral delivery of 50% of drug molecules have thwarted because of high lipophilicity of drug molecules. Approximately 40% of the new drug entities exhibit low aqueous solubility which became a challenge in developing optimum oral dosage forms and enhance the bioavailability of new products of pharmaceuticals. To overcome these problems, many strategies have been used to modify the solubility and maintain the drug in dissolved state throughout gastric transit time (7,8). The strategies may include the addition of surfactants, cyclodextrins, salt formation, micronization process, pH changes, nanonization, solid dispersions and use of permeation enhancers (9-14).

One of the popular and recent approaches to improve the oral bioavailability of poorly water-soluble compounds are lipid-based formulations in which the drug compounds are incorporated into inert lipid vehicles such as oils and surfactant dispersions, self-emulsifying drug formulations and emulsions (15,16). SMEDDS is an emulsion-based formulations containing blend of oils, surfactants in suitable proportions which rapidly forms oil in water micro emulsion (O/W) with moderate gastric motility Many techniques have been adopted to convert liquid conventional SMEDDS into solid SMEDDS such as adsorption on to solid carrier, spray drying, melt extrusion, spray cooling, super critical fluid-based methods etc.

The present study aimed to formulate and evaluate self-micro emulsified drug delivery (SMEDDS) of Pitavastatin using different oils, surfactants and cosurfactants to enhance the solubility of poorly water soluble Pitavastatin. Pitavastatin is used to lower LDL Cholesterol and increases HDL-Cholesterol in adults.

MATERIALS AND METHODS:

Chemicals and Reagents:

Pitavastatin drug was a gift sample form Shasun Pharmaceuticals, Cuddalore, Labrafil 1944 CS, Labrasol and Peceol were obtained as gift sample from Gattefose, Captex 200, Capmul MCM form Abhitec Ingredients company, Silica gel was purchased from SD Fine chemicals. All other chemicals and reagents were of Analytical grade.

Determination of melting point:

Pitavastatin melting point was determined using the open capillary tube method using digital MP apparatus.

Solubility of Pitavastatin:

Pitavastatin Solubility was determined in different solvents like methanol, ethanol, 6.8 phosphate buffer, Dichloromethane, Dimethyl sulfoxide etc.

Fourier Transform Infra-Red Studies (FTIR):

FTIR spectra could be obtained for formulations with the pure drug and excipients used with Shimadzu FTIR spectrophotometer. The drug samples and drug with excipients samples were thoroughly blended using dry powder KBr crystals. Compressed the mixture of drug and excipients and obtained a pellet. The produced disc was placed in spectrophotometer and spectrum was recorded (17).

Differential scanning Calorimetry (DSC):

Accurately weighed Pitavastatin has analyzed using an automatic thermal analyzer system (DSC60 Shimadzu Corporation, Japan) and all the samples were runned 10^{o}C/min from 50^{o}C to 300^{o}C (18).

Determination of λmax:

Standard stock solution containing Pitavastatin was prepared by dissolving 100 mg of Pitavastatin in 10 ml of Methanol in 100 ml volumetric flask to dissolve the drug. Then the volume was made up to 100 ml using phosphate buffer of pH 6.8 to obtain a concentration of 100µg/ml. The stock solution is further diluted using a phosphate buffer pH (6.8) to prepare 10

µg/ml concentration. The resultant solution was scanned in the range of 200-400 nm in UV spectrophotometer (UV -1700 Shimadzu Corporation, Japan) to obtain absorption maximum (λmax) using phosphate buffer as blank (19).

Preparation of standard curves:

From the above prepared stock solution, solutions containing 1 to 10 µg/ml concentrations were prepared using the phosphate buffer pH 6.8 solution. The absorbances of these solutions were measured at λmax by UV-spectrophotometer (UV-1700 Shimadzu corporation Japan).

Determination of solubility of Pitavastatin:

Determined the Solubility of Pitavastatin in various oils (Capryol 90, Captex 200, Labrafil 1944 CS, Isopropyl Myristate), surfactants (tween 80, Labrasol, Transcutol P, Capmul MCM), co-surfactant (PEG 400, Peceol, Captex 500) by dissolving excess amount of Pitavastatin in 2 ml of each of oils, surfactants and co-surfactants selected in stoppered vials. The mixtures were continuously stirred by vortex mixer for 10mins and kept in the water bath shaker at 37^{o}C±0.5^{o}C for 78hrs until equilibrium was attained. The samples equilibrated were centrifuged at 3000rpm for 15mins and filtered the supernatant through 0.45µm membrane filter and diluted using suitable solvent. Determined the drug content using ultraviolet-visible spectrophotometer (20).

Screening of surfactant and co-surfactants:

300 mg of oil phase and 300 mg of surfactant / co-surfactant were weighed and vortexed for two minutes followed by warming at 40- 45^{0}C for 30 seconds. So, an isotropic mixture has been obtained. Small quantity (50 mg) of isotropic mixture was taken and diluted by distilled water which was previously filtered through 0.45µm membrane filter in a volumetric flask Number of flask inversions were observed visually to produce a clear emulsion for which transmittance was observed at 237nm (21).

Construction of pseudo ternary phase diagram:

Ternary phase diagrams were constructed with oil, surfactant/co-surfactant and water using water titration method at room temperature. The procedure consisted of preparing solutions of different ratio of surfactant to co-surfactant by weight such as 1:1, 2:1, 3:1 etc., these solutions then vortexed for 5mins and placed at 50^{o}C for one hour, so that an isotropic mixture was obtained. Each of these solutions were used for preparing a mixture containing oil and Smix (mixture of surfactant and co-surfactant) in the following ratios by weight, 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, 9:1 and after preparation vortexed for 5 mins followed by placing in oven at

50^{o} C for one hour. All the mixtures were then placed at room temperature for 24 hours.

Formulation of Liquid SMEDDS:

Formulations were prepared by preparing optimized ratio of Smix first, for this surfactant and co-surfactant were accurately weighed and then vortexed for 5-10mints. After that Smix was placed in oven at 50^{0}C for one hour. Oil with different ratio was added to Smix. Then these formulations were vortexed for 5-10mints and placed in oven at 50^{o}C for one hour so that an isotropic mixture was formed. The drug was loaded to these isotropic mixtures at the end and vortexed by vortex shaker until a clear solution was obtained (22).

CHARACTERIZATION OF LIQUID SMEDDS:

Visual assessment

Pitavastatin liquid SMEDDS were diluted with purified water (100 ml) and gently stirred with magnetic stirrer by maintaining the temperature at 37^{0} C.

Dispersibility test

The dispersibility test of SMEDDS was carried out using standard USP paddle type dissolution test apparatus, formulation was added to 500 ml of water at 37±0.5^{0}C and the paddle was rotated at 50 rpm.

Determination of self-emulsification time:

The emulsification time of SMEDDS was determined by adding one ml of formulation drop wise to 500 ml distilled water at 37±0.5^{o} C with agitation using dissolution paddle rotating at 50 rpm.

Heating cooling cycle

The optimized SMEDDS formulations were diluted with 100 times distilled water. Six cycles between cooling temperature (4^{o}C) and heating temperature (45^{o}C) with exposure at each temperature for not less than 48 hours were carried.

Centrifugation

Optimized SMEDDS formulations were diluted with 100 times distilled water and centrifuged at 3500rpm for 30 mins.

Freeze thaw cycle

In this study three freeze thaw cycle formulations were exposed between temperatures 21^{o}C-25^{o}C for each temperature cycle not more than 48 hours. For the better estimation six such cycles ran for each batch of formulation (23).

Cloud point measurement:

Dilute the formulation 1 ml with 1000 ml of water in beaker and place it in a water bath with gradually increasing the temperature until the diluted formulation turned to cloudy or turbid.

Robustness to dilution:

Robustness to dilution was studied by diluting SMEDDS to 50, 100, 1000 times with water, phosphate buffer pH 6.8, phosphate buffer pH 7.4. The diluted SMEDDS were stored for 12 hours and observed for any signs of phase separation or drug precipitation.

Refractive index and percent transmittance:

The refractive index was measured using Abbes refractometer. The percent transmittance of the system was measured at wavelength using UV-spectrophotometer keeping distilled water as blank. Stability of micro emulsion formulation with respect to dilution was checked by diluting one ml of formulation with 100 ml of distilled water and measuring transmittance using U-V Spectrophotometer. Transmittance of samples was measured at 638 nm.

Viscosity determination:

The rheological properties of the micro emulsion are evaluated by Ostwald viscometer. Viscosity determinations confirm whether the system was w/o or o/w. If a system has low viscosity, then it is o/w type of the system and if high viscosities then it is w\o type of the system (25).

Absolute drug content in L-SMEDDS:

Liquid SMEDDS containing Pitavastatin, equivalent to 4 mg, was diluted in suitable quantity of methanol. The sample was mixed thoroughly to dissolve the drug in methanol by stirring. The solvent extract is filtered through 0.45 µm membrane filter. Drug content was determined by measuring the absorbance in UV spectrophotometer against the standard solution of drug (26).

Conversion of liquid SMEDDS into solid S-SMEDDS:

Solid SMEDDS were prepared by mixing liquid SMEDDS containing Pitavastatin with silica gel at 1:1 proportion. Liquid SMEDDS was added drop wise over MCC and homogenized using glass rodto ensure uniform distribution in a China dish.

Physiochemical characterization of SMEDDS:

Micromeritic properties:

Prepared solid- SMEDDS were evaluated for micromeritic properties such as angle of repose, bulk density and tapped density, compressibilityindex and Hausner's ratio (27).

a) Angle of Repose

Angle of Repose is defined as the maximum angle possible between the surface of the pile of powder and horizontal plane. Angle of repose has been used as indirect methods of quantifying powder flow ability, because of their relationship with inter particle cohesion.

Angle of Repose (ø) = tan $^{-1}$ (h / r), Where h = height of the heap, r = radius of the heap

b) Bulk Density:

Apparent bulk density is determined by pouring the weighed granules into a graduated cylinder via funnel and measuring the volume.

c) Tapped Density:

A known quantity of sample was transferred to a graduated cylinder and placed on tapped density apparatus and operated for a fixed number of taps (100). It is the ratio of weight of sample to tapped volume.

Tapped density = Weight of the powder (W)

Tapped volume of powder Vf

d) Compressibility (or) Carr's index:

Based on the apparent bulk density and the tapped density, the percentage compressibility of the bulk drug is studied by using

$$\text{Carr's index (\%)} = \frac{\text{Tapped density - bulk density}}{\text{Tapped density}} \times 100$$

e) Hausner's ratio:

Hausner's ratio is defined as the ratio of tapped density to bulk density of the powders. The Hausner's ratio is a number that is correlated to the flow ability of a powder (or) granular material.

Drug content:

The S-SMEDDS containing Pitavastatin, equivalent to 4 mg was diluted in suitable quantity of methanol and sonicated for 10-15 mins. Then it was filtered through a 0.45µm membrane filter. Drug content was analyzed by measuring absorbance using UV spectrophotometer (28).

***In-vitro* drug release from S-SMEDDS:**

The *in-vitro* drug release of prepared S-SMEDDS was assessed in triplicate using United States Pharmacopoeia (USP) Dissolution Type II apparatus (Paddle type) at 37±0.5^{o}C. S-

SMEDDS containing 4 mg equivalent of drug was placed in 900 ml of dissolution medium (phosphate buffer pH 6.8with methanol in 9:1 ratio). The revolution speed of the paddle was maintained at 100 rpm (29). At predetermined time intervals, 5 ml of dissolution medium was collected, filtered and the same volume of fresh dissolution medium was replenished to maintain the sink conditions. The samples were analyzed for the drug concentration using UV-VIS spectrophotometer at 245nm.

RESULTS AND DISCUSSIONS:

Determination of solubility:

The solution of Pitavastatin in various vehicles was screened and the results were presented in **table 1** and **figure 1**. Pitavastatin had significantly higher solubility in Labrafil 1944 CS (96.59±0.22%) and Captex 200 (90.44±0.30%). Among surfactant and co-surfactants, Labrasol (91.34±0.19%), Capmul MCM (91.68±0.37%), Peceol (92.14±0.42%) showed highest solubility.

Table 1: Solubility of Pitavastatin in various Vehicles

S.NO	VEHICLE	SOLUBILITY (%)
1	Capryol 90	77.76±0.22
2	Captex 200	90.44±0.30
3	Labrafil 1944 CS	96.59±0.22
4	Isopropyl Myristate	36.78±0.35
5	Tween 80	45.41±0.27
6	Labrasol	91.34±0.19
7	Transcutol P	60.09±0.42
8	Capmul MCM	91.68±0.37
9	PEG 400	88.73±0.19
10	Propylene Glycol	69.79±0.76
11	Peceol	92.14±0.42
12	Captex 500	74,69±0.58

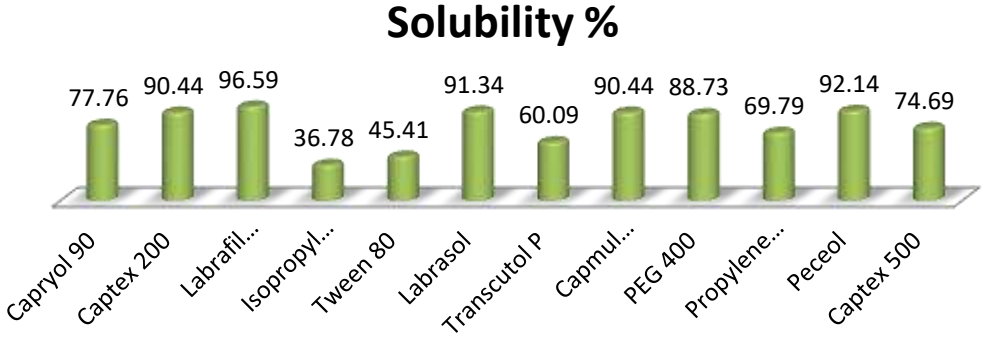

Figure 1: Solubility of Pitavastatin in various Oils

Construction of Pseudo ternary phase diagram:

The micro emulsion region was determined by plotting data in pseudo ternary phase diagram. The selected oil, surfactants and co-surfactants were used to formulate micro emulsion. Nine different combinations of oil and Smix were selected to construct phase diagram for two types of formulation (castor oil and Capryol 90). The ratio of Smix was selected as 1:1, 2:1, 3:1. The diagrams are depicted in **figure 2A, 2B, 2C and 3A, 3B, 3C.** Figures show that castor oil formulation with Smix ratio of 2:1 had more emulsification area compared to Smix ratio of 1:1 and 3:1. And for the Capryol 90 formulation Smix ration of 3:1 had more emulsification area compared to 1:1 and 2:1.

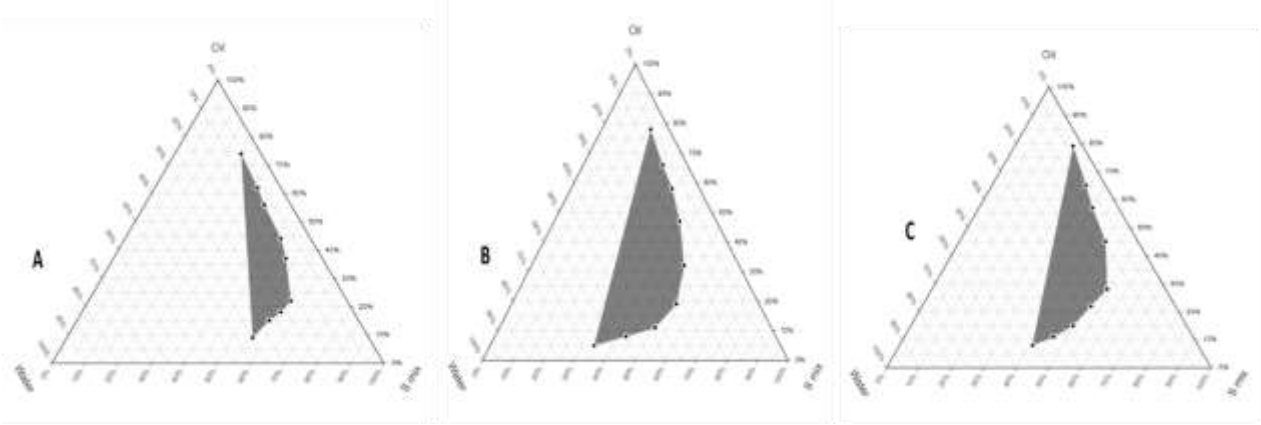

Figure2a, 2b, 2c: Ternary Phase Diagrams 1:1, 2:1, 3:1 ratio with Labrafil 1944 CS

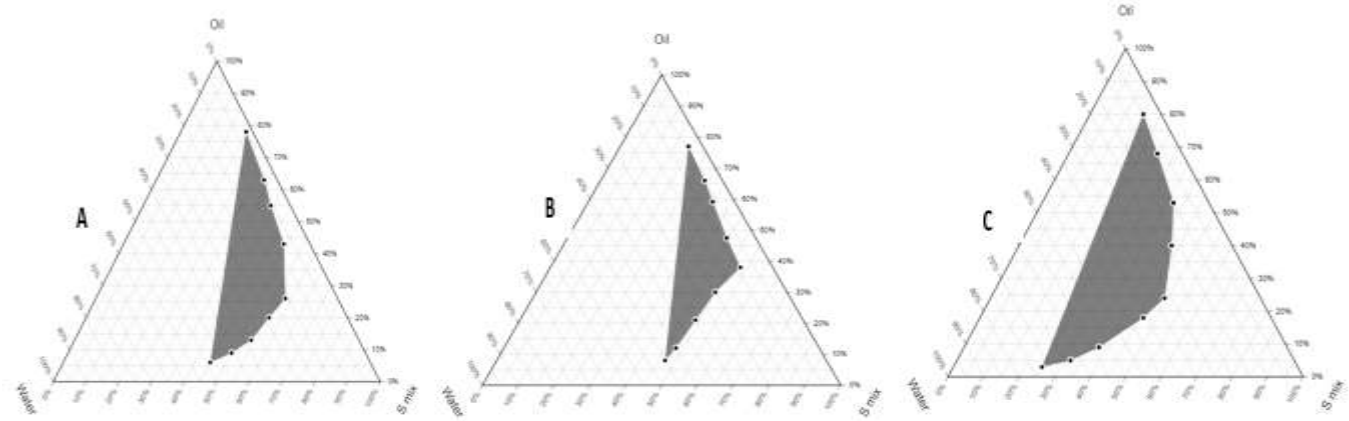

Figure 3a, 3b, 3c: Ternary Phase Diagrams 1:1, 2:1, 3:1 ratio with Captex 200

FORMULATION OF LIQUID SMEDDS:

Based on the pseudo ternary phase diagrams, the formulation with the best self-emulsifying properties, containing Labrafil 1944 CS with Smix of Labrasol and Peceol; and Captex 200 with Smix of Capmul MCM and Peceol were formulated with varying ratios of oil, surfactant and

co-surfactant.

CHARACTERIZATION OF LIQUID SMEDDS:

Dispersibility test and Visual assessment

Pitavastatin liquid SMEDDS was diluted with purified water (100 ml) and gently stirred with magnetic stirrer and maintained at 37^0 C. The results were represented in Table 2.

Table2: Dispersibility Test and Visual Assessment of SMEDDS Formulation

CODE NO.	DISPERSIBILITY AND APPEARANCE	S E TIME	GRADE
PSF1	Clear	Within 2 mints	B
PSF2	Dull	Within 3 mints	D
PSF3	Transparent	Within 2 mints	B
PSF4	Dull	Within 1 mint	C
PSF5	Clear and Transparent	Within1 mint	A
PSF6	Dull	Within 3 mints	C
PSF7	Transparent	Within 2 mints	B
PSF8	clear	Within 2 mints	B
PSF9	clear	Within 1 mint	A
PTF1	Transparent	within 2 mints	B
PTF2	Dull	within 3 mints	C
PTF3	Transparent	within 2 mints	B
PTF4	Dull	within 4 mints	D
PTF5	Clear and transparent	within 1 mint	A
PTF6	Dull	within 4 mints	D
PTF7	Clear	within 2 mints	C
PTF8	Clear	within 1 mint	A
PTF9	Transparent	within 2 mints	B

Thermodynamic stability studies:

SMEDDS are thermodynamically stable systems and are formed at a particular concentration of oil, surfactant and water, with no phase separation, creaming or cracking. Those formulations, which survived thermodynamic stability tests, were taken for further studies. It was observed that formulations PSF2, PSF4, PSF6, PTF2, PTF4 and PTF6 did not pass the thermodynamic stress tests and thus were dropped for further study. The results are shown in Table 3.

Table 3: Thermodynamic Stability Assessment of Labrafil 1944 CS & Captex 200 SMEDDS

Formulation	Heating cooling cycle	Centrifugation	Freeze thaw cycle
PSF1	√	√	√
PSF2	×	×	×
PSF3	×	×	×
PSF4	×	×	×
PSF5	√	√	√
PSF6	×	×	×
PSF7	√	×	×

PSF8	√	×	√
PSF9	√	√	√
PTF1	√	√	√
PTF2	×	×	×
PTF3	×	×	√
PTF4	×	×	×
PTF5	√	√	√
PTF6	×	×	×
PTF7	√	×	√
PTF8	√	√	√
PTF9	×	√	√

√ - Passed × - Failed

Cloud point measurement:

It gives information about the stability of micro emulsion at body temperature. The results were represented in **table 4.**

Table 4: MEASUREMENT OF CLOUD POINT

S.NO	FORMULATION	CLOUD POINT (^{O} C)	FORMULATION	CLOUD POINT (^{O} C)
1	PSF1	88	PTF1	88
2	PSF2	UNSTABLE	PTF2	UNSTABLE
3	PSF3	86	PTF3	84
4	PSF4	UNSTABLE	PTF4	UNSTABLE
5	PSF5	85.5	PTF5	86.5
6	PSF6	UNSTABLE	PTF6	UNSTABLE
7	PSF7	87	PTF7	88
8	PSF8	86	PTF8	86
9	PSF9	88	PTF9	89

Robustness to dilution:

After diluting SMEDDS to 50, 100 and 1000 times with water, buffer pH 7.4 and pH 6.8 and storing for 12hrs, it was observed that there was no sign of phase separation or drug precipitation in formulations except in few formulations and results were shown in Table 5.

Table 5: Results of Robustness to Dilution

S.No	MEDIUM	PHASE SEPARATION								
		PSF1	PSF2	PSF3	PSF4	PSF5	PSF6	PSF7	PSF8	PSF9
1	Distilled water	No	No	No	No	No	No	No	No	No
2	Phosphate buffer pH 6.8	No	No	No	No	Yes	No	No	No	No
3	Phosphate buffer pH7.4	No	No	Yes	No	Yes	No	No	Yes	No

		PTF1	PTF2	PTF3	PTF4	PTF5	PTF6	PTF7	PTF8	PTF9
4	Distilled water	No	No	No	No	No	No	No	No	No
5	Phosphate buffer pH 6.8	Yes	No	Yes	No	Yes	Yes	No	No	Yes
6	Phosphate buffer pH7.4	No	No	Yes	No	Yes	No	No	Yes	No

Refractive index and percent transmittance:

The results of Refractive index and percentage Transmittance were shown in Table 6.

Table 6: Refractive Index and % Transmittance Values

S.No	Formulation	RI Value	Transmittance	Formulation	RI Value	Transmittance
1	PSF1	1.345±0.0007	68.78±0.31	PTF1	1.336±0.0009	88.59±0.32
2	PSF2	UNSTABLE	UNSTABLE	PTF2	UNSTABLE	UNSTABLE
3	PSF3	UNSTABLE	83.24±0.25	PTF3	1.337±0.0007	83.52±0.41
4	PSF4	UNSTABLE	UNSTABLE	PTF4	UNSTABLE	UNSTABLE
5	PSF5	1.343±0.0002	95.68±0.35	PTF5	1.342±0.0006	96.42±0.28
6	PSF6	UNSTABLE	UNSTABLE	PTF6	UNSTABLE	UNSTABLE
7	PSF7	1.342±0.0005	88.57±0.19	PTF7	1.331±0.0005	80.10±0.21
8	PSF8	1.341±0.0006	79.69±0.31	PTF8	1.339±0.0004	73.58±0.29
9	PSF9	1.340±0.0007	90.37±0.41	PTF9	1.338±0.0009	84.49±0.08

Viscosity determination:

Out of 18 formulations, PSF5 and PTF5 show optimum viscosity due to optimum concentration of oil, surfactant and co-surfactant. The results were shown in table 7.

Table 7: Viscosity Measurement of SMEDDS

S. No	Formulation	Viscosity (cps)	Formulation	Viscosity (cps)
1	**PSF1**	0.6321±0.008	**PTF1**	0.6542±0.013
2	**PSF3**	0.6352±0.005	**PTF2**	0.6473±0.006
3	**PSF5**	0.6259±0.011	**PTF4**	0.6499±0.011
4	**PSF7**	0.6198±0.004	**PTF7**	0.6377±0.010
5	**PSF8**	0.6307±0.007	**PTF8**	0.6416±0.007
6	**PSF9**	0.6318±0.005	**PTF9**	0.6509±0.016

Absolute drug content in L-SMEDDS & S-SMEDDS:

The results were represented in Table 8 and figure 4a, 4b, 4c and 4d. From the results, formulations PSF5 & PTF5 showed the highest drug content amongst all the other formulations.

Table 8: Drug content determination in L-SMEDDS & S-SMEDDS

Drug content determination in L-SMEDDS				
S.No.	Formulation	Drug Content (%)	Formulation	Drug Content (%)
1	**PSF1**	95.46±0.11	**PTF1**	95.93±0.09

2	**PSF2**	93.74±0.09	**PTF2**	94.31±0.12
3	**PSF3**	95.86±0.07	**PTF3**	93.16±0.08
4	**PSF4**	95.89±0.16	**PTF4**	93.75±0.21
5	**PSF5**	98.19±0.08	**PTF5**	97.59±0.19
6	**PSF6**	95.04±0.19	**PTF6**	93.71±0.27
7	**PSF7**	94.72±0.08	**PTF7**	94.68±0.41
8	**PSF8**	95.17±0.15	**PTF8**	95.26±0.19
9	**PSF9**	93.68±0.06	**PTF9**	95.49±0.22
Drug content determination in S-SMEDDS				
1	**PSF1**	94.97±0.09	**PTF1**	94.79±0.13
2	**PSF2**	94.09±0.18	**PTF2**	94.65±0.06
3	**PSF3**	95.43±0.21	**PTF3**	93.98±0.15
4	**PSF4**	96.01±0.07	**PTF4**	94.04±0.11
5	**PSF5**	98.27±0.42	**PTF5**	98.04±0.26
6	**PSF6**	94.74±0.36	**PTF6**	94.11±0.19
7	**PSF7**	95.23±0.10	**PTF7**	94.99±0.32
8	**PSF8**	95.58±0.18	**PTF8**	95.87±0.18
9	**PSF9**	94.22±0.14	**PTF9**	95.69±0.27

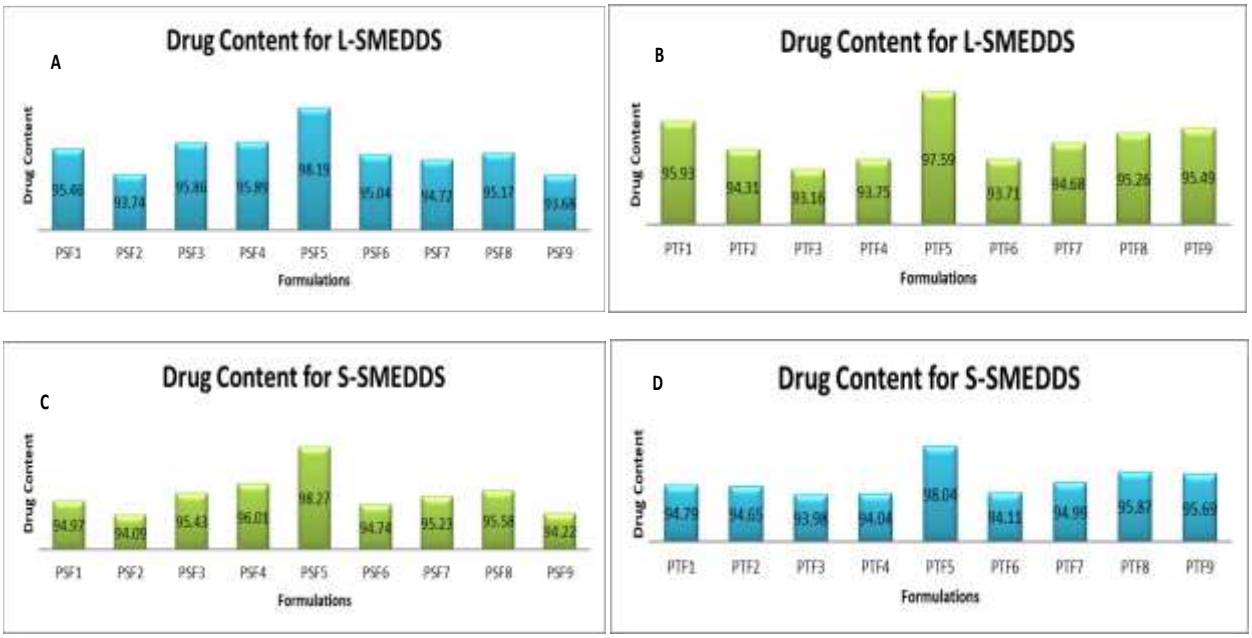

Figure 4: Drug content of - L-SMEDDS (4a & 4b) and S-SMEDDS (4c & 4d)

Characterization of S-SMEDDS:

a) Micromeritic properties:

Angle of Repose

The angle of repose for the best formulation (PSF5 and PTF5) was 26°54' and 28º38' respectively. The results suggested that the powder blend of formulation showed good flow

properties. The results of angle of repose of formulations were shown in **table 9.**

Bulk density

The bulk densities for the best formulations (PSF5 and PTF5) were 0.3441±0.004g/ml and 0.3439±0.012g/ml. The results indicated that the powder blends of formulation had good flow properties. The results were summarized in **table 9.**

Tapped density

Tapped densities for the best formulations (PSF5 and PTF5) 0.4029±0.007g/ml and 0.4035±0.0013g/ml respectively. The results were summarized in **table 9.**

Carr's index

The Carr's index of the best formulations (PSF5 and PTF5) was found to be 14.60±0.007% and 14.77±0.001%, indicating that the powder blend was excellent. The results were summarized in **table 9.**

Hausner's ratio:

The Hausner ratio of the best formulations (PSF5 and PTF5) were found to be 1.17±0.005 and 1.17±0.006. The results were summarized in **table 9.**

Table 9: Micromeritic Characterization of SMEDDS

Parameter	**PSF1**	**PSF2**	**PSF3**	**PSF4**	**PSF5**	**PSF6**	**PSF7**	**PSF8**	**PSF9**
Angle of Repose	27°19'± 0°14'	28°49'± 0°26'	27°56'± 0°45'	28°48'± 0°38'	26°73'± 0°29'	28°62'± 0°25'	27°51'± 0°17'	27°39'± 0°17'	27°86' ± 0°31'
Bulk density g/ml	0.3339± 0.009	0.3402± 0.015	0.3412± 0.017	0.3410± 0.023	0.3469± 0.011	0.3398± 0.009	0.3414± 0.020	0.3476± 0.016	0.3488± 0.019
Tapped density	0.3997 ± 0.009	0.3988 ± 0.013	0.4072 ± 0.008	0.4086 ± 0.016	0.4034 ± 0.014	0.4076 ± 0.012	0.3999 ± 0.008	0.4029 ± 0.013	0.4009 ± 0.020
Carr's index %	15.15 ± 0.008	15.26 ± 0.011	15.18 ± 0.003	15.21 ±0.005	15.08 ±0.007	15.23 ±0.021	15.19 ±0.017	15.22 ±0.009	15.17 ±0.015
Hausner's Ratio	1.19 ±0.022	1.18 ±0.027	1.17 ±0.018	1.18 ±0.026	1.16 ±0.009	1.18 ±0.014	1.19 ±0.018	1.18 ±0.025	1.18 ±0.019
	EBT1	**EBT2**	**EBT3**	**EBT4**	**EBT5**	**EBT6**	**EBT7**	**EBT8**	**EBT9**
Angle of Repose	26o94± 0029'	27o22± 0037'	27o19± 0043'	27013± 0019'	26o25± 0033'	27o37± 0056'	27o43± 0028'	27o38'± 0015'	27o26± 0061'
Bulk Density g/ml	0.3387 ±0.012	0.3436 ± 0.021	0.3496 ± 0.017	0.3387 ± 0.011	0.3405 ± 0.008	0.3467 ± 0.031	0.3459 ±0.0018	0.3473 ± 0.033	0.3455 ±0.009
Tapped Density	0.4067 ± 0.007	0.4019 ± 0.011	0.4058 ± 0.016	0.4064 ± 0.009	0.4009 ± 0.018	0.4055 ± 0.003	0.4049 ± 0.022	0.4024 ± 0.015	0.4051 ± 0.008

Carr's index %	15.23 ± 0.009	15.33 ± 0.011	15.19 ± 0.017	15.34 ± 0.005	15.03 ± 0.006	15.24 ± 0.023	15.18 ± 0.019	15.35 ± 0.027	15.27 ± 0.004
Hausner's Ratio	1.19 ±0.08	1.19 ±0.06	1.18 ±0.08	1.19 ±0.06	1.17 ±0.05	1.18±0.07	1.19 ±0.06	1.18 ±0.11	1.18 ±0.05

***In vitro* drug release from S-SMEDDS:**

The results of *in-vitro* drug release studies from Pitavastatin SMEDDS formulation were represented in Table 10 and figure 5a, 5b, 5c & 5d.

Formulation PSF5 and PTF5 shown the highest percentage drug release of 96.45±0.11% and 96.79±0.27% at the end of two hours respectively.

Table 10: In-vitro Drug Release Studies of S-SMEDDS

Time	**Cumulative % Drug Release**								
	PSF1	**PSF2**	**PSF3**	**PSF4**	**PSF5**	**PSF6**	**PSF7**	**PSF8**	**PSF9**
0	0	0	0	0	0	0	0	0	0
5	65.13±0.38	64.21±0.23	65.79±0.26	66.72±0.34	71.67 ± 0.54	68.16±0.45	66.14±0.42	69.58±0.27	68.52±0.16
10	69.73±0.21	67.52±0.44	68.47±0.31	69.31±0.19	74.34 ± 0.31	70.54±0.17	69.37±0.26	72.48±0.31	71.07±0.27
20	73.19±0.09	72.77±0.30	72.98±0.08	71.17±0.28	78.57 ± 0.08	74.73±0.23	72.56±0.18	74.72±0.07	74.59±0.35
30	76.47±0.11	76.64±0.22	74.75±0.22	73.49±0.32	82.59±0.21	77.58±0.40	75.96±0.47	76.08±0.22	77.86±0.06
45	79.54±0.43	78.25±0.18	78.59±0.36	78.06±0.26	85.46±0.34	80.30±0.05	78.39±0.04	79.14±0.05	80.16±0.22
60	82.61±0.52	82.19±0.36	81.52±0.11	81.99±0.07	88.38±0.29	83.18±0.26	81.63±0.13	82.29±0.27	84.30±0.34
80	85.41±0.36	84.79±0.09	84.76±0.23	85.38±0.12	91.76±0.26	86.72±0.33	84.06±0.08	85.67±0.15	86.29±0.22
100	89.42±0.23	87.08±0.53	88.48±0.32	89.52±0.38	93.42±0.37	89.95±0.54	88.83±0.36	89.39±0.31	89.44.±0.38
120	92.55±0.05	90.57±0.29	92.91±0.19	91.63±0.47	96.45±0.11	91.06±0.25	92.29±0.33	93.06±0.06	92.64±0.03
	EBT 1	**EBT 2**	**EBT 3**	**EBT 4**	**EBT 5**	**EBT 6**	**EBT 7**	**EBT 8**	**EBT 9**
0	0	0	0	0	0	0	0	0	0
5	66.34±0.52	65.23±0.19	66.02±0.08	67.61±0.16	72.17 ± 0.18	67.55±0.24	67.02±0.39	68.95±0.50	68.23±0.22
10	70.15±0.56	68.08±0.32	69.17±0.17	70.26±0.46	76.28 ± 0.57	70.02±0.31	70.13±0.14	71.36±0.29	70.99±0.34
20	73.98±0.22	71.59±0.26	73.48±0.72	72.15±0.19	80.30 ± 0.11	74.67±0.40	73.31±0.12	75.17±0.19	75.67±0.19

30	77.55±0.33	75.47±0.41	75.69±0.35	76.39±0.04	83.13±0.39	78.09±0.38	76.55±0.36	77.62±0.27	78.51±0.23
45	80.38±0.65	78.39±0.29	78.41±0.27	79.79±0.38	86.49±0.52	81.54±0.67	79.29±0.18	80.09±0.38	81.32±0.39
60	83.09±0.71	81.97±0.07	82.46±0.45	82.44±0.31	89.04±0.35	84.33±0.39	82.14±0.44	83.14±0.30	84.89±0.43
80	86.17±0.14	85.16±0.18	85.19±0.08	86.07±0.27	92.58±0.48	87.15±0.15	85.93±0.54	86.59±0.08	87.12±0.21
100	89.42±0.56	87.49±0.38	89.92±0.26	89.96±0.04	94.73±0.16	89.60±0.43	89.67±0.28	90.22±0.27	90.05±0.45
120	92.12±0.19	89.85±0.18	92.06±0.44	91.13±0.33	96.79±0.27	90.52±0.59	91.86±0.19	92.16±0.19	93.01±0.12

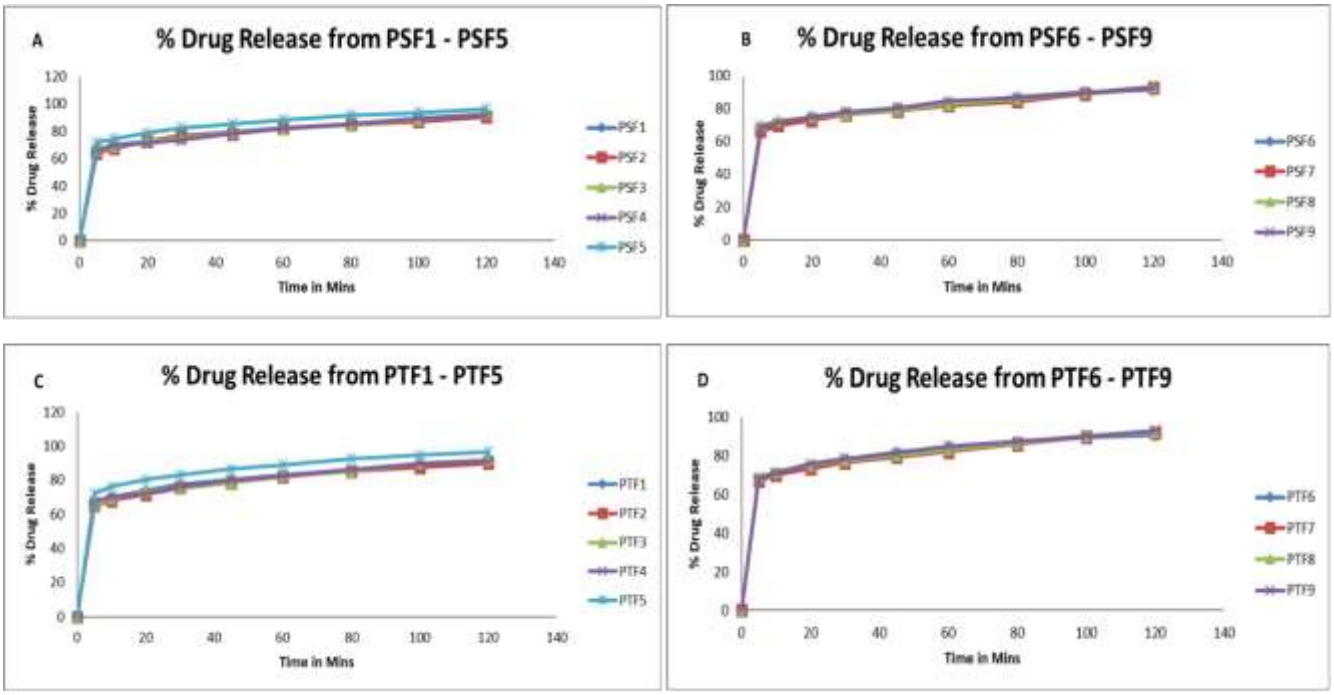

Figure 5: *In vitro* drug release_ A-PSF1-PSF5; B-PSF6-PSF9; C-PTF1-PTF5; D-PTF6-PTF9

CONCLUSION:

Different formulations were prepared using Pitavastatin, oils, surfactants and co-surfactants. Optimized formulations PSF5 and PTF5 were selected and showed increased solubility, dissolution rate and bioavailability. The dissolution profiles of all the formulations showed a drug release of greater than 75% of drug release in 120mins. Among all formulations PSF5 and PTF5 have released drug 96.45% & 96.79%. Thus, our study confirmed that the SMEDDS formulations can be potentially used as an alternative to the traditional oral formulations for the poorly soluble drugs like Pitavastatin to improve its solubility and dissolution.

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