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Formulation and In-vitro Evaluation of Microbially triggered Ibuprofen Delivery for Colon targetting.

A.V.Bhosale[1] , Hardikar S.R. [1], Naresh Patil[1]*, Umang Patel[2] , Yogesh Sumbe[1] , Rajesh Jagtap[1]

[1]Department of Pharmaceutics ,PDEA's SGRS college of Pharmacy ,Saswad,Tal-Purandar. -Pune 412301,M.S.,India

[2]Department of Pharmacology ,PDEA's SGRS college of Pharmacy ,Saswad,Tal-Purandar.Dist-Pune 412301. M.S.,India

Email: nareshpatil1984@gmail.com

ABSTRACT: The purpose of the present investigation was to achieve successful delivery specifically to the colon using guar gum and HPMC K4M as a compression coat over a core tablet of ibuprofen. In this study, Guar gum along with Hydroxy Propyl Methyl Cellulose (HPMC) was used as a compression-coating polymer. The drug delivery system was based on the gastrointestinal transit time concept, assuming colon arrival time to be 6 h. rapidly disintegrating core tablets containing 100-mg ibuprofen were compression coated with guar gum and HPMC. A 3^2 full factorial design was applied for optimization of the formulation. Both variables, coat weight of the tablet (X1) and the proportion of guar gum in polymer blend (X2) and, had an influence on the percent drug release after 6 h of dissolution of tablet in the presence of rat cecal content. The results revealed that for protecting the rapidly disintegrating core of ibuprofen in the physiological conditions of stomach and upper intestine, the core tablet should be coated with 60% of guar gum in coat formulation and at 225 mg coat weight. The proportion of guar gum exhibited predominant action as compared to coat weight. The guar gum–HPMC coating was found to be a promising drug delivery system for colon targeting.

Key words- colon targeting, compression coating, microbially triggered system, guar gum, HPMC K4M,site specific drug delivery, enzyme activated.

INTRODUCTION

Over the last decade there has been increased interest in the development of site specific formulations for targeting drug delivery to the colon, which is a site for local and systemic drug delivery. Basic approaches to achieve colonic site specificity include utilizing pH changes in the gastrointestinal region; designing a system that releases the drug at a predetermined time after administration; and the use of carriers degraded by bacteria located essentially in the colon. The pH approach lacks site specificity [1]. Timed release capsules rely on the reported relative consistency of small intestinal transit times [2], but the overall variability in gastrointestinal transit times may give rise to problems, e.g., bacterial degradation of materials in the colon. A more universal approach in utilizing bacterial degradation of the azo bond to achieve specific release has been the synthesis of a polymer suitable for coating and use of hydrogel with azoaromatic crosslink's [3-6]. A large number of polysaccharides are degraded by colonic bacteria and may form the basis for a suitable carrier. Several polysaccharides such as pectin and its salts, chondroitin sulfate, amylose, and guar gum are being investigated as carriers for colon-specific drug delivery [7-10]. In pharmaceutical formulations, guar gum is used as a binder, disintegrant, suspending agent, thickening agent and stabilizing agent. Guar gum in the form of either a matrix tablet or as a compression coat over a core tablet of drug can target drugs to the colon [11-16]. These studies have shown the drug release retarding property of guar gum in the upper gastrointestinal tract (GIT) and its degradation by the anaerobic bacteria in the colon. Ibuprofen was used as model drugs because it is absorbed at different sites in the human gastrointestinal tract. Ibuprofen is well absorbed throughout the colon [17]. The elimination half-life of model drug is brief, about 2 hours [18-19].

MATERIALS AND METHODS

Guar gum (MW 220,000, particle size o.75 mm) and

Hydroxy Propyl Methyl Cellulose (HPMC K4 M) was obtained as a gift sample from Themis Research lab, Mumbai, Maharashtra, India. Other materials in the study were microcrystalline cellulose (MCC) (Avicel PH 101), Sodium starch glycolate (SSG), magnesium stearate, and talc was of pharmacopoeia grade (USPNF). All chemicals used were of analytical grade.

Preparation of ibuprofen core tablet

Rapidly disintegrating core tablets consisting of ibuprofen (100 mg) and a super-disintegrant Sodium starch glycolate (4 mg) and microcrystalline cellulose (46 mg) as diluents were prepared. A weighed quantity of ibuprofen required for 20 tablets was mixed thoroughly with the required amount of SSG and MCC. The uniformity of mixing was assessed by conducting content uniformity test on the samples of the powder mix. Quantity weighing 150 mg was taken and compressed individual into tablets using a rotary tablet press (Karnawati ,Ahemdabad , India) having a 7-mm die. Weight variation, crushing strength, friability, and thickness were performed for the core tablets.

Experimental design

A 3^2 full factorial design was utilized in the present investigation [20]. The proportion of guar gum in polymer blend (X1) and coat weight (X2) were used as independent variables (Table 1). Among the studied factors were: guar gum to HPMC ratio for compression coating and the amount of coating mixture. This design resulted in 9 batches and it was summarized in (Table 1).

I-A) Factorial design for experiment

Formulation	X1	X2
F1	1	1
F2	1	0
F3	1	- 1
F4	0	1
F5	0	0
F6	0	-1
F7	-1	1
F8	-1	0
F9	-1	-1

I-B) Translation of coded levels into actual units.

	-1	**0**	1
X1:- Weight of total coat on core	225	250	275
X2:- Proportion of guar gum in coating polymeric blend (mg)	60	70	80

Compression coating

Guar gum (GG) polysaccharide being widely used for colon targeting was selected as the ingredient. Guar gum alone has earlier been used in colon specific drug delivery as matrix forming material and as a compression coat[16,21].The core tablets of ibuprofen were compression coated using a uniformly mixed polymer blend of guar gum and HPMC in different ratios at three levels, as mentioned in the 3^2 factorial design layout (Table 1) 45 % of polymer blend was added in a 10-mm die cavity of a rotary tablet press (Karnavati Ahemdabad, India) ibuprofen core tablets were then placed carefully in the center. The rest of the polymer blend was added and tablets were compressed with high compression force. Routine physical parameters for tablet formulation, e.g., weight variation, crushing strength, friability, thickness, and dissolution, were performed for the compression coated tablets.

II) Tablet evaluation parameters

Code	Weight	Thickness	Friability
Core	150±1.55	2.56±0.01	0.16
F1	425±2.78	3.32±0.02	0.03
F2	425± 2.76	3.33±0.02	0.04
F3	425±2.79	3.31±0.03	0.05
F4	400±2.66	3.02±0.03	0.03
F5	400±2.64	3.03±0.02	0.03
F6	400±2.66	3.02±0.02	0.05
F7	375±1.98	2.91±0.03	0.03
F8	375±2.12	2.90±0.02	0.04
F9	375±2.78	2.92±0.02	0.05

Preparation of rat cecal content medium (RCM)

The Industrial animal ethical committee approved the experimental protocol under strict compliances of CPCSAE guidelines. In-vitro drug release testing was investigated in presence of rat cecal content medium. The Albino rat weighing in between 150–200 g were kept on a normal diet and administered 1 ml of 1% w/v solution of guar gum in water with the help of Teflon tubing directly into stomach region via oral cavity. The treatment was continued for 6 days to induce enzyme responsible for guar gum degradation, animal were sacrificed before 30 minutes of commencement of drug release studies and caecum was exteriorized for content collection. The cecal content (anaerobic in nature) were immediately transferred into buffer saline solution pH 6.8 to obtain 4% w/v concentration cecal content equivalent to 8 g were added to 200 ml of buffer (pH 6.8) to give a final cecal dilution of 4%. Solution was previously bubbled with nitrogen gas to maintain an anaerobic environment [22].

In-vitro drug release study

The ability of the prepared tablet to retard drug release in the physiological environment of the stomach and the small intestine was assessed by conducting drug release studies in simulated stomach and small intestinal pH, respectively. The changing pH media [23] for delayed

release tablets was used. The ability of guar gum coat applied on ibuprofen core tablets to remain intact in the physiological environment of stomach and small intestine was assessed by mimicking mouth-to-colon transit. Drug release studies in the presence of cecal content were carried out using USP dissolution test apparatus. However slight modification in the procedure was done. The experiments were carried out in 250 ml beaker immersed in water maintained in the jars of dissolution test apparatus. Initial studies were carried out in 200 ml of 0.1N HCl (pH of 1.2) for 2 h. After this the dissolution medium was replaced with 200 ml phosphate buffered saline (PBS; pH 6.8), and the dissolution continued for another 3 h. Then study at a pH of 6.8 buffer containing rat cecal content medium is carried out till completion of 24 h. The experiments in cecal content media were carried out in presence of a continuous supply of nitrogen. At different time intervals 1 ml sample was withdrawn from the dissolution medium and 1ml of cecal content 4% maintained under anaerobic conditions, was replenished into the dissolution media. The volume of the sample was made up to 10 ml, filtrate which was analyzed using UV-visible spectroscopy at 223 nm.

RESULT

Determination of drug content

The ibuprofen core and compression coated tablets; both were tested for their drug content. The tablets were finely powdered and a quantity of powder equivalent to 100 mg of ibuprofen were accurately weighed and transferred to 100 ml volumetric flasks containing approximately 50 ml of buffer pH 6.8. The flasks were shaken to solubilize the drug. The volume was made up with buffer pH 6.8 and mixed thoroughly. The solutions were filtered through a 0.22 m membrane filter and analyzed for the content of ibuprofen using the UV method at 223 nm.

Core Tablet

The core tablets of ibuprofen were prepared by direct compression of the core mix prepared. The core tablets had a diameter of 7 ± 0.01mm and height of 1.4±0.01 mm. Sodium starch glycholate was added to the tablet core in order to make the core rapidly disintegrating. This would allow the core tablets to disintegrate rapidly once the coat material is digested by the resident microflora of the colon. The hardness of the core tablets was found to be in the range of 3.5–4.0 kg/cm2. These tablets were found to comply with the friability test since the weight loss was found to be less than 0.5%. The disintegration time of the core tablets was found to be 20 s. This may be due to the presence of sodium starch glycholate in these core tablets.

Compression Coated Tablet

The different coat materials were prepared by direct mixing as outlined in (Table 1). The hardness of the tablets was found to be in the range of 4.5–5 kg/cm2. The compression coated tablets had a diameter of 10.0± 0.01mm and height of 5.1 ± 0.01mm when the weight of the compression coat was 275 mg. reducing the coat weight to 250 mg reduced the thickness of the compression coated tablet to 3.02±0.02 mm. Further reduction in coat weight to 225 mg reduces the thickness up to 2.92 ±0.01 mm.

Drug release study

Among the studied factors were: guar gum to HPMC ratio for compression coating and the amount of coating mixture. For drug delivery systems designed for colon targeting, it is desirable that the system remains intact and shows minimal drug release in the physiological environment of the stomach and the small intestine and triggers drug release in the tracts of the colon. Hence an attempt was made to formulate a dosage form, which showed minimal drug release in conditions mimicking mouth-to-colon transit and ensured maximum drug release in the environments of the colon. The compression coat was designed to undergo bacterial degradation in the colon, exposing the rapidly disintegrating drug containing core in the colon. The core tablets were compression coated with coating mixtures outlined in Table 1. 275 mg of coating material at 3 different concentration level of Guar gum (F1, F2 and F3) was applied over the core tablets. The results of the drug release studies carried out on ibuprofen tablets compression coated (275 mg coat weight) with different ratio of the polymers in simulated gastric (pH 1.2) and small intestinal (pH 6.8) are shown in Fig.1.

The compression coated tablet was found to be intact even after 24 h of the dissolution test. However, there was a formation of stiff gel layer and considerable swelling in the tablets. At the end of 24 h of dissolution it was observed that tablets having higher HPMC content showed higher swelling as compared to those with less HPMC content. Similarly tablet having high Guar gum concentration forms stiff gel and tablet with less guar gum concentration forms translucent gel that can be degrade by bacterial enzymes. The cumulative mean percentage of ibuprofen released from the tablet formulation F1, F2 and F3 during the first 5 h of dissolution were 1.63, 1.90, and 2.50 %, respectively. The release of less than 5% in simulated gastric and small intestinal fluids indicates the ability of compression delivery of drugs to the colon. After 24 h of dissolution the mean percent drug release from the formulation F1, F2 and F3 were found to be 13.33 ± 1.23%, 18.33 ± 1.54% and21.22 ± 1.77 %(fig 1). After 24 h of dissolution, upon opening the tablet gels, the core tablets could be seen. Since the drug release rate was highly retarded at a coat weight of 275 mg, it was essential to reduce the coat weight and then evaluate the ability of the compression coating of this polymer mixture for specific drug delivery to the colon. The coat weight of the tablet was reduced to 250 mg (F4, F5 and F6). Drug release studies from compression coated tablets with 250 mg coat weight, showed a drug release in F4,F5 and F6 amounting to 2.312, 3.152, 3.335 respectively, in the first

5 h of dissolution (Fig 2). This included 2 h dissolution at a pH of 1.2 followed by 3 h dissolution at a pH of 6.8. At the end of 24 h of dissolution the amount of drug released was 15.65 ± 1.22%, 19.10 ± 1.89%, and 22.80 ± 2.22% respectively(fig 2), in F4, F5 and F6 tablets. This showed that by reducing the coat weight, the initial drug release was not significantly increased due to formation of viscous gel while the total percent drug released in 24 h was affected. This can be explained on the basis that drug release from the compression coated tablets takes place only upon swelling of the compression coat consisting of guar gum and HPMC K4M. The initial delay in drug coat of this polymer combination for specific release can also be attributed to the time taken for the glassy to rubbery transition by this blend [24]. Once the polymer blend swells the lesser the thickness of the compression coat faster the drug release. This explains the higher drug release from 250 mg compression coat as compared to 275 mg at the end of 24 hours. From this conclusion, we further reduce coat weight to 225 mg which showed a drug release in formulation F7, F8 and F9 amounting to 4.99, 5.31, 6.88 respectively, in the first 5 h of dissolution (Fig 3). This also included 2 h dissolution at a pH of 1.2 followed by 3 h dissolution at a pH of 6.8. At the end of 24 h of dissolution the amount of drug released was 18.21 ± 1.22%, 23.22 ± 1.89%, and 27.30 ± 2.22%.(fig 3) respectively, in F7,F8 and F9 tablets. Earlier studies have shown that guar gum and xanthan gum [22] and starch [25] are digested by the colonic bacteria. However, to evaluate the mixtures of these polymers to carry drug moieties specifically to the colon remains to be studied. Further the rate of drug release from these compression coated tablets in colonic environments needs to be evaluated. So, in order to evaluate the susceptibility of the prepared compression coat to undergo enzymatic action by the colonic bacteria, drug release was carried out in rat cecal content media (4%) for 19 h after 5 h of dissolution in simulated gastric and small intestinal fluids. The cumulative percent drug released from F1, F2 and F3 at 275mg coat weight tablets were found to increase in presence of rat cecal content in the dissolution media (Fig. 1).Thus it concluded that lower concentration of guar gum is most beneficial for site specific delivery of ibuprofen to colon. Cumulative percent drug released after 24 h of dissolution increased from 21.22 ± 1.89% to 64.00 ± 4.34% in presence of 4% cecal content media. Similarly, in case of F6 at 250mg coat weight and 60% GG level, the total cumulative percent drug released in 24 h increased from 22.80±2.22% to 73.50 ±5.23% (fig 2) in presence of 4% cecal content and Considering that the concentration of bacteria present in the colon actually is much higher as compare to 4% rat cecal content. The cumulative percent drug released from F9 at 225 mg coat weight tablets were found to increase in presence of rat cecal content in the dissolution media (Fig. 3). Cumulative percent drug released after 24 h of dissolution increased from 27.30± 1.89% to 88.46 ± 4.34% in presence of 4% cecal content media. Complete drug would be released from these tablets. Based on these studies on compression-coated tablets making use of Guar gum HPMC blend. it may be suggested that these compression coated tablets can be used for carrying chemotherapeutic agents like anti-inflammatory drugs specifically to the site of action in case of rheumatoid arthritis and local inflammatory diseases such as ulcerative colitis and crohns disease. GG: HPMC K4M seems to be a better option for colon specific drug delivery because the compression coat in this case consists of a relatively reduced concentration of degradable polysaccharide which will facilitate a faster drug delivery to the colon.

Figure 1) comparison of release profile on formulation coated with 275 mg coat weight with and without RCM.

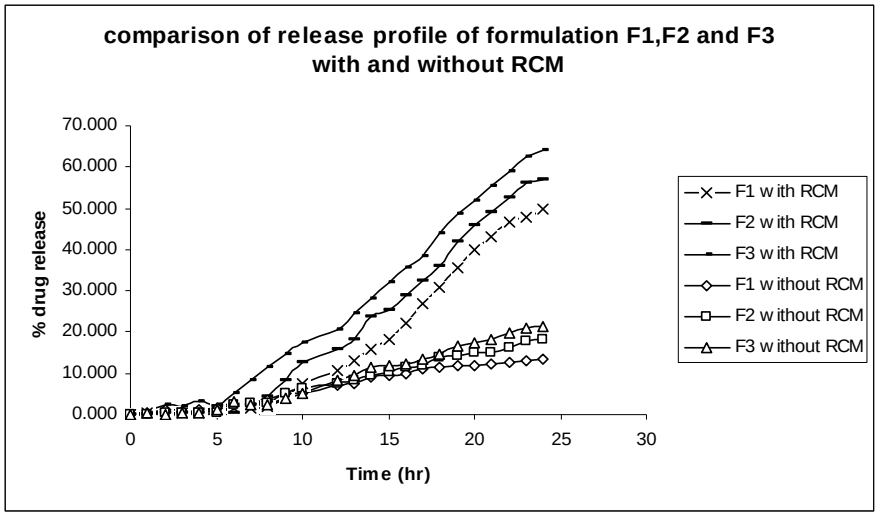


Figure 2) comparison of release profile on formulation coated with 250 mg coat weight with and without RCM.

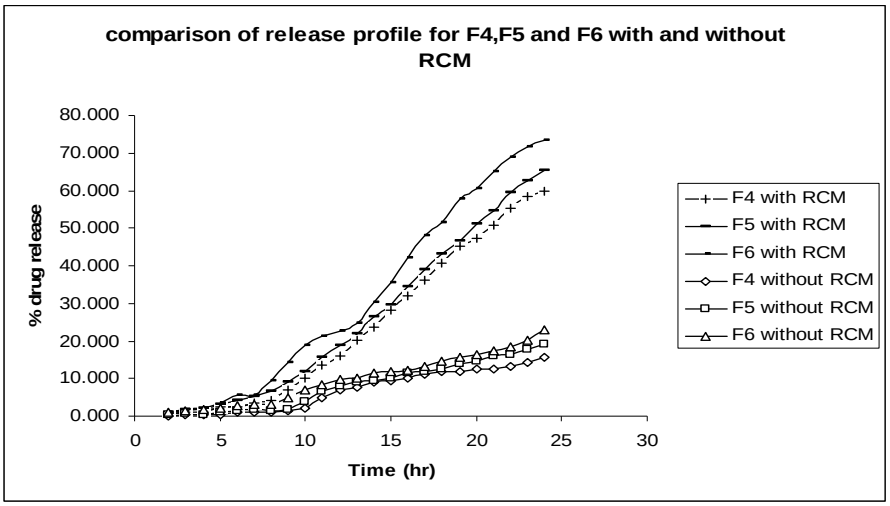
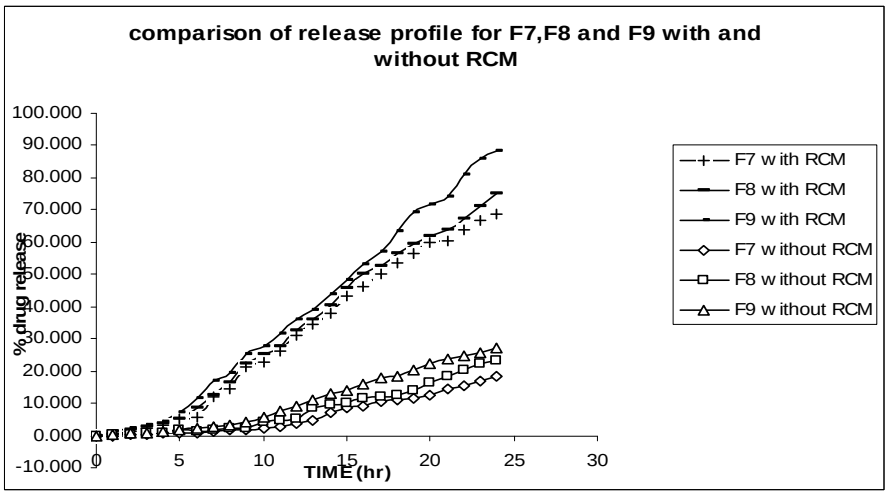


Figure 3) comparison of release profile on formulation coated with 225 mg coat weight with and without RCM



CONCLUSION

This work has shown that tablet systems coated with films composed of guar gum and HPMC offer potential as colonic drug delivery systems. It is possible by careful formulation of the tablet core to achieve different drug release profiles whereby an increase in the amount of drug released can be induced by the action of -glycosidase enzymes produced by rat cecal content. This polymer blend consisting of HPMC K4M as a drug release retarding agent in combination with colon degradable polysaccharide guar gum can be successfully used to protect the drug from being released under conditions mimicking mouth-to-colon transit. This compression coat can carry chemotherapeutic agents with upper gastrointestinal toxicity or side effects specifically to the colon. Drug release from these tablets takes place at a highly retarded rate till the compression coat is digested by the microflora of the colon. So, these systems seem to be site specific. Additionally, containing a relatively lower gum concentration, i.e. 60 % in Guar gum: HPMC K4M (225mg coat weight), the type of formulation we studied has not been described before. Although the formulations are moderately complex, their manufacture is easy, and might also be undertaken on an industrial scale.

ABREVIATION

GG- Guar gum
HPMC- Hydroxy propyl methyl cellulose

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