Research Article

Formulation and Evaluation of Self Micro Emulsifying Drug Delivery System for BCS Class - II Drug Ketoprofen

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ABSTRACT

Ketoprofen, a widely prescribed analgesic drug which belongs to BCS class II and exhibit low and variable oral bioavailability due to its poor aqueous solubility. To enhance the solubility and dissolution rate of poorly water soluble drug Ketoprofen, Self-micro emulsifying drug delivery system (SMEDDS) was developed and evaluated. Solubility study, emulsification ability, ternary phase diagram and central composite design (CCD) were used as primary tools to select the components of the system and optimize the composition of liquid Ketoprofen SMEDDS. The globule size of optimized liquid SMEDDS was 105.08±5.16nm, zeta potential -4.23mV and polydispersity index 0.097, % Transmittance 98.45% and self emulsification time 28 sec. Optimized formulation F3 containing Oleic acid (10%), Tween 80 (30%) and Propylene glycol (60%) was adsorbed onto inert solid carrier Aerosil 200 in 1:1 ratio to form dry, free flowing powder. The liquid crystal phase viscosity increased significantly with increasing amount of aerosil 200 which in turn increases average globule size of solid SMEDDS (303.69±0.933nm) and slowers drug release. S-SMEDDS also characterized for DSC, XRD, SEM etc. The *in vitro* dissolution study indicates improved dissolution characteristics with higher percent drug release for solid SMEDDS (89.78%) compared to marketed preparation (81.26%) and pure drug (71.32%). In conclusion, S-SMEDDS for Ketoprofen holds promise to be developed as potential system for improved oral delivery.

Keywords: Ketoprofen, Liquid SMEDDS, Aerosil 200, Solid SMEDDS, Dissolution.

INTRODUCTION

Approximately 40% of new drug candidate emerging from drug discovery process displays low solubility in water, which leads to poor bioavailability, high intra subject/inter subject variability and lack of dose proportionality. Among lipid based formulations, much attention has been focused on self-micro emulsifying drug delivery system which has successfully improved solubility and bioavailability of poorly water soluble drugs.[1,3]

Self-micro emulsifying formulation comprises isotropic mixtures of natural or synthetic oils with lipophilic or hydrophilic surfactants and co-surfactants, which spontaneously emulsify when exposed to the GIT fluids to form oil-in-water emulsions or microemulsions.[2] SMEDDS is generally prepared as liquid dosage form which has some shortcomings such as incompatibility with the shells of hard or soft gelatine capsules, and complex process of manufacturing.[4] So to overcome these problems, studies on solid self-micro emulsifying drug delivery system (S-SMEDDS) have come into limelight.[8,9] Ketoprofen is a non steroidal anti-inflammatory drug (NSAID) with well-established analgesic and antipyretic properties. It is widely used in the treatment of rheumatoid arthritis, osteoarthritis, and a variety of other acute and chronic musculoskeletal disorders.

Ketoprofen is a poorly water-soluble drug (log P 0.98) and is absorbed rapidly by the oral route. Peak plasma levels occur within 0.5 to 2 hours, after which the therapeutic plasma concentration abruptly falls to very low levels. Different formulation approaches that have been sought to increase bioavailability of Ketoprofen include matrix pellets of nanocrystals, sustained-release microparticles, and floating delivery systems. In the present investigation the solid self-micro emulsifying drug delivery system of Ketoprofen was prepared.

SMEDDS requires lesser excipients to convert in solid dosage forms such as tablets and capsules and may retard the drug release as well. Increasing the amount of co-surfactant was found to increase the drug release.[4,5]

MATERIALS AND METHODS

Materials

Ketoprofen was obtained as gift sample from Sava Pharmaceutical Pvt. Ltd., Pune, India. Methanol (Merck chemicals, Mumbai), Oleic Acid (Merck chemicals, Mumbai), Tween 80 (Molychem, Mumbai), Propylene glycol (Loba chemicals, Mumbai), Aerosil 200 (Research lab) fine Chem Industries Mumbai, other chemicals and solvents was also of analytical grade.

Determination of Aqueous Solubility

The solubility of drug was determined in various solvents by adding excess quantity of drug to the vial containing solvent. The mixture was stirred, sonicated and filtered. Then filtrate was quantified by UV in triplicate.[6,7]

Determination of Saturation Solubility of Ketoprofen in Different Oils, Surfactants, and Co-surfactants

The solubility of Ketoprofen in various oil phases, surfactants, co-surfactants/co-solvents was determined by dissolving an excess amount of drug in 2 ml of each

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selected individual oils, surfactants and co-surfactants contained in stoppered vials (5 ml capacity) separately. The liquids were mixed using a vortex mixer and the vials were then shaken using orbital shaker at 37°C±1°C for 72 hrs to reach equilibrium. The equilibrated samples were removed from the shaker and centrifuged (3000 rpm) for 15 min. The supernatants were taken out and filtered through a membrane. The concentration of Ketoprofen in various phases was determined by UV spectroscopy (Shimadzu 1800) at their respective λmax.[7]

Construction of Pseudo Ternary Phase Diagram

Based on the observations of solubility studies, components of emulsion viz. oil phases, surfactants and co-surfactants indicating highest solubility of Ketoprofen were selected. The surfactants and co-surfactants were blended together in 1:1, 1:2, and 1:3 proportions respectively. These blends of surfactants:co-surfactants (Smix) were mixed with oily phase by adding small amounts with constant stirring. The proportions of oil:Smix were varied as 9:1, 8:2, 7:1, 6:4, 5:5, 4:6, 3:7, 2:8 and 1:9. The resultant blends were titrated with distilled water in 0.5% (w/w) increment was added taking care for proper stirring. Systems were allowed to reach equilibrium and the samples were checked visually for clarity. The pseudo ternary phase diagrams were constructed for each system of oil, surfactant, and co-surfactant. The point indicating the clear and isotropic mixtures were considered. The data obtained was subjected to CHEMIX Software for construction of ternary plot.[8]

Formulation and Optimization using Central Composite Design (CCD)

Central composite design (CCD) is Response surface methodology (RSM) experimental design suitable for formulation and optimization of SMEDDS. CCD determines the influence of the selected variables on the subject responses. Ketoprofen loaded SMEDDS was formulated by simply mixing the drug (1%w/w), with Oleic acid, Tween 80 and Propylene glycol with gentle stirring at room temperature to dissolve properly and observed for clarity. Central composite design (CCD) was used to optimize the formulation of Ketoprofen loaded SMEDDS. Based on the previous preliminary experimental studies, two formulation parameters, the oil percentage and surfactant/co-surfactant ratio, were identified as important factors responsible for the characteristics of SMEDDS. The concentration ranges of these two factors were determined on the basis of feasibility of SMEDDS formation. So the values were as, oil percentage (X1): 10-35%; Smix ratio (X2): 60-90%. Globule size (Y1), % transmittance (Y2) and self emulsification time (Y3) are selected as the response factors for assessing the quality of SMEDDS. A two-factor, five-level CCD was implemented to find out the main effects as well as the interactions of the two independent variables on three responses under study. The data obtained for three responses were fitted using Design expert software 7.1.3 to second order polynomial model, represented as follows:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_1^1 + b_4X_2^2 + b_5X_1X_2 \qquad (1)$$

Where Y corresponds to predicted response, X_1 and X_2 correspond to the studied factors, b_0 is an intercept, and b_1–b_5 is regression coefficient. The response surface graphs were plotted for three responses.[8]

Preparation of Liquid SMEDDS

SMEDDS formulation was prepared with varying ratios of oil, surfactant and co-surfactant. The surfactant and co-surfactant (Smix) tested were taken in the ratio 1:2. A single dose 1% w/w of Ketoprofen was incorporated in all formulations. The formulations were prepared by dissolving the drug in surfactant followed by addition co-surfactant and oil in a glass vial. The mixtures were stirred continuously by vortex mixing and heated at 40°C to obtain a homogenous isotropic mixture. The SMEDDS formulations were stored at ambient Temperature until further use.[7,8]

Characterization of Liquid SMEDDS

Determination of Globule Size

Emulsion globule size was determined by using photon cross correlation spectroscopy Nanophox (NX0088). Emulsion (50µL) was diluted with the 5ml distilled water. Sample was placed in polystyrene cuvette path length 1cm which was placed in thermostatic sample chamber maintained at 25°C and 3 run for 60sec were performed. Detection was carried out at scattering angle of 90°.

% Transmittance

The clarity of the formulation was observed by measuring % Transmittance of all formulations at 638.2nm in UV spectrophotometer using double distilled water as blank.[8]

Determination of Self-Emulsification Time

The assessment of formulation was done by adding 1 ml of each formulation to standard apparatus (USP Type II) containing 100 ml purified water at 37°C, gentle shaking was provided by paddle rotating at 50 rpm. Emulsification time was assessed visually.[9]

Preparation of Solid SMEDDS by Adsorption Method

S-SMEDDS was prepared by mixing liquid SMEDDS containing Ketoprofen with aerosil 200 in 1:1 proportions of F1, F3, F5 formulations.

The liquid SMEDDS of Ketoprofen was adsorbed onto aerosil 200 carrier by physical mixing process.

After each addition, mixture was homogenized by triturating using mortar and pestle to ensure uniform distribution of the formulation.

Resultant damp mass was passed through sieve no. 120 and dried at ambient temperature and stored until further use.[10,11]

Characterization of Solid-SMEDDS

% Drug Content

The content of Ketoprofen in each S-SMEDDS formulation was determined by UV spectrophotometer at λmax 254.60nm.

Powder Flow Properties

Bulk Density

It is the ratio of total mass of powder to the bulk volume of powder.

It was measured by filling the weighed powder into a measuring cylinder and the volume noted in gm/ml.

$$Bulk\ density = Mass\ of\ powder/Bulk\ volume$$

Tapped Density

It is the ratio of total mass of powder to the tapped volume of powder.

The tapped volume was measured by tapping the powder to constant volume and represented with unit gm/ml.

$$Tapped\ density = Mass\ of\ powder/Tapped\ volume$$

Angle of Repose

The angle of repose of S-SMEDDS was determined by funnel method.

Accurately weighed sample were taken in a funnel. Height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of S-SMEDDS powder.

The powder samples were allowed to flow through funnel freely onto the surface.

The diameter of the powder cone was measured and angle of repose calculated using the following equation:

$$\tan \theta = h/r\ (or)\ \theta = \tan^{-1} h/r$$

Where θ - Angle of respoe, h - height, r - radius

Carr's Index

Carr's Compressibility Index is a measure of powder flow properties and was calculated using the following equation:

$$Carr's\ Index = \frac{Tapped\ Density - Bulk\ Density}{Tapped\ Density} * 100$$

Hausner Ratio

A similar index like compressibility index has been defined by Hausner. Hausner's ratio is the ratio of tapped density to bulk density and can be calculated by using the following equation.[12]

$$Hausner\ ratio = Tapped\ Density/Bulk\ Density$$

Globule Size Determination

S-SMEDDS was checked by determining globule size by using photon cross correlation spectroscopy Nanophox

(NX0088).[9,12]

Zeta Potential

The particle is one of the factors determining the physical stability of emulsion and suspension. The particles are equally charged, the higher is the electrostatic repulsion between particles higher is the physical stability. Typically particle charge is quantified by zeta potential. Zeta potential of diluted sample was determined using (Beckman Coulter).[12,13]

Drug-Exicient Compatibility Study Using FT-IR Spectroscopy

The IR spectrum of Ketoprofen, physical mixture and S-SMEDDS was recorded using Fourier transform infra red spectrophotometer (FTIR4100 jasco-japan). Sample preparation done by a mixing the drug with potassium bromide (KBr), triturating it in glass mortar. Finally sample was placed in the sample holder and scanned over a frequency range 4000-400cm^{-1}.[13]

DSC Analysis

The DSC thermo grams were recorded for drug and S-SMEDDS using differential scanning calorimeter. Approximately 2-5 mg of each sample was heated in a pierced aluminum pan (Al-Crucibles, 40 rate of 50ml/min. Thermal data analyses of the DSC thermo grams were conducted using STAR^e software (version 12.10) from 30°C to 300°C at a heating rate of 10°C/min under a stream of nitrogen at flow rate of 50ml/min.[14]

X-Ray Diffraction Study

X-Ray diffraction study of the powder sample of the drug and formulation was performed by Bruker D8 Advanced X-ray diffractometer. Sample was scanned for 2Ɵ values from 5 to 50°. Diffraction pattern for Ketoprofen was obtained.[15]

SEM Analysis

The surface morphology of the S-SMEDDS was studied by scanning electron microscopy (SEM). The sample for SEM were prepared by lightly sprinkling powder on double adhesive tape stuck to an aluminium stub which was then placed in the scanning electron microscope (JEOL JSM-6360 A, Japan) chamber. The sample was then scanned and image was taken and the SEM result obtained.[15]

In-vitro Release Study

Ketoprofen loaded S-SMEDDS formulation was filled in (size 0) hard gelatin capsule. The quantitative in vitro release test was performed in 900ml 0.1N HCl and phosphate buffer pH 6.8 as dissolution medium maintained at 37±0.5°C using USP type II dissolution apparatus. The paddle was rotated at 50 rpm. 5ml aliquots was collected periodically (5, 10, 15, 30, 45, 60, 120, 180, 240, 360, 420, 480, 540 min) and replaced with fresh dissolution medium. Aliquots after filtration through whatman filter paper and diluted with methanol. Analysis was carried out using UV spectrophotometer at 254.60

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PEG 400	61.94 ± 0.823
Propylene glycol	175.17 ± 0.397
Ethanol	154.18 ± 0.737

nm. Results were compared with marketed capsule and pure drug Ketoprofen. The dissolution experiments were carried out in triplicate, and data were expressed as mean ± S.D.[16]

RESULTS AND DISCUSSION

Aqueous Solubility of Ketoprofen

The solubility of drug Ketoprofen in distilled water was found to be 0.11±0.01mg/ml.

Saturation solubility of Ketoprofen in Different Oils, Surfactants, and Co-surfactants

Oil is the important component in SMEDDS because it can solubilize marked amount of the lipophilic drug or facilitates self-emulsification, and must be clear and monophasic when administered into GI lumen. For this purpose solubility of Ketoprofen in different oils, surfactants and co-surfactants was determined. Among these vehicles Oleic acid (89.62±0.877mg/ml), Tween 80 (164.93±0.340mg/ml) and Propylene glycol (175.17±0.397mg/ml) was selected as oil, surfactant and co-surfactant as it shows highest solubility of drug.

Table 1: Saturation solubility of Ketoprofen in different oils, surfactants and co-surfactants (mean ± SD, n=3)

Vehicles	Solubility (mg/ml)
Capryol 90	76.89 ± 0.82
IPM	11.13 ± 0.66
Arachis oil	28.66 ± 0.577
Oleic acid	89.62 ± 0.877
Soyabean oil	26.16 ± 0.733
MCT	51.18 ± 1.51
Labrafac PG	17.84 ± 0.256
Olive oil	18.80 ± 0.249
Tween 20	63.87 ± 1.776
Tween 80	164.93 ± 0.340
Span 20	30.91 ± 1.208
Triethanolamine	51.62 ± 0.632

Construction of Pseudo Ternary Phase Diagram

The pseudo ternary phase diagram of oil (Oleic acid), surfactant (Tween 80), Co-surfactant (Propylene glycol) were constructed (Fig. 1.) with Smix ratio of 1:1, 1:2, 1:3. The shaded portion indicates emulsification region. It was observed that the Smix with ratio 1:2 had shown higher transparency, better stability and self-micro emulsification region.

The design reported that a decrease in oil percentage resulted into decrease of Globule size, increase in % Transmittance and decrease in self-emulsification time which would help to improve solubility and stability. Thus, Formulation (F3) having globule size 105.08nm, % Transmittance was 98.11% and self emulsification time 28 sec was found to be optimized formulation. The composition of optimized formulation (F3) of liquid SMEDDS of Ketoprofen was found to be oleic acid 10%, Smix 90%. The polynomial equation obtained for response globule size (GS), % transmittance (T), and self-emulsification time (SET) was as follows:

$$Y_{GS} = +172.59 + 21.51\ X_1 - 6.61\ X_2 + 13.91\ X_1X_2 - 14.63\ X_1{}^2 - 10.47\ X_2{}^2 \qquad (2)$$

$$Y_T = +85.61 - 6.52\ X_1 + 2.16\ X_2 - 1.55\ X_1X_2 + 0.26\ X_1{}^2 + 2.00\ X_2{}^2 \qquad (3)$$

$$Y_{SET} = +42.80 + 6.28\ X_1 - 2.61\ X_2 + 1.25\ X_1X_2 - 1.34\ X_1{}^2 - 2.84\ X_2{}^2 \qquad (4)$$

Adequacy of model was confirmed for prediction by formulating optimized batch of SMEDDS and evaluating the responses.

The results are represented in Table 3. Since a reasonable agreement existed between the predicted and observed results, the model was proven to be validated.

Table 2: Experimental Runs with Result of Response

Formulation Code	Oil % X_1	Smix % X_2	Globule Size (nm) Y_1	% Transmittance Y_2	Self Emulsification Time (sec) Y_3
F1	10	65	149.12	90.10	36
F2	35	65	154.21	78.30	48
F3	10	90	105.08	98.11	28
F4	35	90	165.08	80.12	45
F5	4.82	77.50	110.52	95.24	32
F6	40.18	77.50	185.66	79.45	47
F7	22.50	59.82	163.08	88.20	40
F8	22.50	95.18	148.65	93.45	33
F9	22.50	77.50	172.59	85.30	39
F10	22.50	77.50	173.59	85.20	45
F11	22.50	77.50	171.02	86.10	43
F12	22.50	77.50	173.51	86.25	42
F13	22.50	77.50	172.24	85.28	45

Table 3: ANOVA and Model Adequacy Determination

ANOVA Result of the Measured Responses (Y)				
ANOVA	Coefficient	Y_1	Y_2	Y_3
	F value	25.72	28.18	17.22
	P value	0.0002	0.0002	0.0008
Model Adequacy Prediction				
	Predicted	**Experimental**		**Bias*(%)**
Globule size (nm)	136.73	112.28		17.88
Transmittance (%)	92.06	97.45		-5.84
Self-emulsification Time (sec)	32	30		6.25

*Bias = predicted-experimental/predicted
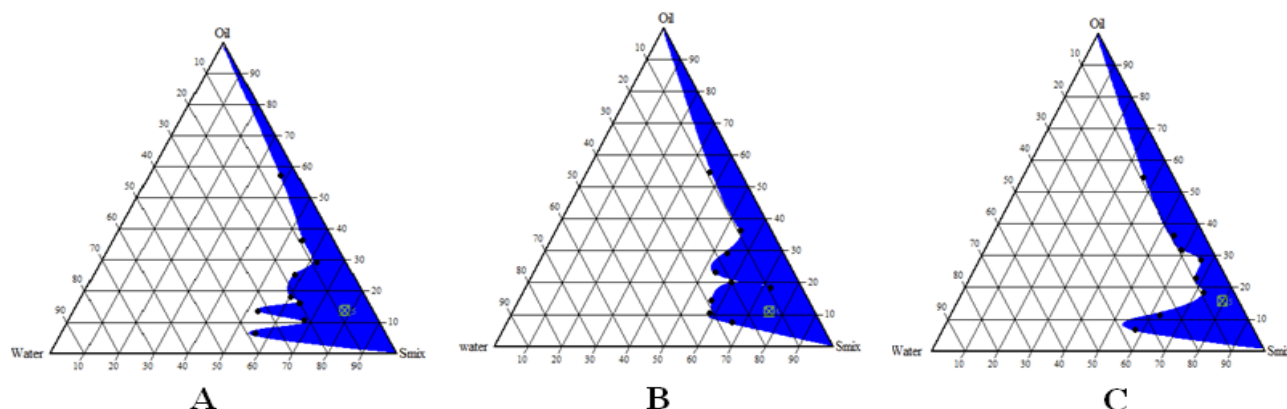
Figure 1: Pseudo ternary phase diagram for different Smix ratio A) 1:1 B) 1:2 C) 1:3
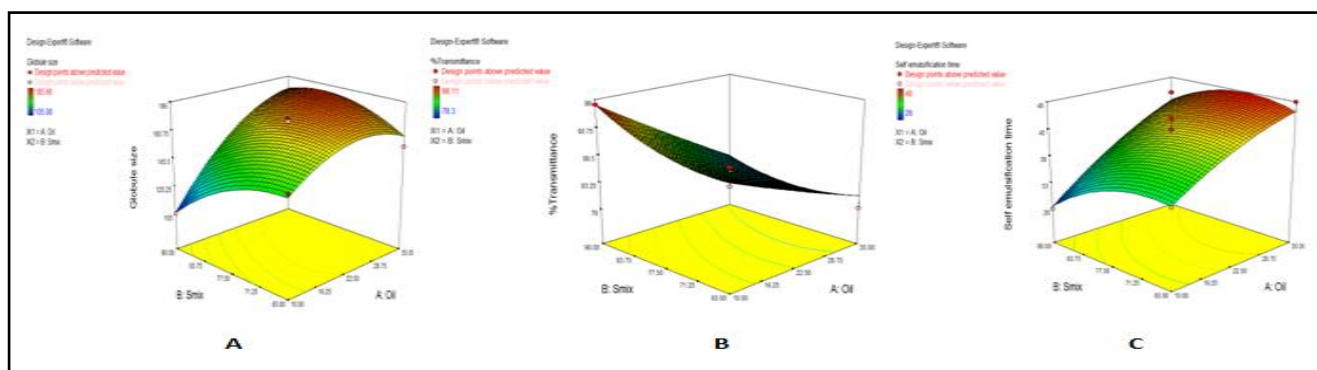
Figure 2: Response surface graph for A) Globule size B) % Transmittance C) Self emulsification time as function of oil % and Smix ratio.
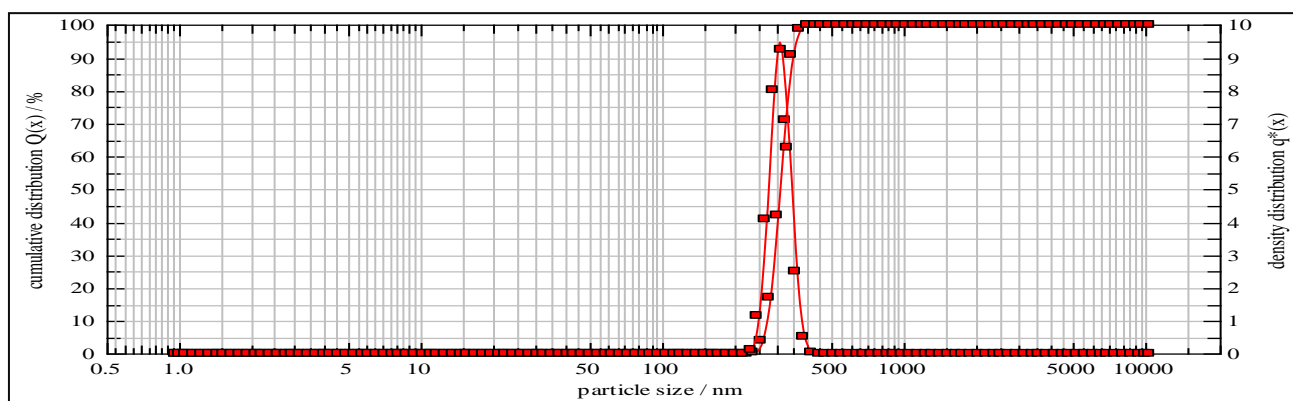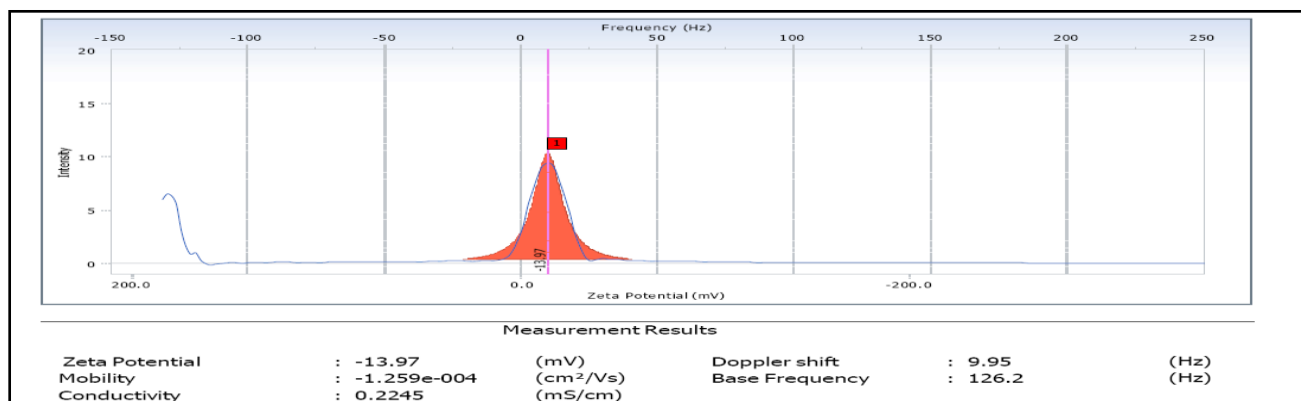

Figure 3A: Globule size of S-SMEDDS

Figure 3B: Zeta potential of S-SMEDDS

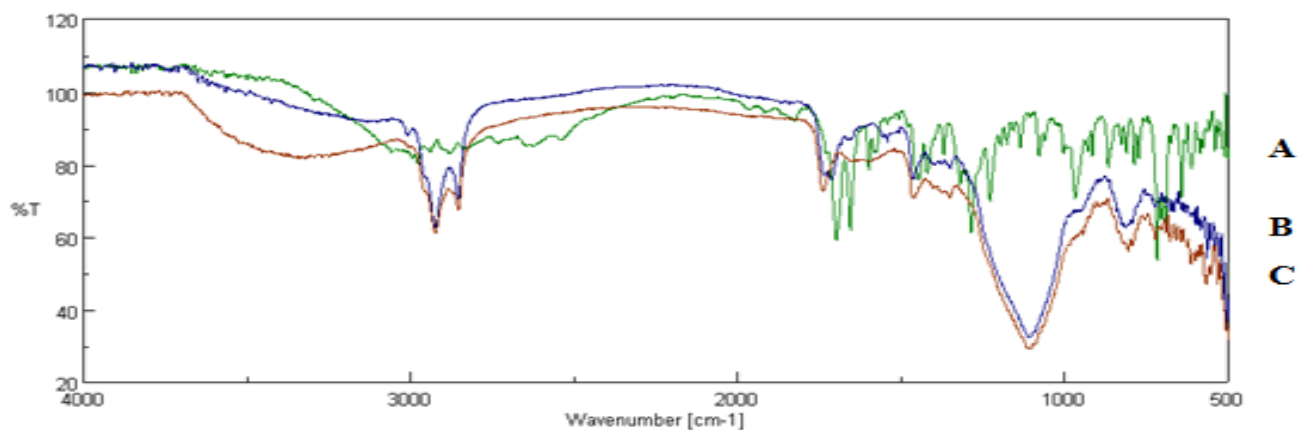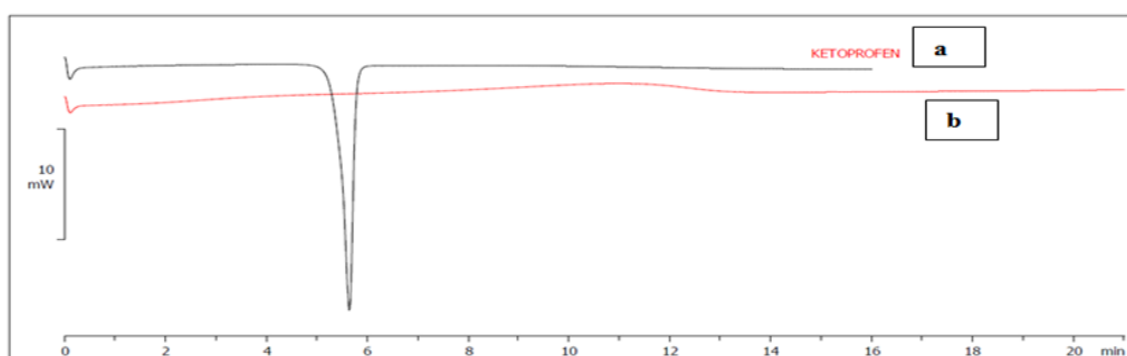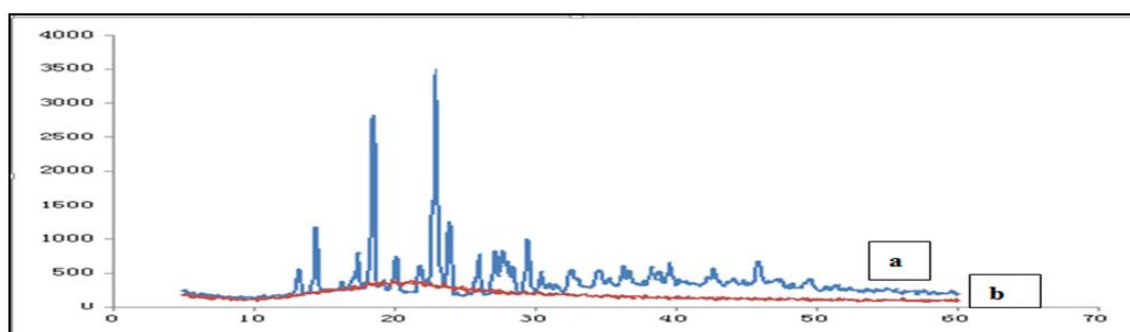**Figure 3:** A) Globule size of S-SMEDDS and B) Zeta potential of S-SMEDDS

Figure 4: FT-IR spectra of A) pure drug Ketoprofen B) physical mixture containing Oleic acid, Tween 80, Propylene glycol C) Ketoprofen S-SMEDDS
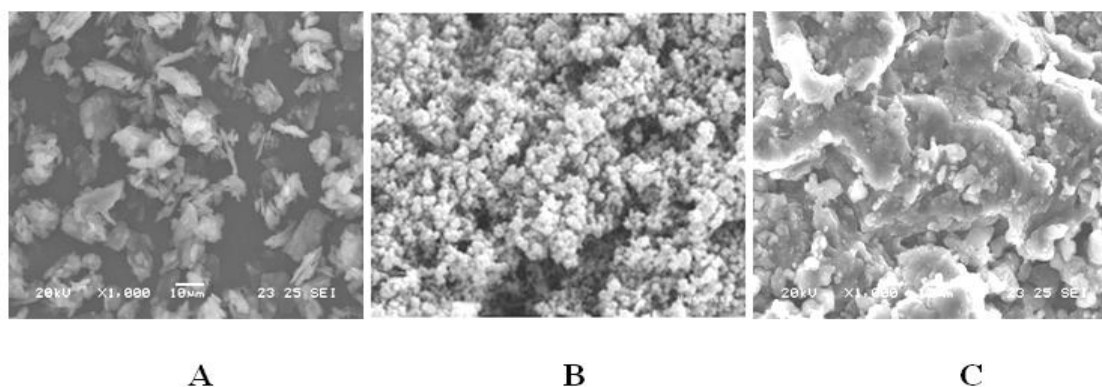

Figure 5: A) DSC Thermo gram of (a) Pure drug Ketoprofen (b) S-SMEDDS (F3); B) XRD Spectra of (a) Pure drug Ketoprofen (b) S-SMEDDS (F3)

Figure 6: SEM image of A) Pure drug Ketoprofen B) Aerosil 200 and C) S-SMEDDS

Characterization of Liquid SMEDDS

Determination of Globule Size

The globule size was found to be less than 200nm for most of the tested formulations in Table 2. The mean globule size of formulation F3 was found 105.08±5.16nm with polydispersity index 0.097.

% Transmittance

The selected formulations were evaluated for its transparency and the results are shown in Table 2. From the results obtained, formulation F3 showed 98.11% transmittance while others showed in the range of 78.30% - 98.11%.

Determination of Self-Emulsification Time

The lowest self-emulsification time was observed for formulation F3 28 sec, and rest of the formulations showed in the range of 28 sec - 48 sec.

Characterization of S-SMEDDS

Drug Content

The result of % drug content of formulation F3 S-SMEDDS was observed 94.92±0.472%.

Powder Flow Properties

Powder flow properties of S-SMEDDS are bulk density, tapped density, angle of repose, carr's index, hausner ratio was found to be 0.714gm/ml, 0.760gm/ml, 24.11, 6.055%, 1.064 respectively of F3 formulation which showed excellent flow property.

Globule Size and Zeta Potential Determination of S-SMEDDS

The mean Globule size of S-SMEDDS (F3) was found to be 303.69±0.933nm in Figure 3: A with polydispersity index (PDI) 0.25, for formulations with particle size less than 200nm PDI must be less than value 0.3 which determines stability of formulation. Therefore, as oil concentration decreases globule size also decreases. Zeta potential of L-SMEDDS was -4.23mV and S-SMEDDS was found to be -13mV in Figure 3: B.

Drug-Exicipent Compatibility Study using FT-IR Spectroscopy

Physical mixture and S-SMEDDS was carried out to identify potential interaction between drug and formulation components. The presence of potential peak of pure drug in thermo gram of physical mixture and as well as in S-SMEDDS reveals the compatibility between drug and exicipents.[16]

DSC Analysis and XRD Study of S-SMEDDS

DSC Analysis

The DSC curve of pure Ketoprofen (Figure 5:A(a)) showed sharp endothermic peak at temperature 95.59°C, corresponding to its melting point and indicate its crystalline nature showing melting has occurred at that temperature, our result shows the disappearance of endothermic peak of the drug in thermo gram of S-SMEDDS (F3) (Figure 5:A(b)) supports the presence of drug in an amorphous state can be due to the drug present in solubilized form into excipients of S-SMEDDS.[14]

X-ray Diffraction Study

X-ray diffraction pattern of S-SMEDDS (Figure5:B(a)) supported the presence of Ketoprofen in amorphous state in S-SMEDDS.

Ketoprofen had sharp peak at the diffraction angles, showing a typical crystalline pattern (Figure5:B(b)) and the disappearance of peak in S-SMEDDS indicates presence of drug in an amorphous state, this change in diffraction is due to change in physical state of drug or it is concluded that drug should be in molecular state in formulation.[18]

Morphological Study by SEM

The scanning electron microscopy of the Ketoprofen S-SMEDDS prepared with Aerosil 200 appeared as spherical smooth surface particles. (Figure 6: C) compared to that of aerosil 200 (Figure 6: B) which are rough in nature.

This observation indicates that the crystalline drug powder (Figure 6: A) is converted into amorphous form, spherical particles with adsorbed aerosil 200 prevents the lots of agglomeration formed by crystal bridges between flaky particles of pure drug.[19]

In-vitro Release Study

To understand the characteristics of drug release from S-SMEDDS (F3), an in-vitro release study was carried out.

As shown in Figure 7. % drug release of Ketoprofen from S-SMEDDS F3 formulation was significantly improved (89.78±0.450%) and $t_{90\%}$ was found at 324.2 min, compared with the marketed capsule (81.26±0.345%) and pure drug powder (71.32±0.32%).

Thus greater the concentration of aerosol 200 (silicon dioxide) increases the viscosity of emulsion and slower the drug release as it is an intermediate sustained release formulation of Ketoprofen and best fitting model was found to be korsmeyer-peppas model.[19,20]
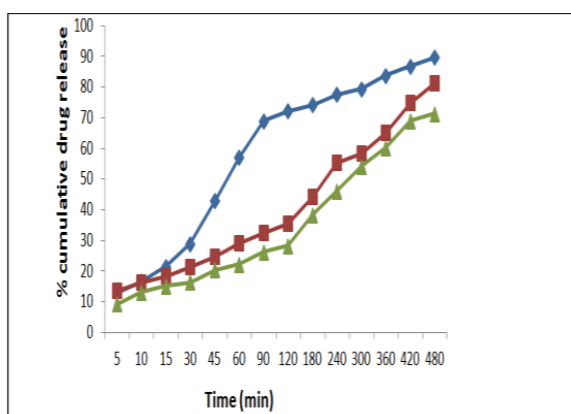

Figure 7: % Drug Release Profile Comparison

CONCLUSION

This study concluded that S-SMEDDS of Ketoprofen prepared using Aerosil 200 by adsorption process showed good flow property and drug content. Dissolution rate limited absorption of Ketoprofen was surrounded by producing globules of nano size range, by which solubility and dissolution rate is enhanced which in turn helps in improving bioavailability. The pseudo ternary phase diagram and central composite design (CCD) were successfully employed as optimized tool to optimize L-SMEDDS. The SEM analysis, DSC measurement and X-ray diffraction analysis suggested that Ketoprofen is present in the dissolved state in S-SMEDDS. *In vitro* dissolution test showed that the S-SMEDDS (F3) had higher *in-vitro* release rate than drug powder and marketed formulation. Thus the solubility and dissolution rate of BCS Class-II Drug Ketoprofen was enhanced which would prove a promising result of increased absorption and oral bioavailability of intermediate sustained release Ketoprofen formulation.

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