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Research Article

Colon targeted drug delivery of propranolol hydro chloride by using different natural polymers

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ABSTRACT

Oral colon targeted drug delivery system have recently gained importance for delivering a variety of therapeutic agents for both local and systemic administration. The successful targeted delivery of drugs to the colon via the gastrointestinal tract requires the protection of a drug from degradation and its release in the stomach and small intestine and then ensures abrupt or controlled release in the proximal colon. This review represents the approaches for formulating colon targeted drug delivery dosage form of Propranolol HCl using polysaccharides like Guar gum, Ceratonia, Chitosan as polymer coating material. The various formulations having Chitosan (F1, F2, F3), Ceratonia (F4, F5, F6) and Guar gum (F7, F8, F9) were prepared using three respective concentrations (i.e 200mg, 250mg, 300mg) of each polymer. These were prepared by direct compression method and were evaluated analytically by *in vitro* method in rat caecal organ. The results from the study clearly shows that 200mg of Guar gum and 200mg of Chitosan in the form of a compression coat is a potential carrier for drug targeting to the colon because at that concentration of these polymer rapidly releases 86.6% (in case of guar gum) and 91.35% (in case of chitosan) of core drug in the colon. Evaluation parameters like Hardness (6.5-7.6kg/cm^2), weight variation, drug uniform content (100±5%), friability (>1%) and *in vitro* dissolution profiles stated that F1 and F7 formulation having 200mg chitosan & 200mg of guar gum was confirmed as a ideal formulation for colon targeting.

Keywords: Propranolol HCl; Guar gum; Ceratonia; Chitosan.

INTRODUCTION

The oral route is considered to be most convenient route and the drug administered by this route dissolves in the stomach or intestinal fluid and absorption from these regions depends upon the physicochemical properties of the drug, residence time of drug, gastrointestinal anatomy and physiology. It is a serious drawback in conditions where localized delivery of the drugs in the colon is required or in conditions where a drug needs to be protected from the hostile environment of upper GIT. The colon has a longer retention time and appears highly responsive to agents that enhance the absorption of poorly absorbable drugs, improves bioavailability and important starting position for the colonic absorption of per orally applied, undigested, unchanged and fully active peptide drugs. The simplest method for targeting of drugs to the colon is to obtain slower release rates or longer release periods by the application of thicker layers of conventional enteric coatings or extremely slow releasing matrices or employing bioadhesive in colonic drug formulation. By these methods delivery dosage form enters the colon can also improve drug uptake by delaying the drug release until it reaches colon. So Propranolol HCl core compressed tablet coated with polymers like Guar gum, Ceratonia, Chitosan was chosen as an experimental drug to get successful colonic delivery of drug without any degradation in GIT because polymers protect the drug core and enhances the epithelial permeability by decreasing the paracellular resistance. This will increase the colonic drug absorption for the treatment of diseases of colon (ulcerative colitis, Chron's disease, etc) whereby high local concentration can be achieved while minimizing side effects that occur because of release of drugs in the upper GIT or unnecessary systemic absorption. Alternatively drug uptake into the lymphatic sinuses of the colon results in delivery directly to the systemic circulation which results in less metabolic breakdown of the absorbed drug.

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MATERIALS AND METHODS

Materials

Propranolol hydro chloride was obtained from Sigma Chemicals.Ltd, Guar gum was purchased from Himedia, Ceratonia (Locust Bean Gum), Chitosan, Microcrystalline cellulose and Magnesium stearate were obtained from Loba Chemidie Pvt.Ltd.

Table 1: Formula for Preparation of Core Tablet

S.NO	Ingredients	For one tablet (mg)
1	Propranolol HCl	10
2	Microcrystalline cellulose	59
3	Starch	5
4	Talc	1.5
5	Sodium lauryl sulphate	4.0
6	Magnesium stearate	0.5

Table 2: Different formulations for compression coating

Formulation code	Coat weight (mg)	MCC (mg)	Magnesium Stearate (mg)	Talc (mg)	Chitosan (mg)	Ceratonia (mg)	Guar gum (mg)
F1	250	45	2	3	200	-	-
F2	300	45	2	3	250	-	-
F3	350	45	2	3	300	-	-
F4	250	45	2	3	-	200	-
F5	300	45	2	3	-	250	-
F6	350	45	2	3	-	300	-
F7	250	45	2	3	-	-	200
F8	300	45	2	3	-	-	250
F9	350	45	2	3	-	-	300

Methods

Preparation of core tablets

Each core tablet (average weight 80 mg) for in vitro drug release studies consists of propranolol HCl (10 mg), microcrystalline cellulose (59 mg), sodium lauryl sulphate (4 mg), talc (1.5 mg) and magnesium stearate (0.5 mg) (Kinget R, 1998). Starch and sodium lauryl sulphate are added to obtain fast disintegration tablets (disintegration time <1 min) of Propranolol hydro chloride. The materials were weighed, mixed and passed through a mesh (250µ) to ensure complete mixing. The tablets were prepared by compressing the thoroughly mixed materials using 0.6 mm round, flat and fine punches on a multi station tablet machine (CADMACH 16 station). The thickness of the core tablet was 0.2mm and their crushing strength was found to be 3 kg/cm^2.

Compression coating of Propranolol hydrochloride tablet

The Propranolol hydrochloride tablets were compressed and coated with different quantities of coating material (Guar gum, Chitosan, Ceratonia) containing different concentrations (Wilding R, 1994). Since the coating material alone gave very soft tablets, microcrystalline cellulose was included in the coat formulations to yield enough hardness. Half the quantity of the coating material was placed in the die cavity; the core was carefully placed in the center of the die cavity and was filled with other half of the coating material. The coating material was compressed around the core at an applied force using 1.2mm round, flat and plain punches. The crushing strength of the compression coat tablet was 6.5 kg/cm^2.

Evaluation of tablets

All the formulated Propranolol hydrochloride core and compression coated tablets were subjected to the following quality control tests.

Weight variation test

The USP weight variation test was run by weighing 20 tablets and then the average weight was determined. All the 20 tablets were weighed individually and compared with the average weight.

Drug Content Uniformity Test

The Propranolol hydrochloride core and compressed coated tablet, both were tested for their drug content. The tablets were finely powdered and a quantity of powder equivalent to 10mg of Propranolol HCl were accurately weighed and transferred to 100 ml volumetric flask containing approximately 50 ml of buffer pH 6.8. The flasks were shaken to solubilize the drug. The volume was made up with buffer pH 6.8 and mixed thoroughly. The solution was filtered and analyzed for the content of Propranolol HCl using UV – spectrophotometer.

Friability test

The Friability test was performed for all the formulated core and compressed coated Propranolol HCl tablets. 20 tablets were taken and their weight was determined. Then they were placed in the friabilator and allowed to make 100 revolutions. The tablets were then dedusted and reweighed. The percentage weight loss was calculated.

Hardness test

Monsanto hardness tester was used for measuring the hardness of the formulated Propranolol HCl core and

Table 3: Evaluation of Drug content uniformity, Friability, Hardness and weight variation of the Formulated core tablets and compression coated tablets

S.NO	Formulations containing	%of Propranolol HCl estimated by UVS-pectrometry	Friability (% of weight loss)	Hardness (Kg/cm2)	Average Wt (mg)	Weight range of tablet(mg)
1	F1	98	0.5	6.8±0.4	79.5	308-313
2	F2	97	0.6	6.6±0.5	312.8	359-364
3	F3	100	0.3	6.5±0.5	359.6	410-413
4	F4	97	0.4	7.1±0.2	411.3	310-314
5	F5	97	0.4	6.9±0.5	313.5	358-362
6	F6	101	0.6	6.7±0.3	361.2	408-413
7	F7	99	0.3	7.0±0.4	409.7	310-312
8	F8	98	0.5	6.8±0.1	311.9	359-354
9	F9	101	0.3	6.5±0.3	362.5	408-411
10	Core Tablet	102	0.3	8.0±0.2	410.6	79-82

Table 4: Medium 0.1Hcl, 7.4pH, 6.8pH, Temperature 37.10°C

Time in hrs	F7	F8	F9
2	-	-	-
4	-	-	-
6	0.98±0.22	0.62±0.08	0.76±0.06
8	1.25±0.32	0.99±0.10	0.95±0.09
10	2.65±0.82	1.20±0.13	099±0.21
12	4.90±0.36	2.25±0.25	1.30±0.24
14	6.70±0.85	3.90±0.86	2.60±0.56
16	8.25±0.96	5.80±0.65	3.90±0.36
18	10.6±0.88	6.95±0.89	5.25±0.49
20	12.8±0.91	8.30±1.04	5.75±0.37
22	13.2±1.02	8.80±0.76	6.42±0.32
24	13.8±1.18	9.54±0.95	7.56±0.26
26	1.45±1.23	10.25±1.21	8.60±0.13

Mean (Standard deviation) Cumulative percentage release of Propranolol hydrochloride on various concentrations of Guar gum (200mg, 250mg, 300mg) without rat caecal content.

compression coated tablets. From each batch 5 tablets were taken and subjected to test. The mean of the 5 tablets were calculated.

Dissolution studies without rat caecal content

The compression coated tablets of Propranolol HCl were evaluated for their integrity in the physiological environment of stomach and small intestine under conditions mimicking mouth to colon transit (Sinha VR, 2002). These studies were carried out using DBK dissolution rate test apparatus.

The tablets were tested for drug release for 2 hours in 0.1 N HCl (900 ml) as the average gastric emptying time is almost 2 hours. Then the dissolution medium was replaced with pH 7.4 phosphate buffer (900 ml) and tested for drug release for 3 hours as the average small intestine transit time is almost 3 hours. At the end of the period 2 samples each of 1 ml were taken, suitably diluted and analyzed spectrophotometrically. Then the dissolution medium was replaced with pH 6.8 phosphate buffer. The drug release studies were carried out for 21 hours (usual colonic transit time is 20-30 hours) and 1 ml samples were taken at different time and replaced with 1 ml of (pH 6.8) phosphate buffer .The samples are diluted and analyzed spectrophotometrically.

Dissolution studies using rat caecal content

The compression coated tablets of Propranolol HCl were evaluated for their integrity in the physiological environment of stomach and small intestine under conditions mimicking mouth to colon transit (Yang L, 2002). These studies were carried out using DBK dissolution rate test apparatus. The tablets were tested for drug release for 2 hours in 0.1N HCl (900 ml) as the average gastric emptying time is almost 2 hours. Then the dissolution medium was replaced with pH 7.4 phosphate buffer (900 ml) and tested for drug release for 3 hours as the average small intestine transit time is almost 3 hours. At the end of the period 2 samples each of 1 ml were taken, suitably diluted and analyzed spectrophotometrically. The drug release studies were carried out using USP dissolution rate test apparatus with slight modification (beaker containing 200 ml of

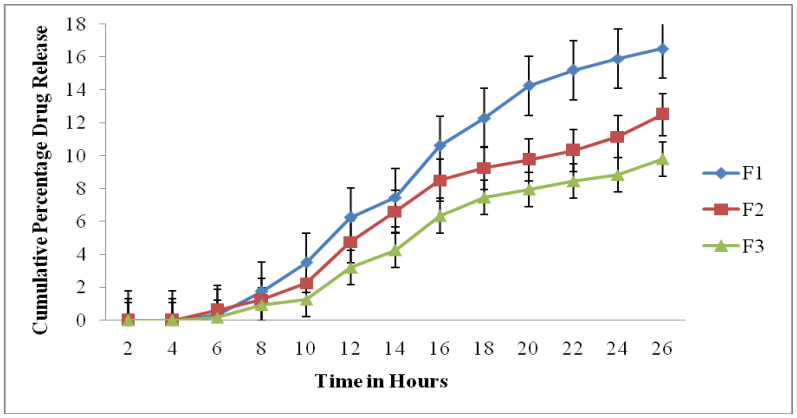

Figure 1: Mean (Standard deviation) Cumulative percentage release of Propranolol hydrochloride on various concentrations of chitosan (200mg, 250mg, 300mg) without rat caecal content

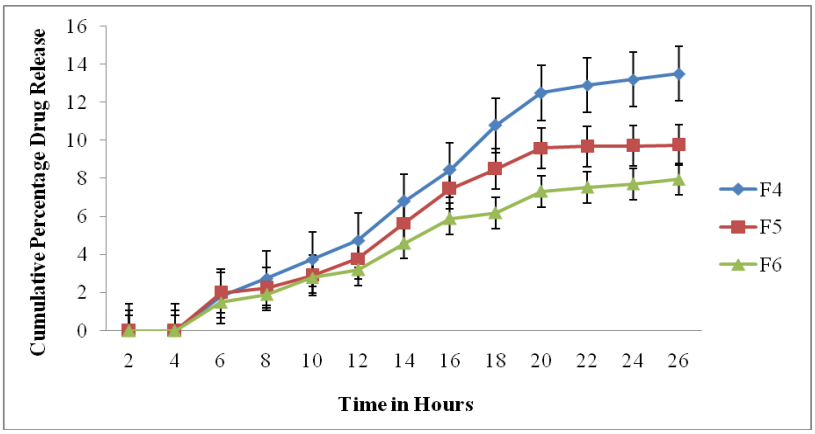

Figure 2: Mean (Standard deviation) Cumulative percentage release of Propranolol hydrochloride on various concentrations of ceratonia (200mg, 250mg, 300mg) without rat caecal content

dissolution medium was placed in the water bath of the apparatus).

RESULTS AND DISCUSSION

Results

Evaluation of tablet parameters

All the batches of propranolol HCl core and compressed coated tablets fulfilled official requirements of uniformity of weight. All the tablets prepared were found to contain the medicament within 100±5% of labeled claim. Hardness of the tablets in all the batches was found to be in the range of 6.5-7.0kg/cm^2 and was satisfactory. The percentage weight loss in the friability test was found to be less than 1% in all the batches**.** All these results were shown in table – 3.

Dissolution studies without rat caecal content

The percentage of drug released at different time periods from propranolol HCl compression coated formulations in 0.1N HCl (2hrs), pH 7.4 phosphate buffer, pH 6.8 phosphate buffer without rat caecal were shown in table - 4 and graphs - 1, 2. The results were found that the formulations F1, F2, F3 of chitosan released 16.5±0.36%, 12.5±0.69%, 9.08±0.45% of drug. Formulations F4, F5, F6 of ceratonia released 13.5±2.23%, 9.75±1.88%, 7.95±1.96% of drug and formulations F7, F8, F9 of guar gum released 14.5±1.23%, 10.25±1.21%, 8.60±0.13% of drug. It shows that percentage of drug released from the propranolol HCl tablet was less in pH 7.4 buffer than the percentage of drug released 6.8 pH buffer phosphate.

Dissolution studies with rat caecal content

The cumulative percentage of drug released at different time periods from propranolol HCl tablets coated formulation in 0.1 HCl and pH 7.4 phosphate buffer (3hrs) and pH 6.8 phosphate buffer containing 2% w/v rat caecal content (21hrs) were represented in the table - 5 and graphs – 3,4. The results were that the formulations F1, F2, F3 of chitosan released 37.5±2.37%, 68.9±6.25%, 91.35±10.25% of drug. Formulations F4,F5,F6 of ceratonia released 25.50±4.36%, 51.55±7.36%, 80.25±8.96% of drug and formulations F7,F8,F9 of guar gum released 31.5±6.52%, 59.25±8.15%, 86.60±8.33% of drug.

From the above results it was found that the rate of drug release from the propranolol HCl tablets decreased with increasing concentration of the coating polymer.

At the end of the 26th hour formulations F3, F6, F9 were found to be intact. The formulations F2, F5, F8 were found broken at one time indicating commence-

Table 5: Medium 0.1Hcl, 7.4pH, 6.8pH, Rat caecal contents 4%w/v

Time in hrs	F1	F2	F3
2	0	0	0
4	0	0	0
6	0.32±0.24	0.61±0.32	0.15±1.06
8	7.5±0.35	10.75±0.47	15.28±1.33
10	10.8±0.42	17.85±0.89	28.5±2.54
12	13.5±0.76	24.55±1.25	37.6±3.69
14	15.25±0.89	33.22±1.89	43.45±4.25
16	20.5±1.56	37.25±2.22	58.25±4.98
18	23.5±2.33	42.65±2.36	66.55±5.36
20	31.45±1.36	53.55±5.24	78.25±7.39
22	33.26±1.56	59.41±5.62	83.52±8.96
24	35.33±2.12	64.2±5.95	87.62±9.54
26	37.5±2.37	68.9±6.25	91.35±10.25

Mean (Standard deviation) Cumulative percentage release of Propranolol hydrochloride on various concentrations of Chitosan (200mg, 250mg, 300mg) using rat caecal content.

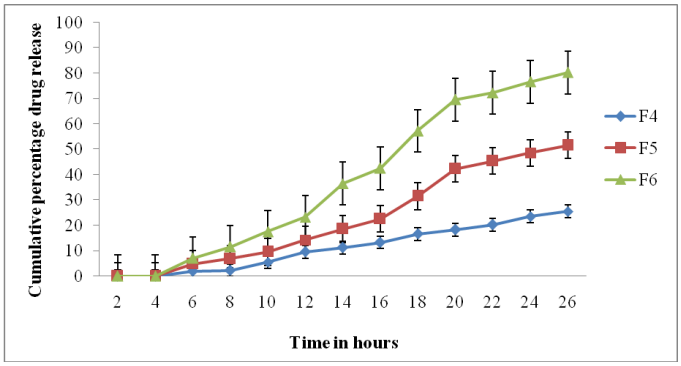

Figure 3: Mean (Standard deviation) Cumulative percentage release of Propranolol hydrochloride on various concentrations of Ceratonia (200mg, 250mg, 300mg) using rat caecal content

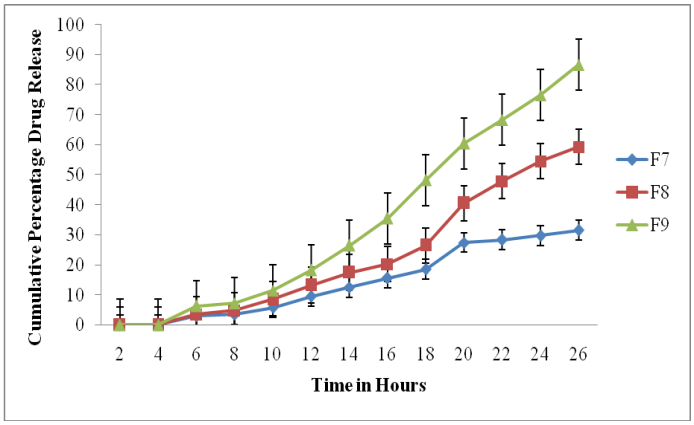

Figure 4: Mean (Standard deviation) Cumulative percentage release of Propranolol hydrochloride on various concentrations of Guar gum (200mg, 250mg, 300mg) using rat caecal content

ment of disintegration of the coat where as the formulations F1, F4, F7 were completely disintegrated.

Discussion

Successful delivery of drugs specifically to the colon requires the protection of the drug form being released in the stomach and small intestine. In this study, polymer in the form of compression coat was applied over Propranolol HCl core tablet and *in vitro* drug release studies were carried out in pH 6.8 phosphate buffer containing 2% w/v of rat caecal contents.

At the end of the 26th hour of testing which includes testing in the simulated gastric and intestinal fluid, formulations F3, F6, F9 were found to be intact. The presence of higher amount of polymer might not have allowed the disintegration of the coat during the period of testing. This also indicates the drug was not being released until the coat is broken.

The percent of drug released from the formulations F2, F5, F8 were found to increase from 18 hours onwards indicating the commencement of breaking of gum

coats where as formulations F1, F4, F7 shows a significant increase in percentage of drug release from 14 hours onwards and at the end the coat was completely degraded by the rat caecal contents in the dissolution medium. Since the polymer content and the thickness of the coat was less as compared to the coat of the other coated formulations. The coat might have completely hydrated and subsequently degraded by the caecal enzyme at a faster rate. An *in vitro* investigation shows the suitability of bacterially triggered delivery system for colon targeting.

CONCLUSION

The delivery of the drugs directly to the colon via the oral route has several therapeutic advantages. The results from the study clearly show that 200 mg of Guar Gum and 200 mg of Chitosan in the form of a compression coat is a potential carrier for drug targeting to the colon. These polysaccharides are capable of retarding the release of the core materials until they reach the colon. An environment rich in bacterial enzymes is the colon in which they degrade the Guar gum and Chitosan allowing the drug release.

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