International Journal of Pharmaceutical Development & Technology

e ISSN - 2248 - 910X

www.ijpdt.com

Print ISSN - 2248 - 9096

FORMULATION AND EVALUATION OF PULSATILE DRUG DELIVERY SYSTEM OF FLURBIPROFEN

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ABSTRACT

The aim of present study is to formulate and evaluate Flurbiprofen Pulsatile Drug Delivery system by press coated method to mimic the circadian rhythm of the disease by releasing the drug with a distinct predetermined lag time of 6 hours. The basic design of the system consists of a rapid release core and controlled release coat. A combination of HPMC K 15M, HPMC K100M, Karaya Gum, Sodium Alginate, was used as a coating material for the tablet. Nine formulations (F1-F6) of the core were prepared by using CCS, SSG and CP as disintegrants in different proportions (5% & 7%) to study the effect of variable concentrations of these on the characteristics of the formulation. Core blend was evaluated for flow properties, hardness, thickness, friability and in-vitro drug release. Among the six formulations, F1 containing CP (5%) as disintegrant showed a better drug release of 100% over 15mins was selected .The core was coated with of HPMC K 15M, HPMC K100M, Karaya Gum, Sodium Alginate with different polymer ratios (P1F1- P8F1). Among these, P8F1was optimized formulation based on the lag time and percent of drug release (98.03% 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, Osteoarthritis, Dysmenorrhoea, Asthama which follows circadian rhythm.

Keywords: Flurbiprofen, HPMC K 15M, HPMC K100M, Karaya Gum, Sodium Alginate, Press coated method, Pulsatile drug delivery.

INTRODUCTION

Oral controlled drug delivery systems represent the most popular form of controlled drug delivery systems for the obvious advantages of oral route of drug administration. Such systems release the drug with constant or variable release rates. The oral controlled release system shows a typical pattern of drug release in which the drug concentration is maintained in the therapeutic window for a prolonged period of time (sustained release), thereby ensuring sustained therapeutic action [1]**.** But there are certain conditions which demand release of drug after a lag time. i.e., Chronopharmacotherapy of diseases which shows circadian rhythms in their pathophysiology.

Recent studies have revealed that diseases have predictable cyclic rhythms and that the timing of medication regimens can improve outcome in selected chronic conditions [2]. Pulsatile system gaining a lot of interest as it is increasing patient compliance by means of providing time- and site-specific drug delivery system, thus providing special and temporal delivery. Pulsed or 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. Recent studies show that diseased have predictable cyclic rhythms and the timing of medication regimens can improve outcome in selected chronic conditions [3,4]. Drugs which exhibit tolerance should not be delivered at a constant rate, since the drug effect decreases with time at constant drug level. In addition drug toxicity increases with time when drug levels are held constant. In such cases it is preferable to opt for dosage form which will provide desired concentration of drug at particular time point only.

Now, concept of chronopharmaceutics has emerged, wherein, research is devoted to the design and evaluation of drug delivery systems that release a therapeutic agent at a rhythm that ideally matches the biological requirement of a given disease therapy. “Chronopharmaceutics” consist of two words chronobiology and pharmaceutics. Chronobiology is the study of biological rhythms and their mechanisms. Recent studies have revealed that diseases have predictable cyclic rhythms and that the timing of medication regimens can improve outcome in selected chronic conditions.

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There are number of diseases which required to be formulated as PDDS as like: hypercholesterolemia, asthma, cancer, duodenal ulcer, arthritis, diabetes, neurological disorders, cardiovascular diseases and colonic delivery. A circadian rhythm occurs during hepatic cholesterol synthesis. Therefore, cholesterol synthesis is generally higher during the night than during daylight. The maximal production occurs early in the morning, i.e. 12 h after the last meal. Studies with HMG CoA reductase inhibitors have suggested that evening dosing was more effective than morning dosing [5,6].

The drugs that undergo first-pass metabolism resulting in reduced bioavailability, altered steady state levels of drug and metabolite, and potential food drug interactions require delayed release of the drug to the extent possible [7,8]. All of these conditions demand for a time controlled therapeutic scheme releasing the right amount of drug at the right time. This requirement is fulfilled by Pulsatile Drug Delivery Systems. The following figures (Fig 1 and Fig 2) are showing the release profiles of drug from pulsatile drug delivery systems.

METHODOLOGY

Method

Drug-Excipient Interaction Studies

This type of interactions was studied with the help of Shimadzu FTIR spectrophotometer, in which KBR pellet method used to determine the interactions.

Formulation

Preparation of core tablets of Flurbiprofen

The tablet formulations were prepared by wet granulation technique. The ingredients Flurbiprofen, croscarmellose sodium, cross povidone, sodium starch glycollate and (previously passed through sieve no. 85) were added, mixed and granulated. Then these were taken and compressed directly in Compression machine (Manesty machineries B3A)

Preparation of compression coated tablets of Flurbiprofen

Four different coating materials were selected for coating of tablets. They were:

1. Hydroxy propyl methyl cellulose K 15M
2. Hydroxy propyl methyl cellulose K 100M
3. Karaya gum
4. Sodium alginate

EVALUATION STUDIES [9,10]

1. Flow Properties

Bulk and Tapped Density

20 g of the granules (W) from each formula were introduced into a 100 ml measuring cylinder, and the initial volume was observed. The cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 Sec intervals. The tapping was continued until no further change in volume was noted.

Bulk density = W / V0

Tapped density = W / VF

Where, W = weight of the granules, V0 = initial volume of the granules, VF = volume of the granules.

Hausner's Ratio

It indicates the flow properties of the granules and is measured by the ratio of tapped density to the bulk density.

Hausner's Ratio = Tapped density/Bulk density

Angle of Repose

The angle of repose of powder blend was determined by the funnel method. The accurately weight powder blend were taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation. Where, h and r are the height and radius of the powder cone respectively.

$\tan \theta = h/r$

Hardness

The hardness of the tablet was determined by using a Monsanto hardness tester. It is expressed in Kg / cm2.

Thickness

The thickness of the tablets was measured by Digital Vernier Calliper. It is expressed in mm.

Weight Variation

Ten tablets were selected randomly from the lot and weighed individually to check for weight variation.

Friability (F)

The friability of the tablet was determined using Roche Friabilator. It is expressed in %. 10 tablets were initially weighed and transferred into the friabilator. The friabilator was operated at 25 rpm for 4 mins. The tablets were weighed again. Friability of tablet should not exceed 1%.

Drug Content

Drug content was estimated at 248 nm spectrophotometrically using a double beam spectrophotometer.

In-vitro dissolution studies of Flurbiprofen

The dissolution test measure the amount of time required for certain percentage of the drug substance in a tablet to go into solution under a specified set of conditions. Dissolution testing of pulsatile delivery systems with the conventional paddle method at 50 rpm and 37±0.5°C has usually been conducted in different buffers for different

periods of time to simulate the GI tract pH and transit time that the pulsatile delivery system might encounter in-vivo. The ability of the coats/carriers to remain intact in the physiological environment of the stomach and small intestine is generally assessed by conducting drug release studies in pH 6.8 phosphate buffer for remaining hours (mean small intestinal transit time) using USP dissolution rate test apparatus. The samples were withdrawn at regular intervals.

Drug Content

Weigh and powder 20 tablets. Weigh a quantity of the powder containing 0.1g of Flurbiprofen, shake with 60 ml of 0.1M Sodium hydroxide for 5 minutes, dilute to 100.0ml with 0.1M Sodium hydroxide, filter if necessary and dilute to 10.0ml of the filterate to 100.0ml with the same solvent. Further dilute 10 ml to 100 ml with the same solvent and measure the absorbance of the resulting solution at the maximum at about 248 nm. Calculate the content of $C_{15}H_{13}FO_2$.

Table 1. Composition of Flurbiprofen core tablets

S No	Ingredients	F1	F2	F3	F4	F5	F6
1	Flurbiprofen	100 mg	100 mg	100mg	100mg	100mg	100mg
2	Cross Povidone	5%	7%	---	---	---	---
3	Cross Carmellose Sodium	---	---	5%	7%	---	---
4	Sodium Starch Glycolate	---	---	---	---	5%	7%
5	Magnesium Sterate	4mg	4mg	4mg	4mg	4mg	4mg
6	Talc	4mg	4mg	4mg	4mg	4mg	4mg
7	Mannitol	87mg	85mg	87mg	85mg	87mg	85mg
8	Total Weight	200mg	200mg	200mg	200mg	200mg	200mg

Table 2. Calibration curve at pH 6.8

Concentration (µg/ml)	Absorbance at 248nm
0	0
2	0.139
4	0.268
6	0.394
8	0.513
10	0.643
12	0.766

Flurbiprofen calibration curve obtained with the regression value R^2= 0.9999 and it obeys Beers Lamberts Law.

Table 3. Calibration curve at pH1.2

Concentration (µg/ml)	Absorbance at 248nm
0	0
2	0.132
4	0.264
6	0.384
8	0.514
10	0.634
12	0.776

Table 4. Evaluation of directly compressible blends of core tablets

Formulation code	Hausner's ratio	Bulk density (g/cc)	Tap density (g/cc)	Angle of repose (θ)	Carr's index (%)
F1	1.21	0.242	0.304	27.23	18.01
F2	1.21	0.232	0.319	22.30	12.13
F3	1.15	0.261	0.307	25.33	14.42
F4	1.13	0.257	0.291	24.46	9.41
F5	1.20	0.238	0.283±	28.72	16.19
F6	1.16	0.261	0.305	27.20	14.42

Table 5. Evaluation of directly compressible blends of coated tablets

Formulation code	Hausner's ratio	Bulk density(g/cc)	Tap density (g/cc)	Angle of repose (θ)	Carr's index (%)
P1	1.11	0.262	0.306	25.64	14.42
P2	1.25	0.252	0.320	23.22	9.65
P3	1.33	0.241	0.354	28.45	14.56
P4	1.25	0.267	0.255	24.96	13.55
P5	1.22	0.228	0.258	25.66	12.48
P6	1.18	0.271	0.306	22.54	13.95
P7	1.19	0.255	0.254	29.06	18.35
P8	1.20	0.285	0.288	28.55	12.52

Table 6. In vitro Drug Release Profile of Flurbiprofen Coated Tablets in 6.8 p^H buffer

Time	Cumulative % Drug Release							
	P1F1	P2F1	P3F1	P4F1	P5F1	P6F1	P7F1	P8F1
1hr	0.044	0.036	0.41	0.027	0.021	0.038	0.021	0.017
2hr	0.156	0.048	0.611	0.033	0.133	0.043	0.1	0.038
3hr	0.266	0.151	0.162	0.075	0.204	0.044	0.129	0.078
4hr	0.269	0.218	0.193	0.363	0.238	0.047	0.232	0.228
5hr	0.372	0.432	0.845	0.415	0.244	0.051	0.235	0.521
6hr	0.382	0.632	0.883	0.674	0.351	0.069	0.304	0.681
7hr	0.388	0.73	--	0.76	0.355	0.076	0.353	--
8hr	0.496	--	--	--	0.468	0.083	0.373	--
9hr	0.502	--	--	--	0.474	0.093	0.476	--
10hr	0.508	--	--	--	0.49	0.209	0.494	--
11hr	0.518	--	--	--	0.509	0.48	0.564	--
12hr	0.556	--	--	--	0.568	0.508	0.576	--

Table 7. Post compressional parameters of coated tablets

Formulation Code	Hardness (kg/cm2)	Friability (%)	Weight variation (%)	Thickness* (mm)
P1	**4.9**	**0.70**	**1.65**	**2.7**
P2	**4.8**	**0.55**	**1.57**	**2.9**
P3	**5.1**	**0.62**	**1.42**	**2.8**
P4	**4.0**	**0.54**	**1.54**	**2.7**
P5	**4.2**	**0.62**	**1.18**	**2.6**
P6	**4.1**	**0.57**	**1.35**	**2.5**
P7	**4.5**	**0.54**	**1.45**	**2.3**
P8	**5.2**	**0.55**	**1.66**	**2.8**

Table 8. Drug content of P1F1-P8F

Formulation code	Drug content (%)
P1F1	98.07
P2F1	105.08
P3F1	87.95
P4F1	109.40
P5F1	97.14
P6F1	73.12
P7F1	88.73
P8F1	104.65

Figure 1. Linearity of Flurbiprofen at pH 6.8

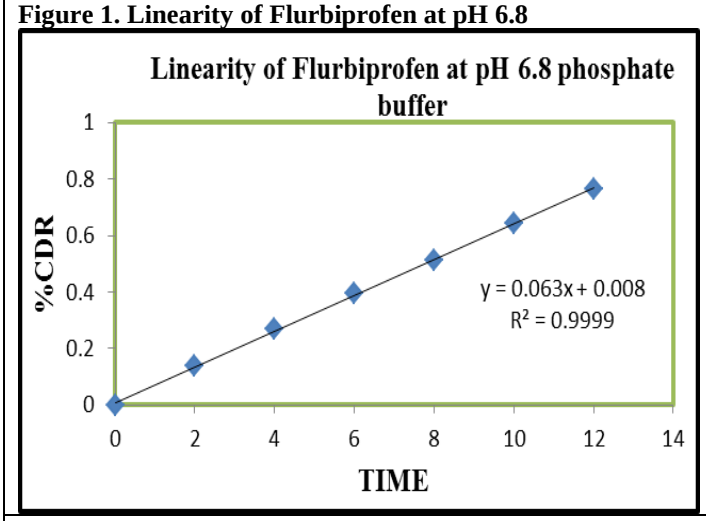


Figure 2. Linearity of Flurbiprofen at pH1.2

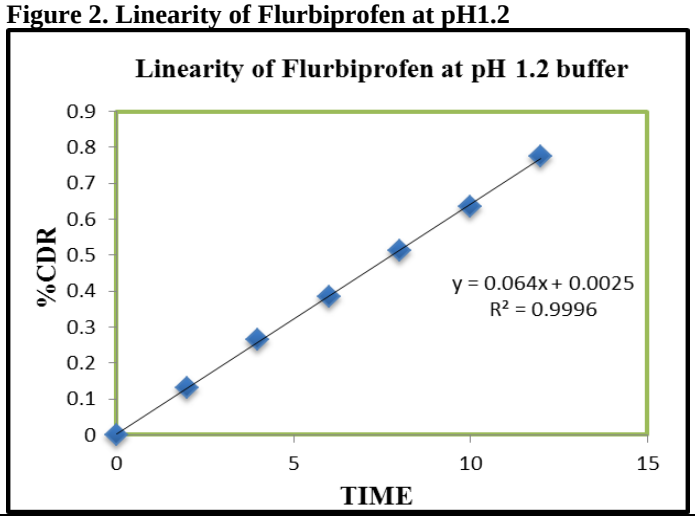


Figure 3. Comparison graphs of F1-F6 Formulations

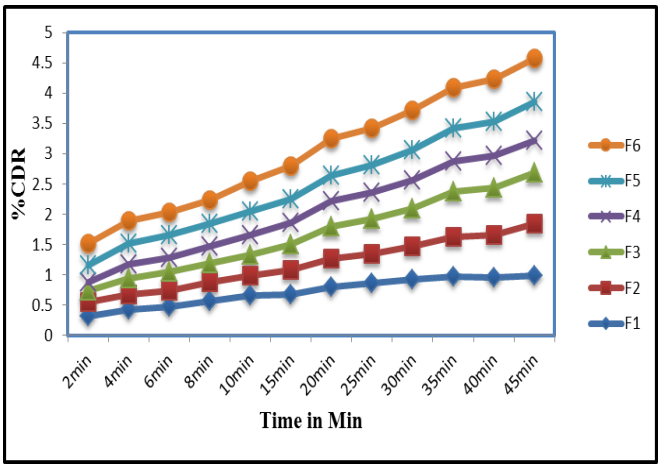


Figure 4. Invitro drug release profile of Flurbiprofen Coated Tablets in 6.8 pH Buffer

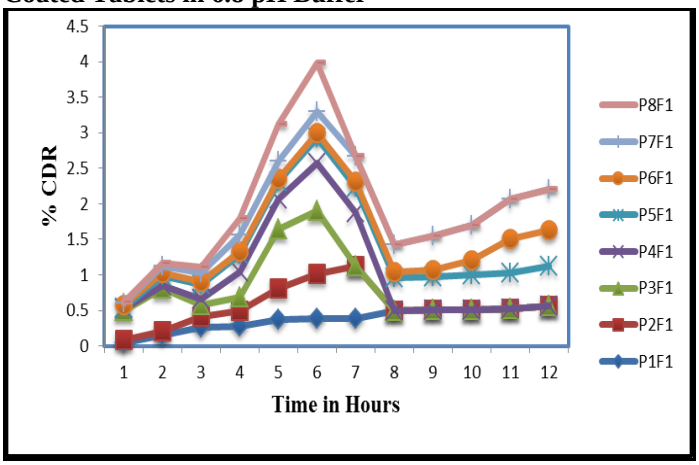
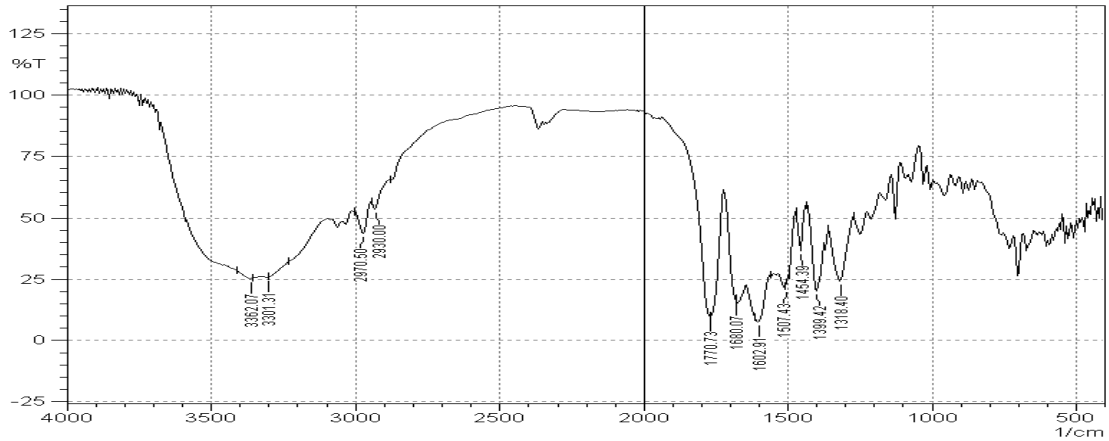


Figure 5. FTIR graph of Flurbiprofen best formulation



CONCLUSION

The characteristic peak stretches of the drug was present in the physical mixture of the drug with the polymers-excipients with no other relevant effects, thus ruling out any interaction between the drug and all the examined components. Hence there are no drug-excipient interactions. Micromeritic properties like bulk density, tapped density, hausner's ratio and angle of repose were inacceptable range indicating flow property excellent to good. The manufactured tablets were evaluated for in process and finished product quality control tests including

appearance, dimensions, weight variation, hardness, friability, drug content uniformity and concluded to be within limits. The drug content was estimated in the table for all the formulations developed from P1F1 TO P8F1. The drug content for the formulations P1F1 to P8F3 were found to be 73.2% to 109.40% respectively. The in-vitro disintegration time were found to be very less for F1. F1 shows 97.06% of drug release with in 15minutes upon contact with dissolution medium.

The results conclusively demonstrated that Pulsatile tablets of Flurbiprofen was effectively prepared by direct compression method with desired prroperties and exhibited better in-vitro druf release profilles. The formulation P8F1 containing a mixture of Sodium alginate and HPMC K 100M exhibit least lag time and maximum rate of drug release. So, this formulation was considered to be optimized formulation. A significant process has been made towards Pulsatile drug delivery system that can effectively treat diseases such as Rheumatoid arthiritis, Osteoarthritis, Asthama, Dysmenohhroea. It can effectively treat diseases with non-constant dosing therapies. Thus the formulated Pulsatile tablets of Flubiprofen offer a superior alternativr to improve the patient compliance over other dosage forms.

ACKNOWLEDGEMENT

We sincerely thank Sri. J.Bhaskar Rao, Chairman, JB Educational Institutions, Moinabad and Spectrum Labs, Hyderabad, Telangana for providing technical support and guidance throughout our studies.

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