

## FORMULATION AND EVALUATION OF PULSATILE DRUG DELIVERY SYSTEM OF ACECLOFENAC FOR TREATMENT OF RHEUMATOID ARTHRITIS

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Received: 24 Mar 2012, Revised and Accepted: 21 May 2012

### ABSTRACT

The objective of the present study was to design and evaluate time and pH dependent multiparticulate pulsatile delivery systems of Aceclofenac. Four batches of microspheres namely A1, A2, A3 and A4 were prepared using combination of Eudragit L-100 and S-100 with core: coat ratio 1:0.5, 1:1, 1:1.5 and 1:2 respectively by solvent evaporation technique. The drug content was uniform and reproducible in each batch of microspheres. FT-IR and DSC studies revealed the absence of drug polymer interactions. The release pattern of Aceclofenac from Eudragit microspheres of A1, A2, A3 and A4 batches were found 96.54, 93.71, 91.20 and 88.29% respectively at the end of 12 hrs. Pulsatile drug delivery system based on pulscap® technology was designed using microspheres from formulation A3 as it showed better drug content, particle size, surface topography, *in-vitro* drug release and release kinetics. Different plugging materials like Sodium alginate, Locust bean gum and Psyllium husk were used in the design of pulsatile capsule. During dissolution studies the pulsatile capsule remained intact in acid buffer of pH 1.2 for 2 hrs due to enteric coat of the system with HPMCP. The enteric coat dissolved when the pH of medium was changed to 7.4. The pulsatile delivery system developed with Sodium alginate as plugging material showed satisfactory lag period when compared to locust bean gum and Psyllium husk.

**Keywords:** Chronotherapeutics; pH and Time dependent; Pulsatile; Aceclofenac; Eudragit microspheres.

### INTRODUCTION

Rheumatoid arthritis is characterized by immunological abnormalities such as hypergammaglobulinaemia, the presence of immune complexes and rheumatoid factors in the serum, and lymphocytic infiltration of the synovial membrane. The activity of certain immune processes varies with the time of day or night at which it is observed. Many symptoms and signs of active rheumatoid arthritis are worse at night or around the time of waking, and objective measurements have confirmed a diurnal variation in joint stiffness, hand volume, and grip strength, also a circadian rhythm in signs and symptoms was suggested. Kowanko *et al* reported that there is a circadian rhythm of disease activity in rheumatoid arthritis, manifested by joint stiffness and grip strength, which is estimated to be maximal between 02:00 and 04:00<sup>1</sup>.

Morning stiffness associated with pain at the time of awakening is a diagnostic criterion of the rheumatoid arthritis and these clinical circadian symptoms are supposed to be outcome of altered functioning of hypothalamic-pituitary-adrenocortical axis. Chronopharmacotherapy for rheumatoid arthritis has been recommended to ensure that the highest blood levels of the drug coincide with peak pain and stiffness<sup>2</sup>. The term "chrono" basically refers to the observation that every metabolic event undergoes rhythmic changes in time. Researchers have concluded that all living organisms are composites of rhythms with varying frequencies that may range from seconds to seasons<sup>3</sup>. Chronotherapeutics refers to a treatment method in which *in vivo* drug availability is timed to match rhythms of disease in order to optimize therapeutic outcomes and minimize side effects<sup>4</sup>.

Aceclofenac is a Non-steroidal anti-inflammatory drug (NSAIDS), belonging to phenyl acetic acid derivatives which effects on a variety of inflammatory mediators. The mode of action of Aceclofenac is largely based on the inhibition of prostaglandin synthesis. Aceclofenac is a potent inhibitor of the enzyme cyclooxygenase, which is involved in the production of prostaglandins. The drug inhibits synthesis of the inflammatory cytokines interleukin (IL)-1 and tumor necrosis factor and prostaglandin E2 (PGE2) production. Effects on cell adhesion molecular from neutrophils have also been noted. *In vitro* data indicate inhibition of cyclooxygenase (Cox)-1 and 2 by Aceclofenac in whole blood assays, with selectivity for Cox-2 being evident. The half-life of Aceclofenac is around 4 hrs, protein binding of 99.7% and the usual dose is 100 mg<sup>5-7</sup>.

A pulsatile drug delivery system that can be administered at night (before sleep) but that release drug in early morning would be a promising chronopharmaceutical system<sup>8</sup>. Drug pharmacokinetics too shows circadian variation for various anti-inflammatory drugs which have greater absorption in morning as compared to evening, and site-specific absorption from small intestine. Therefore, to develop dosage form for chronopharmacotherapy the desired drug release should be time-specific as well as site-specific also<sup>9</sup>. The site-specific delivery of the drugs to the target sites has the potential to reduce the side effects and improved the pharmacological response<sup>10</sup>. The widely used approaches for colon specific targeting are bacterially triggered, pressure controlled, pH dependent and time dependent control drug delivery system<sup>11</sup>.

In this context, Aceclofenac has been found to be suitable drug candidate for the development of time and pH dependent pulsatile drug delivery system. Therefore, the objective of the present study is to develop a pulsatile drug delivery system for aceclofenac which is beneficial for the chronotherapeutic treatment of rheumatoid arthritis.

### MATERIALS AND METHODS

#### Materials

Aceclofenac was gifted from Redson Pharmaceuticals Pvt Ltd, Ahmedabad. pH sensitive methacrylic acid co-polymers (Eudragit L-100 and S-100), Hydroxypropyl methylcellulose phthalate HP 55 and Ethyl cellulose were supplied as gifts by Sunrise remedies Pvt Ltd, Ahmedabad. Redson Pharmaceuticals Pvt Ltd. has also supplied (#00) size hard gelatin capsules as gift. Psyllium husk was purchased from local Ayurvedic store, Gandhinagar. Sodium Alginate and Locust bean gum were gifted by Krystal colloid Pvt Ltd., Mumbai. The rest of chemicals were obtained from S D Fine Chem. Ltd., Mumbai and used as received without further purification: Light liquid paraffin, Span-60, Ethanol, Dichloromethane and Formaldehyde were of analytical grade.

#### Methods

##### Preparation of Microspheres Containing Aceclofenac Drug

Microspheres were prepared by solvent evaporation technique as per formula in Table 1. Accurately weighed quantities of Eudragit L-100 and S-100 in the ratios of 1:2 were dissolved in 8 ml ethanol. Aceclofenac was dispersed with magnetic stirrer. The resulting dispersion was then poured into 250 ml beaker containing the mixture of light liquid paraffin (100 ml) and span60 (0.25% w/w),

stirring at 500 rpm using overhead mechanical stirrer fitted with two blade paddle. Stirring was continued for 4 hrs to allow the completely vaporization of ethanol. The microspheres formed were filtered through Whatman filter paper using Buckner funnel, washed 4-5 times with 50 ml of dichloromethane, dried at room temperature for 24 hrs and stored in a desiccator for the further study <sup>12</sup>. Formulae are given in Table 1.

#### Design of Pulsatile Drug Delivery System Containing Aceclofenac loaded Microspheres

Initially hard gelatin capsule bodies were treated with formaldehyde solution to render them insoluble in gastro intestinal fluids while the caps remained untreated. Twenty-five milliliters of 15% (v/v) formaldehyde was taken into desiccator and a pinch of potassium permanganate was added to it to generate formalin vapors. About 100 numbers of empty bodies of hard gelatin capsule (# 00) were placed over wire mesh and then exposed to formaldehyde vapors. The desiccator was tightly closed, exposed for 12 hrs and dried at

50°C for 30 min to ensure complete reaction between gelatin and formaldehyde vapors. The bodies were then dried at room temperature to facilitate removal of residual formaldehyde. These bodies were joined with untreated caps and stored in a polythene bag.

Then, the microspheres (A3) equivalent to 100 mg of Aceclofenac was loaded in to the bodies by hand filling. Followed by plugging with different amounts (15, 30 and 45 mg) of various polymers, like Sodium alginate, Locust bean gum and Psyllium husk. Then body and cap joined and sealed with a small amount of ethyl cellulose solution (5% w/v ethanolic solution). The sealed capsules were completely coated with 5% w/v HPMCP solution (prepared with mixture of acetone: ethanol) plasticized with 0.75% v/v dibutylphthalate using spray coating to prevent variable gastric emptying. Coating was repeated until to obtain an increase in weight from 8-10%. The % weight gain of capsules before and after coating was determined <sup>13</sup>. Formulae are given in Table 2.

**Table 1: Formulations of different pH sensitive Eudragit microspheres of Aceclofenac**

Code	A1	A2	A3	A4
<b>Core : Coat</b>	1:0.5	1:1	1:1.5	1:2
<b>Ingredients</b>				
Aceclofenac (mg)	500	500	500	500
Eudragit L-100 (mg)	83.33	166.66	250	333.33
Eudragit S-100 (mg)	166.67	333.34	500	666.67
Span 60 (% w/w )	0.1	0.1	0.1	0.1
Ethanol (ml)	8	8	8	8

**Table 2: Composition of Pulsatile Drug Delivery System Based On Design Summary**

Code	Weight of empty body (mg)	Weight of Microspheres*(mg)	Plugging material	Weight of Plugging material (mg)	Total weight of capsule (mg)	Weight after HPMCP Coating (mg)
DS15	78	362	Sodium alginate	15	503	538
DS30	79	362	Sodium alginate	30	519	558
DS45	78	362	Sodium alginate	45	533	570
DL15	80	362	Locust bean gum	15	505	541
DL30	81	362	Locust bean gum	30	521	559
DL45	80	362	Locust bean gum	45	535	573
DP15	80	362	Psyllium husk	15	505	541
DP30	79	362	Psyllium husk	30	519	559
DP45	81	362	Psyllium husk	45	536	574

\*Microspheres equivalent to 100mg of Aceclofenac

#### Evaluation of Microspheres

##### Size Analysis Of Microspheres

Different sizes in a batch are separated by sieving; using a range of standard sieves 20/40, 40/60 and 60/80 and the amount retained on different sieves were weighed. Studies were carried out in triplicate. The average sizes of the microspheres were calculated by using the equation <sup>12</sup>:

$$D_{ave} = \frac{\sum X_i f_i}{\sum f_i} \quad \text{-----} \quad 1$$

Where,

$X_i$  is the mean size of the range

$f_i$  is the percent material retained on the smaller sieve in the size range.

##### Estimation of Drug Content of Eudragit Microspheres Containing Aceclofenac Drug

Crushed microspheres (10 mg) were taken in a 10 ml volumetric flask and volume was made up to mark with phosphate buffer of pH 6.8. The flask was shaken for 12 hrs using water bath shaker. Then the solution was filtered and from the filtrate appropriate dilutions

were made and absorbance was measured at 274 nm by using UV-Visible spectrophotometer <sup>13</sup>.

The encapsulation efficiency was calculated using the formula <sup>15</sup>:

$$\text{Encapsulation efficiency} = \frac{\text{Estimated drug content}}{\text{Theoretical drug content}} \times 100$$

##### In- vitro Dissolution Studies of Eudragit Microspheres Containing Aceclofenac Drug

In vitro dissolution profile of Aceclofenac from each microsphere formulation was determined by employing USP XXIV rotating basket type apparatus (Model TDT-08L-Electrolab). Microspheres equivalent to 100 mg of Aceclofenac were filled into muslin cloth and loaded into the basket of the dissolution apparatus. Acid buffer of pH 1.2 for the first 2 hrs and phosphate buffer of pH 6.8 was used for the next 10 hrs. A 900ml of buffer medium, speed 100 rpm and temperature  $37 \pm 0.5$  °C were maintained. Five milliliters of the sample was withdrawn from the dissolution media at suitable time intervals and the same amount was replaced with fresh buffer. The absorbance of the filtrate was determined at 274 nm by using UV-Visible spectrophotometer, against the respective buffer as blank. The amount of drug present in the filtrate was then determined from the calibration curve and cumulative percent of drug release was calculated <sup>13</sup>.

### Evaluation of Pulsatile Drug Delivery System

#### Test for Formaldehyde Treated Empty Capsule Bodies

Various physical tests such as, identification attributes, visual defects, dimension changes, solubility studies were carried out on the formaldehyde treated empty capsule bodies.

#### Qualitative Chemical Test for Free Formaldehyde

Standard formaldehyde solution used is formaldehyde solution (0.002 w/v) and sample solution is formaldehyde treated bodies (about 25 in number) were cut into small pieces and taken into a beaker containing distilled water. This was stirred for 1 h with a magnetic stirrer, to solubilize the free formaldehyde. The solution was then filtered into a 50 ml volumetric flask, washed with distilled water and volume was made up to 50 ml with the washings. In brief, to 1 ml of sample solution, 9 ml of water was added. One milliliter of resulting solution was taken into a test tube and mixed with 4 ml of water and 5 ml of acetone reagent. The test tube was warmed in a water bath at 40 °C and allowed to stand for 40 min. The solution was not more intensely colored than a reference solution prepared at the same time and in the same manner using 1 ml of standard solution in place of the sample solution. The comparison was made by examining tubes down their vertical axis.

#### *In-vitro* Dissolution Studies of Pulsatile Drug Delivery System Containing Aceclofenac Loaded Microspheres

*In vitro* release of Aceclofenac from the designed pulsatile drug delivery system was investigated by placing device in the basket and followed the procedure described under *in-vitro* dissolution study of

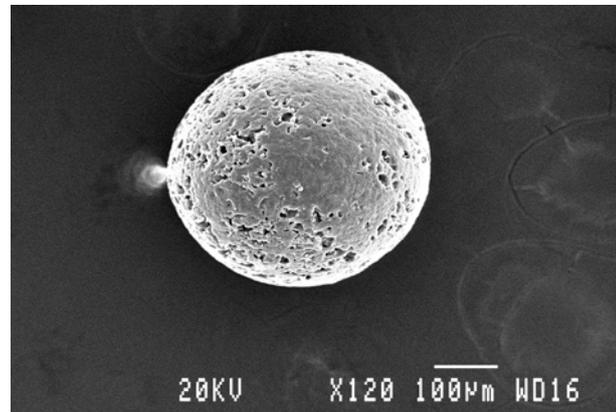
microspheres. However to mimic the physiological conditions of the GIT, dissolution studies were carried out using acid buffer of pH 1.2 for first 2 hrs, phosphate buffer of pH 7.4 for the next 3 hrs and phosphate buffer of pH 6.8 till the end of the study<sup>13</sup>.

### RESULT AND DISCUSSION

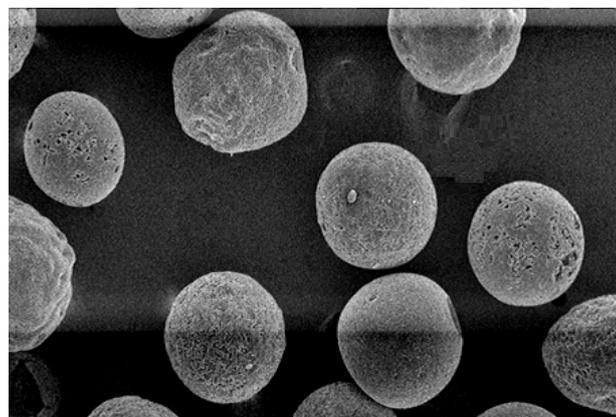
When constant drug plasma levels need to be avoided, as in chronotherapy, time-controlled or pulsed-release formulations are preferable, especially in the treatment of early morning symptoms. By timing drug administration, plasma peak is obtained at an optimal time and the number of doses per day can be reduced. Saturable first-pass metabolism and tolerance development can also be avoided<sup>16</sup>.

Targeted delivery of drugs to the colon has attributed much interest. Recently for local treatment of variety of colonic diseases and also for those drugs where a delay in drug absorption is required from a therapeutic point of view as in case of nocturnal asthma, arthritis and cardiac arrhythmias that are affected by circadian biorhythms<sup>17</sup>. Apparently the colon has a lower pH value (6.5) than that of the small intestine (7.0–7.8). Based on the concept that a formulation on leaving the stomach arrives at the ileocaecal junction in about 6 h after administration and difference in pH throughout GIT, a time and pH dependent pulsatile device proposed for colonic targeting was designed, for achieving the selective delivery of drugs to colon, which is a chronopharmaceutical approach for the better treatment of arthritis.

Thus, Aceclofenac has been found to be a suitable NSAID in the development of time and pH dependent pulsatile drug delivery system for the effective treatment of rheumatoid arthritis.



(I)



(II)

Fig. 1: SEM Photographs of Eudragit Microspheres of Aceclofenac (A3) Group and Single Scanning Electron Microscopy.

The surface topography of optimized formulation (A3) of Aceclofenac loaded Eudragit S100 – L100 combination microspheres (here after called Eudragit microspheres) was investigated by scanning electron microscopy (SEM) and the photomicrographs are shown in Fig 1 (I) and (II). The SEM photographs revealed that, the prepared microspheres were spherical and uniform with a narrow size distribution. Fig 1 (II) showed that the surface of microsphere was little rough, porous, free from cracks and completely covered with coat material. The rough surface can be attributed to the rapid solvent diffusion and quick precipitation during the formation of O/O emulsion. According to the SEM analysis the size of the microspheres was found to be 397.50  $\mu\text{m}$ .

### Size Analysis

The size distribution of the microspheres was found to be narrow in all the batches (A1-A4) with an arithmetic mean size of 425  $\mu\text{m}$ . The average size of the major fraction of microspheres obtained was in the size range of 376-403  $\mu\text{m}$ . The size of the polymeric microspheres was enhanced by increase in the level of core: coat ratio. This could be due to greater amounts of coat material contained in a same volume of liquid droplet. This can be ascribed to an increase in the viscosity resulting in enhanced interfacial tension and demised shearing efficiency<sup>18</sup>. A more viscous solution would require higher shear force for emulsification and lead to larger droplets which would result in larger particles<sup>19</sup>.

**Table 3: Effect of Core: Coat Ratio of Aceclofenac Loaded Microspheres on Yield, Microspheres Particle Size, Drug content, Encapsulation Efficiency, T<sub>50%</sub> and T<sub>90%</sub>**

Code	Core: Coat	Yield* (%)	Particle size* Davg ( $\mu\text{m}$ )	Drug content** (mg)		Encapsulation Efficiency* (%)	T <sub>50%</sub>	T <sub>90%</sub>
				Theoretical	Practical			
A1	1:0.5	78.65±0.82	338.04±0.09	10	8.18±0.678	81.81±0.47	5.19±0.11	10.90±0.07
A2	1:1	82.79±0.78	343.32±0.21	10	8.45±0.696	84.5±0.66	5.43±0.24	11.52±0.12
A3	1:1.5	85.21±0.50	350.04±0.13	10	8.79±0.660	87.96±0.89	5.78±0.31	11.84±0.17
A4	1:2	89.55±0.67	358.84±0.05	10	9.02±0.649	90.2±0.81	6.30±0.19	---

All values are expressed as mean  $\pm$  SD, \*n=3, \*\*Average of 3 determinants.

### Microspheres Yield and Drug Content

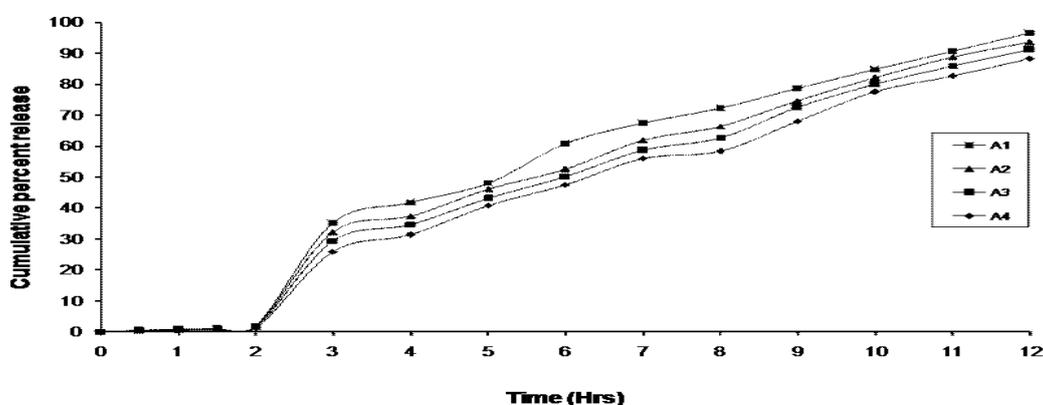
The yield of the microspheres was high ranging from 78.65 to 89.55 %. Little increase in the yield of microspheres was observed with proportionate increase in the core: coat ratio. Similarly encapsulation efficiency was also increased with the proportionate increase in the core: coat ratio. The drug content estimated in microspheres equivalent to 10 mg of Aceclofenac was found to be uniform and reproducible in each batch and is shown in Table 3. The encapsulation efficiency of different batches of microspheres (A1-A4) was in the range of 81.81 to 90.2%. The high encapsulation efficiency could be due to polymer loss by adherence to the container as a result of viscous nature of slurry<sup>13</sup>. Interestingly, encapsulation efficiency was found to be directly proportional to the percentage yield of the microsphere preparation<sup>20</sup>.

### Evaluation of Formaldehyde Treated Empty Capsule Bodies

Formalin treatment has been employed to modify the solubility of gelatin capsules. Exposure to formalin vapors results in an

unpredictable decrease in solubility of gelatin owing to the cross-linkage of the amino groups in the gelatin molecular chain with aldehyde groups of formaldehyde by Schiff's base condensation<sup>13</sup>. The formaldehyde treated empty capsule bodies were evaluated for visual appearance, dimension changes, solubility studies and qualitative chemical test for free formaldehyde.

The capsule bodies after formaldehyde treatment slightly reduced in their size and apart from this no other visual defects were observed. The formaldehyde treatment of the capsule bodies significantly altered their solubility compared to the untreated cap of the capsule. The untreated caps were dissolved within 12 minutes and the treated bodies remained intact over a period of 24 hrs and thus indicating the suitability for the colonic delivery. The qualitative chemical test for the free formaldehyde was carried out. The sample solution was not intensely colored than the standard solution, inferring that less than 20 $\mu\text{g}$  of free formaldehyde was present in 25 capsules used for the test.



**Fig. 2: In-vitro Release of Aceclofenac from Eudragit Microspheres in pH 1.2 and 6.8.**

### In-vitro Dissolution Studies

#### Microspheres

The release of Aceclofenac from the different batches (A1, A2, A3 and A4) of Eudragit microspheres was studied in pH 1.2 for 2 hrs

and pH 6.8 for 10 hrs using USP-XXIV dissolution testing apparatus. All four batches of Eudragit microspheres showed a strong drug release control in acidic medium of pH 1.2. The release pattern of Aceclofenac from Eudragit microspheres of A1, A2, A3 and A4 batches were found 96.54, 93.71, 91.20 and 88.29% respectively at

the end of 12 hrs. The release has occurred after complete swelling of polymer. The swelling was proportionate with polymer concentration resulting retard release. The dissolution study indicated that microspheres were characterized by initial burst effect during first hour after exposure to pH 6.8. The studies showed that the microspheres exhibited both pH sensitive and controlled release properties. Among the various batches of microspheres investigated, A3 with core: coat ratio (1:1.5) was found satisfactory not only with respect to the release behavior but also in regard of size, shape and encapsulation efficiency. The release kinetics of Eudragit microspheres followed zero-order.

**Effect of Different Plugging Materials on *In-vitro* Release**

Reports are not available on the use of natural polymers like Sodium alginate, locust bean gum and Psyllium husk as plugging materials in the development of pulsatile drug delivery systems. Hence these natural polymers were selected in the design of pulsatile delivery system of Aceclofenac. Different concentrations of these polymers were used and their effect on drug release from the designed pulsatile capsule was investigated using the dissolution media mimicking the pH conditions (without enzymes) of the GI tract.

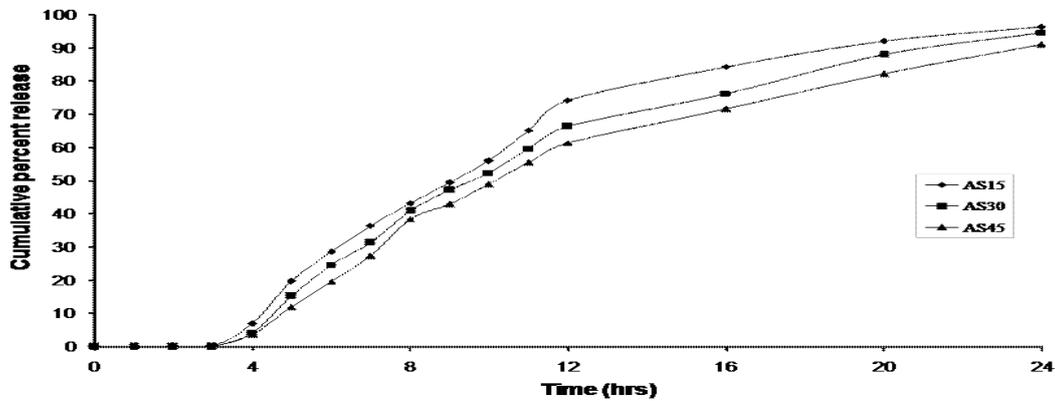


Fig. 3: *In-vitro* Release of Aceclofenac from Pulsatile Device in pH 1.2, 7.4 and 6.8.

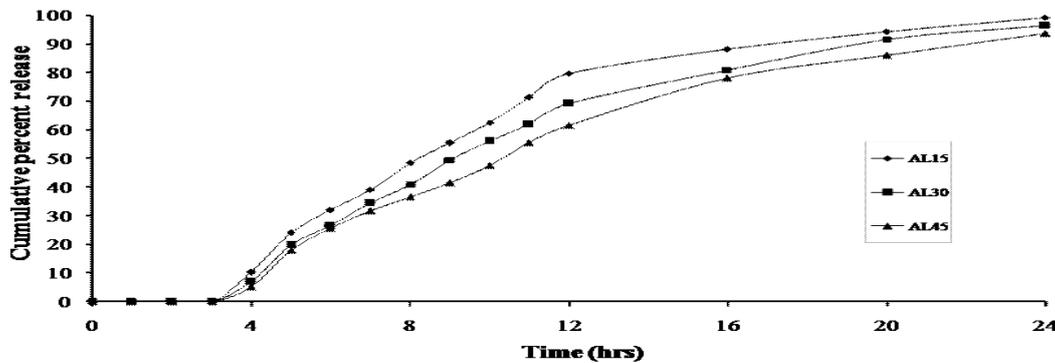


Fig. 4: *In-vitro* Release of Aceclofenac from Pulsatile Device in pH 1.2, 7.4 and 6.8.

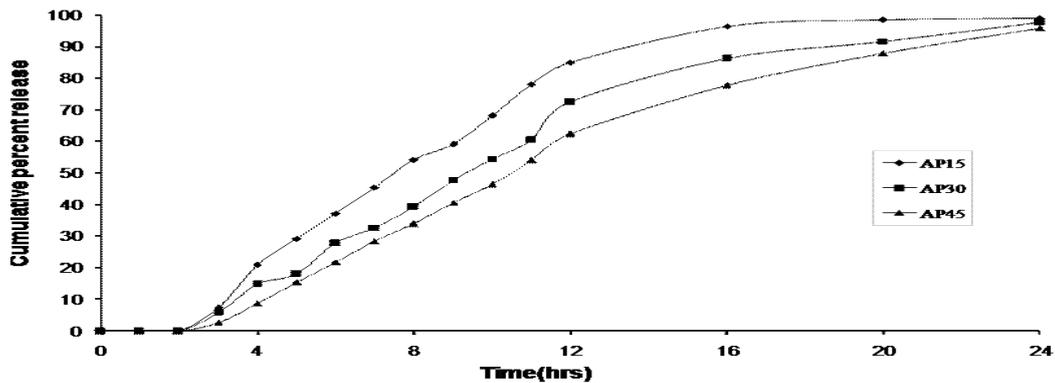


Fig. 5: *In-vitro* Release of Aceclofenac from Pulsatile Device in pH 1.2, 7.4 and 6.8.

### Effect of Sodium Alginate

With all the formulations the concentration of the plugging material was found sufficient to maintain the lag period for a minimum period of 4 hrs. However negligible amount of drug was released at the end of 4th hr. This could be due to diffusion of drug from the microspheres through the swollen hydrogel plug. At the end of 5th hr, the hydrogel plug after complete wetting and swelling was ejected from AS15 and AS30 system and thus releasing the drug containing microspheres in the colonic region (pH6.8). In case of AS45, the polymeric plug was ejected at the end of 6th hr of the dissolution study. This could be attributed to delayed wetting and swelling of the hydrogel material at the higher concentration. At the end of 24 hrs 96.39, 94.74 and 91.16% drug release was observed with AS15, AS30 and AS45 formulation respectively. Overall, with all the formulations containing sodium alginate as a plugging material, a desired lag period of 4hrs was achieved and the release of drug in a controlled manner began after the 5th hr and spread over a period of 24 hrs.

### Effect of Locust Bean Gum

In another set of formulations, locust bean gum as a hydrogel plugging material in three different concentrations like 15, 30 and 45 mg were used in AL15, AL30 and AL45 respectively. The cumulative drug release at the end of 4th hr was negligible and found to be 10.40, 6.99 and 5.13% with AL15, AL30 and AL45 respectively. This could be due to diffusion of drug from the microspheres through the swollen hydrogel plug. The different polymeric concentrations used in the above formulations were found sufficient to maintain the lag period for a minimum period of 4 hrs. During 5th hr, the hydrogel plug after complete wetting and swelling was ejected from AL15 and AL30 formulations and thus releasing the drug containing microspheres in the colonic fluid (pH6.8). In case of AL45, the polymeric plug was ejected during the 6th hr of the dissolution study. This could be attributed to delayed wetting and swelling of the hydrogel material at the higher concentration. At the end of 24 hrs, 99.45, 96.44 and 93.68% drug release was observed with AL15, AL30 and AL45 formulation respectively. Overall, with all the formulations containing locust bean gum as a plugging material, a desired lag period of 4hrs was achieved and the drug was released in a controlled manner after the 5th hr and continued till the end of 24th hr.

### Effect of Psyllium Husk

For the formulations AP15, AP30 and AP45 Psyllium husk was employed as plugging material in three different concentrations like 15, 30 and 45 mg respectively. With all the formulations negligible amount of drug was released at the end of 3rd hr and found to be 20.99, 14.90 and 8.80 % at the end of 4th hr with AP15, AP30 and AP45 respectively. Due to higher water absorbing capacity of Psyllium husk, it swelled rapidly and ejection of the plug was witnessed in between 4th and 5th hr for AP15 and AP30. With these two formulations 96.56 and 86.30% of drug was released at the end of 16th hr. This virtually indicated the failure of these formulations in maintaining the desired lag phase and also failed to maintain the drug release for a period of 24 hrs. However with formulation AP45 containing 45mg of Psyllium husk, the plug was ejected between 6th and 7th hr. This could be due to increased wetting and swelling time and their by delay in the ejection of the plug. About 77.80 and 96% of the drug was released at the end of 16th and 24th hr respectively in case of formulation AP45.

### CONCLUSION

The mechanism of drug release of pulsatile drug delivery systems was diffusion controlled first-order kinetics. With all the above observations, it was found that sodium alginate and locust bean gum as plugging materials were found better in maintaining the desired lag period compared to Psyllium husk. The rank order of sustaining capacity of polymer was Sodium alginate>Locust bean gum>Psyllium husk. The lag period and the drug release could be efficiently modulated by altering the concentration of plugging material to a certain extent. Thus, the study conclusively demonstrated the efficacy and suitability of these natural polymers as plugging materials in the design of pulsatile drug delivery system of Aceclofenac.

### ACKNOWLEDGEMENT

The authors are thankful to Redson Pharmaceuticals Pvt Ltd, Ahmedabad for giving a gift sample of active drug and also very thankful to Sunrise remedies Pvt Ltd., Ahmedabad for providing polymers.

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