WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 7.523
Volume 6, Issue 8, 2242-2256. Research Article ISSN 2277– 7105

PREPARATION AND EVALUATION OF METRONIDAZOLE MATRIX TABLETS FOR COLON TARGETING

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Article Received on
18 June 2017,
Revised on 09 July 2017,
Accepted on 30 July 2017
DOI: 10.20959/wjpr20178-9122

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ABSTRACT

Targeting of drugs to the colon by the oral route could be achieved by different approaches including matrix and coated systems. The method by which the drug release will be triggered by the colonic flora appears to be more interesting with regard to the selectivity. Metronidazole is only one antibiotic used in colonic diseases.[13] Matrix tablets of Metronidazole were prepared by wet granulation method. Xanthan gum, guar gum, and HPMC K100M were used as a carrier, starch was used as diluents and the mixture of talc and magnesium stearate was used as lubricant. Formulations (F1 to F4) contain drug and polymers (xanthan gum, guar gum) ratio in 1:1. Formulations (F5 to F7, F8) contain drug and polymers ratio in 1:1.5, 1:2. Formulations (F9, F10) contain guar gum and HPMC K100M. All the prepared formulations were evaluated and subjected to *in vitro* drug release studies. The amount of metronidazole released from the tablets at different time intervals was estimated by UV spectrophotometer. Metronidazole tablets prepared by using xanthan gum, guar gum as polymers were subjected to dissolution studies. The tablets showed the 100% drug release in less than 5 hours. Formulations (F1 to F4) were subjected to dissolution studies they showed 30% - 60% of drug release in pH 1.2. Formulations (F5 to F7) were able to retard drug release in pH 1.2. Where as they showed 30-40% drug release in pH 6.8 phosphate buffer. Guar gum combination with HPMC K100M (F9, F10) formulations retarded the drug release more than that of guar gum and xanthan gum combination in pH 1.2. The tablets containing guar gum with HPMC K100M (F9 -1.5:0.5) were optimized, showed good lag time of 4 hrs and released 16.87% drug at 4th hr.

KEYWORDS: Colon Targeted, Guar Gum, Xanthan Gum, HPMC K100M, Metronidazole, Matrix Tablets.

INTRODUCTION

Targeted drug delivery into the colon is highly desirable for local treatment of a variety of bowel diseases such as ulcerative colitis, Crohn's disease, amoebiasis, colonic cancer, local treatment of colonic pathologies, and systemic delivery of protein and peptide drugs.[1,2] The colon specific drug delivery system should be capable of protecting the drug en route to the colon i.e. drug release and absorption should not occur in the stomach, the duodenum, as well as the small intestine, and neither the bioactive agent should be degraded in either of the dissolution sites but only released and absorbed once the system reaches the colon.[3]

In recent years, the targeting of drugs to the colon via the oral route could be achieved by different approaches including different formulation systems, for which the drug release is controlled by different pH conditions, transit time and intestinal micro flora. Colon is an ideal site for both systemic and local delivery of drugs. But oral conventional dosage forms basically dissolved in the stomach and gastro intestinal tract (GIT) and also absorption takes place from these regions depend upon the physico-chemical properties of the drug.

Specific targeting of drugs to the colon is recognized to have several therapeutic advantages. Drugs, which are destroyed by the stomach acid and / or metabolized by pancreatic enzymes, are slightly affected in the colon, and sustained colonic release of drugs can be useful in the treatment of nocturnal asthma, angina and arthritis.[4] A local means of drug delivery could allow topical treatment of infectious diseases like amoebiasis and inflammatory bowel disease e.g. ulcerative colitis or crohn's disease.

Metronidazole is an antibiotic and anti protozoal drug and used to treat a variety of infections. It is primarily used to treat bacterial vaginosis and oral infection and infections caused by susceptible anaerobic bacteria. It is also often used to eradicate helicobacter pylori along with other drugs and to prevent infection in people recovery from surgery[5] whereby high colon concentration can be achieved while minimizing side effects that occur because of release of drugs in the upper GIT or unnecessary systemic absorption. The aim of present study is target colon by avoiding systemic absorption in stomach and small intestine.

MATERIALS AND METHODS

Metronidazole was obtained as a gift sample from Aurobindo Pharma Ltd, Hyderabad. Xanthan gum, Guar gum and HPMC K100M were obtained from Alpha Med. Starch, talc and magnesium stearate were obtained from SD fine chem Ltd.

Preparation of metronidazole matrix tablets

The Metronidazole tablets were prepared by manual wet granulation method. The required quantities of the drug, polymer and excipients (Xanthan gum, Guar gum, HPMC K100M[6], and Starch as main filler) were accurately weighed and all the ingredients were screened through sieve no.40, except lubricant all the ingredients were transferred into a mortar, thoroughly blended in a glass mortar with pestle for 15 min and granulated by adding little quantities of starch paste. These prepared damp mass were passed through the mesh no 18 and the granules obtained were dried in a hot air oven at 50^{o}C for 30 minutes. After drying the granules was again passed into sieve no. 18, the fine, almost uniform granules was obtained. Other manufacturing excipients such as talc 2% and magnesium stearate 1% were also added and thoroughly mixed. This ideal lubricated granulation mixture was compressed with 8 mm flat faced punches into tablets weighing 350mg containing 100mg Metronidazole drug by using rotary tablet compress machine. The different batches of Metronidazole compressed tablets were collected and stored in air tight containers.

RESULTS

Table. 1: Formula for the preparation of Metronidazole matrix tablets.

Formulation Code	Drug (MTZ) (mg)	Xanthan gum (mg)	Guar gum (mg)	HPMC K100M (mg)	Starch (diluent) (mg)	Starch paste (mg)	Talc (mg)	Mg. stearate (mg)
XG	100	100	-	-	104.5	35	7	3.5
GG	100	-	100	-	104.5	35	7	3.5
F1	100	60	40	-	104.5	35	7	3.5
F2	100	40	60	-	104.5	35	7	3.5
F3	100	80	20	-	104.5	35	7	3.5
F4	100	20	80	-	104.5	35	7	3.5
F5	100	75	75	-	54.5	35	7	3.5
F6	100	50	100	-	54.5	35	7	3.5
F7	100	100	50	-	54.5	35	7	3.5
F8	100	100	100	-	22	17.5	7	3.5
F9	100	-	150	50	22	17.5	7	3.5
F10	100	-	100	100	22	17.5	7	3.5

Identification of materials by functional group analysis using FTIR spectroscopy

FT-IR spectra of Metronidazole, Guar gum, HPMC K100M, Optimized formula are shown in Figure 1, 2, 3, 4, 5.

Identification of Metronidazole: The peaks observed for H-C-H stretching (Alkane) at 2947.03 cm^{-1}, O-H bending at1076.21 cm^{-1}, C-N bending 1157.21 cm^{-1}, C=C (alkene) stretching 1801.38 cm^{-1},C=N stretching at 1531.37 cm^{-1}, -NO_2 aromatic at 1389.37 cm^{-1} CH_3 bending at 1289.07.

Identification of Guar gum: The peaks observed for O-H stretching at 3406.8, C-C 1652 cm^{-1} stretching, C-O-C stretching at 1220.8 cm^{-1}.

Identification of HPMC K100M: The peaks observed for C-C stretching at 1489.88cm^{-1}, C-O-C stretching at 1089.54 cm^{-1}, O-H stretching at 3600 cm^{-1}, CH_2 at 1489.94 cm^{-1}, CH_3 at 1375.58 cm^{-1}.

Identification of Optimized formula (Metronidazole + Guar gum + HPMC K100M):

The peaks observed for C-N bending at 1383.91 cm^{-1}, C=C (alkene) stretching at 1383.91 cm^{-1}, O-H stretching at 3219.84 cm^{-1}, H-C-H at744.68 cm^{-1}, C-O-C stretching at 1075.10 cm^{-1}. The characteristic peak C-N, C=C, O-H, H-C-H, C-O-C confirms the presence of Metronidazole, Guar gum, HPMC K100M as given in Indian Pharmacopeia. By observing the peaks of drug, Guar gum, and HPMC K100M confirms that there is no interaction between the drug, guar gum, HPMC K100M.

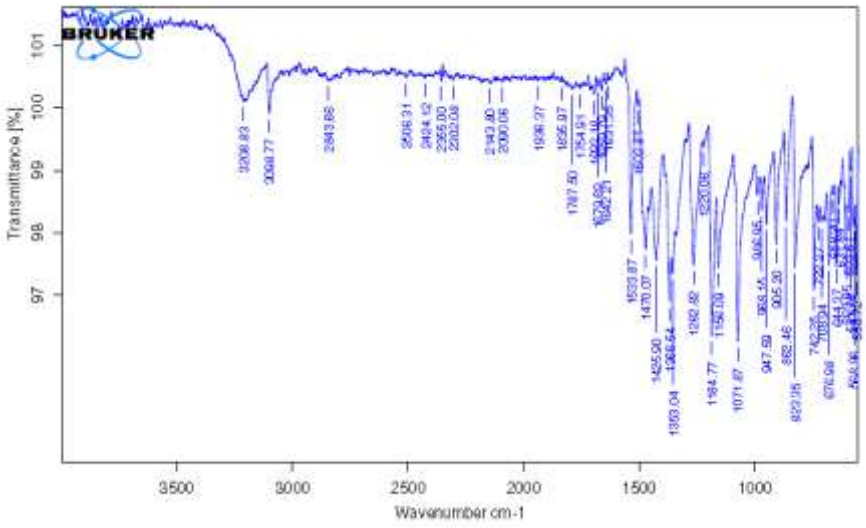

Figure. 1: FTIR spectra of pure drug Metronidazole.

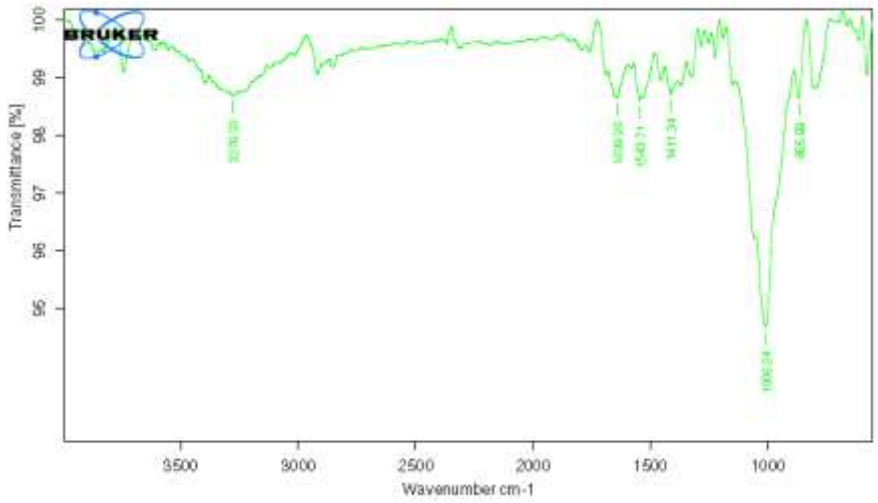

Figure. 2: FTIR spectra of guar gum.

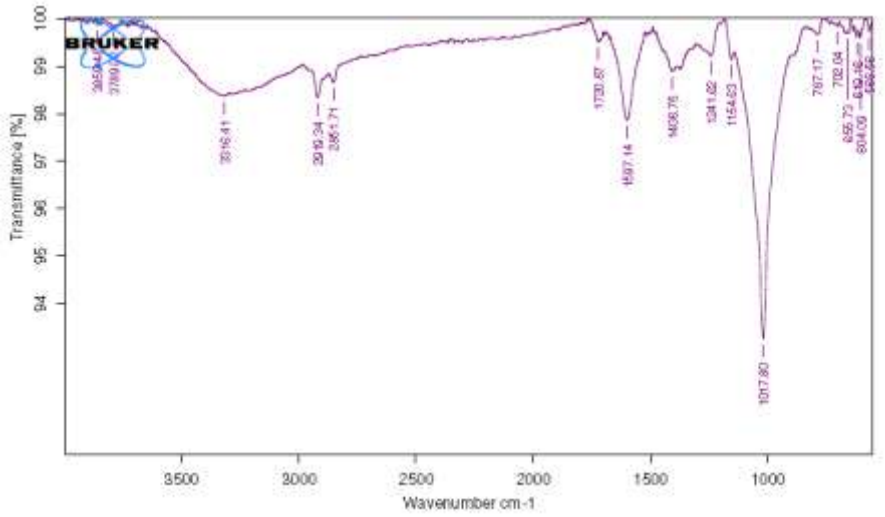

Figure. 3: FTIR spectrum of the Xanthan gum.

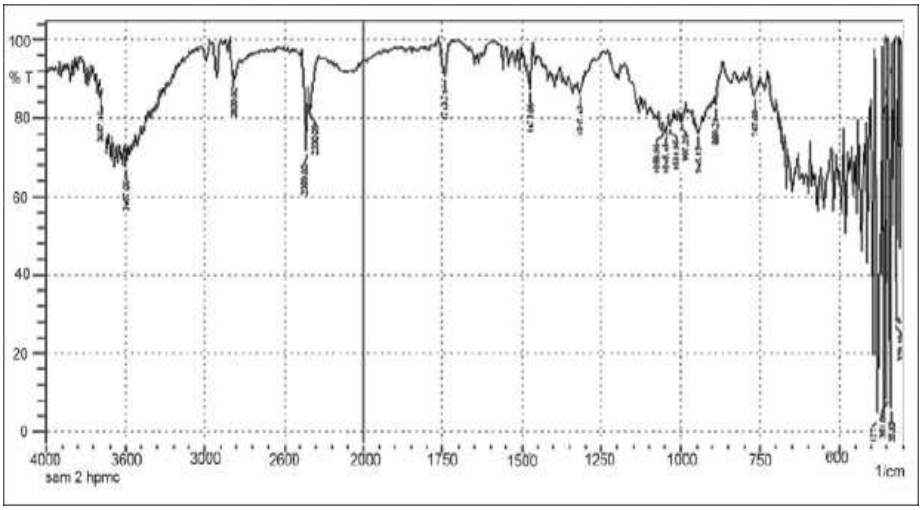

Figure. 4: FTIR spectra of HPMC K100M.

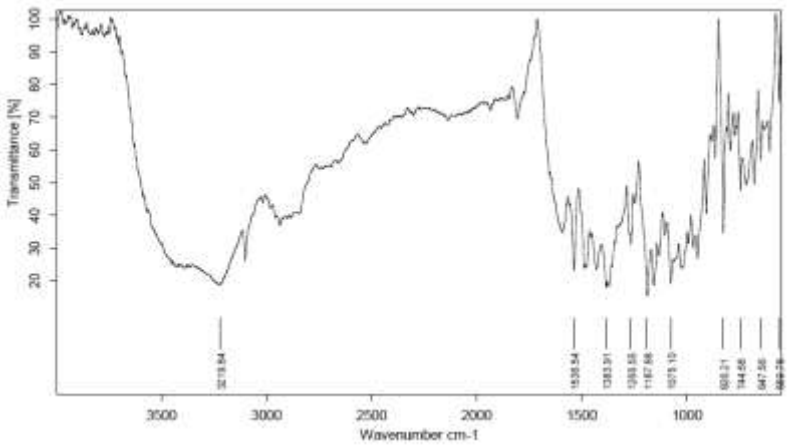

Figure. 5: FTIR spectra of Optimized formulation.

EVALUATION OF METRONIDAZOLE MATRIX TABLETS

The flow properties formulated granules were evaluated for quality parameters like Bulk density, Angle of repose, Tapped density, Compressibility Index, Hausner's ratio, weight variation, and friability.

Assay: Ten tablets were finely powdered; quantities of the powder equivalent to 50 mg of Metronidazole were accurately weighed, transferred to a 100 ml volumetric flask containing 50 ml of pH 7.4 phosphate buffer and allowed to stand for hour with intermittent sonication to ensure complete solubility of the drug. The mixture was made up to volume with pH 7.4 phosphate buffer. The solution was suitably diluted and the absorption was determined by UV-visible spectrophotometer at 277 nm. The drug concentration was calculated from the calibration curve.

***In vitro* drug release studies:** The Metronidazole matrix tablets were evaluated for its *in vitro* dissolution study. The *in vitro* drug release was studied by use of paddle apparatus (USP type II apparatus). In this studies, slight modifications with addition of another pH medium, based on different transit time present from stomach to colon, were carried out with different pH conditions similar to in vitro conditions (pH 1.2 for 2 hrs, pH 6.8 for 2hrs and pH 7.4 for 8 hrs) were maintained for the entire study. 900 ml of 0.1 N HCl was taken in a vessel, formulation was kept in basket after the media attained the temperature of 37 ± 0.5^{o}C. The basket rpm was maintained at 100. 5 ml of sample was withdrawn from the dissolution media at specific time intervals and replaced with a particular medium. After 2 hrs, the 0.1 N HCl was discarded and replaced with 6.8 phosphate buffer and it was maintained for 2 hrs after that pH 7.4 phosphate buffer was used for remaining 8 hrs.

Dissolution results of Metronidazole matrix tablets

The XG[7], GG[8,9] tablets were subjected to dissolution in 0.1 N HCl (pH 1.2), SIF (pH 6.8) and SIF (pH 7.4) shown in Table 2 and Figure 6. The tablets showed high drug release in 0.1 N HCl (pH 1.2) and SIF (pH 6.8) and showed 100% drug release in less than 5 hours.

Table. 2: Cumulative percent drug release of Metronidazole tablets in Simulated gastric fluid (pH 1.2) and simulated intestinal fluid (pH 6.8).

pH	Time(hr)	Cumulative % Drug Release (XG)	Cumulative % (GG)Drug Release
1.2	1	49.6 ±1.25	44.53 ± 1.21
	2	82.48 ± 1.5	74.77 ± 1.02
6.8	3	94.84 ± 0.95	87.08 ± 1.32
	4	106 ± 1.42	100.08 ± 0.97

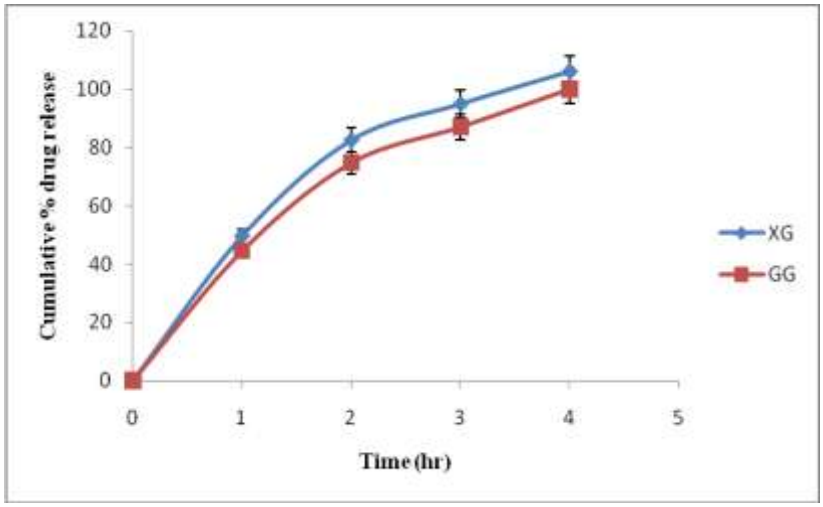

Figure. 6: Percent drug relese of Metronidazole matrix tablets (XG,GG).

Table. 3: Cumulative percent drug release of metronidazole matrix tablets (F1 – F4).

pH	Time (hr)	F1	F2	F3	F4
1.2	1	36 ± 0.828	16.90 ± 0.598	12.72 ± 72	15.08 ± 0.85
	2	59.4 ± 1.03	44.35 ± 0.476	34.7 ± 0.87	37.44 ± 0.97
6.8	3	67.93 ± 1.605	51.11 ± 1.089	40.6 ± 0.76	44.58 ± 0.78
	4	75.61 ± 0.88	57.33 ± 1.469	46.1 ± 1.31	51.8 ± 1.46
7.4	5	77.87 ± 0.79	59.79 ± 1.199	48.26 ±0.77	54.28 ± 1.18
	6	80.87 ± 1.22	64.45 ± 1.388	51.9 ± 1.18	58.16 ± 0.81
	7	90.78 ± 0.87	71.94 ± 1.427	57.92 ±0.92	64.37 ± 1.48
	8	98.24 ± 0.61	84.92 ± 0.988	68.48 ±1.19	74.93 ± 1.0

Data represents mean ± SD, n = 3

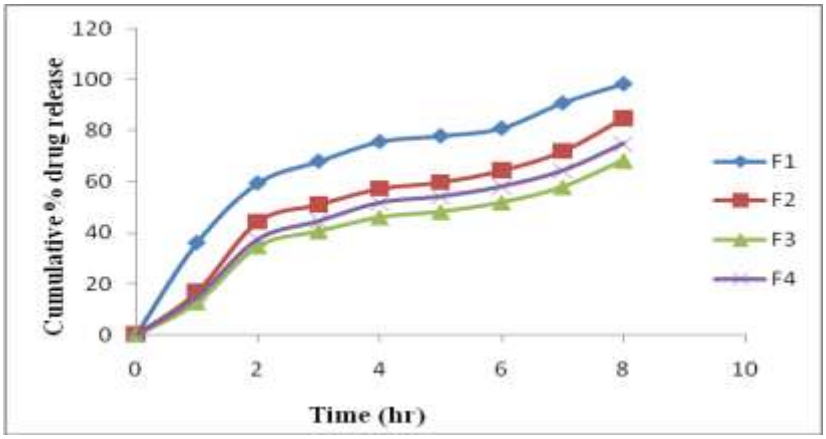

Figure. 7: Cumulative percent drug release of metronidazole matrix tablets (F1 – F4).

From the figure 7, it was observed that the formulations (F1 to F4) had drug release between 30% - 60% in 0.1 N HCl (pH 1.2). And so are not suitable for colon targeting.

Table. 4: Cumulative percent drug release of metronidazole matrix tablets (F5 – F8).

pH	Time	F5	F6	F7	F8
1.2	1	11.45 ± 1.2	4.99 ± 0.93	4.43 ± 0.43	3.87 ± 0.66
	2	24.84 ± 0.69	14.34 ± 1.7	14.27 ± 0.54	13.45 ± 1.01
6.8	3	29.91 ± 1.11	19.79 ± 0.98	20.61 ± 0.9	19.39 ± 0.93
	4	37.24 ± 1.87	27.21 ± 0.69	27.59 ± 0.91	27.29 ± 0.68
7.4	5	44.79 ± 1.49	31.36 ± 1.4	31.36 ± 0.92	32.05 ± 0.77
	6	54.31 ±1.72	37.57 ± 0.91	36.87 ± 1.23	37.82 ± 1.18
	7	70.9 ± 1.5	44.09 ± 1.5	43.06 ± 0.57	46.86 ± 1.3
	8	88.02 ± 0.94	51.64 ± 1.65	52.88 ± 0.83	56.98 ± 1.48
	9	102.5 ± 1.14	65.24 ± 1.24	66.98 ± 0.784	69.18 ± 0.867
	10	_	80.84 ± 1.01	82.46 ± 1.25	84.53 ± 1.25
	11	_	98.29 ± 0.942	99.96 ± 1.54	101.1 ± 1.36
	12	_	_	_	_

Data represents mean ± SD, n = 3.

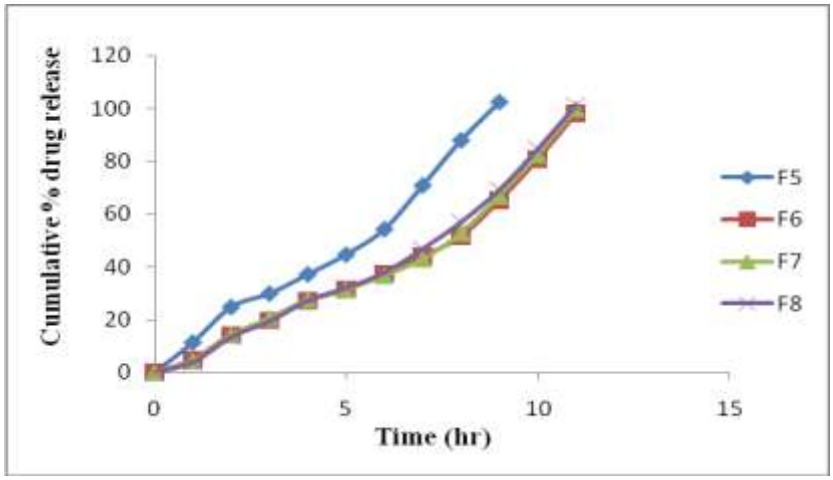

Figure. 8: Cumulative percent drug release of metronidazole matrix tablets (F5 – F8).

From the figure 8, it was observed that the formulations F5 – F8 were able to retard drug release in 0.1 N HCl (pH 1.2) and showed 13% - 24% drug release. But they are not able to retard the drug release in pH 6.8 phosphate buffer.

Table. 5: Cumulative percent drug release of metronidazole matrix tablets (F9, F10).

pH	Time (hr)	F9	F10
1.2	1	1.98 ± 0.43	3.24 ± 0.82
	2	4.95 ± 0.64	6.56 ± 1.11
6.8	3	7.86 ± 0.75	10.03 ± 0.94
	4	16.87 ± 0.96	20.438 ± 0.96
7.4	5	18.19 ± 0.98	21.11 ± 1.08
	6	20.26 ± 1.19	22.78 ± 0.97
	7	29.06 ± 1.36	29.76 ± 1.08
	8	37.95 ± 0.85	37.25 ± 0.98
	9	49.93 ± 1.12	48.39 ± 1.14
	10	65.6 ± 1.14	63.06 ± 0.94
	11	84.12 ± 0.85	80.79 ± 1.13
	12	99.96 ± 1.14	94.38 ± 1.39

Data represents mean ± SD, n = 3.

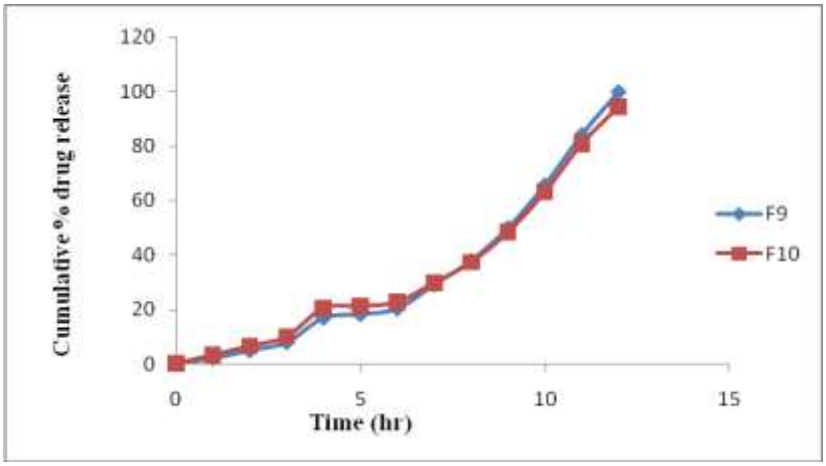

Figure. 9: Cumulative percent drug release of metronidazole matrix tablets (F9, F10).

From the figure 9, it was observed that the two formulations (F9, F10) had no drug release in 0.1 N HCl (pH 1.2). F9 (GG: HPMC K100M - 1.5:0.5) and showed good lag time of 4 hrs than F10 (GG: HPMC K100M), formulation F9 and it released only 16.87% of drug at 4th hr. Only formulation 9 was able to retard the drug release in pH 6.8 buffer and showed significant release (>18%) in pH 7.4 buffer at 5 hrs. Hence formulation 9 was found to be successful in releasing drug at colonic pH and suitable for colon targeting.

DISCUSSION

Various approaches have been used for oral delivery of drug to the colon which includes pH-dependent delivery systems, time-dependent delivery systems, microbially-controlled delivery systems, pressure-dependent delivery systems, enzyme-based delivery systems. The microbially-controlled systems have found practical application. Hence the present study was aimed to develop Metronidazole matrix tablets for colon targeting using polymers Xanthan gum, Guar gum, HPMC K100M.[10] Metronidazole matrix tablets can be used for targeting to colon for the treatment of colonic inflammation.

Metronidazole tablets prepared by using Xanthan gum, Guar gum as polymers were subjected to dissolution studies in SGF (pH 1.2), SIF (pH 6.8) and SIF (pH 7.4). The tablets showed higher drug release in SGF pH1.2 and SIF pH 6.8 and showed 100% drug release in less than 5 hours. It was confirmed that the Metronidazole tablets containing XG, GG as polymers are not suitable for colon targeting.

Hence, attempts were made to minimize the drug release in the physiological environment of stomach and small intestine and to ensure maximum drug release in the physiological environment of colon by using combination of polymers. Different formulations were prepared by wet granulation method using different polymer ratios.

Formulations F1 to F4 were subjected to dissolution studies in 0.1 N HCl (pH 1.2), SIF (pH 6.8) and SIF (pH 7.4). All the formulations showed 30% - 60% of drug release in 0.1 N HCl (pH 1.2). The polymer ratio of 1:1 was not able retard the drug release in 0.1 N HCl (pH 1.2).

Formulations F5 to F8 were able to retard drug release in 0.1 N HCl (pH 1.2). Where as they could release some drug in pH 6.8 phosphate buffer. Because the polymer ratio containing matrix tablets are sensitive in pH 6.8 buffer.

Guar gum combination with HPMC K100M (F9, F10) formulations retarded the drug release more than that of guar gum and xanthan gum combination in 0.1 N HCl (pH 1.2).

The tablets containing guar gum with HPMC K100M (F9 -1.5:0.5) were optimized, showed good lag time of 4 hrs and released 16.87% drug at 4^{th} hr. The tablets containing combination of natural and synthetic polymers showed good results than the formulation containing combination of two natural polymers.

Kinetic studies

The mechanism and kinetics of drug release of metronidazole is determined by the application of zero order, first order, higuchi, and krosmeyer-peppas kinetics as show in table 25. Optimized formulation (F9) follows the first order release as their r^2 value is 0.942.

The mechanisms of drug release are non-fickian diffusion (super case-II), since they fitted well with Korsmeyer-Peppas models as their r^2 value is 0.982 with n value above 1. This indicates that the drug release depends on swelling, relaxation and erosion of polymer with first order release kinetics.

Table. 6: Drug release kinetics.

Formulation code	Zero order	First order	Higuchi	Krosmeyer & peppas	Peppas (n)
F9	0.906	0.942	0.812	0.982	1.892

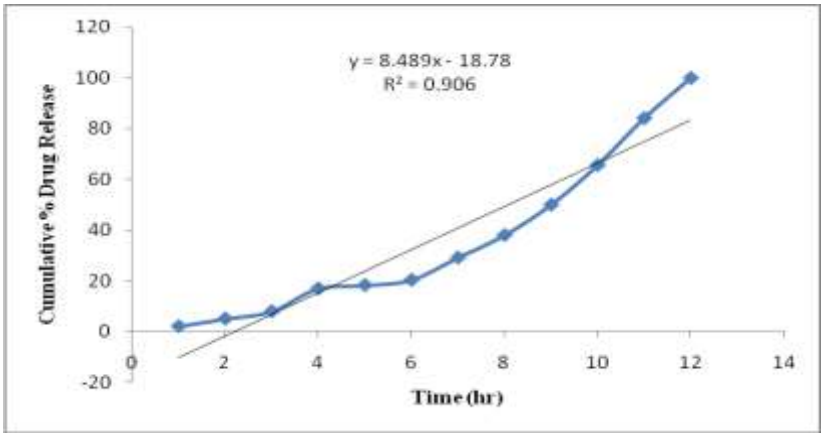

Figure. 10: Zero order release rate kinetics.

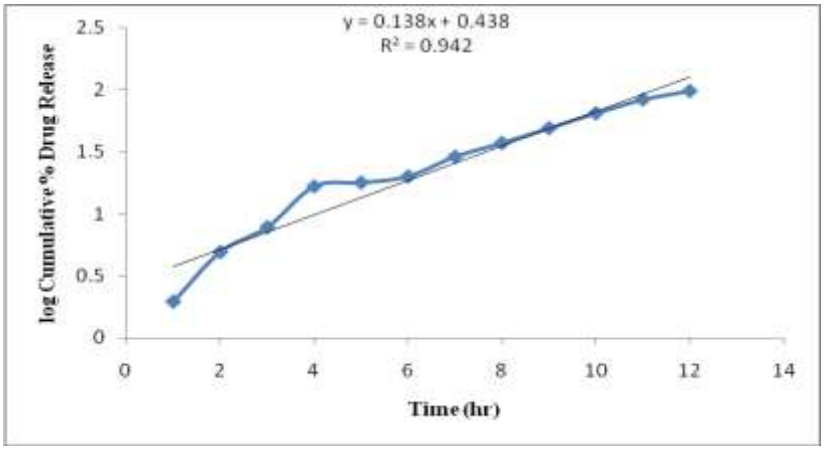

Figure. 11: First order release rate kinetics.

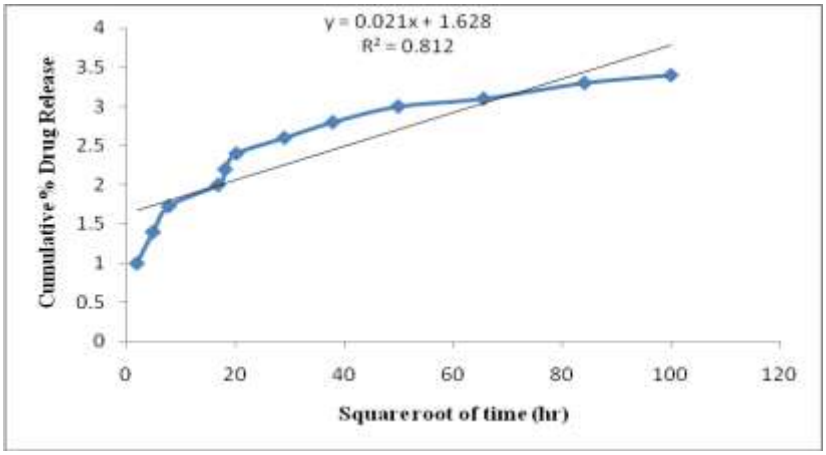

Figure. 12: Higuchi release model.

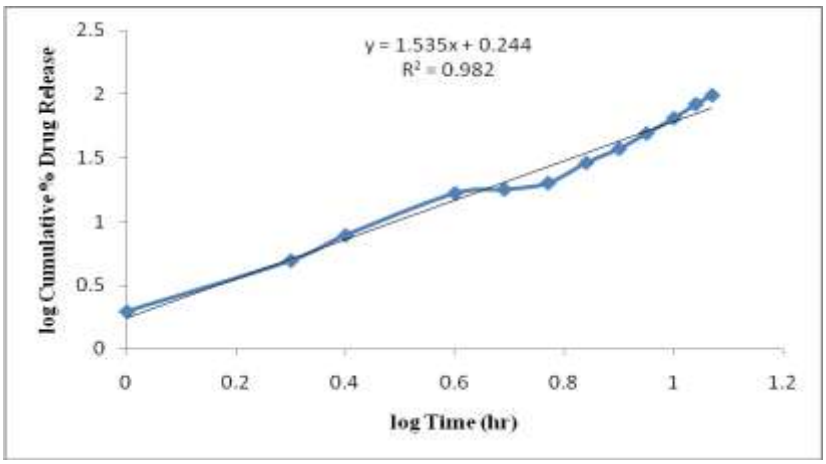

Figure. 13: Korsmeyer and Peppas release model.

SUMMARY

The usual dose of Metronidazole is 500mg to 750mg as anti-amoebic agent which is to be taken three or four times daily. It undergoes rapid first pass metabolism and is unavailable in the GIT as immediate release dosage form. Hence, MTZ was chosen as a model drug with an aim to develop a controlled release system for a period of 12hrs.

The aim of the present work was to formulate and to evaluate the matrix tablets of MTZ by wet granulation technique to sustain the drug release and to reduce frequency of drug administration/dosing.

The microbially-controlled systems have found practical application. Hence the present study was aimed to develop Metronidazole matrix tablets for colon targeting, 12 different formulations were prepared by wet granulation method using natural polymers like xanthan gum (XG), guar gum (GG), and synthetic polymers like HPMC K100M.

Compatibility studies between the drug and excipients such as guar gum, xanthan gum, HPMC K100M, were evaluated by using FT-IR. From the results it is confirmed that there is no interaction between the drug, guar gum, HPMC K100M. The results of angle of repose (< 30) and compressibility index (< 20) indicates good to fair flow properties of the granules.

The XG and GG tablets were subjected to dissolution in 0.1 N HCl (pH1.2), pH 6.8 buffer, and pH 7.4 buffer. The tablets showed high drug release in 0.1 N HCl (pH 1.2) and pH 6.8 and showed 100% drug release in less than 5 hrs. Formulations F1 to F4 had drug release in 0.1 N HCl (pH 1.2) between 30% - 60%, and so they are not suitable for colon targeting. Formulations F5 – F8 released between 13% - 24% of the drug in acidic pH of 0.1 N HCl.

Guar gum combination with HPMC K100M (F9, F10) formulations retarded the drug release more than that of guar gum and xanthan gum combination in 0.1 N HCl (pH 1.2).

During the in vitro drug release studies, all formulations were observed for physical integrity at different time intervals. All the formulations swelled and the outer layer of most of the tablets appeared to be hydrated after being placed in the dissolution medium, with progressive increase in the size of these hydrated matrices. There was also gel formation followed by gradual loss of integrity over a period, resulting from hydrodynamic stress induced by the dissolution apparatus. The quick hydration and subsequent gel formation is a foremost and important property of an excipient intended for use in sustained released formulations.[12]

The release kinetics was fitted to different mathematical models like Zero order, First order, Higuchi's and Korsmeyer-peppas plot. The optimized Formulation F-9 follows super case II transport mechanism since the n value is 1.892. This confirms that the drug release through the matrix was diffusion. The regression coefficient (R^2) values of first order in the optimized formulation F-9 was greater than the R^2 values of zero order. Thus, the drug release follows first order release kinetics.

CONCLUSION

From the results it was concluded that F9 matrix tablet composition was optimized. The tablets containing guar gum with HPMC K100M were optimized. They showed the lag time of 4 hrs and drug release was less than 17% at 4 hrs. The tablets containing combination of

natural and synthetic polymers showed good results than the formulation containing combination of two natural polymers.

The F1 to F8 matrix tablets were not successful to retain the drug release. Hence attempts were made to improve the natural polymer containing with combination of synthetic polymer. The tablets with Guar gum and HPMC K100M showed 4 hr lag time out of all formulations. The matrix protects the formulation from earlier peel off problem in 6.8 pH phosphate buffer. Further pharmacokinetic studies may helpful for the researchers.

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