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pH-responsive dual pulse multiparticulate dosage form for treatment of rheumatoid arthritis

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Abstract

Background: Dual pulse multiparticulate systems may provide relief from circadian disorder rheumatoid arthritis. *Aim*: The aim of this study was to develop a pH-responsive dual pulse multiparticulate dosage form containing a model drug ketoprofen, a nonsteroidal anti-inflammatory drug used for rheumatoid arthritis. *Method*: The pellets were prepared by using extrusion–spheronization method and the core pellets were coated with a pH-sensitive poly(methyl) acrylate copolymer (Eudragit® L100-55, Eudragit® S100) to achieve site-specific drug release with a lag time. The formulated pellets were characterized for shape and size uniformity, friability, surface morphology studies, coating uniformity, and drug–excipient compatibility studies. In vitro dissolution test was used for comparison of drug release profiles of various coated pellets. *Results*: The particle size of core and polymer-coated pellets was found to be in the range of 0.95–1.3 and 1.42–1.61 mm, respectively. The pellets were spherical in shape with smooth texture and uniformity in size. The dual pulse was aimed at release after a lag time of 2 and 5 hours. In vitro dissolution tests were carried out for the first and second dose pellets in a USP type II dissolution apparatus in media-simulating pH conditions of the gastrointestinal tract. The first dose release of the ketoprofen from the formulated pellets was established in pH 1.2 for a period of 2 hours, followed by pH 6.8. The second dose pellets were passed through pH 1.2, pH 6.8 followed by pH 7.5 for the rest of the study. *Conclusion*: The study concluded that the formulated multiparticulate dosage form of ketoprofen was able to relieve circadian symptoms of rheumatoid arthritis during midnight and early morning.

Key words: *Eudragit®; extrusion–spheronization; ketoprofen; lag time; multiple unit; pulsatile release; rheumatoid arthritis*

Introduction

Oral drug delivery is the largest and the oldest segment of the total drug delivery market. It is the fastest growing and most preferred route for drug administration. Sustained and controlled release products provide an immediate release of drug that promptly produces the desired therapeutic effect, followed by gradual release of additional amounts of drug to maintain this effect over a predetermined period. Such a dosage form leads to better management of the acute or chronic disease condition[1]. Recent studies have revealed that diseases have a predictable cyclic rhythm and that the timing of medication regimens can improve the outcome of the desired effect. This condition demands release of drug as a 'pulse' after a lag time and has to be designed in such a way that a complete and rapid drug release should follow the lag. Such systems are called as pulsatile drug delivery systems or time-controlled systems. Circadian rhythm regulates many body functions in time, namely, metabolism, physiology, behavior, sleep patterns, hormone production, and so on[2]. Some circadian disorders like asthma progressively increase at night and osteoarthritis tends to have less pain in the morning and more at night. Gastric acid secretion and cholesterol synthesis increase at night than during day. A cardiovascular rhythm such as platelet aggregation is increased and fibrinolytic activity is decreased in the morning[3].

Rheumatoid arthritis (RA) is a chronic autoimmune disease that affects approximately 2–3% of the world's population. RA is a classic example of circadian disorders starting between the ages of 20 and 40 years in which the lining of the joints becomes inflamed to such an extent

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causing pain and inability to function. In RA, the human proinflammatory Th1-type cytokine production exhibits a diurnal rhythmicity with peak levels during midnight and early morning at a time when plasma cortisol (anti-inflammatory) is lowest and melatonin (proinflammatory) is highest. There is often pain at night and sleep may be disturbed. Early morning stiffness lasting several hours has become a characteristic diagnostic feature in RA[4,5].

Ketoprofen is a nonsteroidal anti-inflammatory drug belonging to a class of propionic acid derivative. Ketoprofen has been used for the treatment of inflammation and pain caused by RA, osteoarthritis, ankylosing spondylitis, and so on by blocking the enzyme cyclooxygenase. It is rapidly eliminated from the blood after dosing (plasma half-life of l–3 hours) with oral bioavailability >90%[6,7]. Therefore, extended release dosage forms of this drug may be beneficial, but constant drug release is not always the optimal choice for its administration, because, owing to the above circadian rhythms, some pathology such as rheumatoid disorders may require different, consecutive pulses of drug.

The objectives of this study were to develop and evaluate a two-pulse multiparticulate pulsatile drug delivery system consisting of a drug core with a swelling agent and osmogent coated with insoluble polymeric membranes. The system was formulated considering pathophysiologies of RA with pain at midnight hours and joint stiffness in early mornings. Administration of such dual pulse dosage form can ensure relief from midnight pain and early morning stiffness of joint without the need to administer the dose at that time.

Materials and methods

Materials

Ketoprofen was a generous gift sample from BEC chemicals, Raigad, Roha, Maharashtra, India. Avicel® PH 101 (Microcrystalline cellulose), Ac-Di-Sol® (croscarmellose sodium), and PVP K30 (polyvinylpyrrolidone) were received as gift samples from Signet Chemicals, Mumbai, India. Water-insoluble coating polymers Eudragit® L100-55 and Eudragit® S100 were received as gift samples from Evonik Degussa Industries, Mumbai, India. All other chemicals were of A.R. grade purchased from S.D. Fine Chemicals Limited, Mumbai, India.

Methods

Preparation of ketoprofen core pellets

Drug-containing core pellets were prepared by extruder–spheronizer (NAOMI, Mumbai, India). Ketoprofen, spheronizing agent Avicel PH 101, filler lactose, superdisintegrant croscarmellose sodium, and osmogent sodium chloride were mixed to form a uniform blend. The binder solution PVP K30 (2.5%, w/v in 50:50 alcohol:water) was slowly added in the powder mixture to achieve a consistency of the damp mass suitable for further extrusion–spheronization process. The composition of core pellets is given in Table 1. The prepared mass was immediately passed through a screw-type extruder using 1 mm diameter screen with the speed set at 15 rpm. The extrudates were then transferred to spheronizer for 15–20 minutes at a rotation speed of 750 rpm. The resultant pellets were dried at 50°C in an oven for 30 minutes.

Preparation of first dose pellets

The core pellets prepared in the above step were evaluated for shape, size uniformity, disintegration study, and friability before proceeding to coating step. The composition of coating solution is given in Table 2. The core pellets were coated with pH-sensitive water-insoluble layer of Eudragit® L100-55 to achieve a weight gain of 2.5%, 5%, 7.5%, and 10%. The coating solution was sprayed onto the core pellets using a spray gun in a pan coater[8]. The conditions for coating are as follows: pellets charged—25 g, preheating temperature—50°C, preheating time—10 minutes, and outlet blower temperature—75°C.

The coating solution was sprayed when the pellet bed in the coating pan reached 30°C. The coating solution was stirred continuously throughout the coating process to prevent sedimentation of insoluble particles. The pellets were coated until the desired film weight was deposited and dried in coating chamber for 20–30 minutes at 50°C after a desired weight gain.

Preparation of second dose pellets

The core pellets were coated with a second pH-responsive copolymer of methacrylic acid and methyl methacrylate

Table 1. Composition of core pellets.

S. no.	Ingredients	Quantity (mg)
1	Ketoprofen B.P.	50
2	Pharmatose (DC lactose)	30
3	Croscarmellose sodium I.P.	10
4	Sodium chloride I.P.	10
5	Polyvinylpyrrolidone I.P. (PVP K30)	2.5
6	Avicel® PH 101 qs* to make	180

*quantity sufficient

Table 2. Composition of coating solution Eudragit® L100-55.

Ingredient	Quantity (%, w/w)
Eudragit® L100-55	5
Dibutyl phthalate	1
Talc	1.3827
Water	5
Isopropyl alcohol qs*	100

*quantity sufficient

Table 3. Composition of coating solution of Eudragit® S100.

Ingredient	Quantity (%, w/w)
Eudragit® S100	5
Dibutyl phthalate	0.5
Talc	1.382
Water	2.469
Isopropyl alcohol qs*	100

*quantity sufficient

Eudragit® S100 (Table 3). The polymer was sprayed onto the core pellets using a spray gun in a pan coater to achieve a weight gain in the range of 2.5–7.5%. The conditions for coating are as follows: pellets charged—25 g, preheating temperature—50°C, preheating time—10 minutes, and outlet blower temperature—65°C. Pellets were dried in coating chamber for 15 minutes at 50°C after a desired weight gain.

Pellets characterization

The pellets were characterized for size and shape using vernier caliper. The diameter of the core pellets, Eudragit® L100-55- and Eudragit® S100-coated pellets, was measured to assess parameters like size and shape uniformity. It was also proposed to evaluate the comparative thickness on polymer coating. Scanning electron microscopy (SEM) pictures of coated pellet showed the uniformity of the coating (Figure 4).

Micromeritic properties

The bulk density and tapped density of pellets were evaluated to assess the packing ability because of tapping. Carr's compressibility index and Hausner's index were computed. Tapped bulk density was performed on 30 g of pellets in 50 mL cylinder followed by 500 toppings.

Friability

Friability studies on core pellets were performed by placing 5 g in a friabilator (Veego, Mumbai, India) and tumbled for 200 revolutions at 25 rpm. Twelve steel balls (diameter 6.3 mm, weighing 1.028 g each) were used as attrition agents. After friability testing, the pellets were sieved through a sieve of 16# size. The weight loss (%F) after friability testing was calculated[9].

Drug content estimation

The Eudragit® L100-55-coated pellets (100 mg each) were weighed accurately, ground in a mortar and pestle, and then transferred to a 100 mL volumetric flask containing methanol. The flask was ultrasonicated for 30 minutes. The solutions were filtered and analyzed spectrophotometrically (UV 1601, Shimadzu, Japan) at 260 nm after suitable dilution. All the experiments were performed in triplicate. A similar experiment was carried out for Eudragit® S100-coated pellets[10].

pH solubility study

The pH solubility study was performed by adding excess amount of ketoprofen to various buffer solutions[11]. The buffer solutions of pH 1.2, 2.4, 6.8, 7, 7.4, and 11 were prepared. The vials containing the drug in buffer solutions were continuously stirred for 24 hours under controlled temperature of 25 ± 1°C. The solubility was determined spectrophotometrically by suitably diluting the aliquot and determining absorbance at 260 nm.

Scanning electron microscopy

The morphology of pellets was examined by SEM. Pellets were spread on an aluminum stub, which was placed later on gold sputtering in an SEM chamber[12,13]. Scanning electron micrographs were taken at various magnifications appropriate to each sample. The cross-sectional view of dried coated pellets was recorded to check the uniformity and thickness of coating layer.

Differential scanning calorimetry

Differential scanning calorimeter (Mettler Toledo DSC 822, Zurich, Switzerland) was used for thermal analysis of samples[14]. Individual samples (drug and excipients) as well as physical mixtures of drug and selected excipients (all passed through 60-mesh sieve) were transferred to the differential scanning calorimetry (DSC) aluminum pan and scanned in the temperature range of 0–400°C under an atmosphere of dry nitrogen[15]. Heating rate of 10°C/min was used and thermograms obtained were observed for any interaction studies.

HPLC analysis

Ketoprofen was determined using reverse-phase high-pressure liquid chromatography (RPHPLC) method (JASCO 2000PLUS; Anatek Services Pvt. Ltd., Mumbai, India)[16]. The column used was HiQ Sil C_{18} (Kromatek, UK) 4.6 × 250 mm (5 μm packing) with Rheodyne injector and UV detector. Mobile phase was developed and analysis was carried out at a flow rate of 1 mL/min at 260 nm.

Dissolution method development

In vitro drug release for first dose pellets

The drug release study was carried out in 0.1 N HCl (pH 1.2) for 2 hours. The pellets were then transferred to phosphate buffer pH 6.8 for the remaining period until complete drug release was achieved. The dissolution studies of the pellets were performed using USP XXIII type II dissolution test apparatus. The volume of dissolution medium was 900 mL with a stirring speed of 50 rpm and the temperature of the medium was maintained at 37.5 ± 0.5°C. These conditions were kept constant for all dissolution studies. Quantification of ketoprofen was performed using UV spectrophotometer

(SHIMADZU 1601; Shimadzu Corporation, Mumbai, India) at a wavelength of 260 nm.

In vitro drug release for second dose pellets

The drug release study was carried out in 0.1 N HCl (pH 1.2) for 2 hours, phosphate buffer (pH 6.8) upper small intestine transit time for 3 hours, and then phosphate buffer (pH 7.5) for the rest of the period. The dissolution apparatus type and conditions were same as mentioned above[17,18].

Stability studies

After evaluating the pellets, the optimized pellets were subjected to accelerated stability studies as per ICH guidelines (25 ± 2°C, 60 ± 5% RH; and 40 ± 2°C, 75 ± 5% RH) for a period of 6 months in stability chamber (Neutonics, Mumbai, India). The samples were taken out at 15, 30, 60, 90, and 180 days and evaluated for the drug content and physical changes.

Results and discussion

Design of complete multiple-unit system

The system consisted of drug-containing core pellets prepared by extrusion–spheronization process. Pulsatile drug delivery aims at the release of drug after a lag time followed by 'burst' release[19]. The drug-loaded core pellets were prepared using a combination of superdisintegrant and osmogent. Superdisintegrant croscarmellose sodium acts by swelling mechanism[20], whereas sodium chloride is used as an osmogent[21]. The osmotic pressure built up in pellets exceeds after a certain threshold value along with swelling causing a burst effect in pellets with t_{90} in 15 minutes. There is a pH gradient in the gastrointestinal tract with values ranging from 1.2 in the stomach through 6.6 in the proximal small intestine to a peak about 7.5 in the distal small intestine[22]. This pH differential between the stomach and the small intestine has been exploited for desired lag time and delivering the drugs directly to small intestine. The pH-responsive polymers are recalcitrant to the acidic conditions of the stomach but ionize and dissolve above a certain threshold pH to burst entire contents into the small intestine.

The superdisintegrant or osmogen alone could not achieve t_{90}% in 15 minutes. An optimized proportion of both the ingredients was required. The anhydrous lactose, Avicel PH 101, and PVP K30 were initially scrutinized for pellets. Anhydrous lactose and PVP K30 were fixed for all the formulation trials whereas batch size was made up with Avicel PH 101. The dissolution patterns of all batches are shown in Figure 1.

The formulation trials revealed that 60%, 65%, and 75% drug release was observed for 5 (A1), 10 (A2), and 15 (A3)mg sodium starch glycolate, respectively, per 180 mg batch. Similarly 5 (A4), 10 (A5), and 15 (A6)mg croscarmellose sodium per 180 mg batch was tried, whereas surprisingly a significant drug release was observed, that is, 80%, with 10 mg croscarmellose sodium. Following batches were tried with 5 (A7), 10 (A8), and 15 mg (A9) concentration of the osmogen sodium chloride to assess the combined effect of superdisintegrant and osmogen. Batch A8 showed good results with more than 90% drug release in less than 15 minutes.

Pellet characterization

It was observed that the pellets were uniform in size and shape. The average size of drug-containing core pellets was 0.95–1.3 mm (n = 100). The size of the layered pellets varied from 1.42 to 1.61 mm for different batches. The uniform size of the pellets indicates good content uniformity, good flow, and ease of capsule filling. The SEM photomicrographs also revealed the uniform coating and spherical shape of the coated pellets.

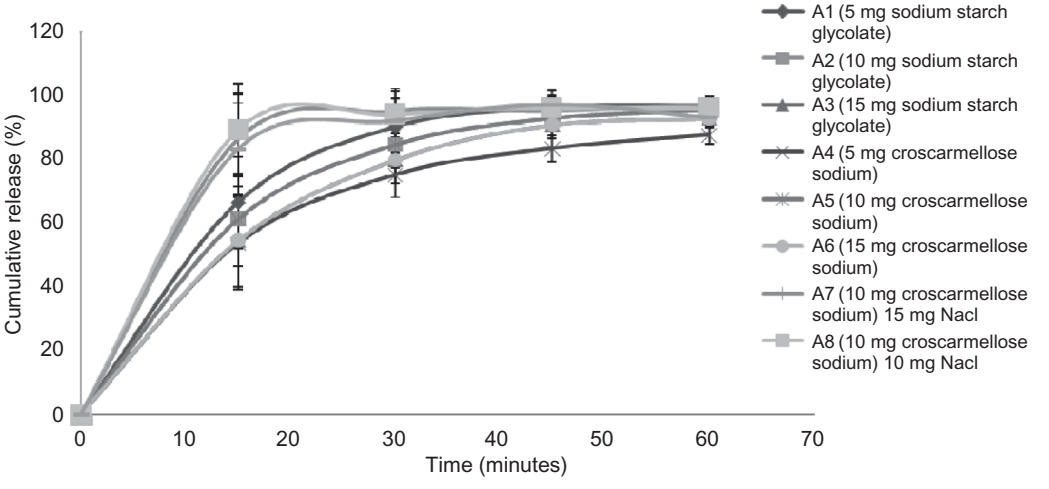

Figure 1. Dissolution profile of core pellets.

Friability

Friability of pellets is an important parameter to withstand handling, shipping, storage, and other processing parameters such as coating. The weight loss (%F) after friability testing was calculated as 0.481 ± 0.13 showing good friability.

Micromeritic properties

The micromeritic properties of pure ketoprofen, Eudragit® L100-55, and Eudragit® S100 are depicted in Table 4. Carr's compressibility index of Eudragit®-coated pellets was significantly improved compared with plain drug in the following order: Eudragit® S100-coated pellets > Eudragit® L100-55-coated pellets>core pellets>drug.

Drug content estimation

The drug content of Eudragit® L100-55-coated pellets was observed in the range of 94–96% whereas for Eudragit® S100-coated pellet it was 94–97%. On an average, the drug content was in the range of 94–98% for all formulations.

pH solubility profile

Ketoprofen had least solubility in lower pH because the drug has acidic nature and has good solubility in basic pH[23]. The official dissolution media of ketoprofen tablet is pH 7.4. The drug had best solubility above pH 8. Considering this behavior, the first pulse of pellets was designed to release drug above pH 5.5 whereas to release the second pulse above pH 7 (Figure 2).

Drug–excipients compatibility study

DSC thermographs were carried out for the drug, Eudragit® L100-55, drug–Eudragit® L100-55, Eudragit® S100, and drug–Eudragit® S100. DSC studies on plain drug showed an endotherm at 95.60°C. Eudragit® L100-55 and Eudragit® S100 showed clear endotherms at 207.53°C and 320.6°C, respectively, which are depicted in Figure 3. The results of drug–Eudragit® L100 and drug–Eudragit® S100 revealed no shift or change in the characteristics of the drug peak indicating no interaction between the drug and these excipients.

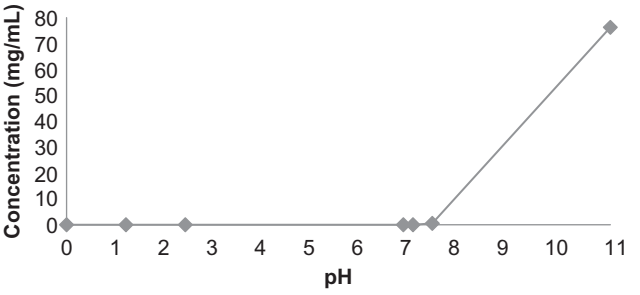

Figure 2. pH solubility profile.

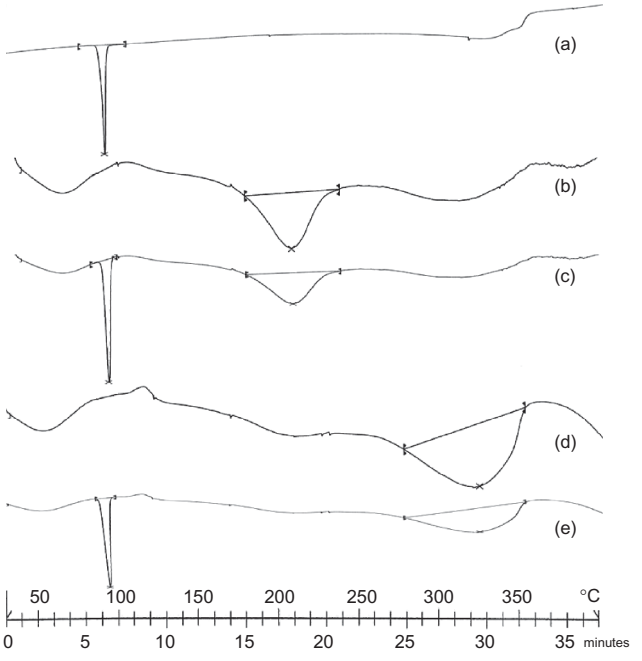

Figure 3. DSC thermographs of (a) drug, (b) Eudragit® L100-55, (c) drug–Eudragit® L100-55, (d) Eudragit® S100, and (e) drug–Eudragit® S100.

SEM study

Scanning electron microphotographs of coated pellets are shown in Figure 4. The shape and surface topography were different for the different coated and uncoated

Table 4. Powder characterization of ketoprofen and coated pellets.

		Results		
S. no.	Parameters	Ketoprofen	First dose coated pellets	Second dose coated pellets
1	Bulk density (g/mL)	0.219 ± 0.002	0.562 ± 0.014	0.638 ± 0.012
2	Tap density (g/mL)	0.346 ± 0.004	0.589 ± 0.015	0.684 ± 0.017
3	Compressibility (%)	36.585 ± 2.407	4.584 ± 0.058	6.72 ± 0.043
4	Angle of repose	38.345 ± 1.41°	13.871 ± 1.124°	12.871 ± 1.684°
5	Flow rate (g/s)	0.085 ± 0.0045	4.813 ± 0.209	4.510 ± 0.369
6	True density (g/mL)	1.253 ± 0.002	1.261 ± 0.018	1.189 ± 0.083
7	Hausner ratio	1.579 ± 0.0604	1.048 ± 0.008	1.07 ± 0.012

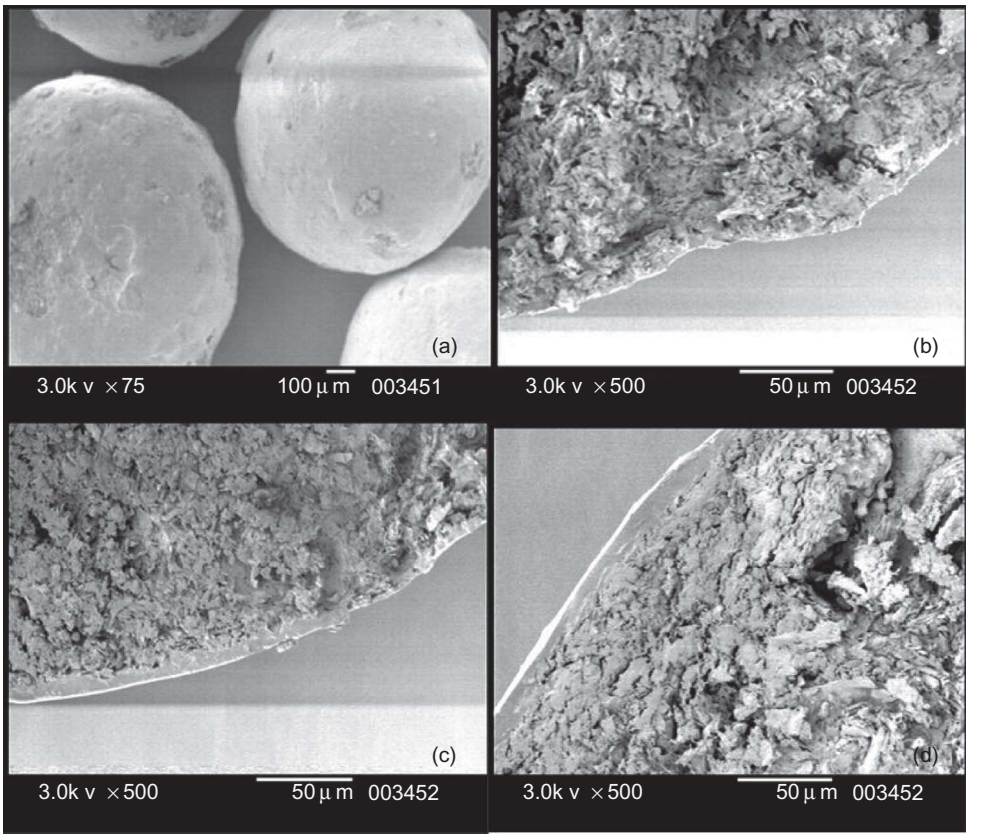

Figure 4. SEM photomicrographs of (a) surface morphology, (b) cross-sectional view of core pellets, (c) cross-sectional view of first dose pellets, and (d) cross-sectional view of second dose pellets.

pellets, which are clearly depicted in Figure 4a and b. The sphericity was increased on gradual coating of polymer. Eudragit® S100-coated pellets were fairly spherical compared with Eudragit® L100-55-coated pellets.

Drug analysis and estimation

RPHPLC method was developed and clear chromatograms were recorded using acetonitrile:methanol:phosphate buffer pH 5.6 (40:20:40%, v/v/v) mobile phase. The different concentrations of drug were analyzed and revealed good linearity in the range of 1–12 µg/mL having the coefficient of regression r^2 = 0.999. The drug showed sharp peak at 4.2 minutes. The optimized formulation was analyzed by RPHPLC and clear ketoprofen peaks were observed at 4.2 minutes; however, excipients' interferences were diminished by blank determination.

In vitro drug release profile of first pulse pellets

The core pellets were first coated with Eudragit® L100-55, an enteric polymer. The lag time was determined by plotting a graph of drug release versus time for different coating of Eudragit® L100-55 pellets. It was revealed that 5% weight gain was found to be optimum to retard drug release in stomach. As the pH rises from 2 to 5, the anionic exchange rapidly increases and the pH-dependent polymer coat slowly dissolves. The polymer Eudragit® L100-55 coat dissolves above pH 5.5 and intrusion of water takes place. The core pellets containing osmogen and superdisintegrant rapidly absorb water and burst the entire contents at duodenum in the next hour (Figure 5). The arthritis pain at midnight can be avoided by the release of drug from the first pulse pellets.

In vitro drug release profile of second pulse pellets

The core pellets for second pulse were coated with Eudragit® S100 with a weight gain of 7.5% that was found to be optimum with desired lag time. The drug release rate depends directly on water uptake by pellets that ultimately relates to osmotic pressure and permeability of coating. This can be attributed to design a longer lag time. Eudragit® S100 dissolves above pH 7, delivering the entire contents in the terminal ileum (Figure 6). However, the transit time in small intestine provides the desired lag time followed by burst release to treat early morning stiffness in RA.

In vitro release profile of combined pulse pellets

Drug release study was carried out to examine the pulsatile release pattern of the designed system. The

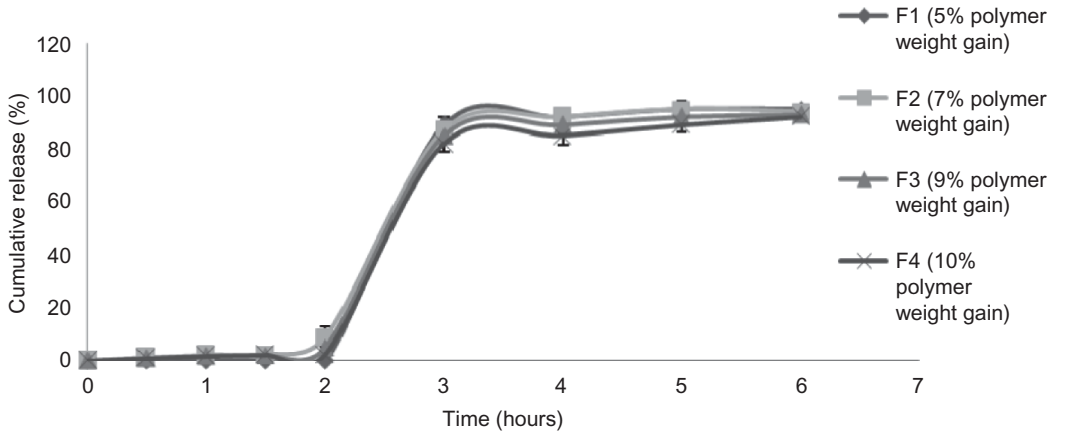

Figure 5. In vitro drug release profile of pellets coated with Eudragit® L100-55.

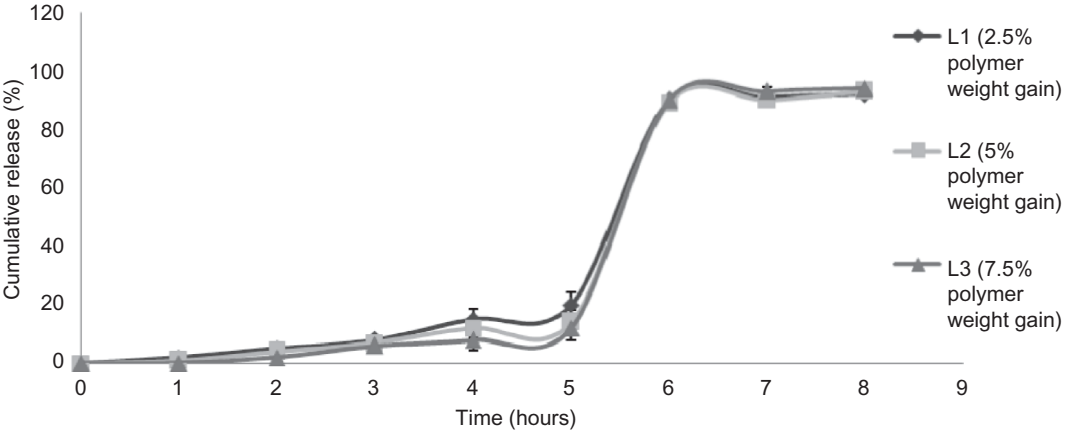

Figure 6. In vitro drug release profile of pellets coated with Eudragit® S100.

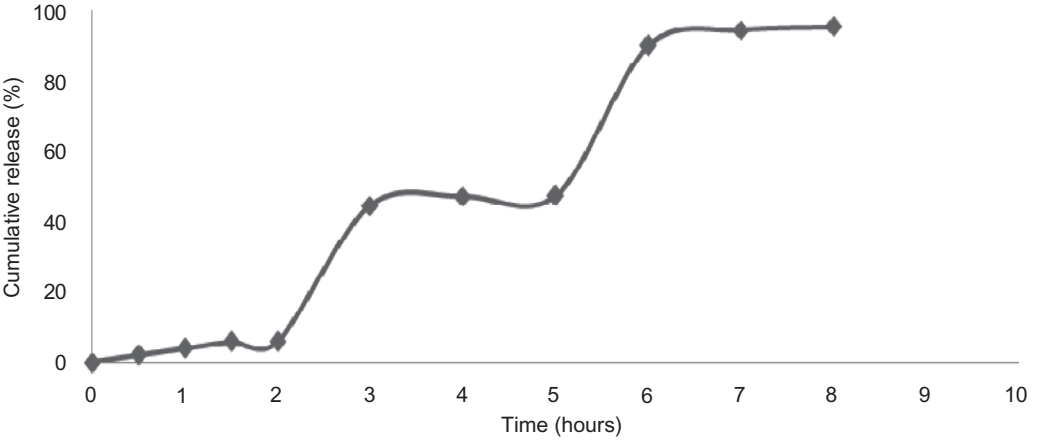

Figure 7. In vitro drug release profile of combined pellets.

release pattern (Figure 7) had a typical pulsatile pattern with initial lag time 2–3 hours followed by burst release. The system again had lag time for 2–3 hours followed by the release of second pulse. The two lag times were effectively designed with sufficient duration to treat rheumatoid arthritic pain chronotherapeutically.

Stability study

The results of accelerated stability studies revealed that pellets did not show any physical changes during the study period and the drug content was found to be more than 95% at the end of 6 months. The percent of drug content (n = 3; mean ± SD) in pellets was as follows: 0 day, 99.89 ± 0.14; 15 days, 99.12 ± 0.56; 30 days, 98.01 ± 0.82; 60 days, 97.21 ± 0.73; 90 days, 96.07 ± 0.33; and 180 days, 95.42 ± 0.29.

Conclusion

It would be concluded that the pH-dependent dual pulse release coated pellets would be a promising drug delivery system for systemic administration of ketoprofen for RA. The pellets were designed to prevent drug release in stomach and to release drug rapidly after the predetermined lag time. The system consists of a core containing a drug (ketoprofen), a swelling agent of croscarmellose sodium, osmogen sodium chloride, and a coating film of Eudragit® L100-55. For the first dose, Eudragit® L100-55 coating gets dissolved in an environment of pH above 5.5 and causes the swelling agent to expand and release the drug. The second dose pellets were coated with Eudragit® S100 polymer desired to dissolve after a lag time of 5 hours. The dissolution method was fabricated keeping gastric physiology in mind. The pellets were passed in 0.1N HCl for 2 hours followed by upper duodenal pH 6.8 for 3 hours, and later, readings were taken in pH 7.5 buffer. The coating was found sufficient to retard the release for 5 hours with maximum release at sixth hour.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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