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DESIGN, DEVELOPMENT AND EVALUATION OF COLON TARGETED MATRIX TABLETS OF IBUPROFEN

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ABSTRACT

In the present work, colon targeted matrix tablet of Ibuprofen was formulated to colon targeted release of Ibuprofen above its site of absorption. Ibuprofen possesses analgesic and antipyretic activities. Its mode of action, like that of other NSAIDs, is not completely understood, but may be related to prostaglandin synthetage inhibition. In clinical studies in patients with rheumatoid arthritis and osteoarthritis, Ibuprofen have been shown to be comparable to aspirin in controlling pain and inflammation and to be associated with a statistically significant reduction in the milder gastrointestinal side Gastroscopic studies at varying doses show an increased tendency toward gastric irritation at higher doses. Ibuprofen is well absorbed throughout the gastrointestinal tract and is therefore suitable as a model drug in relation to study of colon-specific formulations. Tablets of ibuprofen were prepared by direct compression method by rotary tableting machine using 10 mm round, concave punch. Microcrystalline cellulose is used as diluent. Mixture of talc and magnesium state was used as lubricant. Guar gum and pectin were included in various proportions. Various effects of both Guar gum and Pectin on the drug release were noted. Results show that when Guar gum was used alone in a concentration of 10 % in batch-A, the tablets disintegrate within one minute, *i.e.,* these tablets will release 100 % of drug in stomach, this shows that Guar gum in such a low concentration is not able to provide a cohesive strength to tablets. There is significant interaction between Guar gum and Pectin. Effect of Guar gum is less than Pectin in retardation of drug release in first five hours of drug release. So there is a need to study a formulation having medium percentage of both Guar gum and Pectin.

Keywords: Ibuprofen, matrix tablets, colon targeted, NSAIDs, direct compression.

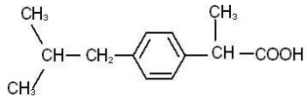
INTRODUCTION

Ibuprofen possesses analgesic and antipyretic activities. Its mode of action, like that of other NSAIDs, is not completely understood, but may be related to prostaglandin synthetage inhibition. In clinical studies in patients with rheumatoid arthritis and osteoarthritis, Ibuprofen have been shown to be comparable to aspirin in controlling pain and inflammation and to be associated with a statistically significant reduction in the milder gastrointestinal side Gastroscopic studies at

varying doses show an increased tendency toward gastric irritation at higher doses.

Ibuprofen (2-(-4-isobutylphenyl)-propionic acid) is almost insoluble in water. Its pKa is 5.3 (Herzfeldt and Kümmel 1983). Ibuprofen is well absorbed throughout the gastrointestinal tract and is therefore suitable as a model drug in relation to study of colon-specific formulations (Wilson *et. al.* 1989a). The elimination half-life of ibuprofen is about 2 hours. Therapeutic concentrations in plasma range from 5 to 50 mg/l (Ritschell 1992). Ibuprofen is a white powder with a melting point of 74-77°C and is very slightly soluble in water (< 1 mg/mL) and readily soluble in organic solvents such as ethanol and acetone. The Molecular formula of Ibuprofen is $C_{13}H_{18}O_2$ and Molecular weight is 206.28. The structural formula of Ibuprofen is given below:

Figure 1: structural formula of Ibuprofen



The Identification test for ibuprofen is Ultraviolet Absorption having respective absorptivities at 264 nm and 273 nm, calculated on the anhydrous basis, do not differ by more than 3.0 %. The concentration of the solution is 250 µg per ml. and the medium used is 0.1 N Sodium hydroxide.

Pharmacokinetics

Table 1: Pharmacokinetics of Ibuprofen

Bioavailability	T_{max} is 1 to 2 h. Bioavailability is less than 80 %.
Plasma Half Life	Plasma $t_{½}$ is 1.8 to 2 h. 45 % to 79 % is eliminated through the urine. Clearance is 30 to 35 L/h.
Plasma Protein Binding	15- 20%
Peak Plasma Conc. (C_{max})	1- 2 hours
Excretion	Renal Excretion (45-79%) Metabolic Excretion (21-55%)
Renal Clearance	500-583 ml/min
Drug Interaction	ACE inhibitors: Antihypertensive effect of ACE inhibitors may be diminished. Aspirin: Protein binding of ibuprofen may be reduced; in addition, the risk of gastric erosion and bleeding may be increased. Beta-blockers: Antihypertensive effect may be decreased. Digoxin: Ibuprofen may increase digoxin serum levels. Diuretics: Diuretic effects may be decreased. Lithium: May increase lithium levels. Methotrexate: May increase methotrexate levels. Warfarin: May increase risk of gastric erosion and bleeding.
Contraindications	Treatment of pre-operative pain in the setting of coronary artery bypass graft surgery; patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs; hypersensitivity to any component of the product.

Adverse effects of Ibuprofen

- Cardiovascular: Edema, fluid retention (greater than 1 % and less than 3 %).
- CNS: Dizziness (3 % to 9 %); headache, nervousness (greater than 1 % and less than 3 %).

- Dermatologic: Rash including maculopapular (3 % to 9 %); pruritus (greater than 1 % and less than 3 %).
- ENT: Tinnitus (greater than 1 % and less than 3 %).
- GI: Epigastric pain, heartburn, nausea (3 % to 9 %); abdominal cramps or pain, abdominal distress, constipation, diarrhea, fullness of GI tract (bloating, flatulence), indigestion, nausea and vomiting (greater than 1 % and less than 3 %).
- Metabolic-Nutritional: Decreased appetite (greater than 1 % and less than 3 %).

MATERIAL AND METHODS

Ibuprofen was received as a gift sample from Belco Pharma, Bahadurgarh, Haryana, India. Guar gum, Pectin and Microcrystalline cellulose were received as a gift from Central Drug House, Mumbai. Magnesium stearate and talc were perchased as a gift from Qualikems Fine Chemicals Pvt Ltd, Delhi. All other ingredients used were of analytical grade.

Experimental methods

Preparation of colon targeted matrix tablets of Ibuprofen

The composition of different formulations of colon targeted matrix tablets of Ibuprofen was shown in table 2. The ingredients were weighed accurately and mixed thoroughly. Tablets of ibuprofen were prepared by direct compression method by rotary tableting machine using 10 mm round, concave punch. Microcrystalline cellulose is used as diluent. Mixture of talc and magnesium state (2:1) was used as lubricant. Guar gum and pectin were included in various proportions. All the components are sieved separately and mixed by spatulation method in mortar and pastel.

Table 2: Composition of different formulations of colon targeted matrix tablets of Ibuprofen

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

In – Vitro evaluation

1. Evaluation of granules

The flow properties of granules before compression were characterized in terms of angle of repose, Carr's index and Hausner ratio. For determination of angle of repose, the granules were poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2.0cm above hard surface. The granules were poured till the time when upper tip of the pile surface touched the lower tip of the funnel. The $\tan^{-1}$ of the (height of the pile/ radius of its base) gave the angle of repose. Granules were poured gently through a glass funnel into a graduated cylinder cut exactly to 10ml mark. Excess granules were removed using a spatula and the weight of the cylinder with pellets required for filling the cylinder volume was calculated. The cylinder was then tapped from a height of 2.0cm until the time when there was no more decrease in the volume. Bulk density and tapped density were calculated.

Table 3: Results of flow properties of granules

Batch No.	Bulk Density	Tapped Density	Angle of Repose	Hausner's ratio	Carr's index
F1	0.350	0.522	32.8,(Good)	1.49,(very poor)	32.95,(very poor)
F2	0.388	0.552	36.8, (fair)	1.42, (poor)	29.71, (poor)
F3	0.410	0.570	40.0, (fair)	1.39, (poor)	28.07, (poor)
F4	0.440	0.504	48.4, (Poor)	1.14, (good)	12.69, (good)
F5	0.425	0.460	45.2, (Passable)	1.08, (excellent flow)	7.6, (excellent flow)

Evaluation of colon targeted matrix tablets

(1) Weight variation tests of tablets

In this test 20 tablets were weighed individually and their average weight was calculated by using electronic balance and the test was performed according to the official method.

(2) Hardness of the tablets

The crushing strength (Kg/ cm^2) of prepared tablets was determined by tablet hardness tester.

(3) 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.

Table 4: Results of physico-chemical characterization of Ibuprofen matrix tablets

Formulations	Average weight/ tablet (mg)	Crushing force	Friability (%)
Batch-A	499 ± 5	2.8-3.2	0.6255
Batch-B	496 ± 3	4.0-5.2	0.2711
Batch-C	502 ± 4	5.1-6.6	0.1279
Batch-D	506 ± 2	6.4-8.2	0.0782
Batch-E	499 ± 7	5.2-6.0	0.1493

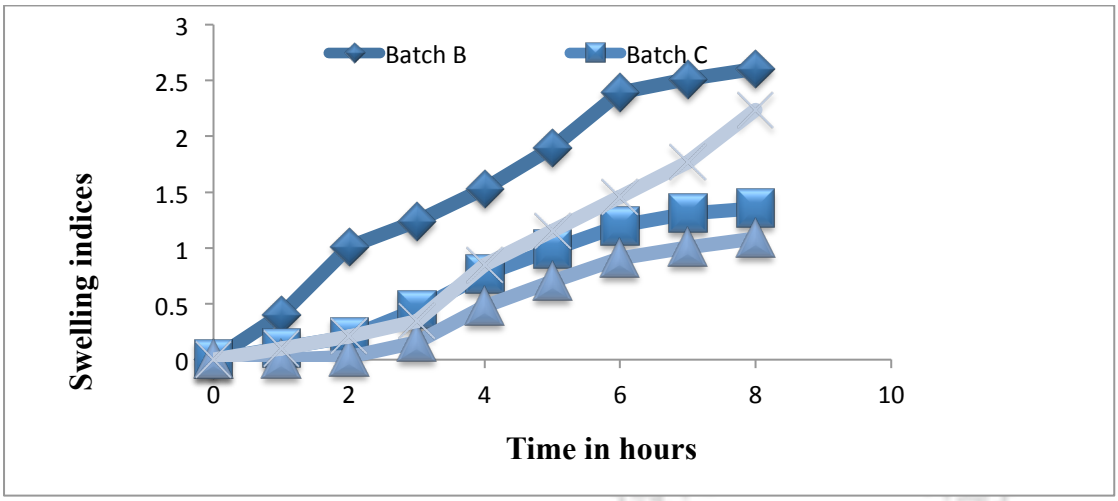
Swelling Behavior studies

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 6.8 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 D2-D1/ D1.

Table 5: Swelling indices of batch-A, B, C, D &E

Time	Batch-A	Batch-B	Batch-C	Batch-D	Batch-E
0	Tablet Disintegrated	0	0	0	0
1		0.3921	0.0935	0	0.0920
2		1.0002	0.1872	0.0230	0.1905
3		1.3110	0.4496	0.1480	0.3265
4		1.4900	0.6918	0.4854	0.7907
5		1.8794	0.9765	0.6935	1.2060
6		2.2910	1.1726	0.8770	1.5100
7		2.430	1.3067	1.0010	1.6990
8		2.5025	1.4060	1.0670	2.1864

Figure 2: Swelling indices of various batches Vs. Time



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.

Table 6: Percentage release of Ibuprofen in 0.1 N HCl from tablets

Time(hrs)	Batch-B	Batch-C	Batch-D	Batch-E
0.0	0.0	0.0	0.0	0.0
0.5	3.9	1.5	0.0	0.6
1.0	8.9	2.7	0.0	1.3
1.5	13.9	4.7	0.0	2.2
2.0	21.0	6.3	0.7	3.4

Results of drug release studies in various dissolution media

Figure 3: Percentage release of Ibuprofen in 0.1 N HCL from tablets

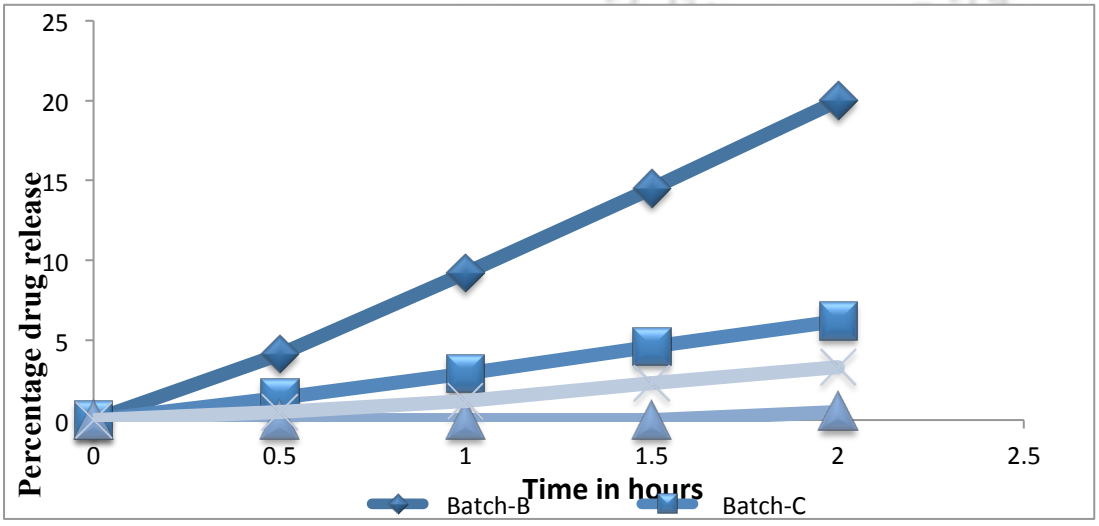


Table 7: Percentage release of Ibuprofen in pH 7.4 phosphate buffer solution from tablets

Time(hrs)	Batch-B	Batch-C	Batch-D	Batch-E
0.0	0.0	0.0	0.0	0.0
0.5	5.9	2.9	1.4	2.0
1.0	12.6	7.4	2.2	3.6
1.5	18.3	11.2	3.6	5.2
2.0	23.9	14.8	4.9	7.6
2.5	28.2	20.0	5.6	9.8
3.0	30.3	24.3	7.0	11.9

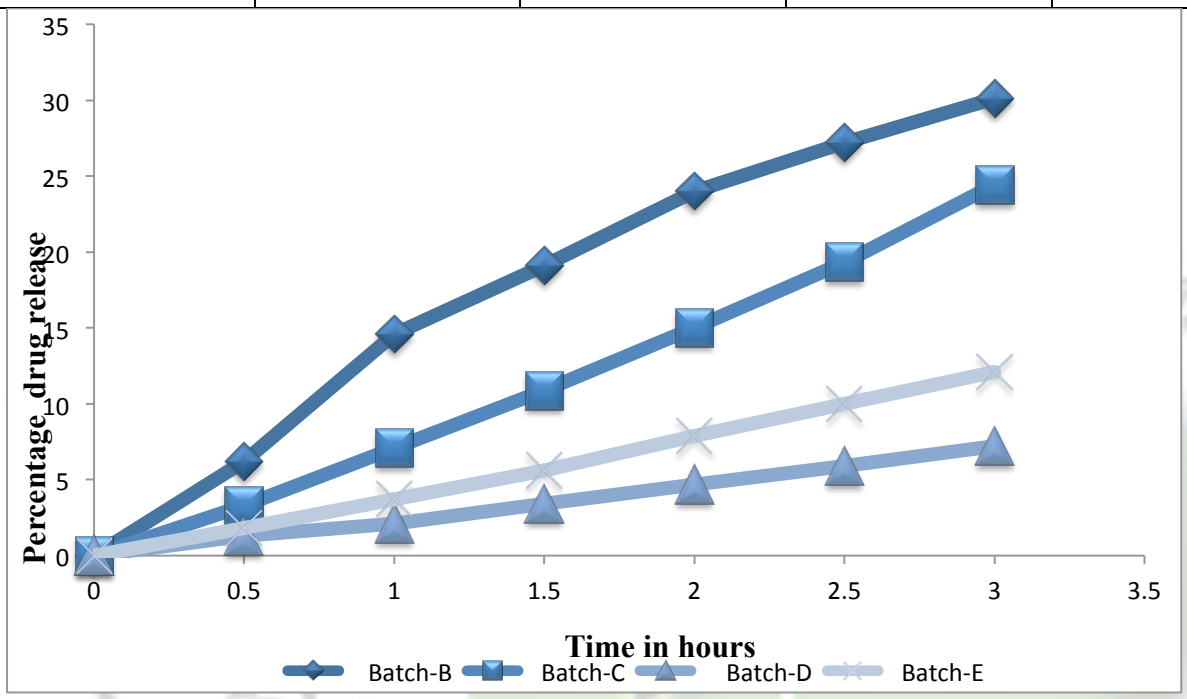


Table 8: Percentage release of Ibuprofen in pH 6.8 phosphate buffer solution with rat caecal contents from tablets

Time(hrs)	Batch-B	Batch-C	Batch-D	Batch-E
0.0	0.0	0.0	0.0	0.0
1.0	15.9	13.0	9.2	12.5
2.0	29.7	21.9	18.5	23.9
3.0	41.8	36.7	28.9	34.6
4.0	44.9	44.9	37.7	47.6
5.0	45.0	51.3	46.9	55.7
6.0	45.2	54.1	55.0	63.9
7.0	45.3	58.0	56.9	71.4
8.0	45.3	59.1	60.8	77.5

Figure 5: Percentage release of Ibuprofen in pH 6.8 phosphate buffer solution with rat caecal contents from tablets

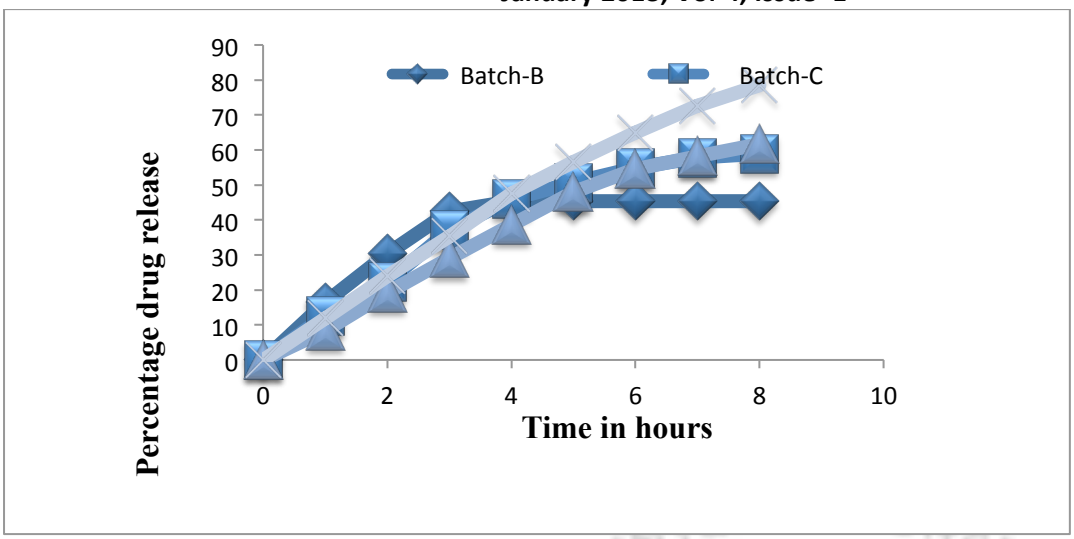
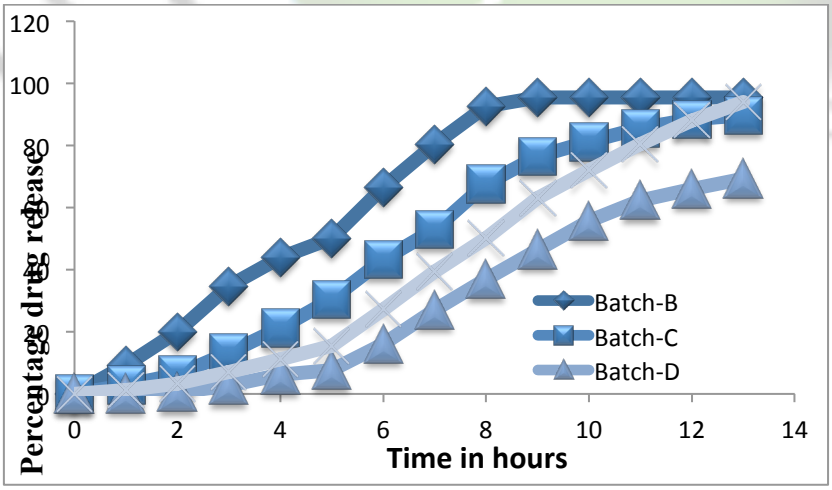


Table 9: Cumulative percentage drug release from tablets

Time	Batch-B	Batch-C	Batch-D	Batch-E
0	0	0	0	0
1	8.9	2.8	0	1.5
2	19.9	5.9	0.7	3.8
3	34.0	12.8	2.6	7.1
4	44.6	20.1	6.6	10.5
5	51.1	30.4	7.0	16.7
6	65.5	42.3	15.7	26.6
7	79.3	52.8	26.8	40.0
8	91.6	66.7	35.8	52.2
9	94.4	75.7	45.6	61.9
10	94.5	80.2	56.8	72.0
11	95.2	84.5	61.9	82.3
12	95.2	87.3	64.8	87.9
13	95.2	88.9	69.8	93.4

Figure 6: Cumulative percentage release of Ibuprofen with time from tablets



CONCLUSION

Four batches of matrix tablets were made using Guar gum and Pectin in their maximum and minimum concentrations. Various effects of both Guar gum and Pectin on the drug release were noted. Results show that when Guar gum was used alone in a concentration of 10 % in batch-A, the tablets disintegrate within one minute, *i.e.,* these

tablets will release 100 % of drug in stomach, this shows that Guar gum in such a low concentration is not able to provide a cohesive strength to tablets. When the percentage of Guar gum was increased from 10 % to 40 % in 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 i.e., these tablets will release 50 % of their drug before reaching colon. This is due to the drug leaching from the swelled tablets because batch-B tablets swell at a highest rate and to a highest extent.

In batch-C when Guar gum 10% and Pectin 30 % was used, the drug release pattern was better than batch-A and batch-B because 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. In batch-D when Guar gum and Pectin was used in their maximum concentrations, i.e., 40 % Guar gum and 30 % Pectin, there was a good retardation of drug release in first five hours. There was only 10 % drug release in first five hours. But when these tablets were studied in simulated colonic fluid, these tablets release drug only up to 70 % of the drug present in tablets. It is due to a very high concentration of gum. Total gum concentration in this batch is seventy percent. Due to this batch-D tablets had hardness up to 8.5 Kg/cm. There is significant interaction between Guar gum and Pectin. Effect of Guar gum is less than Pectin in retardation of drug release in first five hours of drug release. So there is a need to study a formulation having medium percentage of both Guar gum and Pectin. Batch-E was made which was having medium percentages of both Guar gum and Pectin. Ratio of Guar gum and Pectin in Batch –E was 25 % for Guar gum and 15 % for Pectin. When the Guar gum and Pectin were taken in their medium concentrations, Guar gum was 25 % and Pectin was 15 %, these tablets released approximately 15 % drug in first five hours. But the total release of drug from the tablet was approximately 94 percent. This batch releases 79 percent drug in the colon. Batch-E tablets with a Guar gum concentration of 25 % and Pectin concentration of 15 % were showing best drug release profile required for a colon targeted drug delivery system.

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