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THE PHARMA RESEARCH, A JOURNAL

The Pharma Research (T. Ph. Res.), (2011), 5(1); 176-183.
Published on- 15 Jun 2011

Original Article

ISSN 0975-8216

FORMULATION AND EVALUATION OF A COLON TARGETED DRUG DELIVERY SYSTEM USING IBUPROFEN AS A MODEL DRUG

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ABSTRACT

The present investigation aimed to study the influence of Guar gum and Xanthan gum on the drug releasing properties of colon targeted matrix tablets, using Ibuprofen as a model drug. Different batches of matrix tablets were prepared by statistically optimization of drug formulation using factorial design. Matrix tablets were subjected to *in- vitro* drug release studies in simulated colonic fluids after completing the dissolution study in 0.1 M HCl (2 hrs) and pH 7.4 Sorensen's phosphate buffer (3 hrs). In order to understand the dissolution behavior of the drug from the matrices, the swelling studies were conducted under conditions similar to those used under for dissolution studies. Effects of both Guar gum and Xanthan gum on the drug release were studied. There was significant interaction between Guar gum and Xanthan gum so far as dissolution is concerned. Effect of Guar gum was more than Xanthan gum. Matrix tablets with a Guar gum concentration of 25 % and Xanthan gum concentration of 15 % showed best drug release profile required for a colon targeted drug delivery system.

Keywords: Guar Gum, Xanthan Gum, Colon Targeting, Matrix Tablet.

INTRODUCTION

Colonic drug delivery has gained increased importance not just for the delivery of the drugs for the treatment of local diseases associated with the colon but also for its potential for the delivery of proteins and therapeutic peptides (1). To achieve successful colonic delivery, a

drug needs to be protected from absorption and /or the environment of the upper gastrointestinal tract (GIT) and then be abruptly released into the proximal colon, which is considered the optimum site for colon-targeted delivery of drugs (2).

Various approaches are available for colon specific drug delivery, broadly classified as:

1. Coating with pH dependent systems
2. Design of timed release dosage forms
3. Use of carriers that are degraded exclusively by colonic bacteria.

The pH dependent systems are designed to release the drug to above a particular pH of the GIT. The poor site specificity of pH dependent systems, because of large variation in the pH of the GIT, was very well established (3, 4). The timed-release systems release their load after a predetermined time period of administration. The site specificity of these systems is considered poor because of large variations in gastric emptying time and passage across the ileocaecal junction (5, 6). The best alternative approach for colon specific drug delivery is the use of carriers that are degraded exclusively by colonic bacteria. Because of the presence of the biodegradable enzymes only in the colon, the use of biodegradable polymers for colon-specific drug delivery seems to be a more site-specific approach as compared to other approaches (7). These polymers shield the drug from the environments of stomach and small intestine and are able to deliver the drug to the colon. On reaching the colon, they undergo assimilation by micro-organism or degradation by enzyme or break down of the polymer back bone leading to a subsequent reduction in their molecular weight and thereby loss of mechanical strength. So then they release the drug in colon (8, 9).

MATERIALS AND METHODS:

Preparation of matrix tablets:

Tablets of ibuprofen were prepared by direct compression method by rotary tableting machine (PHRMAC-076, Manufactured by-Pharmaceutical Machinery Manufacturing Works, Indore-452006) using 12 mm round, concave punches. Microcrystalline cellulose is used as diluent. Mixture of talc and magnesium state (2:1) was used as lubricant. Guar gum and xanthan gum were included in various proportions. All the components are sieved (250 micro meters) separately and mixed by spatulation method in mortar and pastel.

Formulation of various batches according to factorial design:

In the start of the study four Batches were made, complete formula of various formulations is given in Table 1. Effects of Factor-A, Factor-B and their interaction are calculated below:

- Effect of factor A [i.e., Guar gum] on dissolution:

  = ½ [(ab+a)-b+ (1)]

  = ½ [(10+50)-(30+100)]

  = ½ [60-130]

  = ½ [-70]

  = -35

- Effect of factor B [i.e., Xanthan gum] on dissolution:

  = ½ [(ab+b)-(a+1)]

  = ½ [10+30] - [50+100]

  = ½ [40-150]

  = ½ [-110]

  = -55

Guar gum has got more significant effect on dissolution.

- Interaction:

  = ½ [(1+ab)-(a+b)]

  = ½ [(100+10)-(50+30)]

  = ½ [110-80]

  = ½ [30]

  = 15

There is significant interaction between Guar gum and Xanthan gum so far as dissolution is concerned. Effect of Guar gum is more than Xanthan gum. So there is a need to study a formulation having medium percentage of both Guar gum and Xanthan gum.

A fifth Batch (E) was made which is having medium percentages of both Guar gum and Xanthan gum. Complete formula of all the batches is given in Table 1

Table 1: Complete formula of various formulations including Batch-E (mg):

Ingredient	Batch-A	Batch-B	Batch-C	Batch-D	Batch-E
Ibuprofen	100	100	100	100	100
Guar gum	50	200	50	200	125
Xanthan gum	--	--	150	150	75
Microcrystalline cellulose	335	185	185	35	185
Magnesium sterate	5	5	5	5	5
Talc	10	10	10	10	10
Total	500	500	500	500	500

EVALUATION OF MATRIX TABLETS:

a) Weight variation test
b) Hardness of the tablet
c) Friability of tablets
d) Swelling studies
e) In-vitro drug release studies

(a) Weight variation test of matrix tablets:

In this test 20 tablets were weighed individually and their average weight was calculated. The weight variation in different batches of tablets is given in Table 2.

Table 2: Weight variation test of matrix tablets

Formulation	Average weight/tablet (mg)
Batch-A	496 ± 3
Batch-B	498 ± 5
Batch-C	501 ± 7
Batch-D	504 ± 12
Batch-E	502 ± 6

(b) Hardness of the tablets:

The crushing strength (Kg/ cm^2) of prepared tablets was determined by Pfizer tablet hardness tester. The hardness of tablets in different batches is given in Table 3.

Table 3: Hardness of the tablets

Formulation	Crushing force
Batch-A	3.5-4.2
Batch-B	4.5-5.6
Batch-C	5.5-6.7
Batch-D	6.2-8.3
Batch-E	5.2-6.1

(c) Friability of tablets:

Friability of tablets was determined by Roche Fribilator. Speed of the Fribilator is 25 RPM (rotation per minute). Twenty tablets from each batch were subjected to test for four minutes. Friability of different batches is given in Table 4.

Table 4 Friability of tablets

Formulation	Initial weight (gm)	Final weight (gm)	Friability
Batch-A	9.920	9.855	0.6552
Batch-B	9.960	9.932	0.2811
Batch-C	10.020	10.007	0.1297
Batch-D	10.080	10.072	0.0793
Batch-E	10.040	10.024	0.1593

(d) Swelling studies of tablets:

In order to understand the dissolution behavior of the drug from the matrices, the swelling studies were conducted under conditions similar to those used under for dissolution studies. Tablets of various batches were subjected to swelling studies at a room temperature of 37 ± 0.5 ºC , initial studies were conducted in 0.1 N HCl; followed by pH 7.4 Sorenson Phosphate Buffer. Tablets were photographed on a regular interval after putting them in solution. Diameter of the tablets was measured from the photographs of the tablets using scale. The swelling index is measured as $\frac{(D2-D1)}{D1}$. The swelling indexes of various batches of tablets are given in Table 5 and Figure 1

Table 5 Swelling indexes of various batches of tablets

Time	Batch-A	Batch-B	Batch-C	Batch-D	Batch-E
0	NA*	0	0	0	0
1		0.4021	0.1035	0	0.1020
2		1.0092	0.2020	0.0250	0.2105
3		1.2410	0.4506	0.1560	0.3465
4		1.5300	0.7618	0.4754	0.8507
5		1.9004	0.9860	0.7035	1.1560
6		2.3920	1.2026	0.9070	1.4600
7		2.5130	1.3067	1.0030	1.7690
8		2.6025	1.3560	1.0870	2.2364

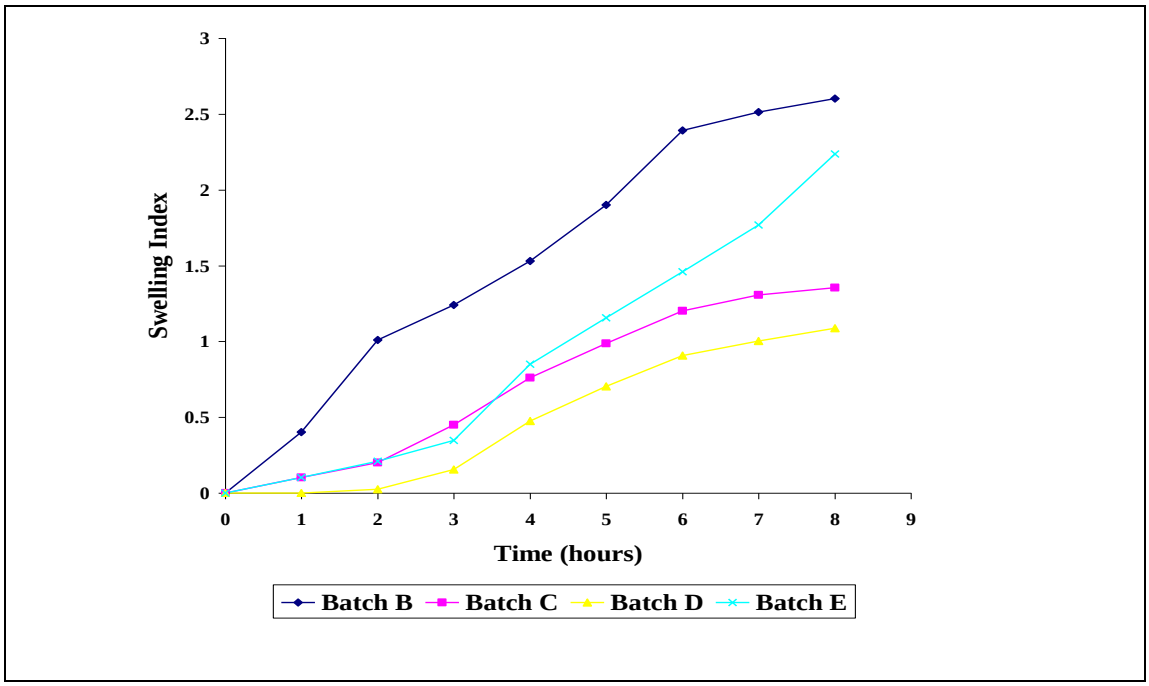
* Tablets of batch-A disintegrated within one minute

(e) *In-vitro* drug release studies:

Studies were carried out using USP-III dissolution apparatus. Drug release studies were performed in 0.1 N HCl (2 hours), pH 7.4 Sorenson Phosphate Buffer (3 hours) and pH 6.8 Phosphate Buffered saline (PBS) with rat caecal contents. Samples of 1 ml were taken from the medium at the definite time intervals and

diluted to ten times by same dissolution media. The samples were assayed by using double beam UV spectrophotometer.

Figure 1: Swelling index of various batches Vs. Time



Preparation of simulated colonic fluid:

Rats were treated with guar gum dispersion for inducing the enzymes specifically acting on the guar gum. The procedure involved oral treatment of rats with 2 % w/v guar gum dispersion for seven days. Thirty minutes before the commencement of the drug release studies, six rats were euthanized, using diethyl ether. The abdomen was opened; the caecai was traced, ligated at both ends, dissected and immediately transferred into the pH 6.8 PBS, previously bubbled with carbon dioxide. The caecal bags were opened; their contents were weighed and then suspended in PBS to give 4 % w/v dilution. Approval for use of animals in this study was taken from IAEC. Percentage drug release with time for different batches is given in Table 6 and Figure 2.

Table 1.6: Cumulative percentage drug release from matrix tablets, using 0.1 N HCl (2 hours), pH 7.4 Sorenson Phosphate Buffer (3 hours) and pH 6.8 Phosphate Buffered saline (PBS) with rat caecal contents.

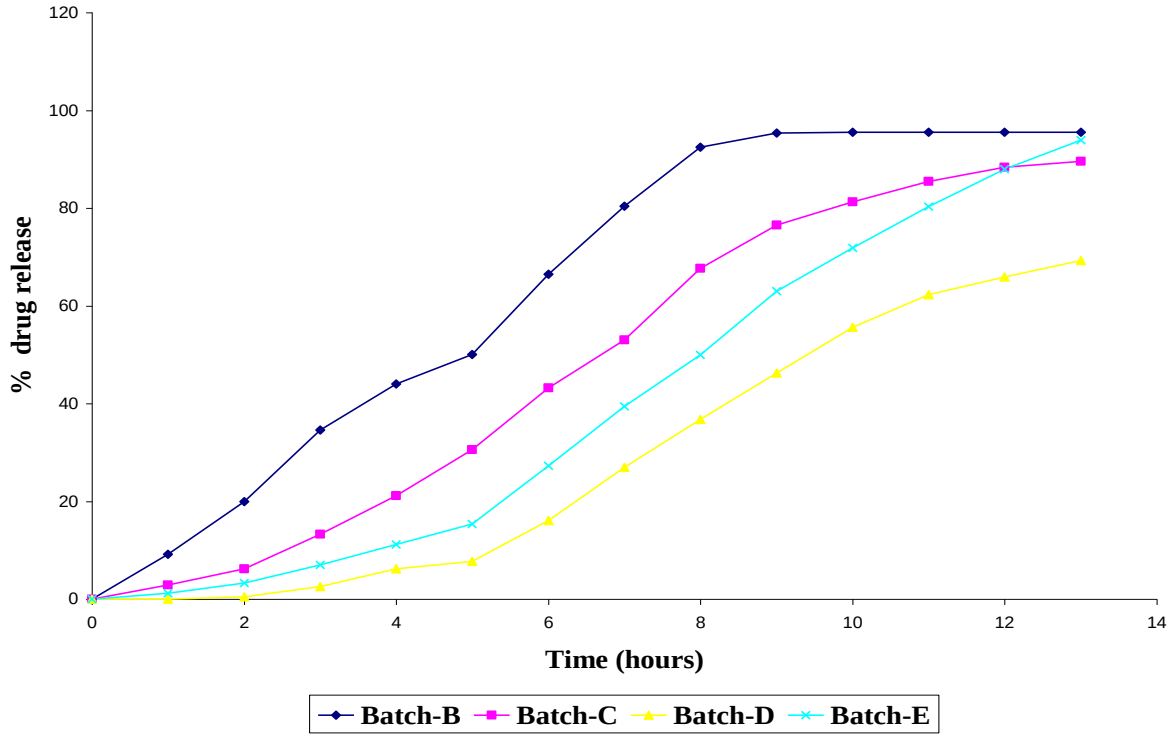
Time	Batch-B	Batch-C	Batch-D	Batch-E
0	0	0	0	0
1	9.2	2.9	0	1.2
2	20.0	6.2	0.5	3.3
3	34.6	13.3	2.6	7.0
4	44.0	21.2	6.2	11.2
5	50.1	30.6	7.7	15.4
6	66.5	43.2	16.1	27.3
7	80.4	53.0	27.0	39.4
8	92.5	67.7	36.8	50.0
9	95.4	76.5	46.3	63.0
10	95.5	81.3	55.6	71.9
11	95.5	85.5	62.3	80.3
12	95.5	88.4	65.9	88.0
13	95.5	89.6	69.3	93.9

RESULTS AND DISCUSSION:

In the start of the study four batches of matrix tablets were made. Guar gum and Xanthan gum were taken in their maximum and minimum concentrations. Effects of both Guar gum and Xanthan gum on the drug release were studied. Results show that:

(a) When Guar gum was used alone in a concentration of 10 % (batch-A), the tablets disintegrate within one minute, *i.e.,* these tablets will release 100 % of drug before reaching colon (Guar gum in such a low concentration is not able to provide a cohesive strength to tablets). So, Guar gum is not appropriate in 10 % concentration for colon targeted matrix tablets.

Figure 2: Cumulative percentage release of Ibuprofen with time from matrix tablets



(b) When the percentage of Guar gum was increased from 10 % to 40 % (batch-B), tablets did not disintegrate in first five hours of drug release studies. But, they release approximately 50 % of drug in first five hours of drug release studies, i.e., these tablets will release 50 % of their drug before reaching colon. This might be due to the leaching of drug from the swelled tablets (it is evident from the swelling

studies that batch-B tablets swell at a highest rate and to a highest extent).

(c) When Guar gum 10% and Xanthan gum 30 % (batch-C) was used, the drug release pattern was better than batch-A and batch-B. There was a release of 30 % of drug in first five hours. However, even 30 % of release is not desirable for colon targeted tablets before reaching colon.

(d) When Guar gum and Xanthan was used in their maximum concentrations, i.e., 40 % Guar gum and 30 % Xanthan gum (batch-D), there was a good retardation of drug release in first five hours. Approximately there was only 10 % drug release in first five hours which is somewhat acceptable. But when these tablets were studied in simulated colonic fluid, these tablets release drug only up to 70 % of the drug in tablets. It might be due to a very high cumulative concentration of gum (70 %). It is also evident from the tablets hardness test (batch-D tablets had hardness up to 8.3 Kg/cm^2). There is significant interaction between Guar gum and Xanthan gum so far as drug release is concerned. Effect of Guar gum is less than Xanthan gum in retardation of drug release in first five hours of drug release studies. So there is a need to study a formulation having medium percentage of both Guar gum and Xanthan gum. A fifth Batch (E) was made which was having medium percentages of both Guar gum and Xanthan gum. Ratio of Guar gum and Xanthan gum in Batch –E was 25 % for Guar gum and 15 % for Xanthan gum.

(e) When the Guar gum and Xanthan gum were taken in their medium concentrations (Guar gum 25 % and Xanthan gum 15 %), these tablets released approximately 15 % drug in first five hours. But the total release of drug from the tablet was approximately 94 % out of which 79 % was alone in colon.

CONCLUSION: There is significant interaction between Guar gum and Xanthan gum so far as drug release is concerned. Effect of Guar gum is less than Xanthan gum in retardation of drug release in first five hours of drug release studies. Tablets having a very high concentration of gum are difficult to manufacture because such produced tablets are very hard. Tablets having a low percentage of gum release their medicament before reaching colon. Matrix tablets with a Guar gum concentration of 25 % and Xanthan gum concentration of 15 % were showing best drug release profile required for a colon targeted drug delivery system.

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