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Research Article

FORMULATION AND EVALUATION OF NAPROXEN PULSATILE TABLETS FOR CHRONOMODULATED DRUG DELIVERY USING CORE IN CUP METHOD

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ABSTRACT

The objective of this research work was to prepare a chrono-modulated drug delivery system to meet chronopharmacological needs of arthritis. In this study naproxen was selected as a model drug. Core in cup tablets is a novel oral pulsatile release drug delivery system based on a core-in-cup dry coated tablet, where the core tablet surrounded on the bottom and circumference wall with inactive material. The system consists of three different parts, a core tablet containing active ingredient, an impermeable outer shell and a top layer-barrier of a soluble polymer. The impermeable coating cup consisted of ethyl cellulose and the top cover layer of hydrophilic swellable material. The system releases the drug after certain period of lag time generally due to the erosion of top cover layer. To meet this objective an initial lag phase for 3-5 hrs and later a rapid release phase was considered. The lag phase in release (2hr) was achieved by coating EC core tablets with release retarding polymers HPMCK4.

Keywords: Pulsatile, chronopharmacological, arthritis, ethyl cellulose, HPMC.

INTRODUCTION

In recent years, oral drug delivery system with zero order sustained-release kinetics have been developed to control drug release using various mechanisms, including matrices with controllable swelling, diffusion, erosion, and osmotically driven systems. Efforts are being made to avoid typical plasma concentration peak through fluctuations and to reduce frequency of drug administration for better patient compliance. Recently, novel systems have been developed that release the drug after a programmable lag time.

Changes in the biological rhythms of the human body (ie, chronobiology) may precipitate serious medical conditions,eg, mycordialinfaction or stroke, in addition to the manifestation and severity of symptoms of chronic diseases, including allergic rhinitis,asthama, nocturnal acid reflux, and arthritis. For such chronopathological conditions chronotherapeutic systems play an important role, because these formulations take into account probable time-dependent variation in risk or symptoms of diseases.Such systems are designed to enable a pulsatile release of drug after a predetermined off–release period (lag time) which mimics the chronopathological symptoms.

A pulsatile therapeutic system can be a single unit (eg, a tablet or capsule) or be multiparticulate (eg, pellets). Capsule-based pulsatile release systems have also been developed which are coated with a water-impermeable or semipermeable membrane containing a hydrogel polymer plug which swells with times after coming into contact with gastro intestinal fluid, an exerts an

internal pressure leading to release of drug after rupture of the membrane.

Pulsatile tablet formulations are manufactured with a rapid-release core (reservoir) encased in a barrier layer formed by a rupturable press coating or liquid coating of erodible and swelling polymer. Polymers like various grades of HPMC or ethyl cellulose have been tested as film coating to achieve the desired lag time. However, a potential problem associated with the film-coated pulsatile systems is delayed drug release after loss of the barrier coat. To get immediate release of the drug after a desired lag time, press-coated systems with a rupturable coat have been suggested. In addition, press coating overcomes the draw bags of liquid coating because it does not required use of a solvent and requires a relatively shorter manufacturing process. With newer technologies, tablet compression and press coating can be achieved in a single step. In addition it is possible to control lag time by changing the coating thickness and composition.

Naproxen, a non steroidalanti inflammatory drug, is used for the symptomatic relief of pain and joint stiffness in patients suffering from rheumatoid arthritis, which is characterized by diurnal variation in circulating levels of proinflommatory cytokimes, interleukin-6 and/or tumour necrosis factor-α. Due to this diurnal variation, many symptoms and signs of active rheumatoid arthritis or manifested in the morning. To coinside with the release of this inflammatory cytokines and peak plasma naproxen levels, a press coated pulsatile tablet (PCPT) formulation was developed to alleviate the symptoms of morning stiffness in patients with rheumatoid arthritis. PCPT, on oral administration at bed-time, release naproxen after a desired lag time of about 360 minutes which correspondes with peak levels of proinflommatory mediators.

The current study illustrates the formulation, characterization, and optimization of a PCPT for naproxen. The system is based on a rupturable coat in which HPMC is incorporated in the coating composition to provide the desired lag time of 360 minutes, and superdisintegrants in the core tablet enables rapid release of naproxen after the coat ruptured.

MATERIALS AND METHODS

Naproxen was donated by MYLCHEM Mumbai, MCC (MYLCHEM Mumbai), SSG (SD Fine CHEM, Bangalore), Ethyl Cellulose (SD Fine CHEM Ltd Mumbai), HPMC (Dr.Reddy's Lab, Hyderabad).

PREPARATION OF CALIBRATION CURVE OF NAPROXEN

1. Stock sample preparation

Accurately weighed 100 mg of drug (naproxen) was first dissolved in 100 ml of phosphate buffer (pH 6.8) in 100 ml of volumetric flask to make a concentration of 1000 µg/ml (primary stock solution)5 ml of primary stock solution was pipette out into 50 ml of volumetric flask and volume was adjusted with phosphate buffer (pH 6.8) to make a concentration of 100 µg/ml (secondary stock solution).

2. Sample preparation

From secondary stock solution various concentrations such as 2, 4, 6, 8, 10, 12, 14, 16 µg/ml were prepared for calibration curve. Standard curve was plotted by taking absorbance of secondary stock solutions in UV double beem spectrophotometer (at 273 nm).

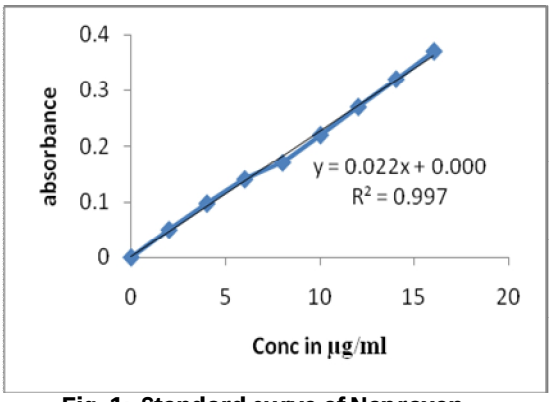


Fig. 1: Standard curve of Naproxen in pH 6.8 buffer

Preparation of core tablets

The core tablet formulations were prepared with drug using 7 mm punches, by using different ratios of superdisintegrants with direct compression.

PROCEDURE

- Naproxen and all other ingredients were individually passed through sieve #60.
- All the ingredients were mixed thoroughly by triturating upto 15 minutes.
- The powder mixture was lubricated with Magnesium stearate.

- The tablets were prepared by using direct compression method according to the formulation table given below.

Ingredients (mg)	F1(mg)	F2(mg)	F3(mg)	F4(mg)	F5(mg)
API	250	250	250	250	250
CCS	30	---	50	----	20
SSG	---	30	0	50	30
TALC	10	10	10	10	10
Mg.Sterate	10	10	10	10	10
MCC	100	100	80	80	80

Evaluation of core tablets

Tablets were evaluated for thickness, diameter, hardness, disintegration, friability and uniformity of weight. The core tablet formulation exhibited uniform thickness and diameter with optimum hardness and friability of less than 1.0 %. The disintegration time for the core tablets was found to be less than 1 minute. Rapid disintegration is desirable to get a rapid release after the coat rupture from core tablet.(The results are shown below in given Table #3)

In vitro Dissolution Studies of tablets

Dissolution parameters

Apparatus	USP-II, Paddle method
Dissolution medium	Phosphate buffer
RPM	50
Sampling intervals (min)	5, 10, 15, 20, 30, 45, 60
Temperature	37±0.5ºC

Dissolution study

900ml of phosphate buffer was placed in the vessel and the USP apparatus-II (Paddle method) was assembled.The medium was allowed to equilibriate to temp of 37 ± 0.5ºC. From the formulations F1, F2, F3, F4, F5, each tablet was placed in the vessel and the vessel was covered, the apparatus was operated for 1 hour at 50 rpm.At definite time intervals, 5ml of the fluid was withdrawn; filtered and again 5ml of the fresh buffer was replaced. Suitable dilutions were done with the dissolution fluid and the samples were analyzed spectrophotometrically at 273 nm.

From all the formulations F1, F2, F3, F4, F5, tablets the best drug release was obtained for F4 with 96.8 %.(This was shown in Table #4).The F4 tablets was further subjected to press-coat method.

Preparation of core in cup tablets

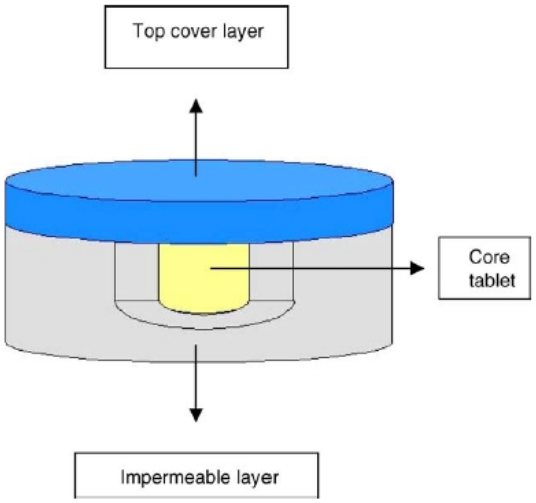


Fig. 2: Schematic representation of " Core in Cup tablet " as a pulsatile drug delivery system

The optimized core tablets were taken for press coating method. The core tablets were taken for 9mm punches are used to prepare core in cup tablets.

The ethyl cellulose was placed at the bottom and gently compacted to make powder bed, core tablet is placed at the center and impermeable ethyl cellulose is placed at the sides of the tablet so that surrounding surface of core tablet was fully covered.On the top a blend hydrophilic soluble polymer material is placed and finally compressed to get a core in cup tablet.

The prepared PCPT tablets were subjected to dissolution in USP-II apparatus using dissolution medium of 0.1 HCL for 2-3 hours and the same tablets were placed in a dissolution medium with phosphate buffer for further release of the drug.

RESULTS AND DISCUSSION

A rapidly releasing core tablets of naproxen was developed by admixing naproxen with different ratios of superdisintegrants. The pattern of release of drug from naproxen is shown in Figure 4.

Drug excipients compatability studies

Naproxen was mixed with all excipients, used in the formulation with different ratios and subjected to physical observation/FTIR in Figure 3.

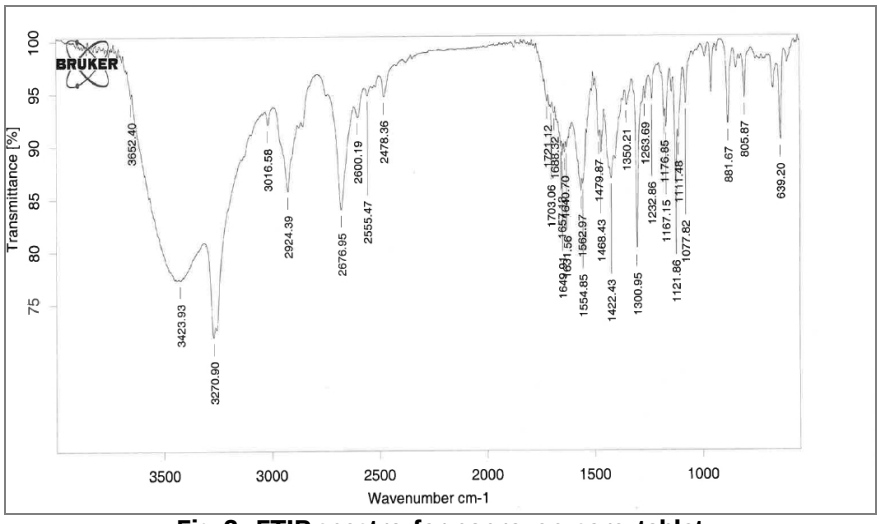


Fig. 3: FTIR spectra for naproxen core tablet

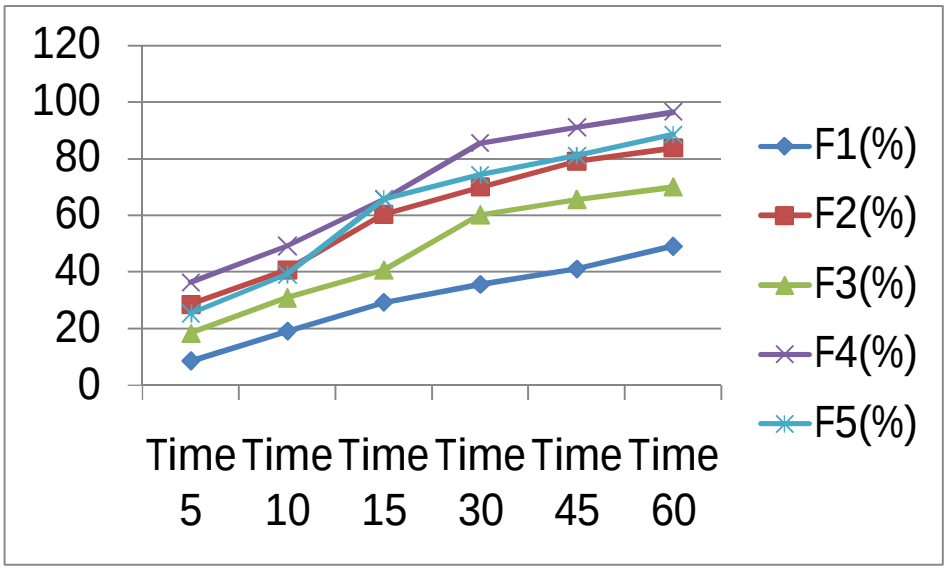
Table 3: Evaluation of core tablets

Formulation	Uniformity of weight ± SD (n=20)	Hardness Mg/cm² ± SD (n=10)	Thickness mm ± SD (n=5)	Friability (%)	Disintegration Time (min)
F1	400±1.5	4.6±0.32	2.94±0.55	0.435	2
F2	399±1.23	4.4±0.24	3.4±0.01	0.392	2.45
F3	383± 1.65	3.8±0.41	2.92±0.01	0.546	3.50
F4	395±1.23	3.6±0.28	2.73±0.6	0.892	2.50
F5	400±1.92	4.2±0.17	3.45±0.8	0.242	3.20

All the values are expressed as mean of sd = standard deviation

Table 4: Percentage drug release of core tablets

TIME	F1(%)	F2(%)	F3(%)	F4(%)	F5(%)
5	8.6	28.6	18.4	36.4	25.4
10	19.2	40.8	30.9	49.2	39.2
15	29.4	60.4	40.7	65.7	65.8
30	35.7	70.1	60.3	85.6	74.4
45	41.2	79.2	65.7	91.2	81.2
60	49.2	83.8	70.1	96.8	88.6



In the above graph % Drug release represents on Y axis and Time on X axis
Fig. 4: Drug release profile graph

Table 5: Formula of core in cup tablets

Ingredients	F1	F2	F3	F4	F5
HPMCK4	50	50	50	50	50
EC	100	150	175	200	250

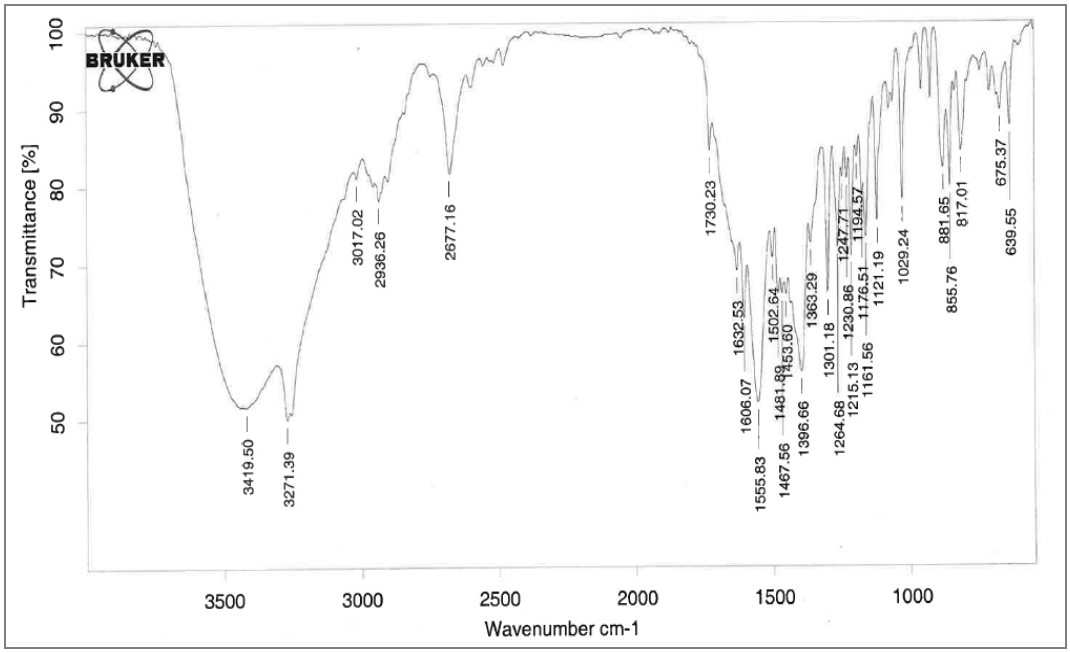


Fig. 5: Compatability studies for API and polymers

Table 6: Evaluation of press-coated tablets

Formulation	Uniformity of weight ± SD (n=20)	Hardness Mg/cm² ± SD (n=10)	Thickness mm ± SD (n=5)	Friability (%)
F1	550±1.5	5.6±0.32	2.84±0.55	0.435
F2	585±1.23	3.4±0.24	3.4±0.01	0.386
F3	600± 1.65	4.8±0.41	3.92±0.01	0.456
F4	595±1.23	4.6±0.28	2.42±0.6	0.692
F5	650±1.92	4.2±0.17	2.45±0.8	0.342

In vitro dissolution of pulsatile press-coated tablets

Dissolution study of resultant press-coated tablets was first carried out in 0.1 HCL, lag phase of 2 to 3 hours when no release of drug was found in 0.1 HCL during this lag phase.

In phosphate buffer (pH 6.8), drug release was found to be more than 99.9 % after 8-9 hours. shown in Table 7.

Table 7: In vitro dissolution of pulsatile press-coated tablets

Time (Hrs)	F1(%)	F2(%)	F3(%)	F4(%)	F5(%)
1	1.68	2.6	3.1	2.5	1.9
2	2.9	3.9	3.9	5.9	3.2
3	7.2	4.2	5.2	6.5	4.1
4	98.44	4.8	6.3	7.04	4.9
5		5.02	7.5	7.2	5.6
6		5.41	7.81	7.6	7.2
7		6.32	8.14	7.8	7.8
8		6.81	8.48	8.2	8.9
9		99.98	101.3	8.6	9.2
10				8.9	9.6

CONCLUSION

In accordance with chronomodulated core in cup method for rheumatoid arthritis, an initial lag phase of 2-3 hours is achieved in pH 0.1 HCL necessary where drug release should be minimal or absent.

Hence it was concluded that naproxen pulsatile press-coated tablets with HPMC and EC of F2, F3 formulations displayed a lag time of 8-9 hours, in dissolution medium of phosphate buffer pH 6.8 followed by rapid release of Naproxen at 99.98%, 101.3% and mimicking the fluctuating symptoms of rheumatoid arthritis.

The Novel PCPT developed for Naproxen could be a promising chronomodulated therapeutic system for the relief of morning stiffness in patients with rheumatoid arthritis. The technology used for the preparation of PCPT is a relatively simple manufacturing process which can be easily adopted in industrial units on a commercial scale.

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