

RESEARCH ARTICLE

PHARMACEUTICS

FORMULATION AND EVALUATION OF COLON TARGETED ORAL DRUG DELIVERY SYSTEMS FOR METRONIDAZOLE IN TREATMENT OF AMOEBIASIS

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ABSTRACT

The aim of study is to develop colon targeted system for metronidazole using guar gum and xanthan gum. Matrix formulations containing various proportions of guar gum and xanthan gum were prepared by wet granulation technique. Later on, multilayer tablets were prepared by using 50 mg and 100 mg of guar gum as release controlling layer on either side of (M5) matrix tablets of metronidazole. The *in-vitro* drug release study was undertaken at 37±0.5°C in 0.1N HCl for 2 h; followed by pH 7.4 phosphate buffer (3h) finally in, simulated colonic fluid pH 6.8 phosphate buffer containing 4%w/v rat ceacal content for 15 h. Results indicated that guar gum was alone failed to control drug release. M5 (GG: XG, 0:100) formulation seemed to quiet promising for colonic drug delivery wherease, other matrices released 12-33% of metronidazole in physiological environment of GIT. When studies were continued in colonic fluids, matrix tablets released almost 100% drug. whereas, multilayer formulations did not release drug in stomach and small intestine, but delivered drug to the colon resulting in slow absorption of the drug and making drug available for local action in the colon.

KEYWORDS

colon-specific tablet, Guar gum, Xanthan gum, matrix tablet, multi-layer tablet

INTRODUCTION

Amoebiasis is an infection of the large intestine caused by *Entamoeba histolytica*, a single celled protozoan parasite. The current estimate shows that *Entamoeba histolytica* causes the 34-50 million symptomatic infections each year and leads to the death of 40-100,000 people which make amoebiasis second only to malaria as a cause of death resulting from protozoan parasite. The trophozoites of *Entamoeba histolytica* can invade the colonic epithelium, causing amoebic colitis¹.

Metronidazole and Ornidazole are the preferred drugs used in treatment of the amoebiasis, giardiasis, trichomoniasis and anaerobic infections. These drugs are to be delivered to the colon for their effective action against trophozoites of *E. histolytica* and *Giardia lamblia* wherein the respective trophozoites reside in lumen of the caecum and large intestine and adhere to colonic mucus and epithelial layers. But pharmacokinetics profile of metronidazole indicates that drug is completely absorbed in approximately 1 h after a single dose of 500 mg. The administration of this drug in conventional tablet dosage form provides a minimal amount of metronidazole for local action in the colon, still resulting in the relief of amoebiasis, but with unwanted systemic side effects².

Various approaches are employed for targeting orally administered drugs to the colon include coating with pH-dependent polymers, design of the timed release dosage forms and the utilization of carriers that are degraded exclusively by colonic bacteria³. The pH-dependent systems are designed to release the drug at particular pH of gastrointestinal tract (GIT), was very well established. The timed

release systems release their load after a pre-determined time period of administration. The time dependent formulation is designed to resist the release of the drug in the stomach with an additional non-disintegrating or lag phase included in the formulation and the release of the drug takes place in the colon. An example of such system is Pulsincap®⁴. Another limitation of time dependent release systems is variation in the gastric emptying time and small intestine transit time. But, due to the use of enteric coating over most of these systems, the large variation in gastric emptying is overcome by most of these systems⁵. However, there is still likely to be a considerable variability in the *in-vivo* performance of the timed-release systems by virtue of the variation in small intestinal transit time⁶⁻⁷.

A variety of metabolic reactions like hydrolysis, reduction, decarboxylation, dealkylation etc. are carried out by the anaerobic bacteria residing in the colon. Colon specific drug delivery system is developed on the basis of metabolic reactions includes prodrugs which are cleaved by colonic bacterial enzymes and releasing the actual drug in the colon⁸. The best alternative approach for colon specific drug delivery is the use of the carriers that are degraded exclusively by colonic bacteria. The micro-flora of the colon is in the range of 10^{11} - 10^{12} CFU/ml consisting mainly of anaerobic bacteria e.g. Bacteroides, Bifidobacteria, Eubacteria, Clostridia, Enterococci, Enterobacteria and Ruminococcus etc. Because of the presence of the biodegradable enzymes only in the colon, the use of the biodegradable polymers for colon specific drug delivery seems to be more site-

specific approach as compared to the other approaches. These polymers shield the drug from the environments of stomach and small intestine and are able to deliver the drug to the colon. On reaching the colon, they undergo degradation by enzyme or breakdown of the polymer back bone leading to a subsequent reduction in their molecular weight and their by loss of mechanical strength⁹.

The present investigation is aimed at using naturally occurring and abundantly available polysaccharides for colon targeted drug delivery. Attempt has been made to formulate a dosage form that

1. retards drug release in the tracts of upper GIT
2. consist of biodegradable polysaccharides as main constituents
3. is degradable by a wider range of microbial species
4. shows a rapid drug release in the tract of colon due to presence of degradable polysaccharides in the tablet, and additionally
5. could be formulated using usual tablet techniques¹⁰.

Working on this rationale, matrices were proposed for the above purpose. A drug release retarding ingredient belonging to polysaccharides, i.e., guar gum and xanthan gum were selected for the study.

Guar gum alone has earlier been used in colon specific drug delivery system as matrix forming material and as a compression coat. Xanthan gum is known to have a greater drug release-retarding property and synergistically enhanced gel properties is presence of glactomannan gums such as guars¹¹. So, a combination of these gums was proposed for achieving these objectives. A mixture of these gums was evaluated for its drug release- retarding properties under simulated gastrointestinal condition^{6, 8, 12-13}. Guar gum (GG) is natural non-ionic polysaccharides derived from seeds

of the *Cyamopsis tetragonolobus* (family *leguminaciae*). It consists of linear chains of (1→4)-β-D-mannopyranosyl units with α-D-galactopyranosyl units attached by (1→6) linkage. Cross linked guar-gum has been used as a drug carrier in matrix tablets. Overall, guar-gum is suitable for preparation of colon specific formulations and is suitable as a carrier for drug that are not soluble in water¹³. Xanthan gum is a high molecular weight polysaccharides gum is produced by pure culture anaerobic fermentation with gram negative bacterium, *Xanthomonas compestris*. It contains D-glucose and D-mannose as a dominant hexose unit, along with D-glucuronic acid. It is used in oral and topical pharmaceutical formulations as a suspending, stabilizing, thickening and emulsifying agents¹⁴.

The present paper describes the development and *in-vitro* evaluation of colon targeted drug delivery systems of metronidazole using guar gum and xanthan gum as a matrixing agent. Matrix tablets and multilayer tablets were prepared by using different ratio of guar gum and xanthan gum. *In-vitro* drug release studies were carried out on metronidazole matrix and multilayer tablets in simulated gastrointestinal (GI) fluids in the presence and absence of rat ceecal contents.

MATERIALS AND METHODS

(i) *Materials*

Metronidazole IP was obtained from M/s J. B Chemical & Pharmaceutical Ltd, Mumbai. Microcrystalline Cellulose (Avicel™ PH-102), Starch Paste was procured from CDH Company, New Delhi. Guar gum and Xanthan gum were procured from S D Fine Chemical Ltd, Mumbai. Magnesium stearate and Talc was also incorporated in tablets as glidant and lubricant was of S D Fine Chemical Ltd, Mumbai. Other excipients used to prepare tablets were of

standard pharmaceutical grade and all chemical reagents used were of analytical grade.

(ii) Preparation of Metronidazole matrix tablets:

Matrix tablets of metronidazole were prepared by wet granulation technique using 10% starch paste

as binder. Microcrystalline cellulose used as diluent and mixture of talc-magnesium stearate (2:1) were used as a lubricant. Guar gum and xanthan gum were included in the formulation in various proportions. The composition of different formulations used in the study containing 100 mg of metronidazole in each case is shown in table 1.

Table 1
Composition of Metronidazole matrix tablets containing various ratios of guar gum and Xanthan gum (total weight = 300 mg)

Ingredients	Quantity (mg) present per matrix tablet				
	M-1	M-2	M-3	M-4	M-5
Metronidazole	100	100	100	100	100
Guar Gum	100	65	55	35	0
Xanthan Gum	0	35	45	65	100
Microcrystalline cellulose	61	61	61	61	61
Starch	30	30	30	30	30
Talc	6	6	6	6	6
Magnesium Sterate	3	3	3	3	3
Total (in mg)	300	300	300	300	300

In all the formulations, guar gum and xanthan gum was sieved (<250 μ m) and mixed with metronidazole (<150 μ m) and microcrystalline cellulose (<250 μ m). The powder was blended and granulated with 10% starch paste. The wet mass was passed through a mesh (1680 μ m) and the granules were dried at 50°C for 2h in hot air oven. The dried granules passed through a mesh (1190 μ m) and these granules were lubricated with a mixture of talc-magnesium stearate (2:1). The lubricated granules were compressed at a compression force of 4500-5500 kg using 9.0 mm size round, flat and plain punches on a single station tableting machine (M/s Cadmuch Machinery, India). The matrix tablets were tested for their hardness, drug content and drug release characteristics with a suitable number of tablets for each test¹⁵.

(iii) Preparation of Multilayer Tablets:

Multilayer tablets of Metronidazole were prepared by using 50 mg and 100 mg of guar gum as release controlling layer on either side of (M5) guar gum matrix tablet formulation of metronidazole. Tablets of matrix formulation (M5) prepared as described above containing GG: XG, 0:100 mg was compressed with either side of 50 mg or 100 mg of guar gum granules as release controlling layer on both sides. The composition of multilayer tablet G1 and G2 is given in table 2 and was compressed with a maximum force of compressing (4500-5500 kg) using 9.0 mm size round, flat and plain punches on a single station tableting machine (M/s Cadmuch Machinery, India) to obtain multilayer tablets¹⁵.

Table 2
Composition of Metronidazole multilayer tablets

Ingredients	Quantity (mg) present each multilayer tablet	
	G1	G2
Guar gum for bottom layer	50	100
GG and XG Matrix tablet (M-5)	300	300
Guar gum for top layer	50	100
Total (in mg)	400	500

(iv) Determination of drug content in tablet formulations:

The metronidazole matrix tablets and multilayer 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 filtered. After filtration, diluted suitably and estimated for metronidazole content at 254 nm by using UV-VIS spectrophotometer and methanol as a blank ¹⁶.

(v) Physical characteristics of fabricated tablets:

The weight variation test was conducted as per specifications. 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 rpm for 4 minutes with 6 tablets dropping from height of 6 inches with each revolution ¹⁵⁻¹⁶.

(vi) In-Vitro Drug Release Studies:

(A) Preparation of simulated colonic fluids:

Male albino rats weighing 105-115 gm was maintained on a normal diet (Bengal gram purchased in local market and soaked in water, 25gm/rat). It is reported earlier that rat ceecal content medium at 4% w/v level is obtained after

7 days of enzymatic induction with 1 ml of 2% w/w guar gum dispersion provides the best conditions 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 days. Thirty minutes before the commencement of drug release studies of six rats were euthanized, using carbon dioxide asphyxiation. 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 saline (previously bubbled with carbon dioxide). The ceecal bag were opened, their contents were individually weighed, pooled and then suspended in the phosphate buffer saline 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 ^{13, 17-18}.

(B) In-Vitro Drug Release studies:

The ability of matrix and multilayer tablets of metronidazole to release in the physiological environment of colon was assessed by continuing the Drug release studies in presence of rat ceecal content medium.were carried out using USP-23 dissolution rate test apparatus ¹⁹ (Apparatus 1, 100 rpm, $37 \pm 0.5^\circ\text{C}$) in 900ml 0.1N HCl for 2h (average gastric emptying time is about 2 h). Then the dissolution medium was replaced with pH 7.4 phosphate buffer saline

(900 ml) and dissolution was continued for 3h (average small intestinal time is about 3 h). The ability of matrix and multilayer tablets of metronidazole to release in the physiological environment of colon was assessed by continuing the drug release studies in the presence of rat ceecal content medium. Drug release studies were also conducted on compression coated matrix and multilayer tablets after completing *in-vitro* dissolution study in 0.1N HCL (2h) and pH 7.4 phosphate buffer (3h) without rat ceecal content in pH6.8 phosphate buffer saline (control study)

The drug release studies were carried out using USP-23 dissolution rate test apparatus (Apparatus 1, 100 rpm, $37\pm 0.5^{\circ}\text{C}$) with slight modifications. A beaker (capacity 150 ml) containing 100 ml of rat ceecal content medium was immersed in the water bath of the 1000 ml vessel, which in turn, was in the water bath of the apparatus. The swollen formulations after completing the dissolution study in 0.1N HCL (2h) and pH 7.4 phosphate buffer saline (PBS) (3h) were placed in the baskets of the apparatus and immersed in rat ceecal content medium. As the caecum is naturally anaerobic, the experiment was carried out with continuous carbon dioxide supply into the beakers. At different time intervals, 5.0 ml of sample was withdrawn and replaced with 5.0 ml of fresh phosphate buffer saline bubbled with carbon dioxide and the experiment was continued for another 15 h as the usual colonic transit time is 20-30 h. This 5.0 ml sample was further diluted with respective medium, filtered and analyzed for metronidazole by UV-VIS Spectrophotometer at 278 nm, 300 nm and 320nm for 0.1N HCL, pH 7.4 PBS and pH 6.4 PBS respectively.

RESULTS AND DISCUSSION

The present study aimed at developing colon targeted formulations of metronidazole using guar gum as matrixing agent. It was reported earlier that guar gum could be used as a carrier for colon specific drug delivery in the form of either a matrix tablet or as a multilayer compression over the core tablet. Guar gum matrix tablets released about 21% of drug (Indomethcin) in the physiological environment of stomach and small intestine, but released the majority of its drug content in the physiological environment of colon¹³. However, the release of such a small percentage of drugs from the surface of matrix tablets in the physiological environment of stomach and small intestine is a serious consideration for drugs showing the deleterious effects on stomach and small intestine (e.g. anticancer drugs in treatment of colon cancer). In such a situation, it was suggested to apply a layer of guar gum over these matrix tablets¹⁷. Hence, attempts were made to minimize drug loss under conditions mimicking mouth to colonic transit and to ensure maximum drug release in the colon by applying guar gum and xanthan gum as a matrixing agents in different proportions.

(i) Matrix tablet of Metronidazole
Since guar gum and xanthan gum has been found to have poor flow properties and is to be incorporated in the matrix tablets in larger proportions, metronidazole tablets were prepared by wet granulation technique using starch paste as a binder. The matrix tablets were prepared by applying maximum force of compression and evaluated for various quality control parameters as shown in table 3. All formulations were complying with IP specifications¹⁶.

Table 3
Physiochemical Characteristics of metronidazole colon specific matrix tablets

#	Matrix code	formulation	Average variation \pm sd	weight	Hardness (Kg/cm ²)	Friability	% drug content uniformity (w/w) \pm sd
1	M-1		301 mg \pm 2.5		5.5 \pm 0.144	0.0306	99.1 \pm 0.0521
2	M-2		305 mg \pm 3.5		5.7 \pm 0.115	0.052	98.6 \pm 0.0341
3	M-3		298 mg \pm 3.5		5.8 \pm 0.158	0.043	99.7 \pm 0.0567
4	M-4		298 mg \pm 4.5		6.1 \pm 0.166	0.052	101.6 \pm 0.0768
5	M-5		302 mg \pm 2.2		6.3 \pm 0.156	0.048	101.4 \pm 0.0435

The matrix tablets were subjected to *in-vitro* drug release studies in 0.1N HCL (2h), pH 7.4 phosphate buffer saline (3h) and simulated colonic fluids (rat ceecal content medium at 4% w/v level, 15h), metronidazole tablets remained intact and swollen at the end of 5h of dissolution study in the physiological environment of stomach and small intestine due to presence of water insoluble diluents such as microcrystalline cellulose. The cumulative percentage drug release versus time profile (figure-1, table-4) of prepared matrices showed that the presence of xanthan gum in the tablet retards the drug i.e., as the amount of xanthan gum in tablet get increased of drug, release from tablets is decreased. In M-5 (GG:XG, 0:100) tablets drug release were highly retarded and only 12.3 \pm 3.9% drug was released in first 5 h of dissolution (the usual upper GIT transit time) as against 33.9 \pm 3.5% drug release observed in case of M-1 (GG:XG, 100:0). In both cases, studies were further performed for 15h in pH 6.8 PBS without the rat ceecal content medium (control). Considering that the usual colonic transit time varies between 20-25h, M-5 released about 79.4 \pm 4.0% of drug and M-1 released about 89.8 \pm 4.0%. Studies were further performed in pH 6.8 PBS with the rat ceecal content medium (test). As M-1 formulation degraded into 2-3 pieces, released 100.2 \pm 4.1% of its drug with in

15 h while M-5 maintain its integrity and released drug 98.76 \pm 3.7% over a period of time. In order to increase degradable portion (making the formulation highly sensitive to arrival into the colon) of the tablet and thereby reduce the portion of non-degradable polysaccharides i.e., XG in the formulation, various combinations of GG and XG were tried for formulation of optimum dosage form, which would show the minimal drug release in the upper GIT and still consist of high percentage of microbially degradable polysaccharides. So, M-2, M-3 and M-4 were formulated. Drug release studies showed that M-2 (GG:XG, 65:35) released 22.8 \pm 2.1% of drug during first 5 h as compared to M-3 (GG:XG, 55:45) which released only 18.8 \pm 1.7% of drug.

From the above results, it can be inferred that guar gum alone failed to control drug release in the physiological environment of stomach and small intestine and the presence of xanthan gum in tablets retards drug release to a much higher as compared to guar gum. The M-5 (GG:XG, 0:100) formulation seems quiet promising for colonic drug delivery. So, it was planned to control the release of metronidazole by applying different amount of guar gum as a release controlling layer over the metronidazole matrix formulations (M-5) (GG:XG, 0:100).

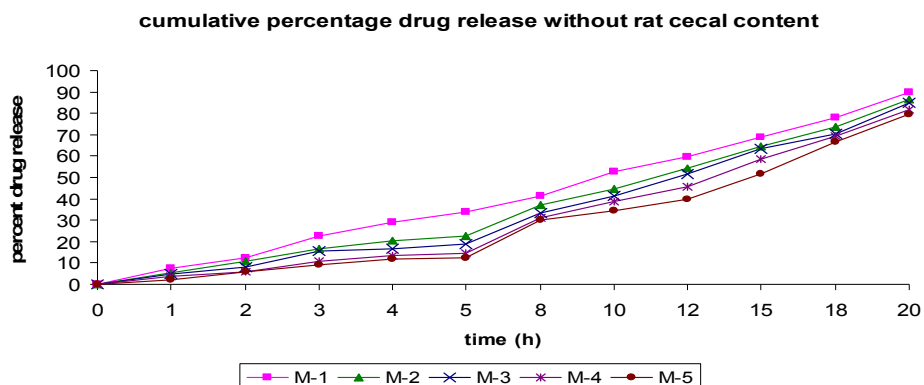


Figure-1
cumulative percentage release from matrix tablets without rat ceecal content medium.

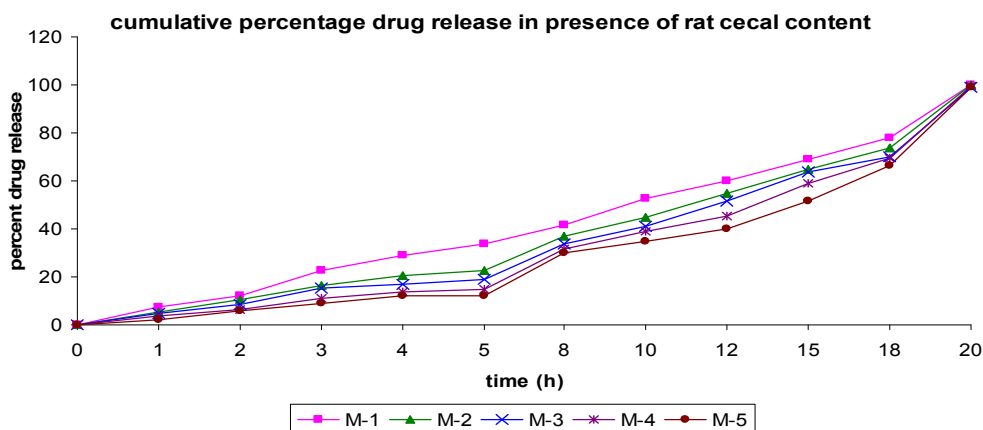


Figure-2
cumulative percentage release from matrix tablets with rat ceecal content medium.

Table 4
Percentage of Metronidazole released from matrix formulation in 0.1 N HCl (2h); pH 7.4 Phosphate buffer (3h) and pH 6.8 PBS (15 h) without rat ceecal content medium (control) and pH 6.8 PBS(15h) with 4%w/v rat ceecal content medium (test)

#	Matrix formulation code	Ratios of Gum	Percentage of Metronidazole released			
			After 2h in 0.1 N HCl	After 5 h in pH 7.4 PBS	After 20 h in pH 6.8 PBS (from initial time)	Control
		GG: XG			Control	Test
1	M-1	100:0	12.2±2.5	33.9±3.5	89.8±4.0	100.2±4.1
2	M-2	65:35	10.6±1.2	22.8±2.1	86.8±1.3	99.87±4.2
3	M-3	55:45	8.3±3.1	18.8±1.7	84.6±4.0	98.96±3.3
4	M-4	35:65	6.1±1.9	14.5±2.8	81.8±3.7	99.56±3.9
5	M-5	0:100	5.8±2.8	12.3±3.9	79.4±4.0	98.76±3.7

(ii) Multilayer tablets of Metronidazole

Multilayer tablets of metronidazole were prepared to control drug release in physiological environment of stomach and small intestine i.e., up to 5 h of dissolution study. Multilayer tablets were prepared by compressing a layer of granules containing either 50 mg or 100 mg of guar gum on either side of metronidazole of

matrix tablet (M-5) (GG:XG, 0:100). The hardness of Multilayer tablet of metronidazole was found to be 6.5-7.0 kg/cm² and metronidazole present in multilayer tablets were ranges from 99.7-101% indicating uniformity of drug content as shown in table-5.

Table 5
Physiochemical Characteristics of Metronidazole multilayer tablets

#	Formulation Code	Average variation \pm sd	weight	Hardness (kg/cm ²)	Friability	% drug content uniformity (w/w \pm sd)
1	G1	398mg \pm 2.3		6.8 \pm 0.114	0.0049	99.7 \pm 0.0341 %
2	G2	501mg \pm 3.3		6.7 \pm 0.163	0.0052	99.1 \pm 0.0568 %

Metronidazole multilayer tablets containing 50 mg (G1) or 100 mg (G2) of guar gum as a release controlling layer retained their physical integrity up to 20 h of the dissolution study conducted without rat ceecal content medium (control), in the dissolution medium. In this first 5h of dissolution study, multilayer tablet of Metronidazole (G1) released about 11 \pm 2.9% of

Metronidazole whereas, (G2) formulations released only 9.0 \pm 1.4% of drug indicating that G2 formulations could effectively control the drug release in the physiological environment of stomach and small intestine. The percentage of metronidazole released from the multilayer tablet of metronidazole with and without rat ceecal content medium is shown in figure-3.

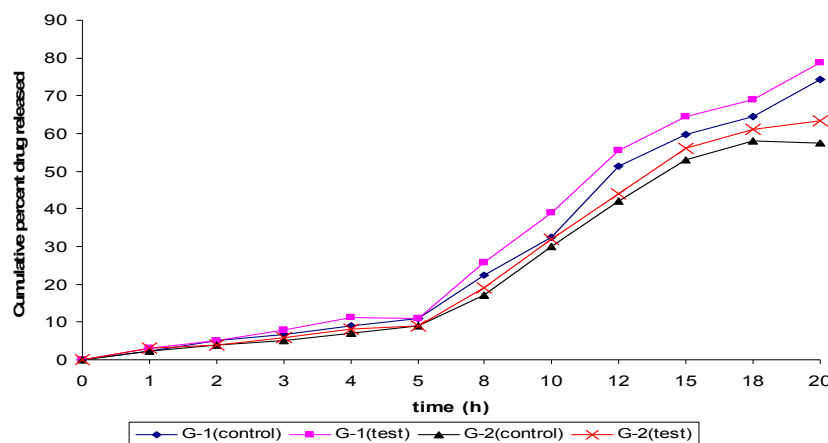


Figure-3

Cumulative percentage release of multilayer tablets with and without rat ceecal content medium

Table 6

Percentage of Metronidazole released from multilayer formulation in 0.1 N HCl (2h); pH 7.4 Phosphate buffer (3h) and pH 6.8 PBS (15 h) without rat cecal content medium (control) and pH 6.8 PBS (15h) with 4%w/v rat cecal content medium (test)

#	Matrix code	formulation	Cumulative Percentage of Metronidazole released			
			After 2h in 0.1 N HCl	After 5 h in pH 7.4 PBS	After 20 h in pH 6.8 PBS	Control Test
1	G1		5.1±1.9	11.0±2.9	74.2±3.7	78.8±3.9
2	G2		3.9±2.1	9.0±1.4	57.6±4.6	63.5±3.7

At the end of 20 h, the percent of metronidazole released from G1 in rat ceacal content medium, was found to be 78.8±3.9% whereas, in control study too, the formulations released were 74.2±3.9%. However, G2 formulation released 63.5±3.7% of metronidazole in rat ceacal content medium, whereas in control study 57.6±4.6% of drug at the end of 20 h was observed. Thus, guar gum in the form of the multilayer over the metronidazole matrix tablet were capable of protecting the drug being released in physiological environment of stomach and small intestine.

CONCLUSION

The present investigation was carried out to develop colon targeted drug delivery system for metronidazole using guar gum and xanthan gum as carrier for an effective of safe therapy of amoebiasis. Matrix tablet of metronidazole containing various proportions of guar gum and xanthan gum were prepared and subjected to *in-vitro* drug release studies. The prepared matrices (GG:XG, 0:100, 65:35, 55:45) M-1, M-2, M-3 form enzyme controlled drug delivery system. M-1 formulation is not suitable for colon targeting as they degraded into 2-3 pieces at the end of dissolution study. M-5 is most promising

for colonic drug delivery. Finally *in-vitro* dissolution studies of multilayer tablet of metronidazole, G1 and G2 formulations shows that G2 formulation is most likely to provide targeted drug delivery of metronidazole to the colon.

However, in certain diseased conditions of the GIT, with a disturbed micro-flora, these can provide a drug delivery to the colon since these additionally from time controlled release system and shall provide a sustained drug delivery to the colon. Under the normal GIT conditions, with a normal microflora they are designed to release the majority of drug in the tracts of the ascending colon e.g., in local pathologies.

The presence of xanthan gum in tablets not only retards initial drug release in upper GIT, but also increases susceptibility of the matrices to microflora, as higher swelling increase surface area available for action of enzymes. So, the matrices prepared using the usual tableting techniques is highly site-specific and proves ideal for delivery of such insoluble molecules to the colon. However, the further studies are planned to assess the utility of these colon targeted drug delivery system of metronidazole in patients suffering from amoebiasis.

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