Research Article

Multi-Approach Colon Targeted Pulsatile Formulation Design For Efficient Chronotherapy

Deepak Shamrao Khobragade[1*], Mohammed Suhail Chowdry[1], Pranav Kumar AVR[1], Sreenivas Reddy Gangi Reddy[1], Mrunali Potbhare[2]
[1]Bharat Institute of Technology, Hyderabad, India.
[2]NNR School of Pharmacy, Hyderabad, India.
***Corresponding author's E-mail:** ksdeepak31@gmail.com

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ABSTRACT

There is a need to develop an effective dosage form Based on chrono-biology of the disease to provide consistent symptomatic relief while ameliorating the ailment. The study was commenced to design chrono-biology based pulsatile drug delivery system of Ketoprofen for the treatment of Rheumatoid arthritis. The formulation was developed by enteric coating the press coated sustained release tablets. Initially formulations for sustained release (SR) tablets were prepared by direct compression with polymers like HPMC K4M and HPMC K100M. The SR tablets were subsequently press coated with IR layer containing the drug and super-disintegrants. Finally, optimized press coated tablets were coated with pH sensitive polymers. Formulation with HPMC K4M (30%) sustained drug release for about 8hrs in 7.4 pH phosphate buffer. Press coated tablets with super disintegrant Crospovidone (5%) released 99.41% drug in 3 min in 7.4 pH phosphate buffer. Coated tablets with Eudragit L100/S100 were having lag time ranged from 4 to 6 hours and In vitro drug release varied from 65.5% to 97.83% in 14 hours based on polymer and coating extent. A novel pulsatile drug delivery system can be successfully developed by coating sustained release core tablet with immediate release layer for enhanced therapeutic benefit in treatment of rheumatoid arthritis.

Keywords: Chronotherapy, Compression coating, Ketoprofen, Pulsatile, Rheumatoid arthritis.

INTRODUCTION

Relevance and Background

Pulsatile drug delivery system is a system of delivery device that has the characteristic mechanism of releasing the drug rapidly and completely after a predetermined time-delay or lag time i.e. a time period of "no drug release".[1] These systems form major role in chrono therapy. The discipline concerned with the Coordination of biological rhythms and medical treatment is called chronotherapy, while the system of delivery of drugs based on the inherent activities of a disease over a period of time is called chronotherapeutics.[2]

The potential benefits of chronotherapeutics have been demonstrated in the management of a number of diseases. In particular there is a great deal of interest in how a particular therapy can benefit patients suffering from allergic rhinitis, rheumatoid arthritis (RA) and related disorders such as arthralgia,[3] cardiovascular diseases, asthma, cancer, and peptic ulcer disease[4] that follow body's circadian rhythm.[5]

Purpose

Based on the chronobiology of the disease an attempt was made in this study to develop a pulsatile drug delivery system for effective treatment of Rheumatoid arthritis.[6] In the treatment of arthritis, the new Cyclo-oxygenase-II (COX-II) inhibitors effectively relieve osteoarthritic symptoms when taken in the morning and better results are obtained when a part of that dose is taken in the evening. The cardinal signs of rheumatoid arthritis are stiffness, fever,[7] swelling and pain in joints[8] which are characteristically most severe in the morning and the pain in joints decreases as the day goes on with less or no pain at night.[9]

Swelling and discomfort of the joints is the characteristic of ankylosing spondylitis. Taking long-acting non-steroidal anti-inflammatory drugs[10-12] like flurbiprofen, ibuprofen, ketoprofen and indomethacin as once-a-day dosage regimen yields improved therapeutic effect and ameliorates their side effects.[13,14]

A pulsatile drug delivery system administered at night (before sleep) that uses the technology of releasing the drug in the early hours of morning would be a promising chronotherapeutic candidate for the effective treatment of rheumatoid arthritis.[15]

Rationale

The motive of this study was to develop press coated tablets for pulsatile drug delivery of ketoprofen. The oral press coated tablet was developed to achieve the time-controlled disintegrating or rupturing function with a distinct predetermined lag time due to pan-coating with enteric polymers on sustained release core which in turn was coated with immediate release layer of drug and super disintegrating agent.

The polymer-compression-coating resulted in release profiles with a distinct lag time depending on the amount of polymer in compression coating.[16] Burst release was obtained by incorporating a layer of drug for immediate release (IR) with a super-disintegrant over the sustained release (SR) core.

MATERIALS AND METHODS

Materials

Ketoprofen was procured from Yarrow Chemical Products, Mumbai. HPMC and Eudragit grades, SSG were obtained from Bright Scientifics, Hyderabad. All other required chemicals procured from SD Fine Chemicals India Ltd. were of LR grade.

Fourier transform infrared (FT-IR) Bruker Alpha T-1020, UV/visible spectrophotometer Shimadzu 1800, tablet punching machine Mini press II (D)-Karnavati Rimek and dissolution test apparatus DS 8000-Lab India were used.

Methods

Drug-excipient Compatibility Studies by FTIR[17]

FT-IR spectroscopy (Bruker Alpha by the conventional KBr pellet method) and physical observation was employed to evaluate the possible incompatibility if any between the drug and the excipients in the solid state. The spectra were scanned over a frequency range 4000-400 cm^{-1}.

Pre-compression Parameters[18]

General Pre-compression parameters like bulk density, Tapped density, Compressibility index (or) Carr's index, Angle of repose (θ) and Haussner's ratio were evaluated as per the procedures well documented and accepted for ensuring acceptable standards for all the formulation batches.

Formulation Development

The process of formulation development was planned in three phases:

Phase 1: Preparation of SR Core Tablet →Phase 2: Compression coating of SR core with IR layer of Drug →Phase 3: Enteric coating of press-coated tablets by pan coating process.

Phase 1-Formulation of sustained release core tablets of ketoprofen

Sustained release (SR) core tablets of ketoprofen were formulated by incorporating drug, different grades of polymer HPMC K4M and K100M, Micro Crystalline Cellulose, lactose, magnesium stearate and talc. All the ingredients were accurately weighed as per the formula and were dispensed in a clean polythene cover, mixed well and sieved through no.60 mesh. Direct compression of core tablets was done in tablet punching machine (Rimek Mini Press IID) using a 8mm concave punch. The composition of the core tablets was selected varying the concentrations of HPMC K4M, HPMC K100M, MCC and Lactose to get optimized batch.

Phase 2-Compression coating of optimized sustained release core tablets with immediate release layer of ketoprofen

The optimized SR core tablets were compression coated with an immediate release layer of ketoprofen. Different IR layers were evaluated using super disintegrants like Crospovidone, Croscarmellose sodium (CCS), Sodium starch glycolate (SSG) and Pregelatinized starch (PGS). Based on the compositions of these super disintegrants concentration 2% and 5% and PGS concentration at 5% and 10% and different blends were prepared. Compression coating was carried out using Cadmach tablet punching machine with 10 mm concave punches. For compression coating, one half of the required quantity was filled in the die, and then optimized SR core tablet is placed exactly in center on top of the fill. The remaining half of the blend was then filled in the die and compression coated.

Phase 3-Formulation of pulsatile tablets of ketoprofen containing optimized IR layer and optimized SR core

The optimized press coated tablets (optimized SR cores compression coated with optimized IR layer) were subjected to pan coating with enteric polymers - Eudragit® L100 and Eudragit® S100 to obtain pulsatile tablets of ketoprofen, in which immediate release of drug is seen after a predetermined lag time then followed by sustained release of the drug from core.

Preparation of coating solution of Eudragit® L100 and Eudragit® S100

Firstly a dispersion of Eudragit® L100 and S100 was prepared by separately taking Eudragit® L100/S100 and mixing with sufficient quantity of isopropyl alcohol in a container.

The dispersion was left undisturbed for 12 hrs by properly closing the container. In a separate container, accurately weighed amount of TiO_2 (opacifier), talc (anti-tacking agent) and dibutyl phthalate (plasticizer) were added to isopropyl alcohol, with constant stirring to prevent settling of talc. Colorants like ferric oxide (red) and erythrosine were added as per requirement. After this, the dispersion of Eudragit® L100/S100 was slowly added to the excipient suspension while constantly stirring with a conventional stirrer.

Finally acetone was added to the above obtained coating solution and stirred to get a final solution that is homogenized.

Coating Procedure

The optimized press coated tablets were pan coated with the Eudragit® L100/S100 coating solutions, by using a R&D coater. In order to increase the bulk of the tablets in the pan, dummy tablets made of MCC having different dimensions to the press coated tablets were taken. Once the desired process conditions were attained, the tablets were coated at different coating levels using Eudragit® L100 (10%, 15%, 20%, 25%)* and Eudragit® S100 (10%, 15%, 20%, 25%, 30%)*.

*Note: The percentages (%) indicate the weight gain of the tablets after pan coating with Eudragit® L100/S100 coating solutions.

Evaluation of Post Compression Parameters

Sustained release core tablets, press coated tablets with immediate release layer on sustained release core and enteric coated pulsatile tablets were evaluated for post compression parameters like thickness, weight variation, hardness, friability, drug content uniformity and in vitro dissolution studies. Enteric coated pulsatile tablets were additionally evaluated for disintegration pH. All the studies were performed in triplicate, and the results were expressed as mean ± SD.

Disintegration pH of the Coated Tablets[19]

Release rate of the model drug from coated (F21-F30) tablets was studied as a function of gradual increase in pH of the dissolution medium[20]. Initially, the tablets were placed in the basket. The test was carried out in dissolution apparatus containing 500 ml of 0.1 M HCl (pH 1.2) as medium stirred at 50 rpm. After an initial, period of 10 min the pH was gradually increased every sixth minute by addition of 10 ml of 0.4 M disodium hydrogen phosphate. Drug concentrations prior to each addition of disodium hydrogen phosphate were measured spectro-photometrically at 260 nm (UV–1601, Shimadzu, Japan). The disintegration pH was considered as the pH at which coated tablets showed the highest amount of drug release at minimum fixed time.

In-vitro Dissolution Studies[21]

Evaluation of SR core tablets

Dissolution test was carried out using USP type-II apparatus at 50 rpm with 900 ml of 7.4 pH phosphate buffer and temperature was maintained at 37±0.5°C. Aliquots of dissolution medium were withdrawn at 30 min, 1 hr, 2 hr, 3 hr, 4 hr, 6 hr and 8 hr intervals.

Evaluation of Press Coated Tablets with the IR layer

Dissolution testing conditions were similar as that for SR core tablet except the time interval for aliquots withdrawal. Aliquots of dissolution medium in this case were withdrawn at 1 min, 2 min, 3 min, 4 min, 5 min, 10 min, 15 min, 20 min, 30 min, 45 min and 60 min intervals. The samples were filtered and the absorbance was determined by UV spectrophotometric method at 260 nm, with 7.4 pH phosphate buffer as the blank.

Evaluation of Pulsatile Tablets of Ketoprofen

The evaluation parameters of pulsatile tablets are similar to those mentioned in the earlier sections. However, in case of dissolution testing, there are variations in the dissolution media used and time points at which the samples are withdrawn, the variations are as described below.

Dissolution test for Pulsatile Tablets of Ketoprofen

Dissolution test was carried out using USP type-II apparatus at 50 rpm with 900 ml of 1.2 pH 0.1N HCl for initial 2 hrs, 4.5 pH acetate buffer for the next 2 hrs and finally in 7.4 pH phosphate buffer for next 10 hrs. The temperature was maintained at 37±0.5°C. Aliquots of dissolution medium were withdrawn at 1, 2, 3, 4, 4.5, 5, 6, 8, 10, 12 and 14 hours.

The samples were filtered and the absorbance was determined by UV spectrophotometric method at 260 nm using 1.2 pH 0.1N HCl as blank for samples taken up to second hour; at 260 nm using 4.5 pH acetate buffer as blank for samples taken up to fourth hour and at 260 nm using 7.4 pH phosphate buffer as blank for samples taken up to fourteenth hour.

Drug release by dissolution followed by diffusion process after lag time diagrammatic representation can be seen in Figure 2.

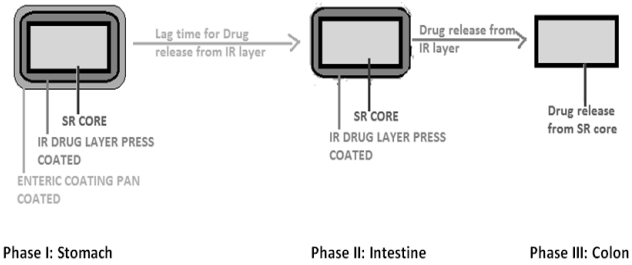

Figure 2: Phases of drug release by dissolution from pulsatile tablets

Scanning Electron Microscopy

The SEM of the cross-section of the final formulation was carried out to evaluate structure and appearance of the formulation.

The cross-section of the tablet was gold coated by sputtering and observed at 500x using Scanning electron microscope JSM-840A SEM, Jeol-Japan with JFC-1100E Ion Sputtering Device.

Stability Studies[22]

Stability studies were carried out by storing the optimized formulation at predetermined conditions of 40°C ± 2°C / 75% ± 5% RH for a period of three months.

RESULTS AND DISCUSSION

Drug-excipient Compatibility Studies by FTIR

It is found that there was no chemical interaction between ketoprofen, HPMC K4M, microcrystalline cellulose, lactose, Crospovidone and Eudragit® S100, L100 used in the formulation of coated pulsatile tablets.

This is attributed to the fact that there were no changes in the characteristic peaks of ketoprofen in the FTIR spectra of coated pulsatile tablets formulation and that of the pure drug. The result can be verified with the spectral peaks of respective samples as shown in Figure 3 below.

Pre Compression Parameters

Evaluation Results of pre compression parameters for sustained release core formulations

The results obtained for angle of repose (θ) vary from 20.2^0 - 27.5^0 which fall within the official range for good

flow i.e. less than 30^0. Therefore the blends have good flow property.

The Bulk and Tapped density of core tablet blend were from 1.21-1.28gm/ml and 1.38-1.47gm/ml respectively. Carr's index calculated showed to vary from 11.50-14.53% indicating that the blend has a good flow property. Whereas Haussner's ratio analyzed is in 1.13-1.17 range representing a good flow.

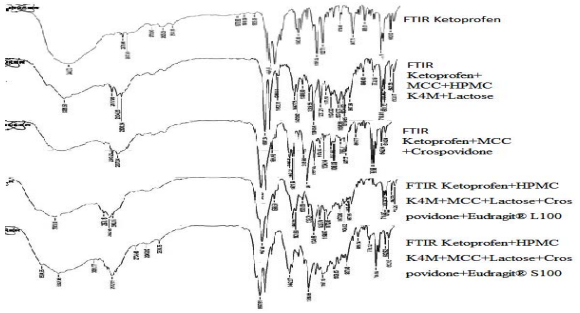

Figure 3: FTIR images of the pure drug, mixture and optimized formulations.

Evaluation results of pre compression parameters for immediate release layer formulations

The results for angle of repose (θ) obtained was found to vary from 20.8^0 - 25.6^0 which indicates the coating material has fairly good flow property and can be used for press coating.

The Bulk and Tapped density of outer coating material blend were from 0.53-0.67gm/ml and 0.62-0.78gm/ml respectively. Carr's index calculated showed to vary from 12.28-19.79% indicating that the blend has an excellent flow property. Haussner's ratio ranged from 1.15 to 1.19 which represents good flow property of the blend.

Post Compression Parameters

Sustained Release core tablets of Ketoprofen

The formulations F1 to F12 represent sustained release core. The hardness of the core tablets in each formulation batch ranges from 1.5-2kg/sq.cm, therefore ensuring appropriate strength. The thickness was kept constant at 2.5mm for all the batches. All the SR core tablets passed the uniformity of weight test. The individual weight of different batch tablets was within official limits of ±10% deviation from average weight. The drug content was in the range of for the formulations.

SR core tablets compression coated with immediate release layer of Ketoprofen

The formulations F13 to F20 represent sustained release core tablets compression coated with immediate release layer of Ketoprofen. For evaluation of IR layer, core tablets were formulated based on the formulation F1 without the drug. These dummy cores were then press coated with IR layer of ketoprofen.

Hardness of the various press coated tablets was in the range of 5.0-6.2 kg/cm^2 enabling good mechanical strength. The thickness observed was 4mm and is even for all batches. The press coated tablets passed the uniformity of weight test. The individual tablet weights when compared with average weight were within the official limit of ±5% deviation. The friability of press coated tablet formulations were within the acceptable limits and ranged from 0.68-0.98%.

Characterization of pan coated pulsatile tablets of Ketoprofen

The formulations F21 to F30 represent coated tablets of Ketoprofen. Pan coating was done in the final stage using enteric polymers Eudragit® L100 and Eudragit® S100 at different coating levels (10%, 15%, 20%, 25% and 30%) respectively. The results of different evaluation parameters for these pan coated tablets such as Thickness (4.20±0.15 mm to 4.45±0.14 mm), Hardness (5.0±0.2 kg/cm^2 to 5.4±0.1 kg/cm^2), Friability (0.88±0.03 % to 0.93±0.06 %), Weight variation (540.60 ± 0.41 mg to 656.23 ± 0.78 mg) and Drug content (96.10 ± 0.45 % to 100.0 ± 0.27) are within the prescribed standard limits enabling good tablet characteristics.

Determination of Disintegration pH[23]

The disintegration pH was considered as the pH at which coated tablets showed the highest amount of drug release at minimum fixed time. The material must be solubilized at alkaline pH to be considered suitable for enteric coating. The disintegration pH increases slightly with the increased percentage of coating. The results for lowest coated percentage (10%) and highest coated percentage (30%) of Eudragit coated tablets are only shown for this test. This is because the time period for the test was very short and time was not adequate for the drug to be released with burst from the tablets with higher coating percentage. It was observed that the coated polymer started dissolving at high pH of at least above 5 in cases of 15%, 20%, 25% coating.

Due to lower extent of coating, small amount of the drug was also found to be released at acidic pH, this may be due to erosion of coat and not solubilisation because the core tablet was intact even after completion of the test. The drug release gradually increased with greater pH levels as can be seen in the Figure 4. The disintegration pH values of pulsatile tablets during disintegration study are shown in Figure 4.

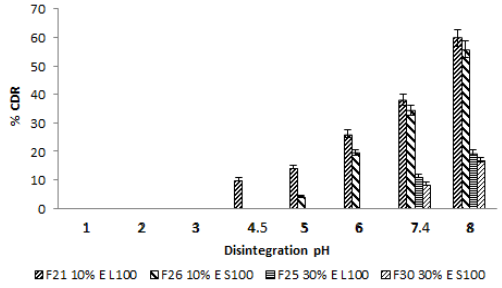

Figure 4: Disintegration pH of SR coated tablet with different levels of polymer.

In vitro drug release profiles of all SR cores of Ketoprofen

The results of *In vitro* drug release from SR core are depicted in Figure 5. Both the polymers show increased sustained action with increase in concentration.

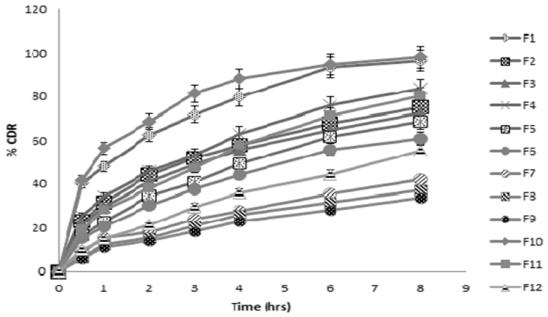

Figure 5: *In vitro* drug release profiles of all SR core tablet formulations (F1 to F12).

From the result it can be observed that the formulations containing only HPMC K4M released the drug quicker compared to the formulations containing only HPMC K100M. This may be due to the fact that the viscosity grade of HPMC K4M is lower than that of HPMC K100M; hence the outer gel layer formed on the tablets offers better permeability of the drug. Moreover, the drug release was becoming more sustained as the concentration of HPMC K4M and HPMC K100M in the formulations was increased.

Based on the results of the dissolution study of the SR core tablets in phosphate buffer (pH 7.4), the core tablet formulation F1, formulated with 30% HPMC k4M (Drug: HPMC in 1:1 ratio) showed 96.49% drug release at the end of 8hrs and therefore selected for further processing of press coating with IR layer of Ketoprofen.

In vitro drug release profiles of immediate release layer formulations

The results obtained from one hour dissolution study of the press coated tablets are depicted in Figure 6. The dissolution study was carried out in phosphate buffer (pH 7.4).

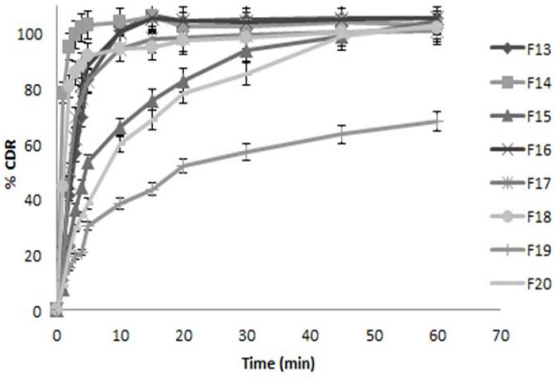

Figure 6: *In vitro* drug release profiles of IR layer formulations (F13 to F20).

Formulation F14 containing 5% Crospovidone as shows faster drug release (99.41% in 3 min) compared to F13 containing 2% Crospovidone (100.97% in 10 min). Formulation F16 (5% SSG) shows 100.45% drug release in 10 min compared to F15 (2% SSG) that shows 98.89% in 45 min. F18 (5% Croscarmellose sodium) releases 85.89% in 3 min and F17 (2% Croscarmellose sodium) releases 77.05% in 3 min.

Both the formulations F20 (10% Pregelatinized starch) and F19 (5% Pregelatinized starch) showed drug release of 103.05% and 68.21% at 60 min.

Since Formulation F14 comprising of 5% Crospovidone showed the fastest drug release of 99.41% by third minute, formulation F14 was further processed for enteric polymer coating to incorporate the desired lag time.

In vitro drug release profiles of pulsatile tablets of Ketoprofen (F21 to F25)

The pan coated tablets were evaluated for in vitro drug release, for starting two hours in 0.1N HCl (pH 1.2), next two hours in acetate buffer (pH 4.5) and in phosphate buffer (pH 7.4) for the remaining duration. In formulations F21 to F30, no drug release was observed for the initial two hours in 0.1N HCl (pH 1.2) medium.

This is consistent with the nature of the enteric polymers Eudragit® L100 and Eudragit® S100 used in the formulations.

The medium was then replaced with acetate buffer (pH 4.5) and drug release was evaluated for the next two hours. Formulation F21 and F22 showed negligible drug release, whereas remaining formulations F23 to F30, showed no drug release in acetate buffer (pH 4.5).

At the end of 4th hour, the dissolution media was replaced with phosphate buffer (pH 7.4) and sampling was done at 4.5 hrs to see whether there is any drug release. It was observed that F21, F22 and F23 showed drug release of 16.25%, 1.43% and 0.29% respectively at the end of 4.5 hrs. The remaining formulations showed no drug release at the end of 4.5 hrs.

At the next sampling point at 5 hrs, F21, F22, F23 formulations released 54.62%, 39.18% and 40.74% which was significantly higher than the drug release for F24, F25 and F26 which was 2.05%, 0.96% and 2.67% respectively. Rest of the formulations did not show any drug release at the end of 5h.

In vitro drug release profiles of pan coated pulsatile tablets of Ketoprofen (F26 to F30)

Formulations, F24 to F26 showed a lag time of 5 hrs. Among these, F24 (25% Eudragit® L100) produced a lag time of 5 hours and released 95.49% of drug at the 14th hrs. Formulation F25 showed a lag time of 6 hrs and released 95.30% of drug at the end of 14th hour.

The increased lag time may be because of two reasons, firstly Eudragit® S100 dissolves at higher alkaline pH and the coating levels applied were high (25% and 30%

respectively). The trend can be observed in Figure 7 and Figure 8.

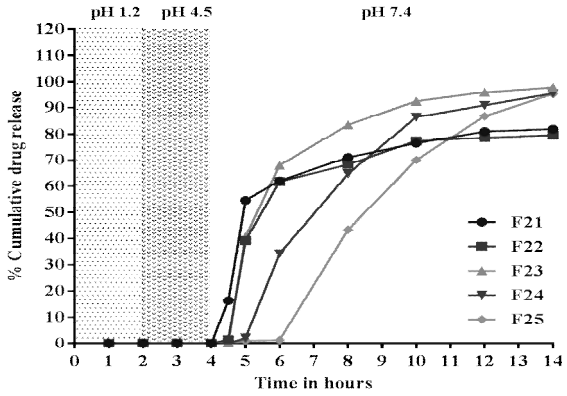

Figure 7: *In vitro* drug release of pan coated pulsatile tablets (F21 to F25).

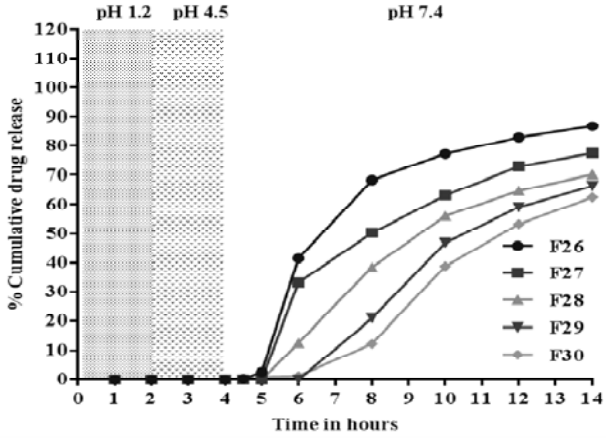

Figure 8: *In vitro* drug release profiles of pan coated pulsatile tablets (F26 to F30).

Overall it was observed that, as the coating levels increased, the lag time increased. Also, Eudragit® L100 based formulations released more drug compared to those coated with Eudragit® S100, at the end of 14th hr of dissolution study.

Kinetic fitting for SR core tablets

Drug release behavior of SR core tablets was fitted as per zero order, first order, Higuchi, Korsemeyer-Peppas, Hixon Crowell models and in case of the optimized formulation F1, the drug release mechanism is found to be following Quasi-Fickian release based on the Peppas (n) value of 0.335.

Scanning Electron Microscopy

The pulsatile release tablet system developed in the present study was a reservoir device, where the tablet cores were surrounded by two consecutive layers, an immediate release drug layer and enteric polymeric coat layer at the top respectively.

Figure 9 shows an SEM photograph of cross section of the pulsatile release tablet. The three parts of the systems are clearly visible, namely the dense tablet core (A), the next layer consists of the immediate release drug layer (B) and then at the surface Eudragit layer as the outer enteric coat(C).

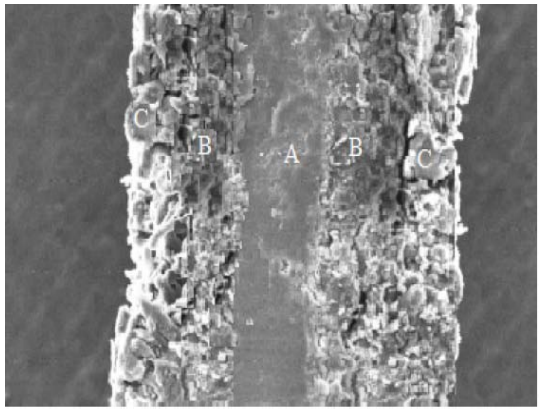

Figure 9: SEM image of formulation F24.

Accelerated Stability Study

There were no physical changes observed during the entire storage period. The % drug content and lag time of F24 after three months on an average was found to be 96.54 ± 0.46 % and 6.5 hours respectively indicating stable formulation.

CONCLUSION

The intention of formulating and evaluating pulsatile tablets of ketoprofen was successfully accomplished and can be used in the chrono-therapeutic treatment of rheumatoid arthritis. The novel concept behind the study was that the outer polymer coating will resist drug release in upper GIT and only after the tablet reaches the alkaline milieu, the polymer coat dissolves and the loading dose gets released from the immediate release layer. Subsequent release for up to 8 hrs will be achieved by the sustained release core. Super-disintegrants in IR layer decides how quickly the drug gets released after lag time.

Polymers like HPMC K4M and HPMC K100M can be employed either singly or in combination to provide the desired sustained release profile. Enteric coating polymers can be used either singly or in combination to provide lag time.

The coating thickness is inversely related to drug release. It could be concluded that a novel pulsatile drug delivery system can be successfully formulated by polymer coating of a sustained release core tablet with immediate release layer for enhanced therapeutic benefit to the rheumatoid arthritis patients.

Abbreviations

SEM-Scanning Electron Microscopy

GIT-Gastro Intestinal Tract

SR-Sustained Release

IR-Immediate Release

%CDR-Percentage Cumulative Drug Release

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