DEVELOPMENT AND EVALUATION OF TIME CONTROLLED RELEASE TABLET OF KETOPROFEN FOR THE TREATMENT OF RHEUMATOID ARTHRITIS

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ABSTRACT

The aim of present study was to develop and evaluate time controlled release tablet of Ketoprofen intended for rheumatoid arthritis. The cardinal sign of rheumatoid arthritis are stiffness, swelling and pain of one or more joints of the body characteristically most severe in the morning. Rheumatoid arthritis shows a significant circadian variation in its symptoms. Time controlled release tablet delivers the drug at definite time or in controlled rate. It consist of core tablet coated with two layers, the inner swelling layer and outer rupturable. Before compression of core tablet, drug- excipients compatibility study and precompression parameters were investigated. Core tablet was prepared by direct compression method. The core tablets are coated with crosscarmellose sodium as inner swelling layer with different coating level. The prepared tablet again evaluated and coated with rupturable layer of ethylcellulose. The free film of ethylcellulose was evaluated for various parameters. The effect of microcrystalline cellulose and coating level of rupturable layer and swellable layer on lag time were investigated. The results shows as the amount of microcrystalline cellulose increase in core tablet the lag time decreases. The lag time increases with increase in coating level of swelling layer and rupturable layer. The water uptake study shows that higher ethylcellulose levels retards the water uptake and prolongs the lag time.

Keywords

Time controlled drug delivery, Ketoprofen, Crosscarmellose sodium, Ethylcellulose, Rheumatoid arthritis

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INTRODUCTION
The impetus for the development of newer drug delivery system, apart from therapeutic efficiency, is the cost. The development cost of a new drug may require about $250 millions (Rs. 900 cores) and takes about 12 - 15 years to reach the market. An existing drug molecule can be developed as a newer drug delivery system in half the time, with 20% cost of new drug discovery [1]. Chronobiology is the science concerned with the biological mechanism of the diseases according to a time structure and chronopharmacology, is the science concerned with variations in the pharmacological actions of various drugs over a period of time and base on this, chronotherapeutics is the discipline concerned with the delivery of drugs according to inherent activities of a disease over a certain period of time [2]

The goal of chronotherapeutics is to match the timing of treatment with the intrinsic timing of illness. The best therapy is that when the right amount of the drug is delivered to the correct target organ at the most appropriate time [3]. Chronotherapy provides ways of increasing the effectiveness and safety of arthritis medications. The chronotherapy of arthritic disease involves determining the best time to take NSAIDs or other types of medicines to improve their desired effects and avoid or minimize unwanted ones. At present, more than 50 different NSAIDs are available on the market and no one is ideal in controlling or modifying the signs and symptoms of inflammation hence Ketoprofen is selected in this work. The time controlled release tablet of ketoprofen intended to approximate the chronobiology of rheumatoid arthritis. It is a chronopharmaceutical approach for the better treatment of arthritic pain.

MATERIALS AND METHODS
Ketoprofen used as an active ingredient gifted by Zim Lab, India. Microcrystalline cellulose gifted Avicel® PH 102, FMC USA, Spray dried lactose gifted by Flowlac® 100 Germany ,Magnesium stearate and talc gifted by Loba chem. India was used as ingredients of core tablet. Croscarmellose sodium gifted by Ac-Di-sol®, FMC was used as swelling agent and PVP gifted by Kollidone® 90F BASF, Germany as binder. The ethyl cellulose (Ethocel® standard 4) gifted by Colorcon Asia Ltd. India was used for rupturable coating and plasticized with Dibutylphthalate Ranchem Ltd. India). All other reagents were of analytical grade.

Preparation and Optimization of Core Tablet
Drug-Excipient compatibility study:
The samples of drug and excipients were evaluated for drug-excipients compatibility study by differential scanning colorimeter (DSC) using Perkin Elmer DSC model-7. The instrument calibrated with indium and zinc prior to analyzing the samples under nitrogen. Sample (1-2mg) was accurately weighed and sealed hermetically in flat bottom open aluminum cells at a scanning rate of 5˚C/min conducted over a temperature range of 30- 250˚C. The samples were heated in sealed aluminum pans under nitrogen flows (50 ml/min) [4] and Fourier transformed infrared spectroscopy (FT-IR) using KBr disc method. Each sample was gently triturated with KBr powder in a weight ratio of 1: 100 and pressed using a hydrostatic press at a pressure of 10 tons for 5 min. The disc was placed in the sample holder and scanned from 4600 to 400 cm-1 at a resolution of 1 cm-1 at zero time [5]

Micromeric properties of core tablet powder blend and Preparation of core tablet:
Before compression, blends were evaluated for their characteristic parameters such as bulk density, tapped density, Hausner’s ratio, compressibility index using a digital tap density apparatus (Electrolab Ltd, India) [6]. Core tablets were prepared by direct compression method as per the composition Table 1. All the excipients first pass through the sieve no. 100. Then Ketoprofen, microcrystalline cellulose, spray dried lactose were simply mixed with each other in a poly bag for 30 minutes for uniform mixing followed by the addition of magnesium stearate and talc. Core tablets were compressed by pilot press tablet machine (Chamunda Pharma Machinery Pvt. Ltd., India) with diameter, 7 mm; biconvex; average tablet Weight 150 mg [7]

| Ingredients         | C1 (mg) (100:0) | C2 (mg) (70:30) | C3 (mg) (50:50) | C4 (mg) (30:70) | C5 (mg) (0:100) |
|---------------------|----------------|----------------|----------------|----------------|----------------|
| Ketoprofen          | 50             | 50             | 50             | 50             | 50             |
| Lactose*            | 98.5           | 68.95          | 49.25          | 29.55          | ----           |
| MCC*                | ---            | 29.55          | 49.25          | 68.95          | 98.5           |
| Magnesium stearate  | 0.75           | 0.75           | 0.75           | 0.75           | 0.75           |
| Talc                | 0.75           | 0.75           | 0.75           | 0.75           | 0.75           |

*Spray dried Lactose & MCC – Microcrystalline Cellulose
Evaluation of core tablet
Core tablet evaluated as per the official tests for tablets mentioned in the pharmacopoeias such as weight variation, as per I.P. Hardness by using Monasanto Hardness tester, thickness by using Vernier calipers and expressed in mm, friability using Roche friabilator. The disintegration time was determined using USP tablet disintegration test apparatus (ED 2L, Electrolab, India). The dissolution study was carried out using USP type II paddle apparatus in 6.8 p H phosphate buffer (900 ml) at 37ºC±0.5ºC at speed 50±5 rpm. At specified time intervals, 5 ml samples were collected and immediately replaced with an equal volume of fresh medium. Samples were suitably diluted & analyzed by using UV spectrophotometer [8].

Coating of core tablet with swellable layer of croscarmellose sodium
The croscarmellose sodium was dispersed in alcoholic solution of polyvinyl pyrrolidone (90F kollidone®) at a ratio of 6:1 w/w. 0.667g Kollidon 90F was dissolved in the 100 ml 96% v/v ethanol by stirring, using a magnetic stirrer till clear solution was obtained. The croscarmellose sodium was passed through the sieved no. 150 and 4g of Croscarmellose (Ac-Di-Sol) were dispersed into the Kollidon 90F solution and agitated for at least 30 minutes to obtain a homogeneous dispersion. The core tablet was coated with coating dispersion to obtained coating level of 10 mg/ cm², 20 mg/cm² and 30 mg/cm². The coating condition were spray rate of 1ml/min., pan speed at 30rpm and inlet hot air temperature of 40˚C. The coated tablet further dried in coating pan for 10 min with hot air after completion of coating process. The tablets were placed in an oven at 40˚C for 2 hours to remove residual solvent [9]. The swellable layer coated tablet again evaluated as per the official tests for tablets.

Coating of swellable layer core tablet with rupturable layer of Ethylcellulose
Preparation and evaluation of free film of Ethylcellulose:
Free film of ethyl cellulose was prepared by mercury substrate technique. The solution of ethyl cellulose was prepared in ethanol by stirring for 30 min. then solution was poured in Petri dish containing mercury and solvent was allowed to evaporate in an oven at 60 °c to 70°C [10]. The thickness of film was determined using Digital Vernier Caliber instrument at a different point throughout the film and the mean of five measurements were recorded. The diffusion study of film was determined by using Keshary-Chein diffusion cell [11]. Moisture Absorption study was carried out in glass desiccators maintained at controlled relative humidity conditions by use of different saturated salt solution such as potassium acetate, potassium carbonate, sodium chloride and potassium nitrate. After equilibrating the desiccators with appropriate concentration of saturated salt solution for three days, accurately weighed film placed in Petri dish were kept in the desiccators undisturbed for 14 days [12]. The difference in weight gives the amount of moisture observed at various relative humidity.

Water vapor transmission rate study (WVTR): The films were cut to a suitable size and thickness of the dry films were determined by Digital Vernier Caliber instrument and were mounted on assembled transmission cell (vials).These vials contains a saturated salt solution of sodium chloride, to provide the relative humidity (RH) condition of 75% and the charged vials were weighed and placed in pre equilibrated desiccators maintained at 0% RH, containing fused calcium chloride. The vials were reweighed in the same manner at 24 h interval for 72 h. The amount of water transmitted through the film was given by the loss of weight of the vials [13]. The rate of water vapor transmission was calculated using the following Utsumi's WVT equation: 

\[ Q = \frac{W}{L} \]

Where W = Gm of water transmitted per 24 hours, L = film thickness in cm, S =Surface area in sq. cm, Q = water vapor transmission in g.cm thickness /cm² areas 24 hours.

To determine mechanical properties of film, a tensile test was performed on Instron (Model - 4467, Instron crop, Carton, MA) instrument based on ASTM standard test principle. The gauge length was kept at 500 mm and crosshead speed was 1.0000 mm / min and the test was performed at 50% RH at room temperature. The mechanical properties viz tensile strength, percentage elongation and modulus of elasticity were automatically computed by the instrument. Each experiment was repeated at least three times [14]

Coating of swellable layer coated tablet of Ketoprofen with rupturable layer
Swellable layer coated tablets were then coated with an ethanolic solution of ethyl cellulose, using dibutyl phthalate as a plasticizer. The coating solution was prepared by dissolving 3.5 g ethyl cellulose in 100 ml of 96% v/v ethanol (3.5% w/w
solution) and stirred on a magnetic stirrer to obtain a clear solution. The plasticizer (5% w/w based on polymer solids) was added into the polymer solution i.e. 0.176 ml and the solution was further agitated for at least 30 min before coating to obtain a homogeneous solution. The homogeneous dispersion was gently stirred throughout the coating process. The polymer solution was sprayed onto the tablets in a conventional coating pan (2.5 inch) and other specification regarding coating conditions were same as described in 2.2.6. The coated tablets were further dried in the coating pan for 15 min at 40°C after the coating process was finished and then placed in the oven at 40°C for 2 h to remove the residual solvent [15]. The coated tablets were equilibrated at room temperature overnight and stored in a closed container before further experiments.

Evaluation of Time Controlled Release Tablet

Scanning Electron Microscopy: The scanning of morphology of a cross-section of the time controlled release tablet of Ketoprofen was carried out by using Scanning Electron Microscopy (JSM-6360). The sample of time controlled release tablet was mounted on stage and coated with gold under vacuum [16].

Rupture test: The rupture test was carried out by using 900ml of phosphate buffer pH 6.8 in the dissolution apparatus USP TYPE-II at 50 rpm and temperature condition 37±0.5°C. The sequence of rupturing of Time controlled release tablet was observed and photographs taken using a digital camera (Sony Ericsson) [17].

Water uptake Study: The water uptake study of time controlled release tablet of Ketoprofen was done using screw-capped container containing 100ml of phosphate buffer pH 6.8. In this container tablet was added and placed in horizontal water bath shaker (Remi equipments Pvt Ltd.) and temperature was maintained at 37±0.5°C. The tablet was withdrawn at predetermined time intervals from dissolution media and weight of tablet was taken after removing the surface water by carefully blotting the tablet with tissue paper and tablet was again added to the medium. The same procedure was repeated until the rupturing of coat occurs [18].

Swelling Index: Swelling index was determined by weighing four tablets separately (m<sub>i</sub>) and each weighed tablet was placed into a beaker containing 6ml of phosphate buffer pH 6.8 at 37±0.5°C. The tablets were removed from beaker at specified time interval and from the surface of tablet excess water was removed using tissue paper. Each swollen tablet was weighed (m<sub>f</sub>) and swelling index was calculated [19].

In – Vitro Dissolution studies: In vitro dissolution studies of time Controlled release tablets of Ketoprofen were performed using USP paddle dissolution apparatus. The other conditions which were maintained throughout the test are paddle speed of 50 rpm at 37°C using 900ml of Ph 6.8 phosphate buffer. Sample of 10 ml was withdrawn at regular interval of 60 minutes by using 10 ml of calibrated pipette upto 6hrs and then regular interval of 15min. The volume withdrawn was replaced by fresh volume of dissolution medium. The sample was analyzed spectrophotometrically at 258 nm. The amount of drug release was determined using calibration curve (PCP-Disso software).

RESULTS AND DISCUSSION

The DSC thermograms Figure 1, shows the endothermic peaks as given in the literature.
The DSC thermograms of samples (pure drug, core tablet mixture and physical mixture core tablet with coating material) show the endothermic peaks as given in literature. It shows there was no considerable change in the endotherm values of Ketoprofen when mixed with excipients which shows no interaction between drug, polymer and excipients [20]. FT-IR spectrum of sample was shown in Figure 2 shows the entire characteristic peak. From the result of FT-IR spectra of pure drug, core tablet mixture and physical mixture core tablet with coating material it was observed that there was no interaction between drug and excipient. All the characteristic absorption peaks of ketoprofen at 3020 cm\(^{-1}\) (C–H stretching of aromatic ring), 2970 cm\(^{-1}\) (C–H stretching of CH\(_3\) group), 1695 cm\(^{-1}\) (C–O stretching of acid), 1655 cm\(^{-1}\) (C-O stretching of ketone), 1595 cm\(^{-1}\) (C-C stretching of aromatic ring), 860 cm\(^{-1}\) (C–H deformation of aromatic ring) were observed [21] variation, friability, drug content and disintegration test [23]. The results of the various tests were mentioned in Table 3. The thickness, hardness, drug content, disintegration time, weight variation and Friability of core tablet of ketoprofen was also found to be within range. The result of dissolution studies of formulation C1, C2, C3, C4, C5 composed of varying concentration of spray dried lactose and microcrystalline cellulose are shown in Figure 3.

Micromeritic properties of core tablet powder blend

The Micromeritic properties or precompression parameter such as angle of repose, bulk density, tapped density, Hausner’s ratio, Carr’s index of core tablet powder was found to be satisfactory and it indicates that powder blend has good flow property with good compressibility and suitable for direct compression method [22]. The core tablets were subjected to various evaluation tests such as thickness, hardness, weight 

| Test              | C1         | C2         | C3         | C4         | C5         |
|-------------------|------------|------------|------------|------------|------------|
| Angle of repose   | 33.09 ±0.16| 30.1967±0.14| 30.0067 ±0.22| 29.4767 ±0.23| 28.89 ±0.17|
| Bulk density      | 0.5979±0.07| 0.5898±0.06 | 0.5958 ±0.0843| 0.6026 ±0.047| 0.6168 ±0.058|
| Tapped density    | 0.7219±0.04 | 0.7198±0.03 | 0.7133 ±0.0467| 0.7199 ±0.03 | 0.7264 ±0.049|
| Carr's index      | 17.17      | 16.53      | 16.47      | 16.29      | 15.08      |
| Hausner's ratio   | 1.22       | 1.22       | 1.19       | 1.19       | 1.17       |

The dissolution study of core tablet was carried out and it was observed that the core tablet without microcrystalline cellulose (spray dried lactose100: 0 Microcrystalline cellulose, 100:0 w/w) showed the steepest slope. As the concentration of microcrystalline cellulose increases in the core it lowers the release rate of drug. According to this result, core tablets consisting of spray dried lactose and microcrystalline cellulose with a 70:30 w/w ratio was used for further studies [24]

Figure 2: Infra red (FT-IR) spectrum of Ketoprofen, physical mixture of core tablet (drug with excipients and physical mixture of optimized time controlled release tablet (core tablet with coating material)

Figure 3: In-vitro drug release profile of formulation C1 to C5
Table 3: Different evaluation parameters of core tablets

| S. No. | Test            | C1              | C2              | C3              | C4              | C5              |
|--------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| 1.     | Thickness (mm)  | 3.32±0.12       | 3.36±0.02       | 3.27±0.08       | 3.32±0.05       | 3.30±0.07       |
| 2.     | Hardness (kg/cm$^2$) | 3.45 ±0.11     | 3.52 ± 0.04     | 3.60 ±0.95      | 3.88±0.51       | 4.23 ± 0.05     |
| 3.     | Friability      | 0.84±0.4        | 0.89±0.2        | 0.87±0.3        | 0.80±0.8        | 0.86±0.6        |
| 4.     | Drug content (%)| 99.13±0.59      | 98.43±0.39      | 98.78 ±0.21     | 99.93±0.4       | 99.53 ± 0.1     |
| 5.     | Weight Variation (mg) | 150±5.5       | 150±6.2         | 150±4.1         | 150±7.2         | 150±3.8         |
| 6.     | Disintegration (min) | 11.8 ± 0.21    | 6.6 ± 0.32      | 5.4 ±0.13       | 4.9 ±0.16       | 4.4 ± 0.12      |

Table 4: Different evaluation parameters of swellable layer coated core tablets of Ketoprofen

| S. No. | Test            | S-1(C2) (10mg/cm$^2$) | S-2(C2) (20mg/cm$^2$) | S-3(C2) (30mg/cm$^2$) |
|--------|-----------------|----------------------|----------------------|----------------------|
| 1.     | Thickness (mm)  | 4.09 ± 0.12          | 4.08 ± 0.02          | 4.09 ± 0.08          |
| 2.     | Hardness (kg/cm$^2$) | 3.73 ± 0.15           | 4.73 ± 0.21          | 5.70 ± 0.95          |
| 3.     | Friability      | 0.01±0.4             | 0.02±0.2             | 0.01±0.3             |
| 4.     | Drug content (%)| 99.13±0.59           | 98.43±0.39           | 98.78 ±0.21          |
| 5.     | Weight Variation (mg) | 170±05              | 190±06              | 210±04              |
| 6.     | Disintegration time (sec) | 44±0.1              | 38±23               | 26±12               |

The core tablets coated with swellable layer were subjected to various evaluation test and the results of the various tests were mentioned in Table 4. The hardness and thickness of core tablet coated with swellable layer of Ketoprofen was found to be high as compared to core tablet. The higher hardness might retard the water penetration through this layer and affect the drug release [25]. The core tablets coated with swellable layer were subjected to various evaluation test and the results of the various tests were mentioned in Table 4. The hardness and thickness of core tablet coated with swellable layer of Ketoprofen was found to be high as compared to core tablet. The higher hardness might retard the water penetration through this layer and affect the drug release [25].

The thickness of prepared ethylcellulose film was shown in Table 5. The thickness of film strongly affects the drug permeability of the film. The increase in the film thickness decreases the permeation rate [26].

Table 5: Thickness of ethyl cellulose film

| S. No. | Polymer concentration of ethyl cellulose film (%) | Thickness (mm) |
|--------|--------------------------------------------------|----------------|
| 1.     | 1.5                                              | 0.05           |
| 2.     | 2.5                                              | 0.07           |
| 3.     | 3.5                                              | 0.09           |
| 4.     | 4.5                                              | 0.10           |

The drug diffusion of prepared ethyl cellulose film was shown in Table 6. From the diffusion study it was found that as the concentration of polymeric film increases the thickness of the film. As the thickness, of the film increases the diffusion rate decreases. The ethyl cellulose film, having a thickness of 0.09 mm was selected for further study [27].

Moisture Absorption capacity of the film increases with an increase in humidity. Moisture will exert a temporal effect on the properties of polymeric film [28]. The Water vapor transmission rate of ethyl cellulose film was determined and

![In-vitro drug release profile of formulation S1 (C2) to S3 (C2)](image-url)
There was no significant difference in the permeability of ethylcellulose films plasticized with dibutyl phthalate. Therefore the ethylcellulose film was suitable as a coating agent. It also offers good protection to water sensitive drugs. In pharmaceutical coating, these films can provide protection from atmospheric moisture [29].

Table 6: Diffusion of ethyl cellulose film

| Polymer concentration of ethyl cellulose film (%) | Thickness (mm) | Time | % Release |
|--------------------------------------------------|----------------|------|-----------|
| 1.5                                              | 0.05           | 15   | 45.44     |
|                                                  |                | 30   | 53.28     |
|                                                  |                | 45   | 63.92     |
|                                                  |                | 60   | 68.36     |
| 2.5                                              | 0.07           | 15   | 43.71     |
|                                                  |                | 30   | 45.23     |
|                                                  |                | 45   | 50.39     |
|                                                  |                | 60   | 52.92     |
| 3.5                                              | 0.09           | 15   | 38.79     |
|                                                  |                | 30   | 41.23     |
|                                                  |                | 45   | 29.66     |
|                                                  |                | 60   | 49.23     |
| 4.5                                              | 0.10           | 15   | 28.87     |
|                                                  |                | 30   | 29.24     |
|                                                  |                | 45   | 32.12     |
|                                                  |                | 60   | 36.04     |

Table 7: Moisture absorption capacity of prepared ethyl cellulose film

| Film                        | Percent moisture absorption at percent relative humidity |
|-----------------------------|--------------------------------------------------------|
| Ethyl cellulose (3.5%)      | 23% 43% 75% 93%                                        |

Table 8: Water vapor transmission rate of prepared ethyl cellulose film

| Film                        | Area (cm²) | Thickness (cm) | WVTR X 10⁴ (gm-cm/cm²) |
|-----------------------------|------------|----------------|-------------------------|
| Ethyl cellulose 3.5%        | 1.24       | 0.09           | 1.37 ± 0.14 1.40 ± 0.20 1.48 ± 0.15 |

Table 9. Mechanical properties of prepared ethylcellulose film

| Film                        | Tensile Strength (MPa) | Percent elongation | Modulus of Elasticity (MPa) | Tensile Strength/Modulus of elasticity (MPa) |
|-----------------------------|-------------------------|--------------------|-----------------------------|--------------------------------------------|
| Ethyl cellulose (3.5%)      | 2.17 ± 0.22             | 4.15 ± 3.0         | 140 ± 14                    | 0.0156                                     |

The mechanical properties of dry film of ethylcellulose show moderate tensile strength, high % elongation, low modulus of elasticity and low tensile strength to elastic modulus ratio. Therefore the prepared films were mechanically weak, brittle and easily ruptured on exposure to dissolution medium also due to internal pressure developed within the tablet core. Dibutyl phthalate increases the % elongation of the ethyl cellulose film. The plasticizers with larger alkyl substituent produced tougher ethyl cellulose films. This phenomenon was due to higher hydrophobicity of the plasticizers, which was more compatible with water-insoluble ethyl cellulose. The dibutyl phthalate plasticized films were smoother and has homogenous surface. The Surface morphology of prepared ethylcellulose film (3.5%) was examined using by scanning Electron Microscopy. The surface morphology of the film was shown in Figure 5.

Figure 5. SEM scanned image of ethylcellulose film

**Evaluation of time controlled release tablet**

The time controlled release table (core tablets coated with swellable layer and further with ethylcellulose) were subjected to various evaluation tests such as rupture test, water uptake study, Swelling index, Scanning electron microscopy and
dissolution study. The thickness, hardness, weight variation, friability, drug content and disintegration test of time controlled release tablet of ketoprofen was also evaluated. The results of the various tests were mentioned in Table 10.

Table 10. Different evaluation parameters of time controlled release tablets of ketoprofen

| Sr. No. | Batch No. | Thickness (mm) | Hardness (kg/cm²) | Friability | Drug content (%) | Weight Variation (mg) |
|---------|-----------|----------------|-------------------|------------|------------------|----------------------|
| 1.      | TC1(S1C2) | 4.12 ± 0.12    | 4.2 ± 0.11        | 0.01±0.11  | 99.18± 0.72      | 175±4.2              |
| 2.      | TC2(S1C2) | 4.11±0.3       | 4.3 ±0.11         | 0.03±0.12  | 99.81± 1.07      | 177±3.8              |
| 3.      | TC3(S1C2) | 4.13±0.5       | 4.2 ±0.10         | 0.01±0.09  | 99.54 ±0.50      | 179±3.5              |
| 4.      | TC4(S2C2) | 4.33±0.1       | 4.5 ±0.12         | 0.00±0.07  | 98.12±0.73       | 195±2.4              |
| 5.      | TC5(S2C2) | 4.40±0.4       | 4.6 ±0.18         | 0.02±0.07  | 99.30 ±0.87      | 197±2.6              |
| 6.      | TC6(S2C2) | 4.41±0.3       | 4.5 ±0.15         | 0.02±0.05  | 99.23 ±0.90      | 199±2.5              |
| 7.      | TC7(S3C2) | 4.62±0.1       | 4.7 ±0.21         | 0.01±0.08  | 99.50 ±0.77      | 216±2.8              |
| 8.      | TC8(S3C2) | 4.66±0.4       | 4.8 ±0.15         | 0.03±0.13  | 99.96 ±0.27      | 218±3.1              |
| 9.      | TC9(S3C2) | 4.71±0.5       | 4.7 ±0.15         | 0.01±0.12  | 99.56±0.76       | 220±2.2              |

Time controlled release tablet of ketoprofen passes all the evaluation parameters of tablet. The thickness and hardness of the tablet increased with an increase in coating level of ethylcellulose rupturable layer of 2.5mg/cm², 3.5mg/cm², 4.5mg/cm².

Lag time determination: To optimized the exact composition of time controlled release tablet, selected batches of core tablets were coated with 10 mg/cm², 20 mg/cm², 30 mg/cm² of Ac-Di-Sol layer and the lag time was determined as per procedure given in the rupture test.

Dissolution study: In vitro dissolution studies of the different batches were carried out and depicted in the graphs. Ketoprofen release from batches TC1 to TC3 has been shown in Figure 7. Ketoprofen release from tablet layered with 10 mg/cm² of swelling layer and coated with ethylcellulose (2.5 mg/cm²) shows the lag time of 4 hours then follows the sigmoidal release pattern with 100% drug release at 10th hour. As the concentration of the ethyl cellulose coating increases to (3.5 mg/cm²) shows the lag time of 5 hours then follows the sigmoidal release pattern with 100% drug release at 12 hour and ethyl cellulose (4.5 mg/cm²) also shows the lag time of 8 hour with 100% drug release at the 15 hour. Ketoprofen release from tablet layered with 20 mg/cm² (TC4 to TC6) of swelling layer and coated with ethylcellulose (2.5 mg/cm²) shows the lag time of 4 hours then follows the sigmoidal release pattern with 100% drug release at 9 th hour. As the concentration of the ethyl cellulose coating increases from 20 to 30 mg/cm² shows the lag time of 6 and 7 hour respectively and the further release profile shows delayed release after an initial lag time of 4 and 5 hour with the 100% drug release at the 10th and 12th hour of as the coating level of ethyl cellulose increases up to 3.5 mg/cm² and 4.5 mg/cm² respectively. Ketoprofen release from tablet layered 20 mg/cm² of swelling layer and coated with ethylcellulose (2.5 mg/cm²) shows with shows the lag time of 2 hours with 100% drug release at 6 th hour. As the concentration of the ethylcellulose coating
increases from 3.5 mg/cm$^2$ and 4.5 mg/cm$^2$ shows delayed release after an initial lag time of 3 hour with the 100% drug release at the 8th hour.

To develop the time release tablet based on swelling and rupturable coatings, several studies were necessary to identify formulation variables, which provided the desired system properties, namely a rapid drug release after a certain lag time. The influence of core composition, level of swelling layer and rupturable coating, and magnesium stearate in rupturable layer was investigated.

**Effect of core composition:** The effect of core composition on lag time of Time controlled release tablets of ketoprofen tablet shown in Figure 8. The amount of microcrystalline cellulose affects the lag time of the tablet. An increase in the concentration of microcrystalline cellulose causes the lag time to decrease. This decrease in lag time is totally independent on the coating level of Ac-Di-Sol and ethylcellulose. The decrease in lag time might be due to the higher disintegration property of microcrystalline cellulose which creates higher disintegration force and spray dried lactose which is highly soluble in water and has high osmotic activity.

Hence the core tablet prepared to use 70:30 w/w ratios of microcrystalline cellulose and Spray dried Lactose showed reproducible result and used as the optimized formulation to provide desired lag time which is essential for time controlled release tablet.

**Effect of swelling layer and rupturable coating on lag time:**
The effect of swelling layer and rupturable layer on lag time shown in Figure 9 and 10. In vitro dissolution studies of time controlled release tablets of Ketoprofen were carried out and it is found that the drug was not released prior to the rupturing of the coating. After rupturing, the drug release from the time controlled release tablets of Ketoprofen with 10.0 mg/cm$^2$ Ac-Di-Sol layer were lower than that from the time controlled release tablets of Ketoprofen with 30 mg/cm$^2$ Ac-Di-Sol layer. A swelling layer level of 10.0 mg/cm$^2$ might not be enough for the complete rupture of the tablets (Flowlac 100: Avicel PH102, 70:30 w/w cores). As observed visually, tablets with
10.0 mg/cm$^2$ Ac-Di-Sol layer showed a lower degree of rupturing than tablets with 30mg/cm$^2$ Ac-Di-Sol layer.

Figure 9. Effect of swelling layer on lag time of Time controlled release tablets of Ketoprofen

The amount of swelling layer was an important variable influencing the rupturing. Unexpectedly, the lag time of tablets with a higher level of swelling layer increased at all ethyl cellulose coating levels. The hardness of the core tablets coated with croscarmellose sodium level 10mg/cm$^2$, 20 mg/cm$^2$, 30 mg/cm$^2$ was found to be high. Core tablets coated with higher levels of croscarmellose sodium (without rupturable membrane) had a higher hardness, which might retard the water penetration through this layer. Croscarmellose sodium swelled when in contact with medium and therefore probably retarded the further water penetration into the core, which by itself had a high disintegration force resulting in short lag times. Croscarmellose sodium layer was also more porous than the core, thus resulting in a lower swelling pressure. In case of pulsatile release tablets, both the tablet core and the swelling layer influenced the rupturing process.

As expected, higher levels of the rupturable ethyl cellulose layer increased the lag time. The lag time increased with increasing ethylcellulose level, the drug was released rapidly and completely at ethylcellulose levels of 2.5 mg/cm$^2$ and 3.5 mg/cm$^2$. At the higher ethylcellulose, level of 4.5 mg/cm$^2$, the drug was released slower after the lag time; this was again caused by the lower degree of rupturing of the thicker coating.

Figure 10. Effect of ethylcellulose coating level on lag time of Time controlled release tablets

Effect of magnesium stearate in rupturable layer:

Time controlled release tablets of ketoprofen containing magnesium stearate in the rupturable coating decreased the lag time significantly compared to tablets without magnesium stearate and the slope of the curve was also less steep, indicating a more robust formulation. The addition of magnesium stearate to the ethylcellulose coating decreased the mechanical properties of film. This may be due to the reduced interaction between polymer chains caused by the presence of the hydrophobic solid particles.

Scanning Electron Microscopy: The scanning of morphology of a cross-section area of the time controlled release tablet of Ketoprofen was carried out by using Scanning Electron Microscopy. The photograph shows the three parts of the tablet which are clearly visible, namely the dense tablet core, (microcrystalline cellulose, lactose and drug) (C), the more porous layer of the Ac-Di-Sol containing swelling layer (B), and the homogenous ethylcellulose coating as the outer rupturable coating (A).

Figure 12. SEM photomicrograph of a cross-section of a pulsatile release tablet with a swelling layer (20 mg/cm$^2$) and a rupturable ethylcellulose coating (3.5 mg/cm$^2$), magnification 150_. (A) rupturable layer (B) swelling layer (C) core

Rupture Test: The rupturing sequence of a time controlled release tablet of Ketoprofen was taken by Digital Camera.
Water influx and the subsequent volume expansion of the swelling agent caused the rupturing of the ethylcellulose coating. The drug was then released rapidly within a short period after a certain lag time due to the strong rupturing of the coating.

**Figure 13.** Rupturable sequence of time controlled tablets of Ketoprofen A to C- Water uptake studies, D- Rupture point, H- Total drug release

**Water uptake study:** The water uptake study of time controlled release tablet of Ketoprofen shows that higher ethyl cellulose levels retarded the water uptake. Interestingly, all curves showed an almost linear water uptake with time until critical water level, where the ethyl cellulose coating ruptured. The critical water uptake level was slightly higher at the higher level of ethyl cellulose.

**Figure 14.** Effect of Ethylcellulose coating level on % water uptake of time controlled Release tablets with 10 mg/ cm² Ac-Di-Sol layer

This could be explained by the higher mechanical strength of the thicker coating requiring a higher degree of swelling (water uptake) for rupturing. Water uptakes prior to rupture of the different batches were investigated as a function of the amount of rupturable ethylcellulose layer.

**Swelling index:** The swelling index of time controlled release tablet of Ketoprofen was shown in Table 11. The swelling index of time controlled release tablet of Ketoprofen was higher at the lower level of ethylcellulose layer. As the coating level increased, the swelling index decreased.

**CONCLUSION**

The prepared time controlled release tablet satisfied the objective of the present research work to synchronize drug delivery to the circadian rhythms of rheumatoid arthritis.
Overlapping of drug release characteristic with the onset of pharmacological symptoms make the drug delivery system ideal for chronotherapy of rheumatoid arthritis, delay the release of drug and hence control the onset of drug action, minimize the frequency of drug administration by developing a once daily therapy administered at bedtime, improved therapy which exerts its action at a time when it is needed most and dose related side effects could be minimized, to achieve patient convenience and compliance.

| Ethyl cellulose coating level (mg/cm²) | Swelling index ± S.D. at Time (hrs) |
|---------------------------------------|-------------------------------------|
|                                       | 1        | 2        | 3        | 4.30     | 5        | 5.30     | 6        | 6.30     |
| 1.5                                   | 12.16 ± 0.01 | 14.81 ± 0.02 | 18.17 ± 0.02 | 22.68 ± 0.03 | R        |
| 2.5                                   | 8.51 ± 0.02  | 10.19 ± 0.01  | 13.88 ± 0.02  | 21.31 ± 0.02  | 24.43 ± 0.01 | R        |
| 3.5                                   | 3.85 ± 0.03  | 6.98 ± 0.03  | 9.91 ± 0.02  | 13.79 ± 0.02  | 18.37 ± 0.03  | 23.2 ± 0.03 | R        |

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Nil

**CONFLICT OF INTEREST**
The authors declare no conflict of interest

**REFERENCES**
[1] Parashar B, Thakur VS, Thakur A, Chauhan A, Prashar D. Novel Drug Delivery System in the treatment of Cardiovascular Disorders International Journal of Institutional Pharmacy and Life sciences. 2, 291–311 (2012).
[2] Jha N, Bapat S. Chronobiology and chronotherapeutics. Kathmandu University Medical Journal, 4, 384–8 (2004).
[3] Gami SV, Gohel MC, Parikh RK, Patel LD, Patel V P. Design and Evaluation Study of Pulsatile Release Tablets of Metoprolol Succinate. Pharma science monitor 4 3947–63 (2013).
[4] Bhavani D, Vani CHSV, Rao VUM. Formulation and Evaluation of Montelukast Sodium Pulsatile Drug Delivery System By Core In Cup Method. Pharmacy Review & Research 5 15–23 (2015).
[5] Latha K, Uhumwangho MU, Sunil SA, Srikanth M V., Ramana Murthy K V. Development of an optimised losartan potassium press-coated tablets for chronotherapeutic drug delivery. Trop. J. Pharm. Res., 10, 551–8 (2011).
[6] Lachmann L, Liberman HA, Kanig JL. Theory and practice of industrial pharmacy. 3.ed.: Varghese Publishing House, Bombay p.297-299 (1987).
[7] Desai M, Jivani RR, Patil LD, Jivani NP, Sonagara B. Development of time controlled chronomodulated tablet with swelling and rupturable layers: Optimization of factors influencing lag-time and drug release. International Journal of Pharmaceutical Investigation. 2 208-212 (2012).
[8] Indian Pharmacopoeia. Govt. of India. Ministry of Health and Family Welfare, The Indian Pharmacopoeial commission, Ghaziabad: 1: 477 2007.
[9] El-maradny HA. Modulation of a Pulsatile Release Drug Delivery System Using Different Swellable / Rupturable Materials.Drug Delivery 8 539–46 (2007).
[10] Kulkarni RV, Mutalik S, Hiremath D. Effect of plasticizer on the permeability and mechanical properties of eudragit films for transdermal application. Indian Journal of Pharmaceutical Science, 64 28-31 (2002).
[11] Bonina, FP. Carelli, V. Cols GD. Montenegro L. and NannipieriE. Vehicle effects on in vitro skin permeation of and stratum corneum affinity for model drugs caffeine and testosterone. International Journal of Pharmaceutics. 100 41-47. (1993).
[12] Mundada AS, Avari JG. Permeability studies of Damar Batu free films for transdermal application. Chemical Industry and Chemical Engineering Quartery 15 83–8 (2009).
[13] Lachman, L. and Drubulis, A. Factors influenceing the properties of films used for tablet coating: I. Effects of plasticizers on the water vapor transmission of cellulose acetate phthalate films. Journal of Pharmaceutical Sciences 53, 639-643 (1964).
[14] American Society for Testing and Materials – ASTM. (2001a). D882- 00: standard test methods for tensile properties of thin plastic sheeting (Annual Book of ASTM Standards). Philadelphia: ASTM. West Conshohocken, PA, (1995)
[15] BK Garg, P. Kothiyal, GG. Formulation and Evaluation of Pulsatile Drug Delivery System of Rosuvastatin Calcium Using Different Swelling Polymers. Pharma Innovation. 1, 61–7 (2012).

[16] Reddy GS, Nayak UY, Deshpande PB, Matalik S. Gastroretentive Pulsatile Release Tablets of Lercanidipine HCl: Development, Statistical Optimization, and In Vitro and In Vivo Evaluation. Scientific World Journal 1–13 (2014).

[17] Sungthangjeen S, Puttipipatkhachorn S, Peeratakul O, Dashevsky A, Bodmeier R. Development of pulsatile release tablets with swelling and rupturable layers. Journal of Controlled Release. 95 147–59 (2004).

[18] Qureshi J, Amir M, Ahuja A, Baboota S, Ali J. Chronomodulated Drug Delivery System of Salbutamol Sulphate for the Treatment of Nocturnal Asthma. Indian Journal of Pharmaceutical Sciences. 70 351-356 (2008).

[19] Efentakis M, Koligliti S, Vlachou M. Design and evaluation of a dry coated drug delivery system with an impermeable cup, swellable top layer and pulsatile release. International Journal of Pharmaceutics. 311 147-56 (2006).

[20] Vittal GV, Deveswaran R, Bharath S, Basavaraj BV, Madhavan V. Formulation and Characterization of Ketoprofen Liquisolid Compacts by Box-Design. International Journal of Pharmaceutical Investigation. 2 150–156. (2012).

[21] Tuan AN, T Chi N, Tran TK, Tuyen Dao TP, Nhan Le NT, Mau Chien D, To Hoai N. Preparation and characterization of ketoprofen loaded eudragit RS polymeric nanoparticles for controlled release. Advances in Natural Sciences: Nanoscience and Nanotechnology. 3 045015 (2012).

[22] Kannan K, Ramya Krishna, Manikandan M. Development and Evaluation of Valsartan Film Coated Tablets. Journal of Pharmaceutical Science and Research. 4 1866 – 1871 (2012).

[23] Rajalakshmi G, Vamsi CH, Balachandar R. Formulation and evaluation of diclofenac potassium effervescent tablets. International Journal of Pharmaceutical and Biomedical Research 2 237-243 (2011).

[24] Lin SY, Lin KH, Li MJ. Influence of excipients, drugs, and osmotic agent in the inner core on the time-controlled disintegration of compression-coated ethylcellulose tablets. Journal of Pharmaceutical Science. 9 2040-6 (2002).

[25] Sunil S, Rao NS, Srikanth MV, Uhumwangho MU, Kumar KSP, Murthy KVR. Development and evaluation of a chronotherapeutic drug delivery system of torsemide. Brazilian Journal of Pharmaceutical Science. 47, 593–600 (2011).

[26] Devi VK, Saisivam S, Maria GR, Deepi, PU. Design and Evaluation of Matrix Diffusion Controlled Transdermal Patches of Verapamil Hydrochloride. Drug Development and Industrial Pharmacy 29 495–503 (2003).

[27] Loos AC, Springer GS, Sanders BA, Tung RW. Moisture absorption of polyester-E glass composites. Journal of Composite Material. 14 142–54 (1980).

[28] Paul WS, Heng LW, Chan, KT. Influence of storage conditions and type plasticizers on ethylcellulose and acrylate films formed from aqueous dispersions. Journal of Pharmacy & Pharmaceutical Sciences. 6 334-344 (2003).

[29] Bussemer T, Dashevsky A, Bodmeier RA. Pulsatile drug delivery system based on rupturable coated hard gelatin capsules. Journal of Controlled Release. 93 331-9 (2003).