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Design And Characterisation Of Pulsatile Capsule Device For Flurbiprofen Using Natural Excipients

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Abstract: *The objective of the present study was to design and characterize pulsatile capsule device for Flurbiprofen using natural excipients. The Flurbiprofen fast disintegrating tablets (FDT) were formulated using superdisintegrants isolated from natural sources. Pulsatile capsules were designed using optimized Flurbiprofen FDT PO4 as core and with different natural materials i.e.,Chitosan, Guar Gum and Plantago Ovata husk as plugging materials in different amounts. Pulsatile capsules remained intact in acid buffer of pH 1.2 for 2 hrs due to enteric coating with hydroxyl propyl methyl cellulose phthalate (HPMCP). In Phosphate buffer of pH 6.8, the enteric coat dissolved. The plug material swelled and ejected out of capsule body, thereby liberating the drug into the alkaline fluid medium. With all the formulations absolutely no drug release was observed in first two hours and negligible drug was released in the third hour. The pulsatile capsules developed with Guar Gum as plugging material showed satisfactory lag time of 285-390 min and percent cumulative drug release (% CDR) of 97.88-98.87% at the end of 6.25 hrs to 7.75 hrs, when compared to Chitosan and Plantago Ovata husk which showed lag time of 180-285 min with % CDR of 98.11-98.49% at the end of 5 hrs to 7.25 hrs and 240-300 min with % CDR of 98.00-98.60% at the end of 5.75 hrs to 7 hrs respectively. The mechanism of drug release from the pulsatile capsule was found to be zero order kinetics. The lag period and the drug release could be efficiently modulated by altering the concentration of plugging material.*

Keywords: *Flurbiprofen, pulsatile capsule device, plugging material, natural excipients, Rheumatoid arthritis*

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I. Introduction

Rheumatoid arthritis is an autoimmune disease that results in chronic, systemic inflammatory disorder that may affect many tissues and organs, but principally attacks flexible (synovial) joints. 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. A circadian rhythm in signs and symptoms was suggested. This disease activity in rheumatoid arthritis is manifested by joint stiffness and grip strength, which is estimated to be maximal between 02:00 and 04:00 a.m [1]. It is a common rheumatological condition in the community as it affects nearly 1% of the population in world [2]. Rheumatoid arthritis can occur at any age, it usually begins after age of 40. The disorder is much more common in women than in men [3]. Flurbiprofen is effective in the treatment of both acute and chronic conditions of pain and inflammation, including osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, gout, sprains, toothache, dysmenorrhoea and ischemic cerebrovascular disorders. A pulsatile drug delivery system that can be administered at night (before sleep) but that releases drug in early morning would be a promising chronopharmaceutic system. Drug pharmacokinetics too shows circadian variation for Flurbiprofen, which has 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 [4]. It can be noted from literature survey that most of Flurbiprofen pulsatile systems are prepared using synthetic, or combination of synthetic and natural plugging materials. Hence, in the present research, it was aimed to prepare novel Flurbiprofen pulsatile capsule device using FDT containing natural superdisintegrants, which can increase the solubility and dissolution of the drug and natural plugging materials that aid pulsatile release of the drug.

II. Materials And Methods

Flurbiprofen was obtained as gift sample from FDC Limited, Mumbai. Hard gelatin capsules (#00) were obtained as gift sample from Redson Pharmaceuticals Ltd., Ahmedabad. Ethyl cellulose, Hydroxypropyl methyl cellulose phthalate, Formaldehyde, Potasium permanganate, Lactose and Dibutyl phthalate were purchased from S.D Fine Chemicals Pvt Ltd, Mumbai. Guar gum was obtained from Hi Media Laboratories Pvt

Ltd, Mumbai. Chitosan was obtained as gift sample from Primex, Iceland. *Plantago Ovata husk* was purchased from local market, Raichur. All other chemicals and reagents used were of pharmaceutical and analytical grade.

2.1. Flurbiprofen fast disintegrating tablets

FDT's of Flurbiprofen were prepared using direct compression method. The natural superdisintegrants *Plantago Ovata*, *Lepidium sativum* and modified Agar were used in concentrations of 2%, 4%, 6% and 8% to formulate the tablets. All the ingredients were co-ground in a pestle and motor and then magnesium stearate and talc were added and mixed for 10 min. The mixed blend of drug excipients was compressed using 10 stations compression machine to produce tablets. The composition of Flurbiprofen FDT's is given in TABLE 1. The formulation and evaluation of Flurbiprofen FDT's and their technical details are described in an earlier publication [5].

Table 1: Composition of Flurbiprofen fast disintegrating tablets

Ingredients (mg)	PO1	PO2	PO3	PO4	LS1	LS2	LS3	LS4	MA1	MA2	MA3	MA4
Flurbiprofen	50	50	50	50	50	50	50	50	50	50	50	50
Microcrystalline cellulose	101	101	101	101	101	101	101	101	101	101	101	101
Spray dried mannitol	40	36	32	28	40	36	32	28	40	36	32	28
Plantago Ovata	4	8	12	16	-	-	-	-	-	-	-	-
Lepidium sativum	-	-	-	-	4	8	12	16	-	-	-	-
Modified Agar	-	-	-	-	-	-	-	-	4	8	12	16
Aerosil200	1	1	1	1	1	1	1	1	1	1	1	1
Magnesium stearate	2	2	2	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2	2	2	2

2.2. Design of pulsatile drug delivery system

Pulsatile device was designed adopting the method reported by Mastiholimath et al [6]. 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 optimized FDT of Flurbiprofen PO4 was loaded in to the bodies by hand filling, followed by plugging with different amounts (30, 40 and 50 mg) of various polymers, like Chitosan, Guar gum and *Plantago Ovata husk* as plugging materials. Then body and cap were 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: methanol in ratio 8:2) plasticized with 0.75% v/v dibutylphthalate using dip 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 using the equation [7]:

$$\% \text{ weight gain} = (Wt - Wo)/Wo \times 100 \quad \text{--- (1)}$$

Composition of Flurbiprofen pulsatile capsule device is given in TABLE 2. The design of Flurbiprofen pulsatile capsule device is shown in Fig. 1.

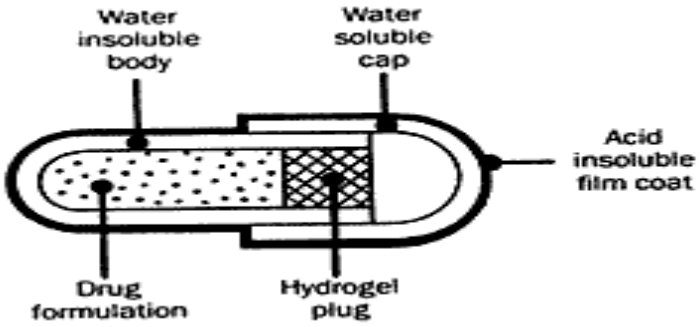

Fig.1: Design of Flurbiprofen pulsatile capsule device

Table 2: Composition of Flurbiprofen pulsatile capsule device

Code	Weight of empty body (mg)	Weight of Core FDT* (mg)	Plugging material	Weight of Plugging material (mg)	Total weight of capsule (mg)	Weight after HPMCP Coating (mg)
CH1	58	201	Chitosan	30	401	438
CH2	59	201	Chitosan	40	419	458
CH3	58	202	Chitosan	50	433	470
GG1	60	202	Guar gum	30	405	443
GG2	61	200	Guar gum	40	421	462
GG3	60	202	Guar gum	50	435	477
POH1	60	200	*Plantago Ovata husk*	30	406	442
POH2	59	203	*Plantago Ovata husk*	40	419	465
POH3	61	202	*Plantago Ovata husk*	50	436	479

*core FDT Contains 50 mg of Flurbiprofen

2.3. Evaluation of Flurbiprofen pulsatile capsule device

2.3.1. Tests for formaldehyde treated empty capsule bodies

The formaldehyde treated and untreated empty capsule bodies were subjected to various physical and chemical tests.

Physical tests [8-12]

i. Identification attributes: The size '00' capsules were one with a dark blue cap and light blue colored body. They were lockable type, odourless, softy and sticky when treated with wet fingers.
ii. Visual defect: Capsule bodies treated with formaldehyde were checked for any kind of distortion, shrink, rupture and crack.
iii. Dimensions: Variations in dimensions between formaldehyde, treated and untreated capsules were studied. The length and diameter of the capsules were measured before and after formaldehyde treatment, using vernier calipers.
iv. Solubility Studies: The solubility tests were carried out for both normal capsules and formaldehyde treated capsules for 24 hrs. Ten capsules were randomly selected. These capsules were then subjected to solubility studies at room temperatures in buffers of pH 1.2 and pH 6.8. 100 ml of buffer solution was taken in a beaker. A single capsule was placed in the buffer solution and stirred for 24 hrs. The time at which the capsule dissolves or forms soft fluffy mass was noted.

Qualitative chemical test for free formaldehyde

Standard formaldehyde solution used was formaldehyde solution (0.002 w/v) and sample solution was 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 hr 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 ml 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.

2.3.2. Tests for formulated pulsatile capsules

Weight variation

An intact capsule was weighed. The capsule was opened without losing any part of shell and the contents were removed as completely as possible. The capsule shell was weighed. The weight of the contents is the difference between the weights. The procedure was repeated with further 19 capsules. The average weight was determined. Not more than two of the individual weights deviate from the average weight by more than the percentage deviation shown in TABLE 3 and none deviates by more than twice that percent [13].

Table 3: IP Limit for capsules

Average weight of capsule contents	Percentage deviation
Less than 300 mg	10%
300 mg or More	7.5%

Disintegration test

One capsule was placed in each tube of disintegration apparatus. The apparatus was operated for 2 hrs without discs in acid buffer pH 1.2. Later the medium in vessel was replaced with phosphate buffer pH 6.8, the discs were added to each tube and the apparatus was operated for further 60 min. The capsules pass the test if no residue remains on the screen or on the underside of discs, or, if a residue remains, it consists of fragments of shell or of a soft mass with no palpable, unmoistened core.

Lag time

Lag time is the total time period after which the plug is ejected out of the capsule body and the drug releases immediately. Lag time was determined visually using phosphate buffer pH 6.8. For lag time determinations USP paddle apparatus was used. Capsules were tied with the paddle by cotton thread; temperature was maintained at 37±05°C at 75 rpm was maintained [14].

In- vitro dissolution study

In-vitro drug release study was carried out in a USP XXIV dissolution apparatus I basket type (TDT-08L plus, Electrolab, Mumbai, India)) in 900 ml medium at 37±05°C at a rotation speed of 75 rpm. The pulsatile capsules were placed in the basket. For simulating conditions of the GI tract, dissolution tests were carried out in media with pH 1.2 first and pH 6.8 phosphate buffers later. The study was performed for 2 hrs for acidic stage in pH1.2 and in the pH 6.8 phosphate buffer later till the end of dissolution. 5 ml samples were withdrawn at predetermined time intervals and replaced with fresh dissolution media. The withdrawn samples were filtered through membrane filter 0.45 μm and analyzed using UV spectrophotometer at λ max 247 nm [15, 16].

Kinetic studies [17-19]

The basic *in-vitro* release data of the Flurbiprofen pulsatile capsule device was tabulated and graphed as:

1. Cumulative percent drug release vs. time.
2. Log cumulative percent drug retained vs. time.
3. Cumulative percent drug release vs. √ T.
4. Log cumulative percent drug release vs. Log time.

In order to analyze the release mechanism, several release models were tested such as:

Zero order: $\mathbf{Qt = Qo + Kot}$ ---------- **(2)**

Where Q_t is the amount of drug released at time *t*, Ko is the apparent dissolution rate constant or zero order release constant and Qo is the initial concentration of the drug in the solution resulting from a burst effect; in this case the drug release runs as a constant rate.

First order: $\mathbf{lnQt = lnQo + K1}t$ ----------**(3)**

Where K_1 is the first order release constant; in this case the drug released at each time is proportional to the residual drug inside the dosage form.

Higuchi: $\mathbf{Qt = KH}\sqrt{t}$ ---------- **(4)**

Where Q_t is the amount of drug released at time *t* and K_H is the higuchi release rate constant; this is the most widely used model to describe drug release from pharmaceutical matrices.

Korsmeyer – Peppas: $\mathbf{Qt/Q\infty = Kk}t\mathbf{n}$ ----------**(5)**

Where K_k is a constant incorporating structural and geometric characteristic of the drug dosage form and n is the release exponent, indicative of the drug release mechanism.

When *n* approximates to 0.5, a Fickian/diffusion controlled release is implied, where $0.5<n<1.0$ (0.5 to 1.0) non-Fickian transport and n=1 for zero order (case II transport). The statistical analysis was performed by calculating the correlation (r) existing between the *in-vitro* release and the model proposed at different *n* values.

IR spectral studies

The compatibility between pure drug and excipients was detected by IR spectra obtained on comp-Bruker, model alpha-T, (USA). The pellets were prepared on KBr press. The spectra were recorded over the wave number range of 4000 to 500 cm^{-1}.

III. Results And Discussion

3.0. Evaluation of pulsatile capsule device

3.1. Test for 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 (Masthiholimath *et al*)[6]. The formaldehyde treated empty capsule bodies were evaluated for physical tests like visual appearance, dimension changes, solubility studies and qualitative chemical test for free formaldehyde.

Physical tests

i. Identification attributes: The size '00' capsule were one light blue colored body before treatment. After treatment very slight colour change was observed and were non sticky when touched with wet fingers.

ii. Visual defect: In about 100 Capsule bodies treated with formaldehyde about 10 were found shrunk or distorted.

iii. Dimensions: Variations were observed in dimensions between formaldehyde treated and untreated capsules. The results are given in TABLE 4.

Table 4: Comparison of dimension of capsule bodies

Parameter	Before treatment	After treatment
Average capsule length (mm)	22.3	22.1
Average diameter of capsule body (mm)	7.5	7.4
Average length of capsule body (mm)	18.4	18.2

iv. Solubility Studies: The solubility tests were carried out for both normal capsules and formaldehyde treated capsules for 24 hrs. The formaldehyde treatment of the capsule bodies significantly altered their solubility compared to the untreated cap of the capsule. Depending upon the duration of exposure to formaldehyde solubility of capsule varied. Solubility of untreated capsule bodies was more than that treated one. The untreated capsule bodies became soft within 4 min and dissolved in 9 min in pH 1.2 where as in pH 6.8 it became soft in 5 min and dissolved in 12 min. The treated bodies (6 hrs and 12 hrs) remained intact over a period of 10 and 24 hrs respectively in pH 1.2 but softened in 4.5 and 9.5 hrs in pH 6.8. The results are given in TABLE 5.

Table 5: Solubility study of formaldehyde treated capsule bodies

Time of exposure with 15% formaldehyde	Observation of solubility in dissolution media	
	pH 1.2	pH 6.8
6 hrs	Intact up to 10 hrs	Softened in 4.5 hrs
12 hrs	Intact up to 24 hrs	Softened in 9.5 hrs

Qualitative chemical test for free formaldehyde

The formaldehyde capsules were tested for the presence of free formaldehyde. The sample solution was not more intensely coloured than the standard solution inferring that less than 20 µg free formaldehyde was present in 25 capsules.

3.2. Tests for formulated pulsatile capsule device

Weight variation

Weight variation was carried out as per method laid down in Indian Pharmacopoeia. % deviation was found to be 2.98 to 5.97% i.e. less than 10% which was within the pharmacopeial limit. The results are given in TABLE 6.

Disintegration test

Disintegration test for pulsatile capsule device containing Flurbiprofen was carried out as per method laid down in Indian pharmacopoeia. None of the capsule showed signs of disintegration or rupture in pH 1.2 for two hours, indicating that enteric polymer i.e. HPMCP was intact and could prevent drug from variable gastric emptying. Later all capsules disintegrated in pH 6.8. The results obtained are given in TABLE 6.

Lag time

Lag time was determined for all prepared batches of Flurbiprofen pulsatile capsule device and the results are given in TABLE 6. Lag time of all formulation CH1-CH3, GG1-GG3, and POH1-POH3 containing Chitosan, Guar gum and *Plantago Ovata* husk respectively, was found to be influenced by type and amount plugging

material. It was observed in all formulation that as the polymer concentration increased the lag time also increased. A lag time of 4-5 hrs is desirable in case of chronotherapeutic treatment of rheumatoid arthritis which is observed in almost all formulation except CH1 andCH2. Out of all these formulations, GG2 (Guar Gum-40 mg) provided ideal lag time of 5 hrs and 15 min needed for pulsatile release of Flurbiprofen.

Table 6: Weight variation, disintegration test and lag time of Flurbiprofen pulsatile capsule device

Batch	Weight variation* (%)	Disintegration test*		Lag time* (min)
		pH 1.2 (min)	pH 6.8 (min)	
CH1	3.05	Intact	50	180
CH2	3.17	Intact	51	225
CH3	5.97	Intact	53	285
GG1	3.85	Intact	52	285
GG2	4.23	Intact	54	315
GG3	3.41	Intact	55	390
POH1	5.12	Intact	51	240
POH2	2.98	Intact	52	270
POH3	3.19	Intact	53	300

*Average of three determinants.

In-vitro dissolution study

In-vitro release studies of the designed Flurbiprofen pulsatile capsule device was carried out in triplicate employing USP-XXIV dissolution testing apparatus (Electrolab, TDT-08L) adopting the pH progression method simulating the gastrointestinal tract conditions. Pulsatile capsule was loaded in to the basket of the dissolution apparatus and pH changes were performed, starting with 900 ml of acid buffer of pH 1.2 for 2 hrs followed by phosphate buffer of pH 6.8 till the end of the study. The % cumulative drug release of all formulations was in the range of 97.88 to 98.87%. Formulations prepared with Guar gum as plugging material gave maximum release 98.87% drug in 6 hrs and 45 min. During dissolution studies the pulsatile capsule remained intact in pH 1.2 for 2 hrs and thus indicated the efficiency of HPMCP (5% w/v) as an enteric coating material. The enteric coat dissolved when the pH of medium was changed to 6.8, leaving the soluble cap of the capsule which also dissolved after few mins. Then, the exposed polymeric plug absorbed the surrounding fluid, swelled and released the drug through the solvent matrix. When polymeric plug was completely wetted by the dissolution fluid, a soft mass was formed which was then easily ejected out of the capsule body, exposing the core tablet to dissolution medium. With most of the formulations absolutely no drug release was observed in first two hrs and negligible drug was released till the third hr. This indicated that, the designed pulsatile capsule could maintain the lag time of no drug release for minimum of three hrs which is desired for the chronotherapeutic delivery of Flurbiprofen in the treatment of rheumatoid arthritis.

Effect of different plugging materials on in-vitro release

Various natural gums like Chitosan, Guar gum and *Plantago Ovata* husk in different concentrations (30, 40 and 50 mg) were used as plugging material in the design of the pulsatile capsules. The effect of plugging materials on drug release was studied.

Effect of Chitosan

Chitosan as a hydrogel plugging material was used in three different concentrations 30, 40 and 50 mg in the formulations CH1, CH2 and CH3 respectively. The cumulative drug release around of third hr was negligible and found to be 15.04, 10.48 and 5.4% with CH1, CH2 and CH3 respectively. The negligible amount of drug released could be due to controlled diffusion of drug from the swollen hydrogel plug. With all the formulations the concentration of the plugging material was found sufficient to maintain the minimum lag period of 3 hrs. After the third hr of the dissolution study, the hydrogel plug was ejected from CH1 after complete wetting and swelling, whereas the ejection of the hydrogel plug was observed around fourth and fifth hr for CH2 and CH3 formulations. The delay in the ejection of plugging material for the later two formulations was attributed to delayed wetting and swelling of the hydrogel material at the higher concentration. At the end of 5 hrs, 98.11% drug release was observed with CH1, at the end of 6 hrs, 98.49% drug release was observed with CH2 and at the end of 7 hrs and 15 min, 98.46% drug release was observed with CH3 formulation. Overall, with all the formulations containing Chitosan as a plugging material, a desired lag period of 3-4 hrs was achieved.

Effect of Guar gum

Guar gum was used as a hydrogel plugging material in three different concentrations like 30, 40 and 50 mg with GG1, GG2 and GG3 formulations respectively. The cumulative drug release at the end of fourth hr was negligible and found to be 16.5, 5.37 and 4.9% with GG1, GG2 and GG3 respectively. This could be due to

controlled diffusion of drug from 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. After 4 hr and 30 min, the hydrogel plug after complete wetting and swelling was ejected from GG1, and after 5 hrs from GG2. In case of GG3 the polymeric plug was ejected after the 6 hrs 30 min 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 6 hrs and 15 min, 98.04% drug release was observed with GG1, at the end of 6 hrs and 45 min, 98.86% drug release was observed with GG2 and at the end of 7 hrs and 45 min, and 97.98% drug release was observed with GG3. Overall, with all the formulations containing guar gum as a plugging material, a desired lag period of 4 hrs was achieved.

Effect of Plantago Ovata husk

Plantago Ovata husk was employed as plugging material in three different concentrations like 30, 40 and 50 mg in POH1, POH2 and POH3 respectively. Similarly as in case of formulations containing Chitosan and Guar gum, negligible amount of drug 19.06, 14.14 and 10.30% was released around fourth hr with POH1, POH2 and POH3. This could be due to controlled diffusion of drug from 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. After 3 hrs and 45 min, the hydrogel plug after complete wetting and swelling was ejected from POH1 and after 4 hrs and 15 min from POH2. In case of POH3 the polymeric plug was ejected after the 4 hrs 45 min 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 5 hrs and 45 min, 97.99% drug release was observed with POH1, at the end of 6 hrs and 30 min, 98.59% drug release was observed with POH2 and at the end of seventh hr 98.29% drug release was observed with POH3. Overall, with all the formulations containing *Plantago Ovata husk* as a plugging material, a desired lag period of 4 hrs was achieved.

With all the above observations, it was found that Guar gum and *Plantago Ovata husk* as plugging materials were found better in maintaining the desired lag period compared to Chitosan. The rank order of sustaining capacity of polymer plug was Guar gum>*Plantago Ovata husk*>Chitosan. 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 capsule device for Flurbiprofen. Out of all the formulations, GG2 (Guar Gum-40 mg) provides lag time of 5 hrs and 15 min with initial drug release of 54.52% and rapid delivery of drug up to 98.87% in next 1.5 hrs and was considered as best formulation. The results of *in-vitro* release study of all formulations are given in Fig. 2.

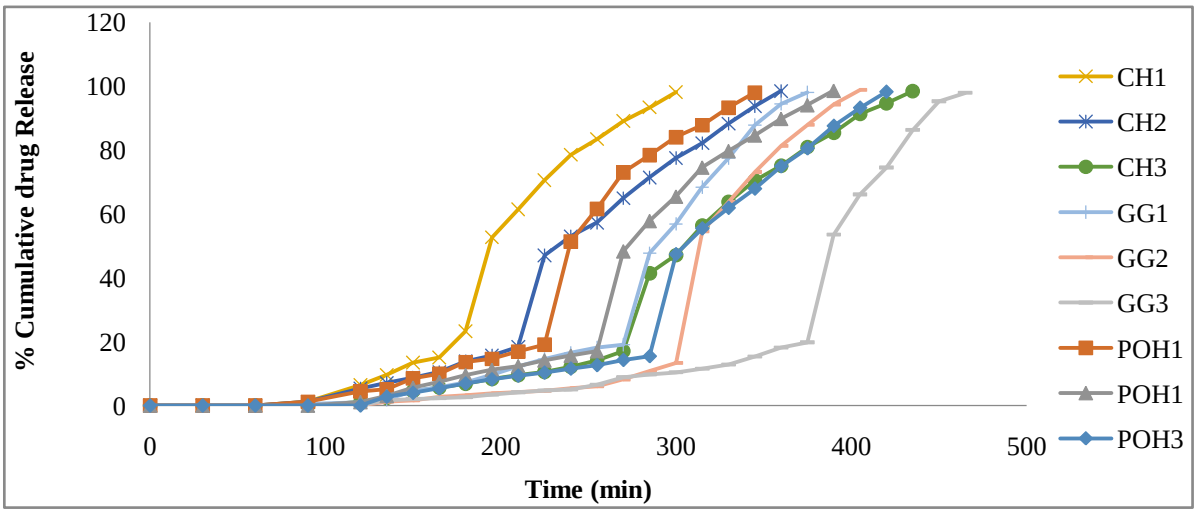

Fig. 2: *In-vitro* dissolution study of Flurbiprofen pulsatile capsule device

Kinetic studies

To investigate the mechanism of drug release from pulsatile capsule device, various kinetics models like zero order, first order, Higuchi's and Korsmeyer-Peppas equations were applied to the *in-vitro* release data obtained from different formulations. As observed from the TABLE 7, the values of correlation-coefficient (r^2) for all the formulations were enough to evaluate the drug dissolution behavior. The value of release exponent (n) is a function of polymer used and the physicochemical property of a drug molecule itself. When the data was plotted in zero order equation, linear plots were obtained for all the formulations with correlation coefficient (r^2)

values ranging from 0.625-0.876. Further when the drug release data put in to Higuchi equation, correlation coefficient (r^2) values ranging from 0.448 to 0.676 were obtained, indicating that drug release followed Higuchi release kinetics. When plotted with Korsmeyer-peppas model the formulations showed (r^2) value ranging from 0.386 to 0.578 with n value approaching to 1. Hence the mechanism of release from formulations was found to be zero order diffusion mechanism.

Table 7: Kinetic studies of Flurbiprofen pulsatile capsule device

Formulation code	Zero order		First order		Highuchi		Korsmeyer-peppas	
	N	r^2	n	r^2	n	r^2	n	r^2
CH1	0.395	0.858	-0.002	0.089	6.814	0.656	0.968	0.548
CH2	0.322	0.874	-0.001	0.115	6.253	0.676	0.975	0.578
CH3	0.266	0.837	-0.001	0.155	5.745	0.637	0.986	0.525
GG1	0.276	0.748	-0.001	0.072	5.297	0.54	0.906	0.491
GG2	0.252	0.876	-0.001	0.090	5.014	0.466	0.852	0.386
GG3	0.187	0.625	-0.001	0.063	4.086	0.448	0.853	0.490
POH1	0.332	0.815	-0.001	0.096	6.173	0.608	0.946	0.547
POH2	0.294	0.811	-0.001	0.127	5.898	0.607	0.962	0.511
POH3	0.257	0.782	-0.001	0.103	5.361	0.579	0.941	0.505

IR spectral studies

Several analytical techniques are presently used in the study of drug formulation. Among such analytical techniques Infrared spectroscopy (IR) technique is quite oftenly used in establishing the identity of drug in formulations. In the present study IR spectra of drug, its core FDT PO4 prepared using natural superdisintegrants (*Plantago Ovata*) and physical mixture of PO4 + Guar gum were taken. The comparative study revealed the fact that there was no marked shift in the position of characteristic absorption band of the functional groups and bonds present in the drug molecule. Hence from the study it was concluded that there was no interaction of the drug with excipients. The IR spectra are given in Fig. 3 and 4.

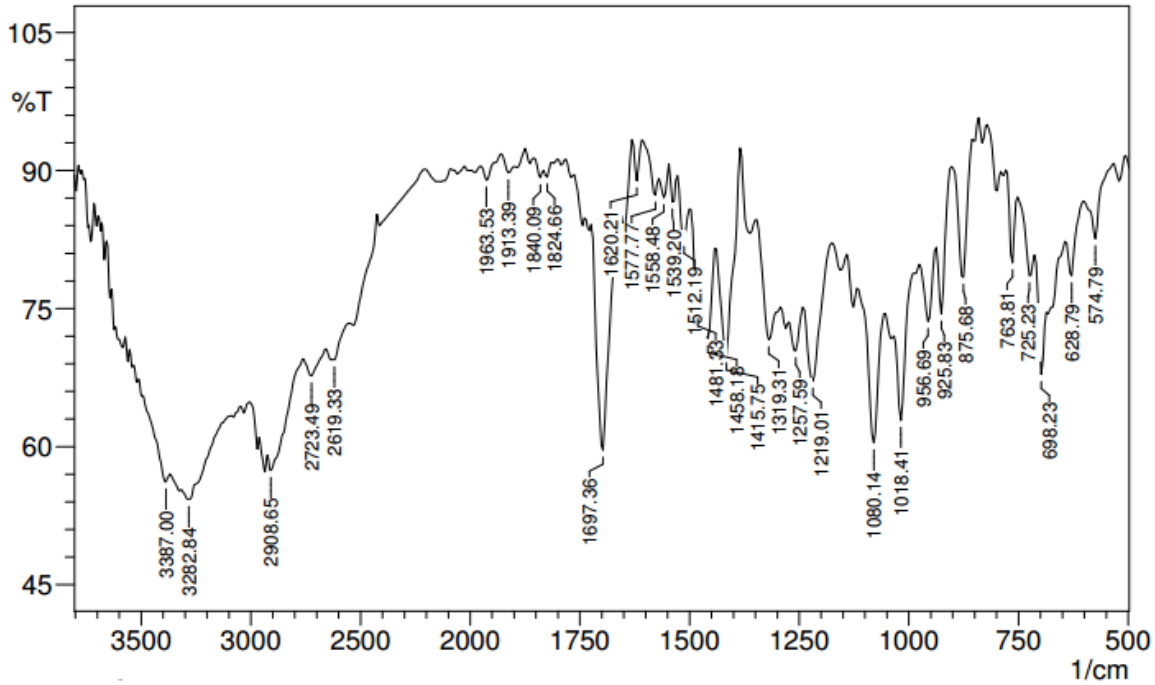

Fig. 3: IR spectra of Core FDT of Flurbiprofen PO4

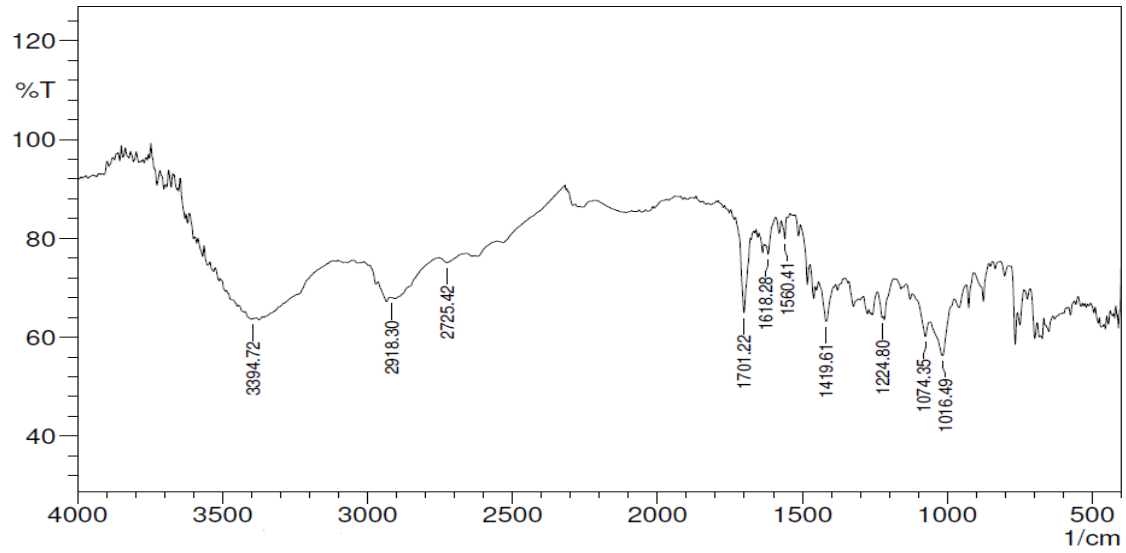

Fig. 4: IR spectra of physical mixture core FDT PO4 and Guar gum

IV. Conclusion

Flurbiprofen pulsatile capsule device were developed using natural sources like isolated natural superdisintegrant *Plantago Ovata* (PO) in the core tablet FDT PO4 and natural plugging materials like guar gum, *Plantago Ovata husk* and chitosan in the pulsatile capsule device. The pulsatile capsules showed acceptable physical characteristics. The capsules were capable enough to control the release of drug in stomach and release the drug in intestine. All plugging materials provided good lag time. Based on lag time and in-vitro release study optimized formulation GG2 showed 315 min of lag time and 98.87% of % CDR in 6 hrs and 45 min. The mechanism of drug release of pulsatile capsules was zero order kinetics. IR studies revealed the absence of drug excipient interactions. It could be concluded that natural excipients can be used in developing pulsatile systems which are cheaper and safe. Further the developed Flurbiprofen pulsatile capsule can be used for Rheumatoid arthritis after pharmacokinetic assessment.

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References

[1]. JAL. Harkness, MB. Richter, GS. Panayi, KV. Pette, A. Unger, R. Pownall and Geddawi, Circadian variation in disease activity in rheumatoid arthritis, *British Medical Journal, 284*, 1982, 551-54.
[2]. www.rheumatology-india.com/rheumatoid-arthritis.html[cited 2017 March 10]
[3]. www.myoclinic.org/diseases-conditions/rheumatoid-arthritis/basic/defination/con-20014868[cited 2017 March 12]
[4]. AP. Pawar, SS. Badve, P. Sher, and A. Korde. Development of hollow/porous calcium pectinate beads for floating – pulsatile drug delivery, *European Journal of Pharmaceutics and Biopharmaceutics, 65*, 2007, 85-93.
[5]. Md. Sarfaraz, S. Surendra Kumar, K. Kalpana, and H. Doddayya, Formulation and evaluation of flurbiprofen fast disintegrating tablets using natural superdisintegrants, *Asian Journal of Pharmaceutical and Clinical Research, 9(6)*, 2016, 1-8.
[6]. VS. Mastiholimath, PM. Dandagi, SJ. Samata, AP. Gadad, and AR. Kulkarni. Time and PH dependent colon specific, pulsatile delivery of theophylline for nocturnal asthma, *International Journal of Pharmaceutics 328*, 2007, 49-56.
[7]. SM. Rajashree, G. Aloknath, and K. Danish. Development and characterization of diltiazem hydrochloride pulsatile drug delivery system for chronomodulated therapy, *Asian Journal of Pharmaceutical and Clinical Research, 4(2)*, 2011, 168-173.
[8]. G. Sharma, and M. Srikanth. Application of modified pulsincap technique for oral controlled drug delivery of Gliclazide, International *Journal of Pharmacy and Pharmaceutical Sciences, 4*, 2012, 618-624.
[9]. D. Patel, and R. Jani. Design and Evaluation of colon targeted modified pulsincap delivery of 5-Fluorouracil according to circadian rhythm, *International Journal of Pharmaceutical Investigation, 1*, 2011, 172-181.
[10]. M. Gohel, and S. Manhapra. Modulation of active pharmaceutical material release from a novel 'tablet in capsule system' containing an effervescent blend, Journal *of Controlled Release, 79*, 2002, 157–164.
[11]. Lachman L, Leiberman H and Kanig J, *The Theory and practice of Industrial Pharmacy* (Bombay: Varghese publishing house, 1987; 395).
[12]. I. Krogel, and R. Bodmeier. Floating or pulsatile drug delivery systems based on coated effervescent cores, *International Journal of Pharmaceutics, 187*, 1999, 175-184.
[13]. Minister of Health & Family Welfare. Indian Pharmacopoeia. New Delhi: The Controller of Publications; 2007; 2: 634.
[14]. T. Bussemer, NA. Peppas, and R. Bodmeier. Evaluation of the swelling, hydration and rupturing properties of the swelling layer of a rupturable pulsatile drug delivery system, *European Journal of Pharmaceutics and Biopharmaceutics, 56*, 2003, 261-270.

[15]. L. Ying-Huan, and J.Zhu, Modulation of combined-release behaviors from a novel tablets-in-capsule system, *Journal of Controlled Release*, *95*, 2004, 381– 389.
[16]. I. Rogel, and R. Bodmeiera, Pulsatile drug release from an Insoluble Capsule Body Controlled by an Erodible Plug, *Pharmaceutical Research*, *15*, 1998, 3.
[17]. P. Costa and JMS. Lobo, Divisability of diltiazem matrix sustained release tablets, *Pharmaceutical Development and Technology*, *6(3)*, 2001, 343-51.
[18]. MS. Reza, MA. Quadir, and SS. Haider, Comparative evaluation of plastics, hydrophilic polymers as matrices for controlled-release drug delivery, *Journal of Pharmacy and Pharmaceutical Sciences*, *6(2)*, 2003, 282-91.
[19]. J. Akbari, A. Nokhodehi, D. Farid, M. Adragul, MRS. Shadbad, and M. Sacedi, Development and evaluation of buccoadhesive propranolol hydrochloride tablet formulations: effect of fillers, *IL Farmaco*, *55*, 2004, 155-61.

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