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In vitro studies on guar gum based colon targeted delivery of aceclofenac

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ABSTRACT

In the present work, colon targeted matrix tablets of aceclofenac and natural polysaccharide-guar gum was prepared to synchronize the morning stiffness of autoimmune disease, rheumatoid arthritis. In colon specific drug delivery, the use of biodegradable polymer holds great promise. Four formulae namely GG_1, GG_2, GG_3, GG_4 were prepared by wet granulation method, keeping the drug concentration constant but varying the polymer concentrations to 36%, 44%, 52%, and 60% w/w with drug respectively. *In vitro* drug release studies of punched tablets were conducted in 3 different media, 0.1 N HCl (stomach pH), pH 7.4 buffer (simulated intestinal fluid) and pH 7.4 buffer with 4% w/v rat cecal contents (simulated colonic fluid). The GG_3 and the GG_4 batches were releasing less than 50% of drug in the simulated intestinal fluid and in colonic fluid the release was up to 93% (GG_3) and 83% (GG_4). Therefore, the GG_3 batch containing 52% guar gum was considered suitable for colon targeting. The optimized batch was given enteric coating with 5% w/v cellulose acetate phthalate in isopropyl alcohol to prevent the drug release in the intestine.

KEYWORDS

Matrix tablet;
Aceclofenac;
Guar gum;
Colon targeting.

INTRODUCTION

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body promptly thereby to maintain the desired drug concentration i.e. the drug delivery system should deliver the drug at a rate desired by the needs of the body over a specified period of treatment[1].

The colon targeting is also exploited for systemic delivery of active drug for certain diseases such as arthritis, nocturnal asthma and angina for delivering the drug consistently with the circadian rhythm of the disease[2].

Arthritic diseases such as rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and gout exhibit profound circadian rhythms in the manifestation and intensity of symptoms. Patients with osteoarthritis tend to have less pain in the morning and more at night whereas, rheumatoid arthritis pain usually peaks in the morning and decreases as the day wears off.

In case of ankylosing spondylitis, back stiffness and pain are prominent between 6 a.m and 9 a.m. Chronotherapy for all forms of arthritis uses standard treatment of NSAID. The drugs are to be delivered to synchronize the circadian rhythms of the above diseases.

The present work exploits the use of polysaccha-

ride- guar gum in the preparation of Colon Specific Drug Delivery (CSDD) system of aceclofenac. The gum hydrates and swells forming viscous colloidal dispersions which retard the drug release from the tablet into the intestine. The *in vitro* release profile confirms that the vast micro flora and the enzymes present in the colon leads to the degradation of the polymer in the colon[3].

MATERIALS AND METHODS

Materials

Aceclofenac was obtained from M/s.Padmaja Pharmaceutical's, Vijayawada., Guar Gum from M/s. Romet labs Pvt.Ltd, Chennai. All other chemicals were of analytical grade.

Methods

Preparation of aceclofenac matrix tablets using guar gum[4]

Granules were prepared by wet granulation method (TABLE 1).

TABLE 1: Preparation of matrix tablets of aceclofenac and guargum

Ingredients	Quantity (mg) present in each tablet			
	GG_1	GG_2	GG_3	GG_4
Aceclofenac	100	100	100	100
Guar gum	180	220	260	300
Microcrystalline cellulose	50	50	50	50
Lactose	122	82	42	30
Starch paste	20	20	20	20

Evaluation of granules and tablets

Granules were evaluated for angle of repose and compressibility index. Prepared tablets were evaluated for weight variation, thickness, hardness, friability, and drug content followed by *in vitro* release studies. *In vitro* release studies of tablets in media of different pH

(a) Simulated gastric fluid (SGF) pH 0.1N HCl

Dissolution test was carried out as per USP XXI rotating basket method. 0.1M HCl was used as the dissolution medium (900ml), at 100 rpm, temperature maintained at $37^0 \pm 1^0$C. Samples of 5 ml were withdrawn at regular time intervals, filtered, diluted suitably and assayed spectrophotometrically at 275 nm (UV-1601 shimadzu).

(b)Preparation of rat cecal content medium (SCF)

The simulated colonic fluids were prepared using rat cecal content as described by sinha[12] et al. Wister rats weighing 150-200 gm and maintained on normal diet were used. To induce enzymes that specifically act on guar gum, the rats were treated with 1 ml of 1%w/v dispersion of guar gum for 7 days.

Forty-five minutes before the commencement of drug release studies seven rats were killed by spinal traction. The abdomen was opened, the ceacum were traced ligated at both the ends, were opened and their contents were individually weighed, pooled and suspended in the buffer (pH 7.4) continuously bubbled with CO_2 and made up to volume with phosphate buffer pH 7.4 to give 4% w/v solution of cecal content. All the above procedures were carried out under CO_2 in order to maintain anaerobic conditions as the ceacum were naturally anaerobic. Animal studies were approved by the institutional animal ethics committe.

(c) Simulated intestinal fluid (SIF)-pH 7.4 and simulated colonic fluid (SCF)-pH 7.4 with rat cecal contents

In SIF (phosphate buffer pH 7.4) the dissolution was carried for 8 hr (Sampling time-1, 2, 3, 4, 5, 6, 7, 8hrs) for GG_1, GG_2 and for GG_3, GG_4 the dissolution was carried out for 24hr (Sampling time-1,2,3,4,8,12, 16,20 and 24 hrs). Then the medium was replaced with 900ml phosphate buffer homogenized with rat cecal contents (SCF) and the dissolution was carried out for 24 hrs. 5 ml of sample was withdrawn at specified time intervals) and analyzed for aceclofenac at 275 nm. 5ml of fresh dissolution medium was replaced after each sample withdrawal.

RESULTS AND DISCUSSION

In vitro release study

1. Simulated gastric fluid (SGF) pH 0.1N HCl

In stomach-simulated condition, the GG_1 batch of tablets released maximum of 40.15% of aceclofenac at the end of 120 minutes which may be due to the less percentage of guar gum added (38%). The GG_2 batch released maximum of 13.43%. The GG_3 batch of tablets did not release the drug up to 90 minutes and 10.95%

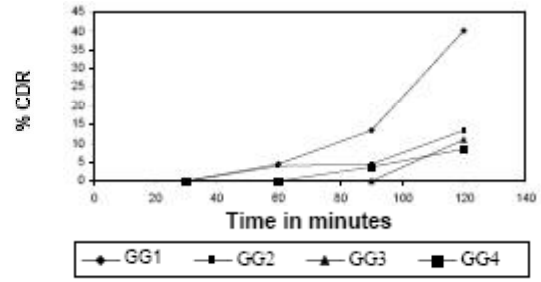

Figure 1: Dissolution profile of GG_1, GG_2, GG_3, and GG_4 tablets in 0.1 N HCL

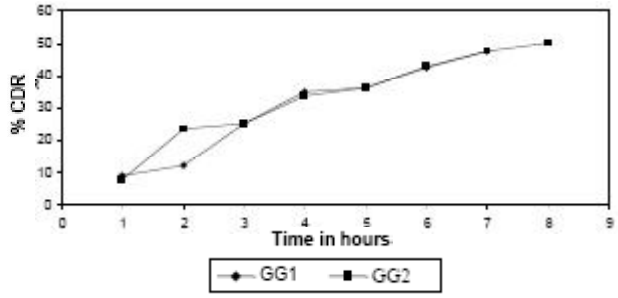

Figure 2: Dissolution profile of GG_1, GG_2, tablets in simulated intestinal fluid (SIF) control study

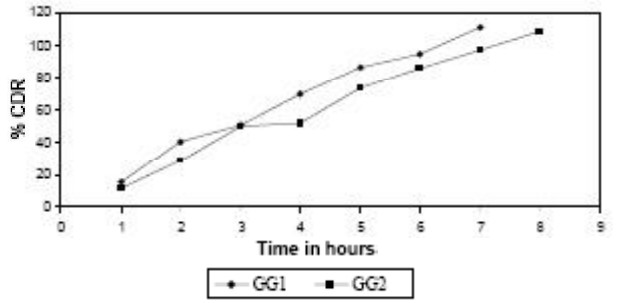

Figure 3: Dissolution profile of GG_1, GG_2 tablets in simulated colonic fluid with rat cecal content (SCF)

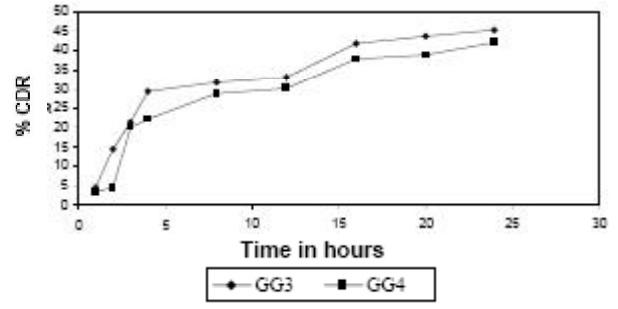

Figure 4: Dissolution profile of GG_3, GG_4 tablets in simulated intestinal fluid (SIF) control study

of the drug was released at the end of 120 minutes. The GG_4 batch of tablets released maximum of 8.46% of the drug at the end of the 120 minutes. From the above results it evident that as the percentage of guar gum

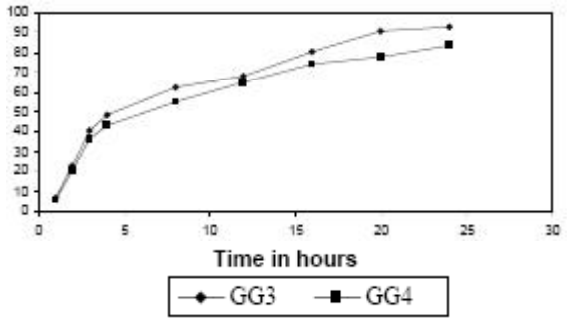

Figure 5: Dissolution profile of GG_3, GG_4 tablets in simulated colonic fluid with rat cecal content (SCF)

increased from the GG_1 to GG_4, the amount of the drug released was found to be less. This was due to the protective effect of guar gum, which swells to form a barrier to release the drug. The datas are represented in figure 1.

2. In simulated intestinal fluid (SIF) and simulated colonic fluid (SCF)

In SIF batch GG_1 showed 47.56% of drug release at the end of 7th h and the tablet remained intact but showed very loose gel like appearance. The cumulative percentage drug release for the batch GG1 in pH 7.4 buffer with rat cecal contents was 111.1%. The amount of drug released from GG_2 matrix tablet at the end of 8th h was found to be 50% (SIF) and 108.78% at the end of 8th h in pH 7.4 buffer with rat cecal contents. The datas are represented in figure 2 and 3.

The amount of drug released from the GG_3 tablets in the simulated intestinal fluid study was found to be 45.20% at the end of 24 h (SIF) and it was found that 92.25% of drug was released at the end of 24h in the SCF dissolution medium containing rat cecal contents. The GG_4 batch of tablets have released 42.13% at the end of 24th h in the stimulated intestinal fluid and it was found that 83.3% of drug was released from the GG_4 batch in the pH 7.4 buffer solution with rat cecal contents. The datas are represented in figures 4 and 5.

It was observed that a drug release of maximum 40.15% was found in 0.1 N HCL from GG_1 and minimum 10.95% and 8.46% from the GG3 and GG_4 batches respectively. It is evident from the data that GG_3 and GG_4 batches release small quantity of drug in the stomach media, so they can be considered as moderate formulae. The release of drug from GG_1, GG_2, GG_3 and GG_4 tablets in SIF, it was found that GG_1 and

GG_2 tablets which were containing 38% and 47% of guar gum could not protect the drug release in the stomach media and 50% of drug was released from both the batches at the end of the studies without rat cecal contents (SIF). The GG_3 and GG_4 batches released 45.20% and 42.13% of drug at the end of 24th hr respectively. The matrix tablets containing 55% and 64% of guar gum in the batches GG_3 and GG_4 were considered suitable for colon targeting but incomparison to the percentage of drug released in the presence of rat cecal matter, the GG_3 batch was releasing a maximum of 92.25% of the drug whereas the GG_4 batch released 83.3% of drug at the end of 24th h of the study.

CONCLUSION

This suggests that the amount of guar gum present in GG_3 batch was enough to retard the drug release in the upper G.I tract Amongst all the approaches used for colon targeting, a microbially controlled delivery system is the most appealing as it relies on a unique enzymatic ability of the colonic microflora and enables a more specific targeting independent of pH variation along the GI tract in the present work 55% of guar gum have been concluded as an optimised percentage in designing colon specific delivery of aceclofenac for the treatment of chronobiological symptoms of arthritis.

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