Development and Characterization of Press Coated Tablet of Flurbiprofen: A Chronotherapeutic Approach

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Abstract

Aim: The main objective of the present investigation was to formulate and characterize an oral pulsatile drug delivery system of flurbiprofen, for time dependent release, based on chronomodulated approach for the management of rheumatoid arthritis. **Settings and Design:** The drug delivery system was designed to deliver the drug with a lag time to release the drug when it could be most needful to patients of rheumatoid arthritis. **Materials and Methods:** Rapid release core tablets of flurbiprofen were prepared by wet granulation method with explotab as superdisintegrant. Then the press coated pulsatile tablets were formulated using different grades of hydroxypropyl methylcellulose (HPMC) E5, E15, and E50 in varying ratios. Pulsatile tablets were evaluated for pre- and post-compressional parameters. Then the tablets were optimized based on *in vitro* dissolution studies and lag time for drug release. **Statistical Analysis used:** One sample *t*-test was computed to compare the mean lag time obtained with different formulations with a standard of 6 h (360 min) as required time lag between administration of the dosage and drug release. **Results:** Core tablet formulated with explotab 4% showed 76.18 ± 0.27% release in 10 min it was suitable for formulating into pulsatile release tablets. The formulation containing HPMC E50 at 1:2 ratio of core to coat has shown lag time of 6 h; thus, it was optimized and compiled with chronotherapeutic objective of rheumatoid arthritis. **Conclusions:** Pulsatile tablets of flurbiprofen were successfully formulated which provided a desirable lag time followed by desirable drug release.

Key words: Chronotherapeutics, flurbiprofen, press-coated tablet, rheumatoid arthritis

INTRODUCTION

To achieve the chronotherapeutic drug delivery, development of pulsatile tablets is one of the promising time specific systems that release the drug after a predetermined lag time.[1] The lag time of developed tablets depends on the nature of therapeutic application and type of polymer and core to coat ratio of tablets.[2] Pulsatile drug delivery is required especially for the treatment of some chronomodulated diseases, such as bronchial asthma, hypertension, angina pectoris, and rheumatoid arthritis with mainly night or early morning symptoms.[3] Compression coating methodology is free of solvents which is safe, inexpensive that does not require special coating equipment and the coating formed through compression offers higher stability as compared with film coating.[4] There is a circadian rhythm in the plasma concentration of C-reactive protein and interleukin-6 of patients with rheumatoid arthritis.[5] Rheumatoid arthritis, the level of C-reactive protein increases early morning leading to enhanced pain and inflammation. Chronotherapy for all forms of arthritis using non-steroidal anti-inflammatory drugs (NSAIDs) should be timed to ensure that the highest blood levels of the drug coincide with peak pain. In the present study, chronomodulated system of flurbiprofen a NSAID is selected for treatment of rheumatoid arthritis. Rheumatoid arthritis requires time-dependent drug release for maximum therapeutic benefit.[6] By considering these factors, press

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coated tablets are developed to achieve the time-dependent release with a distinct predetermined lag time.

MATERIALS AND METHODS

Materials

Flurbiprofen, Explotab, Methocel LV Premium (HPMC E5, E15, and E50) were gift samples from hetero drugs, Hyderabad, India. All other chemicals used were of analytical grade procured from S.D. Fine Chemicals.

Methods

Flowability studies

A quantity of 2 g of blend from each formulation, filled into a 10 ml of measuring cylinder. Initial bulk volume was measured, and cylinder was allowed to tap from the height of 2.5 cm. The tapped frequency was 25 ± 2/min to measure the tapped volume of the blend. The bulk density (BD) and tapped density (TD) were calculated using the bulk volume and tapped volume. The compressibility index (Carr's index) (%) and the Hausner ratio were calculated as follows:[7]

$$\text{Carr's index } (\%) = \frac{TD - BD}{TD} \times 100$$

$$\text{Hausner ratio} = \frac{TD}{BD}$$

Preparation of rapid release core tablets (RRT) by wet granulation method

Accurately measured quantities of drug, polyvinyl pyrollidine, and half the amount of excipients without glidant and antiadherant were taken. Isopropyl alcohol was used as a granulating agent, added until wet mass was formed and passed through 40 sieves to get the required granules; granules formed were dried in oven till the moisture content was below 1%. Further, to the dried granules remaining amount of excipients were added and taken into polybag and blended properly for 15 min. Finally, glidant and antiadherant was added to the granule mix and blended for 5 min.[8] The final blend was compressed using 9 mm flat punches on 16 station tablet punching machine (Cadmach, Ahmedabad, India). Three types of core tablets [Table 1] were prepared containing different ratio of super disintegrant.

Preparation of pulsatile release tablets (PRT)

Best RRT was used for the preparation of pulsatile release tablets, and compression coating of it was done using different grades of Methocel LV Primium (HPMC E5, E15, and E50) at different concentrations [Table 2]. Press coated tablet was prepared by placing 50% of polymer blend in 12 mm die

Table 1: Formulations of flurbiprofen RRT prepared by wet granulation method

Ingredients	RRT1	RRT2	RRT3
Intragranular			
Drug	100	100	100
Explotab	4	6	8
Avicel pH 101	44	42	40
Extragranular			
Explotab	4	6	8
Avicel pH 101	44	42	40
Magnesium stearate	2	2	2
Talc	2	2	2
Total weight (mg)	200	200	200

RRT: Rapid release tablet

and core tablet was placed on it. Further, remaining quantity of polymer blend was added finally then compressed on 16 station tablet punching machine (Cadmach, Ahmedabad, India).

Physical characterization of tablets

The prepared tablets were characterized for various physical parameters such as weight variation, hardness, friability, and drug content uniformity.

Drug content of core and pulsatile tablets

Tablets were finely powdered and quantity of the powder equivalent to 10 mg of flurbiprofen was accurately weighed and transferred to volumetric flask containing 100 ml phosphate buffer (pH 6.8) and mixed thoroughly for 1 h on a rotary shaker and the solution was filtered by passing through 0.45 µm filter and the filtrate obtained was diluted suitably and estimated for flurbiprofen content at 248 nm using double beam ultraviolet (UV) spectrophotometer (Shimadzu Corporation, Japan, UV-1700).

Lag time

The lag time was determined by visual observation of the pulsatile tablet in USP Type II paddle apparatus, medium: pH 1.2 buffer 0.1 N HCl for 2 h followed by phosphate buffer, pH 6.8, maintained at $37°C \pm 0.5°C$, with 50 rpm until the outer press coat was ruptured and removed. Lag time was recorded as the time point when outer coat of pulsatile tablet is ruptured and removed ($n = 3$).[9]

Swelling index and water uptake studies

The swelling index of prepared pulsatile tablets was determined in USP Type I dissolution apparatus employing pH 1.2 buffer 0.1 N HCl for 2 h followed by phosphate buffer,

Formulations	PRT1	PRT2	PRT3	PRT4	PRT5	PRT6	PRT7	PRT8	PRT9
Core tablet (mg)	200	200	200	200	200	200	200	200	200
Methocel LV premium E5 (mg)	200			400			600		
Methocel LV premium E15 (mg)		200			400			600	
Methocel LV premium E50 (mg)			200			400			600
Magnesium stearate (mg)	2	2	2	4	4	4	6	6	6
Talc (mg)	2	2	2	4	4	4	6	6	6

Table 2: Formulations of flurbiprofen pulsatile release tablet prepared by direct compression method

PRT: Pulsatile release tablets

pH 6.8, for 8 h maintained at 37°C ± 0.5°C, with 50 rpm. The initial dry weight was recorded and denoted as Wi, the above tablets were placed in the above-mentioned apparatus and removed at every 1 h, the wet swelled tablet was blotted on filter paper to remove excess water, and wet weight was recorded as Wt.[10-12] Swelling index was calculated using the following formula:[13]

Swelling index (%)=Wt–Wi/Wi×100

Water uptake of the pulsatile tablets was further determined by considering the wet blotted weight of tablet at each stage as Wf then followed by subsequent wet weight of the tablet as Wt. water uptake was calculated using the following formula.[13]

Water uptake (%)=Wt-Wf/Wf×100

The swelling indices of the pulsatile tablets formulated using different polymer grades utilized at same concentrations and increased amounts used were compared.

In vitro dissolution studies of core tablets

In vitro drug release studies of core tablets (RRT) were conducted using USP Type II dissolution apparatus at 50 rpm speed and 37°C ± 0.5°C temperatures in 900 ml phosphate buffer pH 7.4 as dissolution media for 1 h. The Q limit of flurbiprofen was considered in the selection of optimized core formulation. The optimized formulation was further evaluated for drug release study in pH 6.8 phosphate buffer as per previous reports.[2,13]

In vitro dissolution studies of pulsatile release tablets

In vitro drug release studies of press-coated tablets were conducted using USP type II dissolution apparatus at 50 rpm speed and 37°C ± 0.5°C temperature in 900 ml dissolution media (pH 1.2 buffer 0.1 N HCl for first 2 h and then in phosphate buffer pH 6.8 from 3 to 12 h). An aliquot of 5 ml was withdrawn at specific predetermined time intervals and replaced with the same volume of dissolution medium maintained at the same temperature. The withdrawn samples

were filtered by passing through 0.45 μm filter and the filtrate obtained was diluted suitably and estimated for flurbiprofen content at 248 nm using double beam UV spectrophotometer (Shimadzu Corporation, Japan, UV-1700).

Statistical analysis

The statistical treatment of the obtained data was calculated by one-sample *t*-test. The one-sample *t*-test is used to determine whether a sample comes from a population with a specific mean in this the mean lag time of all the developed formulations were compared with standard of 6 h (360 min) as required lag time using SPSS statistical software Version 6.0.

Stability studies

The stability of flurbiprofen in developed optimized formulation was assessed at ambient temperature by placing the tablets at room temperature in a desicator for three months. The physical appearance, physicochemical properties of tablets and drug release studies were conducted at the end of three months to understand the stability of products.[7]

Fourier transform infrared (FTIR) studies

The FTIR spectra of Flurbiprofen, RRT1, PRT6, and PRT8 formulations were recorded between 400 and 4000/cm with FTIR spectrometer (Shimadzu, Model 84005, Japan) to detect the drug-excipients interactions. The FTIR spectra for the test samples were obtained using KBr disk method; the resultant spectra were compared for any possible changes in the peaks of the spectra.[14]

Differential scanning calorimetry (DSC)

The DSC thermograms were recorded for pure flurbiprofen, RRT1, and PRT6, corresponding physical mixture using a DSC (Perkin-Elmer, Shelton, CT). Approximately, 2-5 mg of each sample was heated in an open aluminum pan from 0 to 350°C at a scanning rate of 10°C/min under stream of nitrogen.

RESULTS AND DISCUSSIONS

Precompression parameters of RRT powder blend

The precompression parameters such as BD, TD, Carr's index, and Hausner's ratio of RRT formulation powder blend showed poor flow. To improve the flow characteristics, the wet granulation method was adopted and obtained granular powder blend evaluated for precompressional parameters showed improved flow characteristics [Table 3].

Evaluation of tablets

All the core and compressed coated tablets of different batches compiled with the official requirements of uniformity of weight as their weights were varied within the limits [Table 4]. The hardness of the tablets ranged from 6.4 to 6.8 kg/cm² and the friability values were <0.5% indicating that the tablets were compact and hard. The thickness of the tablets ranged from 3.1 to 5.19 mm. All the formulations showed 97.4-99.75% of flurbiprofen content indicating the suitability of formulation of tablets. The disintegration time of optimized core tablet was found to be 55 ± 5.32 s.

Swelling and water uptake studies

The swelling behavior of optimized formulations containing HPMC E50 was compared with other formulations containing HPMC E5 and HPMC E15. The obtained results showed that the swelling front erodes faster in HPMC E5 and the swelling front erosion was comparably slower in tablets with HPMC E15 and E50 due to their marked viscosity properties [Figure 1]. In swelling index study, an increase in thickness of rubbery layer of pulsatile tablets with HPMC E50 was higher as compared with HPMC E5 and HPMC E15. This result may be attributed to complete penetration and retention of solvent in the matrix because of high viscosity of the HPMC E50. A direct correlation between swelling and lag time was observed and found that the formulation having maximum swelling indices showed higher lag time.[10] Similarly, a formulation having higher water uptake showed higher lag time [Figure 1].

Table 3: Precompression characterization of flurbiprofen RRTs

Formulations	BD (g/cc)	TD (g/cc)	Hausner ratio	Percent compressibility index
Powder blend				
RRT1	0.272	0.499	1.74	40
RRT2	0.312	0.498	1.75	41.5
RRT3	0.311	0.521	1.74	40.2
Granular blend				
RRT1	0.343	0.401	1.18	16.7
RRT2	0.320	0.401	1.23	19.2
RRT3	0.33	0.409	1.24	19.9

RRT: Rapid release tablet, BD: Bulk density, TD: Tapped density

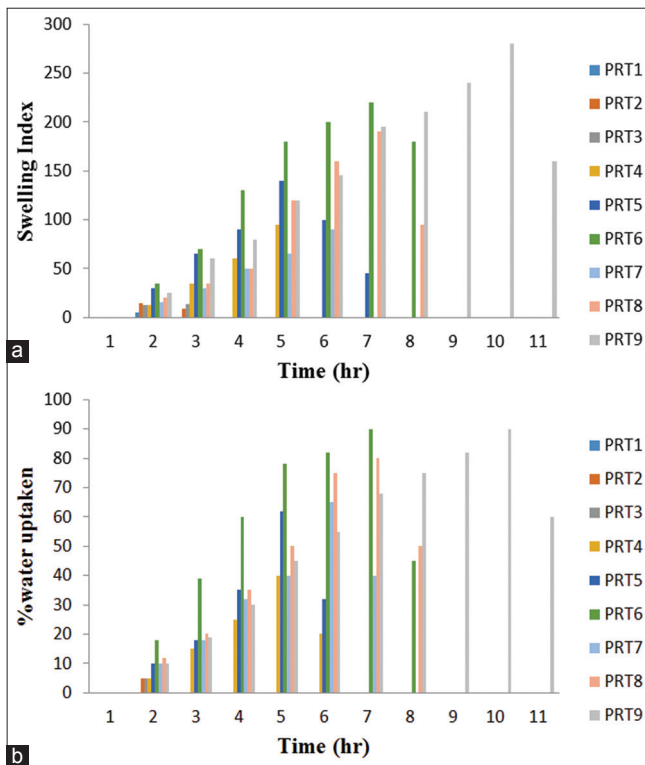**Table 4:** Physical evaluation tests of flurbiprofen core and pulsatile release tablets

Formulations	Weight variation (mg)	Hardness (kg/cm²)	Friability (%)	Thickness (mm)	Drug content (%)	Disintegration time (s)	Lag time (h)
RRT1	198.27±3.67	3.4±0.93	0.38±0.45	3.52±0.21	99.75±0.53	55±5.32	
RRT2	202.31±3.23	3.2±0.52	0.35±0.73	3.48±0.45	99.46±0.82	53±2.39	
RRT3	201.25±4.77	3.2±0.36	0.43±0.32	3.49±0.43	98.26±1.61	50±3.44	
PRT1	401±0.36	6.4±0.66	0.38±0.54	3.14±0.21	99.48±1.49		0.35±0.13
PRT2	403±0.83	6.6±0.29	0.42±0.55	3.12±0.84	98.87±2.13		0.39±0.15
PRT3	400±0.68	6.5±0.18	0.48±0.34	3.27±1.04	99.30±1.23		1.05±0.25
PRT4	603±0.35	6.6±0.31	0.35±0.49	4.12±0.75	98.66±0.67		4.02±0.54
PRT5	607±0.32	6.5±0.56	0.44±0.62	4.17±0.86	98.10±0.55		5.27±0.35
PRT6	602±0.28	6.8±0.46	0.37±0.67	4.17±0.83	99.09±1.54		6.40±0.21
PRT7	810±0.73	6.4±0.21	0.36±0.23	5.15±0.79	99.88±0.32		5.24±0.21
PRT8	809±0.44	6.5±0.52	0.42±0.56	5.19±0.83	97.97±1.73		7.13±0.52
PRT9	809±0.59	6.4±0.13	0.39±0.82	5.14±0.29	97.46±1.45		9.33±0.07

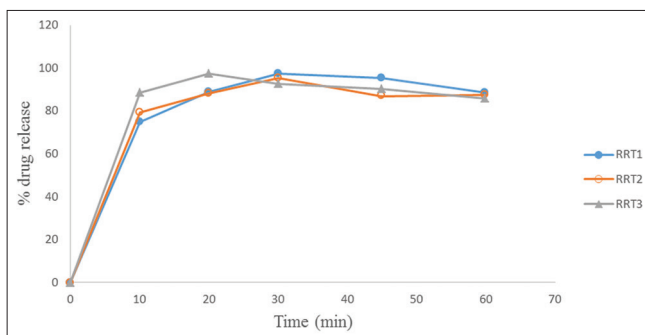PRT: Pulsatile release tablets, RRT: Rapid release tablet

In vitro drug release profile of RRTs

The drug release studies of RRT formulations conducted in pH 7.4 buffer showed complete release of drug within 30 min [Figure 2]. The drug release from RRT1, RRT2, and RRT3 at 10 min was 76.18% ± 0.27%, 79.39% ± 1.34%, and 88.4% ± 3.27%, respectively. RRT1 was considered to be optimized because it contained lower concentration of explotab when compared to RRT2, RRT3 and the drug release revealed more than the Q limit of 75% within 30 min. Further drug release studies conducted in pH 6.8 buffer, which also revealed the similar profile [Figure 3]. Based on above observations formulation, RRT1 was selected to formulate pulsatile release tablets.

Effect of pH on drug release of flurbiprofen: The influence of different pH media, i.e., pH 6.8 and pH 7.4 buffers studied showed similar drug release characteristics in both the media, this could be due to less variation (i.e. of 0.6 pH value) within the two dissolution media studied. However, when further evaluated with similarity factor (f_2) between two dissolution profiles of the RRT1 the (f_2) value of 82 was obtained which is above 50 suggesting the drug release was similar, indicating the drug release is not dependent on dissolution media pH 6.8 and pH 7.4 evaluated.

Lag time and *In vitro* drug release profile of PRTs

Based on release characteristics RRT1 core tablet was utilized in the development of press-coated tablets. The profiles relevant to the coated tablet showed that a lag phase was allowed before rapid release of the active agent. The delayed duration clearly depended on the viscosity grade and amount of hydrophilic polymer (hydroxyl propyl methyl cellulose) which was utilized on the core. In this present study, HPMC E grade polymers of viscosity E5, E15, and E50 used in different concentrations showed as polymer concentration increased in the coat layer the lag time was increased. However, among the polymers studied E50 showed more lag time this would be attributed due high viscosity of this hydrophilic polymer HPMC E50 (40-60 cps) compared to HPMC E15 (10-20 cps) and HPMC E5 (3-6 cps). All the press coated tablets showed erosion mechanism in the dissolution medium to expose the core tablets this may be due to dissolution or erosion of outer low viscosity coat on the core. This facilitated burst release of flurbiprofen in the formulations studied. The lag

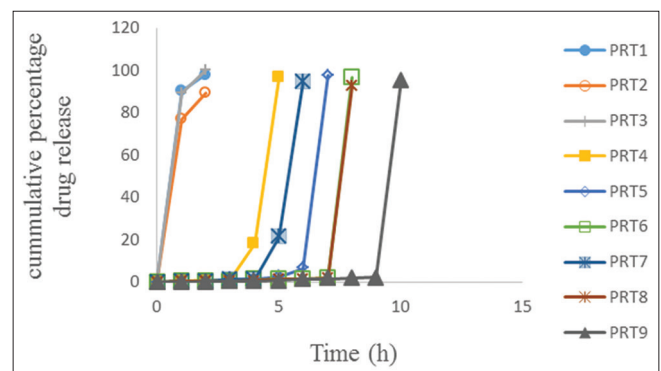**Figure 1:** (a and b) Swelling indices and water uptake studies pulsatile release formulations

Figure 2: Cummulative percentage drug release profile of flurbiprofen from rapid release tablets
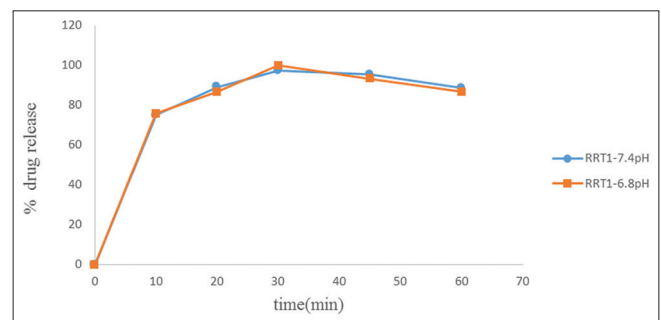
Figure 3: Cummulative percentage drug release profile of flurbiprofen from buffer media of pH 7.4 and pH 6.8

Figure 4: Cummulative percentage drug release of flurbiprofen from pulsatile release tablets's

time of the tablet coated with 400 mg of HPMC E50 (PRT6) was found to be 6 h, and 600 mg of HPMC E15 (PRT8) was found to be 7 h, respectively [Figure 4]. Among the above two formulations, PRT6 was selected for further studies. This is due to low amount of HPMC E50 compared with HPMC E15, i.e., PRT8. These above observations are in accordance with the previous reports where high viscosity HPMC K 4M showed extended release because of high viscosity the drug release would be due to diffusion mechanism.

In fact, it is reported that the hydrophilic matrices rapidly form a surface "gel" layer on exposure to aqueous media. Hydration is accompanied by a progressive plasticization of HPMC leading to swelling and, as the chains uncoil and extend, more locations become available for hydrogen bonding and further molecular entanglements.[15-17] The overall result is an increase in the thickness of the gel layer surrounding the matrix, which retards disintegration and prevents further rapid water penetration into the matrix.[18] The thickness of the gel depends on the rate of water penetration, the movement of water within the matrix, the degree of polymer swelling, the dissolution of drugs and excipients and the rate of gel removal by matrix erosion.[19,20] The outermost layer of gel becomes fully hydrated, the polymer dissolves, and this contributes to the erosion of the matrix surface. As time progresses, water continues to penetrate slowly into the core until the whole matrix has undergone hydration and it eventually erodes completely. It is reported that in contrast to erodible polymers (HPMC E grade), swellable polymers (HPMC K grade) of high viscosity have higher degree of cross-linked macromolecular networks (hydrogels) that fails to dissolve even after extensive water uptake and possess greater mechanical strength.

One-sample statistics

One sample *t*-test was computed using statistical software version 6.0 to compare the mean lag time obtained with different formulations with a standard of 6 h (360 min) as required time lag between administration of the dosage and drug release.

As observed from Table 5 PRT1, PRT2, PRT3 showed a mean lag time of 38.3 min, 36.6 min, 86.6 min, respectively which were far lower when compared to the standard of 360 min (6 h). PRT4 showed further higher mean lag time of 248.3 min when compared to the earlier formulations, however, was insufficient as compared to the standard lag time.

PRT5, PRT6, and PRT7 showed values nearby to the estimated standard lag time with a mean lag time of 316.6 min, 380 min, and 326.6 min, respectively. However, PRT6 was the one that could resonate with the estimated standard values.

Similar comparison PRT8 and PRT9 formulations showed far higher values in the mean lag time when compared to the fixed standard with mean lag time values of 438.3 min and 551.6 min.

From Table 5, we can observe that there was statistically significant difference in the mean lag time values of all the formulations ($P < 0.05$) as compared to the set standard of 360 min, however, there was an exception in this phenomenon with mean lag time obtained with PRT6 which showed no significant difference ($P > 0.05$) from the set standard of 360 min.

Stability studies

The physicochemical parameters of the optimized formulation (PRT6) at an initial time and after 3 months were shown in Table 6. The results reveal that there was no significant change in the physicochemical parameters of the optimized formulations. Further, the dissolution profile of the formulation was observed to be similar with f_2 value of 87.

This suggests the developed PRT6 formulation was stable over the period of study. However, the stability studies as per ICH guidelines are to be conducted.

| Table 5: One sample *t*-test										
Formulation Code for Pulsatile tablets	*n*	Mean (min)	Standard deviation	Standard error mean	Test value=360					
					t	df	Sig. (two-tailed)	Mean difference	95% confidence interval of the difference	
PF1	3	38.33	10.40	6.00	−53.52	2	0.000	−321.66	−347.52	−295.81
PF2	3	36.66	7.637	4.40	−73.32	2	0.000	−323.33	−342.30	−304.36
PF3	3	86.66	20.20	11.66	−23.42	2	0.002	−273.33	−323.53	−223.13
PF4	3	248.33	7.63	4.40	−25.32	2	0.002	−111.66	−130.63	−92.69
PF5	3	316.66	11.54	6.66	−6.50	2	0.023	−43.33	−72.01	−14.64
PF6	3	380.00	17.32	10.00	2.00	2	0.184	20.00	−23.02	63.02
PF7	3	326.66	5.77	3.33	−10.00	2	0.010	−33.33	−47.67	−18.99
PF8	3	438.33	7.63	4.40	17.76	2	0.003	78.33	59.36	97.30
PF9	3	551.66	23.62	13.64	14.04	2	0.005	191.66	132.96	250.36

FTIR studies

FTIR studies were performed to understand the nature of the drug in the formulated tablets and compared in Figure 5. The FTIR spectrum of pure flurbiprofen demonstrated peaks at 1217/cm (C-F stretching), 1699.57/cm (C=O stretching), 3133.50/cm (C-H stretching), and 3726.63/cm (O-H stretching).[21] All the characteristic peaks observed for both drug and excipient remained unchanged with a decrease in intensity of peaks over a range of 4000-400/cm. FTIR spectra of different formulations show no substantial shifting of the position of the functional groups. The peaks are only broadened, indicating no major interaction between flurbiprofen and polymers used, thus showing compatibility.

Table 6: Physical evaluation of the optimized formulation (PRT6) after 3 months						
Formulations	Weight variation (mg)	Hardness (kg/cm²)	Friability (%)	Thickness (mm)	Drug content (%)	Lag time (h)
PRT6 (0 month)	602±0.2	6.8±0.46	0.37±0.67	4.17±0.8	99.09±1.54	6.40±0.21
PRT6 (3 months)	603±0.4	6.4±0.53	0.42±0.28	4.2±0.16	97.34±0.94	6.23±0.37

PRT: Pulsatile release tablets
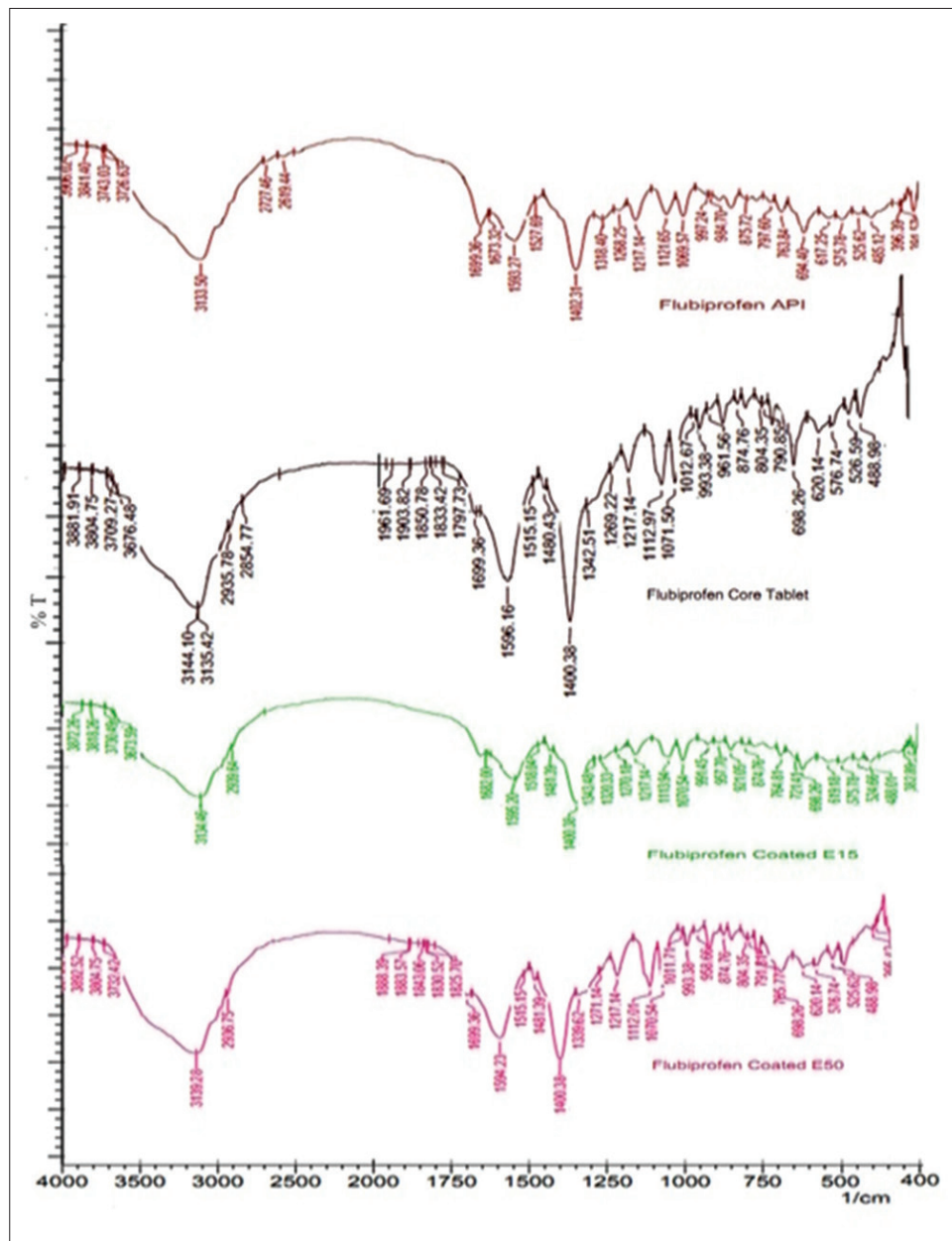
Figure 5: Fourier transform infrared spectra's of Flurbiprofen, rapid release tablet 1, PRT6 and pulsatile release tablets 8
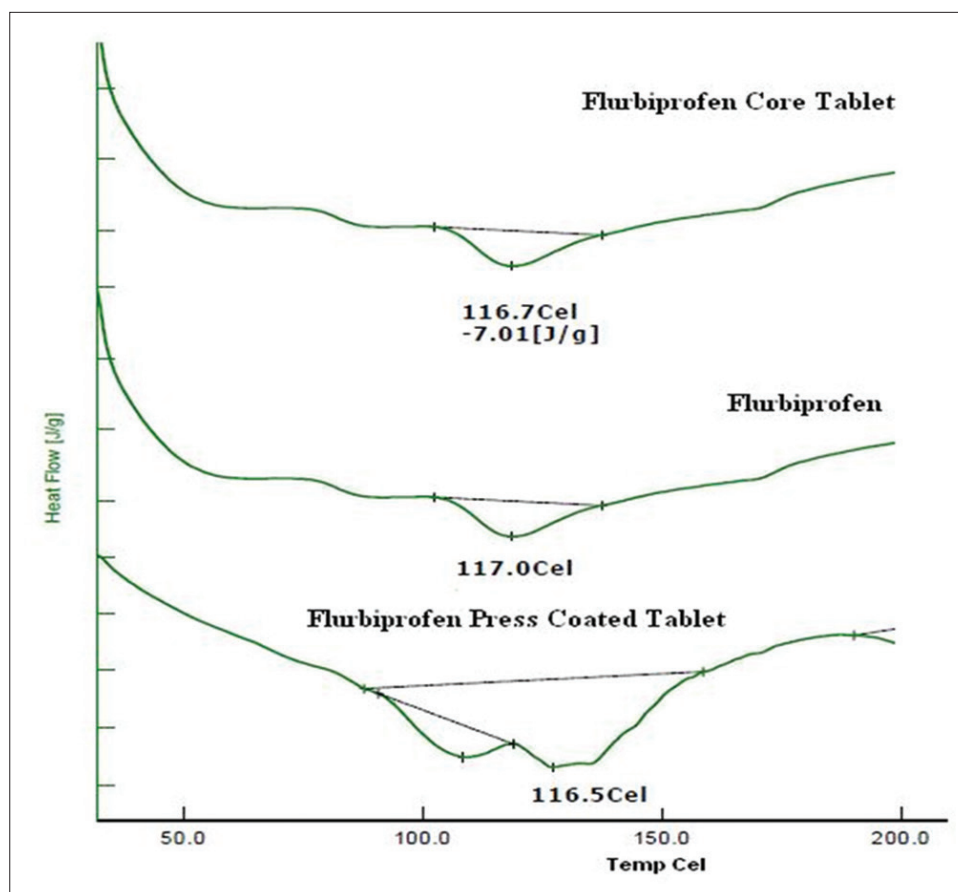
Figure 6: Differential scanning calorimetry of flurbiprofen, rapid release tablet 1 and pulsatile release tablets 6

DSC

The thermograms of the pure drug flurbiprofen, RRT1 and PRT6 are illustrated in Figure 6. DSC thermogram of flurbiprofen shows an endothermic peak at 117.0°C corresponding to the melting point of flurbiprofen. Endothermic peak corresponding to the melting point of flurbiprofen observed in the optimized formulations RRT1 and PRT6 at 116.7°C and 116.5°C, respectively. This suggests that drug was present in its crystalline form in the formulations which was further confirmed from FTIR studies.

CONCLUSION

The chronotherapeutic formulations of flurbiprofen were developed as press coated tablets using different viscosity grades of HPMC polymers. The results revealed that the formulation with HPMC E50 was optimized with concentration of 1:2 core to coat ratio.

The desired lag time of 6.4 h was achieved followed by burst release of flurbiprofen from core tablet in pH 6.8 dissolution medium. The drug excipient compatibility studies showed no evidence of interaction among the ingredients studied. Thus, the flurbiprofen pulsatile release tablets with desired lag time

and time controlled release were developed which would be a strategy for chronotherapy of arthritis.

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