International Journal of Innovative Research and Advanced Studies (IJIRAS)
Volume 4 Issue 5, May 2017

ISSN: 2394-4404

Design, Development And Evaluation Of Pulsatile Tablets Of Flurbiprofen For The Chronotherapy Of Rheumatoid Arthritis

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Abstract: ***The present work conceptualizes the pulsatile principle to develop a drug delivery system, intended for chronotherapy in rheumatoid arthritis. This approach will be achieved by the development of press-coated Flurbiprofen Pulsatile release tablets. Pulsatile delivery system is capable of delivering drug when and where it is required most. By administering the system at bedtime, but releasing drug as a burst after the lag time (during peak morning hours) thereby delivering the drug at the time when it is required most by decreasing side effects and dose size. Flurbiprofen rapid release core tablets were prepared by direct compression method using superdisintegrants such as croscaremellose sodium , crospovidone and further compression coated using hydrophilic erodible polymers such as HPMC E5, HPMC E15 and HPMC E50 which are responsible for the lag phase in the onset of pulsatile release. The prepared press-coated pulsatile tablets were evaluated for various pre-compression and post-compression parameters. Formulation code FP6 with HPMC E5 (200 mg) was selected as the best formulation with a satisfactory release pattern at 5.5 hours***

Keywords: Flurbiprofen, hydrophilic erodible polymers, direct compression, compression coating, pulsatile tablets.

I. INTRODUCTION

Due to poor drug efficacy, the incidence of side effects, and frequency of administration to conventional drug preparations, many traditional drug dosage forms are undergoing replacement by second-generation, modified drug release dosage forms. During the early 1990s, second-generation modified release drug preparations achieved continuous and constant rate drug delivery, in which constant or sustained drug output minimize drug concentration "peak and valley" levels in the blood, promoting drug efficacy and reducing adverse effects.

Recent studies also reveal that body's biological rhythm may affect normal physiological function, including gastrointestinal motility, gastric acid secretion, gastrointestinal blood flow, hepatic blood flow, urinary pH, cardiac output, drug-protein binding and liver enzymatic activity, and biological functions such as heart rate, blood pressure, body temperature, blood plasma concentration, intraocular pressure, stroke volume and platelet aggregation. Most organ functions vary with the time of the day, particularly when there are rhythmic and temporal patterns in the manifestation of a given disease state. The symptoms of many diseases such as bronchial asthma, myocardial infarction, angina pectoris, hypertension and rheumatoid arthritis have followed the body's biological rhythm. Day night variation in asthmatic dyspnoea and variations in the incidence of myocardial infarction occur throughout the early morning hours. Treating these diseases with immediate release dosage forms may be impractical if the symptoms of the disease are pronounced during the night or early morning.

A chronodelivery system, based on biological rhythms, is a state-of-the-art technology for drug delivery; chronomodulated DDSs not only increase safety and efficacy

levels, but also improve overall drug performance. The time-controlled function of third generation DDSs currently under development is finding application in new and improved disease therapeutics. Biological rhythms may be applied to pharmacotherapy by adopting a dosage form that synchronizes drug concentrations to rhythms in disease activity.

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.[11] Pulsatile drug delivery systems can be classified into site-specific systems in which the drug is released at the desired site within the intestinal tract (e.g., the colon) or time-controlled devices in which the drug is released after a well-defined time period. A pulsatile release profile is characterized by a lag time followed by rapid and complete drug release. Most pulsatile systems are reservoir systems and usually covered with a barrier. This barrier can be dissolved, eroded or removed at a predetermined period of time after which the drug is dissolved and rapidly released.

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. A pulsatile drug delivery system that can be administered at night (bed time) but that release drug in early morning would be a promising chronopharmaceutic system.

In the present study an attempt was made to develop chronotherapeutic drug delivery system of Flurbiprofen using various polymers with a predetermined lag time by compression coating technique. The compression coated tablets could be used to provide maximum drug plasma concentration after a desired lag time with a bed-time oral administration.

Flurbiprofen (2RS)-2-(2-Fluorobiphenyl-4-yl) propanoic acid, is an important analgesic and a non-steroidal anti-inflammatory drug (NSAID) also with anti-pyretic properties whose mechanism of action is the inhibition of prostaglandin synthesis. It is chosen as the model drug, as its physico-chemical properties and short half-life make it a suitable candidate for chronotherapeutic drug delivery system.

II. MATERIALS AND METHODS

MATERIALS

Flurbiprofen, HPMC E5, HPMC E15 and HPMC E50 were obtained as gift samples from Orchid chemicals, Chennai. Croscarmellose sodium, crospovidone, were obtained as gift samples from Kniss Laboratories, Chennai. Microcrystalline cellulose was obtained as gift from Pharma French Ltd. All other reagents used were of analytical reagent grade.

METHODS

CALIBRATION CURVE OF FLURBIPROFEN

100 mg of Flurbiprofen was dissolved in a small amount of ethanol and made up to 100 ml with 0.1N Hydrochloric Acid. 10 ml of the solution was pipetted out into a standard flask and made up to 100 ml using 0.1N Hydrochloric Acid. 2 ml, 4 ml, 6 ml, 8 ml and 10 ml of the solution were pipetted into separate standard flasks and made up to 100 ml using 0.1N Hydrochloric Acid. The absorbance of the resulting solutions was measured at 247 nm using UV Spectrophotometer. Calibration curve was plotted using Concentration in x-axis and Absorbance in y-axis. The same procedure is repeated using phosphate buffer pH 6.0.

FTIR STUDIES

The IR spectra of pure Flurbiprofen, HPMC E5, HPMC E15 and HPMC E50 along with physical mixture of polymers and drug were taken separately to check drug-polymer interaction by KBr disc method. A small amount of drug was mixed with the spectroscopic grade of KBr and triturated for uniform mixing. The prepared mixture was placed in the sample cell and was exposed to the IR beam. The spectra were recorded in the range of 400-4000cm^{-1} by using FTIR spectrophotometer (FTIR Shimadzu, Japan).

PREPARATION OF FLURBIPROFEN CORE TABLETS

The inner core tablets of Flurbiprofen were prepared by compression. Different concentrations of various superdisintegrant such as croscarmellose sodium and crospovidone were used. The powder mixtures of Flurbiprofen, superdisintegrant, microcrystalline cellulose, lactose were dry blended, followed by addition of magnesium stearate. The mixtures were further blended. The blend was compressed using 10 station tablet compression machine.

PREPARATION OF FLURBIPROFEN PULSATILE RELEASE TABLET

Pulsatile release tablets were prepared by press-coating method using, HPMC E50, HPMC E15, HPMC E5 (polymers). One half of the coating powder was placed in the 9mm die cavity, then the tablet core was centrally placed on the powder bed, the remaining half of the coating powder was filled on top of the tablet and compressed.

S.No.	Ingredients	F1	F2	F3	F4	F5	F6
1.	Flurbiprofen	100	100	100	100	100	100
2.	Croscarmellose Sodium	2	4	6	-	-	-
3.	Crospovidone	-	-	-	2	4	6
4.	Microcrystalline cellulose	25	25	25	25	25	25
5.	Lactose	20	18	16	20	18	16
6.	Magnesium stearate	3	3	3	3	3	3

Average weight of each tablet = 150mg

Table 1: Formulation of rapid release core tablets

S. No	Ingredients	FP1	FP2	FP3	FP4	FP5	FP6
1.	Optimized core tablet	150	150	150	150	150	150

2.	Guar gum	-	-	-	-	-	-
3.	HPMC E50	150	-	-	120	-	-
4.	HPMC E15	-	175	-	-	200	-
5.	HPMC E5	-	-	175	-	-	200
6.	Lactose	123	98	98	153	73	73
7.	Magnesium stearate	4.5	4.5	4.5	4.5	4.5	4.5
8.	Talc	22.5	22.5	22.5	22.5	22.5	22.5

Average weight of each tablet = 450mg

Table 2: Formulation of Pulsatile release tablets

PRE COMPRESSION STUDIES

a. BULK DENSITY (ρ_b)

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder into a measuring cylinder and it was slightly shaken to break any agglomerates formed. The volume occupied by the powder was measured which gave bulk volume.

Bulk density of the powder was calculated using the formula mentioned below. It is expressed in g/ml.

$\rho_b = M/V_b$

Where, M and V_b are mass of powder and bulk volume of the powder respectively.

b. TAPPED DENSITY (ρ_t)

It is the ratio of weight of the powder to the tapped volume of powder. An accurately weighed powder was introduced into a measuring cylinder with the aid of a funnel. The measuring cylinder was tapped untilno further change in volume was noted which gavethe tapped volume.

Tapped density of the powder was calculated using the formula mentioned below. It is expressed in g/ml.

$\rho_t = M/V_t$

Where, M and V_t are mass of powder and tapped volume of the powder respectively.

c. ANGLE OF REPOSE (θ)

It is defined as the maximum angle possible between the surface of a pile of powder and the horizontal plane. It was determined by the funnel method. The powder mixture was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the formula,

Angle of Repose(θ) = $\tan^{-1}$ (h/r)

Where, h = Height of the pile of powder (in cm)

r = Radius of pile of powder (in cm)

d. COMPRESSIBILITY INDEX (CARR'S INDEX)

Compressibility index is the measure of flow property of a powder. It is measured for determining the relative importance of interparticulate interactions. It is expressed in percentage and calculated by the formula,

$$\text{CompressibilityIndex} = \frac{TD - BD \times 100}{TD}$$

Where, TD is the tapped density and BD is the bulk density

e. HAUSNER'S RATIO

Hausner's ratio is an indirect index of ease of powder flow. Hausner's ratio is the measure of propensity to be compressed and also Interparticulate interactions / Interparticulate friction. It was calculated by the following formula,

$HR = \rho_t / \rho_b$

Where, ρ_t and ρ_b are tapped density and bulk density respectively

POST COMPRESSION STUDIES

a. GENERAL APPEARANCE

The general appearance of the tablets from each formulation batch was observed. The general appearance parameters, shape and colour were evaluated visually.

b. UNIFORMITY OF WEIGHT

Twenty tablets were randomly selected and weighed individually on an electronic weighing balance. The average weight was calculated. The individual weight of tablets is compared with the average weight.

c. THICKNESS AND DIAMETER

The thickness and diameter was measured to determine the uniformity of size and shape. Thickness and diameter of the tablets were measured using Vernier caliper.

d. HARDNESS

Hardness is defined as the force required for breaking a tablet at diametric compression test and it is termed as "Tablet Crushing strength". Hardness of the prepared formulations was determined using Monsanto Hardness Tester. It is expressed in kg/cm^2.

e. FRIABILITY

Friability of the prepared formulations was determined using Rochelle Friabilator. Pre-weighed sample of Tablets was placed in the Friability tester, which was then operated for 100 revolutions, Tablets were de-dusted and re-weighed. The Friability of the Tablets was calculated using the formula,

$$\% \text{ Friability} = \frac{(\text{Initial weight of the tablets} - \text{Final weight of the tablet}) \times 100}{\text{Initial weight of the tablets}}$$

f. DISINTEGRATION TEST FOR FLURBIPROFEN CORE TABLETS

Tablet disintegration was carried out by placing one tablet in each tube of the basket and operated in phosphate buffer pH 6.0 maintained at 37 °C as the medium. The assembly was raised and lowered for 30 cycles per minute. The time taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded.

g. DRUG CONTENT

Twenty tablets were selected randomly, weighed and finely ground. An accurately weighed quantity of powder equivalent to 100mg of Flurbiprofen was transferred to a 100 ml standard flask and dissolved in 60 ml of 0.1M sodium hydroxide and shaken for 5 minutes and the volume was made up to the mark with 0.1M sodium hydroxide. The solution was filtered and 10ml portion of the filtrate was diluted with 0.1M sodium hydroxide in a 100ml standard flask. Further, 10ml portion was diluted to 100ml with 0.1M sodium hydroxide. The absorbance of the resulting solution was measured at 247nm taking 0.1M sodium hydroxide as blank using UV-Visible Spectrophotometer.The drug content was calculated by taking 802 as (A 1%, 1cm).

IN-VITRO DISSOLUTION STUDIES FOR PRT

The release of Flurbiprofen pulsatile tablet was determined using USP Type II (Paddle type) apparatus. The dissolution test was performed using continuous buffer medium (0.1N Hydrochloric acid, pH 1.2 for 2 h followed by phosphate buffer pH 6.0), at 37°C ± 0.5°C. The paddle was rotated at the speed of 50 rpm. A sample (10ml) of the solution was withdrawn from the dissolution apparatus at specific time intervals for 12 hrs. Samples were replaced with fresh dissolution medium. The samples were diluted to a suitable concentration. The absorbance of these solutions was measured at 247 nm using a UV Spectrophotometer.

LAG TIME

Lag time was considered as the time when the tablet burst and core tablet is out of press coating. This is considered as predetermined off-release period.

IN VITRO DRUG RELEASE KINETICS

To illustrate the drug-release mechanism from the prepared compression-coated tablets, the data obtained from the *in vitro* dissolution study was integrated to zero-order, first-order, Higuchi and korsmeyer-peppas models.

III. RESULTS AND DISCUSSION

STANDARD CURVE OF FLURBIPROFEN

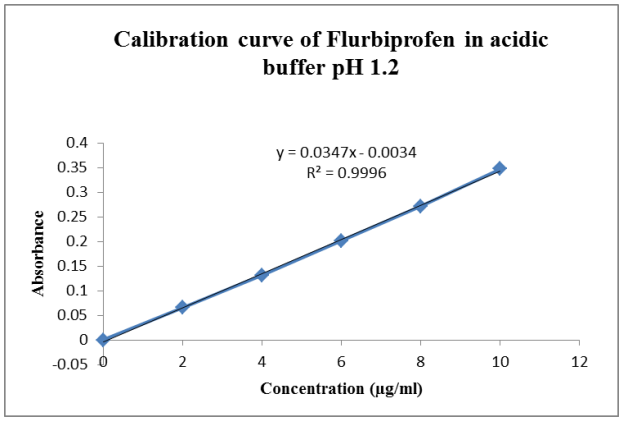

Figure 1: Standard curve of Flurbiprofen in pH 1.2

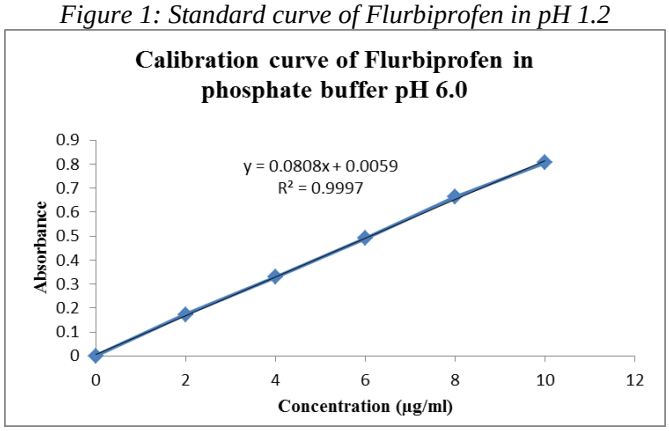

Figure 2: Standard curve of Flurbiprofen in pH 6.0

It was found that the solutions of Flurbiprofen in 0.1N Hydrochloric acid (pH 1.2) and phosphate buffer pH 6.0 showed linearity (R^2 = 0.9996) in absorbance at concentrations of 2 to 10 µg/ml and obey Beer Lambert's Law.

FTIR STUDIES

FTIR was performed for the pure Flurbiprofen, physical mixture of pure drug + HPMC E5,physical mixture of pure drug + HPMC E15, physical mixture of pure drug + HPMC E50 to detect any sign of interaction which would be reflected by a change in the position or disappearance of any characteristic peaks of the compound. The IR spectra are shown in the figures below.

From the infrared spectral analysis, the characteristic absorption peaks of Flurbiprofen were found in physical mixture of drug and polymers. This indicates that there is no interaction between drug and polymers.

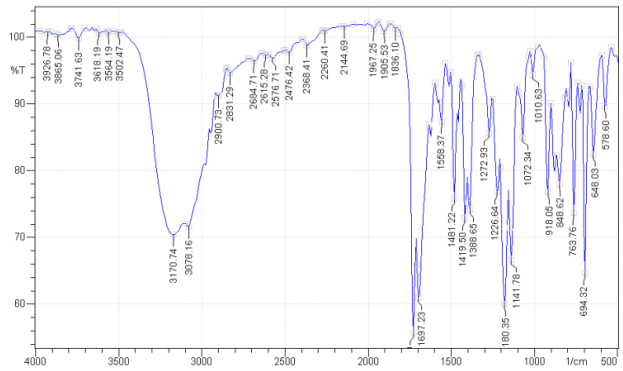

Figure 3: FTIR of Flurbiprofen

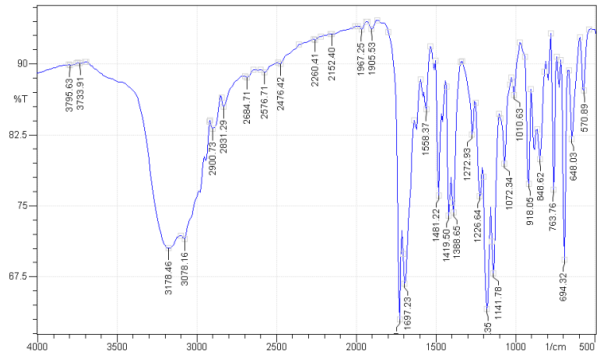

Figure 4: FTIR of Flurbiprofen with HPMC E5

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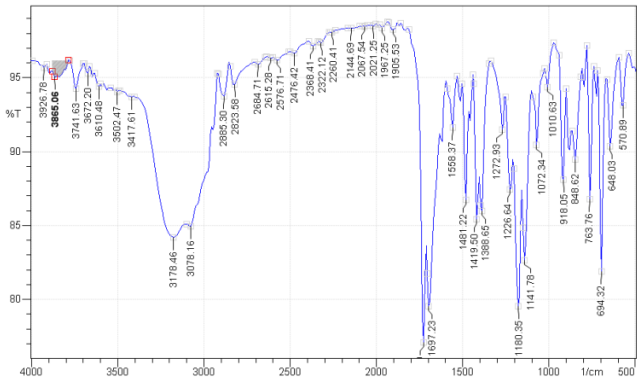

Figure 5: FTIR of Flurbiprofen with HPMC E15

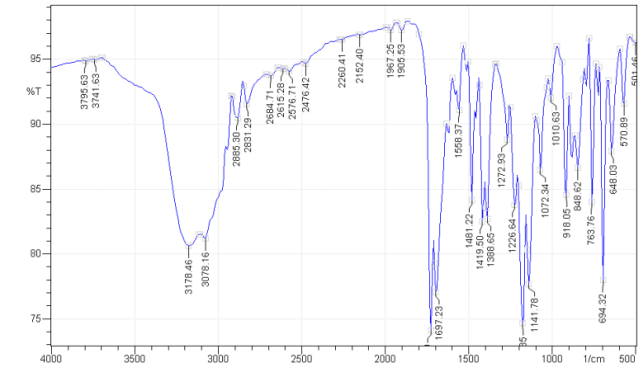

Figure 6: FTIR of Flurbiprofen with HPMC E50

PRECOMPRESSION STUDY OF FLURBIPROFEN CORE BLEND

The formulated blends were evaluated for precompression parameters. The results are given in the table 3.

Drug Formulation	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Compressibility index(%)	Hausner's ratio	Angle of repose*
F1	0.421	0.4677	9.98	1.11	27º38´±1.22
F2	0.4228	0.4933	14.2	1.16	27º09´±1.34
F3	0.4285	0.5041	14.9	1.17	27º54´±0.93
F4	0.4166	0.4861	14.2	1.16	27º39´±0.83
F5	0.444	0.5223	14.9	1.17	27º28´±0.99
F6	0.4214	0.4916	14.3	1.16	28º03´±0.68

**Mean ±S.D (n=3)*

Table 3: Precompression study of formulated blends

The bulk density of Flurbiprofen blends ranged from 0.4166 to 0.444g/cm^3 and tapped density ranged from 0.4677 to 0.5223 g/cm^3. The compressibility index of the Flurbiprofen powder blend ranged from 9.98 to 14.9% and Hausner's ratio ranged from 1.17 to 1.11. F1, showed an excellent flow, F2,F4,F6, showed good flow, and F3,F5, showed good flow. The angle of repose of Flurbiprofen powder blend ranged from 27º09´ to 28º03´ which showed an excellent flow property.

PRECOMPRESSION STUDY OF COATING MATERIAL

The formulated coating material blends were evaluated for Pre-compression parameters. The results are given in the table 4.

Drug Formulation	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Compressibility index (%)	Hausner's ratio	Angle of repose*
FP1	0.4226	0.486	13.04	1.15	26º21´±1.3769
FP2	0.4187	0.4815	13.04	1.15	26º21´±0.9366
FP3	0.4037	0.4614	12.51	1.14	27º39´±0.3105
FP4	0.4016	0.4590	12.50	1.14	26º27´±1.009
FP5	0.4221	0.4855	13.05	1.15	27º37´±0.9591
FP6	0.4008	0.4580	12.48	1.14	27º53´±1.068

**Mean ±S.D (n=3)*

Table 4: Precompression study of formulated blends of coating materials

The bulk density of coating material blends ranged from 0.4008 to 0.4226 g/cm^3 and tapped density ranged from 0.4580 to 0.4860 g/cm^3. The compressibility index of the coating material powder blend ranged from 12.48 to 13.05% and Hausner's ratio ranged from 1.14 –to 1.15. The angle of repose of coating material powder blend ranged from 26°21′ to 27°53′. The formulated coating material powder blend showed excellent flow property.

POST COMPRESSION STUDIES OF FLURBIPROFEN CORE TABLETS

The data obtained from post compression parameters of core tablets are shown in table 5. The hardness of the core tablets of Flurbiprofen were found to be in the range of 3.5 to 4.0 kg/cm^2. The core tablets of Flurbiprofen were found to comply with the friability test since the weight loss was found to be 0.053 to 0.28%. The average weight of Flurbiprofen core tablets were in the range of 148.1 to 150.8 mg. The tablets comply with the official standards for uniformity of weight. The thickness of the tablets was found to be 3.5±0.0 mm. the drug content of Flurbiprofen core tablets was found to be 97.24 to 101.65% w/w indicating uniformity of drug content in the formulation. The core tablets were found to disintegrate within 21 seconds.

Formulation	Thickness* (mm)	Hardness* (kg/cm^2)	Friability (%)	Average weight (mg)	Drug content (%)	Disintegration time (seconds)
F1	3.5 ± 0.0	3.9±0.48	0.053	150.7 ± 0.0028	97.44	59
F2	3.5± 0.0	4.0±0.63	0.28	148.1±0.0064	97.24	51
F3	3.5 ± 0.0	3.7±0.4	0.14	149.1±0.0052	98.10	38
F4	3.5± 0.0	3.5±0.0	0.11	150.8± 0.0057	101.65	36
F5	3.5 ± 0.0	3.6±0.2	0.12	149.9± 0.0058	99.14	23
F6	3.5± 0.0	3.8±0.4	0.14	148.3± 0.0061	98.28	21

Table 5: Data for post compression studies of Flurbiprofen core tablets

POST COMPRESSION STUDIES OF FLURBIPROFEN COMPRESSION COATED TABLETS

The tablets of all the formulations were subjected to post compression tests. The results obtained are represented in table 7. The compression coated tablets were prepared by applying maximum compression force and the hardness of the tablets were found to be in the range of 6.5 to 7.1 kg/cm^2. The friability values which were in the range of 0.03 to 0.10 % showed that the formulations will be physically stable to mechanical shocks during handling and transportation. Test for uniformity of weight was carried out for all the designed

formulations and was found to be within the pharrmacopoeial limits. The tablet thickness of all the formulations was found to be in the range of 5 mm.

Formulation	Thickness* (mm)	Hardness* (kg/cm^2)	Friability (%)	Average weight* (mg)	Drug content (%)	Lag time (hours) $t_{10\%}$
FP1	5 ± 0.0	6.9±0.3741	0.03	445.9± 0.0086	98.56	1
FP2	5 ± 0.0	6.7±0.4000	0.03	444.6 ± 0.0079	99.75	1
FP3	5 ± 0.0	7.1±0.3741	0.03	450.3± 0.0079	97.87	1
FP4	5 ± 0.0	6.5±0.3160	0.03	447.4± 0.0081	99.48	1.5
FP5	5 ± 0.0	6.9±0.2000	0.05	449.1± 0.0078	98.25	3
FP6	5 ± 0.0	7.0±0.3162	0.10	445.4± 0.0071	98.59	3

Table 6: Data for post compression studies of Flurbiprofen pulsatile tablets

IN VITRO DRUG RELEASE STUDIES

a. IN VITRO DRUG RELEASE OF CORE TABLETS

In this study formulations containing crospovidone (F3-F6) showed fast drug release than the formulation containing croscarmellose sodium. This may be because of the fact that crospovidone probably made larger pores with continuous network or skeleton providing enough pressure for faster disintegration and it also had capability to swell at least twice of its original volume when in contact with dissolution fluid. Among six formulations, it was observed that formulation F6 containing crospovidone in concentration 4% showed rapid and complete drug release. F6 was considered as optimized formulation and taken for further studies.

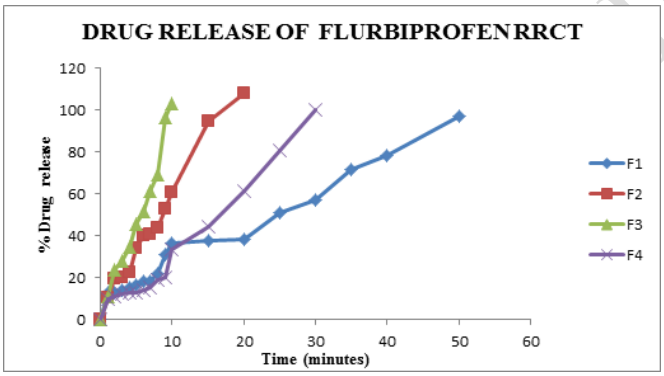

Figure 7: In vitro drug release of flurbiprofen rapid release core tablets

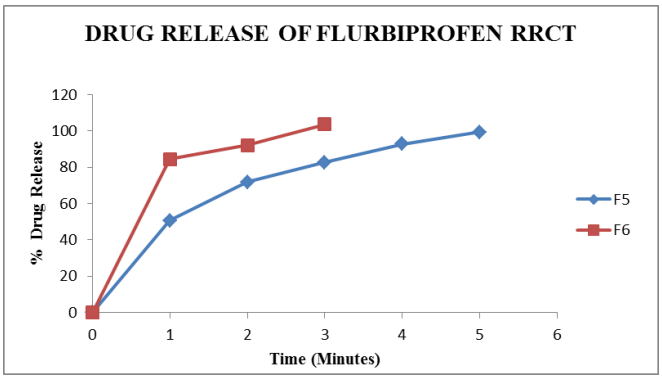

Figure 8: In vitro drug release of flurbiprofen rapid release core tablets

b. IN VITRO DRUG RELEASE OF COMPRESSION COATED FLURBIPROFEN TABLETS

The main aim of the drug delivery system was to release the drug in an immediate release pattern after a non-delivery period (lag time) of 3 h. The lag time before the immediate release of the drug from all the batches is summarized in table7 and figure 3.

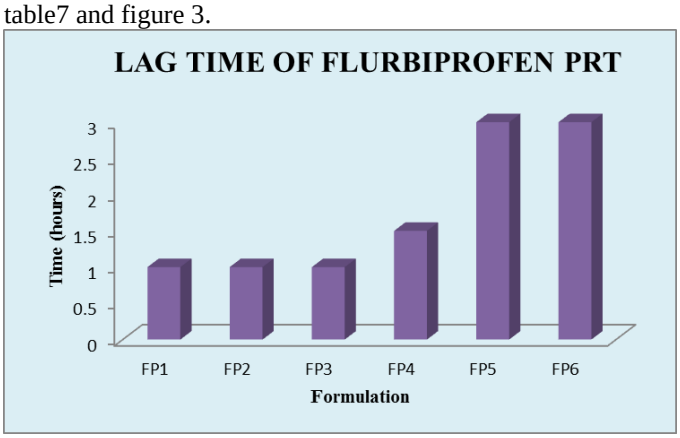

Figure 9: Lag time of the formulated pulsatile release tablets

In vitro drug release (lag time) study of 6 formulations showed differences in drug release pattern (lag time). All the formulations coated with HPMC E50, HPMC E15, HPMC E5 had the lag time of less than 3 hours. Formulations FP1, FP2, FP3 had a lag time of 1 hour (~ 10% drug release). Formulation FP1 and FP2 showed a release of 61.24% and 79.62% at the end of 5.5 hours, while FP3 with a release of 99.86% at the end of 4 hours. FP4 showed a lag time of 1.5 hours with a drug release of 70.91% at the end of 5.5 hours.

Formulations FP5 and FP6 showed a drug release of 9.41% and 10.04% respectively at the end of 3 hours lag time and released 22.54% and 100.2% of the drug respectively at the end of 5.5 hours. This indicated that formulation FP6 could satisfy the criteria for lag time (i.e., considered to be less than 10% drug release within 3 hours) with a complete drug release at the end of 5.5 hours. Hence, FP6 was considered as the optimized formulation as it has shown desired predetermined lag time and a satisfactory release pattern.

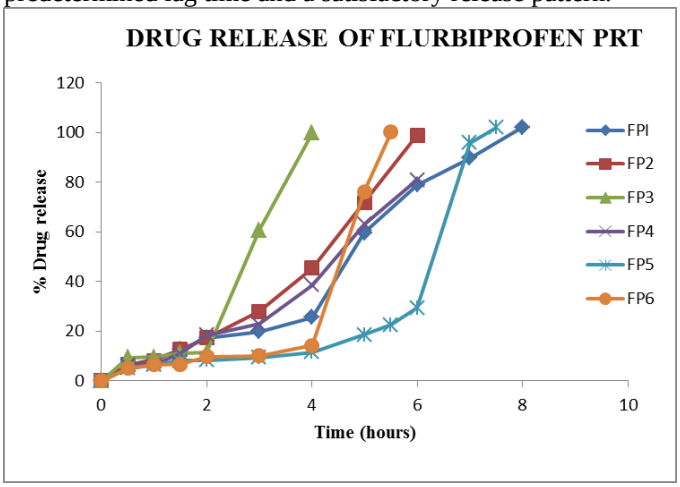

Figure 10: In vitro drug release of flurbiprofen pulsatile release tablets

IN VITRO DRUG RELEASE KINETICS

The drug release mechanism and kinetics of the optimized formulation was determined by the application of Korsmeyer-peppas model, Higuchi's model, Zero order and first order kinetics to dissolution data. The tablet formulation (FP6) follows zero order release as their r^2 values was found to be 0.9574.The drug release mechanism followed non-fickian diffusion (super case II), since it fitted well with Korsmeyer-peppas model. This indicates that the drug release depends on swelling, relaxation, and erosion of polymer with zero-order release kinetics.

Formulation code	Zero order	First order	Higuchi	Hixson-crowell	Korsemeyer-peppas equation	
	R^2	R^2	R^2	R^2	R^2	N
FP6	0.9574	0.9022	0.9574	0.9022	0.9138	0.476

Table 7: Drug release kinetics of optimized formulation (FP6)

IV. CONCLUSION

Formulation of Pulsatile compression coated tablets proved to be the most successful approach to gain a time-controlled release of Flurbiprofen for the chronotherapy of Rheumatoid arthritis in which the symptoms are worse at early morning. In the present study, HPMC E5, HPMC E15 and HPMC E50 were investigated as outer compression coated polymers based on time-dependant approaches.

The pulsatile tablets of Flurbiprofen, a non-steroidal anti-inflammatory drug has been developed to achieve maximum drug release after a predetermined lag time of 3 hours with a complete drug release at 5.5 hours. The *in vitro* drug release studies showed that amongst all the formulations, FP6 could release the drug rapidly and completely at the end of 5.5 hours with a lag time of 3 hours.

ACKNOWLEDGMENT

The authors are thankful to Orchid Chemicals Pharmaceuticals Ltd. For providing gift sample of Flurbiprofen for research work. The authors are highly thankful to College of Pharmacy, Madras Medical College, Chennai, India for providing all the facilities to carry out the work.

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