



**Research Article**

**FORMULATION AND IN VITRO EVALUATION OF METRONIDAZOLE FLOATING TABLETS**

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(Received: 15 April, 2013; Accepted: 21 April 2013; Published: 28 April, 2013)

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**Abstract:** Floating tablets of Metronidazole were prepared by using synthetic and natural polymers in different concentrations. The floating properties and in-vitro drug release properties were optimized and total 4 formulations were developed. The synthetic and natural polymers used are HPMC K4M, HPMC K15M and Xanthan Gum, Guar gum respectively. Each formulation consists of a combination of drug and polymer in the ratio of 1:1. In this study it was confirmed that the formulations containing guar gum, have shown better floating properties and finally the formulation containing guar gum, has shown better in-vitro release properties.

**Keywords:** Floating matrix tablets, Metronidazole, HPMC K4M, Xanthan Gum, Gastric retention.

**INTRODUCTION**

Gastro retentive drug delivery systems are the systems which are retained in the stomach for a longer period of time and thereby improve the bioavailability of drugs that are preferentially absorbed from upper GIT. Floating drug delivery systems (FDDS) offer a number of applications for drugs having poor bioavailability because of narrow absorption window in the upper part of gastrointestinal tract<sup>1</sup>.

The ideal drug candidate for FDDS are drugs that are acting locally in upper gastro intestinal tract (GIT) or drugs that are degrading in lower GIT or drugs that show poor intestinal absorption or drugs that are absorbed only in the initial part of the small intestine and stomach. Acid labile drugs and other drugs that are causing gastric lesions are unsuitable for such formulations<sup>2</sup>. The gastric retention of the dosage form in the stomach depends upon various factors like pH, size of the dosage form, food intake, and biological factors which include age, body mass index, gender, posture, and diseased states. Out of all available gastro retentive systems floating tablets, floating beads, floating granules, and floating microspheres have gained major importance in the formulation development more recently<sup>3</sup>.

Metronidazole, chemically 2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethanol, is a nitroimidazole antibiotic medication used particularly for anaerobic bacteria and protozoa. Metronidazole is an antibiotic, amebicide, and antiprotozoal. It is the drug of choice for first episodes of mild-to-moderate Clostridium difficile infection. Metronidazole is indicated for the treatment of Helicobacter pylori eradication therapy, as part of a multi-drug regimen in peptic ulcer disease<sup>4</sup>. It is usually taken two or three times a day. Unionized metronidazole is selective for anaerobic bacteria due to their ability to intracellularly reduce metronidazole to its active form. This reduced metronidazole then covalently binds to DNA, disrupts its

helical structure, inhibiting bacterial nucleic acid synthesis and resulting in bacterial cell death<sup>5</sup>.

In the present study, Metronidazole floating tablets were prepared to increase the gastric residence time and absorption of drug through gastric mucosa and to decrease the dose frequency. The prepared tablets were evaluated for their floating properties and in-vitro drug release.

**MATERIALS AND METHODS:**

The chemicals used in this study were pure drug like Metronidazole (Venkateswara scientific traders) and polymers like HPMC K4M, HPMC K15M, Xanthan gum, Guar gum (Venkateswara scientific traders) and other excipients like Micro crystalline cellulose, Magnesium stearate, Talc, Sodium bicarbonate (Venkateswara scientific traders).

**1. Preformulation study**

Preformulation studies were conducted to identify the compatibility of drug with polymers. These studies were conducted by using FTIR method. In this method, the sample along with KBr was used to get the IR spectrum. The IR spectra of pure drug and physical mixtures containing drug and polymers were produced and analysed.

**2. Preparation of floating matrix tablets<sup>6</sup>**

Metronidazole was mixed manually in polybags with gastro retentive polymers separately as per formulae and MCC was added as diluent and sodium bicarbonate was added as effervescent agent (Table 1) and mixed for 10 mins. The blend was lubricated with magnesium stearate for 3-5mins and talc was added as glidant. The mixed blend was then compressed into tablets by direct compression method using 10 mm punches on a twelve station rotary tablet punching machine (Cmach machineries). Total four formulations were developed by using four polymers.

**Table 1: Formulation composition of Metronidazole floating tablets of F1 to F4**

Formulation	Drug	HPMC K4M	HPMC K15M	Xanthan gum	Guar gum	MCC	Sodium bicarbonate	Mg stearate	Talc
F1	200mg	200mg	-	-	-	22mg	60mg	12mg	6mg
F2	200mg	-	200mg	-	-	22mg	60mg	12mg	6mg
F3	200mg	-	-	200mg	-	22mg	60mg	12mg	6mg
F4	200mg	-	-	-	200mg	22mg	60mg	12mg	6mg

### 3. Evaluation

#### a) Characterization of tablets for physicochemical parameters

The prepared Metronidazole floating tablets were evaluated for their physicochemical parameters like weight variation, hardness, friability and drug content.

#### b) In vitro floating lag time<sup>7</sup>

The in vitro buoyancy was determined by floating lag time. The tablets were placed in a 100 ml beaker containing 0.1N HCl. The media was kept in stagnant condition and the temperature was maintained at 37°C. The time required for the tablet to rise to the surface and float was determined as floating lag time.

#### c) In vitro floating duration time

The floating capacity of the tablets was determined using USP Dissolution apparatus II containing 900ml of simulated gastric fluid. The time interval between introduction of the tablet in to the dissolution medium and its buoyancy to the dissolution medium was taken as buoyancy lag time and for which time the tablet constantly floats on the surface of the medium was observed visually and taken as floating duration.

#### d) In vitro drug release<sup>8</sup>

The release of Metronidazole from floating tablets was determined by using Dissolution type II test apparatus. The dissolution test was performed using 900 ml 0.1N HCl

solution at  $37 \pm 0.5^\circ\text{C}$  temperature and at 50 rpm. At specified time intervals, samples of 5 ml were withdrawn from the dissolution medium and that amount was replaced with fresh medium to maintain the volume constant. The samples were filtered and diluted to a suitable concentration with 0.1 N HCl. The absorbances of the diluted samples were measured at 278nm for Metronidazole by using UV-Visible double beam spectrophotometer. Cumulative percentage drug release was calculated using an equation obtained from standard curve.

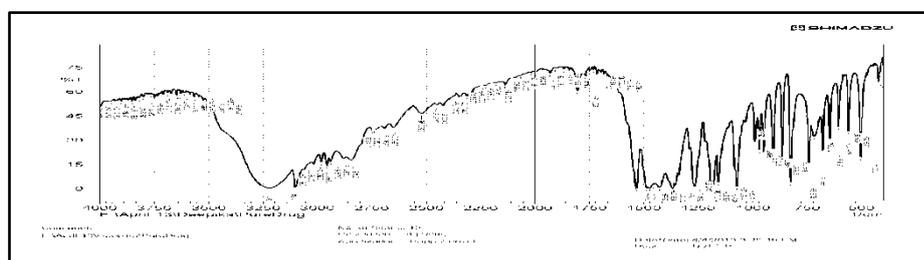
#### e) Characterization of drug in Floating tablets

FTIR studies were conducted for characterization of drug in tablets of selected optimized formulation (F4). The floating tablets were compressed and powdered. The pelletized powder along with KBr was used for FTIR studies. The IR spectra were recorded using Fourier Transform Infrared spectrophotometer. The IR spectra of pure Metronidazole and pelletized powder of tablets were taken, interpreted and compared with each other.

## RESULTS AND DISCUSSION:

### 1. Preformulation study

In IR spectrum (figure 1) of pure Metronidazole, the presence of peaks were characteristic to that of the pure drug and all of them remained unaltered in the IR spectra (figure 2) of physical mixtures containing drug and polymers. IR analysis revealed that there was no evidence to the presence of known chemical interaction of drug with polymers and other ingredients.



**Figure 1: IR spectrum of pure Metronidazole**

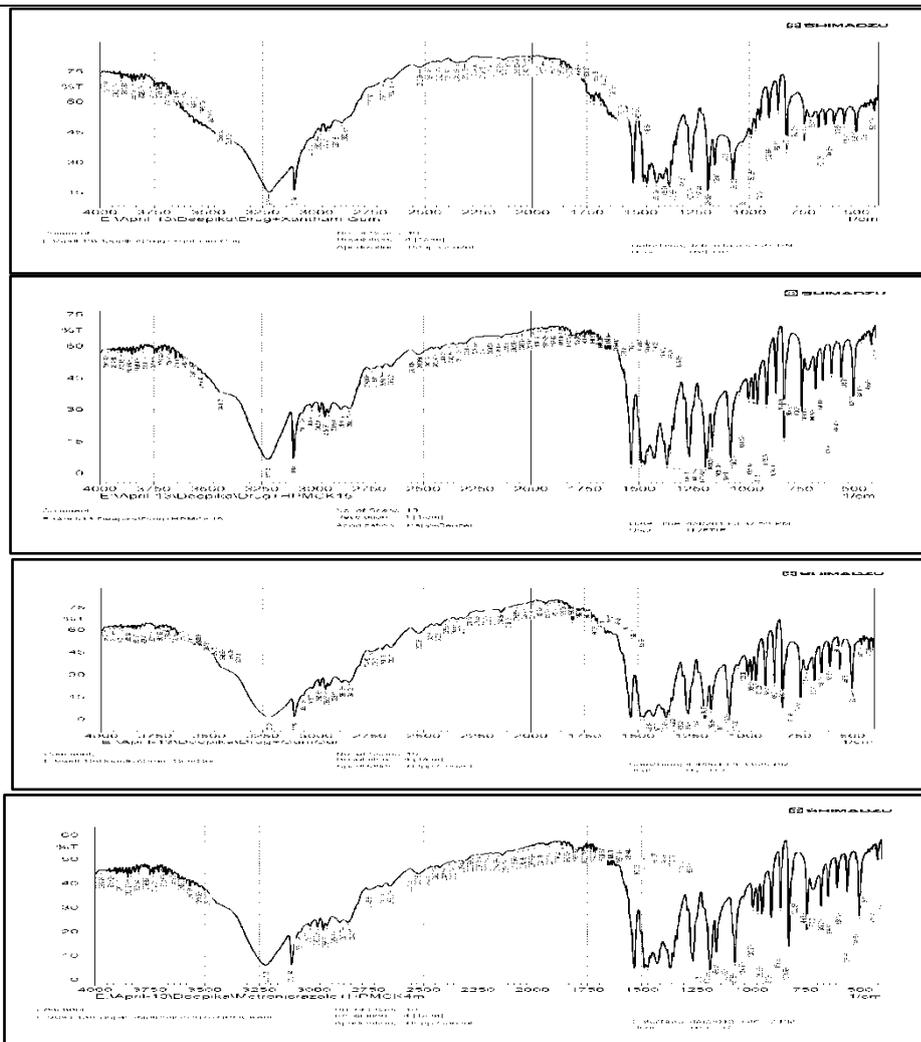


Figure 2: IR spectra of physical mixtures containing drug and polymers

**2. Weight variation, hardness, friability and assay**

The weight variation of the tablets (Table 2) was within the limits of uniformity. The mass ranged from 599.50 to 601.40 mg with SD values 0.69–1.30. The mass of all compressed tablets were within the limits as per USP. The drug content ranged from  $97.50 \pm 0.36\%$  in formulation

F1 to  $90.38 \pm 0.36\%$  in formulation F8 and the friability was ranged from 0.25 to 0.98. Friability and assay of all compressed tablets were within the limits as per USP. The hardness of all prepared tablets was in the range of 3.5 to 4 kgs.

**Table 2: Weight variation, Friability and Assay**

Formulation	Mass (mg) Mean $\pm$ SD	Friability (%)	Assay (%)
F1	599.80 $\pm$ 1.00	0.50	97.50 $\pm$ 0.36
F2	601.70 $\pm$ 0.76	0.25	101.25 $\pm$ 0.47
F3	599.10 $\pm$ 0.69	0.32	109.25 $\pm$ 0.59
F4	600.40 $\pm$ 0.75	0.98	110.88 $\pm$ 1.01

**3. In vitro floating lag time and floating duration**

The formulations like F1, F2 and F3, F4 have shown floating lag times of below 5 minutes (Table 3). From these results it was found that all the formulations have shown less floating lag time.

All the formulations were allowed to float constantly on dissolution medium. The formulations F3 and F4 formulations were floated up to more than 8 hours where as the formulations F1 and F2 containing HPMC K4M, HPMC K15M have shown their floating duration of less than 8 hours.

**Table 3: Floating lag time and Floating duration**

Formulation	Floating lag time (sec)	Floating duration time(hrs)
F1	120 sec	Less than 5hrs
F2	300 sec	Less than 5hrs
F3	120sec	More than 8hrs
F4	120sec	More than 8hrs

This may be due to less capacity of HPMC K4M, HPMC K15M to form hydrophilic barrier around the tablet and to decrease the total density of the tablet. The other reason may be due to inefficiency of 10 % w/w effervescent agent in tablet to reduce its total density in the presence of HPMC K4M, HPMC K15M.

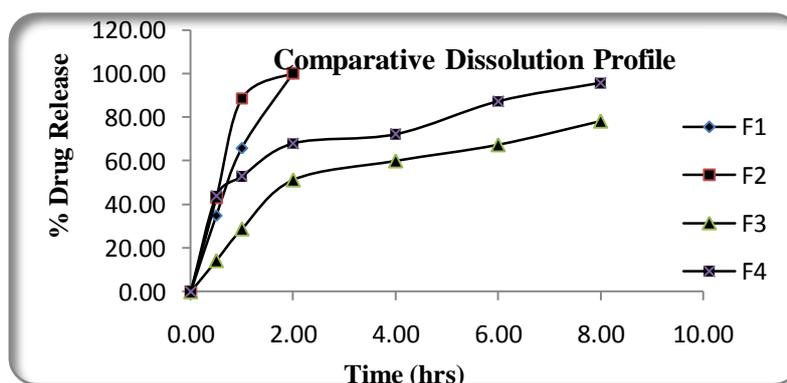
**4. In vitro drug release**

The in vitro dissolution study was performed to all those formulations that have shown better floating properties i.e. F1, F2 and F3, F4. The release of Metronidazole from gastro retentive floating tablets (Table 4 and Figure 3) varied according to the type of matrix forming polymers.

The drug release from the formulations F3 was controlled up to 8hrs. The drug release in case of formulation F1 and F2 was not extended up to 8 hrs and immediate drug release pattern was observed; and incase of formulation F4 the complete drug release was observed at the end of 10 hours. The matrix forming ability was more in case of formulations F3 and F4 containing polymers like Xanthan gum and guar gum, where as matrix forming ability was less in case of formulations F1 and F2 containing polymers like HPMC K4M and HPMC K15M. However the more controlled drug release was observed in the formulation F4 containing a polymer like Guar gum in 1:1 drug, polymer ratio.

**Table 4: In-vitro release profiles of formulations F1, F2 and F3, F4**

Time (hrs)	F1	F2	F3	F4
0	0	0	0	0
1	34.94	43.15	14.29	43.94
2	65.91	88.68	28.85	52.94
4	100.06	100.32	51.35	68.03
6	-	-	60.09	72.26
8	-	-	67.50	87.35
10	-	-	78.35	<b>95.82</b>



**Figure 3: Dissolution Profile of F1, F2 and F3, F4**

In the dissolution study of formulations F1, F2 and F3, F4, it was revealed that only two formulations like F3 and F4, have released the drug in controlled manner up to 10 hours. Hence kinetics of drug release and mechanism of these three formulations were studied. The release data of all four formulations seem to fit better with the first order kinetics and Higuchi model i.e. the release rate in these formulations, is dependent of its concentration or amount of

drug in tablet at given time and the release mechanism is Fickian diffusion.

Based on the results from in-vitro floating studies and in-vitro drug release studies, the formulation F4 containing a polymer like guar gum was selected as best formulation with optimum floating and drug release properties.

### 5. Characterization of drug in floating tablets

IR analysis (figure 4) revealed that there was no evidence to the presence of known chemical interaction of

drug with polymers and other ingredients in selected best formulation.

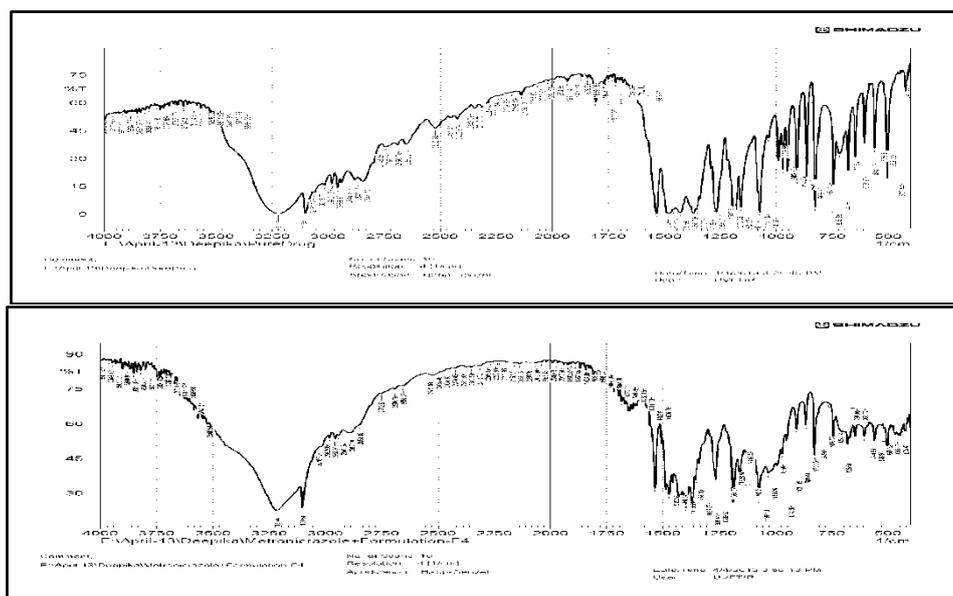


Figure 4: IR spectra of Pure Metronidazole and F4 formulation

### Conclusion:

New gastro retentive delivery systems for Metronidazole were developed and evaluated. The results propose that natural polymer like guar gum in 1:1 drug and polymer ratio can increase the retention time of formulation in stomach and also can control the drug release from formulation due to matrix formation thereby increasing drug absorption and reducing the dose frequency. It can be concluded that the antimicrobial action of Metronidazole may be increased in the stomach due to increased retention and absorption by using formulation F4. The results obtained for used combination and ratio of polymers in the presence of MCC (diluent), were not reported earlier in any work. Further work is needed to claim the results in human beings by in-vivo studies.

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