Original Article

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Guar gum and hydroxy propyl methylcellulose compressed coated tablets for colonic drug delivery: *in vitro* and *in vivo* evaluation in healthy human volunteers

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ABSTRACT: The objectives of the present study are to evaluate guar gum in combination with hydroxy propyl methylcellulose (HPMC) as compression coat for colonic delivery of prednisolone as well as improving the mechanical properties of the compressed coated tablets. The core tablets containing 5 mg prednisolone were compression coated with 125 mg of coating materials consisted of guar gum alone or mixtures of guar gum in combination with different ratios of HPMC. The compressed coated tablets were evaluated for their mechanical properties, *in vitro* drug release and *in vivo* performance in human volunteers. The compressed coated tablets with coats containing HPMC exhibited acceptable mechanical properties. *In vitro* drug release studies in pH 7.4 phosphate-buffered saline medium containing 2% (w/v) rat caecal content have shown that increase in concentration of HPMC in the prepared coats from 10% to 20% resulted in an increase in the release rate. However, further increase in HPMC concentration to constitute 30% caused a reduction in the release rate. Based on the drug release results, tablets coated with coat consisted of 80% guar gum and 20% HPMC were selected for *in vivo* evaluation. *In vivo* gamma scintigraphic study on human volunteers using technetium-99m-diethylenetriamine pentaacetic acid as a tracer was performed. The results showed that tablets remained intact in stomach and small intestine, however partial and complete release of the tracer occurred in the colon. In conclusion, guar gum in combination with HPMC would be successfully used as a carrier for drug delivery to the colon.

Keywords: Guar gum, hydroxy propyl methylcellulose, compressed coated tablets, colonic drug delivery, prednisolone, gamma scintigraphy

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1. Introduction

Colonic drug delivery has gained increased importance not just for the delivery of drugs for the treatment of local diseases of colon such as irritable bowel syndrome, inflammatory bowel disease (IBD) including Crohn's disease and ulcerative colitis but also for its potential for the delivery of proteins and therapeutic peptides like insulin (*1-3*).

Colon as a site offers distinct advantages on account of a near neutral pH, a much longer transit time, reduced digestive enzymatic activity, much greater response to absorption enhancers, and the presence of large amounts of enzymes for polysaccharides which were secreted by a large number of colonic bacteria (*4*). Various systems have been developed for colon-specific drug delivery including covalent linkage of a drug with a carrier, coating with pH-sensitive polymers, time dependent release systems and enzymatically controlled delivery systems (*5*). The most convenient approach for site-specific drug delivery to colon is the enzymatically controlled delivery system (*6*).

Guar gum is a polysaccharide derived from the seeds of *Cyamopsis tetragonolobus*, of the Leguminosae family. It consists of linear chains of (1-4)-β-D-mannopyranosyl units with α-D-galactopyranosyl units attached by (1-6) linkages. In pharmaceutical formulations, it is used as a binder, disintegrant, suspending agent, thickening agent and stabilizing agent. It was reported previously that guar gum as compression coat is a potential carrier for colon-specific drug delivery (*7-10*). From the previous studies a coat of considerable thickness of guar gum is usually required to protect the drug loaded in the core tablets, moreover, using guar gum alone in formulation of the compressed coated tablets gave very soft coats (*7*). In this study, guar gum in combination with hydroxy propyl methylcellulose (HPMC) is used to develop colonic delivery using prednisolone as a model drug. HPMC was used to modify the drug release and improve the mechanical properties of the compressed coated tablets.

The aim of this study is to evaluate a mixture of guar gum and HPMC, in the form of compression coat applied over core tablets for colonic drug delivery.

2. Materials and Methods

2.1. *Materials*

Prednisolone was a gift sample from Al Arabia pharmaceutical Company, Cairo, Egypt. Guar gum was obtained from Sigma-Aldrich, St Louis, MO, USA. HPMC 4000 and Avicel PH101 were obtained from Fluka Biochemika, Buchs, Switzerland. Ethyl alcohol absolute 99% from the United Company for Chemicals and Medical Preparation, Cairo, Egypt. All other materials used were of pharmacopeial grade.

2.2. *Differential scanning calorimetry (DSC)*

In order to investigate the possible interaction between prednisolone and the polymers used, *viz* guar gum, HPMC and Avicel PH101, DSC analysis was carried out on pure substances and their physical mixtures in equimolar ratios using the Shimadzu DSC-50 instrument equipped with a computerized data station (Shimadzu, Kyoto, Japan). Samples (4-5 mg) were placed in an aluminum pan and heated at a rate of 10°C/min with indium in the reference pan in an atmosphere of nitrogen to a temperature of 300°C.

2.3. *Preparation of compression-coated prednisolone tablets*

2.3.1. *Preparation of core tablets*

The core tablets of prednisolone for compression coating were prepared by direct compression technique. Each core tablet (50 mg) consisted of 5 mg prednisolone, 44.50 mg Avicel PH101, and 0.5 mg magnesium stearate. The powders were thoroughly mixed and passed through mesh (149 µm). The uniformity of mixing was assessed by conducting content uniformity tests on the samples of powder mix. The mixture was compressed into tablets using hydraulic press with an applied force of 3,250 kg using 4 mm round concave punches.

2.3.2. *Preparation of compression coated tablets*

The coating materials of 125 mg guar gum alone or mixtures of guar gum in combination with 10%, 20%, and 30% HPMC were used to prepare four coats F1, F2, F3, and F4, respectively. Half the amount of compression coating material was placed in the die cavity followed by carefully centering the core tablet and addition of the remaining coat weight. The coating material was then compressed around the core tablets using hydraulic press at an applied force of 4,000 kg using 8 mm round concave punches. The prepared tablets were tested for the uniformity of weight, drug content, mechanical properties (hardness and friability) and drug release characteristics.

2.4. *Determination of drug content in tablets*

Ten tablets of each formula were finely powdered; 200 mg of the powder were accurately weighed and transferred to 100 mL volumetric flasks containing 50 mL of phosphate buffer pH 7.4. The flasks were shaken to solubilize the drug. The volume was made up with the buffer to 100 mL, mixed well and allowed to stand for 24 h to ensure complete solubility of the drug. The solution was centrifuged and 1 mL of the supernatant liquid was suitably diluted and analyzed for prednisolone content spectrophotometerically at 245 nm.

2.5. *In vitro drug release studies in 0.1 N HCl and phosphate buffer, pH 7.4*

The ability of the prepared tablets to retard drug release in the physiological environment of the stomach and small intestine was assessed by conducting drug release studies in simulated stomach and small intestine pH, respectively. Dissolution test was conducted in USP I apparatus at 100 rpm and a temperature of 37°C. Initial drug release studies were conducted in 700 mL 0.1 N HCl for 2 h, then 200 mL of 0.2 M tribasic sodium phosphate was added to the dissolution vessels and pH was adjusted to 7.4 using 0.1 N NaOH. Samples were withdrawn at 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, and 24 h time intervals and replaced with an equal volume of fresh media (*11*). The content of prednisolone in the withdrawn samples was analyzed spectrophotometerically at 245 nm.

2.6. *In vitro drug release studies in presence of rat caecal content*

In order to assess the ability of the prepared tablets to release drug in the physiological environment of the colon, the drug release studies were carried out in 200 mL of pH 7.4 phosphate-buffered saline (PBS) containing 2% (w/v) of rat caecal contents. Approval to carry out the release studies in presence of rat caecal content was obtained from the Animal Ethics Committee of Faculty of Pharmacy, Helwan University. Guidelines of the ethics committee were followed for the studies.

The caecal contents were obtained from Wistar rats weighing 150-200 g, after pre-treatment with oral administration of 2 mL of 1% guar gum dispersion in water for 3 days (*12*). Thirty minutes before starting drug release studies, each rat was killed by spinal traction, after which abdomens were opened, dissected, and immediately transferred to PBS previously bubbled with CO_2. The caecal bags were then opened; their contents were individually weighed, homogenized, and then suspended in PBS to give the desired concentration of 2% (w/v) of caecal content. As the caecum is naturally anaerobic, all these operations were carried out under CO_2.

Drug release studies in the caecal content were carried out on tablets previously subjected to 5 h-exposure to

conditions mimic the stomach and the small intestine. The obtained tablets were then placed in 200 mL of the dissolution medium (PBS, pH 7.4) containing 2% (w/v) rat caecal content. The release studies were performed using USP I apparatus at 100 rpm and a temperature of 37°C with continuous CO_2 supply into the dissolution media. At specific time intervals, samples were withdrawn and replaced with fresh medium. The experiment was continued up to 24 h. The withdrawn samples were filtered through 0.45 µm membrane filter and analyzed for drug content at 245 nm spectrophotometerically.

2.7. *In vitro release kinetics mechanisms*

In order to determine drug release mechanism from the prepared tablets, the release kinetic data were analyzed according to Korsmeyer-Peppas release model (*13*) given by the following equation:

$$M_t/M_\infty = Kt^n$$

where M_t is the amount of drug released at time t; M_∞ is the amount of drug released at infinite time; K is the kinetic constant related to the structural and geometric characteristics of the drug delivery system (tablet); and n is the release exponent indicative of the release mechanism. The n values used for elucidation of drug release mechanism from the tablets were determined from log cumulative percentage of drug release *versus* log time plots. Values of n near 0.5 indicate predominantly diffusion control and of 1.0 correspond to zero-order release. Another analysis mechanism was used considering that drug release in swellable matrices depends on two processes, drug diffusion into the swollen polymer and matrix swelling due to approximate contribution of the diffusion and relaxation mechanisms. This was carried out by fitting the data to the model proposed by Peppas and Sahlin (*14*) given by the following equation:

$$M_t/M_\infty = K_1t^m + K_2t^{2m}$$

where K_1 and K_2 are obtained from non linear regression curve fitting of the release data using GraphPad prism 4 (GraphPad Software, San Diego, CA, USA). When $K_1 > K_2$, the release is mainly controlled by diffusion, and when $K_2 > K_1$, the release is mostly due to matrix swelling. When K_1 is nearly equal to K_2, the release is a combination of diffusion and polymer relaxation (*15*).

2.8. *Preparation of labeled tablets for in vivo scintigraphic studies*

The core tablet (average weight 50 mg) for *in vivo* scintigraphic study consists of sodium chloride (20 mg), Avicel (29.50 mg) and magnesium stearate (0.5 mg). Sodium chloride was used as filler and 5 millicuri of ^{99m}Tc-diethylenetriamine pentaacetic acid (DTPA), a radiolabelled material, was adsorbed on it. ^{99m}Tc-DTPA was prepared by radiolabelling DTPA with sodium pertechnetate solution. Sodium chloride was dissolved in this solution, evaporated to dryness. The resultant powder was then mixed with the remaining excipients and compressed into tablets using 4 mm round concave punches. The core tablets were then compress-coated with 125 mg of the coating material F3 (80% guar gum and 20% HPMC).

2.9. *In vivo scintigraphic studies*

The study was approved by the University Protection of Human Subjects Committee, and the protocol complies with the declarations of Helsinki and Tokyo for humans. Six healthy male volunteers participated in this study. After overnight fasting, each volunteer orally swallowed the prepared radiolabelled tablets. The tablets were scanned using a PHILIPS AXIS dual head gamma camera (Phillips Medical System, Cleveland, OH, USA). Anterior and posterior images were taken immediately after tablet administration and after 0.5, 1, 1.5, 2, 4, 8, 12, and 24 h.

2.10. *Statistical analysis*

Student *t*-test was used to test the differences between the calculated parameters using SPSS Statistical Package, Version 10 (IBM SPSS, Chicago, IL, USA). Statistical differences yielding $p < 0.05$ were considered to be significant.

3. Results and Discussion

3.1. *DSC study*

DSC thermograms revealed that prednisolone has a single sharp characteristic, endothermic melting peak at 240.94°C (Figure 1, trace A). The sharp endothermic peak reflects the pure crystalline state of the drug. The sharp endothermic peak of the drug was observed at the same melting temperature in case of its physical mixtures with Avicel, guar gum and HPMC but shortened due to the dilution factor (Figure 1). These results demonstrated that prednisolone did not interact with the chosen additives.

3.2. *Physical properties of tablets*

All the prepared tablets met the USP requirements for weight variation, hardness, and drug content (Table 1). The friability of the prepared tablets was within the compendial limits except F1 coated with 100% guar gum which showed high friability percentage (2.20%) that exceeded the pharmacopeial limitation. Therefore, F1 was excluded from any further evaluations.

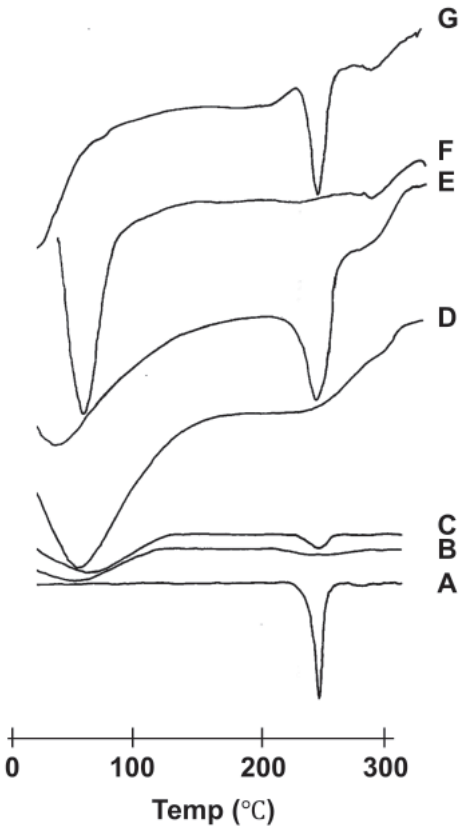

Figure 1. DSC thermograms. A, prednisolone; **B**, Avicel; **C**, prednisolone-Avicel physical mixture; **D**, guar gum; **E**, prednisolone-guar gum physical mixture; **F**, HPMC; and **G**, prednisolone-HPMC physical mixture.

Table 1. Physical properties of the compressed coated tablets

Formulations	Weight (mg ± S.D.)	Hardness (kg/cm^2 ± S.D.)	Friability (%)	Drug content (% ± S.D.)
F1	177.00 ± 1.50	4.50 ± 0.44	2.20	4.90 ± 0.15
F2	176.00 ± 1.13	5.30 ± 0.48	0.42	4.94 ± 0.10
F3	175.40 ± 1.76	5.60 ± 0.51	0.32	5.00 ± 0.05
F4	176.00 ± 1.51	6.10 ± 0.62	0.25	4.98 ± 0.11

3.3. *In vitro release studies*

The mean drug release from the tablets F2, F3, and F4 after the first 5 h was 2.67 ± 0.15%, 6.43 ± 0.54%, and 8.27 ± 0.25%, respectively. At the end of 24 h, the mean % drug release was 37.7 ± 2.7%, 47.2 ± 2.2%, and 31.2 ± 2.0%, respectively, in PBS medium (Figure 2A). While in rat caecal medium, after 24 h, the mean % drug release was increased to 91.0 ± 4.1%, 97.2 ± 2.2% and 82.5 ± 4.1%, respectively (Figure 2B). The maximum drug release after 24 h in rat caecal medium was significantly higher ($p < 0.05$) in comparison with the drug release in control medium. This can be explained as the release of prednisolone in the physiological environment of colon is due to microbial degradation of guar gum (*4*).

The addition of HPMC to constitute 10% to 20% of the coat (F2 and F3, respectively) caused a significant increase ($p < 0.05$) in the mean % drug release from 37.7

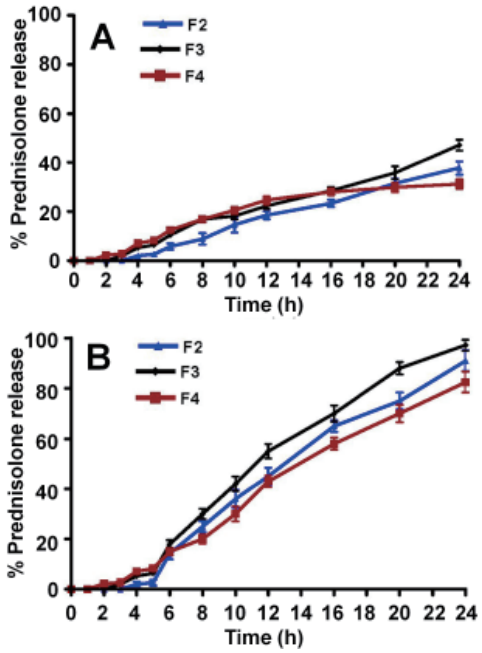

Figure 2. Release profiles of prednisolone from compression-coated tablets F2, F3, and F4. (A) Release profiles in 0.1 N HCl for 2 h and phosphate buffer (pH 7.4) till the end of 24 h. **(B)** Release profiles in 0.1 N HCl for 2 h, phosphate buffer (pH 7.4) for another 3 h, and PBS containing 2% (w/v) rat caecal content till the end of 24 h.

± 2.7% to 47.2 ± 2.2% after 24 h in the physiological environment simulating the stomach and small intestine and from 91.0 ± 4.1% to 97.7 ± 2.2% and in rat caecal medium. The increase in drug release could be explained due to HPMC creates a porous structure of the coat and consequently increases guar gum leaching and drug release. However, further increase in HPMC percent to constitute 30% of the compression coat (F4) caused a reduction in gum leaching, with a consequent decrease in drug release as shown in Figure 2A. These results are well correlated with previous reports (*16,17*) which suggested that higher concentrations of HPMC would reduce the free water volume and increase the viscosity of the coat causing a reduction in the polymer leaching and subsequent reduction in drug release. Based on the previous results, F3 was selected for further *in vivo* evaluation since the cumulative percentage of drug released at the end of 5 h, which is the expected time for the arrival of the dosage form in the colon, was found to be 6.43 ± 0.54% and almost complete drug release was achieved after 24 h.

The kinetics of prednisolone release from the prepared tablets was studied by applying the Korsmeyer model to the release data up to 60% of prednisolone. The release kinetic parameters are listed in Table 2. Increase of the HPMC content in the coat of F2, F3, and F4 results in exponents n values of 1.53, 1.40, and 1.45, respectively, which markedly exceed the value of 0.5 corresponding to diffusion controlled release and furthermore together with the good fitting of the zero-order model indicate significant contribution of erosion.

Table 2. Fitting of release kinetic models to prednisolone release data

Formulations	Zero-order		Korsmey ermodel*		Peppas-Sahlin model		
	R^2	K_o (% h^{-1})	R^2	n	R^2	K_1 (% $h^{-0.45}$)	K_2 (% $h^{-0.9}$)
F2	0.985	4.475	0.987	1.53	0.985	−12.23	8.37
F3	0.982	4.832	0.979	1.40	0.983	−11.11	8.67
F4	0.992	3.902	0.985	1.45	0.993	−9.05	7.06

* Release exponent evaluated for < 60% released drug.

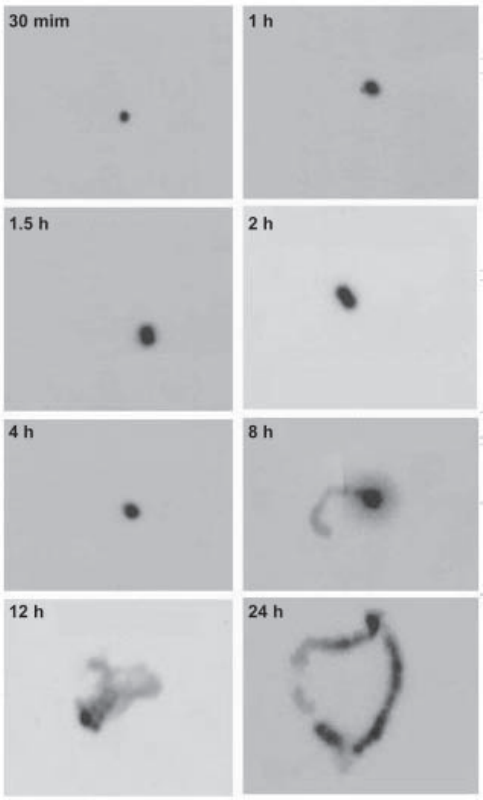

Figure 3. A representative gamma scintigraphs in one volunteer. Tablets remained intact in stomach after 0.5, 1, and 1.5 h; in small intestine after 2 and 4 h. Tablets partially disintegrated in colon after 8 and 12 h, and completely disintegrated and distributed as the tracer throughout the colon after 24 h.

The higher values of n would be a consequence of a plasticization process in the gel layer arising from a reduction of the attractive forces among polymeric chains that increases the mobility of macromolecules (*18*). Further analysis by Peppas and Sahlin model showed higher values of the relaxation constant K_2, compared with the diffusion constant K_1, combined with the low solubility of prednisolone, reflect the prevalence of the erosion as a mechanism for drug release versus swelling mechanism.

3.4. *In vivo γ-scintigraphic studies*

From the images taken at regular time intervals in all volunteers, the observed time for initiation of tablet disintegration and distribution of the tracer through gastrointestinal tract were closely similar. Figure 3 shows a group of representative images for initiation of disintegration of the tablets and distribution of the traces in gastrointestinal tract of one volunteer. From the images, it was found that the tablets remained intact in stomach (30 and 60 min) and small intestine (2 and 4 h). On entering the colon, the tablets began to release the tracer due to partial degradation of the coat (8 to 12 h) and finally the uniform distribution of the tracer along the entire colon after 24 h. These results showed that a coat consists of a mixture of 80% guar gum and 20% HPMC would successfully prevent the release of prednisolone in the stomach and small intestine. However, on arrival to the colon, the tablets started their degradation after 8 h and were completely disintegrated after 24 h as evident from the distribution of the tracer in the different segments of the colon as shown in Figure 3.

4. Conclusion

Based on drug release in the colon as well as *in vivo* gamma scintigraphic study, compressed coated tablets with mixture of 80% guar gum and 20% HPMC could produce a successful drug targeting to the colon with minimal amount released in the gastrointestinal tract.

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