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FORMULATION DEVELOPMENT AND EVALUATION OF A COLON TARGETED TABLET DOSAGE FORM

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ABSTRACT

Oral route has been considered one of the most important getting highest patient compliance for administration of colon targeted drugs. Guar gum was used as a carrier for the model drug aspirin and three formulations were developed. Microcrystalline cellulose was used as routine diluent. The primary variation in the formulations was the percentage of guar gum used and stage of addition during formulation of tablets. Guar gum was either used for making dummy granules without drug or half of it during granulation without drug and half with drug during compression or completely during granulation along with the drug. The preliminary evaluation of the three formulations for in-vitro drug release in pre-colonic environment was carried out. The results revealed that the maximum drug retention was possible in tablets of formulation F-III, when granulation was done using complete quantity of guar gum along with the drug. However split dose addition of guar gum, i.e. half during granulation and half during compression of tablets (Formulation F-II) leads to marginal increase in release of drug in the pre-colonic environments. The drug release from the formulations was limited to 4.5 % in the pre-colonic environment during the tested time period of 5 hr.

INTRODUCTION

Development of a colon specific oral drug delivery system is one of the research areas that has invited attention and intervention of scientific community. Oral route for drug delivery has enjoyed highest patient acceptance. Colonic drug delivery approach for treatment of diseases like ulcerative colitis, Crohn's disease and irritable bowel syndrome is being recently used[1]. Usefulness of colonic drug delivery system for systemic absorption of protein and peptide drugs is well documented[2]. The success of a colon specific oral dosage forms depends on two things: the prevention of delivery in pre-colonic region during gastrointestinal transit and appropriate release of drug in colon. The feasibility of natural polysaccharides as targeting tools of drugs to the colon has been well documented. As compared to the pH-dependent polymers that are used as coating materials to protect the drug from release in gastric environment, exploitation of metabolic activity of the colon is a better alternative to improve the drug carriers' specificity. Azo-reduction, glycosidic bond hydrolysis is common approach and chemically modified polysaccharides can be used as perspectives drug carriers. Of the various approaches, the use of polysaccharide carriers has been successful because the minimal degradation of the carrier in gastric and ileac environments and colonic micro-flora triggered degradation of carrier and hence specific delivery of drug to colon. Guar gum in form of directly compressed tablets is capable of protecting drug from being released completely in the pre-colonic regions [2]. The present investigation was initiated with creating variations in percentage and mode of addition of guar gum in tablet dosage form and carrying out initial studies on protection of drug release in pre-colonic environment.

MATERIALS AND METHODS

Guar gum, Microcrystalline cellulose (MCC), Starch, Talc, Magnesium Stearate, Hydrochloric acid, Potassium Dihydrogen Phoshate, Sodium hydroxide and Aspirin were purchased from standard Indian suppliers and manufacturers. Analytical grade reagents were used for the study.

Formulation of compressed tablets with 100 % Guar gum in dummy granules [F-I]: To prepare dummy granules, pre-weighed quantity of guar gum was taken and mixed with MCC and starch paste in the ratio 100:50:7.5. In the process of dummy granules preparation, guar gum, microcrystalline cellulose and starch paste as binding agent were mixed to form coherent mass. The coherent mass was passed through sieve number 22 to prepare granules which were dried in oven below 60˚C and passed through sieve number 30/40. Amount of model drug Aspirin was

kept 50 % of the amount of guar gum. Dummy granules and model drug were mixed and compressed into tablets in presence of talc (1 %) and magnesium stearate (2 %) using 10 station Rotary Tablet Compression Machine (Rimek RBS-4 – mini press) at an optimum pressure.

Formulation of tablets with 50 % Guar gum in dummy granules [F-II]: While preparing dummy granules, guar gum was added as split fraction, in which, half quantity of guar gum was added during granulation and half was mixed with the model drug. Dummy granules were prepared with ratio of guar gum, MCC and starch paste selected as 50:50:5. In the process of dummy granules preparation, coherent mass was prepared by mixing guar gum, microcrystalline cellulose and starch paste as binding agent. The coherent mass was passed through sieve number 22 to prepare granules which were dried in oven below 60˚C and passed through sieve number 30/40. A mixture of dummy granules, model drug and remaining 50 % of the guar gum was prepared. It was compressed to form tablets in presence of talc (1 %) and magnesium stearate (2 %) using 10 station Rotary Tablet Compression Machine (Rimek RBS-4 – mini press) at an optimum pressure.

Formulation of tablets with 100 % Guar gum and drug in the granules [F-III]: Granules were prepared with 100:50:50:10 ratio of guar gum, model drug Aspirin, MCC and starch paste. In the process of preparation of granules guar gum, model drug Aspirin, microcrystalline cellulose and starch paste as binding agent were mixed to form coherent mass. The coherent mass was passed through sieve number 22 to prepare granules which were dried in oven below 60˚C and passed through sieve number 30/40. Dried granules were compressed into tablets in presence of talc (1 %) and magnesium stearate (2 %) using 10 station Rotary Tablet Compression Machine (Rimek RBS-4 – mini press) at an optimum pressure.

F-I, F-II and F-III formulation batches were prepared in triplicate (n = 3).

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.

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/cm^2. 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 pre-colonic environments: All of the above formulations were tested for their drug release under following simulation conditions. The amount of Aspirin released was determined using the UV spectrophotometer against appropriate blank.

a. Gastric simulation Dissolution parameters:

Medium	:	0.1 N HCl
Volume	:	900 ml
Apparatus	:	Dissolution apparatus type I of USP (Basket)
Speed	:	100 rpm
Temperature	:	37 °C ± 0.5 °C
Sampling time	:	30 min intervals

b. Ileac simulation Dissolution parameters:

Medium	:	Phosphate buffer pH 6.8
Volume	:	900 ml
Apparatus	:	Dissolution apparatus type I of USP (Basket)
Speed	:	100 rpm
Temperature	:	37 °C ± 0.5 °C
Sampling time	:	30 min intervals

RESULTS & DISCUSSION

Guar gum is reported to be widely accepted excipient in colon specific drug delivery systems owing to its release retarding property and susceptibility of microbial degradation in large intestine [3],[4],[5]. The properties and suitability as a colon specific drug delivery excipient of a galactomannan polysaccharide, gaur gum, has been reviewed. The suitability of gaur gum is due

to its high viscosity resulting from its high molecular weight (1,000,000) and long polysachharide chain. Each 100 g gaur gum contains galactomanan 80, water 12, protein 5, acid soluble ash 2 and fat 0.7 g. It consists of high molecular weight hydrocolloidal polysaccharide, composed of galactan and mannan units, combined through glycosidic linkages and is degraded in the large intestine due the presence of microbial enzymes.

The present investigation was initiated with the aim of developing a tablet formulation containing guar gum that shows intactness and minimum drug release in pre-colonic environments. Three types of formulations were tested. F-I formulation contained the complete content of guar gum added in form of dummy granules and compressed with powder of model drug Aspirin after proper lubrication. F-II formulation contained half of the guar gum content in dummy granules and half added along with model drug Aspirin powder during tablet compression. The third formulation, F-III, was prepared using complete guar gum content during granulation along with model drug Aspirin. All the three formulations were evaluated for various physical parameters such as tablet thickness, diameter, hardness, friability, individual weight of tablet and the results have been depicted in Table 1 and found to be well within acceptable limits.

Table 1: EVALUATION OF PHYSICAL PARAMETERS FOR THE FORMULATIONS

Physical Parameters	**F-I**	**F-II**	**F-III**
Tablet Thickness (mm)	3.8 ± 0.05	3.75 ± 0.04	3.8 ± 0.06
Tablet Diameter (mm)	8.2 ± 0.02	8.2 ± 0.02	8.2 ± 0.02
Hardness (kg/cm^2)	4.0 ± 0.5	5.0 ± 0.5	5.5 ± 0.5
Friability (%)	0.83± 0.5	0.77± 0.4	0.64± 0.5
Tablet Weight (mg)	210 ± 6	208 ± 5	213 ± 6

The formulations were tested for the release of drug under gastric and ileac simulation conditions. Formulation F-I was unable to maintain intactness in the liquid medium and disintegrated in the dissolution apparatus within first 30 min.

Formulation F-II remained intact under similar conditions and showed expected swelling in the simulation fluids. The release of drug from the formulation was highly restricted in the gastric environment and seemed to shoot up as the simulation fluid was changed to suit ileac conditions, however, the cumulative % release as seen from Fig.1 did not increase more than 4.5 % during the gastric and ileac transit period i.e. 5 hr.

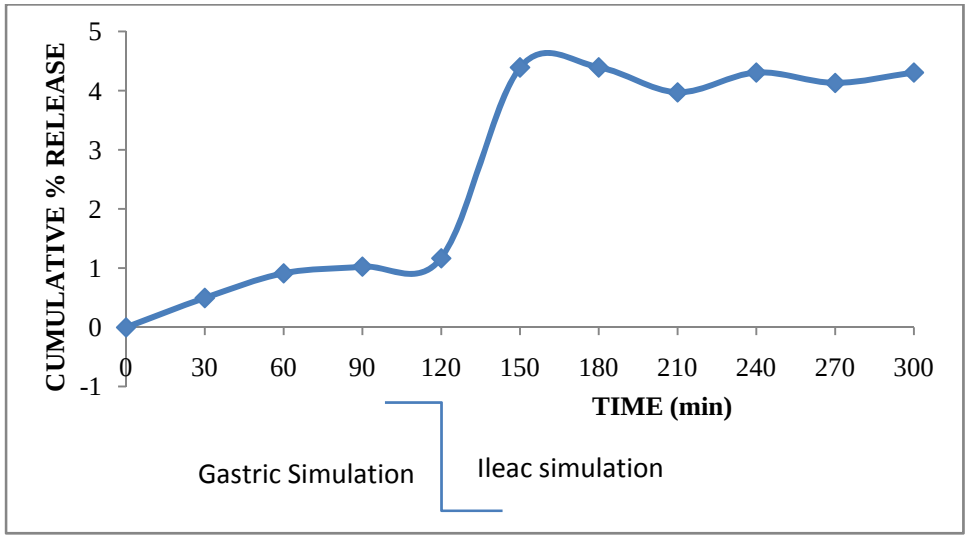

Fig. 1: Cumulative % release of Aspirin from formulation F-II in pre-colonic environment

The results with the formulation F-III were encouraging and the tablets swelled in about 20 min and did not disintegrate throughout the period of dissolution test under gastric (120 min) and ileac simulation (180 min). The results of spectrophtometric analysis of cumulative % release of Aspirin from the formulation F-III under gastric and ileac simulation has been shown in Fig.2.

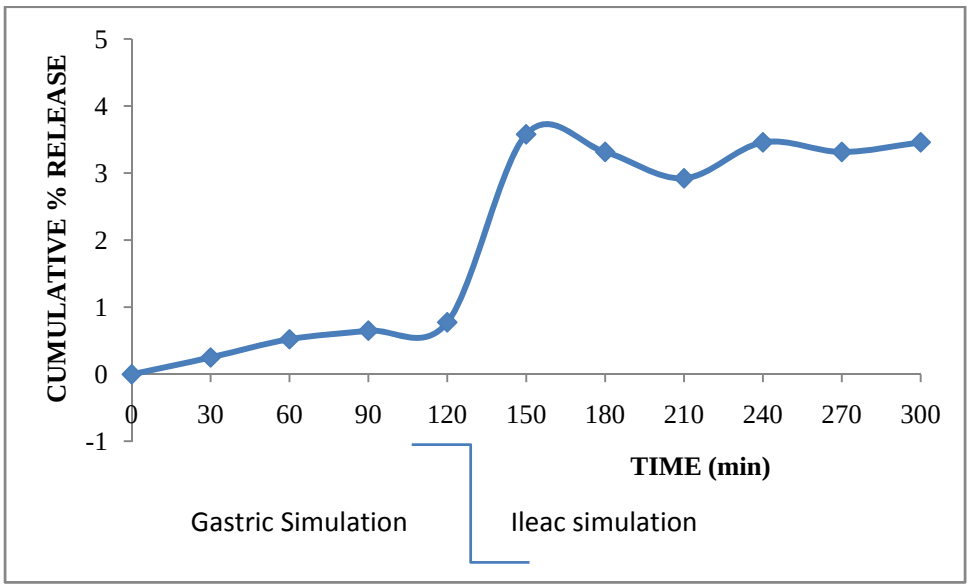

Fig 2: Cumulative % release of Aspirin from formulation F-III in pre-colonic environment

It is evident from Fig.1 & Fig.2 that there was hardly any release from the formulation in the gastric simulation fluid and the cumulative % release was limited to well near 1 %. When the swollen tablets were shifted to ileac simulation fluid for further release studies in the dissolution

apparatus, drug release seemed to be increased. However, the total drug release recorded for the next 180 min in the ileac environment was limited to about 4 %. Formulation F-III seemed to be marginally better in resisting drug release as compared to F-II. Release of drug in the range of 2.5 – 4 % has been reported from guar gum containing compressed tablets in simulated GI fluid[6]. Prevention of release of drug from the formulation for first 5 hrs has been reported when tablet containing pectin was coated with inulin and shellac to enhance colonic specificity [7].

It is indicated from the present results that the formulation is capable of resisting drug release in pre-colonic environments when kept for the normal timings even without requirement of enteric coating and hence suitable for colonic delivery. The usefulness of polysaccharides including guar gum for prevention of pre-colonic delivery of drugs and successful delivery in colon under the effect of colonic microflora has been confirmed as suggested by Pawar et al [8].

CONCLUSIONS

The results suggest the suitability of guar gum as carrier for drugs in tablet dosage forms for prevention of drug delivery in pre-colonic regions of the gastrointestinal tract. Addition of complete content of guar gum along with the model drug Aspirin during granulation (Formulation F-III) gives desirable results, however split dose addition of guar gum, i.e. half during granulation and half during compression of tablets (Formulation F-II) only leads to marginal increase in release of drug in the pre-colonic environments.

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