Research Article

Ketoprofen Loaded Solid Self Emulsifying Drug Delivery System (SEDDS): Development and Optimization.

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Accepted on: 12-05-2015; **Finalized on:** 30-06-2015.

ABSTRACT

The purpose of this study was to formulate a solid self emulsifying drug delivery system (SEDDS) containing Ketoprofen as an intermediate in the development of sustained release solid dosage form. Oleic acid (an oil), Tween 80 (a surfactant), and ethanol (a cosurfactant) were used to formulate SEDDS. Silicon dioxide was used as an adsorbing agent, which may aid in solidification and retardation of drug release. The solubility of Ketoprofen (BCS Class II), as a model drug in this study, was determined in several oils, surfactants and co-surfactants using an UV method. The self emulsifying system of Ketoprofen was constructed by using oil, surfactant and cosurfactant. The ratio of these components in the formulation was 15:28.3:56.7 (w/w) and optimized by a pseudo ternary phase diagram. The droplet size of the optimized liquid with drug was 185.2nm and solid SEDDS was 399nm. Effect of adsorbing agent on emulsification process and *in vitro* drug release was studied. A liquisolid system is formed by converting a liquid formulation into a dry, free-flowing and compressible powder mixture with selected carrier material and coating material. This technique has industrial applications for low dose insoluble drugs. The liquid crystal phase (LC) viscosity increased significantly with increasing amount of silicon dioxide, which in turn caused an increase in average droplet size of resultant emulsion and slower drug release. Drug release from the formulation increased with increasing amount of cosurfactant.

Keywords: SEDDS, Ketoprofen, Solid SEDDS, silicon Dioxide, LC phases.

INTRODUCTION

Most of the new chemical entities and existing drug candidates display low water solubility, which leads to poor bioavailability, high intrasubject/intersubject variability and lack of dose proportionality. Thus the oral delivery of these low soluble drugs is hindered where dissolution is rate limiting step. The various strategies such as solid dispersions, complexation with cyclodextrin, lipid based formulations and self emulsifying drug delivery systems (SEDDS) have been reported in literature. Of various strategies reported SEDDS are found to be the prominent approach to improve solubility.[1] SEDDS are described as isotropic mixtures of oil, surfactant, co-surfactant and lipophilic drug. They form fine oil-in-water emulsions when introduced into an aqueous phase under gentle agitation.

These are able to self emulsify rapidly in the gastrointestinal fluids, forming O/W emulsion. In such a system, the lipophilic drug is present in solution, in small droplets of oil that leads to increase surface area and hence increased absorption.[2,14,15]

Traditional preparations of SEDDS are usually prepared in liquid state. So, the liquid SEDDS are enclosed in hard or soft capsule to facilitate oral administration, but it produces some disadvantages such as stability, incompatibility, drug leakage, precipitation and capsule ageing. The incorporation of SEDDS into solid dosage form is desirable but challenging. Adsorption to solid carriers is one of the techniques to form solid SEDDS. Free flowing powders may be obtained from liquid SEDDS by adsorption to solid carriers. The adsorption process is simple and involved addition of liquid formulation to carriers by mixing in a blender. The resulting powder then filled directly into capsules. A significant benefit of adsorbent technique is good content uniformity. SEDDS can be adsorbed at high levels up to 70%W/W on to suitable carriers.[3] Lipid formulations however may interact with the capsule resulting in either brittleness or softness of the shell. To overcome this problem SEDDS need to convert into solid SEDDS. Numerous reports states that, the major techniques for converting SEDDS to S-SEDDS are spry cooling, spray drying, adsorption onto solid carriers, melt granulation, melt extrusion, super-critical fluid based methods and high pressure homogenization. Out of all these processes the physical adsorption process is simple.[4,16]

Ketoprofen (KPF) is a nonsteroidal 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. KPF 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. KPF is eliminated from the body by first-order kinetics (k 5 0.35/h) and elimination half-life (t1/2) ranges between 1.5 and 2 hours. At a single dose of 150 mg, KPF plasma concentration reaches up to 15 to 25 g/mL, which is much higher than the therapeutic concentration. When

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administered with food in conventional form, the total bioavailability of KPF remains unchanged, but the absorption rate is slowed by 1 to 2 hours. Different formulation approaches that have been sought to increase bioavailability of KPF include matrix pellets of nanocrystals, sustained-release microparticles, and floating delivery systems. In the present investigation the solid self emulsifying drug delivery system of Ketoprofen was prepared. Solid self-emulsifying KPF formulation consisted of oleic acid, Polyoxyethelene 20 Sorbitan monooleate (Tween 80), ethanol and colloidal silicon oxide (A 200). A 200 consists of small silica spheres with 12-nm diameter and a specific surface area of 200 m^2/g and acts as an adsorbing agent for oil-based systems. absorbing agent was incorporated with the intention that SEDDS may require lesser excipients to convert in solid dosage forms such as tablets and capsules and may retard the drug release as well. We observed that the addition of colloidal silicon dioxide caused an increase in the viscosity of the liquid crystal phase, which in turn increased the average droplet size of the emulsion formed and slowed the drug release. Increasing the amount of cosurfactant was found to increase the drug release.[5,17]

MATERIALS AND METHODS

Materials

Ketoprofen was obtained as a gift sample From Inventia Pharma, Thane, Mumbai. Polyoxyethelene 20, Sorbitan Monooleate (Tween 80) was purchased from Gattefosse (Mumbai, India). Colloidal silicon dioxide (Arosil 200) from lupine Aurangabad. Hard gelatine capsules from concept Pharma Aurangabad. All other reagents were of Analytical grade and were used as received.

Methods

Determination of saturation solubility of Ketoprofen in different oils, surfactant, and cosurfactant

The solubility of Ketoprofen in various oil phases, surfactants, cosurfactant/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 72 h 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.[6,11]

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 cosurfactant. The point indicating the clear and isotropic mixtures were considered.[6,21]

Preparation of liquid SEDDS

A series of SEDDS formulations were prepared with varying ratios of oil, surfactant and co surfactant as shown in Table 1. The surfactant and co surfactant (S/Co S) tested were in the ratio of 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 of co surfactant and oil in a glass vials.

The resultant mixtures were stirred continuously by vortex mixing and heated at 40 °C to obtain a homogenous isotropic mixture. The SEDDS formulations were stored at ambient temperature until further use.[1,19]

Table1: Composition of oil, surfactant, and cosurfactant.

Formulation	Oil(ml)	Surfactant (ml)	Cosurfactant (ml)
F1	10	30	60
F2	20	26.5	53.5
F3	30	23.3	46.7
F4	15	28.3	56.7
F5	25	25	50
F6	35	21.6	43.4
F7	20	26.5	53.5
F8	40	20	40
F9	60	13.3	26.7

Characterization of liquid SEDDS

Assessment of Emulsification Time

The emulsification time of SEDDS formulations was determined in a USP dissolution tester. The SEDDS formulation equivalent to 100 mg was added drop-wise to 500 mL of distilled water maintained at 37 ± 0.5°C. Gentle agitation was provided by a paddle rotating at 50 rpm. The emulsification time was recorded manually.

Emulsion Droplet Size Determination

Emulsion droplet size was determined by the zetasizer Briefly, SEDDS formulations (equivalent to 100mg Ketoprofen) were diluted with 500 mL distilled water and thereafter, the droplet size was immediately determined. Each determination was done in triplicate.[7,10]

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Spectroscopic Characterization of Optical Clarity

Each formulation equivalent to 100 mg Ketoprofen was diluted with 500 mL of distilled water.

The absorbance values of each emulsion were measured by a UV spectrophotometer at 400 nm.[7]

Thermodynamic Stability Studies

Heating Cooling Cycle

Six cycles between refrigerator temperatures 4^{O}C and 45^{O}C with storage at each temperature for not less than 48 hours was studied.

Those formulations which are stable at these temperatures were subjected to centrifugation test.

Centrifugation Test

Passed formulations were centrifuged at 3500 rpm for 30 min. Those formulations that did not show any phase separation were taken for freeze thaw stress test.

Freeze Thaw Cycle

Three freeze thaw cycles between -21°C and +25°C with storage at each temperature for not less than 48 hours was done for the formulations.[12,20]

Preparation of Solid-SEDDS

S-SEDDS was prepared by mixing liquid SEDDS containing Ketoprofen with silicon dioxide in various proportions of F1, F4, F8 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.[8,18]

Evaluation of s-Sedds

Micromeritic Properties of S-SEDDS

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. It can be expressed in g/cc:

$$\text{Bulk Density} = \frac{\text{Mass of Powder}}{\text{Tapped density}}$$

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. The equation is represented with the unit g/cc:

$$\text{Tapped Density} = \frac{\text{Total Mass of Powder}}{\text{Tapped volume of powder}}$$

Angle of Repose

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:

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

Carr's Compressibility Index

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

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

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[8,9]:

$$\text{Hausner's Ratio} = \frac{\text{Tapped Density}}{\text{Bulk density}}$$

Drug content

The content of Ketoprofen in the each S-SEDDS formulation was determined by UV Spectrophotometer at ʎ max 260 nm.

In Vitro Dissolution Study

Ketoprofen S-SEDDS (equivalent to 100 mg of Ketoprofen) was filled in size "0" liquid filling hard gelatin capsules.

In vitro release profiles of Ketoprofen S-SEDDS, plain Ketoprofen, were studied using United States Pharmacopeia (USP) XXIII apparatus II (Paddle Type) at 37±0.5°C with a rotating speed of 50 rpm in buffer pH 6.8 as the dissolution media. During the study, 2 ml of aliquots were removed at predetermined time intervals (1, 2, 3, 4, 6, 7, 8 hours) from dissolution medium and replaced with fresh media. The amount of Ketoprofen released in the dissolution medium was determined by UV-VIS spectrophotometer at ʎ max 260 nm.[13]

RESULTS AND DISCUSSION

Solubility Study

Ketoprofen showed highest solubility in oleic acid than other oils Castor oil, Olive oil, lemon oil and dill oil. Ketoprofen showed highest solubility in Tween 20 as Surfactant. Ethanol as a co-surfactant Showed highest solubility Fig. 1. Hence these excipients were selected for SEDDS formulation.

The values are given in Table 2.

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Table 2: solubility values of drug in various oils, surfactant and co surfactant.

Vehicles	Solubility (mg/ml)
Castor oil	32.816 ± 0.000861
Ethanol	65.069 ± 0.001633
Oleic acid	65.069 ± 0.000354
Lemon oil	28.083 ± 0.000707
Tween 80	32.56 ± 0.00707
Dill oil	26.25 ± 0.01767
Olive oil	21.789 ± 0.000707

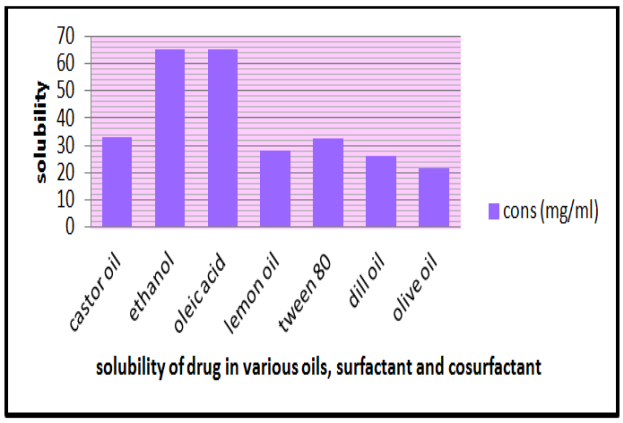

Figure 1: Solubility of drug in various oils, surfactant and co surfactant.

Construction of pseudo-ternary phase diagram

Pseudo-ternary phase diagram were constructed by using a series of SEDDS, to identify the self-emulsifying region and to optimize the concentration of oil, surfactant and cosurfactant in the SEDDS formulation.

The phase diagram of the system containing oleic acid, Tween 80 and ethanol as oil, surfactant and co-surfactant respectively, with different ratios of surfactant and co-surfactant is shown in figure 2.

It was observed that the mixture of surfactant and cosurfactant (Smix) ratio 1:2 [Figure 2(B)] showed the greater self-emulsifying (microemulsifying) region than the other ratios such as, 1:1[Figure 2(A)], and 1:3 [Figure 2(C)].

Emulsification Time

Emulsification time is an important index for the assessment of the efficiency of emulsion formation. SEDDS should disperse completely and rapidly when subjected to aqueous dilution under mild agitation.

Emulsification time of the optimized SEDDS F8 formulations is shown in Table 3. The formulation containing a higher amount of S/CoS has less time to be emulsified.

Emulsification time decreased from 2.25 min to 1.35 min while the S/CoS concentration was increased. It might be due to the presence of a higher concentration of surfactant, which facilitated the self-emulsification process that eventually led to a high emulsification rate.

Microemulsion Droplet Size

Microemulsion droplet size was within the range of 185.4 nm to 572.8 nm of liquid formulation (Table 3), which is slightly larger than usual compared with available literature reports. The presence of Ketoprofen in a very large amount might result in larger emulsion droplets. Reports have also been published about the fact that self-emulsification behaviour of the oil phase may sometimes be altered if it contains drug[7].

Besides, relative concentrations of oil, surfactant, and co-surfactant also play a major role in microemulsion droplet size determination. Gursory and Benita also reported that an increased amount of surfactant concentration led to droplets with smaller mean droplet size[7].

The droplet size of solid SEDDS formulation of F8 shows larger size reported in figure before solidification and after shown in Figure 3(A), 3(B).

Table 3: Emulsification time, Droplet size, drug content and Optical clarity results.

Formulation	Emulsification Time (min)	Droplet Size (nm)	Drug content	Optical clarity	
				Water	0.1N Hcl
F1	2.25	292.7	75.97	0.567	0.550
F2	2.23	471.5	77.19	0.513	0.515
F3	2.24	520.3	81.03	0.879	0.870
F4	2.22	185.4	99.20	0.474	0.477
F5	2.21	451.9	82.47	0.624	0.640
F6	2.19	572.8	72.25	0.593	0.597
F7	2.00	454.9	49.66	0.803	0.808
F8	1.35	267.1	93.85	0.752	0.752
F9	1.40	503.9	22.68	1.009	1.011

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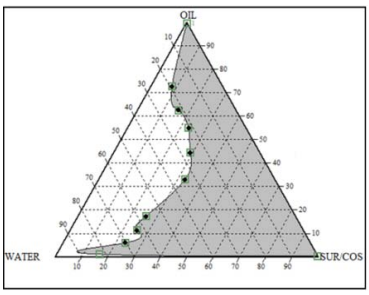

Figure 3(A): Smix 1:1

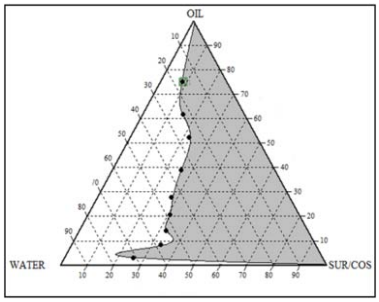

Figure 3(B): Smix 1:2

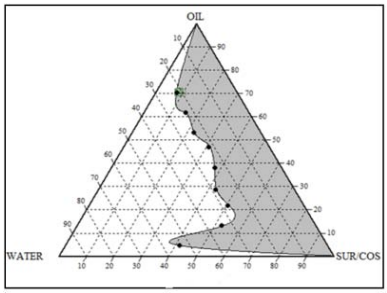

Figure 3(C): Smix 1:3

Figure 2: Pseudo-ternary phase diagram for surfactant and co-surfactant ratios.

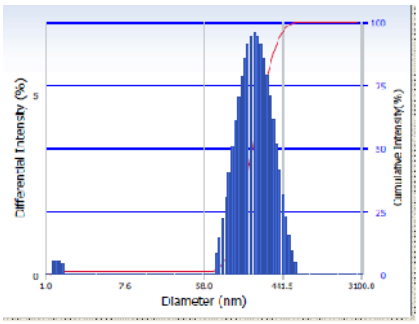

Figure 3(A): Liquid SEDDS

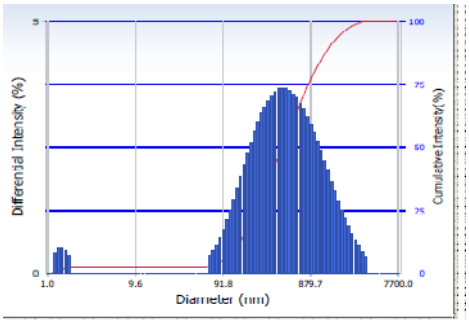

Figure 3(B): Solid SEDDS

Figure 3: Droplet size of solid SEDDS formulation of F8 formulation.

Table 4: % drug release of Ketoprofen loaded solid SEDDS in pH 6.8 phospate buffer.

Time (hour)	% drug release pH 6.8			
	F1	F4	F8	Plain ketoprofen
1	4.501 ± 0.665508	22.858 ± 1.419282	7.773 ± 1.00546	20.154 ± 1.00472
2	7.407 ± 0.824424	26.078 ± 0.967278	10.97 ± 0.93354	25.146 ± 0.95432
3	11.479 ± 0.952599	27.644 ± 1.105663	31.588 ± 0.865452	27.354 ± 0.82345
4	23.166 ± 0.976823	39.87 ± 1.183265	38.967 ± 0.903696	31.245 ± 0.01475
5	41.914 ± 0.998818	40.918 ± 1.132179	42.042 ± 0.510001	47.354 ± 0.69547
6	58.820 ± 1.187625	57.308 ± 0.720331	54.38 ± 1.083264	68.147 ± 0.78964
7	73.746 ± 1.085006	67.023 ± 1.121808	62.388 ± 0.963919	75.145 ± 0.98755
8	78.532 ± 1.53465	79.72 ± 1.07267	62.094 ± 1.448422	89.147 ± 1.00456

Spectroscopic characterization of optical clarity

Absorbance of the studied aqueous dispersion of SEDDS varied between 0.474 to 1.009 and 477 to 1.011 in distilled water and 0.1 N Hcl respectively. As expected, compositions with lower absorbance showed lowest droplet size since, aqueous dispersions with small absorbance are optically clear and oil droplets are thought to be in a state of finer dispersion. The oil mixture provides the largest contribution to the absorbance of the diluted SEDDS and consequently the droplet size of the produced microemulsion.

On basis of dispersibility, appearance and time required to emulsify the SEDDS formulation, results of Visual Assessment of Self-emulsification were also given in Table 3.

Thermodynamic Stability Studies

The thermodynamic stability study was performed three studies like heating cooling cycle, freeze thaw cycle, centrifugation. On the basis of the mentioned three studies formulations were selected. On the basis of the thermodynamic stability studies it was found that F1, F4, F8 formulations were passed and selected for further characterization.

Micromeritic properties of solid SEDDS

The Micromeritic properties of solid SEDDS are bulk density, tapped density, angle of repose, compressibility index, hausner ratio were found to be 0.448gm/ml, 0.586gm/ml, 45, 23.54%, 1.30 respectively of F4 formulation.

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Drug Content

Drug content in various SEDDS formulations were presented in Table 3. The content of drug in various SEDDS formulation varies from 75.97% to 99.20% for F1, F4, and F8. However, it was showed that the F4 and F8 formulation has better drug content.

In Vitro Dissolution Study

Drug release from the all SEDDS formulation was found to be significantly higher as compared with that of plain Ketoprofen as showed in Figure 3. Ketoprofen SEDDS formulation F1, F4, F8 released drug above 60 % within 7hr as showed in Table 5. It could be suggested that the SEDDS formulation resulted in spontaneous formation of a microemulsion with a small droplet size, which permitted a faster rate of drug release into the aqueous phase, much faster than that of plain Ketoprofen and adsorbing of SEDDS in the presence of Arosil may affect the progress of Emulsification as well as the release of drug from the droplets.

Thus greater the concentration of silicon dioxide increases the viscosity of emulsion increases and slower the drug release as it is an intermediate sustained release formulation of Ketoprofen. Drug release of formulation F4 shows better results presented in Table 4.

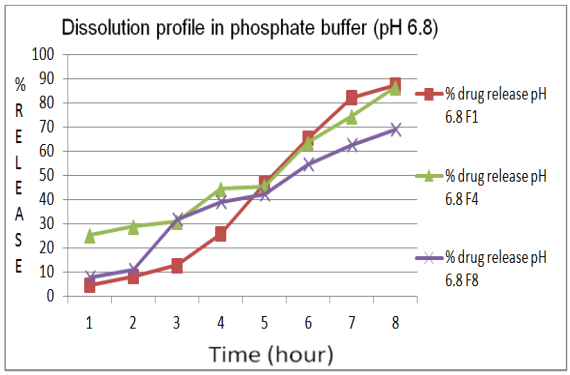

Figure 4: Dissolution of Ketoprofen in phosphate buffer.

CONCLUSION

S-SEDDS formulations of a poorly water-soluble drug, Ketoprofen were formulated for direct filling into hard gelatin capsules for oral administration.

The study concluded that S-SEDDS of Ketoprofen prepared using silicon dioxide by adsorption process showed good flow properties and drug content. The formulations after reconstitution formed good emulsion with drug solubilisation.

Drug releases from S-SEDDS formulation F4 was found to be significantly slow as compared with that of other formulations.

Thus the solubility and the dissolution rate of BCS Class – II drug Ketoprofen was enhanced which would prove a promising result of increased absorption and increased oral bioavailability of intermediate sustained release Ketoprofen formulation.

Acknowledgement: The authors are thankful to the Government College of pharmacy, Aurangabad for providing necessary facilities to carry out the research work.

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Source of Support: Nil, **Conflict of Interest:** None.

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