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Original Article

FORMULATION AND EVALUATAION OF COLON TARGETED MATRIX TABLET OF NAPROXEN

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ABSTRACT

Objectives: The objective of the present study is to formulate the Colon targeted delivery containing Naproxen for chronopharmaceutical drug delivery system (ChrDDS) for treatment of rheumatoid arthritis, which are influenced by circadian rhythm. Chronopharmaceutical drug delivery system is capable of delivering drug when and where drug required most. Naproxen would remain in the GIT Fluid, intestinal fluid and it will liberate only in colonic fluid and gives better absorption.

Methods: The matrix core tablets of Naproxen were prepared by direct compression method by using Crosspovidone as superdisintegrant. From those optimesd batch core tablet is further going for coating. Coating was carried out by using natural gums like Xanthan gum, Guar gum, Chitosan and Pectin alone and in combination.

Results: From the experimental work Crosspovidone shows good drug release. Coating done by combination of Xanthan Gum and Chitosan shows better drug release (98.24%) in sustained release manner than other natural gums like Guar gum and pectin.

Conclusion: From the results obtained, it was concluded that the programmable Chronopharmaceutical drug release has been achieved from Crosspovidone containing core tablet compressed coated by combination of Xanthan gum and Chitosan over a 10 hrs period, consistent with the demands of chronotherapeutic drug delivery for rheumatoid arthritis.

Keywords: Colon targeted drug delivery, Naproxen, Chronopharmaceutical drug delivery, Rheumatiod arthritis, Xanthan gum, Chitosan.

INTRODUCTION

The oral route is considered to be most convenient for administration of drugs to patients[1]. Nearly 50% of drug delivery systems available in the market are oral drug delivery systems and these systems have more advantages due to patient acceptance and ease of administration. In recent years, colon-specific drug delivery system (CDDS) have been developing as one of the site specific drug delivery system.Along with many application in local and systemic delivery of drugs the CDDS would also be advantageous when a delay in absorption is desirable from a therapeutic point of view as for the treatment of diseases that have a peak symptom in the early morning and that exhibit circadian rhythm, such as angina, asthma and rheumatoid arthritis[2].

Chronotherapy coordinates drug delivery with human biological rhythms and holds huge promise in areas of pain management and treatment of asthma, heart disease and cancer. The coordination of medical treatment and drug delivery with such biological clocks and rhythms is termed chronotherapy. The goal of chronotherapeutics is to synchronize the timing of treatment with the intrinsic timing of illness[3].

Theoretically, optimum therapy is more likely to result when the right amount of drug is delivered to the correct target organ at the most appropriate time. In contrast, many side effects can be minimized if a drug is not given when it is needed[4-6]. Naproxen itself is rapidly and completely absorbed from the GI tract with an *in*-vivo bioavailability of 95%. Although Naproxen is well absorbed, the sodium salt form is more rapidly absorbed resulting in higher peak plasma levels for a given dose[7-8]. Arthritis is a chronomodulated disease. The attacks of arthritis is usually occurs in the early morning (4 to 5 o'clock). In this research work, an attempted has been done to develop a dosage form which deliver the Naproxen at colon and get released in the early morning.

MATERIALS AND METHODS

Naproxen was obtained as a gift sample from Devi's laboratories limited, Hyderabad. All other ingredients were used of analytical grade.

Methods

The core tablets were prepared by direct compression technique. All materials were thoroughly mixed with mortar and pestle and passed through the mesh to ensure complete mixing. The powder weighting 180 mg was taken and compressed into tablets using 8mm round, flat and plain punches on a single station tablet punching machine. Then the core tablets were coat compress coated method. For compression coating, 50% of granular material was first placed in the die cavity. Then, the core tablet ease carefully positioned at the center manually, which was then filled with the remaining 50% of granular material. The coating material was then compressed around the core tablet by using 12 mm round, flat, plain punches[9].

Drug-excipients interaction study [10,11]

The technique employed in this study is Fourier transform Infrared spectroscopy using FTIR (IR Affinity-1, Shimadzu, Japan). Fourier Transform Infrared spectroscopy is one of the most powerful analytical techniques which offer the possibility of identifying chemical interaction between drug and excipients. The diffusion reflectance spectroscopy technique was utilized in the mid-IR (400–4000 cm-1) spectral region Powder mixture of drug and polymers in the ratio of 1:1 were prepared in KBr discs. The samples were placed in the light path and the spectra were obtained Infrared was performed in duplicate for each of the samples.

Evaluation

Hardness [12,13]

Hardness indicates the ability of tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Pfizer hardness tester. It was expressed in kg/cm^2.

Friability [14,15]

The friability of the tablets was determined using Roche friabilator. It is expressed in percentage (%). Approximately 6.5 gm (Wo) of deducted tablets were subjected to rotate at 25 rpm for 4 minutes in a rotating drum of 6 inches and are then reweighed (W) The friability was given by following formula.

$$\% \text{ Loss} = \frac{\text{Initial wt. of} - \text{final wt. of tablets}}{\text{Initial wt. of tablet}} \times 100$$

Weight variation test [16]

Twenty tablets were weighed individually on weighing balance (Shimadzu, Japan), average weight was calculated and individual tablet weights were compared to the average weight The stablets met the USP test if no more than 2 tablets are outside the percentage limit and if no tablet differs by more than two times the percentage limit.

***In Vitro* drug release studies in presence of rat caecal material [17, 18] (SIP/IAEC/08/2013-2014)**

Two wistar rats of body weight (150-200g) with no prior drug treatment were used for all the present ex vivo studies and maintained on normal diet and administered 1ml of 2% dispersion of pectin in water and this treatment was continue for 7 days in order to include the enzyme that specifically act on pectin or xanthan gum or guar gum, 30 minutes before starting the study, each rat was sacrificed and abdomen was opened. The caecum was traced, legated at both ends, dissected and immediately transferred in to phosphate buffered saline (PBS) pH 6.8, which was previously bubbled with CO_2. The caecal bag was opened, the contents were weighed homogenized and then suspended in simulated colonic fluid of pH 7.4 to give desired concentration of 2% caecal content. The experiment was carried out with a continuous supply of CO_2 in to the dissolution media. Drug release studies for first 5 hr were performed as described under section describing *In vitro* drug release studies in simulated gastro intestinal fluid. After 5 hrs release studies were carried out in simulated colonic fluid containing rat caecal material. Aliquots of samples were withdrawn periodically and replaced with fresh buffer bubbled with CO_2.The samples were filtered through a whatman filter paper and drug content was determined spectrophotometrically.

Drug content [19]

Ten tablets were weighed and average weight was calculated. All the 10 tablets were crushed in a mortar. The powder equivalent to 10 mg was accurately weighed, dissolved in 5 ml of Methanol & made upto 100 ml of 0.1 N HCl. The volumetric flask was then shaken for approximately 20 minutes. The solution was filtered and 1 ml of filtrate was diluted to 10 ml using 0.1 N HCl. Absorbance was measured at 264.5 nm using 0.1 N HCl as a blank. The amount of drug present in one tablet was calculated.

Stability studies [20, 21]

The optimized formulation was charged for the accelerated stability studies according to ICH guidelines (40 ± 2ºC and 75 ± 5% RH). The tablets were packed in high density polyethylene (HDPE) container and were stored in ICH certified stability chamber for 3 months(zone III conditions as per ICH Q1guidelines) The samples were withdrawn at the end of 1 month for 3 months and evaluated for various parameters.

Formulation Table

Table 1: Composition of colon tablets

Composition of Core tablets							
Ingredients (mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**
Naproxen	150	150	150	150	150	150	150
Crosspovidone	9	9	9	9	9	9	9
MCC	7.5	7.5	7.5	7.5	7.5	7.5	7.5
PVP K30	9	9	9	9	9	9	9
Mg. stearate	2.7	2.7	2.7	2.7	2.7	2.7	2.7
Talc	1.8	1.8	1.8	1.8	1.8	1.8	1.8
Composition of Compress coated tablets							
Xanthan gum	150	-	-	-	75	75	75
Guar gum	-	150	-	-	75	-	-
Chitosan	-	-	150	-	-	75	-
Pectin	-	-	-	150	-	-	75
Starch	1.8	1.8	1.8	1.8	1.8	1.8	1.8
MCC	109.5	109.5	109.5	109.5	109.5	109.5	109.5
PVP K30	15	15	15	15	15	15	15
Mg. stearate	4.5	4.5	4.5	4.5	4.5	4.5	4.5
Talc	3	3	3	3	3	3	3
Total (mg)	480	480	480	480	480	480	480

RESULTS AND DISCUSSION

Drug-excipient interaction study

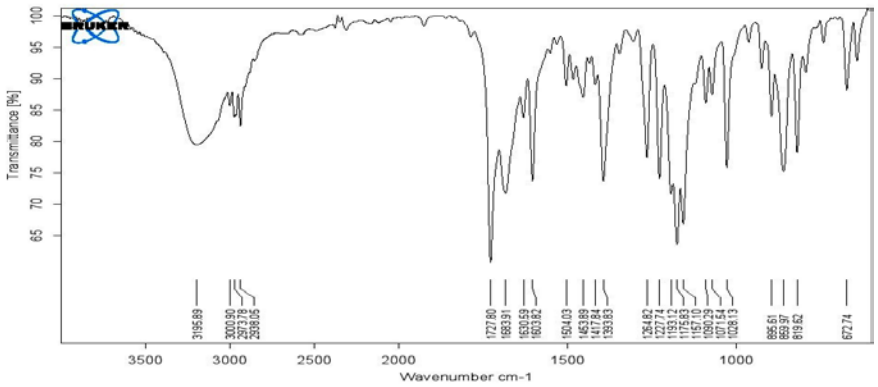

Fig. 1: IR spectral analysis of Naproxen

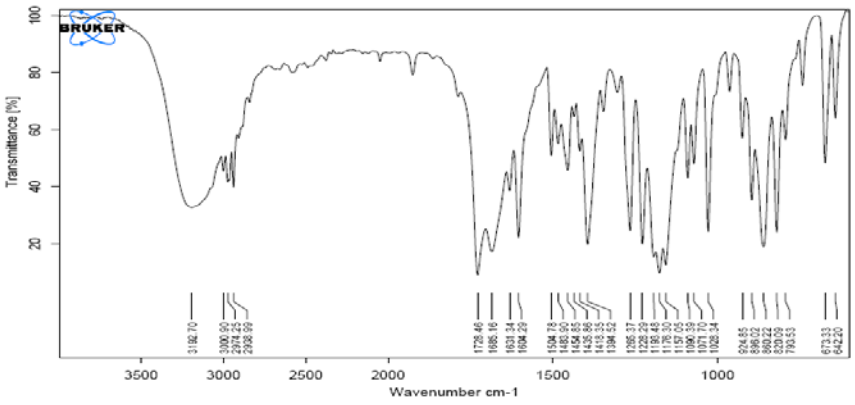

Fig. 2: IR spectral analysis Naproxen + polymer mixture

- No interaction was found between drug and polymer mixture means drug is compatible with the polymer mixture.

Table 2: Evaluation of Compressed coated Tablets

Formulation	Hardness * (Kg/cm²) (n=3)	Friability (%)	Weight variation (mg) (n=20)	Drug Content (%) (n=10)
F1	6.2±0.32	0.84%	482.5±1.22	98.02±0.04
F2	6.1±0.37	0.79%	481.2±1.74	98.44±0.01
F3	6.4±0.39	0.78%	480.2±1.37	99.63±0.5
F4	5.7±0.47	0.74%	478.5±1.75	98.08±0.07
F5	6.4±0.39	0.96%	481.8±1.19	97.51±0.09
F6	5.5±0.42	0.86%	483.5±1.25	98.09±0.07
F7	6.1±0.37	0.91%	478.2±1.20	98.45±0.01

Table 3: Stability study of optimized formulation (F6)

Parameters	Initially	After 1 months	After 2 months	After 3 months
Hardness(Kg/cm²)(n=3)	5.5±0.42	5.4±0.58	5.4±0.74	5.4±0.91
Friability (%)	0.86%	0.88%	0.89%	0.89%
% *In vitro* drug release (10th hrs)	98.24	98.11	97.88	97.34
Drug content (%)	99.26±0.07	98.89±0.11	98.47±0.25	98.43±0.14

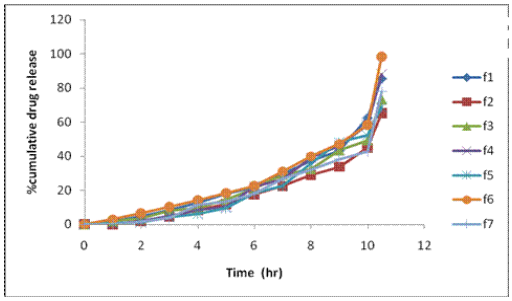

Fig. 3: *In-vitro* drug Release study of Compressed coated colon tablets

- Hardness of the formulations F1-F7 was found to be in the range of 5.5±0.42 to 6.4±0.43 and friability limit for all the formulations were below 1%.
- Drug content of all the formulations was found to be in the range of 97.51±0.09 % to 99.63±1.5 %.
- The *in vitro* drug release was found to be in the range of 65.19 to 98.24 %.

Stability Studies

From the stability studies, it was observed that there were no significant changes in the physical evaluation parameters, drug content and *In vitro* release study of optimized F6 formulation, and therefore the formulation is stable.

CONCLUSION

Based on the result obtained, the F6 was selected as the optimum formulation for colon drug delivery system. Polymers used in this study are suitable for colon targeting. I*n-vitro* drug release in phosphate buffer 7.4pH with rat ceacal material was 98.24%. Compressed coated tablet for colon was able to retard the drug in upper GIT which reduces adverse effect and further sustained release of the drug in the colon was achieved by coat with Xanthan gum and Chitosan in combination. This design can be used for colon targeted delivery of Naproxen for treatment of rheumatoid arthritis.

CONFLICT OF INTERESTS

None

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