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Formulation and Evaluation of Colon Targeted Drug Delivery System

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ABSTRACT: Purpose: The objective of the present study was to develop colon targeted drug delivery system of Metronidazole using guar gum as the carrier. **Methods:** Matrix tablets containing various proportions of guar gum were prepared by direct compression technique. Rapidly disintegrating Metronidazole core tablets were prepared and compression coated with guar gum and 20% of microcrystalline cellulose. The tablets were evaluated for hardness, thickness, drug uniformity and subjected to in vitro drug release studies under conditions mimicking mouth to colon transit. **Results and Conclusions:** The FTIR study indicates no possible interaction between Metronidazole and carriers. The tablets were found within the permissible limits for various physiological parameters. In vitro drug release studies in pH 6.8 phosphate buffer solution containing rat cecal contents have demonstrated the susceptibility of guar gum to the colonic bacterial enzyme action with consequent drug release. The pretreatment of rats orally with 1 ml of 2% w/v aqueous dispersion of guar gum for 7 d induced enzyme specifically acting on guar gum thereby increasing drug release. Dissolution studies were performed in 0.1N HCl for 2 h, in pH 7.4 buffer for 3 h and pH 6.8 up to 24 h. The cumulative percentage of drug release of Metronidazole after 24 h in pH 6.8 phosphate buffers was found to be 98.51±0.02, 86.69±0.02, 84.55±0.04, 39.31±0.02, 24.60±0.02, 18.85±0.02 for formulation F1, F2, F3, F4, F5 and F6. It can be concluded that formulation F1 is considered a potential formulation for targeting the drug to the colon. The results showed that guar gum protects the drug from being release completely in the physiological environment of stomach and small intestine.

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INTRODUCTION

Colon drug delivery system refers to targeted delivery of drugs into the lower GI tract, which occurs primarily in the large intestine (i.e. colon). The site-specific delivery of drugs to lower parts of the GI tract is beneficial for localized management of several colonic diseases, mainly inflammatory bowel disease (Crohn's disease and ulcerative colitis), colon cancer and irritable bowel disease. Other possible applications of colonic delivery include chronotherapy, prophylaxis of colon cancer and treatment of nicotine addiction. It has also gained importance not just for the delivery of drugs for the treatment of local diseases but also potential site for the systemic delivery of therapeutic proteins and peptides which are being delivered by injections. These delivery systems when used orally, allow drugs to release the drug from the delivery system once the delivery system arrives into the colon [1]. These delayed mechanisms are designed to improve the efficacy of the drug by concentrating the drug molecules where they are needed mostly and also minimize the potential side effects and drug instability issues associated with premature release of drug in the upper parts of the GIT, namely stomach and small intestine [1].

Colon targeted drug delivery would ensures direct treatment at the disease site, low dosing and less side effects. Also, the colon can be used as a portal for the entry of drugs into the

systemic circulation. For example, molecules that are degraded or poorly absorbed in the upper gut, such as peptides and proteins, may be better absorbed from the more benign environment of the colon. Overall, there is less free fluid in the colon than in the small intestine and hence, dissolution could be difficult for poorly water soluble drugs. In such instances, the drug may require to be delivered in a pre-solubilized form, or delivery should be directed to the proximal colon, as a fluid gradient exists in the colon with more free water present in the proximal colon than in the distal colon. The stability of the drug in the colonic environment is an additional issue that warrants attention. The drug could bind in a nonspecific manner to dietary residues, intestinal secretions, mucus or general faecal matter, thereby reducing the concentration of free drug. Moreover, the resident microflora could also affect colonic performance via degradation of the drug [2]. The colon is reach in lymphoid tissue uptake of antigens into mast cells of the colonic mucosa produces rapid local production of antibodies and this helps in efficient vaccine delivery [3].

Metronidazole, the drug of choice for intestinal amoebiasis, has to be delivered to the colon for its effective action against *Entamoba histolytica*. Metronidazole is rapidly and completely absorbed after oral administration of conventional tablet dosage forms. The administration of this drug in conventional tablet dosage forms provide a minimal amount of Metronidazole for local action in the colon, still resulting in the relief of amoebiasis but with unwanted systemic side effects. In a pharmacokinetic evaluation of guar gum based colon targeted oral drug delivery system of Metronidazole in healthy volunteers, demonstrated that colon targeting of Metronidazole resulted in a slow absorption of the drug and increased its availability for local action in the colon. Therefore, colon-targeted delivery of Metronidazole could play a crucial role in providing effective and safe therapy for amoebiasis [4].

Various approaches have been proposed for targeted colon drug delivery, namely pH and time dependent systems, pressure-controlled release system, osmotic system, prodrugs and polysaccharide based delivery system. The pH approach has been shown to lack site-specificity because of inter/intra subject variation and the similarity of the pH between the small intestine and the colon. Timed-release systems depends on the relative consistency of the small intestinal transit time, but the high variability in gastric retention times makes prediction of the accurate location of drug release difficult. Prodrugs and polysaccharide-based delivery systems depend on the enzymatic degradation carried out by the inherent bacterial flora present in the colon, thereby resulting in drug release. The enzyme-trigger mechanism in such delivery system makes them highly site- specific. Prodrugs, however are considered as new chemical entities from a regulatory perspective which requires a detailed toxicological study to be performed, before being used as drug carriers. Natural polysaccharides, including chitosan, pectin, guar gum, xanthan gum, dextran and insulin remain undigested in the stomach and small intestine and are degraded by the huge numbers of anaerobic microflora in the colon [5,6].

Polysaccharides, the polymer of monosaccharide retains their integrity because they are resistant to the digestive action of gastrointestinal enzymes. The matrices of polysaccharides are assumed to remain intact in the physiological environment of stomach and small intestine but once they reach in the colon, they are acted upon by the bacterial polysaccharides and results in the degradation of the matrices. A large number of polysaccharides such as amylose, guar gum, pectin, chitosan, insulin, cyclodextrins, chondroitin sulphate, dextrans, dextrin and locust bean gum have been investigated for their use in colon targeted drug delivery. The most important fact in the development of polysaccharide derivatives for colon targeted drug delivery is the selection of suitable biodegradable polysaccharide. As these polysaccharides are usually soluble in water, they must be made water insoluble by cross linking or hydrophobic derivatisation. Very important are an optimal proportion of the hydrophobic and hydrophilic parts respectively and the number of free hydroxyl groups in the polymeric molecule [7,8].

MATERIALS AND METHODS

Materials

Metronidazole was obtained as a kind gift sample from J. B. Chemical and Pharmaceutical Ltd., Mumbai. Microcrstryalline cellulose, crosspovidone, magnesium stearate and guar gum were purchased from Loba Chemie Pvt. Ltd., Mumbai.

Methods

Preparation of compression coated tablets

Preparation of core tablets

All the materials were accurately weighed, mixed and passed through a mesh (250µm/sieve no. 60) to ensure complete mixing. The tablets were prepared by compressing the through mixed materials using 6mm round, flat and plain faced punches. The composition of the core tablets is given in **Table 1**.

Table 1: Formula for Metronidazole core tablet

Sr. No.	Ingredients	Quantity taken per tablet
1	Metronidazole	100 mg
2	Crosspovidone	6.25 mg
3	Microcrstryalline cellulose	15 mg
4	Talc	2.5 mg
5	Magnesium stearate	1.25 mg

Preparation of compression coated tablets

After passing the quality control tests of drug content uniformity, hardness, friability, disintegration and dissolution rate, core tablets were compression coated using different coat: core ratios (**Table 2**). Half the quantity of the coating

material was placed in a die cavity, the core tablet was then carefully positioned in the centre of the die cavity, the other half of the coat was added and tablets compressed using 8, 10 and 12mm round concave punches [9,10].

Table 2: Formula for core:coat concentration ratio

Formulation	Core:coat ratio	Coat weight	Guar gum	20% MCC	Total weight of tablet
F1	1:1	125 mg	100 mg	25 mg	250 mg
F2	1:1.4	175 mg	160 mg	35 mg	300 mg
F3	1:1.8	225 mg	180 mg	45 mg	350 mg
F4	1:2.2	275 mg	220 mg	55 mg	400 mg
F5	1:2.6	325 mg	260 mg	65 mg	450 mg
F6	1:3	375 mg	300 mg	75 mg	500 mg

Determination of drug content in tablet formulations

The Metronidazole core tablets were tested for their drug content. Ten tablets were finely powdered; 100 mg of the powder were accurately weighted and transferred to a 100 ml volumetric flask containing 50 ml of methanol and allowed to stand for 6 h with intermittent sonication to ensure complete solubility of drug. The solution were made up to volume and then filtered. After filtration, diluted suitably and estimated for Metronidazole content at 254 nm by using UV spectrophotometer and methanol as a blank [11].

Physical characterization of tablets

The tablets were characterized for weight variation, thickness and friability. The weight variation test was conducted as per specification. The crushing strength (Kg/cm^2) of prepared tablets of Metronidazole was determined by using Monsanto tablet hardness tester. Friability test of tablets was determined by Roche friabilator at 25 r/min for 4 min and content uniformity was determined by method as specified in Indian Pharmacopoeia [12,13]. The results of physical characterization of core and compression coated tablets were shown in table 3 and 4.

***In vitro* drug release studies**

Preparation of simulated colonic fluids

All experiments were conducted according to the institutional animal ethics committee and they were maintained at proper animal housing facility following standard ethical measures. Male albino rats weighing 150-200 g was maintained on a normal diet. It is reported earlier that rat cecal content medium at 4% w/v level is obtained after 7 d of enzymatic induction with 1 ml of 2% w/w guar gum dispersion gives the supreme environment for assessing the susceptibility of guar gum to colonic bacterial degradation. Hence, the rats were treated with guar gum dispersion for inducing the enzymes specifically acting on guar gum. The procedure involved oral treatment of rats with 1 ml of 2% w/v guar gum dispersion for 7 d [14,15].

Before the commencement of drug release study, six rats were euthanized using Methanol. The abdomen were opened, the caecai were traced, ligated at the both ends with thread, dissected and immediately transferred into pH 6.8 phosphate buffer solution (previously bubbled with carbon dioxide). The cecal bag were opened, their contents were individually weighed, pooled and then suspended in the phosphate buffer solution to give 4% w/v dilution. As the caecum is naturally anaerobic, all the operations were carried out under carbon dioxide. The care of the rats was in accordance with institutional guidelines [16].

***In vitro* drug release study in the absence of rat cecal contents**

The ability of matrix tablets of Metronidazole to release in the physiological environment of colon was assessed by continuing the drug release study in absence of rat cecal content medium were carried out using USP-23 dissolution rate test apparatus (Apparatus 1, 100 r/min, 37±0.5°C) in 900 ml 0.1N HCl for 2 h (average gastric emptying time is about 2 h). Then the dissolution medium was replaced with pH 7.4 phosphate buffer solution (900 ml) and dissolution was continued for 3 h (average small intestinal time is about 3 h) without rat cecal content in pH 6.8 phosphate buffer solution (control study) and the experiment was continued for another 24 h as the usual colonic transit time is 20-30 h. At different time intervals, 5.0 ml of sample was withdrawn and replaced with 5.0 ml of fresh phosphate buffer solution [17,18].

RESULTS AND DISCUSSION

A colon targeted drug delivery system should not only protect its load from being released in the physiological environment of the stomach and small intestine but also deliver its load to the colon. Conventional dissolution testing is less likely to accurately predict *in vivo* performance of colon delivery systems triggered by bacteria residing in the colon. Hence, release studies were performed in an alternate release medium called rat caecal content release medium. The ability of guar gum to retain the integrity of tablets in the physiological environment of stomach and small intestine was assessed by conducting drug release study in 0.1N HCl for 2 h and in pH 7.4 phosphate buffer for 3 h conditions mimicking mouth to colon transit [19].

The use of blend of polymers represents a potential way of achieving the required release properties. Mixtures of non ionic and ionic polymers have been used previously to give different viscosity efficiencies and provide delivery systems with modified drug release.

Hence, guar gum and microcrystalline cellulose in combination, in the form of compression coated tablets is

capable of protecting Metronidazole from being release in the upper region of GI system, i.e. stomach and small intestine [20,21].

Guar gum compression coated tablets prevent the drug from being released in the physiological environment of the stomach and small intestine. On exposure to the dissolution fluids, the gum gets hydrated and forms a viscous gel layer that slow down further seeping-in of dissolution fluids towards the core of the tablets. The hydration of guar gum seems not to be affected by the pH of the dissolution medium.

With the diffusion of medium into the polymer a hydrogel layer forms. When there is an enzyme in the environment, it breaks out the polymer chains and as a result dissolution of tablet increases with the increase of diffusion of dissolution medium.

The initial drug release may be credited to the dissolution of the drug present on the surface of the tablet and the lag time required for total hydration of guar gum to form viscous gel layer around the tablet [22,23].

The core tablets from the F1 to F6 formulations were subjected for weight variations, hardness, friability and drug content as shown in **Table 3**. All the tablets were within ± 5% deviation range and pass the weight variation test. The harness of the tablet was found in the range between 3.0±0.04 to 2.3±0.65 Kg/cm^2. The friability of the tablets was found within the desired range 0.3-0.6 and hence the tablets passed the friability test. The drug content of tablets was found to be in the range 98.55-99.52%. Hence, the tablets complied with the IP standards.

The tablets were compression coated using different core:coat ratio (**Table 4**). The hardness of the tablets was found to be in the range of 4.16±0.28 to 7.5±0.50 Kg/cm^2. All the tablets were within ± 5% deviation range and pass the weight variation test. The friability of the tablets was found within the desired range 0.34-0.74 and hence the tablets passed the friability test. The drug content of tablets was found to be in the range 98.67±0.30 – 101.1±0.61%. Hence, the tablets complied with the IP standards.

The compression coated formulation of F1 to F6 subjected to *in vitro* release in 0.1 N HCl, pH 7.4 and pH 6.8 in the presence and absence of rat cecal contents (**Table 5, 6, 7 and 8**).

Table 3: Physical properties of Metronidazole core tablets

Formulation	Hardness Kg/cm^2	Weight variation	Friability	Content uniformity (%)
F1	2.5±0.64	122±2.5 mg	0.39	99.17±0.20
F2	2.3±0.65	121±1.5 mg	0.43	99.52±0.32
F3	2.9±0.09	120±3.5 mg	0.31	98.73±0.20
F4	3.0±0.04	122±2.0 mg	0.42	99.22±0.12
F5	2.8±0.03	122±1.0 mg	0.45	98.55±0.15
F6	2.9±0.06	123±2.5 mg	0.55	99.32±0.16

N = 3, Values are expressed in Mean ± SD

Table 4: Physical properties of Metronidazole coated tablets

Tablet Formulation	Hardness Kg/cm^2	Weight variation	Thickness	Friability	Content Uniformity (%)
F1	5.5±0.28	251±3.5 mg	3.20 ±0.26	0.34	99.65±0.39
F2	7.5±0.50	302±2.2mg	4.26 ±0.15	0.42	99.52±0.57
F3	5.5±0.50	352±1.5 mg	5.23 ±0.05	0.47	100.4±0.41
F4	4.5±0.50	403±2.5 mg	5.26±0.05	0.63	99.57±0.15
F5	4.33±0.28	453±2.3 mg	5.13±0.05	0.69	98.67±0.30
F6	4.16±0.28	501±3.3 mg	4.26±0.05	0.74	101.1±0.61

N = 3, Values are expressed in Mean ± SD

Table 5: % of Metronidazole release from matrix formulation in 0.1 N HCl for 2 h and pH 7.4 Phosphate buffer for 3 h without rat cecal content medium (Control)

Sr. No.	Tablet Formulation	In 0.1 N HCl for 2 h	In pH 7.4 for 3 h
1	F1	1.14±0.01	7.17±0.03
2	F2	1.64±0.01	7.51±0.01
3	F3	1.04±0.03	4.26±0.01
4	F4	0.51±0.02	3.82±0.01
5	F5	0.50±0.02	1.74±0.01
6	F6	0.83±0.02	3.10±0.01

N = 3, Values are expressed in Mean ± SD ($p \leq 0.0001$)

Table 6: % of Metronidazole release from matrix formulation in pH 6.8 Phosphate buffer for 24 h without rat cecal content medium (Control)

Sr. No.	Time (h)	F1	F2	F3	F4	F5	F6
1	3	9.08±0.01	8.41±0.03	7.25±0.02	4.93±0.02	2.26±0.02	2.46±0.03
2	6	12.76±0.01	12.05±0.03	11.73±0.01	6.68±0.03	4.19±0.01	3.12±0.02
3	8	26.77±0.01	13.32±0.02	14.49±0.02	8.71±0.01	5.73±0.02	4.07±0.03
4	10	28.22±0.01	16.23±0.02	16.38±0.02	10.09±0.01	7.06±0.03	5.21±0.02
5	20	52.61±0.01	32.35±0.02	29.47±0.02	19.94±0.02	14.57±0.02	11.12±0.04
6	22	63.84±0.01	35.15±0.01	32.57±0.02	22.08±0.02	16.26±0.03	11.93±0.03
7	24	70.47±0.01	39.13±0.02	34.52±0.01	26.59±0.02	19.83±0.01	13.51±0.02

N = 3, Values are expressed in Mean ± SD ($p \leq 0.0001$)

Table 7: % of Metronidazole release from matrix formulation in 0.1 N HCl for 2 h and pH 7.4 Phosphate buffer for 3 h with rat cecal content medium (Test)

Sr. No.	Formulation	In 0.1 N HCl for 2 h	In pH 7.4 for 3 h
1	F1	1.11±0.01	7.19±0.02
2	F2	1.56±0.02	7.51±0.01
3	F3	0.95±0.04	4.23±0.02
4	F4	0.54±0.02	3.89±0.01
5	F5	0.46±0.01	3.50±0.01
6	F6	0.84±0.01	3.16±0.03

N = 3, Values are expressed in Mean ± SD ($p \leq 0.0001$)

Table 8: % of Metronidazole released from matrix formulation in pH 6.8 Phosphate buffer for 24 h with rat cecal content medium (Test)

Sr. No.	Time (h)	F1	F2	F3	F4	F5	F6
1	3	22.40±0.01	19.50±0.02	16.35±0.02	6.76±0.02	4.94±0.02	2.72±0.02
2	6	28.22±0.01	23.61±0.02	21.25±0.02	7.17±0.02	7.93±0.02	5.20±0.02
3	8	36.29±0.01	34.25±0.02	31.93±0.03	15.75±0.02	8.73±0.02	6.06±o.02
4	10	43.17±0.05	51.14±0.03	49.57±0.01	21.64±0.02	9.45±0.02	8.05±0.03
5	20	89.58±0.01	76.03±0.02	73.96±0.03	36.47±0.01	15.92±0.01	14.58±0.02
6	22	91.50±0.01	80.42±0.02	79.35±0.03	37.17±0.02	18.67±0.01	15.24±0.02
7	24	98.51±0.02	86.69±0.02	84.55±0.04	39.31±0.02	24.60±0.02	18.85±0.02

N = 3, Values are expressed in Mean ± SD ($p \leq 0.0001$)

The matrix tablets of Metronidazole containing various proportion of guar gum and 20% microcystalline cellulose were prepared and subjected to *in vitro* release study showed that the percentage of Metronidazole release from F1 at the end of 24 h was found to be 98.51% in presence of 4% w/v rat cecal content. The matrix tablets when subjected to *in vitro* dissolution study in absence of rat cecal contents, the percentage of drug release was found to be 70.47%.

The percentage of Metronidazole release from F2 at the end of 24 h was found to be 39.12 % in presence of 4% w/v rat cecal content. When the matrix tablets from F2 formulation subjects to *in vitro* study in absence of rat cecal contents, it was found to be 86.69%. When the *in vitro* study were carried out in the presence of rat cecal content medium, the cumulative percent release of Metronidazole from F3 at the end of 24 h was found to be 84.55%. The matrix tablets from F3 subjected to control *in vitro* study in absence of rat cecal contents at the end of 24 h were found to 34.51.

The cumulative percent release of Metronidazole from F4 at the end of 24 h in presence of rat cecal contents was found to be 39.31%, whereas in control, it was found to be 26.59%. The cumulative percent release of Metronidazole from F5 at the end of 24 h was found to be 24.60% in presence of 4% w/v rat cecal content, whereas in the control, it was found to be 19.83%. At the end of 24 h of dissolution studies in presence of rat cecal content, the cumulative percent release of Metronidazole from F6 was found to be 18.83%,whereas in the control i.e. in absence of rat cecal content it was found to be 13.48%.

Statistical analysis was performed using student t – test (paired) as only two parameters i.e. drug release of control and test formulations were compared with each other. Statistical analysis performed by using student t- test (non parametric Test) in GraphPad Prism software version 6.04. Percentage of drug release form matrix formulation F1 to F6 was statistically significant ($p \leq 0.0001$) which indicates a significant difference between the control and test formulation.

CONCLUSION

The present study was carried out to develop colon targeted drug delivery system for Metronidazole using effective binder system of guar gum and microcrystaline cellulose. The compression coated tablets of Metronidazole were shows the ability to protect the tablet core from drug release premature in the physiological environment of stomach and small intestine and subjected to dissolution studies.

From the *in vitro* study conducted in 0.1 N HCl, pH7.4 and pH 6.8 in presence and absence of rat cecal contents, it was concluded that the matrix formulation F1 released almost entire quantity of drug at the end of 24 h dissolution study. Significant difference was observed in the amount of drug release at the end of 24 h with rat cecal content medium when compared with the dissolution study without rat cecal contents. The results showed that, formulation F1 may be acted upon by colonic bacteria within 5-6 h of entering the colon and release most of the drug in the colon.

As the concentration of the guar gum increases in formulation F2 to F6, it forms a stiff gel resulting in decrease drug release from the matrix tablet. Hence, form the results it can be concluded that, formulation F1 is considered potential formulation for targeting the drug release to the colon, which is the specific site of drug delivery system.

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DATA AVAILABILITY

Not declared

ETHICS STATEMENT

The authors have taken all the necessary permissions as per ethical guidelines wherever applicable. The authors will be

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CONFLICTS OF INTEREST

The authors have no known conflict of interest concerning the present article.

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AUTHORS' CONTRIBUTION

All the authors were contributed for manuscript preparation, conducting of the experiments, data collection, interpretation and analysis of the result.

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