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DEVELOPMENT , OPTIMIZATION AND CHARACTERIZATION OF SMEDDS OF POORLY SOLUBLE DRUG

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Abstract: Lipophilic drugs' low aqueous solubility and low bioavailability make oral delivery a significant challenge. The capacity of self-micro emulsifying drug delivery systems (SMEDDSs) to improve solubility and bioavailability has drawn attention to this issue. Numerous formulation-related factors, including droplet size, charge, oil/surfactant ratio, and surfactant concentration, affect how well the drug compound from the SMEDDS is absorbed orally. Ibuprofen a BCS class II drug with poor aqueous solubility was selected for development of SMEDDS. Ibuprofen's solubility in various oils, surfactants, and cosurfactants was examined. Capmul MCM (oil), Cremophore RH 40 (surfactant), and polyethylene glycol 400 (cosurfactant) were used to prepare the Ibuprofen SMEDDS. Several Evaluation parameters were performed to determine the optimization of Ibuprofen SMEDDS.

IndexTerms **- Ibuprofen, SMEDDS, Bioavailability, Capmul MCM, Cremophore RH 40, PEG 400.**

I. INTRODUCTION

Self-emulsifying drug delivery systems (SEDDS) are defined as an isotropic mixture of natural or synthetic oils, solid/liquid surfactants, one or more hydrophilic solvents, and cosolvents/surfactants. When these formulations are mixed with gastric fluid after oral administration, fine oil-in-water (O/W) emulsions or microemulsions (SMEDDS) can be formed. Self-emulsifying nanoscale drug delivery systems (SNEDDS) are a novel technology consisting of oils, surfactants, and cosurfactants/cosolvents that spontaneously form oil-in-water nanoemulsions upon exposure to gastric fluid. Self-emulsifying drug delivery microsystems are desirable for maintaining hydrophobic drugs dissolved in the lipid matrix, and the formed micelles provide a large surface area for drug absorption. Therefore, SMEDDS formulations can enhance the absorption of drugs with low water solubility and limited dissolution rates, thereby enhancing the therapeutic efficacy of the drugs.[1]

I.1. Advantages of SMEDDS [2]

- Improved oral bioavailability
- Ease of production and scale-up
- Reduced inter- and intra-subject variability and food effects
- Peptide delivery potential
- Increased drug loading capacity

I.2. Biopharmacological aspects of SMEDDS

Although not fully understood, it is now generally accepted that lipids can enhance bioavailability through several potential mechanisms, including: Altering (reducing) gastrointestinal transit, thereby slowing the rate of delivery to the site of absorption and increasing the time required for dissolution; Increasing the effective solubility of the drug in the lumen: - The presence of lipids in the gastrointestinal tract increases the secretion of endogenous bile acid lipids, including bile acids (BS) and phospholipids (PL) and cholesterol (CH), resulting in: Formation of mixed BS/PL/CH micelles in the intestine and increased solubilizing capacity of the gastrointestinal tract. However, when (exogenous) lipids are introduced into these structures, either directly (if sufficiently polar) or by secondary insertion following digestion, the micellar structures swell, further increasing the solubilizing capacity. Stimulation of intestinal lymphatic transport: - For highly lipophilic drugs, lipids can indirectly increase bioavailability by enhancing the extent of lymphatic transport and reducing first-pass metabolism. Alterations in the biochemical barrier function of the gastrointestinal tract: - It is clear that some lipids and surfactants can attenuate the activity of intestinal efflux transporters, as demonstrated by the p-glycoprotein efflux pump, and may also reduce the extent of enterocyte-based metabolism. Alterations in the physical barrier function of the gastrointestinal tract: - Various combinations of lipids, lipid digestion products, and surfactants have

been shown to have properties that enhance permeability. However, in most cases, passive intestinal permeability is not considered a major barrier to bioavailability for most poorly water-soluble and especially lipophilic drugs. [3,4]

I.3. Criteria for selecting suitable drug candidates

- Lipid formulations provide a potential platform for improving oral bioavailability of drugs, particularly those classified in Biopharmacology Classification System (BCS) Class II and IV.
- A key indicator of the potential utility of a lipid formulation is the evaluation of the drug's lipophilicity (log P) and its solubility in pharmaceutically acceptable lipid excipients. The partition coefficient (log P) is an important criterion in designing lipid systems.
- Another indicator of the potential success of a lipid formulation is that a strong positive food effect is observed when the drug is taken with a fatty meal, compared to when taken on an empty stomach.
- SMEDDS can provide reproducible blood concentration profiles by improving the rate and extent of absorption.
- SMEDDS systems generally offer the advantage of increased drug loading capacity compared to lipid solutions due to the solubility of poorly soluble drugs in water with intermediate partition coefficients [5].

Ibuprofen is the drug that belongs to the class of Non-Steriodal AntiInflammatory Drugs. It is often used to relieve the symptoms of Headaches, Painful periods, Sprain & Strain.Generally, the dose of the Ibuprofen present in marketed preparations are higher (dose). The Higher dose of Ibuprofen leads to minor & major side effects such as kidney damage i.e called Nephritis. Ibuprofen is a less water soluble drug. As the Self-Microemulsifying Drug Delivery System enhances the bioavailability of drug, therapeutic dose can be reduced. [6]

Present study focuses on development of Self microemulsifying drug delivery system in order to enhance the bioavailability and reduce dose of the targeted drug.

II. MATERIAL

Ibuprofen was received as a gift sample from Amoli chemicals Ambernath. Capmul MCM, Cremophor RH 40, and polyethylene glycol 400 were purchased from GATTEFOSSE. All other reagents and chemicals used were of analytical grade.

III. METHODOLOGY

III.1. Preformulation Study

III.1.1 Melting Point Melting point of the drug Ibuprofen was determined by a capillary method for the determination of any impurity. The obtained result was compared with the reported data.

III.1.2. FTIR Spectroscopy

The identification of plain Ibuprofen powder was carried out using FTIR. The FTIR spectra of the drug was determined by ATR technique. A background scan was taken followed by the IR scan of the sample in the range of 4000-400 cm-1.

III.1.3Ultraviolet Spectroscopy Identification of Ibuprofen was performed by UV spectrophotometry using a Shimadzu UV-1800 spectrometer (Shimadzu Corp. Japan). Accurately weighed 50 mg of Ibuprofen was transferred to a 50 ml volumetric flask. After dissolving in a sufficient amount of methanol, the volume was made up to 50 ml by adding methanol. Exactly 10 ml of stock solution was pipetted and diluted to 100 ml with methanol (10 µg/ml). The spectra were recorded in the range of 220–370 nm. The λmax of ibuprofen was obtained at 263 nm.Calibration curve was established using suitable concentration range[7]

III.1.4 Selection of lipid phase [8]

A suitable amount of Ibuprofen was added to the vial containing 1 gm of prewarmed oil and the solution was vortexed using the cyclomixer for 4-5 min to facilitate uniform mixing. To ascertain the degree of the drug solubility in the first aliquot, mixes in vials were visually inspected. The second portion was added to this vehicle where the first portion of the drug was completely dissolved, and the same procedure was repeated until the vehicle became completely saturated with the drug. The entire amount of API added to completely saturate the vehicle was reported

III.1.5 Emulsification Efficiency study [9,10]

Selection of Surfactant

The emulsifying efficiency of various surfactants was tested using the shake flask method. 1 g of the selected oil and 1 g of the preheated surfactant were placed in a vial, circulated for 5 minutes, and heated at 40–50°C. 50 mg of the solution was placed in a beaker, 50 ml of distilled water was added, and the mixture was slowly shaken and transferred to an iodine flask. The number of inversions required to obtain a clear solution was recorded. After the flask was left to stand for 2 hours, phase separation was observed. If no phase separation was observed, the transmittance (%) was observed at 638.2 nm using distilled water as a blank.

Selection of co-surfactant:

Mixing 1 gm of oil, 1 gm of surfactant and 1 gm of co-surfactant, the mixture is then homogenized using mild heat (40-50^{0}c). 50 mg were accurately weighed and diluted with 50 ml distilled water to create a fine emulsion. The relative turbidity of the

produced emulsion was evaluated visually. Emulsions showing no phase separation after 2 hours were screened for % Transmittance

III.2. Formulation of Liquid SMEDDS

From preformulation study, Capmul MCM, Cremophor RH 40, and polyethylene glycol 400 were selected as oil, surfactant and cosurfactant respectively. Nine trial batches of liquid SMEDDS were prepared by taking various ratios of oil, surfactant and cosurfactant as given in Table no.1. Oil, surfactant and cosurfactant were mixed a vial and vortexed by cyclomixer. A fixed amount of drug was loaded in all formulations.

Table No: 1 Trial batches of Ibuprofen Liquid SMEDDS

Formulation Codes	Ratio of excipients (%w/w)	
	Oil : Mix	Surfactant: Co-surfactant
F1	1 : 1	1 : 1
F2	1 : 1	2 : 1
F3	1 : 1	3 : 1
F4	1 : 1.5	1 : 1
F5	1 : 1.5	2 : 1
F6	1 : 1.5	3 : 1
F7	1 : 2	1 : 1
F9	1 : 2	2 : 1
F9	1 : 2	3 :1

III.3 Optimization of trial batches

III.3.1 Spontaneity of emulsification and Phase separation [11]:-
The formulation was heated to 50°C to homogenize the components. 50 mg of each formulation was placed in a glass-stoppered conical flask and diluted with 50 ml of distilled water. Ease of emulsification was assessed by counting the number of flask inversions required to obtain a homogeneous emulsion. The formed emulsion was allowed to rest for 24 hrs and observed for phase separation.

III .3.2 %Transmittance [12]
Emulsions which have not shown phase separation after 24hrs were assessed for their % Transmission. The percent transmittance of the system is measured at wavelength 638.2 nm using an ultraviolet-visible spectrometer. The percent transmittance can be analyzed by appropriately diluting 1 ml of the SMEDDS formulation.

III.3.3 Freeze-thaw cycles[13]
Formulations showing good % Transmission were subjected to freeze-thaw cycles. In this study, the SMEDDS formulation was diluted with deionized water at a ratio of 1:20 and subjected to two freeze-thaw cycles between -20°C and 25°C and stored at each temperature for 48 h. After 48 h, the samples were observed for phase separation (or) precipitation.

III.3.4 Dilution Resistance[14]
The dilution stability of SMEDDS was studied using a slight modification of the method of Date and Nagarsenker. SMEDDS was diluted 100-fold and 1000-fold using various dissolution media such as water, pH 1.2 buffer, pH 4.5 buffer and pH 6.8 buffer. The diluted microemulsions were stored for 24 h and observed for any signs of phase separation or drug precipitation.

III.3.5 Globule Size & Zeta Potential Measurement[15]
Formulations which were stable to freeze thaw cycle and robust to dilution were selected for globule size and zeta potential measurement. This is an accurate method to assess stability. Particle size & zeta potential of the microemulsion was measured using Photon Correlation Spectroscopy (PCS) using a Horiba Zeta Sizer. Before measurement, the microemulsion is diluted twice with double distilled water and filtered just before placing it in the cuvette. Measuring the size of the spheres helps to maintain the size distribution within the desired range. For Zeta potential,The sample is placed in a transparent disposable zeta cell and the results are recorded.
The zeta potential value indicates the surface charge of the dispersed spheres. The higher the zeta potential value, the more stable it is. Particles with a zeta potential greater than 30 mV or greater than or equal to -30 mV are generally considered stable.

III.4. Characterization of the optimized formulation.

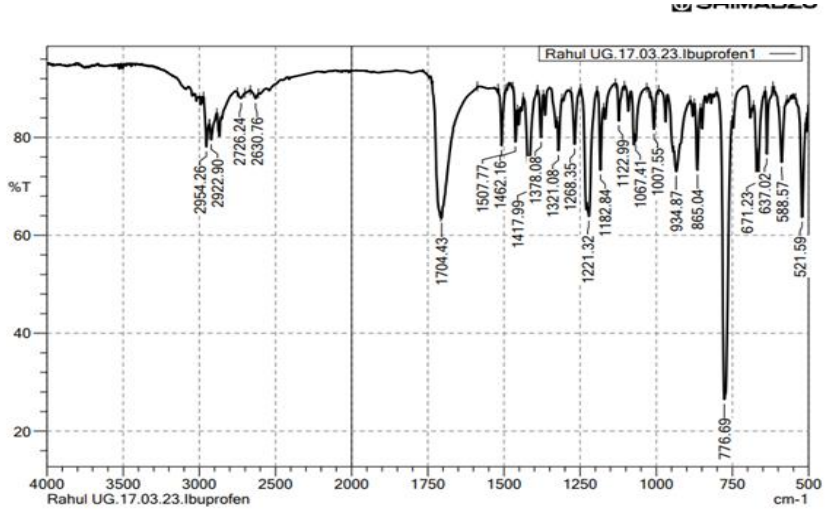
III.4.1.Drug content analysis [16]:
The drug content was calculated using the UV-Vis Spectophotometer. Formulation containing known concentration of Ibuprofen was dissolved in methanol. To extract Ibuprofen in the methanol solution, it was ultrasonicated for 10–15 minutes and then filtered. The absorbance of the filtrate was measured at 263 nm using an ultraviolet-visible spectrometer. The amount of Ibuprofen was determined using the Beer-Lambert equation of the drug standard curve in methanol.

III.4.2. Cloud point measurement. [17]
The L-SMEDDS diluted 1:250 in phosphate buffer pH 6.8 was placed in a water bath and the temperature was gradually increased while visual inspection was performed until turbidity was formed. The cloud point is the temperature at which emulsion shows turbidity..

III.4.3. Accelerated stability study [18];
An accelerated stability study was performed to determine the storage life. The SMEDDS formulation was stored at constant temperature and ambient humidity conditions (40 ± 0.5) for 7 days. 9. Study on dissolution in phosphate buffer solution, pH 6.8.[19] The in vitro release of ibuprofen SMEDDS was tested using a USP-2 paddle apparatus. The ibuprofen microemulsion was placed in the paddle and placed in 900 ml of phosphate buffer solution, pH 6.8 as the dissolution medium at 37 °C. The blade rotation speed was maintained at 50 rpm. At specified intervals, 5 ml samples were taken and an equal volume of fresh dissolution medium was added.

IV. RESULUT AND DISCUSSION

IV.1. Preformulation studies:
IV.1. 1. Melting point
Melting point of the drug Ibuprofen was found to be 76 c+-1. At temperature 74'C the slight changes in the consistency of drug powder filled in the capillary tube was observed. Melting was started at 74'C and at 76'C it was observed that the drug was completely melted.
IV.1. 2.Fourier Transform Infra-Red (FTIR) Spectroscopy:
FTIR shows the alkane, carboxylic acid and alcohol functional group. IR spectra match with standard spectra of Ibuprofen confirming the purity of the drug.



Stretch bond	Wavelength (cm-1)
Alkane C-H (medium peak)	2726.24
Carboxylic acid CO	1704.43
Alcohol O-H stretch (weak broad)	2954.26

Fig 1: Fourier Transform Infra-Red (FTIR) Spectra of Ibuprofen.

IV.1. 3.Ultraviolet visible (UV-Visible) spectroscopy:
The absorbance maxima for the drug was found to be 263 and 223 nm in methanol and 6.8 pH phosphate buffer respectively. Calibration curve is obtained in the concentration range of 10-70 ppm in methanol and phosphate buffer 6.8 pH and it has shown the r2 value of 0.96.

IV.1. 4. Selection of lipid phase

Solubility of Ibuprofen was assessed in various oily phases as given in figure 2. On the basis of solubility, Capmul MCM was selected as the lipid phase for formulation of SMEDDS.

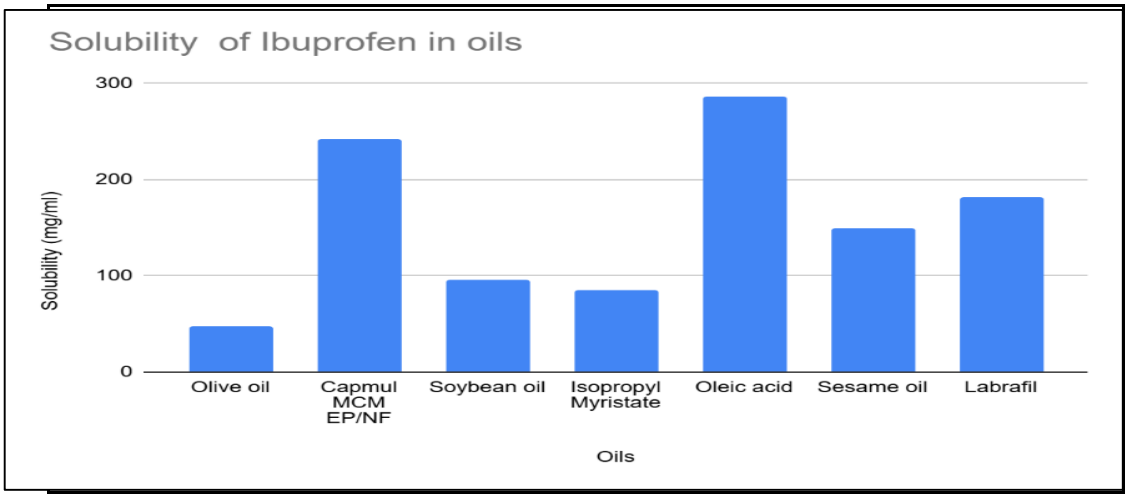


Fig 2: Solubility of Ibuprofen in various lipid phases

IV.1. 5.Selection of Surfactant:

The surfactants were compared for their clear emulsification efficiency for the selected oil phase. Cremophor El and cremophor RH 40 show clear emulsion after minimum number of flask inversion and high % Transmittance. other surfactants after the many inversions didn't show clear emulsion. Hence, cremophor El and cremophor RH 40 were selected for further selection of co-surfactant by spontaneity of emulsification study

Table No 2: Emulsification of Capmul MCM with different surfactant

Surfactant	No of flask inversions	Results	% Transmittance
Tween 20	17	Turbid Solution	63
Tween 60	16	Milky appearance	75
Tween 80	30	Turbid Solution	58
Kolliphor p-188	22	Turbid Solution	62
Kolliphor p-407	20	Milky appearance	65
Cremophor EL	15	Clear	72
Cremophor RH 40	12	Clear	80

IV.1. 6. Selection of Co-surfactant:

Addition of co surfactant to the surfactant containing formulation lowers the interfacial tension and fluidizes the hydrocarbon region of the interfacial film. Co surfactants were added to increase the spontaneity of self emulsification efficiency of selected surfactants.

PEG 400 with Cremophor RH 40 displayed better transmittance of 91.59% with lower number of flask inversion. Hence, PEG 400 was selected as co surfactant

Table No 3: Emulsification of Capmul MCM & Cremophore RH40(1:1) with different Co-surfactant

Co-surfactant	No of flask inversions	% Transmittance (1 to 10 dilution)
Propylene glycol	6	90.07
PEG 200	9	92.09
PEG 400	5	96.59
Transcutol	11	86.71
Ethanol	7	84.06
Labrafac	8	87

IV.2. Optimization of trial batches:

IV.2.1 . Spontaneity of emulsification ,Phase separation & % Transmission

Table No 4: Phase separation, Ease of emulsification and % Transmittance of the trial batches

Formulation	Phase separation after 24 hrs.	No. of F.I.	% Transmittance
F1	Phase separation	8	-
F2	No Phase separation	5	92.68
F3	No Phase separation	5	93.54
F4	No Phase separation	5	93.75
F5	No Phase separation	3	95.71
F6	No Phase separation	3	93.97
F7	No Phase separation	2	93.97
F8	No Phase separation	2	95.49
F9	No Phase separation	2	97.29

Except F1, all other formulations were stable after 24hrs of emulsification. The % transmittance of formulation F2-F9 was found to be above 90%, so all were subjected to the Freeze Thaw Cycle.

IV.2.2.Freeze Thaw cycle:

L-SMEDDS were subjected to a freeze thaw cycle and ease of emulsification, phase separation & % Transmittance of formulations after 3 cycles was checked. It was observed that there was no precipitation or phase separation seen for all formulations but only formulations F2, F3, F4, F6 have shown turbidity and transmittance has dropped below 90%. So formulations F5, F7, F8, F9 with no phase separation and no significant change in % Transmittance were considered stable formulation and were subjected for assessment of robustness to dilution.

IV.2.3. Dilution Resistance

Formulations F5, F7, F8 and F9 were diluted to 100 & 1000 folds with 0.1N HCL and Phosphate buffer of pH 6.8. % Transmittance of resulting solution was checked.as per table no 6, F5 is rejected and the remaining formulations were evaluated by zeta potential and globule size.

Table No 5: % Transmittance of trial batches on dilution with 0,1N HCl and Phosphate buffer of pH 6.8

Formulation	0.1N HCL (% T)		Phosphate buffer 6.8 pH (%T)	
	1:100	1:1000	1:100	1:1000
F5	77.7	95.5	57.01	91.83
F7	80.9	97.1	54.62	107.89
F8	76.9	96.6	53.33	92.68
F9	85.8	96.2	52.23	94.18

IV.2.4 Globule Size & Zeta Potential Measurement

After a particular concentration of surfactant, the particles start coagulating. Hence, particle size increases or globule size increases that's why the F9 shows bigger particle size than the F7 and F8. F7 has particle size under the range of 100 nm so F7 formulation shows better results. Oil carries a negative charge due to the existence of free fatty acids. Therefore, SMEDDS also shows negative potential. Particles with zeta potential more positive than +30 mV or more negative than -30 mV are normally considered stable.

F7 has zeta potential -34.5 mV which is outside the range of -30 mV to +30 mV so F7 was selected as optimized formulation

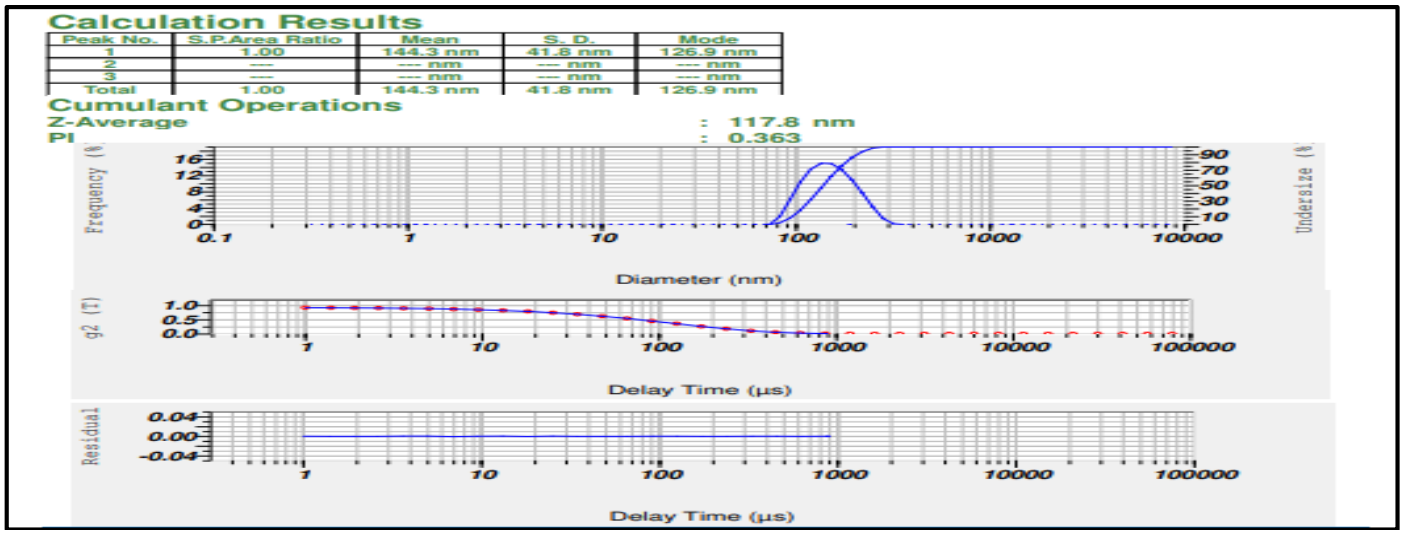


Fig 3: Globule size of F8

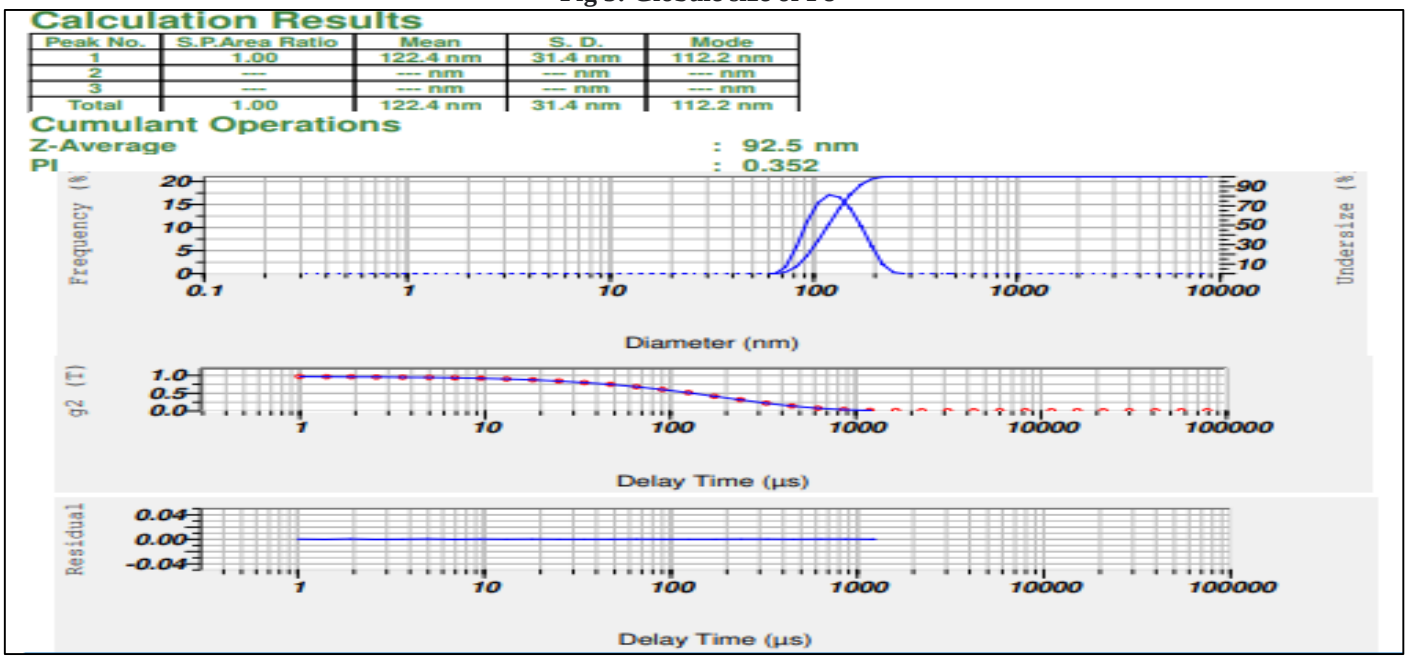


Fig 4: Globule size of F7

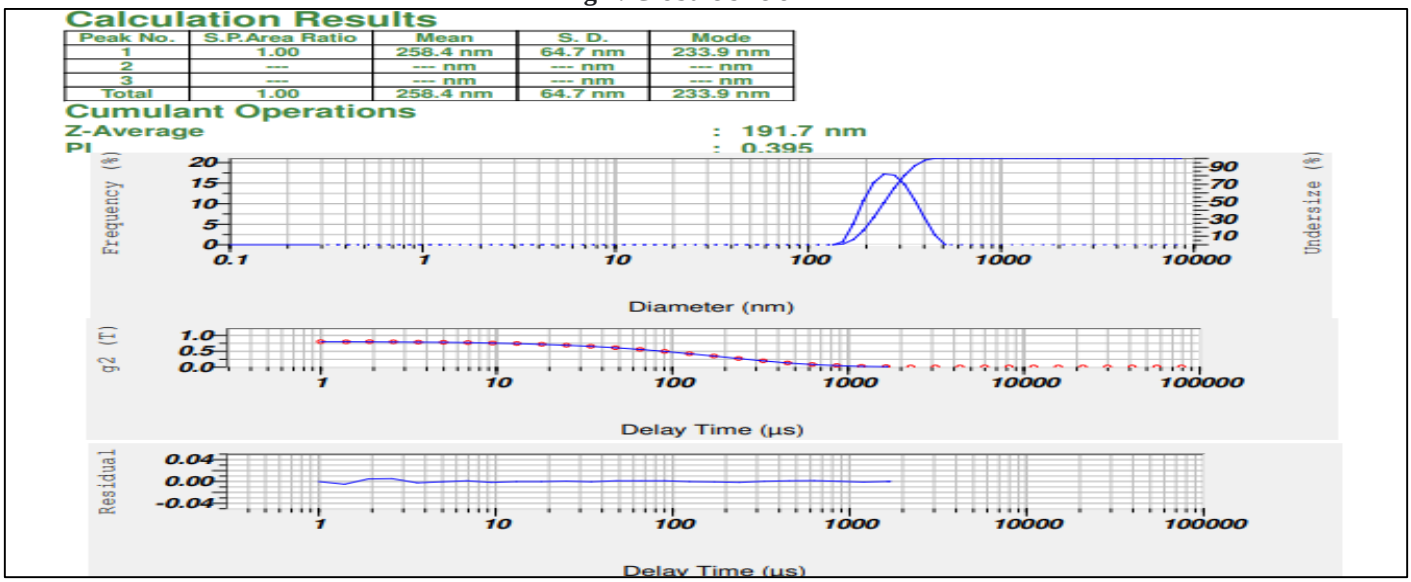


Fig 5: Globule size of F9

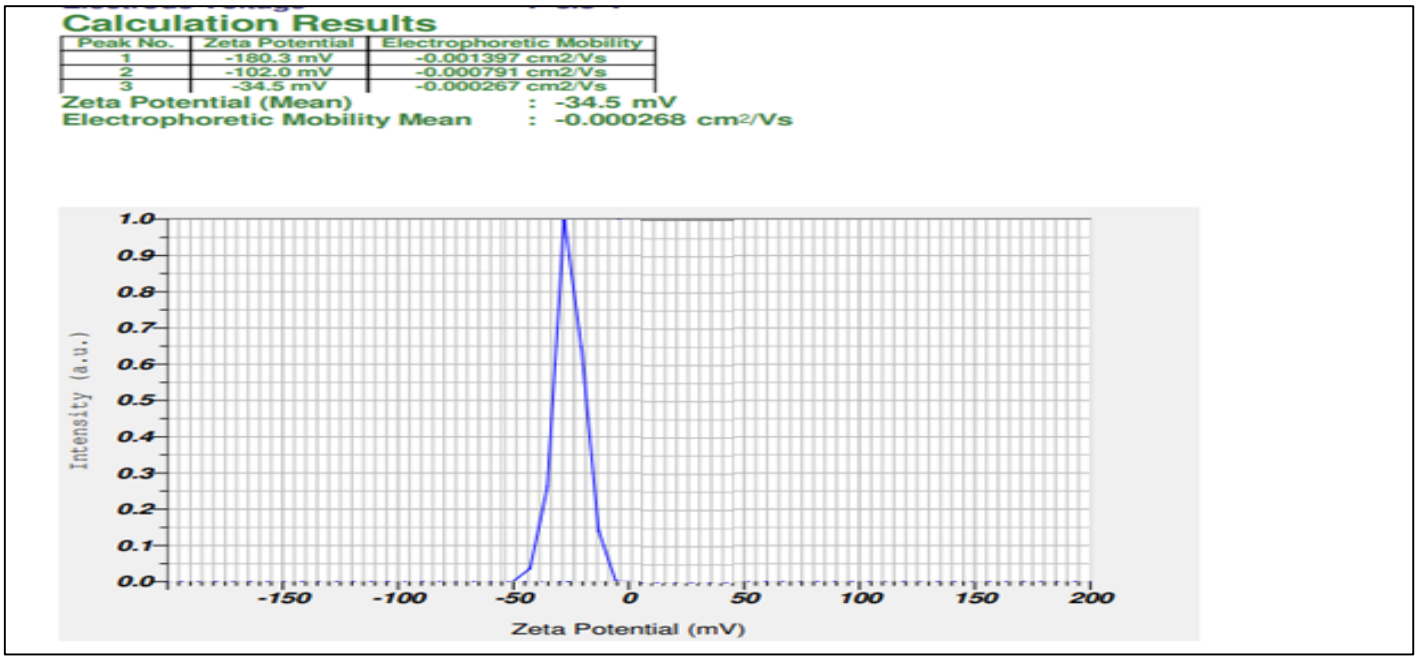


Fig 6: Zeta potential of F7

IV.3. Characterization of Optimized formulation

IV.3.1 Determination of drug content

Drug content of the optimized batch of L-SMEDDS was found to be as 104.23 %w/w.

IV.3.2 Cloud point measurement

The cloud point for SMEDDS should be above 37°C to avoid difficulties with instability. The optimized SMEDDS formulation's cloud point was discovered to be 65 ° ± 1.0°C. As a result, in-vivo delivery of the SMEDDS should result in the formation of a stable microemulsion.

IV.3.3. Accelerated stability Studies:

In order to evaluate accelerated stability, L-SMEDDS were kept in a stability machine for 7 days with constant temperature. After 7 days it was discovered that there was no precipitation or phase separation seen. Hence, it was considered to be a stable formulation.

IV.3.4. In -Vitro drug dissolution study

Cumulative % release of L-SMEDDS filled in hard gel capsule was compared with cumulative % release of plain ibuprofen filled in capsules. L-SMEDDS shows faster and higher dissolution of the drug indicating improved absorption of drug *in-vivo*.

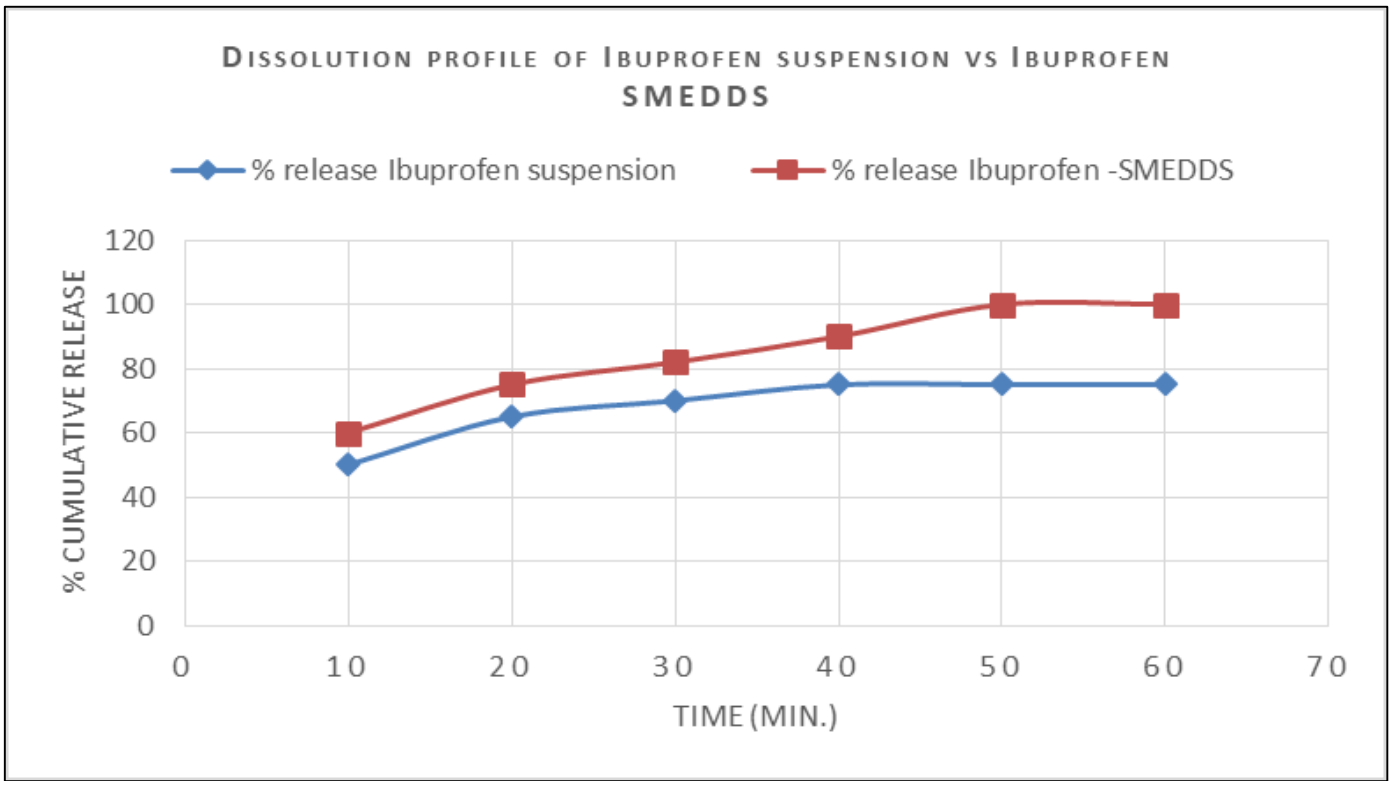


Fig. 7: Dissolution profile of Ibuprofen suspension vs Ibuprofen L-SMEDDS

V. CONCLUSION

A self micro emulsifying drug delivery system of Ibuprofen was developed with Capmul MCM as an oily phase, Cremophor RH 40 serving as the surfactant and PEG 400 as a co-surfactant. According to the result of the investigation, the liquid SMEDDS that had been created was physiologically stable, had good self-emulsification efficiency and was thermodynamically stable. As a result, the lipid based self micro emulsifying formulation was prepared, characterized & Optimized

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