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ORIGINAL CONTRIBUTION

Formulation and Roentgenographic Studies of Naproxen-pectin-based Matrix Tablets for Colon Drug Delivery

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A study has been carried out to assess the potential use of pectin in combination with two added hydrocolloids, i.e., hydroxy-propyl-methyl cellulose and hydroxyethyl cellulose in varied concentrations and coated with ethyl cellulose and cellulose acetate phthalate. The results of in vitro *drug release showed that the matrix tablets prepared with pectin, hydroxy ethyl cellulose (20 percent) when coated with ethyl cellulose and cellulose acetate phthalate were found to be 63.0 percent, 8.4 percent, and 4.5 percent, respectively, in after eight hours during drug release study period. These results were confirmed with the results of roentgenographic studies in nine healthy human volunteers to find the shape and integrity of the dosage form. The X-ray photographs revealed that the enteric-coated tablet was visible only up to 5.5 hours and at the end of eighth hour, the photograph has not shown any presence of tablet indicating the loss of shape and size by the microflora present in the colon region. So, the results of* in vitro *and roentgenographic studies revealed that pectin, hydroxy ethyl cellulose (20 percent) base coated with ethyl cellulose and cellulose acetate phthalate was found to be a promising carrier for naproxen to colon.*

INTRODUCTION

Adkin, Kenyon, et al. [1] studied the use of scintiography as proof of concept data in man using gamma scintiography for calcium pectinate preparations for drug delivery to colon. Kenyon et al. [2] tested the ability of the naturally occurring polysaccharide guar gum to deliver a corticosteroid, dexamethasone to colon using pharmaco-scintography. Ashford et al. [3], 1993, have demonstrated the lack of site specificity of tablets in pH dependent systems by using gamma, scintiographic technique in healthy human volunteers. Wilding et al. [4] have evaluated an enteric-coated naproxen tablet formulation using gamma scintiography in 12 healthy male subjects. In recent past, an intense interest has been elicited by different

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authors for finding out a suitable drug carrier material for colon targeting. Slany and Mandak [5] studied the functional action on citrous pectin in tablets on the dissolution of phenobarbital sodium and sodium para-amino salicylic acid. They attributed the retardation of dissolution rates due to the formation of pectin hydrogel barrier. Rubeinstein A et al. [6] studied chondroitin sulphate as potential biodegradable carrier for a colon-specific drug delivery. The same authors have evaluated calcium pectinate as a potential colon drug delivery carrier. Munjeri et al. [7] evaluated the suitability of hydrogel beads based on amylated pectin for its potential use in film forming polymers for colon drug delivery. Turkoglu et al. [8] designed pectin hydroxypropylmethyl cellulose matrix tablets to find out their erosion property for colon targeting. The above citations revealed that pectin as a carrier for colon targeting has not been fully explored. In 1999, Basit et al. [9] reported and studied the use of amylase coating as a means of delivering drugs to the human colon. Amylase, a high-molecular weight component of starch can be digested by bacterial amylase enzymes in the colon. Amylase, has therefore, been applied as a coating, in combination with water-insoluble polymerethyl cellulose to conventional dosage forms for the purpose of colon targeting. So, the present investigation was designed to study pectin in combination of hydroxypropylmethyl cellulose, hydroxyethyl cellulose as a gelbased matrix systems for colon drug targeting by using roentgenographic studies in healthy human volunteers by taking naproxen as a model drug.

MATERIALS AND METHODS:

1. Naproxen: Divi's Laboratories, Hyderabad-India.
2. Pectin powder: Loba Chemicals Pvt. Ltd., Mumbai-India.
3. Hydroxyethyl cellulose and hydroxy propyl methyl cellulose: Himedia Laboratories Ltd., Mumbai-India.
4. Ethylcellulose and cellulose acetate phthalate: SD Fine Chemicals Pvt., Ltd., Mumbai-India

And other required laboratory chemicals used are of analar grade.

Preparation of Matrix Tablets: The formulation details and ingredients used are shown in Table 1.

Matrix tablets containing each 150 mg of naproxen and 150 mg of pectin were prepared by conventional wet granulation method using pectin alone and in combination with hydroxpropylmethyl cellulose and hydroxyethyl cellulose was drug

Table 1. Formula and ingredients to prepare naproxen-pectin-based matrix tablets.

	Formulations						
Ingredients in mg/tab	P1	A1	A2	A3	B1	B2	B3
Naproxen	150	150	150	150	150	150	150
Pectin	150	150	150	150	150	150	150
Lactose	200	150	125	100	150	125	100
Hydroxy propyl methyl cellulose	—	50	75	100	—	—	—
Hydroxy ethyl cellulose	—	—	—	—	50	75	100
Total weight of the tablet (mg)	500	500	500	500	500	500	500

Each tablet contains 150 mg of the drug.
P1 = Plain naproxen-pectin tablet.
A1, A2, A3 = 10, 15, and 20 percent hydroxy propyl methyl cellulose naproxen-pectin tablet.
B1, B2, B3 = 10%, 15% and 20% hydroxy ethyl cellulose naproxen-pectin tablet.

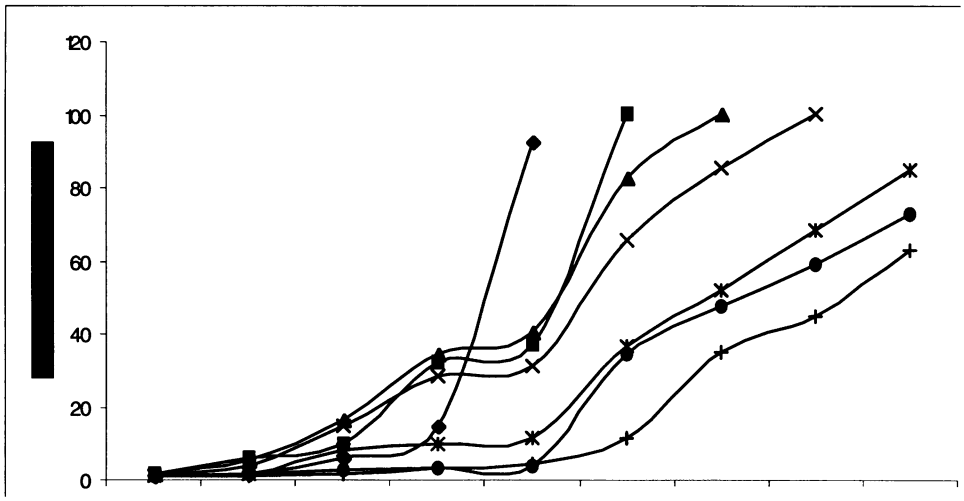

Figure 1. Comparative *in vitro* percent drug release of various uncoated naproxen-pectin-based tablets.

regarding swelling gel systems using 10 percent starch paste as binder, talc 2 percent, and mg stearate 2 percent as lubricants. The tablet required amounts of lactose as diluent. To cover all the variables, seven different batches of formulations were studied.

Preparation of tablets

The granules were compressed into tablets of each 500 mg using 10 station rotary tablet punching machine. The tablets were compressed to a hardness of 5 to 6 kg/cm^2. Some selected formulations were coated with 5 percent ethyl cellulose and 5 percent cellulose acetate phthalate solutions by pan-coating technique.

In vitro *drug dissolution studies*

The *in vitro* release of naproxen was carried out by using dissolution test apparatus of USP XXIII using 900 ml of dissolution fluid at varied pH dissolution media of 2 hours in 1.2 pH, 4 hours in 4.5 pH and 2 hours in 7.4 pH buffer solution. The basket speed was adjusted at 50 ± 2 rpm at a temperature of 37 ± 1°C. Five ml of aliquote of samples were withdrawn at each hourly interval and were replaced with fresh dissolution fluid to maintain the sink conditions. The samples withdrawn were suitably diluted and absorbance was measured at 261 nm in 1.2 pH, 269 nm in 4.5 pH, and 271 nm in 7.4 pH dissolution media.

Drug content uniformity

Ten tablets from each formulation were powdered, and a quantity equivalent to 50 mg of drug content was dissolved in 100 ml of methanol and filtered. 10 ml of filtrate was suitably diluted and analyzed for drug content spectro-photometrically.

Roentgenographic studies

Ethical committee permission was obtained for this study in consultation with radiologist, using our teaching and general hospital facilities. In these studies, nine healthy male subjects in the age group of 20 to 25 years and having a body weight between 50 to 65 kg participated in this study without any prior medication. The volunteers were divided into three groups of each three members. The first group was given plain uncoated tablets; the second groups was given ethyl cellulose coated tablets; and the third group was given

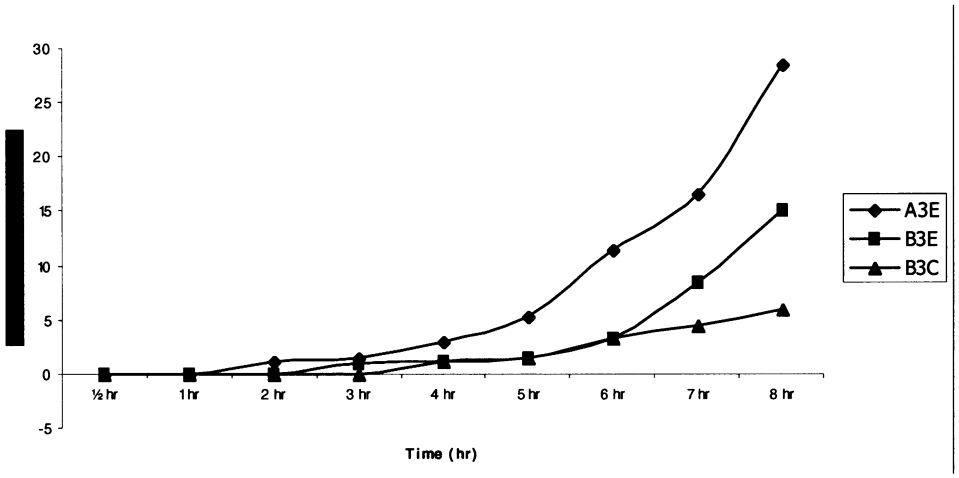

Figure 2. *In vitro* drug release of HPMC 20 percent and HEC 20 percent naproxen-pectin tablets coated with 5 percent ethylcellulose solution and 5 percent cellulose acetate phthalate solution.

ethyl cellulose and cellulose acetate phthalate-coated tablets. The volunteers were required to fast for at least 10 hours before the study. The volunteers were given one test tablet each followed by sufficient water along with 200 ml of barium meal. At different time intervals of 1, 3.5, 6, and 8 hours. The subjects were X-ray photographed to observe shape and integrity and position of the tablet. The photograph of X-ray studies revealed that the enteric coated tablet was visible only up to 5.5 hours. At the end of eighth hour, the photograph has not shown any presence of tablet.

Table 2. Comparative *in vitro* release naproxen from various uncoated matrix tables.

Sl. no.	Time (hr)	Percent naproxen released						
		P1	A1	A2	A3	B1	B2	B3
1	0.5	1.20	1.00	1.50	1.20	1.08	1.20	0.90
2	1.0	1.50	6.00	5.40	3.60	1.50	1.50	1.08
3	2.0	6.00	10.00	16.50	15.00	8.40	3.00	1.50
4	3.0	15.00	32.58	34.50	28.50	9.90	3.30	3.30
5	4.0	92.50	37.08	40.50	31.50	11.40	3.90	4.50
6	5.0	—	100.01	82.50	66.00	36.90	34.50	11.50
7	6.0	—	—	100.50	85.50	51.90	47.40	35.10
8	7.0	—	—	—	100.30	68.40	59.40	45.00
9	8.0	—	—	—	—	84.90	72.90	63.00

Each tablet contains 150 mg of the drug.
P1 = Plain naproxen-pectin tablet.
A1, A2, A3 = 10, 15, and 20 percent hydroxy propyl methyl cellulose naproxen-pectin tablet.
B1, B2, B3 = 10%, 15% and 20% hydroxy ethyl cellulose naproxen-pectin tablet.

Table 3. *In vitro* drug release of Naproxen from pectin, HPMC (20 percent) and HEC (20 percent) combined matrix tablets coated with EC and CAP.

Sl. no.	Time (hr)	Percent naproxen released		
		P1	A1	A2
1	0.5	—	—	—
2	1.0	—	—	—
3	2.0	1.20	—	—
4	3.0	1.50	0.90	—
5	4.0	3.00	1.08	1.20
6	5.0	5.25	1.50	1.50
7	6.0	11.40	3.30	3.30
8	7.0	16.50	8.40	4.50
9	8.0	28.50	15.00	6.00

Each tablet contains 150 mg of the drug.
A3E: Naproxen-pectin tablets containing 20 percent Hydroxypropylmethyl cellulose coated with 5 percent ethyl cellulose solution.
B3E: Naproxen-pectin tablets containing Hydroxy ethyl cellulose 20 percent coated with 5 percent ethyl cellulose solution.
B3C: Naproxen-pectin matrix tablet containing Hydroxy ethyl cellulose 20 percent coated with ethyl cellulose and 5 percent cellulose acetate phthalate solution.

RESULTS AND DISCUSSION

The basic data of *in vitro* release of naproxen for all the seven batches studied are shown in Table 2 and Figure 1. The result showed that plain naproxen, pectin uncoated tablets gave complete release at the end of fifth hour whereas pectin with increased concentrations of hydroxy propyl methyl cellulose (10, 15, 20 percent w/w) were found to be released completely by the end of 6, 7, and 8 hours, whereas the pectin-hydroxy ethyl cellulose system was found to extend the release even after the eighth hour, at the end of which an amount of 84.9 percent, 72.9 percent, and 63.0 percent of drug was found to be released from these uncoated tablet formulations. So, these formulations were further coated with 5 percent ethyl cellulose and 5 percent cellulose acetate phthalate solutions to control the drug release up to 6 hours. The results indicated that, after 8 hours release study, 8.4 percent drug release from ethyl cellulose coating and 4 percent drug release from ethyl cellulose and cellulose acetate phthalate coatings from 20 percent hydroxy ethyl cellulose matrix tablets. The results showed that the uncoated tablet systems are not suitable to be used as colon targeted drug delivery systems. The aim of the present work is to achieve the disintegration of the tablet only after reaching colon. From these studies, it can be presumed that the ethyl cellulose and cellulose acetate phthalate coated (Table 3, Figure 2) tablet after reaching colon at the end of 7.5 hours might have degraded by the resident anaerobic microflora present in the colon of human volunteers. So the results of roentgenographic studies clearly revealed the transit of the selected matrix tablet up to the colon. The disappearance of the tablet in colon region as shown in photograph has revealed unambiguous evidence for the degradation of the tablet in the colon, which can be considered as a significant finding for the utilization of pectin, hydroxy ethyl cellulose system with ethyl cellulose, cellulose acetate phthalate coatings as a potential carrier for the delivery of the drug at the specific targeted site of colon.

DISCUSSION

Among the two selected hydrocolloids, hydroxy propyl methyl cellulose due to its high hydrophilicity was found to be inferior to hydroxy ethyl cellulose in achieving colon-targeted drug delivery. So, the results have conclusively proved that addition of hydroxy ethyl cellulose (20 percent w/w) along with pectin coated with ethyl cellulose and cellulose acetate phthalate will be an ideal carrier for colon targeted drug delivery.

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