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RESEARCH PAPER

Studies of Guar Gum Compression-Coated 5-Aminosalicylic Acid Tablets for Colon-Specific Drug Delivery

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ABSTRACT

The aim of this study was to develop colon-specific delivery systems for 5-aminosalicylic acid (5-ASA) using guar gum as a carrier. Core tablets containing 5-ASA were prepared by wet granulation with starch paste and were compression coated with coating formulations containing different quantities of guar gum (300, 200, 150, and 125 mg). In vitro drug release studies were carried out in simulated gastric and intestinal fluids and in pH 6.8 buffer containing rat cecal contents. The application of 175 mg of coating formulation containing 150 mg of guar gum over 5-ASA core tablets resulted in the release of less than 2% drug in simulated gastric and intestinal fluids and about 93% of 5-ASA in pH 6.8 buffer containing rat cecal contents. Differential scanning calorimetric (DSC) studies showed the absence of any interaction between 5-ASA and the excipients on storage at 45°C for 12 weeks. The study confirmed that selective delivery of 5-ASA to the colon can be achieved using guar gum as a carrier in the form of a compression coating over the drug core.

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INTRODUCTION

The targeting of drugs to the colon for local action is very much desirable for an effective and safe therapy of inflammatory bowel diseases (IBDs) such as ulcerative colitis and Crohn's disease. Inflammation of the colon is usually treated topically by enema administration. The spreading of enema solutions within the large intestine is highly variable even in healthy subjects (1). These preparations often fail to reach even the transverse colon. Oral dosing, therefore, may be an appropriate route for drug delivery to the proximal colon. Sulfasalazine is the drug of choice in the treatment of IBD by the oral route. It is a conjugate of 5-aminosalicylic acid (5-ASA) and sulphapyridine (SP), linked by a diazo bond. Studies have shown that 5-ASA is the active component in sulfasalazine, and SP acts as a carrier (2,3). Most of the side effects, such as nausea, headache, malaise, anorexia, reversible male infertility, leukopenia, and the like, associated with the use of sulfasalazine are because of SP, which gets absorbed systemically from the colon. If 5-ASA alone is given orally, it gets absorbed rapidly from the proximal gastrointestinal tract (GIT) and metabolized to acetyl-5-ASA and eliminated renally without eliciting any therapeutic effect (4,5). Hence, delivery of 5-ASA alone to the colon without the production of unwanted effects by other carriers is needed.

Olsalazine is a prodrug containing two molecules of 5-ASA linked by a diazo bond, and it delivers 5-ASA to the colon without the use of SP (6,7). Balsalazide and ipsalazide are investigational drugs in which 5-ASA is joined to an unabsorbed inert vehicle (7,8). Different prodrugs based on the cleavage of azo bonds by the colonic bacteria were investigated in which 5-ASA was linked either to a polymer or to a spacer, which in turn was linked to a polymer (9,10). Other approaches that attempt to deliver 5-ASA to the colon include the use of pH-dependent polymers to coat the tablets, sustained-release granules coated with ethyl cellulose (6,7,11) and Eudragit-RS-based microspheres (12).

Several polysaccharides are being investigated as potential carriers for colon-specific drug delivery. These include pectin and its salt (13–15), chondroitin sulfate (16), amylose (17), inulinHP (18), chitosan (19,20), and guar gum (21–25). These polysaccharides were formulated into matrix tablets (14,16,21,22), compression-coated tablets (13,26), capsules (19,20), hydrogels (25), and film coatings (24,27). Earlier, we reported the usefulness of guar gum, in the form of matrix tablets, as a potential carrier for colon-specific drug delivery using indomethacin as a model drug (28). Based on these studies, colon-specific delivery systems of 5-ASA were developed using guar gum as a carrier.

Guar gum is a polysaccharide derived from the seeds of *Cyamopsis tetragonolobus*, family Leguminosae. It consists of linear chains of (1 → 4)-β-D-mannopyranosyl units with α-D-galactopyranosyl units attached by (1 → 6) linkages (29). In pharmaceutical formulations, guar gum is used as a binder, disintegrant, suspending agent, thickening agent, and stabilizing agent. In the present investigation, guar gum was applied as a compression coating over 5-ASA core tablets, which were subjected to in vitro drug release studies.

MATERIALS

5-Aminosalicylic acid (98–100% purity) was a gratis sample from Sun Pharmaceutical Industries Limited, Mumbai, India. Guar gum (viscosity 1% w/v, aqueous dispersion, 2300 cps at 25°C) was obtained form Dabur India Limited, New Delhi, India, and was of USNF quality. Other materials, namely, microcrystalline cellulose (MCC: Avicel, FMC Type pH-195), croscarmellose sodium (AcDiSol), starch, magnesium stearate, talc, and colloidal silicon dioxide (Aerosil) were USNF quality.

METHODS

Preparation of 5-ASA Compression-Coated Tablets

The core tablets (average weight 285 mg) of 5-ASA, for compression coating with guar gum, were prepared by a wet granulation technique using starch paste as a binder. Each core tablet consisted of 5-ASA (250 mg), MCC (18 mg), croscarmellose sodium (8 mg), starch (5 mg), colloidal silicon dioxide (2 mg), and magnesium stearate (2 mg). Croscarmellose sodium was included in the formulation to obtain 5-ASA tablets with fast disintegration characteristics (disintegration time < 1 min). Half the quantity of croscarmellose sodium (4 mg/tablet) and 5-ASA and MCC was mixed thoroughly and granulated with starch paste. The wet granulation mass was passed through a mesh (1680 μ) and dried at 60°C for 2 hr in a tray dryer. The dried granules were sized by passing through a sieve (1190 μ) and were mixed with colloidal silicon dioxide, magnesium stearate, and the remaining quantity of croscarmellose sodium (4 mg/tablet). The lubricated granules were compressed into tablets at an applied force of 4000 kg using 9-mm round, flat, and plain

punches on a single-station tablet machine (Cadmach Machinery Co. Pvt. Ltd., Ahmedabad, India).

After passing the drug content uniformity and disintegration tests, the core tablets were compression coated with different coating formulations C1, C2, C3, and C4 containing 300, 200, 150, and 125 mg of guar gum, respectively (Table 1). Half the quantity of the coating material was placed in the die cavity; the 5-ASA core tablet was carefully positioned in the center of the die cavity and was filled with the other half of the coating material. The coating material was compressed around the core tablet at an applied force of 5000 kg using 11-mm round, flat, and plain punches as described above.

Determination of Drug Content

The 5-ASA core tablets were tested for their drug content. The tablets were finely powdered, and quantities of the powder equivalent to 50 mg of 5-ASA each were accurately weighed and transferred to 100-ml volumetric flasks. The flasks were filled with Sorensen's phosphate buffer (pH 7.4) and mixed thoroughly. The solutions were made up to volume and filtered. One milliliter of the filtrate with suitable dilution was estimated for 5-ASA content at 330 nm using a double-beam ultraviolet (UV) spectrophotometer (Shimadzu Corporation, Kyoto, Japan, UV-150-02).

Preparation of Rat Cecal Content Medium

Male albino rats (supplied by M/s Ghosh Enterprise, Calcutta, India) weighing 150–200 g and maintained on a normal diet (Bengal gram purchased in the local market and soaked in water, 25 g/rat) were used. To induce enzymes acting specifically on guar gum, the rats were intubated with Teflon tubing, and 1 ml of 2% w/v aqueous dispersion of guar gum was administered directly into the stomach. The tubing was removed, and this treatment was continued for 7 days. Thirty minutes before the commencement of drug release studies, 5 rats were killed by spinal traction. The abdomen were opened, the cecai were traced, ligated at both ends, dissected, and immediately transferred into pH 6.8 phosphate buffered saline (PBS) previously bubbled with CO_2. The cecal bags were opened; their contents were individually weighed, pooled, and then suspended in PBS to give a final cecal dilution of 4% w/v. As the cecum is naturally anaerobic, all these operations were carried out under CO_2.

Drug Release Studies

The ability of the compression-coated tablets to remain intact in the physiological environment of the stomach and small intestine was assessed by conducting drug release studies under conditions mimicking mouth-to-colon transit. Drug release studies were carried out using a USP dissolution rate test apparatus (apparatus 1, 100 rpm, 37°C) for 2 hr in 0.1 N HCl (900 ml) as the average gastric emptying time is about 2 hr. Then, the dissolution medium was replaced with pH 7.4 Sorensen's phosphate buffer (900 ml) and tested for drug release for 3 hr as the average small intestinal transit time is about 3 hr. At the end of the time periods, two samples each of 5 ml were taken and analyzed for 5-ASA content at 330 nm as described above.

The susceptibility of the compression coatings to the enzymatic action of colonic bacteria was assessed by continuing the drug release studies in rat cecal content medium because of the similarity of the microflora of the rat cecum to that of the human colon (30). The drug release studies were carried out using USP dissolution rate test apparatus (apparatus 1, 100 rpm, 37°C) with slight modifications. A beaker (capacity 150 ml) containing 100 ml of rat cecal content medium was immersed in the water maintained in the 1000-ml vessel, which, in turn, was in the water bath of the apparatus. The tablets were placed

Table 1

Guar Gum Coats: Composition and Thickness

Coat Formulation	Composition (mg)				Coat Weight (mg)	Coat Thickness (mm)
	Guar Gum	MCC	Magnesium Stearate	Talc		
C1	300	38	3	4	345	1.49 ± 0.02
C2	200	25	2	3	230	0.91 ± 0.03
C3	150	20	2	3	175	0.61 ± 0.04
C4	125	45	2	3	175	0.55 ± 0.02

in the baskets of the apparatus and immersed in the rat cecal content medium. As the cecum is naturally anaerobic, the experiment was carried out with continuous CO_2 supply into the beakers. At different time intervals, a 1-ml sample was withdrawn without a prefilter and replaced with 1 ml of fresh PBS bubbled with CO_2, and the experiment was continued up to 21 hr as the usual colonic transit time is 20–30 hr. The volume of the sample was made up to 10 ml with PBS and centrifuged; the supernatant was filtered through a bacteria-proof filter (G-5, Borosil, Glass Works, Ltd., Mumbai, India). The filtrate was analyzed for 5-ASA content at 330 nm. The above studies were carried out on 5-ASA tablets compression coated with coating formulations C1, C2, and C3 and also without rat cecal contents in pH 6.8 PBS (control). To assess the stability, drug release studies in simulated gastric and intestinal fluids and in rat cecal content medium were also carried out on 5-ASA tablets compression coated with coating formulation C3 after storage at 45°C for 12 weeks.

Differential Scanning Calorimetry

The possibility of any interaction between 5-ASA and the excipients used in the formulation of core tablets and also with guar gum was assessed by carrying out thermal analysis on pure 5-ASA, guar gum–5-ASA physical mixture, and powdered 5-ASA core tablets using a differential scanning calorimeter (DSC) (DSC 220, Seiko Instruments, Inc., Chiba, Japan). The samples (5 mg) were accurately weighed into aluminum pans and then hermetically sealed with aluminum lids. The thermograms of the samples were obtained at a scanning rate of 10°C/min conducted over a temperature range 30°C–400°C. The thermograms of 5-ASA–guar gum mixture and 5-ASA core tablets after storage at 45°C for 12 weeks were also obtained.

RESULTS AND DISCUSSION

The mean drug content of the 5-ASA core tablets was found to be 249.87 ± 2.23 mg. This indicates that the tablets passed the content uniformity test as they contained 100% ± 5% of 5-ASA. The drug delivery system targeted to the colon should remain intact in the physiological environment of the stomach and small intestine and should release the drug load in the colon. Hence, attempts were made to minimize the drug loss under conditions mimicking mouth-to-colon transit and to ensure maximum drug release in the rat cecal content medium by applying guar gum as a compression coating over the 5-ASA core tablets. The core tablets of 5-ASA were made to disintegrate within 1 min by inclusion of croscarmellose sodium. This was to ensure fast release of the drug from the core tablets after the degradation of the coating by the cecal enzymes. The core tablets were compression coated with coating formulations C1, C2, C3, and C4 (Table 1). The thickness of the coatings was found to be between 1.49 ± 0.02 (C1) and 0.55 ± 0.02 mm (C4). The coating thickness was taken as half the difference between the core and coated tablet thickness.

The results of the drug release studies carried out on 5-ASA tablets compression coated with different quantities of coating material in simulated gastric and intestinal fluids and in pH 6.8 PBS are shown in Fig. 1. The coatings of the tablets were found to be intact even after 26 hr of testing, but hydration resulted in the swelling of the coatings. The cumulative mean percentages 5-ASA released from the tablets compression coated with coating formulations C1, C2, and C3 were 0.46 ± 0.14, 0.78 ± 0.05, and 1.21 ± 0.09, respectively after 5 hr of testing in simulated gastric (2 hr) and intestinal (3 hr) fluids. The release of less than 1.5% of 5-ASA in simulated gastric and intestinal fluids indicates that guar gum

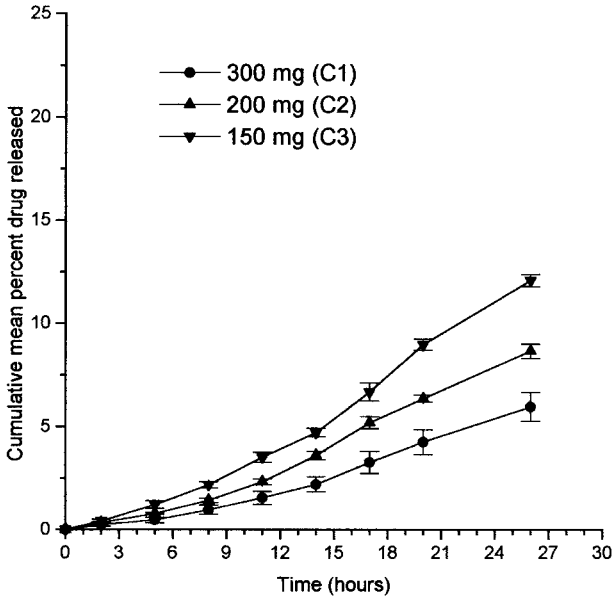

Figure 1. Mean percentage (±SEM) of drug released from 5-ASA tablets (n = 3) compression coated with coating material containing 300 (C1), 200 (C2), and 150 mg (C3) guar gum in 0.1 N HCl (2 hr), pH 7.4 buffer (3 hr), and pH 6.8 PBS (21 hr).

in the form of a compression coating is capable of minimizing drug release in the physiological environment of the stomach and small intestine. After 26 hr of testing, the cumulative mean percentages drug released from 5-ASA tablets compression coated with coating formulations C1, C2, and C3 were found to be 5.98 ± 0.70, 8.67 ± 0.35, and 12.09 ± 0.29, respectively. Further decrease in gum content to 125 mg (coating formulation C4) resulted in the disintegration of the coated tablets within 5 min in simulated gastric fluids. This may be due to the decreased gum content and increased MCC of coating formulation C4, which failed to hold the coating intact. Hence, further studies on 5-ASA tablets compression coated with C4 were not carried out.

The susceptibility of guar gum coatings to the enzymatic action of colonic bacteria was assessed by continuing the drug release studies in rat cecal content medium for 21 hr after 5 hr of testing in simulated gastric and intestinal fluids. The percentage drug released from the tablets coated with coating formulation C1 after 26 hr of testing was found to be 23.85 ± 3.13 (Fig. 2). The coating of the tablets was eroded to some extent, but a thin cover of gum coating over the core tablets was observed after the time period of testing. The presence of more guar gum (300 mg) in the coating might not have allowed

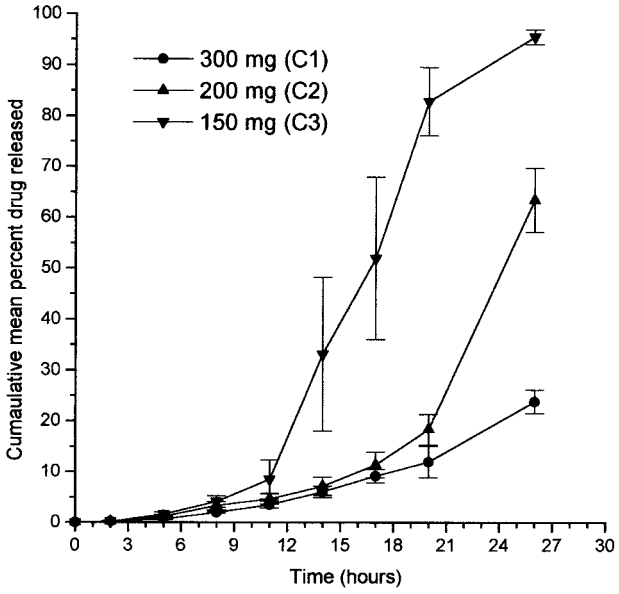

Figure 2. Mean percentage (±SEM) of drug released from 5-ASA tablets (n = 4) compression coated with coating material containing 300 (C1), 200 (C2), and 150 mg (C3) of guar gum in 0.1 N HCl (2 hr), pH 7.4 buffer (3 hr), and rat cecal content medium (21 hr).

complete degradation of the coating by the cecal enzymes during the time period of testing. This also indicates that the coating will not permit the release of the bulk of the drug unless degraded completely. Hence, the gum content was decreased to 200 mg in coating formulation C2. The percentage drug released from these tablets was found to increase from 20 hr onward (Fig. 2), indicating the commencement of the disintegration of the coating by the cecal enzymes and a consequent drug release. At the end of 26 hr of testing, the tablet coatings were found to be broken, and the percentage drug released was 63.43 ± 6.30. However, there was still about 36% of drug to be released from the tablets (C2). Hence, the coating weight was further decreased to 175 mg (C3), which contained 150 mg of guar gum. This resulted in the release of 95.51% ± 1.50% of 5-ASA after 26 hr of testing. The percentage drug released from these tablets increased considerably from 11 hr, and the tablets were found to be completely disintegrated at the end of the experiment. Since the gum content of coating formulation C3 was less (150 mg) than that of coating formulation C1 (300 mg) and C2 (200 mg), the coating might have been degraded by the cecal enzymes at a faster rate, resulting in the release of about 95% of 5-ASA. Based on the results of the drug release studies on compression-coated tablets, it may be suggested that the application of guar gum coating over the drug core in the thickness range 0.61 mm (C3) to 0.91 mm (C2) is sufficient to deliver 5-ASA selectively to the colon.

In the above study, coating formulation C3 was found to be optimal since the lag time required for the coating to burst was less (11 hr) than that of coating formulation C2 (20 hr). Hence, these formulations were assessed for their stability of drug content and drug release characteristics by storing at 45°C for 12 weeks. The drug content of 5-ASA tablets compression coated with C3 after storage was found to be 245.07 ± 2.42 mg. The decrease in drug content of tablets was found to be less than 5% of the labeled amount (250 mg), which indicates the absence of degradation of the drug on storage. The cumulative mean percentage drug released from the 5-ASA tablets coated with coating formulation C3 was found to be 93.75 ± 2.21 after 26 hr of testing, and the lag time required for the bursting of the coating was about 14 hr. As the total percentage drug released from the tablets did not change much on storage, these formulations may be considered stable with respect to their drug release characteristics.

The occurrence of any drug-excipient interactions in the formulations was predicted by conducting DSC studies. Thermograms of the samples of the pure drug, the

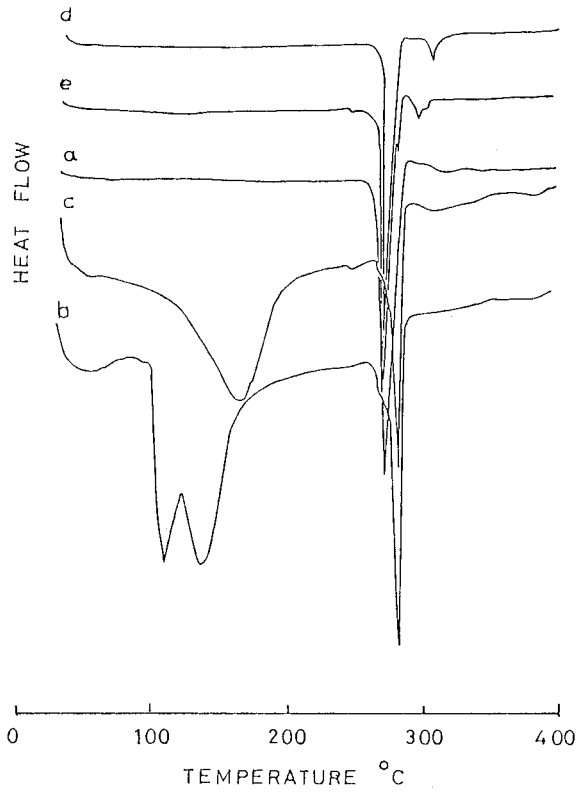

Figure 3. DSC thermograms: (a) 5-ASA; (b) 5-ASA–guar gum mixture before storage; (c) 5-ASA–guar gum mixture after storage; (d) 5-ASA core tablets before storage; and (e) 5-ASA core tablets after storage.

drug-guar gum mixture, and the 5-ASA core tablet are shown in Fig. 3. A sharp endothermic peak corresponding to the melting point of crystalline 5-ASA was found at 270.1°C for the drug sample. The endothermic peak corresponding to the melting point of 5-ASA in the sample of core tablets was observed at 269.4°C, which is almost the same as that of the pure drug (270.1°C). The appearance of the endothermic peak of 5-ASA at 267.6°C in the sample of core tablet after storage at 45°C for 12 weeks also clearly indicates the absence of any possible interaction of 5-ASA with the excipients used in the core formulation. The guar gum–5-ASA mixture exhibited the endothermic peak corresponding to 5-ASA at 281°C together with a broad endothermic peak corresponding to the moisture present in the guar gum. The endothermic peak corresponding to 5-ASA in the mixture after storage at 45°C for 12 weeks was observed at 281.9°C, which is almost the same as that observed before storage. This indicates the absence of any interaction between 5-ASA and guar gum on storage. The results of the drug content estimation and drug release studies indicate that 5-ASA tablets compression coated with coating formulation C3 did not undergo any degradation during storage. DSC studies indicated the absence of any possible drug excipient interaction.

CONCLUSIONS

Guar gum coatings applied over 5-ASA core tablets successfully protected the drug from being released under conditions mimicking mouth-to-colon transit. In vitro drug release studies on 5-ASA tablets compression coated with 175 mg of coating material containing 150 mg of guar gum in simulated gastric, intestinal, and colonic fluids resulted in the release of about 95% of the drug, thereby establishing the susceptibility of gum coatings to the enzymatic action of colonic bacteria. Storage of tablets at 45°C for 12 weeks did not alter either the drug content or drug release characteristics of the formulations. Interactions between drug and excipients, including guar gum, were absent as observed by DSC. Thus, the study established that selective delivery of 5-ASA to the colon could be achieved using guar gum as a carrier in the form of a compression coating over the drug core.

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