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DESIGN & DEVELOPMENT OF NOVEL LIPID BASED CARRIER SYSTEM FOR DELIVERY OF PITAVASTATIN CALCIUM

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Keywords:

SMEDDS, Pitavastatin calcium, self-emulsification region, Smix, Pseudo ternary phase diagram

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ABSTRACT: The aim of this work is to prepare self-micro-emulsifying drug delivery system (SMEDDS) for oral bioavailability enhancement of a poorly water soluble drug, Pitavastatin. Solubility of Pitavastatin was determined in various vehicles. SMEDDS is mixture of surfactants, oils and co-surfactants, which are emulsified in aqueous media under conditions of digestive motility and gentle agitation that would be take place in the gastro-intestinal (GI) tract. Pseudo-ternary phase diagrams were made to detect the efficient self-emulsification region and particle size distributions of the resulting micro-emulsions were resolute using a laser diffraction sizer. Optimized formulations for in vitro dissolution and bioavailability assessment were Capmul PG 8, Tween 80 and Transcutol P. The release rate of Pitavastatin from SMEDDS have significantly higher than the conventional tablet. These suggest the superiority of prepared SMEDDS of Pitavastatin calcium for *In-vitro* drug release that may further in enhancement of bioavailability. Our studies illustrated the prospective use of SMEDDS for the delivery of hydrophobic compounds, such as Pitavastatin by the oral route.

INTRODUCTION: Pitavastatin calcium is a novel, deliberately-engineered HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme A) reductase inhibitor with a novel synthetic cyclopropyl group. The synthetic cyclopropyl group binds tightly to HMG-CoA reductase, allowing it to constrain cholesterol synthesis to the same degree as atorvastatin, simvastatin and pravastatin, but at a several-fold lower dose. [1]

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Pitavastatin thereby offers a highly effective low-dose alternative to other statins. It falls in BCS class II hence, it required enhancement of solubility to become bioavailability of Pitavastatin calcium. [2-3] Many approaches have been explored for the delivering poorly soluble drug candidates; viz particle size reduction, co-precipitation, using wetting agents and preparation of solid dispersion etc. [4-5] Various lipid based formulation were developed to improve the solubility and bioavailability of poorly water soluble drug. [6-7]

Amongst many such options, surfactant dispersion, emulsions and liposomes; self-micro emulsifying drug delivery systems (SMEDDS) is one of the promising approach.[8-9]

Self-micro emulsifying drug delivery systems (SMEDDS) are isotropic, thermodynamically stable transparent system of oil, water and surfactants with droplet size in range of 20 nm to 200nm. [10-11] Microemulsion provides protection against oxidation, enzymatic degradation and improves the solubilisation of the lipophilic drugs and enhances their bioavailability. Microemulsion has been utilized to improve the bioavailability of the poorly soluble drugs such as Atorvastatin, Simvastatin, Cyclosporine and Paclitaxel. [12-13]

Self-Micro emulsifying drug delivery systems (SMEDDS) have many applications as improvement in solubility and bioavailability, protection against biodegradation, controlling the release rate of drug etc.[14]

2. MATERIALS AND METHODS:

2.1 Materials: Pitavastatin calcium was obtained as gift sample from Matrix Hyderabad, India. Transcutol P, Captex 200, Lauroglycol 90, Labrasol, Labrafil M1944CS, Labrafac CC were gifted by Gattefosse SAS, France. Different frades of Propylene Glycol (200, 400) were obtained as gift samples from Thermo Fisher scientific, USA. Different grades of Tween 80 & Tween 20, Tetra hydro furan were gifted by S D Fine-Chem, Mumbai, India. Deionized double distilled water was used throughout the study obtained from Milli-Q-water purification system Millipore (Massachusetts, USA), while all other chemicals and reagents used were of analytical reagent grade.

2.2 Methods:

2.2.1 Preformulation studies: The drug sample characterization is done by various tests like organoleptic evaluation, Melting point determination, Microscopic evaluation, FTIR spectrophotometry, and UV Visible spectrophotometry analysis.

2.2.2 Solubility studies: Aqueous solubility studies of Pitavastatin calcium were determined by using hand shake method. An excess amount of Pitavastatin calcium was added individually in each vehicle placed in screw capped vials. Then the vial was placed in Wrist action shaking machine for 48 hr in order to facilitate saturable mixing of drug with the vehicles. The vials containing the solutions were then kept at 25±1ºC. The sample were removed from shaker and centrifuged at 3,000 rpm for 10 min to remove un-dissolved drug. The supernatant was then filtered through membrane filter (0.45μm). The Sample was diluted with suitable reagent and drug concentration was quantified using UV spectroscopy at λ_{max} of 245nm.[15]

2.2.2.1 Solubility analysis in oil, surfactant and co-surfactant: The solubility of Pitavastatin calcium in selected oil, surfactant and cosurfactant were determined by using shake flask method. An excess amount of drug (Pitavastatin calcium) was added separately in 2mL of each oil, surfactant and co-surfactant in capped vials. The capped vials were then shaking with the help of vortex mixer. The mixture vials were than kept at 25± 1°C in a hand shake for 2 days to reach equilibrium. The sample were removed from shaker and centrifuged at 10,000 rpm. Undissolved drug was removed by filtering through membrane filter (0.45 μm). Samples were suitably diluted with suitable reagent, and drug concentration was quantified using UV spectroscopy at specific λ_{max}.[16-17]

2.2.3 Drug excipient compatibility study: Compatibility study of the drug was carried out with the selected oil, surfactant and cosurfactant for determining the possibility of any drug excipient interaction. Drug was mixed with each excipient in 1:10 ratio in screw capped vial. These vial placed at 40±2°C/75±5% RH for 30 days. Result was analyzed for any incompatibility via physical and chemically.[18]

2.2.4 Construction of pseudo ternary phase diagrams: The pseudo-ternary phase diagrams of surfactant, oil, cosurfactant and water were developed using water titration method as shown in **Table 1**. The surfactant and co surfactant (Smix) were taken in the ratio of 3:1, 2:1, 1:1, 1:2, 3:1. The oil and Smix were taken from 1:9 to 9:1 ratios. For each mixture, the three components were weighed into glass vials and mixed by using vortex mixer at room temperature. 1gm of this solution was transferred to a glass beaker and 250 ml of water was added at 37°C under gentle stirring at 25 rpm. The dispersion was inspected visually for transparency or turbidity or any phase separation.

A mixture was defined suitable micro- or nano-emulsion on the basis of impulsive emulsification or by development of clear transparent solution. From phase diagram, different formulations were selected showing the Microemulsion region so that drug could be incorporated into the oil phase. For each percentage of oil with minimum concentration of S_{mix} was selected for the formulations.[19]

TABLE 1: WATER TITRATION CHART OF PITAVASTATIN CALCIUM

Smix Ratio	Composition		
	Capmul PG 8	Tween 80	Transcutol P
3:1	10	67.5	22.5
	20	60	20
	30	52.5	17.5
	40	45	15
	50	37.5	12.5
	60	30	10
	70	22.5	7.5
	80	15	5
	90	7.5	2.5
2:1	10	60	30
	20	53.3	26.70
	30	46.70	23.30
	40	40	20
	50	33.30	16.70
	60	26.70	13.30
	70	20	10
	80	13.30	6.70
	90	6.70	3.30
1:1	10	45	45
	20	40	40
	30	35	35
	40	30	30
	50	25	25
	60	20	20
	70	15	15
	80	10	15
	90	5	5
1:2	10	30	60
	20	26.70	53.3
	30	23.30	46.70
	40	20	40
	50	16.70	33.30
	60	13.30	26.70
	70	10	20
	80	6.70	13.30
	90	3.30	6.70
1:3	10	22.5	67.5
	20	20	60
	30	17.5	52.5
	40	15	45
	50	1	37.5
	60	10	30
	70	7.5	22.5
	80	5	15
	90	2.5	7.5

2.2.5 Formulation of drug loaded self-micro-emulsifying drug delivery system (SMEDDS): The Pitavastatin calcium was weighed and mixed with Capmul PG 8 by vortexing followed by sonication until a clear solution was obtained. The S_{mix} was added to the mixture of drug and oil. The mixture was then stored for further evaluation and stability studies.[20]

2.2.6 Evaluation of SMEDDS: A number of tests were carried out for characterization and evaluation of SMEDDS.

2.2.6.1 Drug Content: One capsule of each formulation was taken in 100 mL volumetric flask and 100mL methanol was added as extracting solvent. Pitavastatin drug content in the methanolic extract was determined by UV spectrophotometer at λ_{max} of 245 nm, using methanol as blank.

2.2.6.2 Percentage Transmittance: Each formulation was diluted with 500 ml distilled water. The clarity of the formulation was observed by measuring % transmittance by UV spectrophotometer at 650 nm, using distilled water as blank.

2.2.6.3 pH Measurement: The apparent pH of the formulation was measured by a pH meter at 25°C

2.2.6.4 Robustness to Dilution: SMEDDS were diluted to 50, 100, 500 time with water. The diluted micro emulsions were stored for 12 hr and observation for any sign of phase separation or drug precipitation.

2.2.6.5 Droplet size Analysis & Particle size Measurements: Photon correlation spectroscopy (PCS) or dynamic light scattering (DLS) or Laser Diffraction Techniques was used to determine droplet size of micro emulsion. A number of various equipment's are available for measurement of Droplet size viz. Particle Size Analyzer, Mastersizer, Zetasizer etc. which are able to measure sizes between 10 and 5000 nm. The samples were analysed by using Zetasizer. The samples were diluted suitably with distilled water and analysed using Zetasizer.

2.2.6.6 Self-Emulsification Time: The self-emulsification time is determined by using USP dissolution apparatus II at 50 rpm, where 0.5 g of

SMEDDS formulations is introduced into 250 ml of Phosphate buffer solution. The time for emulsification at which transparent formulation was formed at room temperature is indicated as self-emulsification time for the formulation.

2.2.6.7 *In-vitro* Drug Release Studies: *In-vitro* drug release is a test used by the pharmaceutical industry to characterize the dissolution properties of the active drug, the dissolution of a drug from the formulation and the active drug's release. *In-vitro* drug release of Pitavastatin calcium SMEDDS was determined using USP Dissolution apparatus I (basket type). The dissolution test was performed using 900 mL of 0.05 M phosphate buffer (pH 6.8) at 37°C ± 0.5°C. The speed of rotation of basket was set at 35 rpm. 5 mL of sample was withdrawn at regular intervals of 5, 10, 15, 30, and 45 min and same volume was replaced with fresh media to maintain the sink conditions. Samples were filtered through 0.45µm and absorbance of solution was checked by UV-visible spectrophotometer at 245 nm and drug release was determined.

2.2.6.8 Stability Study: The stability studies were carried out to check the stability of the optimized formulation during storage. The optimized formulation was filled in hard gelatin capsules and packed in HDPE bottles. The bottles were sealed and placed in stability chamber at 40±2°C/75±5% RH as per ICH guidelines. Samples were withdrawn every month for 3 months and evaluated for the physical parameters and the *in-vitro* drug release.

2.2.6.9 Comparison of optimized formulation with marketed formulation: After stability a study, the optimized formulation was compared with marketed formulation Pivasta, 4 mg, for % drug release. Drug was bought from local market with batch number- ZHR2077, manufacturing date 5/15 and expiry date 4/17. The % drug release data was compared with the optimized formulation.

3. RESULT AND DISCUSSION:

3.1 Preformulation study:

Drug sample was found to be white to off white color. Its melting point was found to be 183±0.9°C. Also it was found that the drug substances have acicular shaped crystals.

3.2 Solubility Studies:

3.2.1 Aqueous Solubility studies: From this study the solubility it was suggested that Pitavastatin Calcium was practically insoluble in water and more soluble in methanol and phosphate buffer. By this study it was concluded that drug was highly lipophillic drug.

3.2.2 Solubility studies of drug for preparing SMEDDS in oil, surfactant and cosurfactant: The self-emulsifying formulation contains oil, surfactants, cosurfactants, and drug which should be a clear and monophasic liquid at ambient temperature when introduced to aqueous phase and should have good solvent properties to allow presentation of the drug in solution. The solubility of drug in various vehicles is presented in **Table 2-4**. From this data, it was depicted that the Pitavastatin Calcium was more soluble in Capmul PG8, Tween 80 and Transcutol P, and these excipients were selected for the SMEDDS preparation as oil, surfactant and cosurfactant respectively.

TABLE 2: SOLUBILITY OF PITAVASTATIN CALCIUM IN VARIOUS OILS

Oil	Solubility (mg/mL)
Soyabean oil	0.881 ± 0.21
Castor oil	0.532 ±0.270
Oleic acid	3.465 ±0.04
Captex 200	1.436 ±0.14
Capmul PG 8	6.959 ±0.04
Labrafac-cc	2.463 ± 0.04

Values represented as mean ± SD (n=3).

TABLE 3: SOLUBILITY OF PITAVASTATIN CALCIUM IN VARIOUS SURFACTANTS

Surfactants	Solubility (mg/mL)
Tween 20	9.471 ±0.03
Tween 80	70.63 ± 1.55
Labrafil M 1944	40.55 ± 0.91
Labrasol	34.420 ±0.34
Lauroglycol 90	54.830 ±1.30
Kolliphore EL	68.04 ±1.06

Values represented as mean ± SD (n=3)

TABLE 4: SOLUBILITY OF PITAVASTATIN CALCIUM IN VARIOUS COSURFACTANTS

Cosurfactants	Solubility (mg/mL)
Propylene glycol	2..191 ± 0.05
Propylene glycol 200	19.655 ± 0.45
Propylene glycol 400	15.790 ± 0.14
Transcutol P	21.655 ± 0.04

Values represented as mean ± SD (n=3).

3.3 Drug Excipient Compatibility Study: Compatibility study of drug was carried out with Capmul PG 8 (Oil), Tween 80 (surfactant), and Transcutol P (cosurfactant) to determine possibility of any drug-excipient incompatibility. Drug excipient compatibility study was performed *via* two ways i.e. physical compatibility and chemical compatibility.

3.3.1 Physical observation:

TABLE 5: PHYSICAL COMPATIBILITY DATA OF DRUG EXCIPIENTS

Sample	Initial	Final	Inference
Pitavastatin calcium	White to off white powder	White to off white powder	Compatible
Pitavastatin calcium + Campul PG 8	Transparent solution	Transparent solution	Compatible
Pitavastatin calcium + Tween 80	Pale-yellow solution	Pale-yellow solution	Compatible
Pitavastatin calcium + Transcutol P	Transparent solution	Transparent solution	Compatible
Pitavastatin calcium + Capmul PG 8 +Tween 80 + Transcutol P	Yellowish Solution	Yellowish Solution	Compatible

From this studies in **Table 5**, Pitavastatin calcium depicted that the drug was compatible with selected excipient and no change in appearance &color so, selected excipients would be used for further preparation of SMEDDS.

3.3.2 Chemical compatibility: In Chemical compatibility, drug and excipients combination were stored for one month at 40±2°C/75±5% RH. After one month storage the drug sample and API excipient mixture were analyzed using FTIR spectroscopy. FTIR spectrum of pure drug and combination of Pitavastatin calcium with excipients was shown in **Fig. 1** and **Fig. 2.** It was suggested that there was no such change in the chemical integrity of the drug and hence drug and excipients can be chemically compatible with each other.

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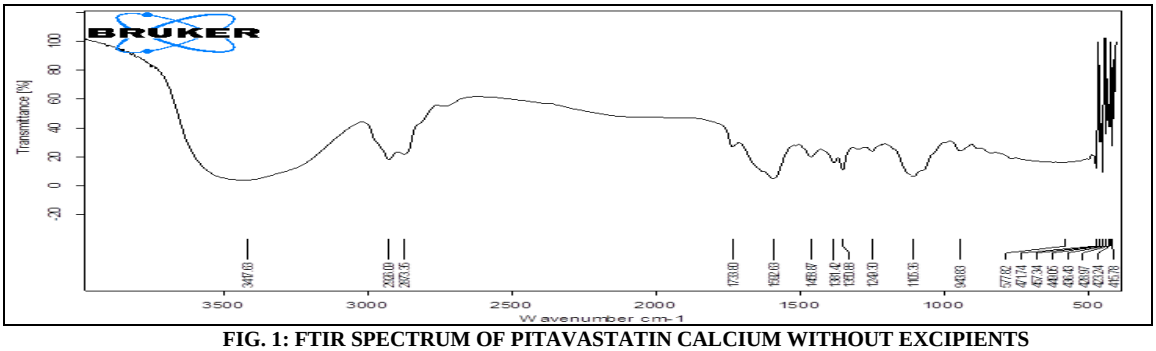

FIG. 1: FTIR SPECTRUM OF PITAVASTATIN CALCIUM WITHOUT EXCIPIENTS

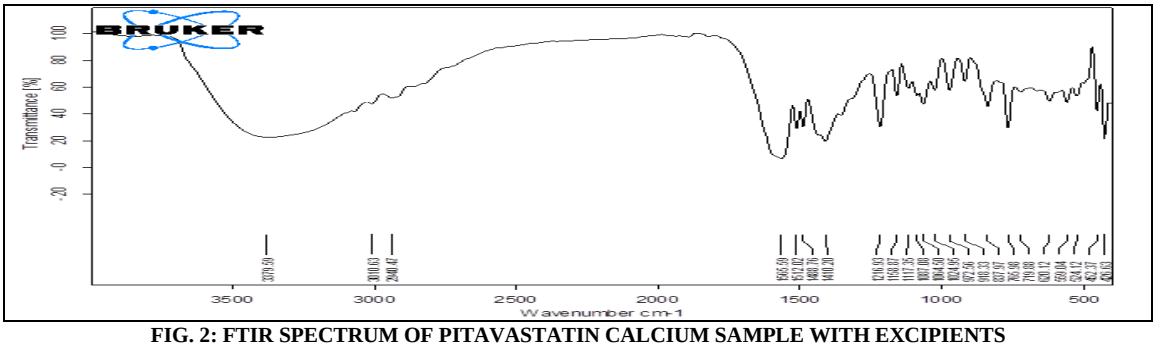

FIG. 2: FTIR SPECTRUM OF PITAVASTATIN CALCIUM SAMPLE WITH EXCIPIENTS

3.4 Pseudo ternary phase diagrams: Pseudo-ternary phase diagrams were constructed to identify self-micro-emulsifying regions and to select suitable concentrations of oil, surfactant and co-surfactant for the SMEDDS formulation. Oil, surfactant and co-surfactant were grouped in different combination for phase studies. Pseudo-ternary phase diagrams were constructed separately for each group so that SMEDDS regions could be identified. Pseudo ternary diagrams of different combinations of oil, surfactant and co-surfactant were tried with different ratios of Capmul PG8, Tween 80 and Transcutol P were constructed as shown in **Fig. 3-7**. The combination with ratio 3:1, 2:1, 1:1, 1:2 of Capmul PG 8, Tween80: Transcutol P was selected for formulation. Therefore by these results, we choose sixteen formulations as described in **Table 6** becauseonly these sixteen formulations were in the range of micro emulsions.

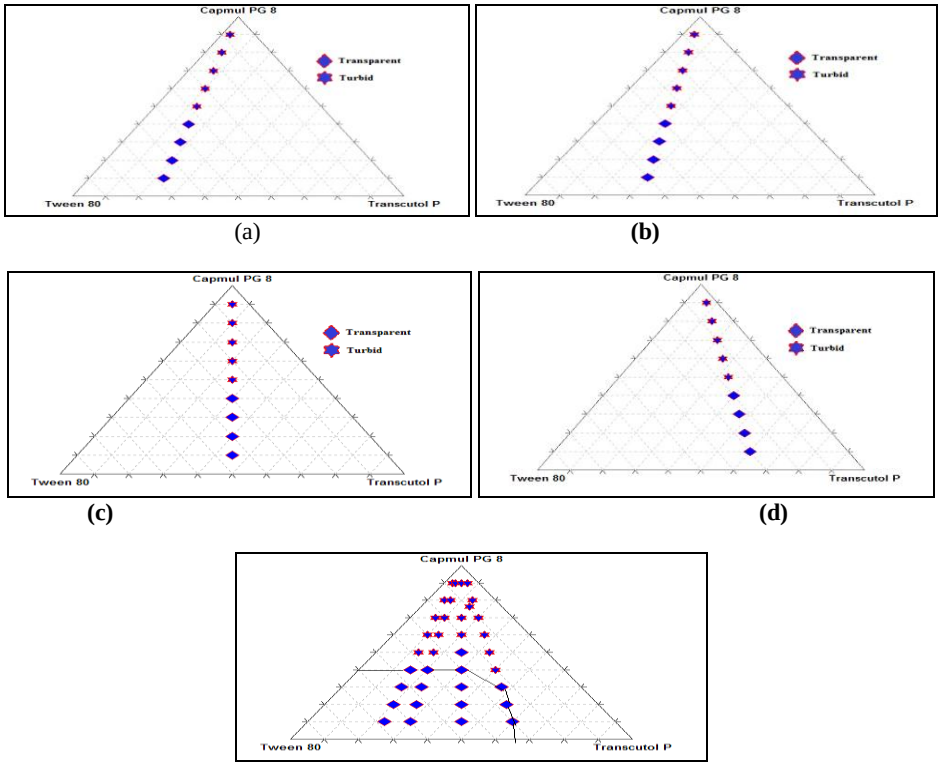

FIG. 3: PSEUDO-TERNARY PHASE DIAGRAMS INDICATING THE EFICIENT SELF-EMULSFICATION REGION (S/CoS = 3:1 (w/w) (a), 2:1 (w/w) (b), 1:1 (w/w) (c), 1:2 (w/w) (d), AND THE AREA REPRESENTS MICROEMULSION REGION (e)

TABLE 6: COMPOSITIONS OF SMEDDS FORMULATIONS WITH DIFFERENT CONCENTRATIONS OF OIL, SURFACTANT AND CO-SURFACTANTS

Formulation	Capmul PG 8	Tween 80	Transcutol P	Drug
F1	10	45	45	4
F2	20	40	40	4
F3	30	35	35	4
F4	40	30	30	4
F5	50	25	25	4
F6	10	60	30	4
F7	20	53.3	26.70	4
F8	30	46.70	23.30	4
F9	40	40	20	4
F10	10	67.5	22.5	4
F11	20	60	20	4
F12	30	52.5	17.5	4
F13	40	45	15	4
F14	10	30	60	4
F15	20	26.70	53.3	4
F16	30	23.30	46.70	4

3.5 Drug Content: The drug content of SMEDDS formulation was measured using UV spectroscopic method. In all the sixteen formulations, drug content was found to be highest in the formulation F4 and in other formulations there was no significant difference in drug content.

3.6 Percentage Transmittance: The clarity of micro-emulsions was checked by transparency, measured in terms of transmittance (%T). % transmittance of formulation (F4) has value greater than 99%; these results indicate the high clarity of micro-emulsion. In case of other systems %T values were about 94% suggesting less clarity of micro-emulsions. This may be due to greater particle size of the formulation. Due to higher particle size, oil globules may reduce the transparency of micro-emulsion. The results of %T are as shown in **Table 7**.

TABLE 7: DRUG CONTENT AND TRANSPARENCY OF SMEDDS FORMULATION

Formulation	Drug content	Transmittance (%)
F1	98.23 ± 1.05	96.98
F2	98.76 ± 0.76	97.98
F3	98.22 ± 0.48	96.76
F4	99.98 ± 1.00	99.26
F5	97.82 ± 1.04	95.03
F6	97.03 ± 0.95	95.67
F7	98.04 ± 0.52	94.68
F8	98.67 ± 0.68	95.82
F9	96.44 ± 0.49	94.30
F10	97.50 ± 0.91	98.74
F11	97.84 ± 0.57	97.56
F12	97.02 ± 1.10	96.54
F13	97.59 ± 0.08	97.51
F14	97.98 ± 0.98	98.27
F15	97.94 ± 1.14	98.11
F16	94.39± 0.99	94.33

% Transmittance of all formulation was above 90% which shows that all formulations were clear and transparent in nature.

3.7 Determination of pH: The pH of all formulations was studied using digital pH meter (Thermo electron, USA) and was found to be in the range of 6.3 to 8.2 which was compared with the pH of GIT & that was in the acceptable range. The pH of formulation is an important parameter as deviation from the pH of GIT; the formulations may cause gastric irritation so the formulations should have pH comparatively equal to gastric pH.

3.8 Robustness to dilution: Robustness of SMEDDS formulation containing drug was studied by diluting it by 50, 100 and 500 times of prepared formulations with water as shown in **Table 8.** In all formulation except F4, showed no satisfactory result but in the diluted micro-emulsion of formulation F4 showed better result i.e. no phase separation or drug precipitation, which implies formulation F4 showed stable Microemulsion.

TABLE 8: OBSERVATION FOR ROBUSTNESS TO DILUTION

Formulation	Observation (dilution)		
	50	100	500
F1	+	+	-
F2	+	+	-
F3	+	+	-
F4	+	+	+
F5	+	+	-
F6	+	-	-
F7	+	-	-
F8	+	+	-
F9	+	+	-
F10	+	-	-
F11	+	+	-
F12	+	+	-
F13	+	+	-
F14	+	-	-
F15	+	-	-
F16	-	-	-

\+ No phase separation
\- Phase separation

3.9 Droplet size analysis & Particle size measurements: Droplet size after micro-emulsion was the most essential criteria of SMEDDS. It may affect the release and absorption of drug in GI tract. In the study, the droplet size increases in all prepared formulations except F4 formulation as shown in **Table 9**. F4 formulation shows better micro-emulsion because the decrease in the droplet size which reflects the formation of a better closed packed film of surfactant at the oil-water interface there by stabilizes the oil droplets.

Polydispersity (PDI) is the ratio of standard deviation to the mean droplet size. The higher the value of PDI, the lower is the uniformity of the droplet size. The polydispersity value of all formulations except F4 shows less value as shown in Table. Due to this data; it was found that F4 formulation formed stable micro-emulsion. **Fig. 4** showed that droplet size of formulation F4 was found to be stable.

TABLE 9: AVERAGE GLOBULE SIZE AND POLYDISPERSIBILITY INDEX OF SMEDDS

Formulation	Polydispersibility index (PDI)	Droplet size (nm)
F1	0.501±0.13	39.5±1.12
F2	0.392±0.13	39.8±0.49
F3	0.329±0.24	38.7±0.32
F4	0.484±0.51	37.2±0.02
F5	0.223±0.81	42.8±0.14
F6	0.384±0.18	48.6±0.15
F7	0.289±0.12	52.8±0.23
F8	0.462±0.24	53.1±0.04
F9	0.537±0.20	51.8±0.37
F10	0.575±0.15	63.2±0.19
F11	0.254±0.51	63.7±0.12
F12	o.393±0.37	59.2±0.28
F13	0.313±0.89	48.9±0.34
F14	0.231±0.22	62.4±0.51
F15	0.483±126	75.8±0.121
F16	0.440±0.029	69.3±0.007

Values represented as mean ± SD (n=3).

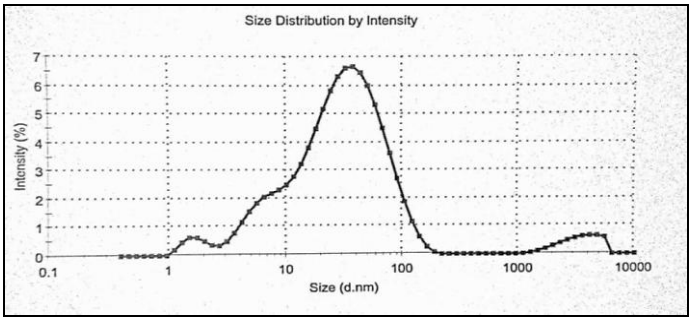

FIG. 4: DROPLET SIZE OF FORMULATION F4

3.10 Self-Emulsification Time: The Self-Emulsification Time was measured with the help of dissolution apparatus type II. The time taken to form micro emulsion was to be 24 second. Hence concluded that the micro emulsion of formulation F4 was found to be Grade a formulation.

3.11 *In-vitro* dissolution studied: Dissolution results showed that 99.6% of drug dissolved from self-microemulsifying formulation (F4) after 45 minutes as compare to others formulations. It suggest that F4 formulation showed better in-vitro drug release and selected this formulation as optimized. Also, the *in-vitro* drug release studies for marketed tablet (Pitavastatin calcium 4mg) and selected micro-emulsion was determined in USP dissolution medium pH 6.8. It means that prepared formulation (F4) showed better result than marketed formulation because of the surfactant molecules increases the solubility of the drug in dissolution medium.

3.12. Comparison of optimized formulation with marketed formulation: The % drug release of the optimized formulation was compared with marketed formulation (Pivasta, 4 mg). The results of comparison of the two formulation suggested that the SMEDDS had remarkably increased dissolution rate as compared to coated tablets. The results of comparative studies are given in **Fig. 5.**

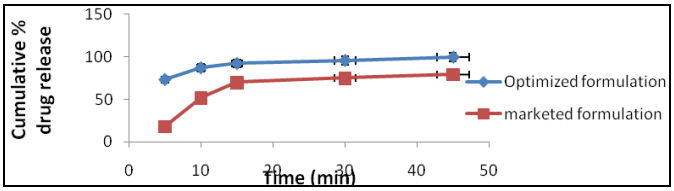

FIG. 5: *IN VITRO* DISSOLUTION PROFILE OF OPTIMIZED FORMULATION, MARKET FORMULATION

In vitro release of all formulation suggested rapid release within few minutes. Formulation (F4) depicted 99.6 % release in 45 min, while with marketed formulation drug release was 79.1% in 45 min. These suggest the superiority of prepared SMEDDS of Pitavastatin calcium for *In-vitro* drug release that may further in enhancement of bioavailability.

3.13 Stability Study: The stability study of the batch was conducted at 40±2°C/75±5% RH for 3 months. The hard gelatin capsules containing the SMEDDS formulation were removed every month from stability chamber and were analyzed for the parameter. After stability study, there were no significant changes in the appearance, drug content and dissolution. Hence stability study confirmed that optimized formulation was found to be stable as per ICH guideline.

CONCLUSION: The self-emulsifying drug delivery system was developed as novel techniques to efficiently deliver poorly water soluble drug candidates with objective of enhance bioavailability. Pitavastatin calcium was selected as a drug which has poor aqueous solubility. Compound with poor aqueous solubility are posing challenge in the development of new drugs. Bioavailability determines the efficacy of the drug as well influences the dose, dosing frequency and untoward effects of drug. Hyperlipidemia is a chronic disease; there for always patient follows maintenance therapy remains on.

In this project it was decided to increase the solubility and dissolution profile Pitavastatin calcium whose solubility is often related to its bioavailability. Lipid based delivery system like self-micro emulsifying drug delivery system (SMEDDS) is one of the promising approaches to improve the oral bioavailability of (BCS) class II and IV drugs.

CONFLICT OF INTEREST: The authors declare that there are no personalor financial conflicts of interest with individuals or organizations.

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