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DEVELOPMENT, OPTIMISATION, AND CHARACTERISATION OF SNEDDS OF ANTI-LIPASE INHIBITOR

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Keywords:

Anti-lipase inhibitor, *In-vivo*, Orlistat, SNEDDS

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ABSTRACT: Background: Self-Nanoemulsifying Drug Delivery System (SNEDDS) has been employed extensively by the formulation of scientists to tackle the low solubility issues of various drugs and lift the bioavailability profile. But the potential of SNEDDS is not limited to augment the dissolution profile only. **Objective:** The objective of the study was to develop, optimization, and characterization of SNEDDS of anti-lipase inhibitors. **Method:** Orlistat was added in an accurately weighed amount of oil into a screw-capped glass vial and heated in a water bath at 40 ºC. The surfactant and co-surfactant were added to the oily mixture using positive displacement pipette and stirred with a magnetic bar. The formulation was further sonicated for 15 min and stored at room temperature until its use in subsequent studies. A 2^3 full factorial design was selected because an experiment may be designed to focus attention on a single independent variable or factor. **Results:** The drug loading efficiency for all Orlistat SNEDDS formulae was found in the range of 92.37% ± 0.75% (PF1) to 99.09% ± 0.56% (PF4), indicating uniform drug dispersion in formulae. To optimize and select a self-emulsifying region with minimum globule size (<300 nm), the concentration of the oil, surfactant, and co-surfactant in the isotropic mixture was determined by constructing a ternary phase diagram. Fourier-transform infrared spectroscopy was optimized Orlistat, indicating no existence of the interaction between the Orlistat and polymer. The Differential Scanning Calorimetry study also confirmed for orlistat (45.77 ºC and formulation F1 to F4 (45.21 ºC, 45.61 ºC, 45.41 ºC, and 45.61 ºC) respectively. In the present study observation of acute toxicity study carried out, and none of the rats showed observable signs of toxicity upon single administration of test drug. The HFD treated rats showed a significant increase ($p<0.05$) in HDL-c compared to control group, while significant ($p<0.05$) increase were observed in standard (orlistat 12 mg/kg), and formulation treated groups (30 and 60 mg kg) when compared to HFD treated rats. **Conclusion:** This technique can minimize cost and cut short the number of formulations needed to identify the optimum composition. The Orlistat SNEDDS formulation was successfully developed, optimized, and characterized.

INTRODUCTION: In the previous decade, Self-Nanoemulsifying Drug Delivery System (SNEDDS) has been employed extensively by the formulation of scientists to tackle the low solubility issues of various drugs and lift the bioavailability profile.

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But the potential of SNEDDS is not limited to augment the dissolution profile only. Research is now heading towards some novel applications of SNEDDS, *e.g.*, solid SNEDDS, supersaturated SNEDDS, self-double emulsions (w/o/w), controlled release SNEDDS, SNEDDS for overcoming mucus gel barrier, delivery of biomolecules and even drug targeting [1]. Researchers are also interested in developing some reliable *in-vivo* correlation for these formulations [2].

Commonly 'Trial and Error' and 'Ternary Phase Diagram' approaches are used in the development

of SNEDDS [3]. Several errors and shortcomings are associated with these 'titration' based methods. This technique consists of fixing the oil, surfactant and co-surfactant concentrations while varying the concentration of one parameter at one time and gradually adding the aqueous phase to judge the nanoemulsion formation from the formulation transparency [4, 5]. In this process, when the aqueous phase is limited, then concentrated nanoemulsions are generated, which are milky, opaque, and are not transparent. Further addition of aqueous phase (mostly water) leads to a bluish, transparent, and translucent nanoemulsion formulations. This change from opaque to transparent formulation is referred to as 'phase transition' which is a wrong interpretation. These two systems are actually 'concentrated' and 'diluted' nanoemulsions, respectively [6]. This misinterpretation raises questions about the validity of the 'Ternary phase diagrams' build this way. These techniques are time-consuming, costly, and demand a greater number of experiments [7].

The solubility of drugs in lipidic excipients is the factor that determines the loading dose of drugs in pre concentrates [8]. As the lipidic content of SNEDDS is reduced, the solubilizing capability of SNEDDS is declined *in-vivo* due to dispersion and digestion, leading to precipitation of the drugs [9]. Drugs that are more soluble in surfactant or co-surfactant than lipophilic phase are at risk of precipitation because the solvent capacity of surfactant and co-surfactant decreases upon dilution. This is why most SNEDDS contain drug less than equilibrium solubility (50-90% of Seq). In one such study, researchers concluded that the presence of a higher quantity of hydrophilic surfactants also leads to greater drug precipitation [10]. To surmount this problem, SNEDDS containing hydrophilic precipitation inhibitors have been introduced successfully.

The emulsions formed from SMEDDS have a mean droplet size that falls within the micrometric scale, which ranges between 2-100 nm. The main difference between common emulsions and micro emulsions is the mean droplet size. SMEDDS are thermodynamically stable. They form optically transparent emulsions. Because of the small droplet size, the surface area for absorption and dispersion are increased significantly, and it easily penetrates the gastrointestinal tract and can be absorbed [11]. In this system, the surfactant was soluble in both oil as well as water phase, and droplet was dispersed in both oil as well as water phase [12].

Hence, it is desirable to evaluate the self nano emulsification time as well as the characteristics of the resultant nanoemulsion in aqueous phases with varying pH and/or electrolyte concentration (depending on the type of application). Therefore, in addition to plain water, Ringer's solution, simulated gastric fluid (pH 1.2), simulated intestinal fluid (pH 6.8), and phosphate-buffered saline are used as an aqueous phases to evaluate the spontaneous nano-emulsification of SNEDDS [13].

The objective of the study was to development, optimization, and characterization of SNEDDS of anti-lipase inhibitor.

MATERIALS AND METHODS:

Materials: Caproic acid was procured from Qualikems Fine Pvt. Ltd. Vadodara, Transcutol P was procured from Lubrizol, Labrafac PG was procured from Thermo Fischer Scientific India Pvt. Ltd., Mumbai, Olive oil and Sunflower oil was procured from Thomas baker (chemicals) Pvt. Ltd. Mumbai, India, n-Octanol, PEG 90 and PEG400 was procured from SDFCL, Mumbai, Tween 80 was procured from Molychem, Mumbai, Kolliphor ER and Polysorbate 80 was procured from BASF, Mumbai.

Methods:

Solubility Studies: The maximum solubility of Orlistat in different oils, surfactants, and co-surfactants were assessed. Briefly, in screw-capped glass vials, 3 mL of each vehicle was placed and an excess amount of the drug was added. These vials were shake-well and placed in a thermostatically controlled water bath shaker (Model 1031; GFL Corporation, Burgwedel, Germany) at 25 ± 0.5 °C for 72 h. The content of each vial was filtered using ministar single-use syringe filter (Sterile-ED, non-pyrogenic hydrophilic 0.45µm, Sartorius Stedim Biotech GmbH 37070 Gottingen, Germany) and the supernatant was collected. Drug concentration in the filtrate was quantified spectrophotometrically (6705 UV/Vis spectrophotometer; JENWAY) at 203 nm following successive dilution with methanol that was used as blank. Drug content for each run was carried out in triplicate.

Formulation of Orlistat SNEDDS: Here, Castor oil, Sunflower oil, Olive oil, Labrafac PG were used as oil phase, and Transcutol P, Tween 80, Kolliphor ER, Caproic acid and Polysorbate 80, PEG 400, PEG 90 were used as surfactant and co-surfactant respectively. The compositions are given in **Table 1.** Orlistat was added in an accurately weighed amount of oil into a screw-capped glass vial and heated in a water bath at 40 ºC. The surfactant and co-surfactant were added to the oily mixture using positive displacement pipette and stirred with a magnetic bar. The formulation was further sonicated for 15 min and stored at room temperature until its use in subsequent studies.

TABLE 1: COMPOSITION OF FORMULATION BATCHES

S. no.	Formulation	Ingredients	Quantity
1	PF 1	Castor oil	12.30 ml
		Transcutol P	4.65 ml
		Polysorbate 80	6.17 ml
		Orlistat	120 mg
2	PF 2	Sunflower oil	2.5 ml
		Tween 80	18 ml
		PEG 400	4.5 ml
		Orlistat	120 mg
3	PF3	Olive oil	3.75 ml
		Caproic acid	8.75 ml
		PEG 90	11.25 ml
		Orlistat	120 mg
4	PF4	Labrafac PG	2 ml
		Kolliphor ER	14.4 ml
		PEG 400	3.6 ml
		Orlistat	120 mg

Experimental Design: A 2^3 full factorial design was selected because, an experiment may be designed to focus attention on a single independent variable or factor. An alternative approach is to study the influence of one independent variable in conjunction with variations in one or more additional independent variables. We can study not only the effects of the two independent variables separately but also how they combine to influence the dependent variable. Three-factors (X1, X2 and X3), two-level (-1, +1) design can be developed. Three-factor were evaluated each at two-level and experimental were performed for all 8 possible combinations.

Emulsification time, % transmittance and % Drug release were selected as dependent variables. The actual and coded formulation design of SNEDDS formulation according to factorial design (2^3) layout is shown in **Table 2** and **3**.

TABLE 2: ACTUAL AND CODED FORMULATION DESIGN OF SNEDDS FORMULATION

Independent Variable	Level	
	Low (-1)	High (+1)
X1: Labrafac PG	1	2
X2: Kolliphor ER	7.2	14.4
X3: PEG 400	1.8	3.6

TABLE 3: COMPOSITION OF FACTORIAL BATCHES

Factorial Batches	Drug Orlistat	Factor 1 A:Labrafac PG 2 ml	Factor 2 B: Kolliphor ER 14.4 ml	Factor 3 C: PEG 400 3.6 ml
F1	120 mg	1	7.2	3.6
F2	120 mg	1	7.2	1.8
F3	120 mg	2	14.4	1.8
F4	120 mg	1	14.4	1.8
F5	120 mg	2	7.2	1.8
F6	120 mg	1	14.4	3.6
F7	120 mg	2	14.4	3.6
F8	120 mg	2	7.2	3.6

Drug Loading Efficiency: For determining the Orlistat content, 1 mL of SNEDDS formulae (equivalent to 20 mg of Orlistat) was diluted with methanol in a volumetric flask and mixed well by shaking or inverting the volumetric flask two to three times. Samples were prepared in triplicate, and absorbance was measured after suitable dilutions at 203 nm using UV-Vis Spectrophotometer (UV/Vis spectrophotometer). The amount of Orlistat present in each formula was calculated from a calibration plot [14].

Construction of the Ternary Phase Diagram: The concentration of oil, surfactant, and co-surfactant in SNEDDS was determined by plotting the ternary phase diagram, which was helpful to identify the self-emulsifying region with minimum globule size on dilution with water followed by gentle agitation. Batches were prepared by using Castor oil, Sunflower oil, Olive oil, Labrafac PG were used as oil phase, and Transcutol P, Tween 80, Kolliphor ER, Caproic acid and Polysorbate 80, PEG 400, PEG 90, PEG 400 were used as surfactant and co-surfactant respectively.

Batches were prepared by varying concentration of the oil, surfactant, and co-surfactant mixture ratio. Only batches with minimum globule size were taken into consideration for the ternary phase diagram. The isotropic mixture (50µL) was added in 50 ml of distilled water, followed by gentle stirring by a magnetic stirrer. Finally, the prepared emulsions were subjected to the globule size analysis. Mixtures, which were clear, or slight

turbid with minimum globule size (≤ 300 nm) were selected to determine emulsion region [15].

Characterization:

Fourier-Transform Infrared Spectroscopy Analysis (FT-IR): A baseline correction was made using dried potassium bromide. A weighed amount of orlistat *i.e.,* 1 mg was mixed thoroughly with potassium bromide (dried at 40°-50°C), which was then compressed under 10-ton pressure under the hydraulic press to form a pellet which was then scanned from 4000–400 cm^{-1} using FTIR spectrophotometer. The same procedure was repeated for polymers and different formulations. The FTIR spectrum of Orlistat was compared with the reference FTIR spectrum of orlistat [16, 17].

Differential Scanning Calorimetry (DSC): The DSC Study also confirmed as per the raw orlistat formulation F1 to F4 was determined by Differential Scanning Calorimetric (DSC-60, Shimadzu). Accurately weighed samples (5-10 mg) were sealed in an aluminum pan and scanned at a temperature range of 30 °C to 400 °C at the rate of 10 °C/min under dry nitrogen atmosphere purge of 50 mL/min.

Animal Study (*in-vivo* Study): Wistar rats of either sex weighing 180-220g are procured from Central Animal House, J.S.S. College of Pharmacy, Ootacamund. The temperature in the experimental room is at 22 ºC (± 4 ºC) with 60% ±2 relative humidity with appropriate lighting (12h light and dark cycle). Animals are housed in polycarbonate cages with stainless steel metal grades in the bottom. Animals are accessed to unlimited water supply and food. The experimental protocol was approved from the Institutional Animal Ethical Committee (JSS/IAEC/OT/03/2018-19) and carried out as per CPCSEA guidelines

EXPERIMENTAL:

Phase-I: Acute oral toxicity studies (OECD 423):

Procedure: Female Wistar Albino rats of weight (180-220g) were taken for the study and kept for overnight fasting. The next day, bodyweight was taken, and the test drug was administered orally at a dose of 2000mg/kg in distilled water. Then the animals were observed for mortality and morbidity at 0, ½, 1, 2, 4, 6, 8, 12, and 24 h. Feed was given to the animals after 4 hr of the dosing, and the body weight was checked at 6 hr after dosing. Morbidity like convulsions, tremors, grip strength, and pupil dilatation were observed. The animals were observed twice daily for 14 days, and body weight was taken. The same experiment will be repeated once again on 3 rats (preferably female) if there is no observable clinical toxicity for the animals on the acute toxicity study.

Phase-II: High Fat Induced Obesity in Rats:

Grouping of Animals: Wistar rats of 180-220g are divided into 5 groups with 6 animals in each group.

G1- Control (NFD)

G2 – High fat diet (HFD)

G3 – HFD+ Orlistat (12 mg/kg),

G4 – HFD+ Formulation (30 mg/kg)

G5 – HFD +Formulation (60 mg/kg)

Procedure: High-fat diet (HFD) induced obesity in rats is considered to be a reliable tool for the evaluation of the antiobesity activity. The study comprises 5 groups with 6 animals in each group. Group 1 represents the normal control in which the animals will receive feed on a normal diet (NPD) and had free access to water. Group 2 represents a negative control in which the rats will receive feed on a high-fat diet (HFD) for a period of 8 weeks. Group 3 represents standard control in which rats will be treated with Orlistat (12mg/kg, i.p), group 4 and 5 represents test treatment in which rats will be treated with the 30 and 60 mg/kg along with high-fat diet for 8 weeks respectively. As shown in **Table 4**.

TABLE 4: COMPOSITION OF HIGH FAT DIET

S. no.	Ingredients	Diet g/kg
1	Powdered NPD	365
2	Lard	310
3	Casein	250
4	Cholesterol	10
5	DL-methionine	03
6	Yeast powder	01
7	Sodium chloride	01

The body weight (gm) was recorded on day initially and then weekly consecutively for 8 weeks days using a digital weighing balance, and food consumptions were measured weekly per cage and mean food consumptions by individual rats were

calculated. At the end of the study of the experiment, all the animals were sacrificed by anesthesia using diethyl ether, and blood samples were collected by a sino-orbital puncture. The clear serum was separated at 3000 rpm for 10 min using a centrifuge. The levels of total cholesterol (TC), triglycerides (TG), high-density lipoproteins (HDL-c), and low-density lipoproteins (LDL-c) were determined to analyze using autoanalyzer [18, 19].

Statistical Analysis: Data obtained from this study were expressed as mean+-SEM. Statistical analysis was performed using one way ANOVA followed by Tukey's post hoc test. $p<0.05$ implies significance using graph pad version 5.0

RESULTS AND DISCUSSION:

Solubility Studies: In order to develop SNEDDS containing orlistat, the solubility of orlistat in different solvents was determined. It was clear from the results that there were three optimal excipients: Labrafac PG, Kolliphor ER, and PEG 400. Labrafac PG was selected as the oil phase of SNEDDS for the higher solubility of orlistat (113.0 mg/ml) compared to Castor oil (103.9 mg/ml). Kolliphor ER also emerged as the appropriate excipient as it showed the dual advantages in enhancing the solubility of orlistat and emulsifying Labrafac PG in water. Finally, PEG 400 was chosen as co-solvent because it offered the highest solubility of orlistat (around 350.1 mg/ml). This co-surfactant not only increased the orlistat solubility but also made it easier for the oil phase to disperse into the water phase due to its miscibility with both the oil and water phases. Given the advantages of these excipients, SNEDDS would be more stable when emulsifying into the water medium, and the risk of orlistat precipitation during the dilution of SMEDDS might be limited. The results are tabulated as graphical representation is shown in **Fig. 1, 2,** and **3**.

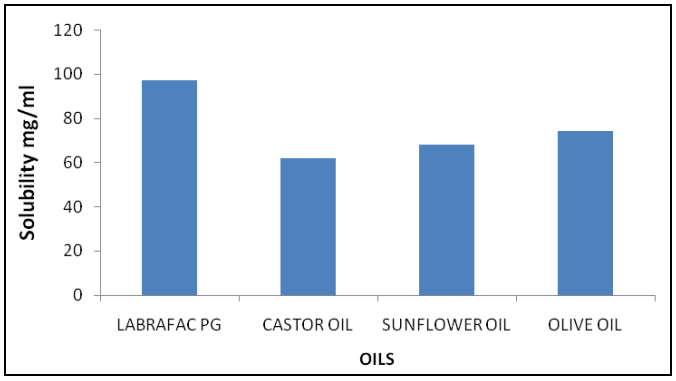

FIG. 1: SOLUBILITY STUDIES OF ORLISTAT IN OILS

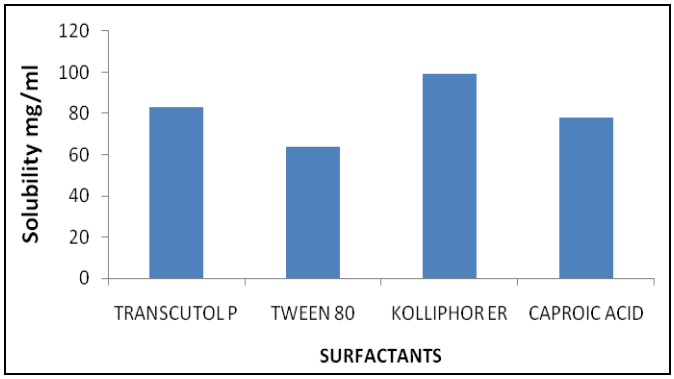

FIG. 2: SOLUBILITY STUDIES OF ORLISTAT IN SURFACTANTS

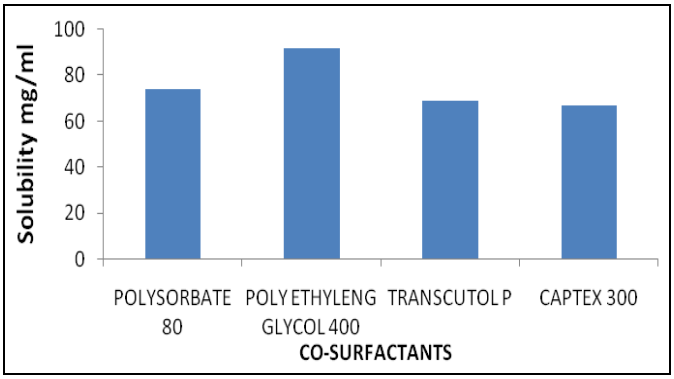

FIG. 3: SOLUBILITY STUDIES OF ORLISTAT IN CO-SURFACTANTS

Construction of the Ternary Phase Diagram: To optimize and select a self-emulsifying region with minimum globule size (<300 nm), the concentration of the oil, surfactant, and co-surfactant in the isotropic mixture was determined by constructing a ternary phase diagram. The self-emulsifying property was identified visually, which confirmed with minimum globule size after size analysis by Nanotrac R-150 ULTRA, Microtrac Inc. The ternary phase diagram for all the batches with a composition of oil, surfactant, and co-surfactant was prepared **Fig. 4 - 7**.

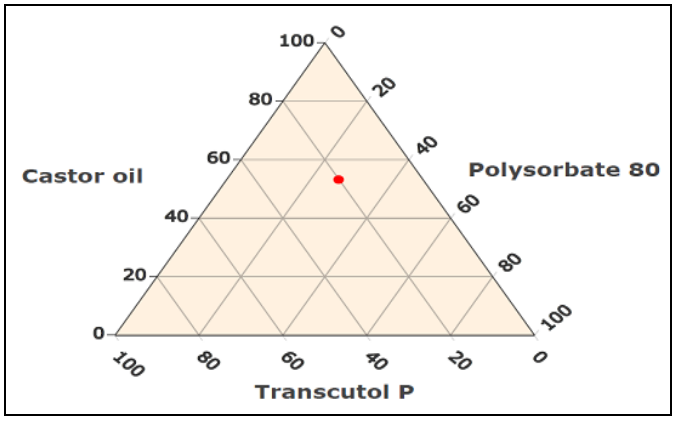

FIG. 4: TERNARY PHASE DIAGRAM FOR PF1

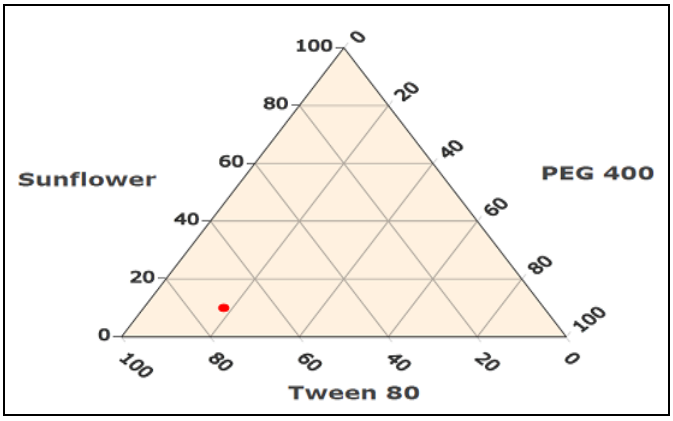

FIG. 5: TERNARY PHASE DIAGRAM FOR PF2

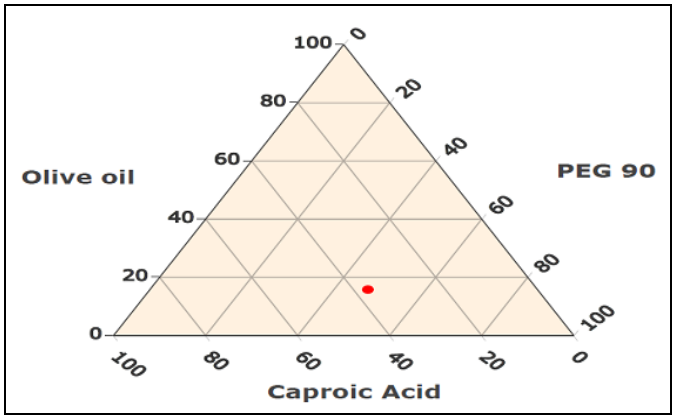

FIG. 6: TERNARY PHASE DIAGRAM FOR PF3

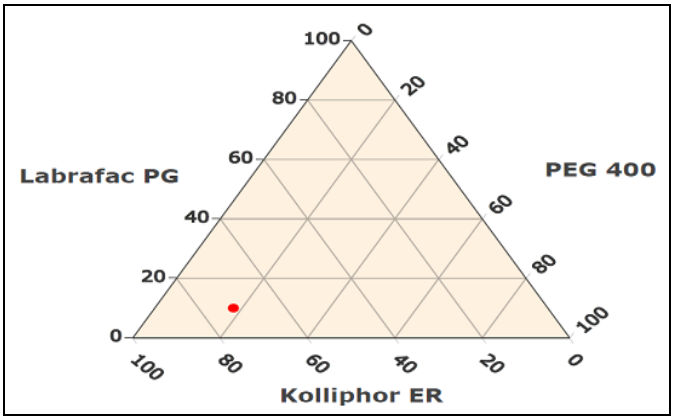

FIG. 7: TERNARY PHASE DIAGRAM FOR PF4

Drug Loading Efficiency: The drug loading efficiency for all Orlistat SNEDDS formulae was found in the range of 92.37% ± 0.75% (PF1) to 99.09% ± 0.56% (PF4), indicating uniform drug dispersion in formulae. It was observed that formula PF4 has the highest drug content.

The drug loading efficiency for all Orlistat SNEDDS formulae was found in the range of 95.87% ± 0.24 % (F1) to 99.89% ± 0.56% (F6), indicating uniform drug dispersion in formulae. Statistically, it was further justified that there was no significant difference in drug content among the various formulae. It was observed that formula F6 has the highest drug content. This may be attributed due to a higher concentration of surfactant and co-surfactant in these two formulae that possess a high solubilizing capacity of Orlistat.

Characterization:

FTIR Study: These values remained very close in the FTIR spectra of optimized Orlistat, indicating no existence of the interaction between the Orlistat and polymer shown in **Fig. 8 - 12**.

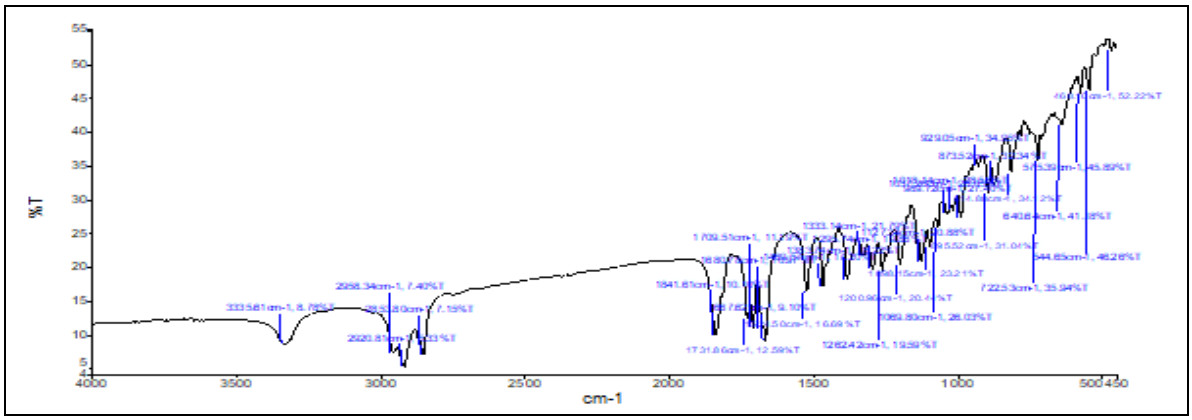

FIG. 8: FTIR OF ORLISTAT

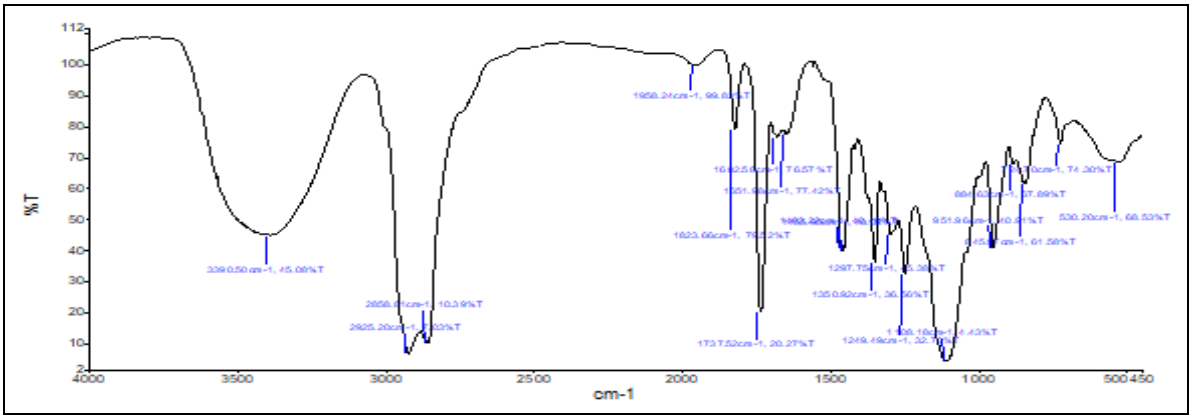

FIG. 9: FTIR OF LABRAFAC PG

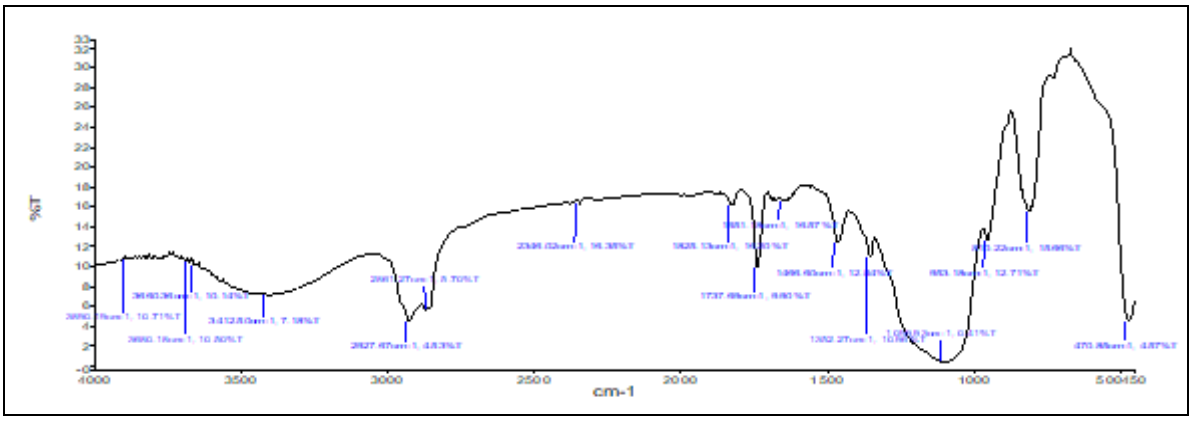

FIG. 10: FTIR OF KOLLIPHOR ER

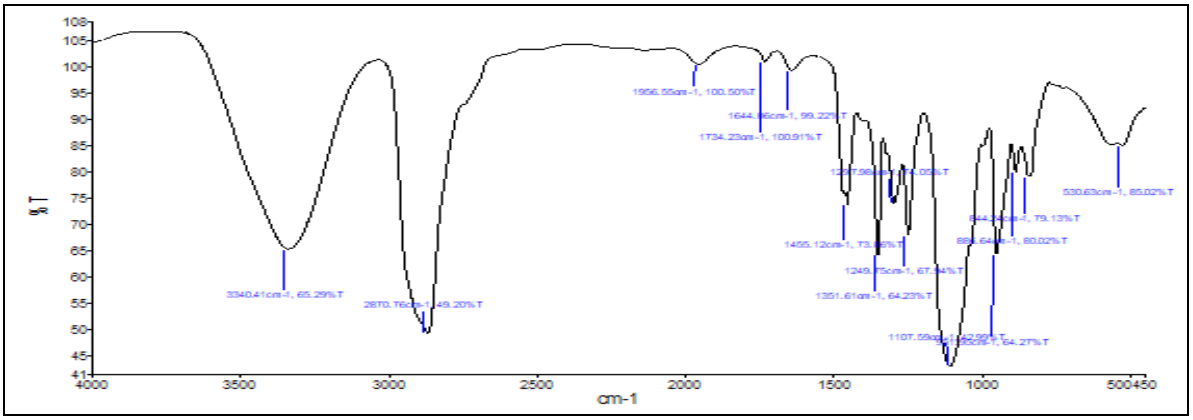

FIG. 11: FTIR OF PEG 400

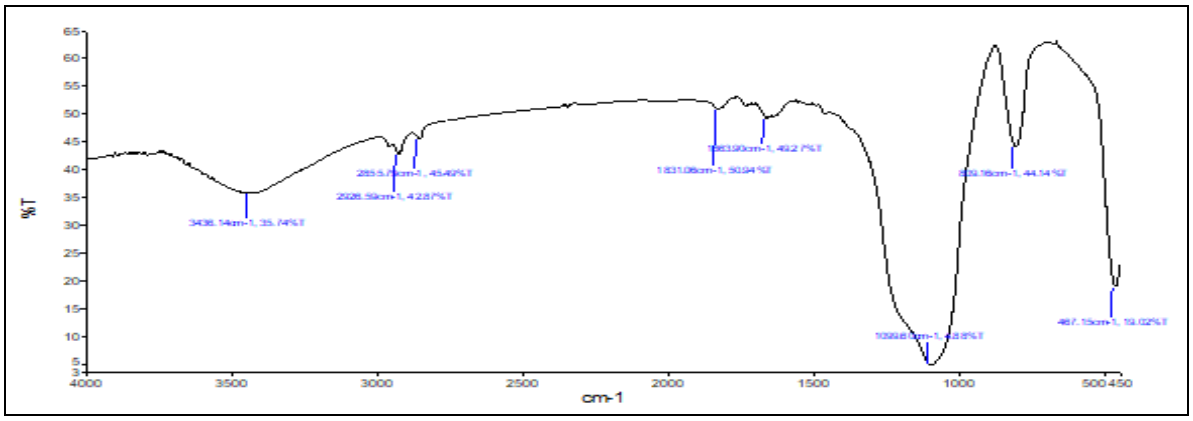

FIG. 12: FTIR OF ORLISTAT FORMULATION

Differential Scanning Calorimetry (DSC): The reported melting point of orlistat is 43 to 46 ºC. The DSC Study also confirmed as per the **Fig. 13** for orlistat (45.77 ºC and formulation F1 to F4 (45.21 ºC, 45.61 ºC, 45.41 ºC, and 45.61 ºC) respectively.

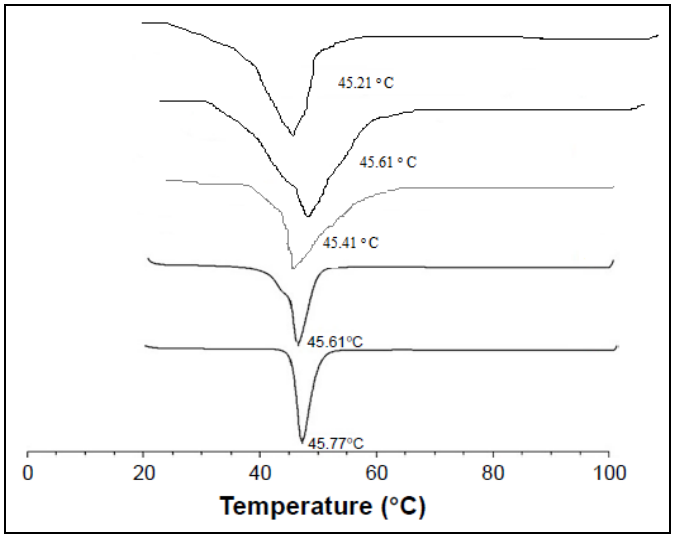

FIG. 13: DSC OF BATCHES

Animal Study (*in-vivo* Study): In present study observation of acute toxicity study carried according to OECD guideline 423, none of the rats showed observable signs of toxicity upon single administration of test drug (2g/kg, p.o.) on day one. Observations twice daily for 14 days also did not reveal any drug-related observable changes. The study was repeated with another set of animals for 14 days, and no signs of toxicity were observed.

Body Weight and Food Intake: Table 5 shows the initial and final body weights (g) and food intake (g)/week after feeding rats for 8 weeks with a neutral fat diet, high-fat diet, and high-fat diet supplemented with orlistat, formulation. The HFD treated rats of showed a significant increase ($p<0.05$) in body weight compared to control group, while significant ($p<0.05$) decrease was observed in standard (orlistat 12 mg/kg) and formulation treated groups (30 and 60 mg kg) when compared to HFD treated rats. Besides, there was a significant ($p<0.05$) increase of food intake in HFD group when compared to the normal group, while significant ($p<0.05$) decrease was observed in standard (orlistat 12 mg/kg) and formulation treated groups (30 and 60 mg kg) when compared to HFD treated rats.

Serum Lipid Profile: Table 5 and **6** shows the serum lipid profile results. The HFD treated rats showed a significant increase ($p<0.01$) in TC, TG and LDL-c compared to control group, while significant ($p<0.001$) decrease were observed in standard (orlistat 12 mg/kg) and formulation treated groups (30 and 60 mg kg) when compared to HFD treated rats. The HFD treated rats showed a significant increase ($p<0.05$) in HDL-c compared to control group, while significant ($p<0.05$) increase were observed in standard (orlistat 12 mg/kg), and formulation treated groups (30 and 60 mg kg) when compared to HFD treated rats.

TABLE 5: EFFECT OF FORMULATION AND ORLISTAT ON BODY WEIGHT IN HIGH FAT DIET INDUCED RATS

Parameters	Control	HFD	Orlistat (12mg/kg)	Formulation (30 mg/kg)	Formulation (60 mg/kg)
Initial body weight (g)	182.83 ± 2.10	184.5 ± 1.78#	186.33 ± 2.33*	192.5 ± 1.20	190.5 ± 1.20
Final body weight (g)	215.5 ± 2.27	249 ± 1.52#	167 ± 2.46*	182.83 ± 1.10*	189.33 ± 1.05*
Food intake (g/week)	175.2 ± 1.22	264.3 ± 1.08#	224.2 ± 1.85*	231.5 ± 0.95*	226 ± 1.55*

Values are expressed Mean ±SEM (n=6), # P<0.05 compared with control, *P<0.05 compared with HFD, One way ANOVA followed by Tukey's post hoc test

TABLE 6: EFFECT OF FORMULATION AND ORLISTAT ON LIPID PARAMETERS IN HIGH FAT DIET INDUCED RATS

Parameters	Control	HFD	Orlistat (12mg/kg)	Formulation 30 mg/kg	Formulation (60 mg/kg)
TC (mg/dl)	72.83 ± 0.79	111.8± 0.83#	83.17 ± 0.87 *	92.17 ± 0.83*	80.67 ± 1.90*
TG (mg/dl)	215± 1.52	264.2± 1.16#	231.5 ± 1.33*	247.2 ± 1.72*	236.7 ± 1.62*
HDL-c (mg/dl)	65.83± 1.55	38.35 ± 0.98#	51.2 ± 1.03*	43.83 ± 1.51*	52.67 ± 1.52*
LDL-c (mg/dl)	102.7± 1.66	130.2 ± 1.40#	110.2 ± 1.07*	125.0 ± 1.31*	115.3 ± 1.02*

Values are expressed Mean ±SEM (n=6), # P<0.05 compared with control, *P<0.05 compared with HFD, One way ANOVA followed by Tukey's post hoc test.

CONCLUSION: Low water solubility of BCS class II and IV drugs is responsible for poor oral absorption and has been fixed through a "key strategy" called lipid-based drug delivery system. With the arrival of low energy and self-emulsification method have regained their importance as SNEDDS.

The gap between SNEDDS and their commercial products is due to lack of complete understanding of their *in-vivo* behavior and so far has been filled by the development of a reflective in-vitro test. Despite advancement mentioned above and modifications in SNEDDS, there are still areas that need to be focused on making SNEDDS a future drug delivery carrier. Although different efficient and predictive *in-vivo* tests were developed to understand SNEDDS, but still we lack enough *in-vivo* information. This technique can minimize cost and cut short the number of formulations needed to identify the optimum composition. The Orlistat SNEDDS formulation was successfully developed, optimized, and characterized.

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