Formulation and Evaluation of Press-Coated Pulsatile Delivery of Flurbiprofen Tablets

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Abstract - **The objective of present study is to formulate and evaluation of press-coated pulsatile delivery of flurbiprofen tablets for treatment of rheumatoid arthritis. The press coated method to mimic the circadian rhythm of the disease by releasing the drug with a distinct predetermined lag time of 4 hours. The design of the system consists of a rapid release core and controlled release coat. A combination of HPMC K 15M and eudragit RL 100, was used as a coating material for the tablet. The formulations (F1-F3) of the core were prepared by using crospovidone (CP) as disintegrants in different proportions (10%, 15% and 20%) to study the effect of variable concentrations of these on the characteristics of the formulation. Among these formulations, F1 containing CP (20%) as disintegrant showed a better drug release of 98% over 1hr was selected. The core was coated with of HPMC K 15M and eudragit RL100 with different polymer ratios (F1- F6). Among these, F6 was optimized formulation based on the lag time and percent of drug release (96% of drug release in 6 hours). Thus, compression coated tablets with a clear lag time before drug release is a potentially useful formulation for the treatment of rheumatoid arthritis.**

1.INTRODUCTION

Pulsatile drug delivery systems are gaining lot of interest and attention these days. These systems have a peculiar mechanism of delivering the drug rapidly and completely after a "lag time," i.e., a period of "no drug release" (1). Though most delivery systems are designed for constant drug release over a prolonged period of time, pulsatile delivery systems are characterized by a programmed drug release, as constant blood levels of a drug may not always be desirable (2). Pulsatile release exploited to target proximal and distal colonic regions via the oral route based on a time-dependent strategy. For this purpose, *in vivo* lag periods are sought that would roughly correspond to the relatively reproducible small intestinal transit time of dosage forms (3). Pulsatile drug release is defined as the rapid and transient release of a certain amount of drug molecules within a short time period immediately after a predetermined off-release period i.e. lag time, thus provide spatial and temporal delivery (4).

Flurbiprofen, a nonsteroidal anti-inflammatory agent (NSAIA) of the propionic acid class, is structually and pharmacologically related to fenoprofen, ibuprofen, and ketoprofen, and has similar pharmacological actions to other prototypica NSAIAs. The anti-inflammatory effect of flurbiprofen occurs via reversible inhibition of cyclooxygenase (COX) (5). The drug used in treatment of rheumatoid arthritis (RA).

It is a chronopharmaceutical for better treatment of early morning stiffness and symptomatic relief from pain in patients with rheumatoid arthritis. Based on the concept of press coated technique, in which the core tablet is compression coated with different concentrations of polymers (HPMC and Eudragit). When this tablet comes in contact with the stomach fluids it produces a lag time of drug release up to 6hrs, after lag time the core tablet contains super disintegrant, the tablet disintegrates in few minutes and burst release of drug present in it. This approach helps in the treatment of rheumatoid arthritis after the consumption of dug at the bedtime, it releases drug after 6hrs (6).

2. MATERIALS AND METHODS

2.1. Materials:

Flurbiprofen is obtained gift sample from Merk pvt.ltd. The polymer of eudragits purchased from Merck Specialities Pvt Ltd, Mumbai, India. The HPMC polymer purchased from Merk pvt.ltd. The excipients like MCC, magnesium stearate, MCC,

dicalcium phosphate, sodium crospovidone and talc purchased from Merck Specialities Pvt Ltd, Mumbai, India. Opadry orange obtained from Ryce Yash India ltd.

2.2 Methods

2.2.1 Preformulation studies

Preparation of calibration curve in 7.4 pH phosphate buffer

An accurately weighed amount of flurbiprofen equivalent to 100mg was dissolved in small volume of ethanol, in 100ml volumetric flask and the volume was adjusted to 100ml with 7.4 pH phosphate buffer and further dilution were made with 7.4 pH phosphate buffer. A series of standard solution containing Beer's Lambert's range of concentration from 2 to16 µg/ml of flurbiprofen were prepared and absorbance was measured at 247nm against reagent blank. All spectral absorbance measurement was on Shimadzu 1700 UV-visible spectrophotometer [(7)].

Drug polymer interaction

FT-IR spectra of the flurbiprofen, Eudragit RL 100, and HPMC K15M were determined by using KBr pellet press technique. Samples were scanned over the 500-4000cm^{-1} Spectral region at a resolution of 4cm^{-1}. The ratio of the sample in KBr disc was 1% (shimadzu FT-IR spectrometer). To ensure no interaction has been occurred between the drug polymers [(8)].

2.2.2. Preparation of flurbiprofen press coated tablets

Preparation of flurbiprofen core tablets:

Accurately weigh all the ingredients and mix thoroughly by using motor and pestle and pre weighed amount of formulation was direct compressed using tablet punching machine. The composition of core tablets was given in table 1.

Preparation of press coated tablets of flurbiprofen:

A compression-coated or press coated tablet is a system in which the all surface of an inner core is completely surrounded by coat. These coats prevent drug release from the core until the polymeric coat is entirely eroded, dissolved or removed. Different drug release fashion could be obtained depending on coating layer and core composition. The process of compression coating is half the quantity of outer coating material was transferred into the die and core tablet was placed manually in the centre of the die and pressed a little bit to fix in the lower part of coating material. Then the remaining half quantity of outer coating material was added into the die and compressed using rotary tablet punching machine [(9)]. The composition of press coated tablets was given in table 2.

2.2.3. Evaluation of core and coated tablets

Weight variation

Randomly selected 20 tablets of each formulation batch were weighed using an electronic digital balance and the test was performed according to the Indian Pharmacopeia.

Hardness

The tablet crushing strength, which is the force required to break the tablet by compression in the diametric direction was measured in triplicate using Monsanto tablet hardness tester. A tablet was placed between the anvils and the crushing strength which causes the tablet to break was recorded. Three tablets from each formulation batch were tested randomly and the average readings were expressed as mean values of triplicates [(10)].

Friability

Randomly selected dedusted tablets of weight equivalent to 6.5g were placed in a Roche friability test apparatus and rotated 100 times at 25 ± 1 rpm. Then the tablets were removed, dedusted and re-weighed [(11)]. The % friability were calculated by the given formula,

$$\% \text{ Friability} = \frac{\text{Initial weight - Final weight} \times 100}{\text{Initial weight}}$$

Thickness

Three tablets were selected randomly from each batch and the thickness of the tablets was measured using vernier caliper.

Drug content determination

Ten core tablets were weighed, triturated and powdered. Powder triturated equivalent to average weight of tablet was weighed and transferred to a 100 ml volumetric flask. Initially about 50 ml of methanol was added and the flask was shaken thoroughly and the volume was made up to 100 ml with the methanol. The resulting solution was diluted suitably and the drug content was estimated spectrophotometically

(Shimadzu, Japan, UV-v1701) at 247 nm using UV spectrophotometer against 7.4 pH phosphate buffer as blank. The drug content was calculated using calibration curve [12].

Core erosion test

Compression coated tablets were separately immersed in the Petri plate containing 7.4 pH Phosphate buffer at 37ºC for 3 h.9 After the tablets were removed from the medium, the gelated portion of the outer layer and the dissolved or gelated portion of each core tablets were carefully removed to obtain the non-eroded residual core. The dry mass of each non-eroded residual core was measured after drying for 20 h at 40ºC. The initial mass of each core tablet and the mass of each non-eroded residual core were used to calculate the core erosion ratio [13].

In-vitro drug release studies

Drug release studies were carried out using USP XXIII dissolution test apparatus, rotating paddle method (Lab India, Mumbai, India). The study was conducted at 37±0.5ºC and 50 rpm using 900 ml of 1.2 pH buffers for 2 hr followed by 7.4 pH buffers until completion of the studies. Aliquots of sample (2 ml) were withdrawn at regular pre-determined time intervals, diluted suitably and the drug content was measured spectrophotometically at 247 nm, using 7.4 pH phosphate buffers as blank [14].

3. RESULTS AND DISCUSSION

3.1. Standard calibration curve of flurbiprofen

Standard calibration curve of flurbiprofen was carried out in 7.4 pH buffer at 247nm. The r^2 value in the entire medium shows nearly 1, which signifies linearity (Fig 1).

3.2. FT IR studies

Drug polymer interaction study was carried out for pure drug and physical mixtures of drug and polymers. The physical mixture showed identical spectrum with respect to the spectrum of the pure drug, indicating there is no chemical interaction between the drug molecule and polymers (Fig 2). The FT-IR spectra study showed no change in the finger point of pure drug spectra, thus confirming absence of the drug and polymer interaction.

3.3. Evaluation of core tablets

Flurbiprofen core tablets were prepared by using with super disintegrant like crospovidone by direct compression method using 8mm dies and punches in tablet punching machine. Here developing three formulations of core tablets in that formulation (F3) considered as optimized core tablet of flubiprofen. The study based on disintegration time with different concentrations of super disintegrants.

The core tablets were evaluated for the following parameters like weight variation, hardness, thickness, friability and drug content. In that formulation F3 requires less time to release the drug from core tablet. The results are given table 3.

In vitro dissolution study of flurbiprofen core tablets

The *in vitro* dissolution study of flurbiprofen core tablets F1, F2 and F3 were done for 1hr in pH 7.4 phosphate buffer as dissolution medium. The results indicated that F1 and F2 formulations less amount of drug release in 1hr period of time, these formulations containing less amount of superdisintegrant. Whereas formulation F3 containing higher concentration of super disintegrant (Crospovidone 20mg) showed greater drug release (98%) than all other two formulations F1 and F2. Hence the formulation F3 is selected as the optimized core tablet formulation. The results are shown in figure 3.

3.5. Evaluation of press-coated tablets of flurbiprofen

The press-coated tablets were evaluated for the following parameters like weight variation, hardness, thickness, friability and core erosion. The results are given table 4.

In Vitro dissolution studies of press coated tablets

The in vitro dissolution studies of flurbiprofen press coated tablets were performed by using 7.4 pH phosphate buffer in dissolution apparatus for different formulations, the comparative % cumulative drug release study of different formulations were shown in fig 4. Shows the time in hrs v_s % cumulative drug release of press coated tablets of different formulations from F1-F6. The % cumulative amount drug release from formulation (F6) shows highest percentage of drug release (96% in 6 hrs).

4. CONCLUSION

Flurbiprofen press coated tablets were prepared by using eudragit RL 100 and HPMC K 15 M in different ratios by press coating technique. The core tablets were prepared by direct compression method using crospovidone as super disintegrant. The formulation (F3) of core tablet shows disintegration time 12sec and percentage of drug release was found to be 98% within 1hr dissolution study. Based on the lag time results, the F6 (lag time 4hrs) press-coated tabled as optimized formulation. The lag time increased with increasing outer coating level. The formulation (F6) after desired lag time, the drug release (96%). The result obtained promises the development of pulsatile delivery system for time dependent drug release for the treatment of rheumatoid arthritis.

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TABLES AND FIGURES

Table 1: Formulation design of flurbiprofen core tablets

SL.No.	Ingredients	Formulation code Quantity (mg)		
		F1	F2	F3
1.	Flurbiprofen	100	100	100
2.	Microcrystalline cellulose	20	25	30
3.	Dicalcium phosphate	15	20	25
4.	Crospovidone	10	15	20
5.	Opadry orange	03	03	03
6.	Talc	01	01	01
7.	Magnesium stearate	01	01	01
	Total weight of core tablet (mg)	150	165	180

Table 2: Formulation of press coated tablets

SL.No	Ingredients	Formulation code (Quantity in mg)					
		F1	F2	F3	F4	F5	F6
1	Core tablet (Drug)	180	180	180	180	180	180
2	HPMC K 15 M	45	60	80	-	-	-
3	Eudragit RL 100	-	-	-	45	60	80
4	Microcrystalline cellulose	75	60	40	75	60	40
Total weight (mg)		300	300	300	300	300	300

Table 3: Evaluation of core tablets parameters

F.Code	Weight variation (mg)	Thickness (mm)	Hardness (Kg)	Friability (%)	Disintegration time (Sec)	Drug content (%)
F1	150.30±2.8	2.6±0.5	2.4±0.6	0.29	35	95.81±1.27
F2	165.15±2.6	2.9±0.3	2.6±0.5	0.27	28	97.74±1.82
F3	180.10±2.1	3.1±0.1	2.9±0.5	0.24	12	99.13±1.65

Table 4: Evaluation of press coated tablets of flurbiprofen

Formulation code	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm2)	Friability (%)	Core erosion (%)
F1	318±4.81	5±0.15	6±0.35	0.61±0.05	35±2.5
F2	298±5.13	5±0.16	5.5±0.28	0.72±0.02	19±3.7
F3	305±4.91	6±0.12	6±0.42	0.64±0.04	5.9±1.8
F4	310±3.57	5±0.09	5±0.51	0.71±0.03	6.9±1.5
F5	315±3.78	6±0.18	6±0.26	0.54±0.04	4.2±0.5
F6	308±2.94	6±0.19	6±0.39	0.26±0.02	1.5±0.3

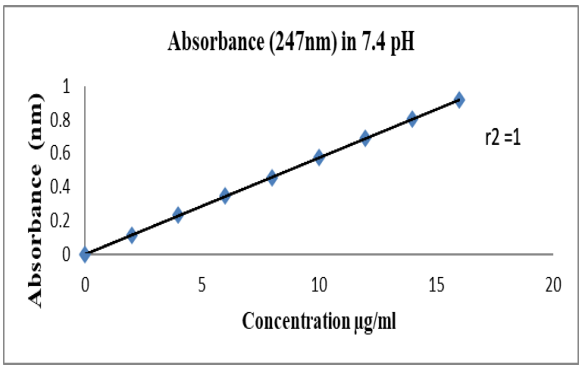

Fig. 1: Standard calibration curve of Flurbiprofen in 7.4 pH buffer at 247nm.

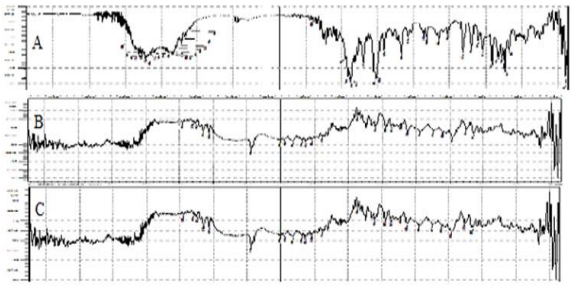

Fig. 2: FTIR spectrum of (A) Flurbiprofen; (B) Flurbiprofen+HPMC K 15 M; (C) Flurbiprofen + Eudragit RL100

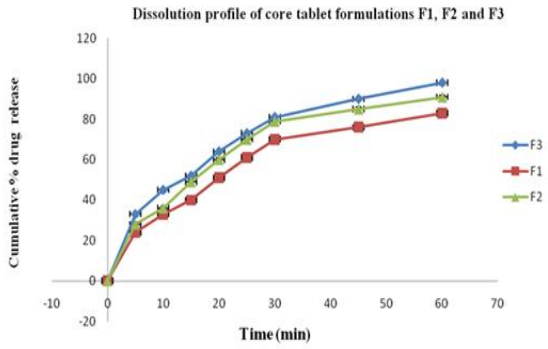

Fig 3: In vitro dissolution profile of core tablets in pH 7.4 phosphate buffer

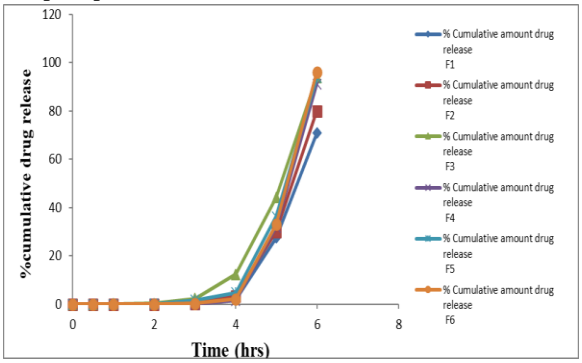

Fig 4: In vitro dissolution study of different formulations of press coated tablets F1-F6