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# Formulation and Evaluation of Colon Targeted Drug Delivery System

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**Keywords:** Ketoprofen, SMEDDS, Chronotherapy, pulsincap, Rheumatoid arthritis.

**ABSTRACT**

Present study was aimed at the design of pulsincap of ketoprofen in the form of SMEDDS which will release the drug according to the circadian rhythm. Capsule body was coated with ethyl cellulose and made water insoluble. Hydrogel plug was used to close the capsule body and to achieve a predetermined lag time. Ketoprofen showed the highest solubility in oleic acid as oil, Tween 80 as Surfactant. Polyethylene glycol 400 as a co-surfactant, phase diagram showed Smix ratio 2:1 have the greatest self-Micro emulsion region. FTIR and DSC showed no interaction occurred in between drug and formulation. The capsule cap was coated with cellulose acetate phthalate for pH specific solubility. Solid SMEDDS was prepared with drug and quantity equivalent to 150 mg of ketoprofen was filled into treated capsule bodies and closed by plugging it with different polymers like hydroxyl ethyl cellulose, HPMC K 100 M and chitosan at a different amount. Batch F4 containing SMEDDS have good flow properties. In dissolution studies, the enteric coating of the capsule was intact for 2 hours in pH 1.2 and dissolved in phosphate buffer 7.4 followed swelling of the plug releasing minor optimum lag time of 5-6 h to eject the plug out of capsule body amount of drug. After sufficient swelling of plug ejected out of the capsules body at the end of, released drug into colon fluid of phosphate buffer 6.8 according to a circadian rhythm. The % cumulative drug release of solid SMEDDS formulation was found to be 97.90 % after 180 minutes compared with drug release of pure drug was found to be 70.51 %.Puls-in-cap device has been specially designed as a colon targeted drug delivery system which may maintain the chronopharmacological anti-arthritis action of the drug.

## INTRODUCTION

The local and systemic delivery of drugs can take place in the colon. Colon targeted drug delivery is useful in the treatment of nocturnal asthma, angina, and arthritis[1,2,3]. A major objective of chronotherapy in the treatment of nocturnal asthma, angina, and arthritis is to deliver the drug in higher concentrations during the time of greatest need generally early in the morning according to the circadian peak symptoms of the disease or syndrome[10]. To follow this principle one must have to design the dosage form such that it can be given at the convenient time for example before going to bed and the drug will release and reach systemic circulation early in the morning [11].

Pulsatile drug delivery technologies are the most widely used[4]. It means that these types of delivery systems will deliver the drug at a time when the disease shows it's a most morbid and mortal state within a circadian cycle of 24 hours. This delivery system releases the drug in such a way that in the initial hours there will be no drug release followed by an immediate or controlled drug release. Thus, by the use of such approach drug can be delivered at the needed time, in the desired amount and at the accurate site[12].

Osteoarthritis and Rheumatoid arthritis are considered chronic diseases which cause destruction in the integrity of joints. In patients with rheumatoid arthritis, symptoms such as joint stiffness and functional disability mainly persist in the early morning hours[10]. It has been recommended to treat rheumatoid arthritis by using the concept of chronopharmacotherapy to ensure the highest concentration of drug in the bloodstream when the excessive stiffness and pain of the disease persist. Therefore, we developed a novel pulsincap formulation to enable arthritis treatment with ketoprofen that is coordinated with biological rhythms[25,18].

In the present work, we prepared SMEDDS (self microemulsion drug delivery system) of ketoprofen and filled in pulsincap for targeting to colon[13,14].

SMEDDS are isotropic mixtures of oils and surfactants, sometimes containing co-solvents, and can be used for the design of formulations in order to improve the oral absorption of highly lipophilic compounds. SMEDDS emulsify spontaneously to produce fine oil-in-water emulsions when introduced into GI fluid under gentle agitation (GI motility)[15].

Ketoprofen belongs to class II drug in BCS classification. One of the major problems with this drug is its low solubility in biological fluids, which results in poor and variable bioavailability after oral administration. Hence we formulated and evaluated a pulsincap containing Ketoprofen loaded SMEDDS, to release the drug rapidly in the early morning to target rheumatoid arthritis[23].

## MATERIALS AND METHODS

### Material:

**Table No. 1: Material and sources [20,26]**

| Sr. No. | Chemicals | Supplier |
|---|---|---|
| 1 | Ketoprofen | Yucca Chemicals, Mumbai |
| 2 | Oleic acid | N.N. Scientific Traders, Dahisar, Mumbai |
| 3 | Tween 80 | N.N. Scientific Traders, Dahisar, Mumbai |
| 4 | Polyethylene glycol 400 | N.N. Scientific Traders, Dahisar, Mumbai |
| 5 | Microcrystalline cellulose | N.N. Scientific Traders, Dahisar, Mumbai |
| 6 | Cellulose acetate phthalate | N.N. Scientific Traders, Dahisar, Mumbai |
| 7 | Ethyl cellulose | N.N. Scientific Traders, Dahisar, Mumbai |
| 8 | Hydroxyl propyl methyl cellulose K 100 M | N.N. Scientific Traders, Dahisar, Mumbai |
| 9 | Hydroxyl ethyl cellulose | N.N. Scientific Traders, Dahisar, Mumbai |
| 10 | Chitosan | N.N. Scientific Traders, Dahisar, Mumbai |
| 11 | Phosphate buffer 7.4 | Freshly Prepared |
| 12 | Phosphate buffer 6.8 | Freshly Prepared |
| 13 | 0.1 N HCl | Freshly Prepared |
| 14 | Acetone | N.N. Scientific Traders, Dahisar, Mumbai |
| 15 | Propylene glycol | N.N. Scientific Traders, Dahisar, Mumbai |
| 16 | Ethyl alcohol | N.N. Scientific Traders, Dahisar, Mumbai |

**Methods:**

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

The solubility of Ketoprofen in various oil phases, surfactants, cosurfactant/co-solvents was determined by dissolving an excess amount of ketoprofen in 2 ml of selected individual oils, surfactants and co-surfactants contained in stoppered vials (5 ml capacity) separately. The liquids were mixed using a vortex mixer at 37°C±1°C for 72 h to reach equilibrium. The equilibrated samples 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 at their respective λmax[15].

**Construction of Pseudoternary Phase Diagrams:**

Pseudo-ternary phase diagrams were constructed to identify the self-micro emulsifying regions and to optimize surfactant to cosurfactant ratio and the concentration of oil. The microemulsion regions in the diagrams were plotted, and the wider region indicated better self-microemulsification efficiency. Pseudo-ternary phase diagrams of oil, surfactant/ co-surfactant, and water were developed using the water titration method. The mixtures of oil and S/CoS at certain weight ratios were diluted with water in a dropwise manner. For each phase diagram at a specific ratio of S/CoS, transparent and homogenous mixture of oil and S/CoS was formed by vortexed for 5 minutes. Then each mixture of oil and S/CoSwas titrated with water and visually observed for phase clarity and flowability. The concentration of water at which transparency-to-turbidity and turbidity-to-transparency transitions occurred was derived from the weight measurements. These values were then used to determine the boundaries of the self-emulsifying domain corresponding to the chosen values of oils, as well as the S/CoS mixing ratio[15].

**FTIR studies:**

For the study of the interaction of a drug with excipients the samples of a pure drug (ketoprofen)and a formulation containing ketoprofen, oleic acid, tween 80, PEG 400, Microcrystalline cellulose were analyzed on FTIR (Agilent Carry 630) at Diya lab, Airoli, New Mumbai.

**DSC studies:**

For the study of the compatibility of the drug and in the formulation, samples of drug Ketoprofen and Physical Physical mixture of Ketoprofen, oleic acid, tween 80, PEG 400 and Microcrystalline cellulose were analyzed on DSC (Differential scanning colorimeter) METTLER TOLEDO at Diya lab, Airoli, New Mumbai.

**Preparation of SMEDDS:**

We took three different ratios of surfactant and co-surfactant, 1:1, 1:2 and 2:1 respectively. SMEDDS were prepared with varying ratio of oil (oleic acid) to surfactant + cosurfactant mixtures (Tween 80 + PEG 400) as 9:1 to 1:9 for each surfactant and co-surfactant ratio. The amount of ketoprofen was kept constant in all formulation and area for microemulsion was determined using a pseudo-ternary phase diagram. The surfactant to co-surfactant ratio 2:1 gave good microemulsion region. Therefore taking this ratio SMEDDS were prepared by dissolving the drug in surfactant followed by addition of co-surfactant and oil in a glass vial. The resultant 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[16].

**Preparation of S-SMEDDS**:

S-SMEDDS was prepared by mixing liquid SMEDDS containing ketoprofen with microcrystalline cellulose. In brief liquid SMEDDS was added dropwise over microcrystalline cellulose contained in a broad porcelain dish. After addition, the mixture was homogenized using a glass rod to ensure uniform distribution of formulation. Resultant damp mass was passed through sieve no. 120 and dried at ambient temperature and stored until further use[20,21].

**Preparation of water-insoluble hard gelatin cap body:**

Weighed required quantity of ethyl cellulose dissolved in sufficient qty of acetone (1:10 proportion). Dipped body of hard gelatin capsule in the above solution, took out, dried, again dipped .repeated this procedure of coating up to 50% weight gain.

**Preparation of enteric coated cap of hard gelatine capsule**:

Weighed accurate qty of cellulose acetate phthalate, propylene glycol, tween 80 and dissolved in ethyl alcohol and acetone. Dipped cap of hard gelatin capsule in the above solution, took out, dried, again dipped .repeated this procedure of coating up to 20 % weight gain.

**Preparation of polymer plugs:**

The polymer plugs which were used for plugging the opening of capsule bodies were selected by swelling index (hydroxyl ethyl cellulose, hydroxypropyl methylcellulose K 100 M, chitosan[26].

**Development of Pulsincap dosage form of ketoprofen:**

The capsule body and cap was completely coated with water-insoluble ethyl cellulose and cellulose acetate phthalate respectively. Dip coating method was employed for coating the capsule body and cap. This coating was given in order to prevent variable gastric emptying. This procedure for coating was continued until a 50% increase in the weight of the body and a 20% increase in weight of the cap. SMEDDS equivalent to 150 mg of ketoprofen were filled manually into the ethylcellulose treated capsule bodies. The opening of capsule bodies containing SMEDDS was then closed by plugging it with different polymers like hydroxyl ethyl cellulose, HPMC K 100 M and chitosan at a different amount. Further, a small amount of 5 % ethanolic solution of ethyl cellulose was used to seal the joint between the capsule body and cap[17,18,22,25].

**Table No. 2: Formulation table for SMEDDS**

| Ingredient | Quantity |
|---|---|
| Ketoprofen | 100(mg) |
| Oleic acid | 0.8(ml) |
| Tween 80: PEG 400 (2:1) | 1.5(ml) |
| Microcrystalline cellulose | 460(mg) |

**Table No. 3: Composition of the Pulsincap drug delivery system of ketoprofen**

| Formulation code | Wt of SMEDDS(mg) | Polymer used as a plug | Wt of the plug(mg) | Wt of treated capsule body(mg) | Wt of the treated cap(mg) | Total wt of the capsule(mg) |
|---|---|---|---|---|---|---|
| F1 | 560 | HEC | 50 | 89 | 51 | 750 |
| F2 | 560 | HEC | 70 | 85 | 56 | 771 |
| F3 | 560 | HPMCK100M | 50 | 81 | 53 | 744 |
| F4 | 560 | HPMCK100M | 70 | 87 | 54 | 771 |
| F5 | 560 | Chitosan | 50 | 88 | 55 | 753 |
| F6 | 560 | chitosan | 70 | 86 | 52 | 768 |

**RESULTS AND DISCUSSION:**

**Solubility profile of Ketoprofen in oils, surfactants, and co-surfactant:**

Solubility profile of Ketoprofen showed the highest solubility in oleic acid followed by other oils such as isopropyl myristate, sunflower oil, castor oil. Ketoprofen showed the highest solubility in Tween 80 as Surfactant. Polyethylene glycol 400 as a co-surfactant Showed the highest solubility.

**Construction of pseudo-ternary phase diagram**:

The phase diagram of the system containing oleic acid, Tween 80 and PEG 400 as oil, surfactant, and co-surfactant respectively, with different ratios of surfactant and cosurfactant is shown in the figure. It was observed that the mixture of surfactant and cosurfactant (Smix) ratio 2:1 showed the greatest self-micro emulsion region than the other ratios such as 1:1 and 1: 2.

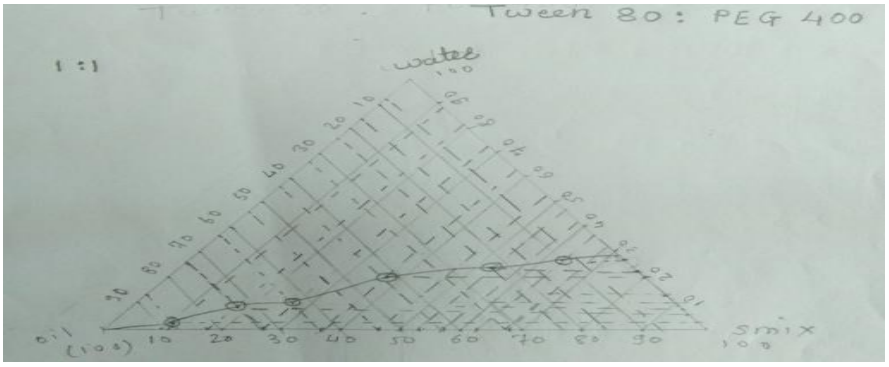



**Figure No. 1: (Smix 1:1) pseudo-ternary phase diagram**

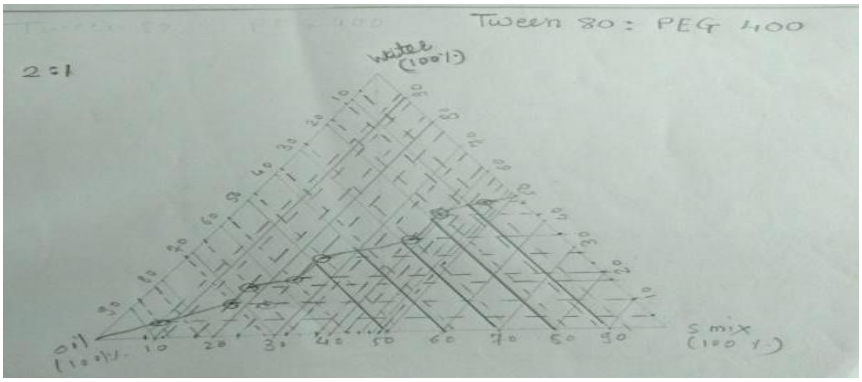



**Figure No. 2: (Smix 2:1) pseudo-ternary phase diagram**

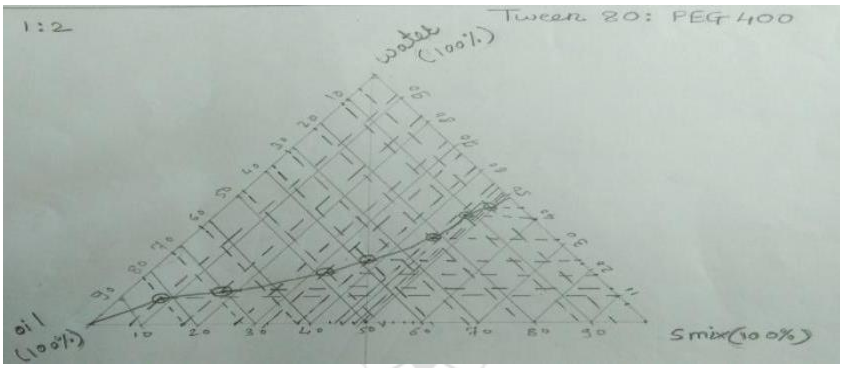



**Figure No. 3: (Smix 1:2) pseudo-ternary phase diagram**

**Fourier Transform Infrared Spectroscopy (FT-IR) Interpretation:**

The interaction studies were carried out to ensure that there is no interaction occurred in between drug (ketoprofen) and formulation.

**Table No. 4: Interpretation of the FT-IR spectrum**

| IR Spectrum | Groups | Peaks |
|---|---|---|
| Ketoprofen | $-CH_2$ | 717.54 |
| | C=O | 1654.98 |
| | $CH_3$ | 1443.98 |
| | OH | 3421 |
| Formulation | $-CH_2$ | 721.4 |
| | C=O | 1654.98 |
| | $CH_3$ | 1456.3 |
| | OH | 3417.98 |

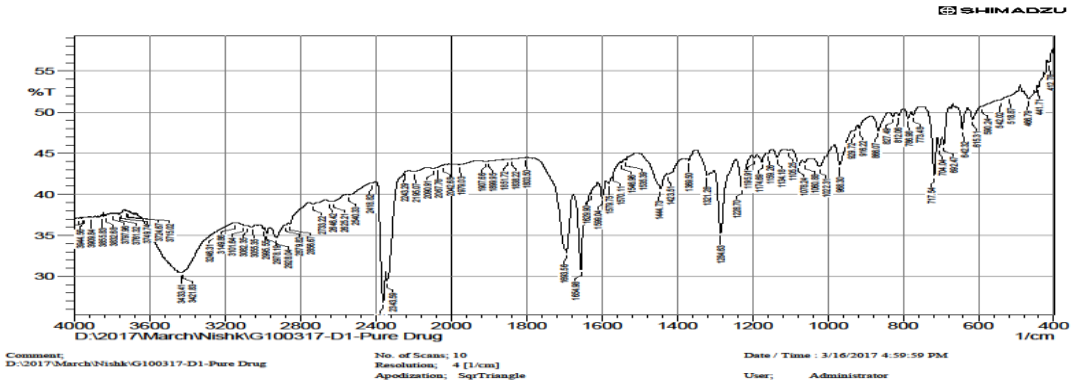



**Figure No. 4: FT-IR Spectrum of ketoprofen**

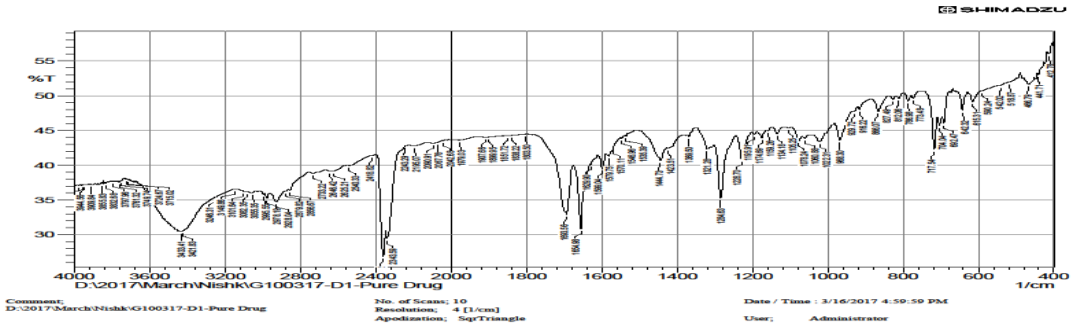



**Figure No. 5: FT-IR spectrum of a physical mixture of drug + Excipient**

**Differential Scanning Calorimetric (DSC) Studies:** The absence of interaction was confirmed with the help of DSC. There is no definite change in peak of pure drug and formulation. Ketoprofen peak was found at 98.19$^{o}$C and formulation was found at 103$^{o}$C.

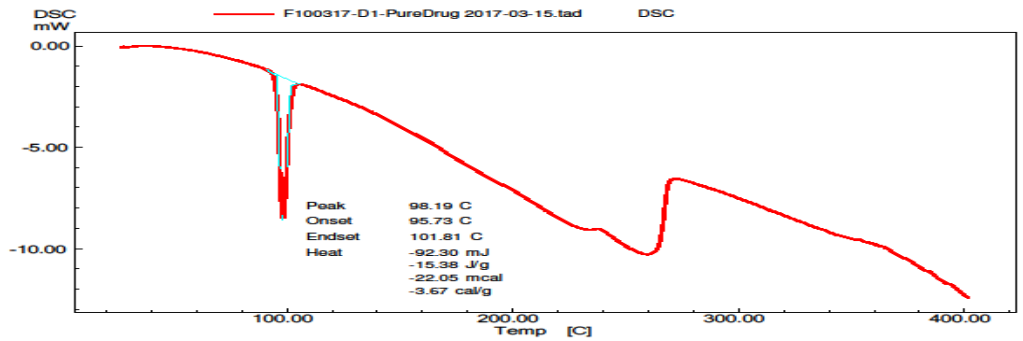



**Figure No. 6: DSC of pure drug**

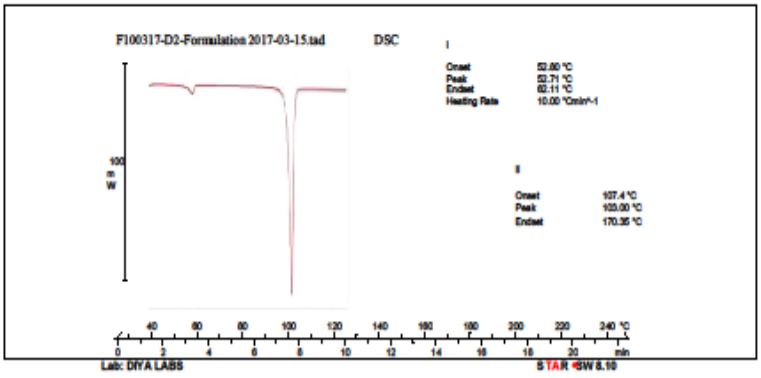



**Figure No. 7: DSC Of formulation**

**Graded system for better stable liquid formulation or dispersibility test and Self emulsification time:**

The optimized formulation F4 and F5 emulsifies rapidly (in less than a minute) having a clear and transparent appearance. Formulation code F1 and F2 emulsifies in less than 2 min having rapidly forming, slightly less clear emulsion, having a bluish white appearance and F3, F6 emulsifies in less than 3 min having rapidly forming, slightly less clear emulsion, having a bluish-white appearance.

**Flow properties of S-SMEDDS:**

Flow properties for various formulations were performed and are represented in Table 5.4.1. The optimized formulation F4 has an angle of repose of 24.10 indicating good flow properties and formulations F5, F1 has an angle of repose 24.13, 24.41 resp. Indicating good flow properties.

**Table No. 5: Flow properties of S -SMEDDS**

| Sr. No. | Formulation code | Bulk density(gm/ml) | Tap density (gm/ml) | Carr's index(%) | Hausner's ration | Angle of repose$^0\Theta$ |
|---|---|---|---|---|---|---|
| **1** | **F1** | 0.21 | 0.24 | 12.5 | 1.14 | 24.41 |
| **2** | **F2** | 0.13 | 0.15 | 13.33 | 1.15 | 25.22 |
| **3** | **F3** | 0.17 | 0.20 | 15 | 1.17 | 26.56 |
| **4** | **F4** | 0.22 | 0.26 | 15.38 | 1.18 | 24.10 |
| **5** | **F5** | 0.27 | 0.33 | 18.18 | 1.22 | 24.13 |
| **6** | **F6** | 0.21 | 0.24 | 12.5 | 1.14 | 27.47 |

**Physicochemical properties of the plug:**

Physicochemical properties for various polymer were performed and are represented in Table The optimized formulation of F4 indicating 298 min required to eject the plug out of capsule body. The optimum lag time of about 5-6 h.

**Table No. 6: Physicochemical properties of the plug**

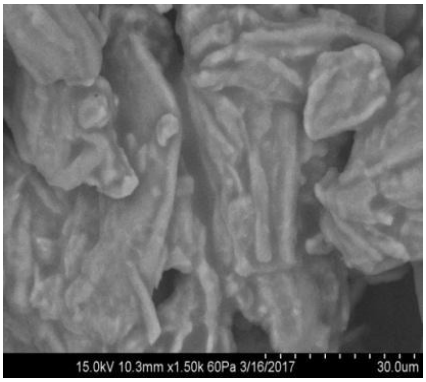
| Sr. No. | Formulation code | Polymer name | Weight (mg) | Lag time (min) |
|---|---|---|---|---|
| 1 | F1 | HEC | 50 | 280 |
| 2 | F2 | HEC | 70 | 289 |
| 3 | F3 | HPMC K 100 M | 50 | 285 |
| 4 | F4 | HPMC K 100 M | 70 | 298 |
| 5 | F5 | Chitosan | 50 | 290 |
| 6 | F6 | Chitosan | 70 | 285 |

**Swelling index:**

**S**welling index for various hydrogel plugs were performed and are represented in Table 8. Hydroxyethylcellulose, hydroxypropyl methylcellulose K 100 M and chitosan indicating more swelling index as compared to other polymers. Therefore these polymers are selected for plug.

**Scanning electron microscopy of S-SMEDDS:**

Figure showed that S-SMEDDS appeared as smooth surfaced S-SMEDDS particles, indicating that the liquid SMEDDS is adsorbed or coated inside the pores of microcrystalline cellulose with a lesser amount of aggregation.



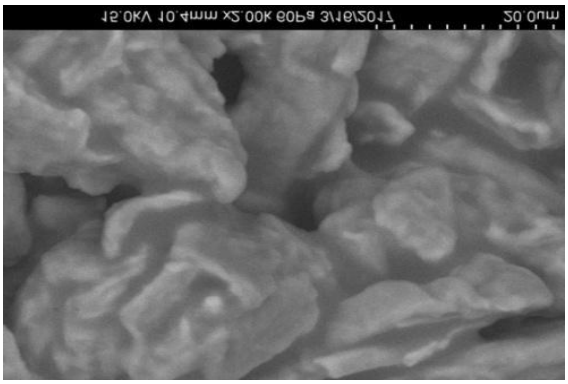



**Fig A** **Fig B**

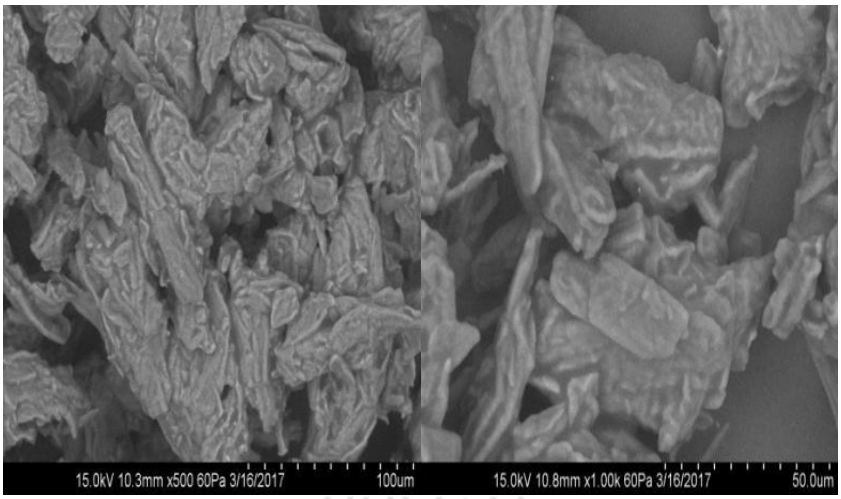



**Fig C** **Fig D**

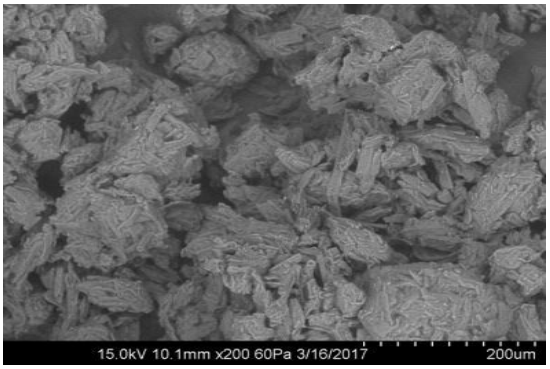



**Fig E**

**Figure No. 8: SEM images**

**Mean globule size determination or droplet size**:

Mean droplet size of optimized formulation was found to be 834.1 nm with polydispersity index 0.652.

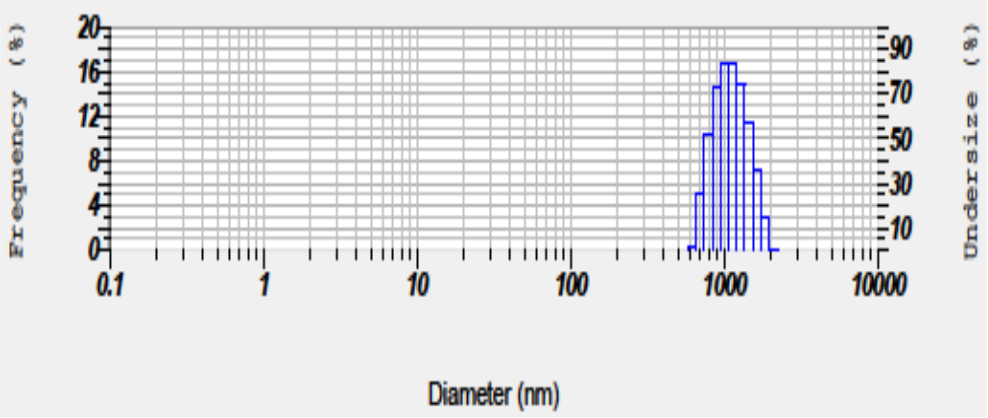



**Figure No. 9: Mean globule size determination or droplet size**

**Zeta potential measurement:**

Zeta potential of optimized formulation was found to be -7.8 mV. The particles did not exhibit any flocculation and the formulation was found to be stable.

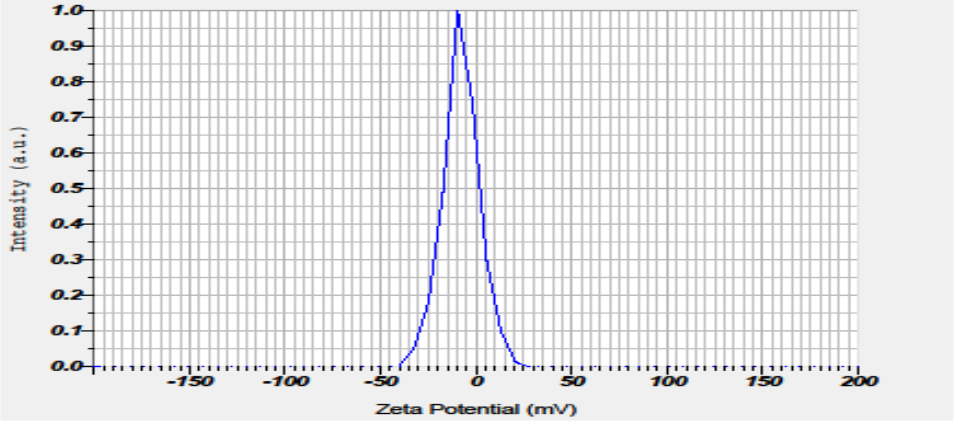



**Figure No. 10: Zeta potential measurement**

**Drug content determination:-** Drug content of optimized formulation F4 was found to be 97.12 %.

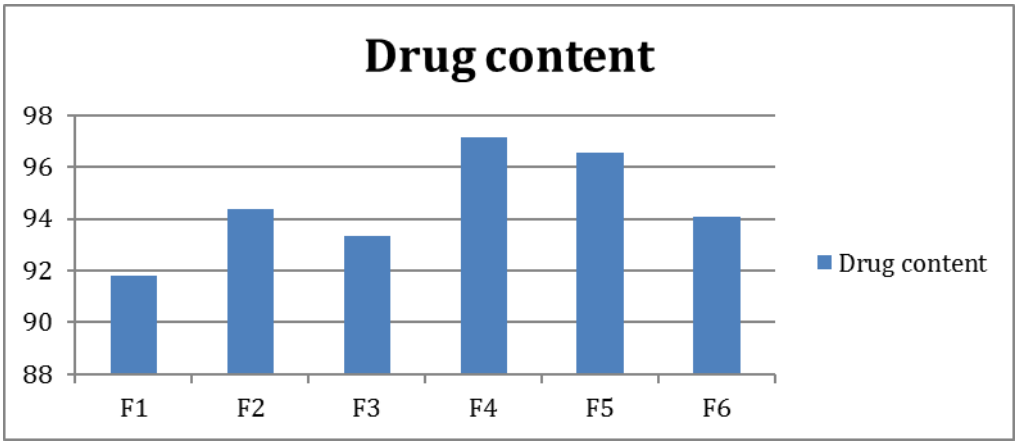



**Figure No. 11: Drug content determination**

**3.13 Comparative *in-vitro* release profile of pure drug and S-SMEDDS: -**The % cumulative drug release of solid SMEDDS formulation was found to be 97.90 % after 180 minutes compared with drug release of pure drug was found to be 70.51 %. Drug release of ketoprofen from solid SMEDDS formulation was significantly improved. As ketoprofen is a BCS class II (poor soluble, high permeable), by improving the solubility of the drug, the bioavailability of the drug can be increased.

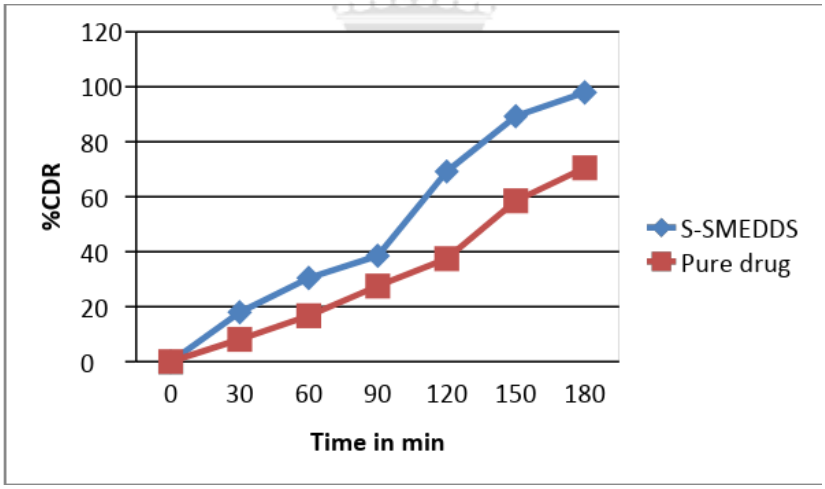



**Figure No. 12: Comparative *in-vitro* release profile of pure drug and S-SMEDDS**

***In-vitro* drug release study:**

In drug dissolution study of pulsincap drug delivery system indicate that drug release from pulsincap was taken over a period of 9 hr. During dissolution studies, it was observed that the enteric coating of the cellulose acetate phthalate was intact for 2 hours in pH 1.2. The enteric coated cap of pulsincap was dissolved in phosphate buffer 7.4 and then the polymer plug

absorbed the surrounding fluid, swelled and released a minor amount of drug through the swollen matrix. After complete swelling of a plug, it ejected out of the capsules body, released the drug into colon fluid of phosphate buffer 6.8.
In accordance with the chronotherapy of arthritis, the lag time criterion of 5 hours was satisfied by formulation F4.

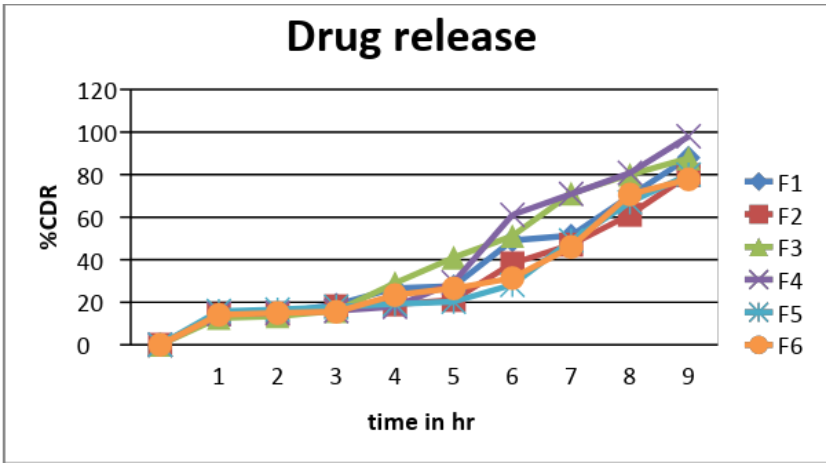



**Figure No. 13: *In-vitro* drug release study**

**CONCLUSION:**

From the above study, one can predict that in the coming year colon targeted drug delivery system would be used to targeted the chronopharmacological anti-arthritis action of the drug.

Novel pulsincap formulations have been successfully developed by filling of S-SMEDDS in a water-insoluble capsule body. The capsule body containing S-SMEDDS after plugging with a polymer, sealed with a cap which was completely enteric coated with cellulose acetate phthalate. Formulations had shown a complete lag time of 5 hours and released drug thereafter up to 4 hours respectively. Thus, S-SMEDDS filled pulsincap formulations are suitable for optimum colonic delivery of ketoprofen in the treatment of rheumatoid arthritis as per chronotherapy requirement.

Ketoprofen drug belongs to class II drug in BCS classification. One of the problems with this drug is its low solubility in biological fluids, which results in poor bioavailability after oral administration. Hence to improve its bioavailability we prepared SMEDDS.

**ACKNOWLEDGMENT:**

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