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Guar Gum Based Colon Targeted Drug Delivery System: *In-Vitro* Release Investigation

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ABSTRACT

A novel 5-Aminosalicylic acid matrix tablets was developed using guar gum for colon targeting coated with two different polymeric layers to protect the matrix tablets from gastrointestinal environment. The in-vitro drug release was conducted in 0.1N HCl for 2 hours indicated no change in the enteric coating. This showed that the enteric coating membrane prevented inner film coat from erosion or pore forming. The medium was replaced with phosphate buffer pH 6.8 for 3 hours and at the end of 3 hour, the enteric coating was dissolved. The test was continued for 7 hours by replacing the medium with phosphate buffer pH 7.4 containing 4% rat cecael content, the drug was released in the range of 57.8 to 68.38%, due to the microbial enzymatic activity and therefore site specificity of the dosage form consequently sustained the release of the drug over a period of 12 hours. Among the four formulated batches, batch I had retarded release of about 57.8% at 12th hours with that of other batches, hence batch I sustain the release up to 100% over 24 hours. The results showed that developed guar gum based formulation had a high potential for colonic drug delivery.

Keywords: Guar gum, 5-Aminosalicylic acid, colonic drug delivery, enzymatic activity.

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INTRODUCTION

The targeting and delivery of drugs to the colonic region of the gastrointestinal tract has been the focus of considerable research effort in recent years [1, 2, 3, 4]. Colonic drug delivery is intended for the local treatment of ulcerative colitis, irritable bowel syndrome and can potentially be used for colon cancer or the systemic administration of drugs that are adversely by the upper gastro-intestinal tract [3]. The advantages of local treatment in the colon have been described: reduced incidence of systemic side effects, administration of lower doses of drug, and maintenance of the drug in its intact form as close as possible to the target site. [5]. Drugs for which the colon is a potential absorption site [for example, peptides and proteins] can be delivered to this region for subsequent systemic absorption. The digestive enzymes of the gastrointestinal tract generally degrade these agents. However, these enzymes are present significantly in lower amounts in the colon compared with the upper portion of the gastrointestinal tract [6]. There has been considerable research into the design of colonic delivery systems and targeting has been achieved by several ways [7]. The primary approaches include prodrugs, pH-sensitive and time-dependent systems. Nevertheless, these parameters [pH, time] can vary from one individual to the next and also according to the pathological and dietary conditions. So these systems can lead to premature and non-specific drug delivery in the colon and they had limited success. Precise colon drug delivery requires that the triggering mechanisms in the delivery system only respond to the physiological conditions particular to the colon [3].

Several polysaccharides like, pectin and its salts, chondroitin sulphate, amylase and guar gum are being investigated as carriers for colon specific drug delivery. In pharmaceutical formulations, guar gum is used as a binder, disintegrant, suspending agent, thickening agent and stabilizing agent [8, 9]. Guar gum and pectin are reported to be potential carriers for colon specific drug delivery. Colon specific drug delivery systems for 5-ASA and mebendazole have been developed using guar gum as a carrier [10, 11]. The guar gum matrix tablets of albendazole were found degraded by colonic bacteria of rat caecal contents and released about 44% of albendazole in simulated colon fluids at the end of 24h indicating the susceptibility of the guar gum formulation to the rat caecal contents. Compression coated tablets of 5-ASA and matrix tablets of mebendazole have been prepared using guar gum as a carrier. Matrix tablets containing various proportions of guar gum were prepared by wet granulation technique using starch paste as a binder.

5-Amino Salicylic Acid [5-ASA] is an anti-inflammatory drug commonly used in the treatment of Crohn's disease and ulcerative colitis, which may provide protection against the development of colorectal cancer in patients suffering from inflammatory bowel disease [IBD] [12]. 5-ASA inhibits colonic mucosal sulfidopeptide leukotriene synthesis, which may contribute to GI anti-inflammatory activity. Mesalamine also may inhibit conversion of 12-hydroperoxyeicosateraenoic acid [12-HPTE] to 12-HETE and 5, 12-di-HETE, which appear to be chemotactic stimuli for polymorphonuclear leukocytes, and the drug has been shown to inhibit migration of leukocytes into inflamed tissue.

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With this information, it is planned to develop novel 5-ASA matrix tablets using guar gum for colon targeting followed by coating with two different polymeric layers to protect the matrix tablets from gastrointestinal environment.

MATERIALS

5-Aminosalicylic acid [5-ASA] was procured from S.D. Fine Chemicals, Guar gum [Loba Chemie Pvt Ltd.], Cellulose Acetate [Loba Chemie Pvt Ltd.], Starch [S.D. Fine Chemicals], PEG-400 [Qualigens], Eudragit L 100 [Fourts India Ltd], Magnesium Stearate [Burgoyne Burbidges and co.], Acetone [Chemspure], Methanol [Sisco Research Laboratory]

METHODS

PREPARATION OF 5-ASA MATRIX TABLETS

Matrix tablets of 5-ASA were prepared by wet granulation method. Magnesium stearate was added as lubricant. Guar gum was included in the formulation in various proportions [20-50%]. The compositions of the different formulations were given in Table 1.

Table 1: Composition of granule preparation

S.NO.	INGREDIENTS (MG/TABLET)	F1	F2	F3	F4
1	5-ASA	100	100	100	100
2	Guar Gum	100	80	60	40
3	Starch Solution (10%)	q.s.	q.s.	q.s.	q.s.
4	Magnesium Stearate	2	2	2	2

In all the granulation the ingredients were screened through sieve no 16, mixed and granulated using 10%w/v as starch paste. The wet mass was passed through a sieve no 16 and dried for 6 hours at 40°C. The dried granules were mixed with magnesium stearate and compressed the granules into tablet by instrumented tablet press using flat punches with 9.2mm diameter.

PREPARATION OF COATED TABLETS

PREPARATION OF INNER COATING [POLYSACCHARIDE] SOLUTION

The polysaccharide polymeric solution was prepared in four different concentrations of guar gum [0.2, 0.4, 0.6 and 0.8%] by dissolving in 2% of cellulose acetate polymeric solution, prepared by using acetone and methanol as solvents with 0.39% of PEG-400 as plasticizer. The Composition of inner [polysaccharide] coating of tablet was given in Table 2.

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Table 2: Composition of inner (polysaccharide) coating of tablet

S.NO.	INGREDIENTS	A	B	C	D
1	Cellulose Acetate (g)	2	2	2	2
2	Guar gum (g)	0.2	0.4	0.6	0.8
3	PEG-400	0.39	0.39	0.39	0.39
4	Acetone (ml)	80	80	80	80
5	M ethanol (ml)	20	20	20	20

COATING OF TABLETS [INNER COATING]

A batch size weighing 250g of tablets were coated in pan coater. The coating parameters were as follows:

1. Pan speed: 25 rpm
2. Inlet temperature: 40˚C
3. Bed temperature : 30˚C
4. Pressure of hot air blower: 50lb

The flow rate of coating solution was 6mg/ml and it was continued until a theoretical weight increase of 8% had been achieved. The tablets were dried after coating at the same temperature for 5 min.

PREPARATION OF OUTER COATING [ENTERIC] SOLUTION

The enteric coating polymeric solution was prepared by dissolving 50 g of Eudragit S 100 in 1000 ml of acetone. Triethyl citrate was used as plasticizer at a concentration of 2%.

COATING OF TABLETS [ENTERIC COATING]

A batch size weighing 250g of tablets were coated in pan coater. The coating parameters were same as that of inner coating. The flow rate of coating solution was 6mg/ml and it was continued until a theoretical weight increase of 4% had been achieved. The tablets were dried after coating at the same temperature for 5 min.

EVALUATION OF TABLETS

Both the coated and uncoated tablets were evaluated for their physical characteristics as per standard methods. The thickness, crushing strength, friability were measured using Vernier caliper, Pfizer Hardness tester and Roche Friabilator respectively.

DETERMINATION OF DRUG CONTENT IN TABLET FORMULATION

The tablets [50 mg] were finely powered, weighed and dissolved in phosphate buffer [pH 7.4], and mixed thoroughly. The volume was made up to 100 ml and filtered. 1 ml of filtrate solution was diluted to 10ml with phosphate buffer [pH 7.4], and analyzed at 332nm using a double beam UV Spectrophotometer.

IN-VITRO DRUG RELEASE STUDY

A] IN-VITRO RELEASE STUDY IN BUFFER MEDIUM

Drug release from enteric-coated 5-ASA tablet was carried out by USP 23 dissolution rate test apparatus. [Basket type, 50 rpm, 37°C]. The tablets were tested for their drug release for 2 h in 0.1N HCl [900 ml]. The dissolution medium was replaced with suitable buffer solution [pH 6.8 and 7.4]. The samples [5 ml] were collected at predetermined time points and replaced it to maintain the sink conditions. The samples were analyzed for 5-ASA content either at 303 nm [pH 1.2] or at 332nm [pH 6.8 and 7.4].

B] IN-VITRO RELEASE STUDY UNDER COLONIC CONDITION [RAT CECAEL MEDIUM]

1] PREPARATION OF RAT CECAEL CONTENT MEDIUM

The Albino rats weighing 150-200g were maintained on a normal diet [soaked gram]. 45 minutes before the commencement of drug release studies, the seven rats were killed by spinal traction. The abdomen was cut opened traced the cecae ligate at both the ends, dissected and immediately transferred into pH 6.8 buffer previously bubbled with CO_2. The cecael bags were opened, weighed their contents individually, pooled and suspended in the buffer continuously bubbled with CO_2. These were added to the dissolution media to give a final cecael dilution of 4% W/V. All the above procedures were carried out under CO_2 to maintain anaerobic conditions. [13, 14, 15].

2] DRUG RELEASE STUDIES IN PRESENCE OF CECAEL CONTENT

The drug release studies were conducted in cecael content medium using USP dissolution test apparatus with slight modification made in the procedure.

Medium of 850 ml of 0.1N HCl [pH 1.2] for 2 h, followed by 50 ml of 0.2 M trisodium phosphate [adjusted to pH 6.8] for 3 h. After which, cecael content equivalent to 8g was added to give a final ceceal dilution of 4%.

The dissolution was carried out in cecael content media upto 12h in phosphate buffer pH 7.4 medium. 5ml of samples were withdrawn at different time intervals, maintained under anaerobic conditions, and is replenished into the dissolution media. The samples were centrifuged and micro filtered before analyzing in UV spectrophotometer. [14].

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RESULTS AND DISCUSSION

The present study was aimed at developing novel matrix tablet of 5-ASA for colon targeting using guar gum as a matrixing agent. The prepared matrix tablets were evaluated and results were shown in the table 3.

Table 3: Evaluation of coated and uncoated matrix tablets

Evaluation of uncoated tablets	Parameters	Batch I	Batch II	Batch III	Batch IV
	Weight Variation (g)	0.253±1.84	0.257±2.41	0.249±2.67	0.259±2.21
	Tablet Thickness (mm)	3.08±0.024	3.15±0.28	3.06±0.041	3.09±0.012
	Tablet Hardness (kg/cm^2)	4.32±0.69	4.46±0.77	3.44±0.46	5.08±0.24
	Friability (%)	0.6377	0.4975	0.337	0.3419
	Drug Content (%)	92	96	94	98
Evaluation of Cellulose Acetate coated tablets (Inner Coating)	Weight Variation (g)	0.269±1.25	0.274±1.89	0.273±1.29	0.271±1.94
	Tablet Thickness (mm)	3.24±0.28	3.13±0.52	3.16±0.04	3.16±0.03
	Tablet Hardness (kg/cm^2)	6.96±0.46	6.48±0.899	5.64±0.34	7.08±0.54
	Drug Content (%)	93.4	95.1	94	96
Evaluation of Eudragit L-100 coated tablets	Weight Variation (g)	0.28±1.25	0.281±1.89	0.28±0.956	0.282±1.29
	Tablet Thickness (mm)	3.36±0.28	3.58±0.431	3.25±0.04	3.37±0.24
	Tablet Hardness (kg/cm^2)	7.56±0.48	7.28±0.28	6.3±037	7.4±0.387
	Drug Content (%)	93.5	94.7	99.2	97.3

The coated and uncoated tablets were subjected to in-vitro drug release study at different pH conditions. The in-vitro release of the uncoated tablets of various formulations F1 to F4, showed that F1 containing 50% of guar gum as matrixing agent, is hydrated more and forms a viscous gel layer that slows down the further entry of dissolution fluids than the other formulations. Hence F1 was chosen and coated with inner and outer coating materials and evaluated for further studies.

Eudragit L 100 was used as enteric polymer. This enteric polymer dissolves above pH 7, hence the result shown the lag period of 5h for all the formulations coated with Eudragit L 100 [Fig 1]. The results have shown enteric coating protects the tablets from acidic condition and lower pH medium. The lag time indicates that the formulation was protected from gastric and intestinal pH. Upon reaching pH 7 [the distal end of small intestine or proximal part of large intestine] enteric coating got dissolved to expose polysaccharide polymer coat that in turn degraded by colonic microflora, since there was no release in the buffer medium.

Because of the presence of the inner coating material made up of cellulose acetate and guar gum, retarded the release of the drug from the core tablet. The results of this study

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showed that increase in the concentration of the guar gum in the inner coating leads to fast erosion of guar gum thereby increased release of the drug into the dissolution medium.

The results of batch I showed 0.45% cumulative release of 5-ASA at the end of first hour in the colonic condition, and 57.86% cumulative release at the end of 12th hour. The amount of 5-ASA release from batch II tablets at the end of 12th hour was found to be 67.71%. On exposure to the dissolution fluids, the guar gum in the core tablet The study shows that the release of 5-ASA in the physiological environment of colon is due to the microbial degradation of the guar gum in the presence of rat ceacal content. The tablets containing 0.6g of guar gum [batch III] released 5-ASA only 63.83% at the end of 12th hour. Batch IV showed 68.38% drug release in the colonic medium at the end of 12th hour.

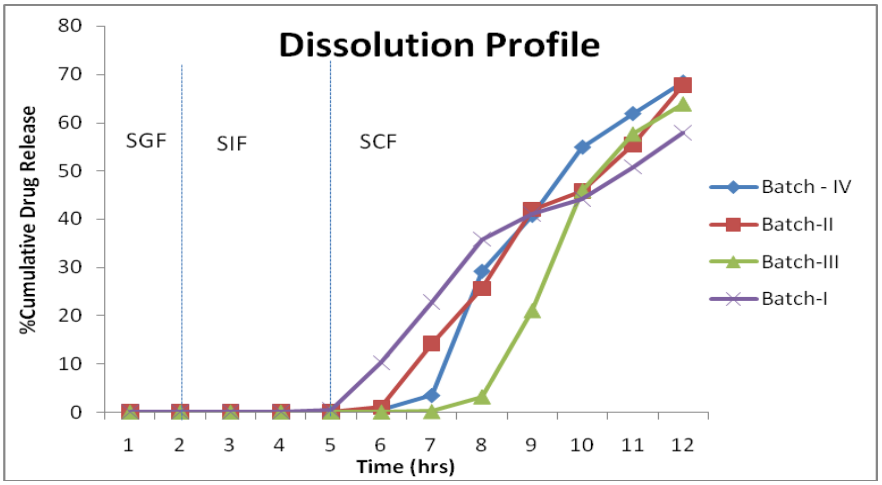

Figure 1: Dissolution profile of drug release from the colon targeted tablets containing various concentrations of guar gum.

The result indicates that the microbial enzymatic activity on polysaccharide polymer coat and guar gum in matrix tablets, improved the percentage of drug release at different time intervals. Even though there was an improvement in the percentage drug release with 4% W/V rat cecael matter, there was 40% of the drug still to be release from the dosage form.

Batch I showed the retardation in the release hence it is chosen for release kinetics study. Dissolution data of the batch I was fitted to various mathematical models [zero-order, first-order, Peppas, Hixon-Crowell and modified cube root] in order to describe the kinetics of drug release after 12th hour. The Residual sum of squares, Co-efficient of determination [R^2] and correlation co-efficient [r] were taken as criteria for choosing the appropriate model. Drug release from batch I fitted well into modified cube root equation [Table 4]. The reason for the fitting of the drug release to modified cube root is that the geometric shape of the dosage form remained intact and the drug release was erosion based means decrease in surface area and diameter of the particle with polymer erosion. This erosion is due to degradation guar gum in the inner coating polymer cellulose acetate lead to the formation pores and leach out the drug into surrounding medium. When guar gum in the inner coating film and the core tablet was

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fully degraded by the colonic microflora enzymes it would form channels through which the drug release could happen. This study confirmed that guar gum in the inner film coat was accessible to enzymatic attack; therefore its degradation was a rate-limiting factor.

Table 4: Fitting of drug release data of optimized formulation according to various mathematical models.

Model	Parameters used to assess the fit of model								
	Slope	Y-intercept	R^2	R	S(y)	F	df	Regression Sum of Squares	Residual Sum of Squares
Zero-order	5.4635	-12.5567	0.8851	0.9408	8.0056	84.7669	11	5432.6828	704.9864
First-order	0.1941	-0.3726	0.8015	0.8953	0.3929	44.4382	11	6.85839	1.6977
Peppas	-0.0256	-0.2847	0.0238	-0.1544	0.6676	0.2689	11	0.11981	4.9022
Hixon-Crowell	0.4113	-0.6513	0.8971	0.9471	0.5667	95.8573	11	30.7892	3.5332
Modified cube root	1.5005	-3.0628	0.9002	0.9488	2.0318	99.2568	11	409.7602	45.4111

CONCLUSION

The present study was carried out to develop a colon targeted drug delivery of 5-Amino salicylic acid based on the combined approach of a pH-dependent coating and a specifically biodegradable core matrix tablet.

In-vitro drug release from enteric coated 5-ASA tablets, tested in 0.1N HCl for 2 hours indicated no change in the enteric coating and the medium was replaced with phosphate buffer pH 6.8 for 3 hours and at the end of 3 hour, the enteric coating was dissolved. The test was continued, replacing the medium with phosphate buffer pH 7.4 for 7 hours, no release was found up to 7^{th} hour, as the polysaccharide polymeric coating can be degraded only by colonic microflora. Hence the release study was conducted using rat cecael content.

The in-vitro drug release under colonic condition was conducted in 0.1N HCl for 2 hours indicated no change in the enteric coating. This showed that the enteric coating membrane prevented inner film coat from erosion or pore forming. The medium was replaced with phosphate buffer pH 6.8 for 3 hours and at the end of 3 hour, the enteric coating was dissolved. The test was continued for 7 hours by replacing the medium with phosphate buffer pH 7.4 containing 4% rat cecael content, the drug was released in the range of 57.8 to 68.38%, due to the microbial enzymatic activity and therefore site specificity of the dosage form consequently sustained the release of the drug over a period of 12 hours.

Among the four formulated batches, batch I showed the retardation in the release of about 57.8% up to 12 hours when compared to that of other batches. Hence batch I is expected

to sustain the release up to 100% over 24 hours. The results showed that developed guar gum based formulation had a high potential for colonic drug delivery.

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