Influence of Beta-cyclodextrin and Chitosan in the Formulation of a Colon-Specific Drug Delivery System

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Influence of Beta-cyclodextrin and Chitosan in the Formulation of a Colon-Specific Drug Delivery System

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Key words
- colon drug delivery
- enzymatic digestion
- inclusion complex
- in vitro drug release
- polysaccharide

Abstract

The increase in diseases of the colon underscores the need to develop cost-effective site-directed therapies. We formulated a polysaccharide-based matrix system that could release ibuprofen under conditions simulating those in the colon by employing a wet granulation method. Tablets were prepared in a series of formulations containing a polysaccharide (beta-cyclodextrin and chitosan) matrix system along with ethylcellulose. We characterized physicochemical properties and performed an in vitro drug release assay in the absence and presence of digestive enzymes to assess the ability of the polysaccharides to function as a protective barrier against the upper gastrointestinal environment. Fourier transform infrared spectroscopy studies revealed no chemical interaction between ibuprofen and polysaccharides; however, spectrum analysis suggested the formation of an inclusion complex of beta-cyclodextrin with ibuprofen. The formulations contained 50% ethylcellulose and 50% beta-cyclodextrins (1:1) were proven to be the better formulation that slowly released the drug until 24 h (101.04±0.65% maximum drug release in which 83.08±0.89% drug was released in colonic medium) showed better drug release profiles than the formulations containing chitosan. We conclude that a beta-cyclodextrin drug carrier system may represent an effective approach for treatment of diseases of the colon.

Abbreviations

BP	British Pharmacopoeia
F	formulation without polyvinylpyrrolidine
FP	Formulation with polyvinylpyrrolidine
GI	gastrointestinal
kN	kilonewton
kPa	kilopascals
MCC	microcrystalline cellulose
PVP	polyvinyl pyrrolidine
SCF	simulated colonic fluid
SGF	simulated gastric fluid
SIF	simulated intestinal fluid
USP	United States Pharmacopoeia

Introduction

The site-specific targeted drug delivery system has gained importance for the treatment of local disease associated with gastrointestinal regions of the body. Because of the increasing prevalence of colon cancer, ulcerative colitis, irritable bowel disease, and Crohn's disease [1], there is an urgent need to develop drug delivery systems that specifically target the colon. The most difficult challenge with such delivery systems is preservation of the formulation during its passage through the gastrointestinal (GI) tract until it reaches the colon. For formulation of a colon-specific drug delivery system, the physicochemical properties of the drug molecule and the excipients in the delivery system must be well understood in relation to known physiological attributes of the GI tract, such as pH gradients and transit times [2]. Systems employing pH-sensitive and time-dependent approaches have been unreliable because of individual variability in the gastric and intestinal transit times and differences in pH between the distal intestine and the colon [3].

The polysaccharide-based microbial enzyme triggering system is considered as the most reliable colonic delivery [4,5]. These polysaccharides are fermented by the large number of hydrolytic and reducing enzymes [6]. In this process, the drug is released inside the colon region. The

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upper part of gastrointestinal tract, that is the stomach and duodenum has a microflora of less than 103–104 CFU/mL and the microflora of colon is in the range of 1 011–1 012 CFU/mL [7], thus providing selectivity for the colon drug delivery.

Current strategies for targeting drug delivery to the colon involve utilization of complexes of conjugated polysaccharides, including carboxymethylchitosan-g-poly(acrylic acid) hydrogel [8] pectin-4-aminothiophenole [9] cyclodextrin [10], and nanoparticles of carboxymethyl starch with chitosan [11]. Other approaches involve coating calcium-chitosan pellets with pectin or alginate [12], and complexing chitosan-Ca-alginate microspheres with hydroxypropyl-β-cyclodextrin-polyvinylpyrrolidone [13]. However, manufacturing costs preclude the use of these strategies for large-scale production. Thus, there remains a need to develop cost-effective colon-specific drug delivery systems.

In this study, an attempt has been made to contribute in the efforts of developing a suitable dosage form for the safe delivery of drug inside the colon region. Here, chitosan, beta-cyclodextrin and ethylcellulose were utilized to formulate a matrix system by wet granulation, which can deliver a maximum drug release inside the colon region. Chitosan [14–17] and beta-cyclodextrin [18–20] have been extensively tested in formulations that permit the sustained release of drugs, particularly in the colon. In this study, however, the inclusion complex forming property of the beta-cyclodextrin was utilized to carry the drug into the colon region. Because both chitosan (**Fig. 1**) and beta-cyclodextrin (**Fig. 2**) are hydrolyzed by *alpha-amylase* in the colon [21,22], it is plausible that this will enhance the delivery of the payload drug to its intended site of action. Thus, the aim of this study was to investigate the ability of beta-cyclodextrin and chitosan as components in tablet matrix formulations to maximize the release of a drug under conditions simulating those in the colon, while minimizing drug release under conditions simulating those in the upper GI tract.

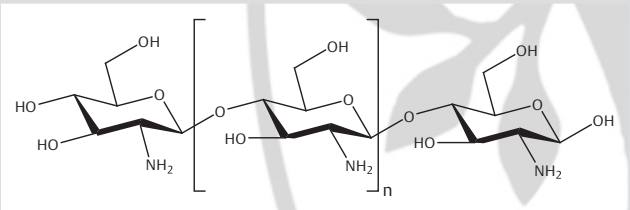

Fig. 1 Structure of chitosan.

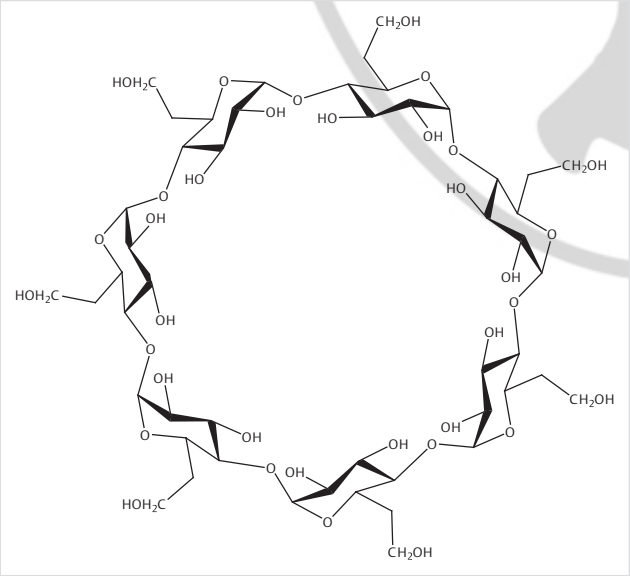

Fig. 2 Structure of betacyclodextrin.

Materials and Methods

Materials

Ibuprofen was purchased from Shasun Chemicals and Drugs (China). Microcrystalline cellulose, ethyl cellulose (10 cps viscosity grade), magnesium stearate, polyvinylpyrrolidone (PVP), chitosan (medium molecular weight, 75–85 % deacetylated), beta-cyclodextrin, potassium dihydrogen phosphate, sodium chloride, *alpha-amylase*, *pancreatin* from porcine and *pepsin* were purchased from Sigma-Aldrich (USA). Ethanol (absolute alcohol), methanol, hydrocholoric acid, and sodium hydroxide were purchased from Merck (Germany). All materials used were of analytical grade.

Drug-polysaccharides interaction study

Fourier transform infrared spectroscopy (FTIR)

FTIR spectroscopy of ibuprofen, polysaccharides, and ibuprofen-polysaccharide mixtures was conducted by the KBr disc method using a Perkin Elmer FTIR (USA) instrument. Mixtures containing equal amounts (25 g each) of ibuprofen and polysaccharide were prepared using a tumbling mixer (Glas-Col, USA), and scanned from 4 000 to 500 cm^{-1}.

Preparation of tablet matrix

A series of ibuprofen formulations (**Table 1**) were prepared prior to compression. All the excipents were passed through 1 mm mesh size screen to remove the lumps in the bulk materials. Then, the materials were weighed according to the batch size (100 tablets) and mixed in a spiral mixer (GRT-HS50) for 15 min. Then binder was added to the mixture. The formulations with and without PVP are identified as FP and F, respectively (as shown in **Table 1**). The wet mass was passed through 1 mm sieve to produce the granules and air-dried for 24 h. After drying, the dried granules passed through the sieve. Talc and magnesium stearate were then added to the formulation and mixed for 5 min. The granules were compressed at 5 kN compression force by using a rotary tabletting machine (ZP-5 China) with a specialized mould consisting of a 12-mm punch and die; the average weight of the tablets was 500 mg.

Characterization of prepared tablets

Friability test

Tablet friability test is to investigate the fragility of tablets. 10 tablets were placed in the friabilator (Sotax F1, Switzerland) and spun for 100 rotations or for 4 min at 25 rpm rotation rate.

Hardness test

Hardness (in kPa) was assessed in 10 tablets randomly selected from each formulation by using a tablet harndess tester (PTB 311E, Pharmatest, Germany).

Drug content determination

The assay of the randomly selected 20 tablets of all the batches was conducted to determine the content of ibuprofen in the tablets.

Table 1 Formulation ingredients of tablets.

	Formulation mg/tablet							
ID FP[c],F[d]	Ibuprofen	MCC [a]	Beta cyclodextrin	Chitosan	Ethyl-Cellulose	PVP[b]	Magnesium stearate	Talc
FP1	100	285	–	75	25	5	5	5
FP2	100	285	75	–	25	5	5	5
FP3	100	285	–	50	50	5	5	5
FP4	100	285	50	–	50	5	5	5
FP5	100	285	–	25	75	5	5	5
FP6	100	285	25	–	75	5	5	5
F1	100	290	–	75	25	–	5	5
F2	100	290	75	–	25	–	5	5
F3	100	290	–	50	50	–	5	5
F4	100	290	50	–	50	–	5	5
F5	100	290	–	25	75	–	5	5
F6	100	290	25	–	75	–	5	5

a) microcrystalline cellulose
b) polyvinyl pyrrolidine
c) Formulations containing PVP as a binder
d) Formulations without PVP as a binder

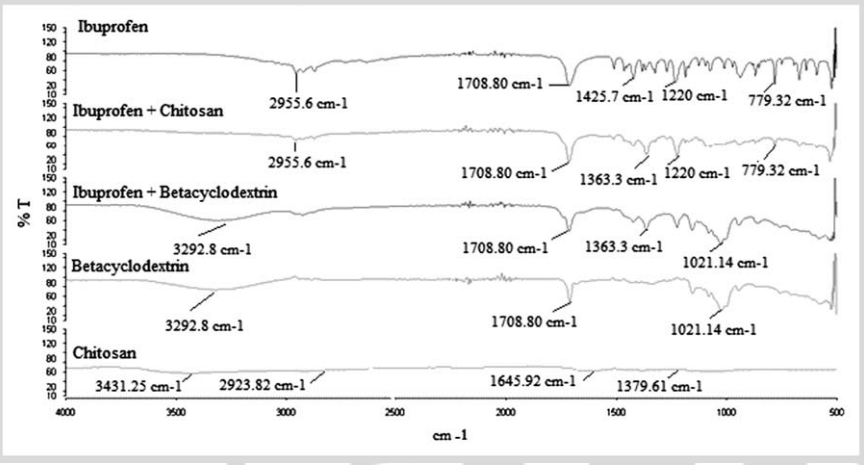

Fig. 3 Chitosan, betacyclodextrin and ibuprofen FTIR analysis.

According to United States Pharmacopoeia (USP) 2009, the content uniformity of ibuprofen tablets should be between 90–110%.

In-vitro drug release study

In vitro release of ibuprofen from tablets composed of the different formulations was conducted using dissolution apparatus (DT 70 Pharmatest, Germany) operated at 50 rpm. Drug release was assessed at 37 °C sequentially in simulated gastric fluid pH 1.2 (SGF), simulated intestinal fluid pH 6.8 (SIF), and simulated colonic fluid pH 7.2 (SCF) at 37 °C [21–23] in the absence or presence of pepsin (in SGF), pancreatin (in SIF), and 1% alpha amylase (in SCF). 5-ml aliquots were withdrawn at 2, 5, 8, 12, 16, 20, and 24 h, and replaced with equal volumes of dissolution solution, filtered through a 0.45-µm filter, diluted, and assayed at 221 nm (according to B.P 2012) by using a UV/VIS spectrophotometer (Shimadzu UV 1800, Japan); data are expressed as the percentage of ibuprofen released over the sampling times. The formulations that disintegrated quickly or released more than 20% of the drug content in SGF and SIF were excluded from the in vitro enzymatic drug release study.

Statistical analysis

The amount of ibuprofen released in the enzymatic medium and non-enzymatic medium were analyzed by using a paired student's t-test at all points of the drug release. The influence of polysaccharides (beta-cyclodextrin and chitosan) concentration along with ethylcellulose was also determined using paired student's t-test at all points of the drug release. A difference was considered as statistically significant if the *P* value is less than 0.05.

Results and Discussion

Fourier transform infrared spectroscopy

The FTIR spectra from 4000 to 500 cm^{-1} for ibuprofen, polysaccharides, and ibuprofen-polysaccharide mixtures are shown in **Fig. 3**. There were no appreciable changes in the nature and position of the functional group bands in the spectrum for the ibuprofen-chitosan mixture. This suggests that ibuprofen is not affected by chitosan and that it does not chemically interact with chitosan. Conversely, the spectrum for the ibuprofen-beta-cyclodextrin mixture reflected an inclusion complex, suggesting that beta-cyclodextrin may be a suitable drug carrier. The peaks at 500–1200 cm^{-1} and at 3000–3500 cm^{-1} in the ibuprofen spectrum were substituted by the beta-cyclodextrin peaks. The region from 1000–1200 cm^{-1} represents the C-O stretch, while the peak at 3350 cm^{-1} represents the -OH stretch from beta-cyclodextrin (**Fig. 3**).

Table 2 Characterization of tablet formulations.

Tests	FP1	FP2	FP3	FP4	FP5	FP6
Hardness (kPa)	14.44 ± 0.86	15.22 ± 0.32	13.81 ± 0.53	19.93 ± 0.51	15.8 ± 1.80	17.63 ± 1.80
Friability	0.26	0.18	0.41	0.26	0.20	0.32
Assay (%)	104.31	104.45	107.89	105.44	101.39	105.10
Tests	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Hardness (kPa)	13.89 ± 0.58	13.99 ± 0.42	12.12 ± 0.97	14.89 ± 0.71	14.36 ± 0.76	14.19 ± 0.89
Friability	0.22	0.21	0.18	0.21	0.29	0.32
Assay (%)	103.46	101.33	104.89	102.82	102.10	102.34

*kPa = Kilopascals

Characterization of prepared tablets

All tablet formulations were characterized in terms of their hardness, friability, and content uniformity (**Table 2**). All formulations passed the friability test (< 1%; British Pharmacopoeia, 2012), and the uniformity of content was within the limits specified by the US Pharmacopoeia (90–110%). Beta-cyclodextrin-containing tablets were harder than those containing chitosan (**Table 2**). This was most likely because of the high compactability of beta-cyclodextrin [24]. Ethylcellulose may also contribute to tablet hardness because of its high compressibility and low viscosity [25]. Accordingly, we found that tablet strength was the highest in the formulations containing beta-cyclodextrin and ethylcellulose at a ratio 1:1 with and without PVP (**Table 2**). The increased strength of tablets may be beneficial for slowing drug release as observed in FP6 (17.63 ± 1.80 kPa) and F6 (14.19 ± 0.89 kPa).

In vitro drug release study

In order to simulate the pH changes and transit time of gastrointestinal tract, the drug release from the tablets were first analyzed in simulated gastric fluid at pH 1.2 for 2 h and then the dissolution medium was changed to simulated intestinal fluid at pH 6.8 and conducted the analysis for 3 h. After simulated intestinal fluid drug release study, the dissolution medium was changed to simulated colonic fluid at pH 7.2 and the drug release study was continued until 24 h. To ensure tablets integrity was not disturbed during the change of dissolution medium, the tablets were recovered after draining the medium from the flask and the tablets were blotted dry before transferring into next stage dissolution medium [26]. In the absence of enzymes, the formulations containing beta-cyclodextrin did not rapidly disintegrate and exhibited controlled release of ibuprofen (**Fig. 4, 5**). This may be due to the ability of beta-cyclodextrin to form an inclusion complex with ibuprofen. We observed that chitosan tended to swell in a basic medium, leading to the disintegration of the tablets and the release of more than 20% of ibuprofen in SIF, the lone exception being FP5 (**Fig. 4, 5**). Formulations FP2, FP4, FP5, FP6, F4, and F6 did not release 100% of the ibuprofen (**Fig. 4, 5**), suggesting that some of the drug was trapped inside the polysaccharide matrix system which could only be released if the enzymes are present inside the dissolution medium to hydrolyze the polysaccharides.

In the presence of enzymes, all formulations except FP4 released 100% of the ibuprofen by 24 h. The failure of FP4 to completely release ibuprofen may be because of the tablet's increased hardness conferred by the presence of the PVP binder and of an equal amount of ethylcellulose (**Fig. 6**). It was also observed that there is a significant increase in drug release in the simulated colon fluid pH 7.2 in the presence of 1% *alpha-amylase* for all the formulated batches as compared to non-enzymatic drug release study. F4 and FP4 formulations were proved to be better formulations in terms of delaying the release of the drug as both formulations contained 1:1 ratio of beta-cyclodextrin and ethyl cellulose. During the non-enzymatic drug release study F4 and FP4 released 86.63 ± 1.50% and 75.29 ± 2.93% of the drug respectively until the 24 h of the drug release study. The drug released in the colonic medium was 70.87 ± 1.67% and 64.45 ± 2.79% for

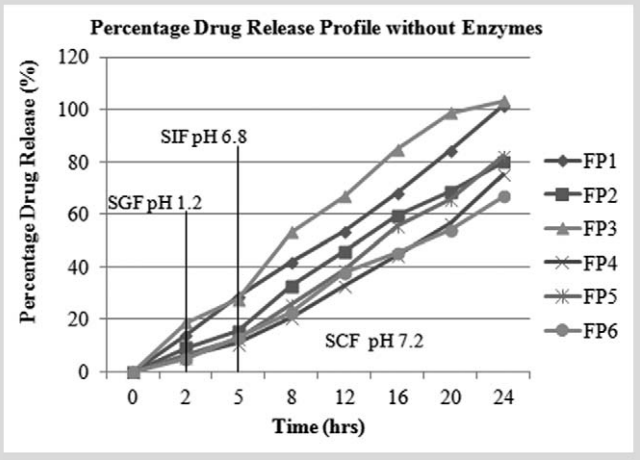

Fig. 4 In vitro Drug Release Profile of Formulations (with PVP binder) under non-enzymatic conditions (n = 6). (SGF) drug release in simulated gastric fluid, (SIF) drug release in simulated intestinal fluid, (SCF) drug release in simulated colonic fluid.

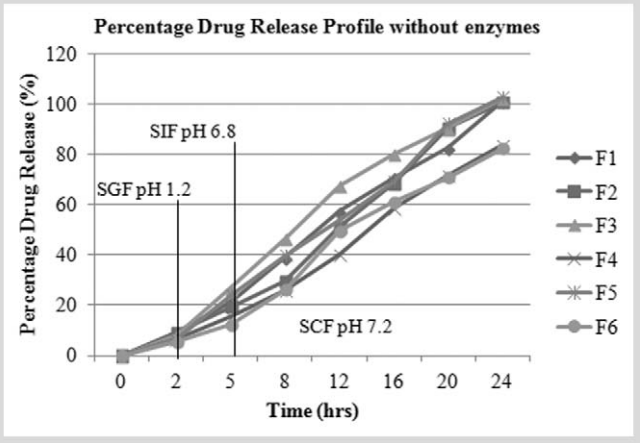

Fig. 5 In vitro Drug Release Profile of Formulations (without PVP binder) under non-enzymatic conditions (n = 6). (SGF) drug release in simulated gastric fluid, (SIF) drug release in simulated intestinal fluid, (SCF) drug release in simulated colonic fluid.

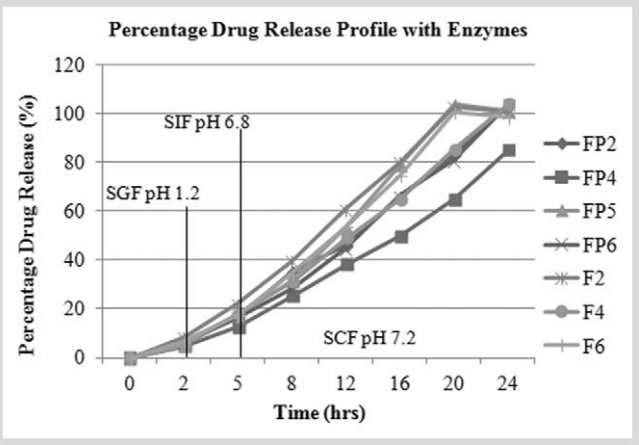

Fig. 6 In vitro Drug Release Profile of Tablet Formulations under enzymatic conditions (n = 6). (SGF) drug release in simulated gastric fluid, (SIF) drug release in simulated intestinal fluid, (SCF) drug release in simulated colonic fluid.

F4 and FP4 respectively (**Fig. 4, 5**). There was a significant increase in drug release in the enzymatic medium as F4 released 101.04 ± 0.65% and FP4 released 85.10 ± 1.79% of the ibuprofen until the 24 h of study. The ibuprofen released in the simulated colonic medium was 83.08 ± 0.89% for F4 and 72.38 ± 1.47% for FP4, which was more than the drug release observed in the absence of enzymes (**Fig. 5**). In order to analyze the influence of polysaccharide and ethyl cellulose concentration in the drug release under enzymatic and non-enzymatic conditions, a paired student's t-test was conducted at all points of the drug release. A difference was considered as statistically significant if the *P* value is less than 0.05. The statistical analysis revealed that the difference between the drug release in enzymatic conditions and non-enzymatic conditions is statistically significant for all the batches, which were analyzed for both stages where $P < 0.05$ for all the batches.

Influence of chitosan

Our results suggest that formulations containing beta-cyclodextrin are superior to those containing chitosan for ibuprofen delivery to the colon. Chitosan provided a weak protective barrier against the upper GI environment and less resistance to drug release, most likely because of the swelling of chitosan, resulting in the release of ibuprofen before it reached its intended site of action. The only chitosan formulation that showed drug-carrying capability inside the colon was FP5, for which the mass ratio of chitosan to ethylcellulose was 1:3; the concentration of the chitosan was the least among all the chitosan formulations and also contained polyvinyl pyrrolidone as binder (**Table 1**). Hence, FP5 tablets did not rapidly disintegrate as compared to other chitosan-containing formulations.

Influence of beta-cyclodextrin

Beta-cyclodextrins tablets proved to be the best formulations in this study for the purpose of colon drug delivery. Formulations FP2, FP4, FP6, F2, F4 and F6 had shown to have potential use for protecting the drug from upper gastrointestinal environment and for the controlled release drug delivery system. The better protection and control drug release is because of the inclusion complex forming tendency of the beta-cyclodextrin and its structural features. Beta-cyclodextrin has a unique structure, in which the cyclodextrin molecule possess a hydrophilic outer surface and the inner surface which is hydrophobic and is capable of hosting a large variety of guest molecules by forming a non-covalent inclusion complex [27]. These inclusion complexes were also observed during the FTIR analysis (**Fig. 3**). The polysaccharides are generally considered as more water soluble [28]. So the addition of hydrophobic polymer such as ethylcellulose helped the inclusion complexes to be less soluble in water and resulted into more delayed drug release [18,19]. The difference in control of the drug release was statistically significant with the changing percentage ratio between beta-cyclodextrin and ethylcellulose. These inclusion complexes were stable enough to carry the drug load to the large intestine and once they reached the simulated colon medium (SCF), enzymatic degradation of beta-cyclodextrin occurred by the *alpha-amylase* enzymes. The *alpha-amylases* enzymes hydrolyse the alpha-1, 4- glucoside bonds of the beta-cyclodextrin. Beta-cyclodextrin are believed not to be hydrolyzed during their transit along the small intestine, but are degraded by colonic microflora [29]. The inclusion complex forming nature of beta-cyclodextrin may help the bulk of the drug to be directly released inside the colon; it may also produce the localized effect and less systemic action as compared to absorption from the small intestine. Having said that, it also important to observe the non-disintegrating nature of the tablets influenced by the presence of ethylcellulose, chitosan and polyvinyl pyrrolidone in all formulations that may also be the determining factor for the colonic delivery of ibuprofen.

Conclusion

A beta-cyclodextrin polysaccharide matrix system is better than chitosan for drug delivery to the colon based on the ability of beta-cyclodextrin to form an inclusion complex. Formulations with equal amounts of beta-cyclodextrin and ethylcellulose yield the most stable carrier systems. In addition, the presence of ethyl cellulose and polyvinyl pyrrolidone may contribute to the non-disintegrating nature of the tablets that assist the delivery of the drug into the colon. There is a scope for beta-cyclodextrin inclusion complex to be employed in large scale manufacturing for cost effective colon drug delivery systems.

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Conflict of Interest

The writers have shown no conflict of interest.

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