



In-vitro Evaluation of Guar Gum Mediated Colon Specific Tablet Dosage form Containing Aspirin

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ABSTRACT

Colon specific drug delivery system containing Aspirin as model drug was developed by varying amount of guar gum in the formulation. Granules containing different quantities of guar gum were prepared without changing the amount of Aspirin, microcrystalline cellulose and starch paste. The amount of starch paste was kept at 5 % of the combined amount of guar gum, microcrystalline cellulose and Aspirin. A decrease in rate of release of drug was observed with increase in guar gum content from formulation AG1 to AG3. The effect of presence of induced colonic microflora during *in-vitro* evaluation for colonic delivery of the formulations was studied and found to enhance the rate of degradation of carrier polysaccharide facilitating drug release.

Keywords: Guar gum, colon targeting, colonic simulation fluid, induced colonic microflora, microbial polysaccharidases.

INTRODUCTION

Incorporation of polysaccharides in formulating colon specific oral drug delivery systems is one of the well documented approaches. A variety of polysaccharides used for the purpose include chitosan, pectin, chondroitin sulphate, cyclodextrin, dextrans, guar gum, inulin, amylose and locust bean gum (Pawar et al 2011)¹. Guar gum in form of directly compressed tablets is capable of protecting drug from being released in the pre-colonic regions (Rama Prasad et al 1998)². The researchers have also suggested addition of induced rat caecal contents in the colonic simulation fluids during *in-vitro* drug release studies to increase drug release in colonic environment. However, the rat caecal contents do not imitate the human colonic microflora and hence the results have to be extrapolated for human conditions. Polysaccharide breakdown by mixed populations of human fecal bacteria has been compiled by Englyst et al (1987). Presence of polysaccharide degrading activity in the washed bacterial load has been reported. Various polysaccharidases detected include amylase, pectinase and xylanase as major enzymes and arabinofuranosidase, xylosidase, galactosidase, glucosidase in minor quantities. They reported fermentation of starch, pectin, xylan and arabinogalactan by mixed populations of bacteria found in human feces³. Shah (2011) has developed a method for enrichment of colonic microflora under anaerobic incubation and utilization of the enriched culture contents for degradation of variety of polysaccharides successfully under aerobic and anaerobic conditions⁴. Use of enriched human fecal bacteria in colonic simulation fluid has been suggested by Pawar et al (2012) for *in-vitro* evaluation of the colon specific drug delivery systems containing natural polysaccharide excipients⁵. It was decided to develop tablet formulations containing varying amounts of guar gum in granules and to evaluate the

importance of presence of induced colonic microflora for enhancement of drug release from such formulations during *in-vitro* evaluation.

MATERIALS AND METHODS

All routine chemicals and reagents like Guar gum, Microcrystalline cellulose (MCC), Magnesium stearate, Talc, Starch, Hydrochloric acid, Potassium Dihydrogen Phosphate, Sodium hydroxide, Fluid Thioglycolate medium and Aspirin were of analytical grade and procured from standard Indian suppliers.

Formulation of tablets

Granules were prepared with different amounts of Guar gum during granulation with Aspirin, MCC and Starch. Three formulations were prepared in which increasing amounts of guar gum was added keeping fixed concentration of Aspirin and MCC. The details of the formula are given in Table 1. A mixture of Aspirin, guar gum and microcrystalline cellulose was prepared. A wet mass of this mixture was prepared using starch paste as binding agent. The wet mass was passed through sieve number 16 to prepare granules. These wet granules were dried in oven below 60°C and passed through sieve number 22/40. Dried granules were lubricated with 1 % talc and 2 % magnesium stearate and compressed at an optimum pressure using 10 stations Rotary Tablet Compression Machine (Rimek RBS-4 – mini press).

Evaluation of the compressed tablets for physical parameters

Tablet Dimensions

Thickness and diameter were measured using a calibrated vernier caliper. Five tablets of each formulation were picked randomly and parameters (Thickness and Diameter) measured individually.



Table 1: Composition of tablets

Ingredients (mg)	Formula 1 [AG1]	Formula 2 [AG2]	Formula 3 [AG3]
Aspirin	50	50	50
Guar gum	100	150	200
MCC	50	50	50
Starch (for paste)	10	12.5	15

AG1, AG2 and AG3 formulation batches were prepared in triplicate (n = 3).

Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm². Five tablets were randomly picked and hardness of the tablets was determined.

Friability Test

The friability of tablets was determined by using Roche Friabilator. It is expressed in percentage (%). A pre-weighed sample of 20 whole tablets was taken and put in the friabilator drum and operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again. The % friability was then calculated.

Weight Variation Test

Twenty tablets were selected randomly from each batch and average weight of twenty tablets determined. Each tablet was weighed individually to check for variation in weight from average weight of tablet.

In-vitro evaluation of drug release in colonic environment

Tablets were kept in the dissolution apparatus in gastric simulation fluid for 2 hr. Thereafter, the fluid was changed to ileac simulation fluid and experiment continued for further 3 hr. After that, the colonic simulation fluid was used in two variations for testing the efficiency of drug release in presence and absence of induced human fecal culture. The details of simulation fluids and dissolution test parameters are as under:

a. Gastric simulation Dissolution parameters (2 hr):

Medium : 0.1 N HCl
 Volume : 900ml
 Apparatus : USP apparatus type I (Basket)
 Speed : 100 rpm
 Temperature : 37 °C ± 0.5 °C
 Sampling time : 1 hr intervals

b. Ileac simulation Dissolution parameters (3 hr):

Medium : Phosphate buffer pH 6.8
 Volume : 900ml
 Apparatus : USP apparatus type I (Basket)
 Speed : 100 rpm
 Temperature : 37 °C ± 0.5 °C
 Sampling time : 1 hr intervals

c. Colonic simulation fluid (A) (4 hr)

Medium : Phosphate buffer pH 6.8
 Volume : 900ml
 Apparatus : USP apparatus type I (Basket)
 Speed : 100 rpm
 Temperature : 37 °C ± 0.5 °C
 Sampling time : 1 hr intervals

d. Colonic simulation fluid (B) (4 hr)

Medium : Phosphate buffer pH 6.8
 (supplemented with enriched colonic microflora)
 Volume : 900ml
 Apparatus : USP apparatus type I (Basket)
 Speed : 100 rpm
 Temperature : 37 °C ± 0.5 °C
 Sampling time : 1 hr intervals

The human fecal microflora was enriched as described by Pawar et al (2012) with modification by incorporating guar gum as polysaccharidase inducer⁵. The release profile of Aspirin was followed by UV spectroscopy against an appropriate blank.

RESULTS AND DISCUSSION

The aim of present study was to prepare and evaluate a guar gum containing tablet dosage form for colon specific drug delivery. Additionally, the suitability of incorporation of induced human fecal microflora for rapid drug release in colonic simulation fluid was evaluated. All the three formulations were evaluated for various physicochemical parameters and the results have been depicted in Table 2 and found to be within acceptable limits.

Table 2: Evaluation of physical parameters for the formulations

Parameters	AG1	AG2	AG3
Tablet Thickness (mm)	3.8 ± 0.05	4.2 ± 0.06	4.66 ± 0.05
Tablet Diameter (mm)	8.2 ± 0.02	8.2 ± 0.02	8.72 ± 0.02
Hardness (kg/cm ²)	5.5 ± 0.5	6.0 ± 0.5	7.0 ± 0.5
Friability (%)	0.61 ± 0.4	0.57 ± 0.5	0.44 ± 0.5
Tablet Weight (mg)	213 ± 5	267 ± 5	324 ± 6

Natural polymers have been routinely evaluated for their drug delivery potential because of their abundant availability at affordable costs and compatibility with human system. Beneke et al (2009) highlighted one of the well studied aspects i.e. use of natural polysaccharides as excipients and components of prodrugs in order to achieve colon specificity⁶. The importance of microbial polysaccharidases in colon specific drug delivery of formulations containing polysaccharide excipients is well reported. Sinha and Kumaria (2003) have reported guar gum along with inulin as naturally occurring polysaccharide obtained from plant and categorized as 'generally regarded as safe' (GRAS) as they are broken down by colonic microflora to simple saccharides⁷.

Pawar et al (2011) presented a compilation of the important polysaccharide excipients, along with their metabolism in human colon, the mechanism of action of the degrading enzymes and genetic aspects of polysaccharide degrading colonic microflora. It was also suggested by the researchers that polysaccharidase based in-vitro evaluation systems are few and there is a need of substantial research to develop an ideal and economically feasible system for *in-vitro* evaluation of orally administered formulations containing polysaccharide excipients to achieve colon specificity.

Precise colon drug delivery requires that the triggering mechanism in the delivery system respond to the physiological conditions particular to the colon. For a formulation to act as an effective colon specific drug delivery system, the primary condition is that a minimum amount of drug should be released in the environment of the upper gastrointestinal tract, *i.e.*, in stomach and small intestine (Pawar et al 2012). At same time, on entry in colon, where the transit time is quite sufficient *i.e.* about 20 to 30 hr, the polysaccharide excipient should facilitate drug release under the degradative action of colonic micro flora.

The developed formulations were evaluated for their success in achieving colon specificity. The results have been shown in figures 1 to 3. Sample tablets from all the three formulations *i.e.* AG1, AG2 and AG3 were subjected to dissolution studies in gastric simulation fluid for first 2 hr followed by ileac simulation for next 3 hr. Thereafter, the fluid was changed to Colonic simulation fluid in two variations; one with and another without supplementation of induced human fecal microflora. It is well obvious from the figures that the release of drug was highly restricted from all the tested formulations in the pre-colonic milieu. The purpose of using guar gum in formulation seems to be fulfilled. The figures clearly depict that as the amount of guar gum increases (AG1 < AG2 < AG3), the release of drug is slowed down which can be explained on the basis of diffusion limitations created due to high concentration of polysaccharide matrix around the drug.

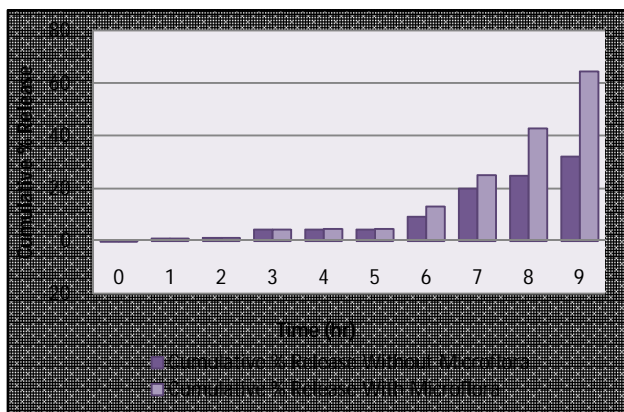


Figure 1: Comparison of release of Aspirin from AG1 formulation in colonic simulation fluid with and without supplementation of induced human fecal microflora.

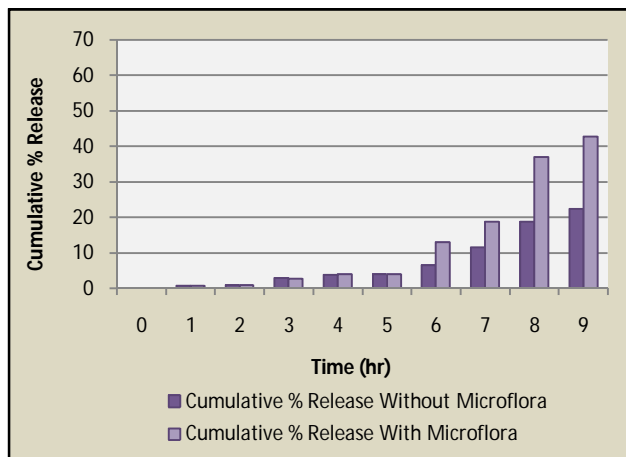


Figure 2: Comparison of release of Aspirin from AG2 formulation in colonic simulation fluid with and without supplementation of induced human fecal microflora.

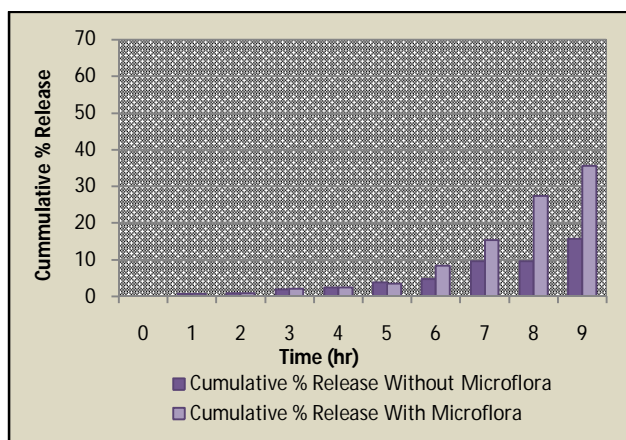


Figure 3: Comparison of release of Aspirin from AG3 formulation in colonic simulation fluid with and without supplementation of induced human fecal microflora.

One of the important observations is that as the pH of simulation fluid is increased, the drug release is significantly improved owing to better solubility of Aspirin in the aqueous medium in neutral and slightly alkaline pH. A high level retardation of drug release from the oral dosage forms in the pre-colonic environments is by incorporation of guar gum in the formulations has been frequently reported (Shyale et al, 2005; Kotadiya et al 2008)^{8,9}.

Anaerobic bacteria of the colon are able to react to the constantly changing mixture of complex carbohydrates entering the colon by recognizing a variety of substrates and producing digestive enzymes accordingly (Slayers et al 1978)¹⁰. Hence polysaccharide based drug delivery systems have been developed for drug delivery to this part of the gastrointestinal tract. Shah (2011) has optimized the enrichment medium for human fecal microflora for different polysaccharide excipients. Presence of inducer polysaccharide in the anaerobic growth medium was reported to improve the relevant enzymatic activity in the culture. Further, the induced enzymatic activity did not require anaerobic incubation for degradation of target polysaccharide. Applying the

findings in the present case, the colonic simulation fluid was appropriately supplemented with human fecal culture enriched anaerobically in fluid thioglycollate medium containing inducer guar gum. The culture was directly added as supplement in the colonic simulation fluid where the condition was kept aerobic. As expected, the release of Aspirin in the supplemented colonic simulation fluid was higher as compared to the non supplemented fluid (Figs 1, 2, 3). The results are fairly encouraging as the requirement of setting up anaerobic conditions during dissolution experiments in colonic simulation fluids was not required. He Wei et al (2008) have reported the importance of maintaining anaerobic conditions during in-vitro evaluation in colonic environment of pectin/ethyl cellulose film-coated pellets of 5-fluorouracil for colonic targeting¹¹. The requirement of anaerobic incubation during colonic simulation studies is emphasized by Rama Prasad et al (1998). The formulations tested in the present study are found to remarkably improve the colon targeting of Aspirin. However, further experimentation is required to optimize the time required to achieve complete drug release from the formulation.

CONCLUSION

The tested formulations were efficient in restricting release of Aspirin in pre-colonic environments. The increase in amount of guar gum in the formulation effectively reduced drug release. The release of model drug Aspirin from all the tested formulations was highly limited in pre-colonic environments. Presence of guar gum induced human fecal microflora in the colonic simulation fluid remarkably enhanced the drug release in colonic environment from the formulation, confirming the suitability of the formulations for colon specific drug delivery.

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