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FORMULATION AND EVALUATION OF NAPROXEN CHRONOMODULATED PULSATILE DRUG DELIVERY SYSTEM

M Nalini Krishna Reddy[1], T Ramya Krishna[2] and A Jaswanth[3]

[1]Talla Padmavathi Pharmacy College, Urus, Kareemabad, Warangal.

[2]St Peters Institute of Pharmaceutical Sciences, Hanamkonda, Warangal.

[3]Procadence College of Pharmacy, Pragnapur, Gajwel, Madak.

*Corresponding Author Email: mnalinireddy@yahoo.com

ABSTRACT

The objective of present work was to formulate and evaluate an oral pulsatile drug delivery system to achieve time release of Naproxen, based on chronomodulated approach for management of pain in Rheumatoid Arthritis. Core tablets (CR) of Naproxen were prepared by direct compression method using optimum concentration of superdisintegrant. CR tablet was then press coated using different grades of HPMC like E5, E15 and E50 in varying ratios. Pulsatile tablets were evaluated for pre-compressional and post-compressional parameters. CR tablet formulated with 4% explotab showed 75.79±0.56% release in 10min it was suitable for formulating it into pulsatile release tablets. On the basis of in-vitro release profile it was found that the optimized formulation F6showed the lag time of about 6hrs which showed compliance with chronotherapeutic objective of rheumatoid arthritis. Solid state characterization studies indicated that there was no interaction between drug and excipients. The lag time and time controlled behavior of Naproxen from press coated tablets could be modulated by changing the viscosity of HPMC, coating weight and polymer concentration. Drug is released as a burst after a lag time (during peak morning hours), hence pulsatile drug delivery of Naproxen can be helpful for the arthritis patients in giving relief from morning surge.

KEY WORDS

Naproxen, lag time, pulsatile drug delivery.

INTRODUCTION

It is evident that drug delivery and therapy should be modified to achieve an efficient drug level at an optimum time, rather than maintaining constant drug concentrations. Recently, chronotherapy has been extensively applied in clinical therapy by modulating the dosing regimen of drug administration according to physiological needs[1]. Chrono-pharmaceutics includes pharmaceutical application of "Chronobiology" in drug delivery.Chronobiology is the study of biological rhythms and their responses to other metabolic functions of body[4]. Chronopharmaceutics is a branch of pharmaceutics devoted to the design and evaluation of drug delivery systems that release a bioactive agent at rhythm that ideally matches the biological requirement of a given disease therapy[2]. Pulsatile drug delivery systems (PDDS) are gaining importance as these systems deliver the drug at specific time as per the pathophysiological need of the disease, resulting in improved patient therapeutic efficacy and compliance. 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. Numerous studies, suggest that pharmacokinetics, drug efficacy and side effects can be modified by following therapy which matches with the biological rhythm[5]. Specificity in delivering higher amount of drug in a burst at circadian timings should correlate with specific pathological disorder which is a key factor to achieve maximum drug effect[5]. Oral drug delivery is typically considered as the favorable and the most preferable route having the highest degree of patient compliance. If the timing of dosage regimen is adjusted according to cyclic rhythm of diseases effective management can be achieved.

Diseases such as bronchial asthma, hyper-cholestremia, ulcer, diabetes, arthritis, myocardial infarction, angina and hypertension show symptomatic changes due to circadian rhythmicity.The chronobiology, chronopharmacology and chronotherapeutics of pain have been extensively reviewed. For instance, there is a circadian rhythm in the plasma concentration levels of C - reactive protein and interleukin-6 in patients with rheumatoid arthritis. In rheumatoid arthritis, levels of C – reactive protein increases early in the morning leading to enhanced pain and inflammation. Chronotherapy for all forms of arthritis using NSAIDs should be timed to ensure that the highest drug levels in the blood should coincide with peak pain[7]. The oral press coated tablet was developed to achieve the time-controlled disintegrating or rupturing function with a distinct predetermined lag time. By considering these factors, Naproxen press coated tablets was developed to achieve the time-dependent release with a distinct predetermined lag time.

MATERIALS

Naproxen, Explotab, Methocel LV Premium E5, E15, E50 was gift sample from Hetero drugs, Hyderabad, India. All other chemicals used were of analytical grade.

EXPERIMENTAL METHODS

Preparation of rapid release core tablets by direct compression method: Accurately measured quantities of drug, superdisintegrant, diluent, glident and antiadherant were taken and blended properly for 15 min, then the blend was compressed using 9mm flat punches on 16 station tablet punching machine. (Cadmach, Ahmedabad, India). Three types of core tablets (Table 1) were prepared containing different ratio of superdisintegrant.

Preparation of pulsatile release tablets (PRT): Best rapid release core tablet was used for preparation of pulsatile release tablets using different grades of Methocel LV Primium (HPMC E5, E15 and E50) at different concentrations (Table 2). Press coated tablet was prepared by placing 50% of polymer in 12mm die and core tablet was placed on it. Further remaining quantity of polymer was added and finally compressed using 16 station tablet punching machine. (Cadmach, Ahmedabad, India)

Evaluation of tablets:

The prepared tablets were evaluated for various physical parameters like weight variation, hardness, friability and drug content uniformity.

Drug Content of Core Tablet: Tablets were finely powdered and quantity of the powder equivalent to 10 mg of Naproxen was accurately weighed and transferred to volumetric flask containing 100 ml phosphate buffer (pH 6.8) and mixed thoroughly. One milliliter of filtrate with suitable dilution was estimated for Naproxen content at 245nm using double beam spectrophotometer (Shimadzu Corporation, Japan, UV-1700).

Infrared Spectroscopy FTIR analysis measurements of Naproxen, core formulation & press coated formulation were obtained by JASCO V5300 FT-IR (Tokyo, Japan). The pellets were prepared on KBr-press (Spectra Lab, Pune, India) under hydraulic pressure of 150 kg/cm^2

In vitro drug release study In *vitro* drug release studies were conducted using USP type II

dissolution apparatus at 50 rpm speed and 37 C ± 0.5 C temperature in 900 ml dissolution media (0.1 N HCl for first 2 h and then in phosphate buffer pH 6.8 from 3 to 8h). An aliquot (5 ml) was withdrawn at specific time intervals and replaced with the same volume of pre-warmed fresh dissolution medium. The withdrawn samples were filtered and analyzed by using UV spectrophotometer at 245 nm.

RESULTS AND DISCUSSIONS

Precompression Parameters of Core Tablet Powder Blend: Powder blends of all formulations were characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio. The angle of repose was less than 25^{o} and Carr's index values were more than 15 - 20 indicating good to fair flow ability compressibility(Table 3). Hausner's ratio was less than 1.3 for both the batches indicating good flow properties.

Evaluation of tablets: All the tablets of different batches compiled with the official requirements(Table 4). The weights varied within the limits for both core & coated tablets The hardness of press coated tablets ranged from 6.2 to 6.8 kg/cm2 and the friability values were less than 0.5% indicating that the tablets were compact and hard. The thickness of the tablets ranged from 3.1 to 4.17 mm (Table 6). All the formulations satisfied the drug content as they contained 98.4 to 99.5 % of naproxen and good uniformity in drug content was observed.

In vitro drug release profile: As the superdisintegrant concentration increased complete drug release within 15min was observed. The drug release from the core tablets containing 4%explotab resealed 75% of the drug within 15 min it was suitable for formulating into pulsatile release tablets (Table 5) (Figure1). As the coated tablet was placed in the medium, it was observed that the hydrophilic polymeric layer started swelling, which underwent progressive modification in terms of thickness and consistency. In gradually starts to erode up to a limiting thickness. After this stage, a rupture of the shell was observed under the pressure applied by the swelling of the core tablet releasing drug from core tablets. All of this process corresponded to a lag time capable of exhibiting a pulsatile release of the drug. The profiles relevant to the coated tablet showed that a lag phase was allowed by the quick delivery of the active agent (Table 7). The delayed duration clearly depended on the kind and amount of hydrophilic polymer which was applied on the core. The lag time of the tablet coated with 400 mg of HPMC E50 (F6) was found to be 6h. A significant lag time followed by brust release of drug is seen in all the formulations (Figure 2).

Fourier transform infrared spectroscopy (FTIR): FTIR spectra of the drug, excipients and the optimized formulation were recorded in range of 4000-400 cm^{-1}. Naproxen exhibits sharp bands at 1227cm-1 due to C-O stretching(ether), 1264cm^{-1} due to C-O stretching(acid), 1394cm-1 to 1363cm-1 due to CH3 bending, 3420cm^{-1} due to aromatic stretching, 2963cm-1 and 2938cm-1 due to aliphatic stretching and 3002cm^{-1} and 2838cm^{-1} due to C-H aliphatic stretch. In the optimized formulations, the presence of all the characteristic peaks of the Naproxen indicates lack of any strong interaction between the drug and the excipients which are indicated in figure 3, 4 & 5 for formulations naproxen pure drug, CF1 & F6 respectively.

CONCLUSION

The lag time and time-controlled release behavior of naproxen from press-coated tablets could be modulated by changing the viscosity of the polymer and coating weight. Formulation F6 compression coated tablets achieve a burst release after 6h lag time which is applicable pulsatile drug delivery of naproxen

Table 1: Formulations of naproxen rapid release core tablet prepared by direct compression method.

Ingredients	CF_1	CF_2	CF_3
Drug	100	100	100
Explotab	8	12	16
Avicel pH 102	88	84	80
Magnesium stearate	2	2	2
Talc	2	2	2
Total Weight (mg)	200	200	200

Table 2: Formulations of naproxen pulsatile release tablet prepared by direct compression method.

Formulations	PF1	PF2	PF3	PF4	PF5	PF6
Core tablet (mg)	200	200	200	200	200	200
METHOCEL LV Premium E5 (mg)	200	--	--	400	--	--
METHOCEL LV Premium E15 (mg)	--	200	--	--	400	--
METHOCEL LV Premium E50 (mg)	--	--	200	--	--	400
Magnesium stearate (mg)	2	2	2	4	4	4
Talc (mg)	2	2	2	4	4	4

Table 3:Characterization of powder blend of Naproxen Core tablet

Formulations	Angle of Repose	Bulk Density (g/cc)	Tapped Density(g/cc)	Hausner Ratio	Percent Compressibility Index
CF1	22.97	0.344	0.408	1.18	15.6
CF2	24.84	0.324	0.401	1.23	19.2
CF3	25.21	0.33	0.411	1.24	19.7

Table4: Physical evaluation tests of Naproxen core tablets

Formulations	Weight Variation (mg)	Hardness (Kg/cm^2)	Friability (%)	Thickness (mm)	Disintegration Time(sec)	Drug Content (%)
CF1	200.2 ±4.67	3.5±0.3	0.42±0.5	3.5±0.2	60±5.32	98.97 ± 0.6
CF2	200.31±3.52	3.3±0.2	0.39 ±0.8	3.48±0.4	43±2.39	98.88 ±0.9
CF3	200.25±3.47	3.6±0.3	0.44±0.6	3.49±0.4	40±3.44	99.09 ± 1.2

Table 5: Cummulative percentage drug release of Naproxen from core tablets in 6.8 pH buffer.

Time (min)	CF1	CF2	CF3
0	0	0	0
10	74.92±0.47	79.39±0.49	88.4±0.72
20	88.97±1.56	88.04±0.92	97.29±1.84
30	97.25±0.16	95.41±1.16	92.78±2.49
45	95.32±3.48	86.88±1.14	90.08±1.60
60	88.56±4.68	87.39±2.39	85.73±5.12

Figure 1: Cummulative percentage drug release of Naproxen from core tablets in 6.8 pH buffer.

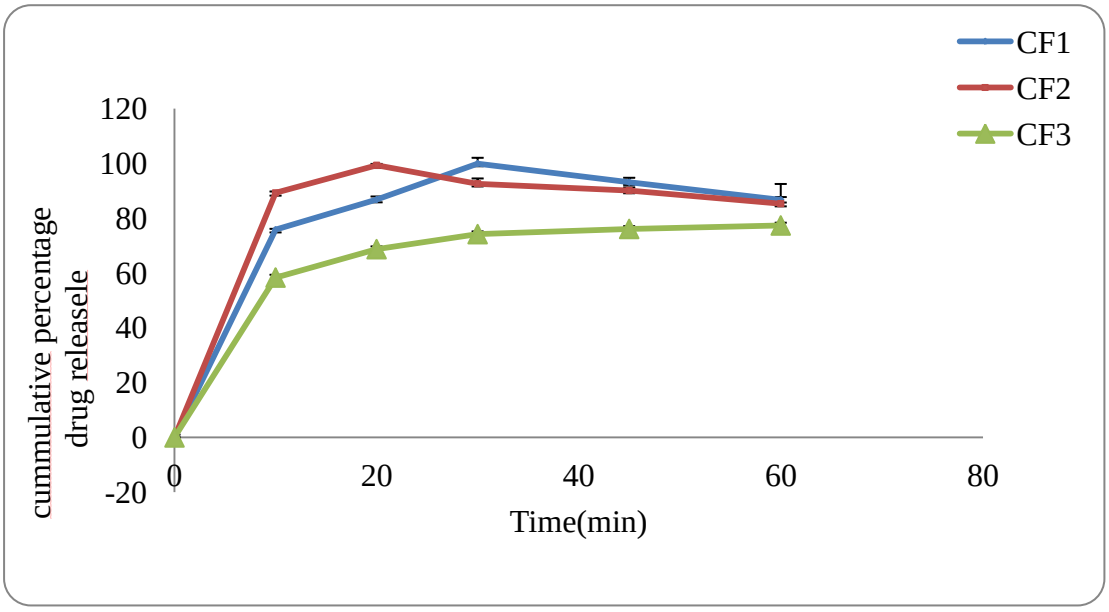


Table 6: Physical evaluation tests of naproxen compression coated tablets

Formulations	Weight Variation (mg)	Hardness (Kg/cm^2)	Friability (%)	Thickness (mm)	Drug content (%)	Lag time (hr)
PF1	404±0.7	6.8±0.65	0.35±0.49	3.1 ± 0.2	99.10±1.21	0.35±0.13
PF2	404±0.6	6.2±0.21	0.38±0.34	3.12 ± 0.8	98.66±2.00	0.3 ±0.15
PF3	404±0.4	6.6±0.34	0.36±0.23	3.2 ± 1.0	98.20±1.46	1.05 ± 0.25
PF4	608±0.5	6.5±0.81	0.37±0.67	4.12 ± 0.7	99.30±0.33	4.02±0.54
PF5	608±0.2	6.2±0.45	0.32±0.55	4.17 ± 0.8	98.87±0.56	4.27±0.35
PF6	608±0.3	6.8±0.35	0.38±0.54	4.17 ± 0.8	99.48±1.31	5.40±0.21

Table 7: Cummulative percentage drug release of naproxen from compression coated tablets

Time(hr)	PF1	PF2	PF3	PF4	PF5	PF6
0	0.00	0.00	0.00	0.00	0.00	0.00
1	90.30	76.80	89.20	0.25	0.22	0.36
2	98.00	89.00	99.80	0.79	0.45	0.23
3	--	--	--	1.10	1.06	0.43
4	--	--	--	96.29	1.31	1.07
5	--	--	--	99.09	89.93	1.16
6	--	--	--	--	93.6	96.33
7	--	--	--	--	--	97.02

Figure2: Cumulative percentage drug release of naproxen from press coated tablets

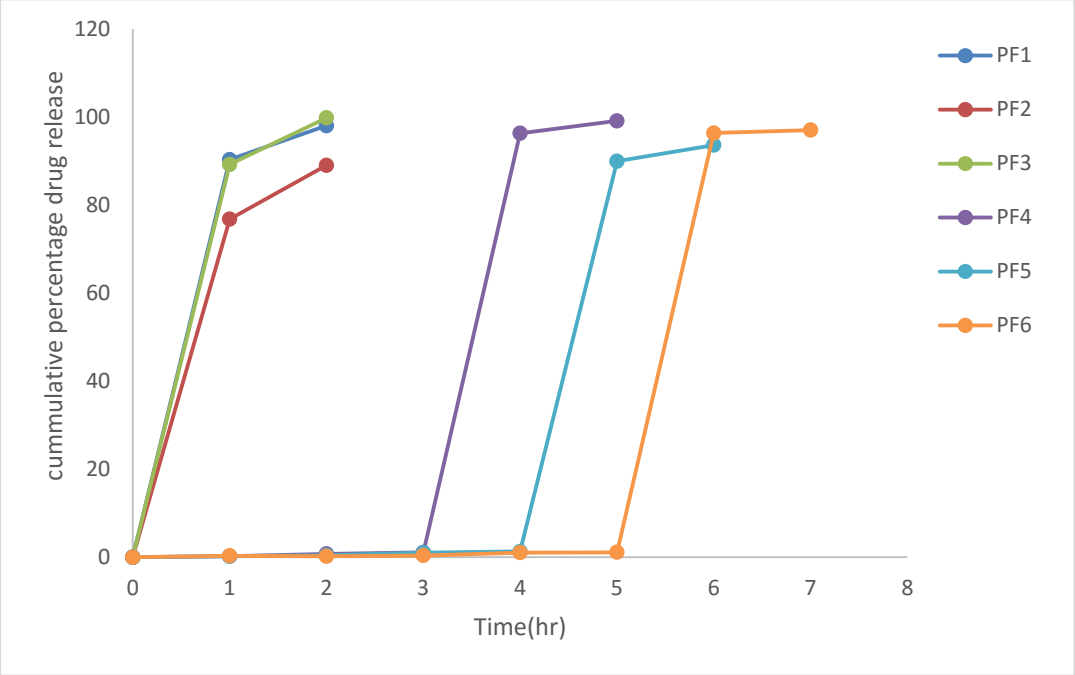


Figure 3: FTIR of Naproxen

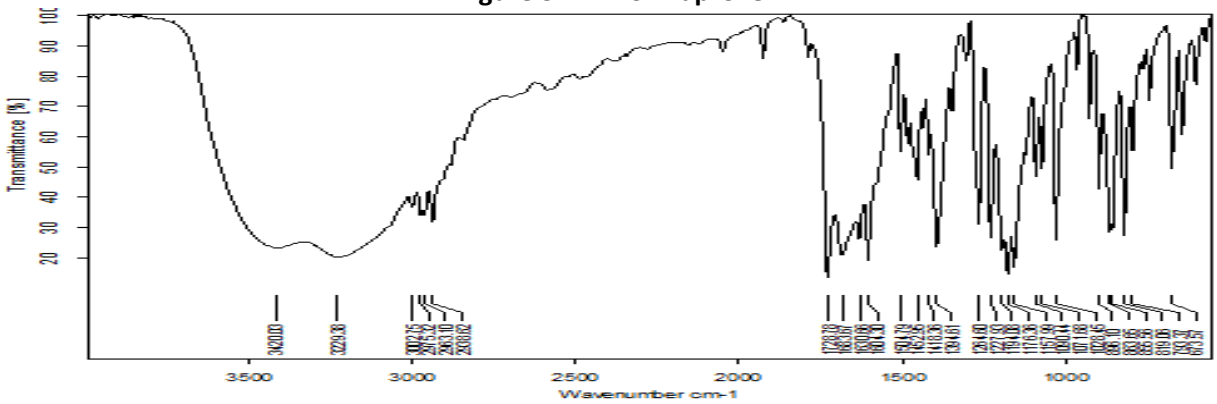


Figure 4: FTIR of core (CF1)

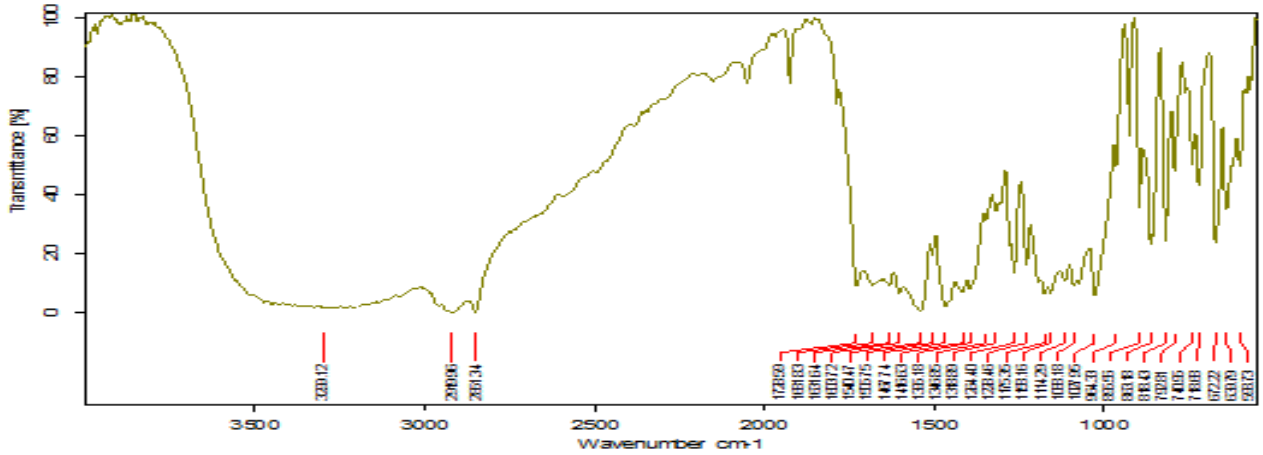
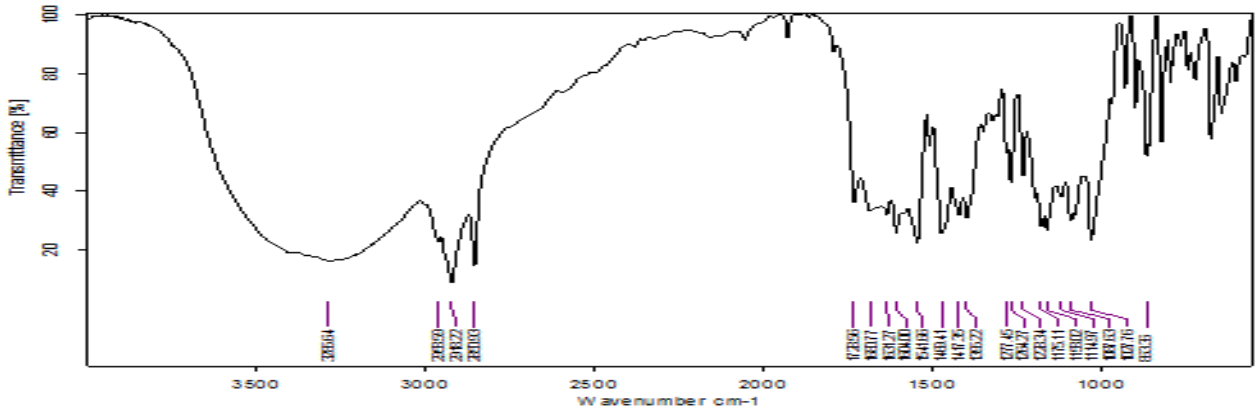


Figure 5: FTIR of Press coated formulation (F6)



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*Corresponding Author:
mnalinireddy@yahoo.com