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Original Article

Design, development and evaluation of pulsatile drug delivery system using tablet in tablet formulation

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ABSTRACT

Tablet in tablet formulation, containing Aceclofenac (API) in core tablet and coated with hydroxylpropyl cellulose (HPC) was evaluated for time drug release with predetermined lag time and subsequent rapid release phase. Various types of press coated tablets were prepared using single punch tablet machine. They were evaluated for various physicochemical properties and *in vitro* dissolution study was carried out by USP type II (paddle) apparatus. Initially, drug release was slow for 3-6 hr followed by a burst release. Lag time of tablet increased with increasing viscosity of the HPC and load of outer shell. However, the compression load had little effect.

Keyword: Aceclofenac, hydroxylpropyl cellulose (HPC), lag time, press coated tablet

INTRODUCTION

Chronotherapy or Chronopharmacology has been successfully used for the treatment of ischemic heart disease, asthma, rheumatoid arthritis, diabetes mellitus and peptic ulcer. For the treatment of these diseases drug should maintain therapeutic blood level only at specific time when disease symptom are at peak. Therefore drug release pattern should be controlled by time rather than rate. For diseases like rheumatoid arthritis in which pain is increased during early morning, various types of systems i.e. time clock systems and sigmoid release systems have been used to. By using pulsatile system, the drug is released rapidly and completely after a defined lag time where no drug releases occurs (Fig. 1). Alternative terms used for pulsatile drug delivery is delayed release or sigmoidal release. Single pulse or multi pulse systems are also available [1, 2].

The application of press coated technology can be advantageous to design a formulation to meet chronopharmacological needs. It can also be utilized to target a drug to a specific site in the gastrointestinal tract (GIT), e.g. to the colon. Pulsatile drug delivery systems (PDDS) can be classified as site-specific and time-controlled systems[3,4].PDDS system can be used for many drugs that require modification of drug release, protection of volatile substance and masking bitter taste of drugs[4,5]. Time-controlled pulsatile delivery has been achieved mainly with drug-containing cores, which are covered with release-controlling layers. The cores serve as reservoirs, which protected from the environment by the release controlling coat.

Hydroxypropyl cellulose (HPC) has been used as pharmaceutical additive for various purposes like binders in tablet, film-coating material and thickeners for syrup. It is also used in controlled release formulation or bioadhesive formulation due to its swelling and adhesive properties. However HPC is not used for preparation of time-release formulations. In this study HPC was used as functional material for controlling release time in press coated tablet. Other water soluble polymers such as hydroxyethylcellulose and hydroxypropyl methylcellulose can also be used for controlling release. In this study core tablet was coated with water insoluble but permeable polymer [5, 6]. Aim of the present study was to develop a pulsatile release tablet of aceclofenac using hydrophilic and/or hydrophobic polymers to meet the requirements of drug release as per the chronobiologic rhythm of arthritis. The target was to release drug rapidly in a short period i.e. in pulse manner after a predetermined lag time of 6 hrs.

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MATERIALS AND METHODS

Materials: API Aceclofenac was obtained from Shefa Healthcare Pvt. Limited Mumbai.Diluent microcrystalline cellulose (Avicel PH-102), binder polyvinyl pyrrolidone (PVP-K30) and lubricant Magnesium stearate are obtained from LOBA Chemie laboratory reagents and fine chemicals, superdisintegrant cross povidone for burst release after predetermined lag time from THOMAS BAKER (chemical) pvt Limited Mumbai. Two viscosity grade of HPC (Hydroxypropyl cellulose) i.e. HPC-L & HPC-M having viscosity 6-10 mPa.s and 150-450 mPa.s respectively from Nippon soda co. Ltd, Japan supplied by Arihant Trading Co. Lower parel (W), Mumbai - 400 013 India as a gift sample. HPC where used for the hydrophilic outer layer of time release press coated tablet.

Methods

Excipients selection: Physical mixture of drug and various excipients were kept at 40 ±2° C and RH 75% ± 5% for 1 month and their FTIR spectrum was recorded initially and after 1 month using FTIR spectrometer over the range of 400 to 4000 cm^{-1} at a resolution of 2 cm^{-1}

Preparation of core tablets: Core tablet containing 100 mg of aceclofenac per tablet was prepared as shown in table no.1.Wet granulation method was used to prepare the granules for the core tablet. Individual ingredients were passed through sieve no. 60 and mixed for 10 min then 5% aqueous solution of PVP was used to bind the ingredients. The wetted mass was passed through a sieve no. 10.Then granules were dried at to 50^0C for 45 minutes in tray dryer and sized by passing through sieve no.22 to prepare granules ready for compression. Magnesium stearate was mixed with the granules for 10 min. Tablets were manufactured under a compression force of 2 tons using a single punch machine flat face bevelled edge punch 8 mm in diameter. Weight of Core tablets was maintained at 150 mg.

Press-coating of core tablets: HPC-L and HPC-M were passed through sieve no.60 and blended in different proportions as shown in table no.2. For the outer shell 450mg of polymer blend was used. Different proportions were used to attain a variable lag time. Press-coated tablets were prepared using single punch tabletting machine. Half amount of the polymer (200mg) was filled into the die to make a powder bed, on the centre of which was placed the core tablet. Then, the remaining half (250 mg) of the HPC powder was filled in the die, and the contents were compressed under a compression force of 2 tons, using a flat face bevelled edge punch 12mm in diameter.

EVALUATION [7, 8, 9, 10]

General Appearance: The general appearance of a tablet, its visual identity and over all "elegance" is essential for consumer acceptance. These include tablet's size, shape, colour, presence or absence of an odour, taste, surface texture, physical flaws and consistency and legibility of any identifying marking. Cross section of press coated tablet was also examined. For the ease of identification colored core tablet were prepared. .

Tablet thickness: Tablet thickness is an important characteristic in reproducing appearance and also in counting by using filling equipment. Three tablets were taken and their thickness was recorded using vernier calliper.

Weight variation: Twenty tablets and ten tablets were taken from core tablet and coated tablet respectively for this test, their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet is determined from the collective weight.

Hardness (Crushing load): Tablet hardness was measured using Monsanto hardness tester. A tablet was placed in the hardness tester and load required to crush the tablet was measured.

Friability: Friability is a measure of mechanical strength of the tablet. If a tablet has more friability it may not remain intact during packaging, transport or handling. Roche friabilator was used to determine the friability by following procedure. Pre weighed ten tablets were placed in the Friabilator. The tablets were rotated in the Friabilator for 4 minutes. At the end of test tablets were dusted and reweighed; the loss in the weight of tablet was determined as:

% Friability = (loss in weight / Initial weight) X 100

Percent drug content: Twenty tablets were accurately weighed and finely powdered, the mean weight was determined. A weight of the powder equivalent to 100 mg Aceclofenac was transferred to a 100 ml volumetric flask containing 50 ml methanol and the mixture was sonicated for 30 minutes and then diluted to 100 ml with methanol (1000µg/ml).The solution was filtered and 2 ml of filtered solution was diluted to 100 ml with phosphate buffer pH6.8 to furnish a concentration of 20µg/ml. Concentration of the drug and content per tablet were determined using UV absorbance at 275.

In vitro dissolution studies: The aim of present pulsatile release was to achieve lag time up to 6 hours during which the tablet should not release the drug or release should be less than 10%. To see the effect of combination of different proportions of HPC polymer on release pattern all the formulations (F1 to F6) were subjected for dissolution in acidic media (pH 1.2) for first 2hr and after that in phosphate buffer pH 6.8.

a. In vitro drug release study of core tablets: The *in vitro* release pattern of core tablets was studied in 900 ml of Phosphate buffer pH 6.8 solution using USP-II paddle apparatus by withdrawing samples at an interval of 5 minutes followed by replacement with fresh media; till 30 minutes at 100 rpm and 37±0.5^{0}C. The samples were analyzed at 275 nm using a UV spectrophotometer, after filtration.

b. In vitro drug release study of press-coated tablets: The release rate of Aceclofenac from pulsatile release tablet was determined by using USP dissolution testing apparatus type II (paddle type). The dissolution test was performed using 900 ml of Hydrochloric Acid pH 1.2 at 37±0.5^{0}C for 2 Hrs followed by phosphate buffer pH 6.8 at 100 rpm. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus every 60 min for 8 hrs and the samples were replaced with fresh dissolution medium. The samples were filtered through whatman filter paper. Absorbance of these solutions was measured at 275 nm using UV spectrophotometer. Cumulative percent drug release was calculated by using an equation obtained from a standard calibration curve [8].

Optimization study by factorial design: To find the optimized batch 3^2 factorial design was used. Two factors HPC-L and HPC-M were used in three different concentrations high, medium and low as shown in table no.3.

Stability study: Optimized batch of tablets was packed in high density polyethylene containers and stored under the following conditions for a three month period as prescribed by ICH guidelines for accelerated studies at 40 ±2° C and RH 75% ± 5%. The tablets were withdrawn after a period of 90 days and analyzed for physical characterization, dissolution and drug content.

RESULTS AND DISCUSSION

Drug excipients compatibility study: The drug excipients compatibility studies that were carried out on different combination of drug and excipients showed that there was absence of any interaction with excipients used in the formulation as the IR peaks of aceclofenac were identified.

Formulation of Pulsatile release tablet: Core tablet of Aceclofenac was prepared as per formula given in Table no. 1. Core tablets were then coated with HPC using press coating technique. Pulsatile release tablet were prepared as per formulation table no.2.The pulsatile drug delivery tablets consisted of inner core tablet and outer coating layer of HPC. HPC was chosen because of its eroding behavior. Two grades of water soluble HPC i.e HPC-L and HPC-M (both are hydroxypropyl cellulose derivatives varying in molecular weight and apparent viscosity) were used in the present research work. To see the effect on pulsed release of Aceclofenac. To achieve desired pulse release, both polymers were used in combination with varying concentration as shown in Table no.2.

Tablet evaluation result

Photographs of core and coated tablet: Placebo tablet were prepared with pink core. The presence of core inside coated tablet can be confirmed by pink shade in the centre of coated tablet which after bisection can be seen clearly as in fig no.2.

Tablet thickness: Thickness of all formulations including core tablet was measured and are as shown in Table 4. Thickness of core tablet was found to be 3.5 mm where as coated tablet formulation F1 to F6 showed thickness from 4.70 mm to 4.93 mm.

Weight variation: Tablets demonstrated no weight variation.

Tablet hardness: The hardness of core tablet was maintained below 4 Kg/cm^2. After press coating with different proportions of HPC combination the hardness was found to be in the range of 6 Kg/cm^2 to 8 Kg/cm^2 (Table no. 4).

Friability: As per IP specifications, percentage friability of core tablet and press coated tablets was maintained below 1%. Friability for press coated tablet it was 0.06 to 0.17% (Table no.4).

Percent drug content: The % drug content of the tablet was found 99.38%; and passes as per IP limit.

Dissolution study result: Dissolution profile of the formulations F 1 to F 6 is shown in figure no.3. None of the formulations showed drug release as expected. Incorporation of core tablet into press coated tablet produce a lag time prior to drug release. When the dissolution medium reaches the core after eroding the outer barrier layer rapid drug release was observed. There is increase in lag time from 3 hrs to 7 hrs with increasing concentration of HPC-M polymer in 45 mg to 270mg in the coating blend. A further increase in amount of HPC-M retarded the total drug release resulting in no dissolution of tablet. The tablets in dissolution jar were found intact even after 8 hrs Dissolution studies [10].The study also suggested that the drug

release rate was further suppressed as the viscosity of the polymer increased. This reveals that the release rate was dependent on the dissolution rate of the polymer from the tablets. The factors affecting the drug release from such matrix tablets seemed very complicated, since water penetration into polymer matrix, hydration and gelation of the polymer, diffusion of drug through the formed gel layer, erosion of the gel layer etc. could be involved in the process of drug release [11].

Optimization study by factorial design result: The lag time was found in the range of 3 to 8 hrs for formulations F1to F6, thereafter there was no release. Therefore to determine optimum batch, a 3^2 factorial design was used. The three levels are low, medium, high weight of HPC mixture and two factors are HPC-L and HPC-M in table no. 3. Using factorial design batch F12 was optimized having lag time 6 hr (in fig no.4). The aim of this study was to design a pulsatile drug release system of aceclofenac for Rheumatoid Arthritis. In this condition there is a severe pain in the morning causing muscle stiffness retarding the movement of patient. Thus if developed formulation (F12) is administered to arthritis patient at 10-11 pm, it will release drug after 6 hrs. i.e. at 4-5 am; consequently the drug will be available before awakening of patient and provide relief from the symptoms.

Stability studies result: The results of accelerated stability studies carried out according to ICH guidelines indicated that the tablets did not show any physical changes (color change, friability and hardness), assay and dissolution characteristics during the study period

CONCLUSION

Press-coated tablets were manufactured using hydroxypropyl cellulose in the outer shell. They demonstrated a time-release pattern of drug release i.e. an initial lag phase of 6 hrs followed by rapid drug release. The lag time could be controlled by altering the HPC viscosity grade in the outer shell. From the results it can be concluded that.

- Prepared tablet had a uniform drug content, thickness & hardness. The weight variation, was within the limits specified in IP.
- From *in vitro* dissolution studies it can conclude that formulation F12 has excellent drug release as compared to other formulations. It may be due to combination effect of polymers.
- Stability studies shown that there are no changes found during study period. Thus it can be concluded that formulation was stable. Finally Press coated pulsatile release tablet of Aceclofenac can be formulated by using different grade of HPC having varied viscosities. Press coating may be an alternative technique over conventional pulsatile release systems where spray or dip coating is employed.

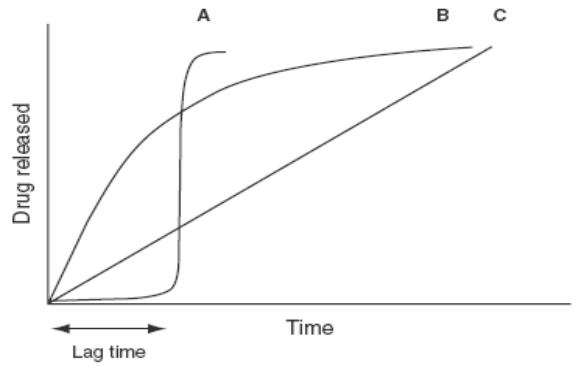

Fig. No .1. Drug release profiles: (A) pulsatile, (B) and (C) conventional extended release[12]

Fig.no.2: Tablet photo

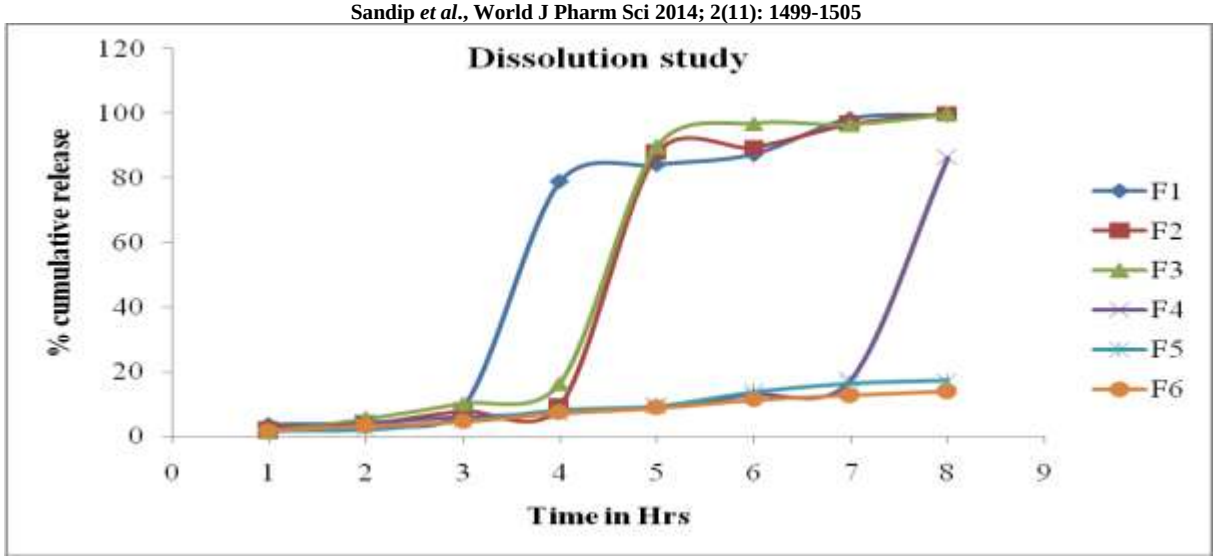

Figure No.3.In vitro drug release study of formulations F 1 to F 6 in 1.2 pH and Phosphate buffer pH 6.8 solution

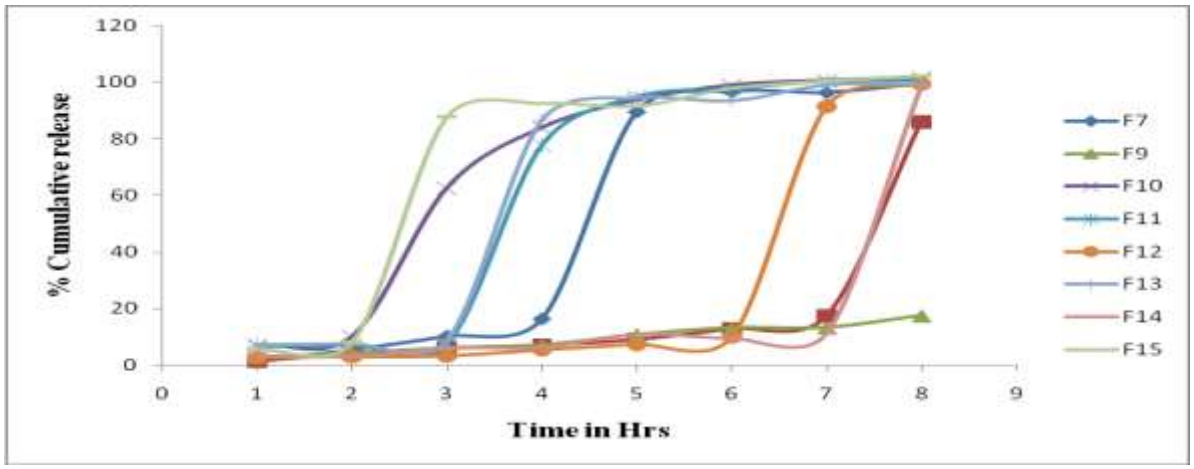

Figure No.4. In vitro drug release study of formulations F 7 to F 15 in 1.2 pH and Phosphate buffer pH 6.8 solution

Table No. 1. Composition of core tablet (Batch no F0)

Sr. No.	Material	Quantity(mg)	% w/w
1	Aceclofenac	100	66.66
2	Microcrystalline Cellulose	32.25	21.5
3	Cross povidone	9.5	6.33
4	Polyvinyl Pyrrolidone(5% solution)	6	4
5	Magnesium stearate	2.25	1.5
	Core tablet weight (mg/tablet)	150	100

Table No. 2. Formulation table (all the quantities mentioned below in mg)

Formulations / Ingredients	F0	F_1	F_2	F_3	F_4	F_5	F_6
Core tablet	150	150	150	150	150	150	150
HPC-L	0	405	360	315	270	225	180
HPC-M	0	45	90	135	180	225	270
Total	**150**	**600**	**600**	**600**	**600**	**600**	**600**

Table no. 3 Factorial design table

Formulations / Ingredients	F7	F_8	F_9	F_{10}	F_{11}	F_{12**}	F_{13}	F_{14}	F_{15}
	HL	**LH**	**HH**	**LL**	**MM**	**HM**	**LM**	**MH**	**ML**
Core tablet	150	150	150	150	150	150	150	150	150
HPC-L	315	270	315	270	292.5	315	270	292.5	292.5
HPC-M	135	180	180	135	157.5	157.5	157.5	180	135
Total	**600**	**600**	**645**	**555**	**600**	**622.5**	**577.5**	**622.5**	**577.5**

❖ H=high, M=medium, L=low

Table No. 4. Physical Evaluation of tablet formulations

Formulation Code	Weight Variation ±SD(mg)	Hardness ±SD (kg/cm^2) (n=3)	Thickness ±SD (mm) (n=3)	Friability%	Drug Content (%)
CORE	154.1±4.19 (20 tablets)	3.93±0.09	3.5±0.00	0.84 (10 tablets)	100.40
F1	604±5.50 (10 tablets)	6±0.34	4.7±0.08	0.14 (6 tablets)	99.49
F2	604±5.81	6.4±0.33	4.73±0.04	0.06	99.35
F3	601.6±6.87	8±0.28	4.86±0.04	0.06	99.93
F4	603.2±5.68	7±0.57	4.93±0.04	0.17	98.58
F5	603.7±7.21	6±0.52	4.93±0.04	0.17	100.70
F6	601.8±6.22	6±0.33	4.86±0.09	0.08	98.87

Table No.5 dissolution profile data of Aceclofenac pulsatile release tablet in pH 1.2 and phosphate buffer pH 6.8 solution

Time in Hours	Cumulative Drug Release (%)					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
1	3.704	2.567	1.430	1.429	1.755	1.917
2	4.395	3.895	5.507	4.207	2.099	3.075
3	8.830	7.837	10.279	6.041	4.721	4.571
4	78.860	9.233	16.403	7.082	8.210	7.221
5	84.040	87.789	89.688	9.109	9.414	8.762
6	87.24	89.41	96.85	12.94	13.74	11.29
7	98.30	96.70	96.50	17.50	16.30	12.6
8	99.48	99.89	99.68	86.22	17.32	13.83

Table No.6 dissolution profile data of Aceclofenac pulsatile release tablet in pH 1.2 and phosphate buffer pH 6.8 solution

Time in Hours	Cumulative Drug Release (%)								
	F7	**F8**	**F9**	**F10**	**F11**	**F12##**	**F13**	**F14**	**F15**
1	1.430	1.429	2.891	6.953	6.628	2.567	7.116	3.217	5.816
2	5.507	4.207	4.223	10.153	7.026	2.758	7.519	2.927	8.155
3	10.279	6.041	6.057	62.738	7.591	3.113	8.739	5.884	87.848
4	16.403	7.082	7.098	83.992	77.854	5.259	86.813	6.111	92.558
5	89.688	9.109	10.749	93.811	94.962	7.266	94.760	10.726	91.625
6	96.85	12.94	13.165	99.058	97.792	9.782	93.688	9.381	97.980
7	96.50	17.50	13.298	100.778	100.479	91.440	99.252	11.100	100.496
8	99.68	86.22	17.510	101.855	100.910	99.438	99.669	98.748	102.216

##= Formula with desired release profile

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