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FORMULATION AND EVALUATION OF FLURBIPROFEN PULSATILE DRUG DELIVERY SYSTEM

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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 7 hours. The basic design of the system consists of a rapid release core and controlled release coat. A combination of Manucol, Carbopol and Ethyl cellulose was used as a coating material for the tablet. Nine formulations (F1-F9) of the core were prepared by using CCS, SSG and CP as disintegrants in different proportions (2, 4 and 6%) 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 nine formulations, F3 containing CP (6%) as disintegrant showed a better drug release of 100% over 45 mins was selected .The core was coated with Manucol, Carbopol and EC with different polymer ratios (P1F3- P6F3). Among these, **P6F3** was optimized formulation based on the lag time and percent of drug release (98% of drug release in 7 hours). Thus, compression coated tablets with a clear lag time before drug release is a potentially useful formulation for the treatment of RA which follows circadian rhythm.

Key words: Flubriprofen, Manucol, Carbopol, Ethyl cellulose, Press coated method, Pulsatile drug delivery.

INTRODUCTION

Pulsatile drug delivery systems (PDDS) are gaining importance in the field of pharmaceutical technology as these systems deliver the right dose at specific time at a specific site. In pulsatile drug delivery system drug release is programmed by external stimuli like magnetism, ultrasound, electrical effect and irradiation etc [1]. However, there are certain conditions for which normal release pattern is not suitable. These conditions demand release of drug after a lag time. In other words, it is required that the drug should not be released at all during the initial phase of dosage form administration. Such a release pattern is known as pulsatile release [2-4]. Flurbiprofen, a nonsteroidal anti-inflammatory agent (NSAIA) of the propionic acid class, is structually and pharmacologically related to fenoprofen, ibuprofen, and ketoprofen [5]. Similar to other NSAIAs, the anti-inflammatory effect of flurbiprofen occurs via reversible inhibition of cyclooxygenase (COX), the enzyme responsible for the conversion of arachidonic acid to prostaglandin G2 (PGG2) and PGG2 to prostaglandin H2 (PGH2) in the prostaglandin synthesis pathway. This effectively decreases the concentration of prostaglandins involved in inflammation, pain, swelling and fever. Flurbiprofen is rapidly and almost completely absorbed following oral administration. Peak plasma concentrations are reached 0.5 - 4 hours after oral administration. Greater than 99% is protein bound, primarily to albumin.

So, the aim of present study is to develop a time-controlled release formulation of Flurbiprofen to increase the lag time of the drug with reduced dose and dosing frequency.

MATERIALS AND METHODS

Materials

Flurbiprofen was obtained from Spectrum Lab, Hyderabad. Cross Povidone, Cross carmellose sodium, Sodium starch glycollate, Magnesium stearate, Carpobol, Manucol, Karaya , Tragacanth and Talc were obtained as a gift sample from S.D Chemicals Pvt.Ltd, Mumbai. Lactose monohydrate was purchased from Merck specialties Pvt.

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Ltd, Mumbai. Ethyl cellulose was purchased from Oxford Laboratory, Mumbai. All solvents used were of analytical grades and were used as obtained.

METHODS

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 lactose (previously passed through sieve no. 85) were added, mixed and granulated using IPA solution as granulating agent. The wet mass was passed through sieve no. 12 and the granules obtained were dried at 45ºC for 30 min.

The dried granules were subjected to dry screening by passing through sieve no. 16 and then the granules were blended with the mixture of talc and magnesium stearate. The granules were compressed into tablets using 6 mm round, concave shaped punch in a rotary tablet press (Rimek RSB-4 minipress, Cadmach).

Preparation of compression coated tablets of Flurbiprofen

Three different coating materials carbopol, manucol, ethyl cellulose were selected for the compression.

EVALUATION STUDIES

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.

$$\text{Bulk density} = W / V_0$$

$$\text{Tapped density} = W / V_F$$

Where,

W = weight of the granules, V_0 = initial volume of the granules, V_F = volume of the granules.

Hausner's Ratio

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

$$\text{Hausner's Ratio} = \text{Tapped density/Bulk density}$$

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.

$$\tan \theta = h/r$$

Where, h and r are the height and radius of the powder cone respectively.

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 Caliper. It is expressed in mm.

Weight Variation

Ten tablets were selected randomly from the lot and weighed individually to check for weight variation. The following %deviation in weight variation is allowed.

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 245nm 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 7.4 phosphate buffer for remaining hours (mean small intestinal transit time) using USP dissolution rate test apparatus. The samples were withdrawn at regular intervals.

RESULTS AND DISCUSSION

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 in

acceptable 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 P1F3 TO P6F3. The drug content for the formulations P1F3 to P6F3 were found to be 92.03±0.80 to 99.36±0.57 respectively. The in-vitro disintegration time were found to be very less for F3. F3 shows 97.7% of drug release with in 45minutes upon contact with dissolution medium.

Fig 1. *In-vitro* drug release for P1F3-P6F3

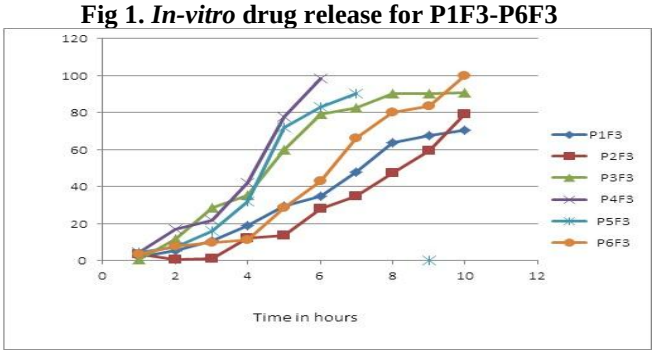

Table 1. Evaluation of directly compressible blends of core tablets

Formulation code	Hausner's ratio*	Bulk density* (g/cc)	Tap density* (g/cc)	Angle of repose* (θ)	Carr's index* (%)
F1	1.21±0.23	0.242±0.012	0.304±0.006	27.23±0.681	18.01±0.721
F2	1.21±0.23	0.232±0.011	0.319±0.012	22.30±0.450	12.13±1.50
F3	1.15 ±0.15	0.261±0.06	0.307±0.0025	25.33±0.486	14.42±0.45
F4	1.13±0.18	0.257±0.009	0.291±0.012	24.46±0.271	9.41±0.201
F5	1.20±0.80	0.238±0.015	0.283±0.015	28.72±0.450	16.19±0.371
F6	1.16±0.90	0.261±0.006	0.305±0.019	27.20±0.632	14.42± 0.24
F7	1.15±0.15	0.250±0.023	0.289±0.023	23.94±0.187	13.49±0.307
F8	1.18±0.19	0.211±0.011	0.322±0.08	21.17±0.121	11.74±0.386
F9	1.13±0.18	0.221±0.007	0.366±0.09	28.05± 0.28	16.66±0.415

Table 2. Post compressional parameters of core tablets

Formulation Code	Hardness* (kg/cm2)	Friability* (%)	Weight variation*(%)	Disintegration time	Thickness* (mm)
F1	4.9	0.70±0.04	1.65±0.7	3min	2.7±0.15
F2	4.8	0.55±0.34	1.57±0.6	2.5min	2.9±0.20
F3	5.1	0.62±0.05	1.42±0.4	1min	2.8±0.67
F4	4.0	0.54±0.67	1.54±0.5	4min	2.7±0.45
F5	4.2	0.62±0.49	1.18±0.2	3.45min	2.6±0.18
F6	4.1	0.57±0.34	1.35±0.3	2.3min	2.5±0.15
F7	4.7	0.55±0.23	1.44±0.5	4.15mim	2.9±0.56
F8	4.5	0.62±0.34	1.23±0.6	3min	2.4±0.67
F9	4.4	0.52±0.34	1.48±0.6	3.5min	2.6±0.81

Table 3. Data for post compression studies of the prepared coated formulations

Formulation Code	Hardness* (kg/cm2)	Friability* (%)	Weight variation* (%)	Swelling index* (%)	Thickness* (mm)
F1	6-7	0.45±0.04	1.65±0.12	280±18.0	7.52±0.67
F2	6-7	0.53±0.12	1.57±0.09	108±8.0	7.45±0.87
F3	6-7	0.62±0.14	1.42±0.80	139±9.0	7.12±0.34
F4	6-7	0.48±0.04	1.54±0.67	192±12.0	7.02±0.23
F5	6-7	0.43±0.08	1.18±0.12	267±16.0	7.21±0.56
F6	6-7	0.48±0.04	1.26±0.17	112±7.7	7.11±0.21
F7	6-7	0.53±0.12	1.57±0.09	232±12.0	7.23±0.34
F8	6-7	0.58±0.14	1.11±0.11	176±14.0	7.87±0.47
F9	6-7	0.43±0.04	1.26±0.17	109±11.0	7.80±0.36

Table 4. Drug content of PF1-PF6

Formulation code	Drug content (%)
P1F3	93.84±0.45
P2F3	92.03.±0.80
P3F3	94.62±0.63
P4F3	96.84±0.45
P5F3	97.36±0.57
P6F3	99.36±0.57

Table 5. Composition of Flurbiprofen core tablets

Sl.No	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Flurbiprofen	100	100	100	100	100	100	100	100	100
2	Cross Povidone	4	8	12	---	---	---	---	---	---
3	Cross carmellose Sodium	---	---	---	4	8	12	---	---	---
4	Sodium starch glycollate	---	--	---	---	---	---	4	8	12
5	Magnesium stearate	3	3	3	3	3	3	3	3	3
6	Talc	2	2	2	2	2	2	2	2	2
7	Lactose	91	87	83	91	87	83	91	87	83
	Total Weight	200	200	200	200	200	200	200	200	200

Table 6. Composition of compression coated tablets

Formulation	Formulation code					
	P1	P2	P3	P4	P5	P6
Core	200	200	200	200	200	200
Carbopol	400	----	----	125	125	----
Ethyl cellulose	-----	400	-----	275	-----	275
Manucol	-----	-----	400	-----	275	125
Total Weight	600	600	600	600	600	600

Table 7. Dissolution of rapid release core tablet

Formulation	Cumulative percentage of drug release from core tablet						
Time	5min	10min	15min	20min	30min	45min	60min
F1	19.54	35.32	46.67	55.88	68.4	71.4	80.2
F2	23.21	39.78	50.23	60.21	78.44	80.91	85.55
F3	33.35	41.50	66.41	73.56	83.99	97.7	-
F4	22.9	37.61	52.91	65.83	70.42	70.7	80.6
F5	24.30	39.91	54.43	60.11	71.32	74.34	81.80
F6	26.23	42.34	58.01	67.99	74.33	77.42	84.18
F7	22.90	37.61	49.40	59.31	67.84	78.85	86.11
F8	24.33	36.68	51.77	62.20	71.37	82.22	92.31
F9	27.63	41.59	48.41	57.72	72.21	78.14	86.58

Table 8. Cumulative % of drug release from coated tablets

Time	Cumulative % drug release						
	P1F3	P2F3	P3F3	P4F3	P5F3	P6F3	P1F3
1	02.2±0.3	03.4±0.5	0.56±0.7	04.4±0.50	4.55±0.3	03.3±0.5	1
2	05.4±0.2	0.61±0.3	11.6±0.8	16.78±0.7	7.27±0.1	07.6±1.1	2
3	10.6±4.8	0.91±0.1	28.6±1.2	21.74±1.0	16.09±0.9	09.7±1.2	3
4	18.7±0.1	12.2±0.12	35.2±1.3	42.17±2.8	32.07±0.4	11.1±1.1	4
5	29.4±1.1	13.4±0.40	59.8±0.5	77.61±1.8	71.71±0.3	28.4±1.2	5
6	34.6±1.1	28.2±1.40	79.2±2.1	98.37±3.3	83.12±0.2	43.2±1.1	6
7	47.9±0.9	34.6±1.18	82.3±2.1	-	90.17±1.1	66.1±0.8	7
8	63.8±1.1	47.4±1.13	90.3±1.1	-	-	79.9±1.1	8
9	67.7±1.1	59.2±1.14	90.4±1.1	-	-	83.4±3.1	9
10	70.5±0.6	79.0±0.90	90.6±4.1	-	-	99.8±3.8	10

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