eISSN: 2231-0541 CAS CODEN: PHARN8 An EMBASE, EMcare Covered Journal

PHARMANEST

An International Journal of Advances in Pharmaceutical Sciences

Volume 5 | Issue 1 | January-February 2014 | Pages 1751-1760

Original Research Article

FORMULATION AND *IN VITRO* EVALUATION OF COLON SPECIFIC DRUG DELIVERY OF NAPROXEN SODIUM BY USING PULSINCAP TECHNOLOGY

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Received: 10-11-2013 Revised: 27-11-2013
Accepted: 09-12-2013 Available online: 01-01-2014

ABSTRACT

The purpose of the present study was to design and evaluate an oral, site specific, and pulsatile drug delivery system containing Naproxen sodium as a model drug, which can be targeted to colon in a pH and time dependent manner, to modulate the drug level in synchrony with the circadian rhythm of Rheumatoid arthritis based on chronopharmaceutical considerations.The basic design consists of an insoluble hard gelatin capsule body, filled with powder blend and sealed with a hydrogel plug. The powder blend containing Naproxen sodium, sodium starch glycolate, sodium bicarbonate, vivapur302 and talc was prepared and evaluated for flow properties and FTIR studies. From the obtained results, G7 powder blend formulation was selected for further fabrication of pulsatile capsules. Hydrogel plug was formulated in a combination of hydrophobic polymer like ethyl cellulose with hydrophilic polymers like guar gum, xantural and HPMC K100M in 1:1, 1:1.5, 1:2, 1:2.5 and 1:3 ratios to maintain a suitable lag period and it was found that the drug release was controlled by the proportion of polymers used.The prepared pulsincaps were evaluated for drug content, weight variation and *Invitro* release studies. FTIR studies confirmed that there was no interaction between drug & polymers and *Invitro* release studies of pulsatile device revealed that increasing hydrophilic polymer content resulted in delayed release of Naproxen sodium from the pulsincap after a predetermined lag time of 6hrs. Based on *invitro* studies performed, F18 was found to be optimized formulation.

Key words: Pulsatile system; colon specific; pH and time dependent delivery; Naproxen sodium; Rheumatoid arthritis; Chronopharmaceutics.

INTRODUCTION

Site specific drug delivery systems offer several advantages over the traditional drug therapies and due to this, a great deal of research has been carried out on these systems during the last few decades. The colon, as a site for drug delivery, offers distinct advantages like longer transit time, relatively low proteolytic enzyme activity, and a much greater responsiveness to absorption enhancers[1]. Successful colonic drug delivery requires careful consideration of a number of factors, including the properties of the drug, the type of delivery system and its interaction with the healthy or diseased gut. Several approaches have been developed for targeted colonic drug delivery. Most of them utilize the physiological properties of the GIT and colon such as pH of GIT, transit time of small intestine, luminal pressure of the colon, and the presence of microbial flora localized in the colon[2].Pulsatile release pattern has gained most popular form of controlled drug delivery system because conventional systems with a continuous release are not ideal[3, 4]. Pulsatile systems are achieving a lot of interest as they deliver the drug at the right site of action at the right time and in the right amount, thus providing spatial and temporal delivery and increasing patient compliance. These systems are designed based on the circadian rhythm of

the body. The principle rationale for the use of pulsatile release is for the drugs where a constant drug release, i.e., a zero-order release is not desired. Pulsatile release systems are formulated to undergo a lag-time of predetermined span of time of no release, followed by a rapid & complete release of loaded drugs. The approach is based on the principle of delaying the time of drug release until the system transmits from mouth to colon[5, 6]. So by developing the pulsatile device for specific colonic delivery, plasma peak is obtained at an optimal time, number of doses per day can be reduced; saturable first pass metabolism and tolerance development can also be avoided. Naproxen Sodium (widely used NSAID) was frequently used for treating rheumatoid arthritis, which had apparent circadian rhythms and peak symptoms in the early morning. When orally administering Naproxen Sodium conventional formulation, it was difficult to achieve the desired clinical effect, because it elicited patient's incompliance of administration in the early morning to coordinate the rhythm of rheumatoid arthritis, due to rapid absorption of the conventional formulation. However, colon specific Naproxen Sodium delivery is not only effective, but also more convenient for administration than the conventional formulation to get the drug release after desired time period because of the few physiological facts like :- (a) Transit time to colon, (b) Colonic bacteria triggered degradation and (c) pH triggered effect. Naproxen sodium possesses good oral bioavailability and adequate colon absorption. Hence it was selected as an ideal candidate for the colon drug delivery system. This system when administered in night was aimed to achieve an elevated Naproxen sodium levels overnight where the risk of Rheumatoid arthritis was found to be maximum[7]. People with rheumatoid arthritis (RA), usually experience peak pain in the morning, which decreases throughout the day. In this scenario, an evening once-a-day nonsteroidal anti-inflammatory drug (NSAID) schedule is recommended. If pain is worse during early afternoon or at night, however, a morning or an evening once a day NSAID schedule may be recommended. The exact dose depends on the severity of the patient's pain and their individual physiology[8]. The Pulsincap system, developed and registered by R.P. Scherer International Corp., is a special dosage form comprising a water insoluble capsule body enclosing a drug reservoir. The body is closed at the open end with a swellable hydrogel plug, which consists of insoluble, but permeable & swellable polymers (e.g., Polymethacrylates), erodible compressed polymers (e.g., HPMC, PVA, polyvinyl acetate), congealed melted polymers (e.g., saturated polyglycolated glycerides, glyceryl monooleate) and/or enzymatically controlled erodible polymers (e.g., pectin). When this capsule comes in to contact with the dissolution fluid, it swells and, after a lag time, the plug pushes itself outside the capsule and rapidly releases the drug. The length of the plug and its position of insertion into the capsule control the lag time[9].In our study, a modified Pulsincap device containing Naproxen sodium was developed to target drug release in the colon. This is a site specific and time dependent formulation; by administering the formulation at 10.00 pm, symptoms that are experienced early in the morning are avoided. The study objective was to explore the time-and pH dependent controlled drug delivery of Naproxen sodium using the pulsincap system.

MATERIALS AND METHODS

MATERIALS:

Naproxen sodium was received as a gift sample from Qualitech Pharma, Hyderabad, India. Ethyl cellulose, Guar gum, Xantural, HPMCK100M, sodium starch glycolate, sodium bicarbonate, vivapur 302 and talc was obtained from Spectrum pharma research solutions, Hyderabad, India.

METHODS:

PULSINCAP DESIGNING: Designing or preparation of pulsincap capsules involves 3 steps:

A. Preparation of cross-linked gelatin capsule.

B. Preparations of powder blend for filling into capsules.

C. Formulation of pulsincap of naproxen sodium.

A. PREPARATION OF CROSS-LINKED GELATIN CAPSULE[10]:

Formaldehyde treatment: About 100 hard gelatin capsules size '0' were taken. Their bodies were separated from the caps and placed on a wire mesh. The bodies which were placed on a wire mesh were spread as a single layer. 25 ml of 15% v/v of formaldehyde solution was prepared and placed in a desiccator. To this 5 g of potassium permanganate was added. The wire mesh containing the bodies of the capsules was kept on the top of dessicator containing formaldehyde liquid at the bottom in equilibrium with its vapor and immediately the dessicator was tightly closed and sealed. The bodies of capsules were made to react with formaldehyde vapors by exposing them for varying periods of time viz., 3, 6, 9 and 12 hrs. Then they were removed and kept on a filter paper and dried for 24 hrs to ensure completion of reaction between gelatin and formaldehyde vapors, afterwards the capsules were kept in an open atmosphere, to facilitate removal of residual formaldehyde. These

capsule bodies were capped with untreated cap and stored in a polythene bag.

OPTIMIZATION OF FORMALDEHYDE TREATED CAPSULE BODIES:

Formaldehyde treated capsule bodies which were exposed at various time intervals viz., 3, 6, 9 and 12hrs were optimized by conducting Disintegration test. The test was performed on both untreated and treated capsules. Formaldehyde treated bodies joined with untreated caps and was tested for disintegration. Disintegration test was carried out by using Hiccon disintegration test apparatus. pH 1.2, pH 6.8, pH 7.4 buffers were used as medium and maintained at 37°C throughout the experiment. The time at which the capsules disintegrate are noted.

EVALUATION OF FORMALDEHYDE TREATED EMPTY CAPSULES[11]: Various physical tests such as identification attributes, visual defects, dimensional changes and solubility studies were carried out.

Qualitative chemical test for free formaldehyde:

Standard formaldehyde solution used is formaldehyde solution (0.002, w/v) and sample solution is formaldehyde treated bodies (about 25 in number) were cut into small pieces and taken into a beaker containing distilled water. This was stirred for 1hr with a magnetic stirrer, to solubilize the free formaldehyde. The solution was then filtered into a 50ml volumetric flask, washed with distilled water and volume was made up to 50 ml with the washings. To 1ml of sample solution, 9ml of water was added. 1ml of resulting solution was taken into a test tube and mixed with 4ml of water and 5ml of acetone reagent. The test tube was warmed in a water bath at 40 ◦C and allowed to stand for 40 min. The solution was not more intensely colored than reference solution prepared at the same time and in same manner using 1ml of standard solution in place of the sample solution. The comparison should be made by examining tubes down their vertical axis.

B. PREPARATION OF POWDER BLEND FOR FILLING INTO CAPSULES:

Different blend formulations of Naproxen sodium, sodium starch glycolate, sodium bicarbonate, vivapur302 and talc were accurately weighed and passed through the mesh No.60 and punched as a tablet and disintegration test was conducted and the time at which the tablets disintegrate was noted. The tablet which disintegrates in short time was selected and that particular formulation in the form of powder blend was chosen for filling into the pulsincap capsules.

Table.1.Formulae for preparation of blend for filling of Naproxen sodium

Ingredients	G1	G2	G3	G4	G5	G6	G7
Naproxen Sodium (mg)	250	250	250	250	250	250	250
Sodium Starch Glycolate (%)	2	2	2	2	4	6	8
Sodium Bicarbonate (%)	1	2	3	4	4	4	4
Talc (%)	2	2	2	2	2	2	2
Vivapur (mg)	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Total wt (mg)	400	400	400	400	400	400	400

Micromeritic properties of powder blend:

a. Angle of Repose: The angle of repose of powder blend was determined by the funnel method. The accurately weighed powder blend was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powder. The powder was allowed to flow through the funnel freely onto the surface[12]. The diameter of the powder cone was measured and angle of repose was calculated using the following equation:

$$\tan \theta = h/r \quad \text{..... (1)}$$

Where h = height and

r = radius of the powder cone.

b. Bulk Density: Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 2 g of powder from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a 10 ml measuring cylinder. After 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-second intervals[12]. The

tapping was continued until no further change in volume was noted. LBD and TBD were calculated using the following formulas.

LBD = weight of the powder/volume of the packing ..... (2)

TBD = weight of the powder/ tapped volume of the packing..... (3)

c. Compressibility Index compressibility index of the powder blend was determined by Carr's compressibility index:

Carr's Index (%) = *(TBD-LBD) × 100]/TBD ..... (4)

C. FORMULATION OF PULSINCAP OF NAPROXEN SODIUM:

Preparation of powder blend:

Hard gelatin capsules of 'size 0' which were hardened with formaldehyde treatment for 6hrs were chosen for the formulation. The bodies and caps separated manually. The drug Naproxen sodium 400mg along with the excipients like sodium starch glycolate (super disintegrant), sodium bicarbonate (gas generating agent), Vivapur302 (diluent) and Talc (lubricant) were accurately weighed and passed through mesh no.60. All the ingredients were mixed together in a mortar to obtain a homogeneous mixture by using geometric dilution technique.

Table.2.Various formulations of Naproxen sodium pulsincaps

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16	F17	F18
Ethyl Cellulose	25	25	25	50	50	50	40	40	40	33.33	33.33	33.33	28.5	28.5	28.5	25	25	25
Guar gum	25	-	-	50	-	-	40	-	-	66.66	-	-	71.5	-	-	75	-	75
Xantural	-	25	-	-	50	-	-	40	-	-	66.66	-	-	71.5	-	-	75	-
HPMC K100M	-	-	25	-	-	50	-	-	40	-	-	66.66	-	-	71.5	-	-	-

Drug-Naproxen Sodium-250mg, Sodium starch glycolate-32mg, Sodium bicarbonate-16mg, Vivapur 302-94mg, Talc-8mg is common for all the prepared formulations

Preparation of Hydrogel plug:

Plug was prepared as a compressed tablet and placed at the opening of capsule body. The capsule body was closed by a cap. Hydrogel plug was prepared by using combination of hydrophobic and hydrophilic polymers like Ethyl cellulose: Gaur gum; Ethyl cellulose: Xantural; Ethyl cellulose: HPMC K100M; in different ratios like 1:1, 1:1.5, 1:2, 1:2.5 and 1:3. Various formulations of Naproxen sodium pulsincaps were given in table no.2. A tight fit between the plug and impermeable capsule shell is essential to regulate water penetration into the capsule content and the drug release prior to complete erosion of plug material. Ideally plug should erode only from the surface exposed to the release medium. Plug ejection can be done by swelling on contact with aqueous fluids (or) pushing out by increased internal pressure (or) erosion (or) by enzyme degradation.

Capsule filling:

Homogeneous mixture of drug and excipients were filled into the 6th hr formaldehyde treated capsule body manually by filling method. Then, hydrogel plug in the form of a tablet is placed above the mixture i.e., at the opening of capsule body. The capsule body was closed by a cap.

Capsule sealing:

The joint of the treated capsule body and untreated cap of the capsules was sealed with a small amount of 5% ethyl cellulose ethanolic solution.

EVALUATION OF DESIGNED PULSINCAP:

Estimation of drug content: From each batch of the prepared pulsincaps of Naproxen sodium

ten pulsincaps were randomly selected and the contents were removed and powdered. From this sample 100 mg powder was accurately transferred into a 100 ml volumetric flask. Then 10 ml of methanol was added to dissolve Naproxen sodium. The solution is made up to volume with pH 7.4 phosphate buffer. The resulted solution was filtered through 0.45µm filter paper and suitably diluted and the drug content was estimated spectrophotometrically by measuring the absorbance at 232nm. The studies were carried out in triplicate[13].

***Invitro* release studies:** Dissolution study was carried out to measure the release rate of the drug from the pulsincap formulation. *Invitro* dissolution profile of each formulation was determined by employing USP I apparatus by rotating basket method. In order to stimulate the pH changes along GI tract three different dissolution media with pH 1.2, 6.8, 7.4 buffers were sequentially used, and therefore referred to as "Sequential pH change method". The dissolution media were maintained at a temperature of 37 ± 0.5°C throughout the experiment and the speed of rotation of basket maintained at 50 rpm. 900ml of dissolution medium was used at each time. Naproxen sodium Pulsincaps was placed in basket in each dissolution vessel to prevent floating. While performing experiments, stimulated gastric fluid (SGF) pH 1.2 buffer was first used for 2 hrs (since the average gastric emptying time is 2hrs) and then removed and the fresh stimulated intestinal fluid (SIF) pH 7.4 buffer was added and used for 3hrs (average small intestinal transit time is 3hrs). Then the medium was removed and the fresh colonic fluid (CF) pH 6.8 buffer was added and used for subsequent hrs. 5 ml samples of dissolution fluid were withdrawn at predetermined time intervals with the help of a syringe. The volume withdrawn at each time interval was replaced with 5ml of fresh dissolution medium maintained at same temperature. The filtered samples were suitably diluted whenever necessary and assayed for Naproxen sodium by measuring absorbance at 232nm by UV absorption spectroscopy and cumulative percentage release was calculated over the sampling times[14].

KINETICS OF DRUG RELEASE:

The results of *invitro* release profile obtained for all formulations were plotted in modes of data treatments as follows: Zero-order kinetic model (cumulative percent drug released versus time), First order kinetic model (log cumulative percent drug remaining versus time), Higuchi's model (cumulative percent drug released versus square root of time) and Peppas model (log cumulative percent drug released versus log time) [15].

RESULTS AND DISCUSSION

1. **Formaldehyde treatment of hard gelatin capsule:**

Formalin treatment has been employed to modify the solubility of the gelatin capsules. Exposure to formalin vapors results in an unpredictable decrease in solubility of gelatin owing to the cross linkage of the amino groups in the gelatin molecular chain with aldehyde groups of formaldehyde by Schiff's base condensation.In about 100 capsule bodies treated with formaldehyde, about ten were found to be shrunk or distorted. Formaldehyde treated capsule showed a significant decrease in length and diameter after treatment. The solubility tests were carried out for normal capsules and formaldehyde treated capsules for 24 h. It was observed that in all the case of normal capsules, both cap and body dissolved within 15 min where as in formaldehyde treated capsules, only the cap dissolved within 15 min, while the capsule body remained intact for about 24 h and hence indicates the suitability for colon targeting. The formaldehyde capsules were tested for the presence of free formaldehyde. The sample solution was not more intensely colored than the standard solution inferring that less than 20µg/ml of free formaldehyde per 25 capsules, taken for test.

2. **Optimization of formaldehyde treated capsule bodies:**

Basing on the disintegration studies, it was observed that the hardened bodies of capsules which were exposed to formaldehyde vapors for 3hrs (M1) got softened and became very sticky masses in 1.2pH medium within 2hrs but the capsule bodies exposed for 6hrs, 9hrs, 12hrs (M2, M3, M4) to formaldehyde treatment did not disintegrate for more than 7hours. As the required lag time is 6hrs, M2 (6th hr treated capsule) was selected as optimized time for formaldehyde treatment for further studies.

Table.3.Disintegration test for formaldehyde treated capsules

Code	Disintegration Time (hrs)		
	pH 1.2 (2hrs)	pH 6.8 (3hrs)	pH 7.4 (upto24hrs)
M1 (3rd hr)	2	_	_
M2 (6th hr)	2	3	3
M3 (9th hr)	2	3	7
M4 (12th hr)	2	3	19

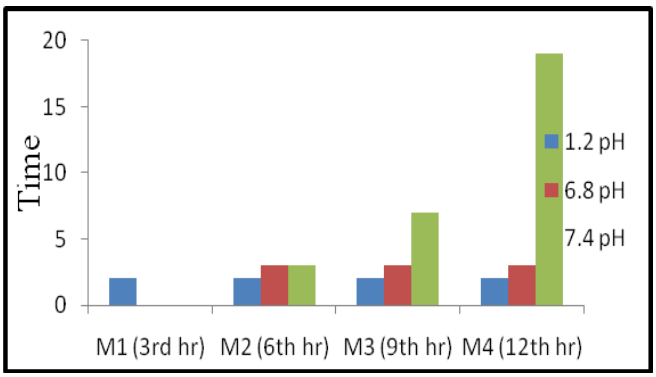

Fig.1.Graph representing disintegration time for treated capsules

3. Micromeritic properties of powder blend:

The results of micromeritic properties of powder blend were given in Table 4. The values of angles of repose were in the range of 26.31±0.23 to 29.41±0.23 degrees and the values of compressibility indices were in the range of 10.81±0.17 to 13.51±0.17 indicates an overall good free flowing nature of powder blend of all batches. Values of angle of repose <30 usually indicate a free flowing material while values of compressibility index <25 give rise to good flow characteristics.

Table.4.Micromeritic properties of powder blend

Code	Angle of Repose±SD	Bulk Density (g/ml)±SD	Tapped Density (g/ml)±SD	Carr's Index. (%)±SD	
G1	27.53±0.38	0.378±0.019	0.424±0.021	10.81±0.17	
G2	28.57±0.23	0.388±0.025	0.437±0.018	11.11±0.12	
G3	26.31±0.23	0.368±0.032	0.424±0.025	13.15±0.26	
G4	27.83±0.58	0.388±0.022	0.437±0.032	11.11±0.21	
G5	26.42±0.28	0.378±0.017	0.437±0.029	13.51±0.17	
G6	28.98±0.23	0.378±0.013	0.424±0.024	10.81±0.26	
G7	29.41±0.23	0.368±0.011	0.424±0.019	13.15±0.12	

4. Preparation of powder blend for filling into capsules:

The disintegration time taken for G1 to G6 ranges from 15.34±12 to 9.39±12 minutes but the time taken for G7 to disintegrate was 34±8 seconds. As the disintegration time of G7 is shorter than the blends from G1 to G6, therefore powder blend of G7 containing sodium starch glycolate and sodium bicarbonate in ratio 2:1 was selected for filling into the capsules.

Table.5.Disintegration time of Naproxen Sodium Tablets

Formulation code (%)	Disintegration time (minutes)±SD
G1	15.34±12
G2	15.91±16
G3	14.51±13
G4	13.55±18
G5	9.39±12
G6	4.42±15
G7	34±8 sec

5. **Drug content:** The results of drug content were given in table no.6 and the maximum drug content among all formulations was found to be 100.70±2.50% and minimum % drug content among all the formulation was found to be 96.64±1.82%. The drug content for all the formulations was found to be within the limits.

Table.6.Content uniformity of different formulations (F1 to F18)

Formulation code	pH 1.2 (%)	pH 7.4 (%)	pH 6.8 (%)
F1	98.77	98.79	96.64
F2	98.14	98.04	98.77
F3	100.07	99.82	97.55
F4	100.33	100.22	100.22
F5	98.37	98.10	97.35
F6	99.37	99.07	100.33
F7	97.55	97.35	98.10
F8	100.70	100.45	97.35
F9	98.77	98.79	99.37
F10	98.14	98.04	98.37
F11	100.07	99.82	98.14
F12	100.33	100.22	100.22
F13	98.37	98.10	99.37
F14	99.37	99.07	100.70
F15	97.55	97.37	99.37
F16	100.70	100.45	99.37
F17	99.37	99.07	98.14
F18	97.55	97.35	98.37

6. ***Invitro* release studies:** All the 18 formulations of Naproxen sodium pulsincaps were subjected to dissolution studies. The results of *invitro* release studies were given in table no.7 & 8 and the graphs were shown in figure no.2, 3 & 4. Formulations F1 to F3 contain the hydrogel plug with combination of hydrophobic polymer and Hydrophilic polymer i.e., Ethyl cellulose: Gaur gum, Ethyl cellulose: Xantural, Ethyl cellulose: HPMC K100M in the ratio of 1:1 of total 50mg weight of the plug. In the first 2hrs of the dissolution study in pH 1.2, formulations F1 to F3 showed a release of about 97.49±0.275, 100.32±0.202, and 98.51±0.350 respectively. As complete release was seen with this 1:1 ratio of 50mg weight plug further work was done with increase in the weight of the plug.

Formulations F4 to F6 contain the hydrogel plug with combination of hydrophobic polymer and Hydrophilic polymer i.e., Ethyl cellulose: Gaur gum, Ethyl cellulose: Xantural, Ethyl cellulose: HPMC K100M in the ratio of 1:1 of total 100mg weight of the plug. In pH 6.8, at the end of 3rd hour the drug release was 94.05±0.625, 98.99±0.535 and 100.14±0.50 respectively. So, further work was done with increase in the polymer ratio. Formulations F7 to F9 contain the hydrogel plug in ratio 1:1.5, showed released rates of 99.26±0.901, 98.47±0.620, and 99.12±0.868 respectively at the end of 4th hour in pH 6.8 buffer. So, further the ratio of hydrogel plug polymer was increased to 1:2 and the drug released from F10 to F12 was 95.50±0.851, 97.49±1.081, 96.57±1.293 by the end of 5th hour respectively. Then further increasing the hydrogel polymer plug ratio to 1:2.5, the drug released from F13 to F15 was 97.58±0.929, 99.83±0.350, 95.50±0.993 by the end of 6th hour in pH 7.4 buffer respectively. When the ratio of hydrogel plug polymer increased to 1:3, the drug released from F16 and F17 was 97.99±0.594, 99.52±0.404 by the end of 8th hour in pH 7.4 buffer respectively. But F18 showed the drug release of 98.28±0.861 at the end of 7th hour and maintained the required lag time of 6hours. There was minimum drug release during the lag time and the burst release occurred after predetermined lag time i.e., during 7th hour, therefore formulation F18 was considered as best formulation.

As the polymer ratio was increased it was observed that the rate of drug release in pH 1.2 buffer and pH 6.8 phosphate buffer was decreased which is one of the important parameter for designing colon targeted drug delivery system, to have minimum drug release in upper GIT. It was observed that as the concentration of Hydrophilic polymer was increased the release rate of drug was delayed and finally burst release of drug from the

formulation occurred after lag time. So basing on these observations, of all the 18 pulsincap formulations, F18 formulation containing hydrogel plug of ethyl cellulose & HPMC K100M in 1:3 ratio was selected as optimized pulsincap formulation for colon targeting to treat rheumatoid arthritis.

Table.7.*Invitro* dissolution data of formulations F1 to F9

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	97.49	100.3	98.51	3.97	7.59	9.00	4.94	7.02	8.42
2	_	_	_	71.10	90.38	83.37	41.44	36.19	31.24
3	_	_	_	94.05	98.99	100.14	80.15	90.25	84.12
4	_	_	_	_	_	_	99.26	98.47	99.12
5	_	_	_	_	_	_	_	_	_

Table.8.*Invitro* dissolution data of formulations F10 to F19

Time (hrs)	F10	F11	F12	F13	F14	F15	F16	F17	F18
0	0	0	0	0	0	0	0	0	0
1	5.38	6.48	5.64	3.70	7.41	8.87	8.51	4.40	3.00
2	9.35	11.32	13.28	11.07	12.53	15.71	10.50	9.40	5.24
3	58.25	49.46	45.06	12.66	15.35	17.74	15.57	16.37	11.38
4	82.20	84.70	86.02	15.57	17.47	18.93	22.95	22.33	16.37
5	95.50	97.49	96.57	90.12	86.46	85.57	26.52	24.09	18.31
6	_	_	_	97.58	99.83	95.50	49.34	47.31	19.50
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8	_	_	_	_	_	_	97.99	99.52	_

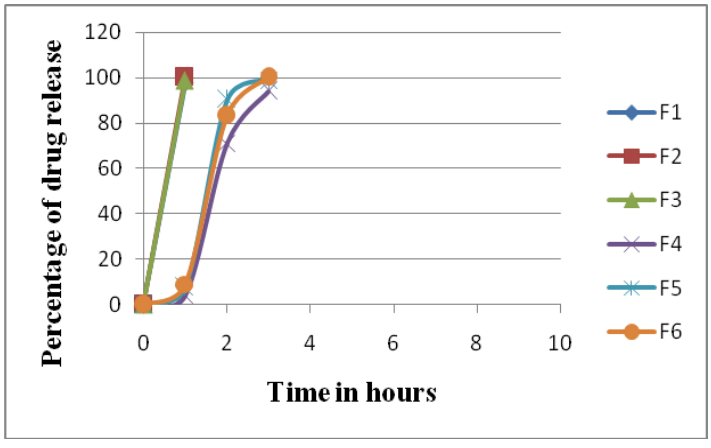

Fig.2.Dissolution plots for formulations F1 to F6

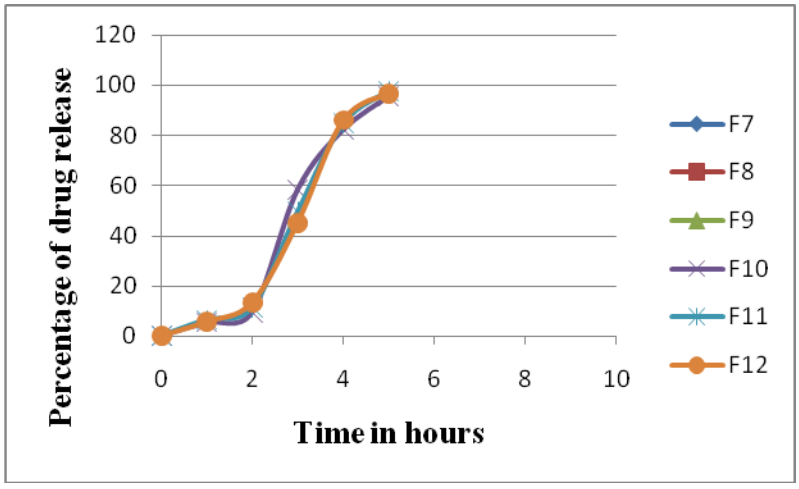

Fig.3.Dissolution plots for formulations F7 to F12

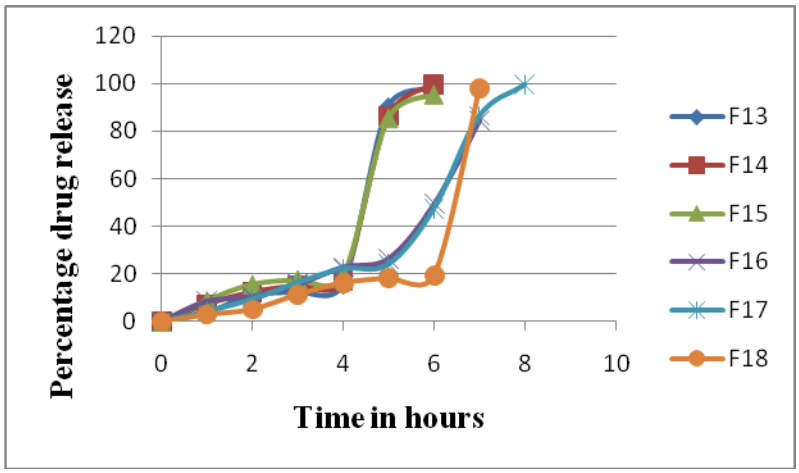

Fig.4.Dissolution plots for formulations F13 to F18

RELEASE KINETICS:

To analyze the mechanism of drug release from optimized F18 pulsincap formulation, data obtained from the drug release studies was subjected to different kinetic treatments. The correlation coefficient (R) was used as indicator of the best fitting for each of the models considered. The drug release kinetics for the optimized formulation F18 followed the first order kinetics. Higuchi correlation clearly indicates that the mechanism of drug release was erosion.

Table.9.Correlation coefficient "R" values of F18 optimized formulation

Models	R values
Zero order	0.555
First order	0.918
Higuchi	0.393
Koresmayer peppas	0.876

CONCLUSION

In conclusion, this system can be considered as one of the promising formulation technique for preparing colon specific drug delivery systems and in Chronotherapeutic management of rheumatoid arthritis. Increase in hydrophilic polymer concentration decreases the drug release but increases the lag time. Among HPMC K100M, guar gum and Xantural as hydrophilic polymers, HPMC K100M shows good retarding ability. As the concentration of polymer was increased, the drug release rate was decreased. Among all the formulations formulated, F18 containing ethyl cellulose and HPMC K100M in 1:3 delayed the drug release for 6hrs by maintaining a predetermined lag time and fulfilled the objective of this work. From the preliminary trials it was concluded that it is possible to formulate the colon targeted drug delivery system by the design of time and pH dependent modified chronopharmaceutical formulation.

ACKNOWLEDGEMENT

We would like to thank the management and principal of CMR College of pharmacy for their encouragement and support to the work and also wish to thank P. Vishnu, faculty in department of pharmaceutics, CMR College of pharmacy, Hyderabad for helpful comments and advice during the project work.

CONFLICT OF INTEREST

The Authors declare no conflict of interest

REFERENCES

1. Macfarlane GT, Cummings JH, Macfarlane S and Gibson GR. Influence of retention time on degradation of pancreatic enzymes by colonic bacteria grown in 3-stage continuous culture system. J. Appl. Bacteriol 1989; 6: 521-527.
2. Abdul B and John B. Perspectives on colonic drug delivery. Business Briefing L: Pharmatech; 2003: 185–190.
3. S. Sarasija and A. Hota. Indian Journal of Pharmaceutical Sciences. 2000; 62(1): 1-8.
4. N.K. Jain, editor. Advances in controlled and novel drug delivery. New Delhi: CBS publishers and distributors: 89-112.
5. Vyas and Khar. Controlled drug delivery concepts and advances. Vallabha prakashan publishers: 218-253.
6. M. K. Chourasia, S. K. Jain. Pharmaceutical approaches to colon targeted drug delivery systems. Journal of Pharmaceutical Sciences 2003; 6(1): 33-66.
7. Micheal J.Rathbone, Jonathan, Micheal S.Roberts, Majella E.Lane. “Part IV Colonic techonologies” Modified release drug delivery. 2nd ed. New York: Informa health care USA; 2006: 217-248.
8. A.J. Swannell, Br. J. Clin. Pract 1983; 38: 16–19.
9. R. Kinget, J. Drug Target 1998; 6(2): 129–149.
10. Abraham S, Bharath S, Basavaraj BV, Deveswaran R, Madhavan V. Modified pulsincap drug delivery system of diclofenac sodium. Pharma Rev 2007: 142-144.
11. Krogel I, Bodmeier R. Floating or pulsatile drug delivery systems based on coated effervescent cores. International Journal of Pharmaceutics 1999; 187: 175-184.
12. Kumar and Rajyalakshmi. Formulation and evaluation of metoprolol succinate pulsatile drug delivery system for chronobiological disorder: Anti-hypertension. IJPSR 2012; 3(10): 4004-4009.
13. Sangalli ME, Maroni A, Foppoli A, Zema L. Different HPMC viscosity grades as coating agent for an oral time and/or site-controlled a process parameters and in vitro performances. Eu J Pharm Sci 2004; 22: 469-476.
14. Mastiholimath VS, Dandagi PM, Jain SS, Gadad AP, Kulkarni AR. Time and pH dependent colon specific pulsatile delivery of theophylline for nocturnal asthma. Int. J. Pharm 2007; 328: 49-56.
15. Korsmeyer, R.W. Gurny, R. Doelker, E. Buri, Peppas, N.A. Mechanisms of solute release from porous hydrophilic polymers. Int. J. Pharm 1983; 15: 25–35.

HOW TO CITE THIS ARTICLE

G. Sanjana Reddy, B.Sirisha, Dr.V. Uma Maheshwar Rao, P. Vijaya Lakshmi, A. Ajitha.(2014 January 1).Formulation and *In Vitro* Evaluation of Colon Specific Drug Delivery of Naproxen Sodium by Using Pulsincap Technology. *PHARMANEST*,*5(1)*,1751-1760. http://www.pharmanest.net