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Formulation and evaluation of self-emulsifying drug delivery system for BCS Class - II Drug

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ABSTRACT

The oral route by so far, has always been the preferred route of drug delivery because it was the easiest and most convenient of non-invasive administration. But oral route possesses problems such as to poor bioavailability, hepatic metabolism, lack of dose proportionality.Therefore, developing suitable formulation for such active pharmaceutical ingredients (API) present a major challenge to pharmaceutical scientist. The purpose of study was to formulate solid self emulsifying drug delivery system containing Ketoprofen as sustain release dosage form. The aim of present research was to formulate Liquid SEDDS which contains the drug ketoprofen, oleic acid (oil), Tween 80 (surfactant) and Ethanol (Co-surfactant). The ratio of this component in this formulation was 22.50:25.8:51.6 9(w/w) and optimized by pseudo ternary diagram. The droplet size of optimized liquid with drug was 111.11nm and solid SEDDS 965nm. Silicon dioxide was used as adsorbent agent. The formulation was characterized for in-vitro studies. The work was aimed to increase dissolution rate as compared to other oral dosage forms.

Keywords: Ketoprofen, SEDDS, Silicon dioxide, Solid SEDDS

INTRODUCTION

The oral route by so far, has always been the preferred route of drug delivery because it is the easiest and most convenient of non-invasive administration [1]. 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. Furthermore, oral delivery of numerous drugs is hindered owing to their lipophilic nature[2, 3].Therefore, developing suitable formulation for such active pharmaceutical ingredients (API) present a major challenge to pharmaceutical scientist. This is because when they are administered orally, the dissolution rate in gastrointestinal lumen becomes the rate limiting step for their absorption [4].

According to the Biopharmaceutical Classification system[5] (BCS), drug is classified into four categories depending upon the solubility and permeability of the drug. Among these classes of drug, BCS class II possesses poor solubility and reasonable permeability. Developing a formulation for a drug belonging to BCS II is often challenging as it requires improved dissolution characteristics.

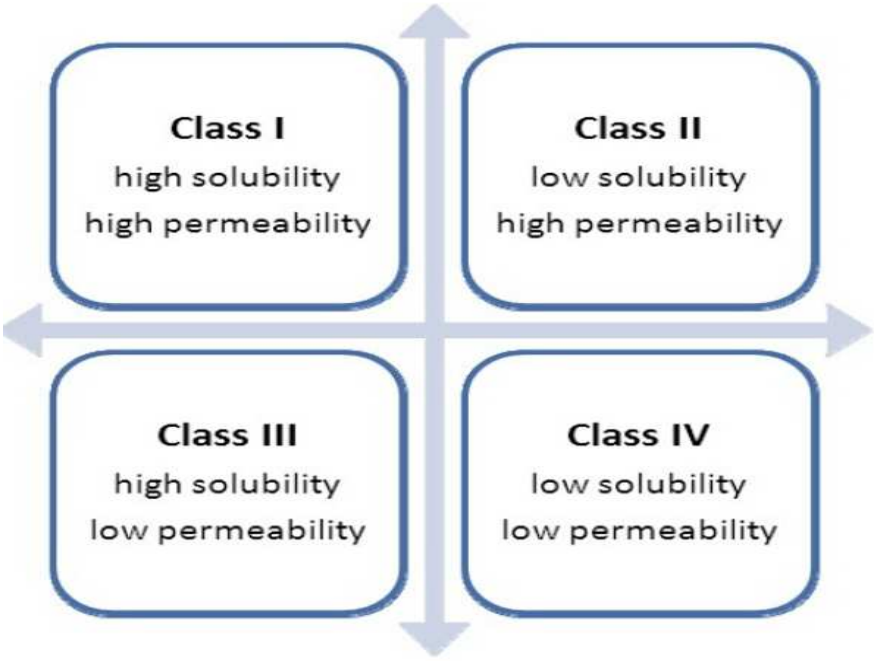


Fig 1. Biopharmaceutical classification system (BCS)

MATERIAL AND METHODS

Materials

Ketoprofen was obtained as gift sample from Sava Pharmaceutical Pvt Ltd, Pune. Oleic Acid (Loba chemicals, Mumbai), Tween 80 (Loba chemicals, Mumbai), Ethanol (Loba chemicals, Mumbai), Aerosil 200 (Research lab fine Chem Industries Mumbai

Methods

Aqueous solubility determination

The solubility of drug was determined in methanol, ethanol, and chloroform by adding excess quantity of drug to the vial containing methanol, ethanol, and chloroform.

Determination of saturation solubility of Ketoprofen in different oils, surfactant, and co- surfactant

The solubility of Ketoprofen in various oil phases, surfactants, co surfactant/co solvents was determined by dissolving an excess amount of drug in 2 ml of each 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 72h 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.[6]

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 (S mix) 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.[7,8]

Preparation of Liquid SEDDS

SEDDS formulation was prepared varying ratio of oil, surfactant and co-surfactant shown in Table 1. The surfactant and co-surfactant (Smix) in the ratio 1:2. A single dose 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 $40^{0\,C}$ to obtain a homogenous isotropic mixture. The SEDDS formulations were stored at ambient Temperature until further use. [7, 8]

Table1 Composition of drug, oil, surfactant and co-surfactant

Formulation Code	Drug (Mg)	Oleic Acid (ml)	Tween 80: Ethanol ml (1:2)
F1	100	22.50	95.18
F2	100	22.50	77.50
F3	100	22.50	77.50
F4	100	22.50	77.50
F5	100	40.18	77.50
F6	100	10.00	65.00
F7	100	35.00	65.00
F8	100	10.00	90.00
F9	100	35.00	90.00
F10	100	22.50	59.82
F11	100	22.50	77.50
F12	100	22.50	77.50
F13	100	8.93	77.50

Characterization and evaluation of Liquid-SEDDS [9]

Emulsion Droplet Size Determination

Emulsion droplet size was determined by using photon cross correlation spectroscopy (Nanophox). 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 25^0 C and 3 run for 60sec were performed. Detection was carried out at scattering angle of $90^{0.}$ Form resulting correlation curves, second order equation was applied to obtain the mean droplet size.

Determination of self-emulsification time

The assessment of formulation was done by adding 1 ml of each formulation standard apparatus (USP Type II) containing 100ml purified water at 37^0 C, gentle was provided by paddle rotating at 50 rpm.

Spectroscopic Characterization of Optical Clarity

Each formulation equivalent to 100 mg Ketoprofen was diluted with 500 mL of distilled water. he absorbance values of each emulsion were measured by a UV spectrophotometer at 400 nm.

Preparation of Solid SEDDS by Adsorption Method

S-SEDDS was prepared by mixing liquid SEDDS containing Ketoprofen with silicon dioxide in various proportions of F2, F5 formulations. The liquid SEDDS of Ketoprofen was adsorbed onto Silicon dioxide 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]

Characterization and evaluation Solid-SEDDS

% Drug Content

Pre weigh formulation was analyzed for % drug content by making dilution with methanol 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.

$$\text{Bulk density} = (\text{Mass of powder})/(\text{Bulk volume})$$

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.

$$\text{Tapped density} = (\text{Mass of powder})/(\text{Tapped volume})$$

Angle of Response
The angle of repose of S-SEDDS 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-SEDDS 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:

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

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:

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

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

$$\text{Hausner ratio} = (\text{Tapped Density})/(\text{Bulk Density})$$

Droplet size
S-SEDDS was checked by determining droplet size by using photon cross correlation spectroscopy (Nanophox NX0088).

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 as called zeta potential. Zeta potential of diluted liposomal sample was determined using (Beckman Coulter).

DSC analysis
The DSC thermo grams were recorded for drug and S-SEDDS 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 5.21).Al) from 30^0C to 300^0C at a heating rate of 10^0C/min under a stream of nitrogen at flow rate of 50ml/min.

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 2Q values form 5 to $50^{o.}$ Diffraction pattern for ketoprofen was obtained.

SEM analysis
The surface morphology of the S-SEDDS was studied by scanning electron microscopy (SEM). The sample for SEM were prepared by lightly sprinkling powder on double adhesive tape stuck to an aluminum 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.

In- vitro release study

Ketoprofen loaded S-SEDDS formulation was filled in (size 0) capsule. The quantitative in vitro release test was performed in 900ml (0.1N HCL) maintained at 37±0.5^0 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 nm. Results were compared with marketed capsule and pure ketoprofen. The dissolution experiments were carried out in triplicate, and data were expressed as mean ±S.D. The drug release data was further analyzed to investigate release kinetic from S-SEDDS by different mathematical models.

Accelerated Stability study

The stability test was carried out according to the ICH guidelines on the topics Q1 A (R2): stability testing of new drug substances and product. The hard gelatin capsule filled with the S-SEDDS (A2) were stored in air tight glass container and protected from light. Samples maintained in a stability chamber under accelerated condition (45^{0}C±2^{0}C, 75^{0}C±5% RH) with humidity and temperature control, were taken at 0, 1, 2 and 3 month. Droplet size, drug content, X-ray, DSC, Zeta potential, Flow properties of S-SEDDS were evaluated.

RESULTS AND DISCUSSION

Aqueous solubility of ketoprofen

Table 2 Aqueous solubility of ketoprofen

Sr. No	Solvent	Solubility (mg/ml)
1	Methanol	62
2	Ethanol	55
3	Chloroform	57

Solubility of ketoprofen in different oil surfactant and co-surfactant

Oil is the important component in SEDDS because it can solubilize marked amount of the lipophilic drug or facilities self-emulsification. Thus at least one dose should be sufficiently solibilize in the oil to be emulsified. For this purpose solubility of ketoporfen in different oil was determine and The solubility of ketoprofen in various surfactant and co-surfactant (Span 80, Tween80, Triethylmine, Labryfacpg, ethanol, PEG 400, PEG 200) was determined

Table3. Solubility of ketoprofen in different oil surfactant and co-surfactant

Sr No		Solubility(mg/ml)
1	Soya bin oil	3.231±0.01
2	MCT	6.951±1.02
3	Arachin oil	2.7804±0.368
4	Oleic acid	17.280±1.677
5	Capryol 90	3.987±0.378
6	Olive oil	0.45±0.167
7	Span 80	9.121±0.939
8	Tween 80	12.841±1.068
9	Triethylamine	4.085±0.500
10	Labryfacpg	6.329±0.775
11	Ethanol	11.731±0.818
12	PEG400	11.109±0.514
13	PEG 200	6.487±0.520

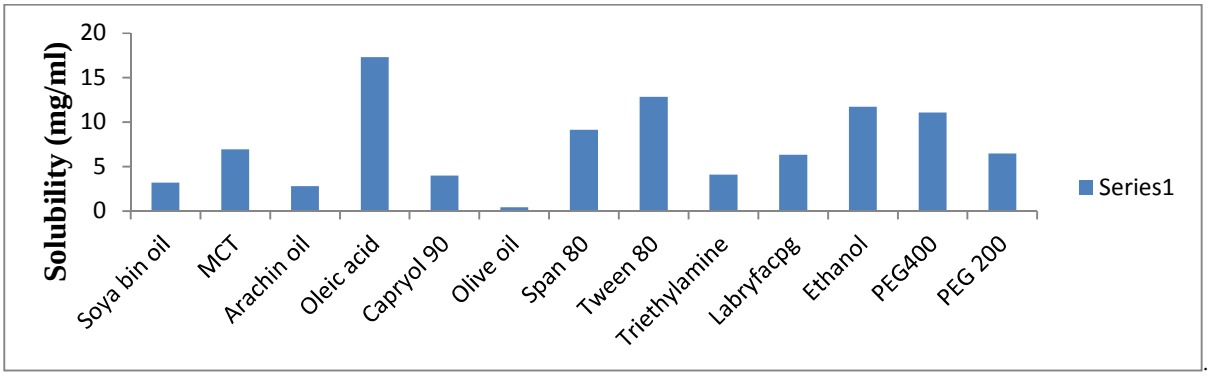
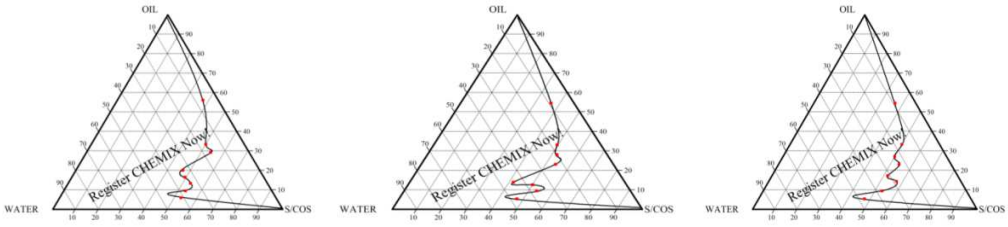


Fig2. Solubility of ketoprofen in different oil surfactant and co-surfactant

Construction of pseudo ternary phase diagram

The pseudo ternary phase diagram of oil (Oleic acid), surfactant (Tween80), Co-surfactant (Ethanol) were constructed (fig.13) with surfactant/co-surfactant ratio of 1:1, 1:2, 1:3



A **B** **C**

Fig 3. Pseudo ternary phase diagram for different Smix ratio A) 1:1 B) 1:2 C) 1:3

Evaluation parameters of Liquid SEDDS

Table 4 evaluation parameters of Liquid SEDDS

Formulation code	Droplet size (nm) Y_1	Self emulsification Time (sec) Y_2	Optical clarity (nm)	
			water	0.1 HCL
F1	350	42	0.109	0.126
F2	163.80	40	0.045	0.181
F3	215	90	0.053	0.100
F4	210.10	35	0.121	0.246
F5	111.11	22	0.043	0.165
F6	300	75	0.032	0.479
F7	245	55	0.057	0.074
F8	230	85	0.136	0.050
F9	320	90	0.070	0.049
F10	163.80	40	0.045	0.181
F11	163.80	40	0.045	0.181
F12	163.80	40	0.045	0.181
F13	163.80	40	0.045	0.181

The design reported that a decrease in oil percentage resulted into decrease of droplet size, an decrease self emulsification time and a increase optical clarity which would help to improve solubility. Thus, Formulation (F5) having droplet size 111.11nm, self emulsification time 22sec and optical clarity 0.043nm was found to be optimized. The composition of optimized formulation (F3) of liquid SEDDS of ketoprofen was found to be oleic acid 22.75%, Smix 77.50%

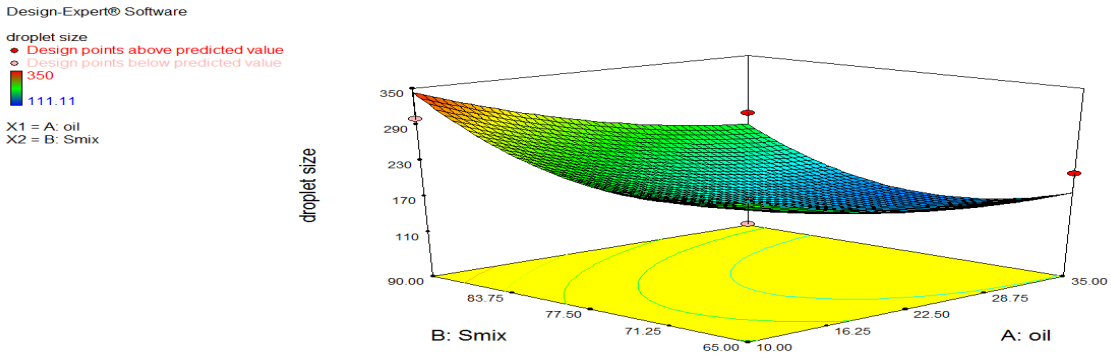


Fig 4. Response surface graph for droplet size analysis

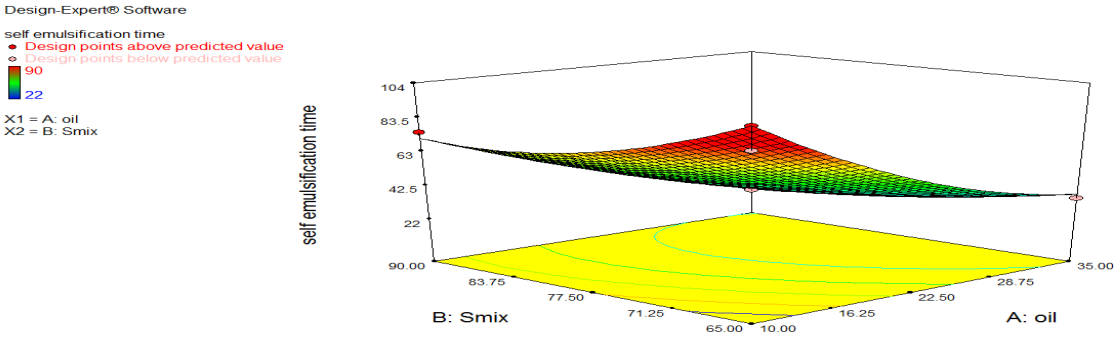


Fig 5. Response surface graph for Self emulsification time

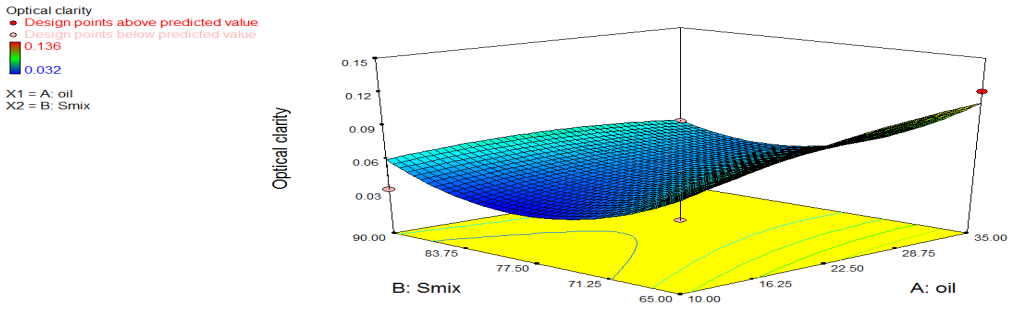


Fig 6. Response surface graph for Optical clarity

Evaluation parameters of Solid SEDDS

% drug content

The result of % drug content of F5 S-SEDDS formulation is 96.951± 0.652

Powder flow properties

Table5. Flow properties of S-SEDDS

	F5 S-SEDDS formulation
Bulk Density (gm/ml)	0.552
Tapped Density (gm/ml)	0.59
Carr's Index%	6.77
Hasuner ratio	1.07
Angle of repose (^{0})	25.42
Flow property	Excellent

Solid formulation F5 had shown excellent flow properties. Hence F5 was found to be optimized S-SEDDS formulation.

Droplet Size determination

The mean droplet size for S-SEDDS (F5) was found to be 965nm with polydispesity index 0.30. The droplet size of S-SEDDS further conformed

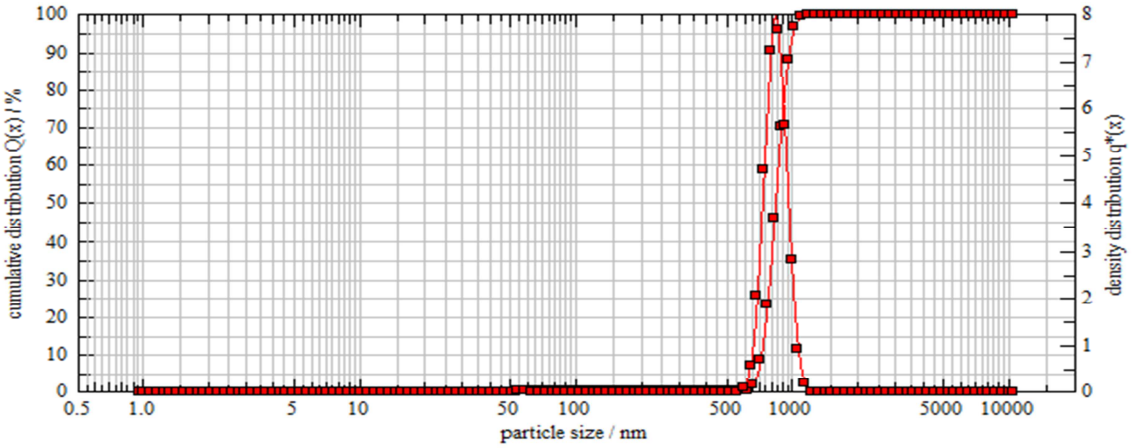


Fig7. Droplet size determination (F5)

Zeta Potential

Many studies have reported the zeta potential played an important role in the interaction with mucus of the gastrointestinal tract. According to the report, the intestinal cell interior carry negative charge with presences of mucosal fluid, positive charge droplet could have better interaction with the mucus of the gastrointestinal tract. Zeta potential of formulations increased with increase in surfactant concentration. Surfactant decreases the globule size that makes higher surface area, lead to increase in zeta potential value. Zeta potential was observed -8.66 mv[11,12]

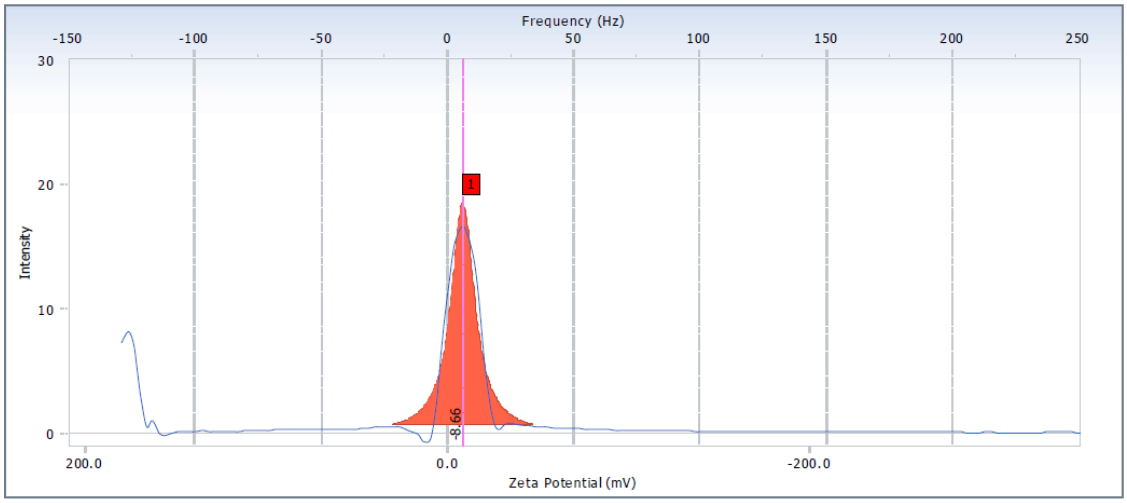


Fig 8. Zeta potential of solid SEDDS

Morphological study by SEM

The scanning electron micrographs of the ketoprofen S-SEDDS prepared with aerosil 200 appeared as spherical smooth surfaced particles. (Fig9C) compared to that of aerosil 200 (Fig. 9B) which are rough in nature. This observation indicates that the crystalline drug powder (Fig9A) is converted into amorphous form or drug must be present in dissolved state in S-SEDDS.[13]

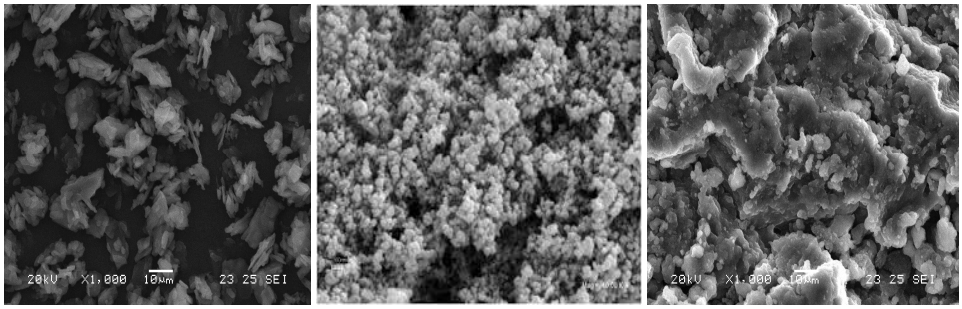


Fig 9. SEM image A) Pure drug, B) aerosol 200 and C) S-SEDDS

6 DSC analysis

The DSC curve of pure ketoprofen (Fig.10A) showed sharp endothermic peak at temperature 95.59^{0}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-SEDDS supports the presence of ketoprofen in an amorphous form in S-SEDDS (fig.10B). [14, 15]

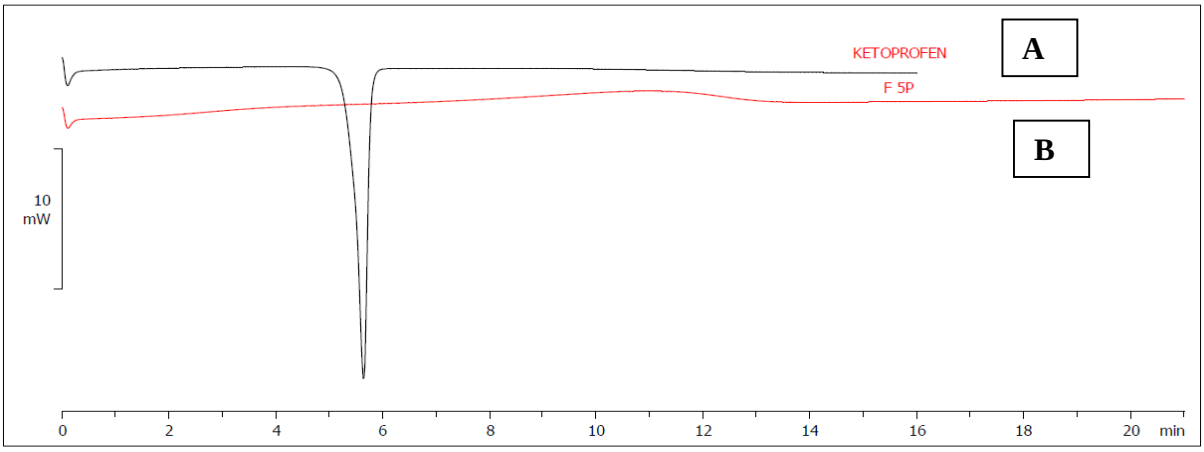


Fig 10.DSC thermo gram of A) Ketorpofen B) S-SEDDS

X-ray diffraction study

X-ray diffraction pattern of S-SEDDS (fig.11B) supported the presence of ketoprofen in amorphous state in S-SEDDS. Ketoprofen had sharp peak at the diffraction angles, showing a typical crystalline pattern (fig.11A) and the disappearance of peak in S-SEDDS indicates presences of drug in an amorphous state.

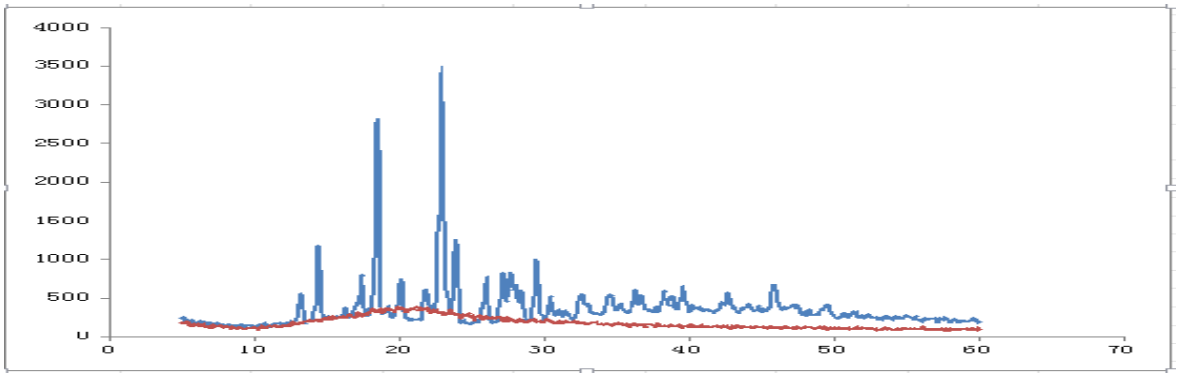


Fig 11 .XRD spectra of A) pure Ketoprofen B) S-SEDDS

8 *In –vitro* release study

To understand the characteristics of drug release from SEDDS, an in vitro release study was carried out. As shown in fig12, the release performance of ketoprofen form S-SEDDS formulation was significantly improved compared with the marketed capsule and pure drug powder.

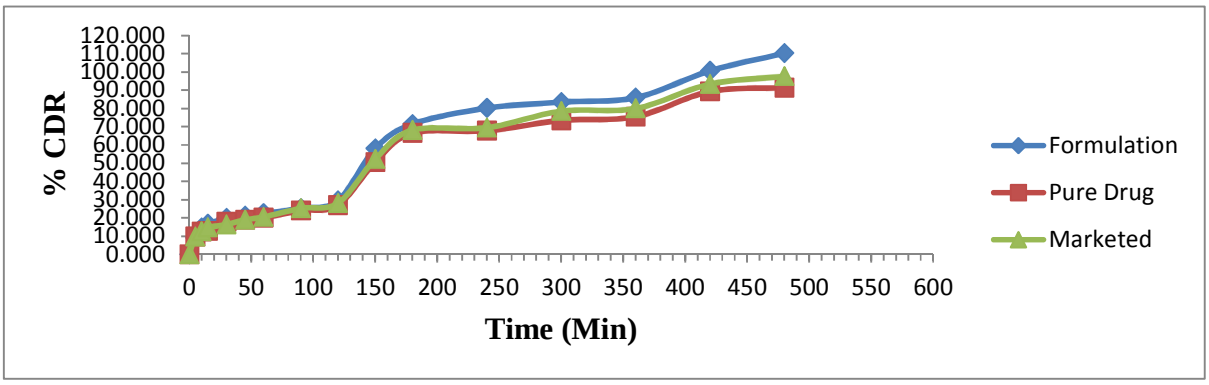


Fig12. In Vitro Drug release

Accelerated stability study

Table7. Accelerated stability study

Month	Droplet size	Drug content
0 Month	965 ±1.00	96.951±0.652
1 Month	967 ±1.527	91.951±1.151
2 Month	965.5±1.322	93.170±1.039
3 Month	966±1.755	94.390±0.632

CONCLUSION

In this study, the S-SEDDS of ketoprofen was successfully formulated in an attempt to increase its solubility and dissolution rate. The pseudo ternary phase diagram and central composite design (CCD) were successfully employed as optimized tool to optimize L-SEDDS. Adsorption method was found to be useful solidification technique which produced uniform and free flowing particles of S-SEDDS. The SEM analysis, DSC measurement and X-ray diffraction analysis suggested that ketoprofen is present in the dissolved state in S-SEDDS. In vitro dissolution test showed that the S-SEDDS had a higher in vitro release rate than drug powder and marketed formulation. A significant improvement in dissolution is obtained for the drug. SEDDS for ketoprofen holds promise to be developed as useful oral dosage form.

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