Innovare Academic Sciences

International Journal of Pharmacy and Pharmaceutical Sciences
ISSN- 0975-1491 Vol 6, Issue 9, 2014

Original Article

PREPARATION AND EVALUATION OF METRONIDAZOLE SUSTAINED RELEASE FLOATING TABLETS

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Received: 15 Jul 2014 Revised and Accepted: 20 Aug 2014

ABSTRACT

Objective: The objective of the present study is the preparation of metronidazole (MZ) floating tablets that are designed to retain in the stomach for a long time for better eradication of *Helicobacter Pylori (H. pylori)*, a main cause of peptic ulcer disease.

Methods: Synthetic and natural polymers were studied for their floating potential in the presence of sodium bicarbonate, namely: hydroxypropyl methylcellulose (HPMC), carbopol 974P, sodium alginate {low and medium viscosity (LV & MV) grades}, locust gum and guar gum. Hardness, floating ability, release profiles and kinetics as well as DSC / FT-IR were studied.

Results: Results of both DSC and FT-IR spectroscopy revealed that there was no interaction between the drug and any of the proposed polymers. Carbopol 974P based tablets showed an unacceptable floating lag time (2 h) and did not maintain good tablet integrity. All other formulas were able to float after few seconds and showed buoyancy for more than 24 h. Meanwhile, sustained profiles of MZ release were obtained. After 6 h the amount of MZ released were: 75.11 %, 61.26 %, 54.56 %, 54.25 % and 43.42 % from sodium alginate-LV, HPMC-K4M, guar gum, locust gum and sodium alginate-MV based tablets, respectively. Kinetically, among the 5 assessed models, the release pattern of MZ from the tablets fitted best to Zero order and Hixson & Crowell Cube-Root models.

Conclusion: These stomach targeted dosage forms could maintain the minimum inhibitory concentration for sufficient time to allow for local eradication and thereby achieve better efficiency of therapy with improved patient compliance, reduced costs and minimized side effects caused by immediate release dosage forms.

Keywords: Metronidazole, Floating tablets, HPMC-K4M, Alginates, Gums, Drug-polymer interaction, Release kinetics.

INTRODUCTION

Oral delivery of the drug is the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in the formulations. Recent technological advancements have been made in controlled oral drug delivery systems by overcoming physiological difficulties, such as short gastric residence time (GRT) and highly variable gastric emptying time [1]. Gastric residence time is the major physiological constrain which is responsible for the reduction in efficacy of oral controlled release dosage forms. GRT considerably affects the bioavailability of pharmaceutical dosage forms [2].

Variable and short gastric emptying time results in incomplete drug release from the oral controlled release dosage forms (OCRDF) which leads to diminished efficacy of the administered dose [3]. GRT is affected by both the fasting as well as fed states of the stomach. Gastric emptying studies revealed that the short GRT and unpredictable gastric emptying rate have altered the performance of OCRDF [4]. To improve the performance of OCRDF, scientists have discovered a new concept in drug delivery, that is, gastroretentive drug delivery systems (GRDDS). A GRDDS can be defined as a system which remains in the stomach for a sufficient time interval against all the physiological barriers, releasing the active moiety in a controlled manner, and finally becomes metabolized in the body [5].

A GRDDS can be a useful tool in delivery of drugs that are primarily absorbed in the duodenum and upper jejunum or those that have an absorption window in the gastrointestinal tract (GIT) [6-8]. Such delivery system is appropriate for drugs which are locally active in the gastric mucosa, for example, antibiotic administration for *Helicobacter pylori* (*H. pylori*) eradication [9,10] and in the treatment of peptic ulcer and gastritis [11,12]. Drugs that are less soluble in or are degraded by the alkaline pH may get benefit by being incorporated in GRDDS for prolonged gastric retention and consequent improved oral bioavailability and therapeutic efficacy by possible reduction of dose size [13,14].

Floating systems are more popular in comparison with the other described GRDDS [15-17] because they do not have any adverse effect on the motility of the GIT [18]. Floating drug delivery systems have lower density compared with gastric fluid which enables them to float over the surface of gastric fluid [19]. Drug release from the system takes place slowly at the required rate which results in reduced fluctuation in the plasma concentration along with increased GRT [20].

Hydrophilic polymers are actually one of the most used excipients to control drug delivery from an oral pharmaceutical dosage form including GRDDS and may be classified as either synthetic or natural. Carbopol 974P-NF is the oral pharmaceutical grade of the carbomers and is an example of polymers with highly crosslinked structure [21]. Carbopol and hydroxypropyl methylcellulose (HPMC-K4M), a semi-synthetic cellulose derivative, have been used by other authors to prepare MZ floating matrix tablets [22-25].

In spite of the advent of many synthetic polymers, use of natural polymeric materials has gained a lot of importance during the last two decades in drug delivery field. Incorporation of natural polymers in various drug delivery systems seems to be an active area of research and development due to obvious advantages including being biocompatible, inexpensive and ready availability [26]. These polymers, particularly those with pronounced swelling properties have been frequently employed in the formulation of different gastroretentive products [27]. Drug delivery systems targeted to stomach which are based on the utilization of various natural polymer offer superiority over other systems. Moreover, these polymers are safe, nontoxic, capable of chemical modification and gel forming nature. Natural polymers which have been explored for their promising potential in stomach-specific drug delivery include alginates

[28], xanthan gum [29], chitosan [29], locust gum [30], guar gum [31,32], pectin, gellan gum, karaya gum, psyllium husk, starch, etc [33,34].

In the last decade, the number of patients suffering from peptic ulcer and gastric cancer due to *H. pylori* infection has increased tremendously. *H. pylori* are spiral, gram-negative, microaerophilic rod-shaped bacteria with multiple flagella [35,36]. *H. pylori* which remains on the luminal surface of the gastric mucosa under mucous gel layer, is highly motile, and produces enzyme urease to alter the surrounding pH to protect itself from gastric acid [36]. The current therapy for the treatment of *H. pylori* involves use of proton pump inhibitors with antibiotics and has drawbacks like poor patient compliance and increased bacterial resistance due to higher multiple dosage of antibiotics [37,38].

There could be one or several reasons for the failure of antibiotic therapy against *H. pylori*. Firstly, the organism resides in the mucus gel close to the acidic environment of the gastric fluid. Many antibacterial agents, such as penicillin and erythromycin, degrade rapidly in acidic medium. Secondly, the drug must diffuse into the mucus layer and the bacterial glycocalyx to furnish concentrations sufficient for antibacterial activity. For eradication of *H. pylori* in the stomach the concentrations of antibacterial agents reaching the site of infection from tablets or capsules might not be bactericidal against organisms located in the mucus layer and protected by the glycocalyx. Lastly, the contact time of antibacterial drugs with the organism needs to be sufficiently long for successful eradication of *H. pylori* from the gastric mucosa, that can be achieved through a GRDDS [39,40]. Delivering drug at the site of infection for a longer period of time is one of the approaches to improve the efficacy of antibiotic therapy [41,42]. Metronidazole (MZ) is an active adjunct in treatment of *H. pylori* [43] with the commonly reported side effects including anorexia, nausea, vomiting, and epigastric pain. Metallic taste, mouth dryness, probably caused by the presence of high concentrations of the drug in the saliva, and furring of the tongue are also reported [44]. Therefore, certain MZ floating systems were developed for better eradication of *H. pylori*, including: floating MZ tablets [22-25,45] and beads [28,46-50]. Such dosage forms for MZ would be beneficial in delivering higher concentrations of the antibacterial agent in the gastric mucosa where *H. pylori* resides ensuring better microorganism eradication. Furthermore, such treatment may lead to drug dose reduction which will be an additional valuable advantage [48].

In our previous work, the one year bench stability studies for the prepared MZ double layer floating tablets, containing PEO (M. W. 8,000,000) in the gas generating layer and PEO (M. W. 900,000) in drug release layer, revealed a pronounced increase in MZ release rate, between fresh and stored tablets, with "f_2" value equal to 25.0. This means that the product was not stable upon storage [40]. These results directed us to search for other alternatives and the need for investigating other polymers (especially the natural ones) regarding their feasibility to be used as release retarding and floating agents for the preparation of MZ floating tablets of improved stability.

The objective of the present study was to prepare MZ floating matrix tablets based on a hydrophilic polymer and a gas-former namely sodium bicarbonate ($NaHCO_3$). Such tablets will help to achieve higher concentrations of the antibacterial agent in the gastric mucosa. The hydrophilic polymers used were either synthetic: Carbopol 974P-NF and HPMC (K4M), or natural: sodium alginate (Na alginate), guar gum and locust gum. The mechanism of release was elucidated to obtain a general kinetic model for drug release profile-. The *in vitro* release and floatability studies for the prepared MZ tablet formulations were performed. The results will increase our understanding of the tablets' floatability and the release control from these types of matrices.

MATERIALS AND METHODS

Materials

Metronidazole (MZ; Batch no. 10053 F090020, Exp. date 5/2014) was kindly supplied by EIPICO, Egypt. Hydroxypropyl methylcellulose [HPMC-K4M, the viscosity of 2 % water solution is 4000 cps] was purchased from Aldrich, Germany. Sodium alginate (low and medium viscosity) and locust gum were purchased from Aldrich (Germany). Guar gum and carbopol 974P-NF were gifted from Novartis (Egypt). Sodium bicarbonate ($NaHCO_3$) was from Kahira Pharm. (Egypt). Methanol (HPLC grade) was from Prolabo (France). Distilled water was used for all experiments (Milli RO plus 10, Millipore, USA). All other reagents were of analytical grade.

Methods

Tablet preparation

MZ tablets were prepared using a rate controlling polymer and a gas-generating excipient. Each formula contained 250 mg MZ, 20 % (w/w) of a single polymer as shown in Table 1 and sodium bicarbonate as the gas-generating agent. Locust gum and guar gum based formulas were uncompressible as such therefore; avicel was added to these two formulas to aid compression. All ingredients (for each formula) in their specified ratios (Table 1) were sieved through 710 µm sieve (mesh number 25). Blending of all ingredients was carried out simultaneously using polyethylene bag [51], after which tablets were prepared from different blends by direct compression at 1.5-tons compression force (Single Punch Press Tablet Machine, Stokes- Merrill Model 511-7-A, USA). For such formulas, a round die (13 mm internal diameter) with flat-faced punches were employed to give round flat-surface tablets.

Table 1: Composition of metronidazole floating tablets (250 mg/tablet).

	Composition:% (w/w)/tablet					
	M1	**M2**	**M3**	**M4**	**M5**	**M6**
HPMC-K4M	20	0	0	0	0	0
Na alginate (medium viscosity)	0	20	0	0	0	0
Na alginate (low viscosity)	0	0	20	0	0	0
Locust Gum	0	0	0	20	0	0
Guar Gum	0	0	0	0	20	0
Carbopol 974P	0	0	0	0	0	20
$NaHCO_3$	10	10	10	20	20	10
Avicel	0	0	0	20	20	0

Characterization of the prepared tablets

Physical parameters

PTB (311E) 3 in 1 Hardness, Diameter and Thickness Tester (PTB 311E Tablet Testing Instument, Pharma Test Apparatebau AG, Germany) was used for determination of thickness, diameter, weight, and hardness of the prepared tablets (mean of twenty tablets for each formula was calculated).

Content uniformity

Twenty tablets of each formula were weighed, grinded, and the weight equivalent to one tablet was transferred quantitatively into 250 ml volumetric flask.

About 100 ml dilute HCl (1 in 100) were added to each flask and then the flasks were shaken for 30 min using "temperature-controlled shaking water-bath (Lab-Line, USA)" at 37 °C. The volume

was then completed to the mark with dilute HCl (1 in 100) followed by mixing [52]. The solution was then filtered and appropriate dilutions were done to the filtrate using dilute HCl (1 in 100). The absorbance was then measured spectrophotometrically (UV-Visible spectrophotometer, Beckman, DU-650, USA) at the predetermined λ_{max} at 277 nm for MZ.

Determination of floating lag time and floating duration of the prepared tablets

The time required for the tablets to emerge on the dissolution medium surface (floating lag time) and the time the tablets remained floating on the dissolution medium surface (floating duration) were inspected visually in 1L jacketed jar connected to Julabo circulator (F10-VC, Germany), filled with 400 ml 0.1 N HCl, pH 1.2 [53], at 37 ± 0.5 °C [54]. The results were registered as an average of three repetitions.

***In vitro* release studies**

These studies were carried out using the closed system of the flow-through cell, USP Apparatus 4, which is composed of Dissotest CE-6 equipped with a CY 7-50 piston pump (Sotax, Switzerland). Each tablet was placed into the large dissolution cell (22.6 mm diameter) according to the cell design shown in Fig.1. This design was chosen as it allowed for floating observations while studying the release profile. Built-in filtration system (0.7 µm Whatmann GF/F and GF/D glass micro-fiber filters, and glass wool) was used throughout the study. The dissolution medium was 900 ml 0.1N HCl (pH 1.2), which was filtered (on 0.45 µm filter), degassed and then pumped at a laminar flow rate of 16.0 ± 0.2 ml/min. Temperature of the dissolution medium was kept constant at 37 ± 0.5 °C. At predetermined time intervals, 10 ml samples were collected and replaced by the same volume of the fresh dissolution medium. Collected samples were then analyzed spectrophotometrically (UV-Visible spectrophotometer, Beckman, DU-650, USA) for MZ content by measuring the absorbance at the corresponding λ_{max} (277 nm) against 0.1N HCl (pH 1.2) as blank. Each formula was tested in triplicate for up to 6 h and the mean value was calculated.

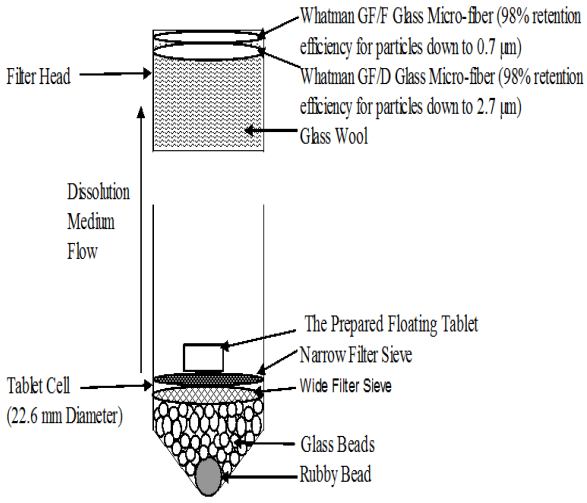

Fig. 1: Dissolution cell design used for the prepared floating tablets: laminar flow with free tablet position (glass beads filling the entry cone).

Comparison between different release profiles

The similarity factor (f_2), as proposed by Moore and Flanner [55] was calculated from the mean release data and used to compare between the different release profiles. f_2 is — given by Eq. (1):

$f_2 = 50 \times \log \{[1+ (1/n) \Sigma t=1n (Rt - Tt) 2] - 0.5 \times 100\}$ Eq. (1)

Where, n is number of data time points collected during the in vitro release test, Rt and Tt are the cumulative release percentages released at the selected (n) time point of the two tested formulas. The f_2 value is a measure of the similarity between two dissolution curves and its value ranges from 0 and 100. A high f_2 value indicates high similarity between two release rate profiles. FDA suggests that two dissolution profiles are considered similar if the similarity factor f_2 is between 50 and 100 [55,56].

Kinetic study of drug release data

In order to describe the kinetics of MZ release from the prepared sustained release tablets, various mathematical equations were applied;

Zero-order Equation [57,58]: $Q_t = k_0 . t$ Eq. (2)

First-order Equation [57-60]: $ln (100 - Q_t) = ln 100 - k_1 . t$ Eq. (3)

Second-order Equation [58]: $1 / (100 - Q_t) = k_2 . t$ Eq. (4)

Higuchi model Equation [57,59,60]: $Q_t = k_H . t^{1/2}$ Eq. (5)

Hixson–Crowell model Equation [57,59,60]: $(100 - Q_t)^{1/3} = (100)^{1/3} - k_{HC} . t$ Eq. (6)

where, Q_t is % drug release at time t; k_0, k_1, k_2, k_H, and k_{HC} are release rate constants for zero-order, first-order, second-order, Higuchi square root of time model, and Hixson–Crowell cube root model equations [Eqs. (2-6)], respectively. MZ release data obtained was subjected to different drug release models in order to establish the drug release mechanism and kinetics. The criteria for selecting the most appropriate model was based on the best goodness of fit and the smallest sum of squared residuals (SSR) [61,62].

Physico-chemical interaction studies

Differential scanning calorimetry (DSC) studies

DSC was performed for pure MZ, pure polymers and crushed tablets of each batch to detect any possible chemical interactions between the drug and polymers and other excipients employed in tablet formulations. DSC thermograms were performed using an automatic thermal analyzer (DSC-50, Shimadzu, Japan). Sealed and holed aluminum pans heated in an atmosphere of nitrogen were used in the experiments for all samples and an empty pan, prepared in the same way was used as a reference. Samples of pure drug and powdered tablets of 5 mg each were weighted directly into the aluminum pans and the thermal analysis was carried out using heating ramp from 25 to 300 °C at 10 °C/min scale up rate. A nitrogen purge (20 ml/min) was maintained throughout the run.

Fourier transform-infra red (FT-IR) analysis

FT-IR spectra were obtained using Jasco FT-IR-6100 spectrometer (Jasco, Japan). The samples (pure MZ, pure polymers and crushed tablets of each batch) were previously ground and mixed thoroughly with potassium bromide, an infrared transparent matrix, at 1:5 (sample:KBr) ratio, respectively. The KBr disks were prepared by compressing the powders at a pressure of 5 tons for 5 min in a hydraulic press. Scans were obtained at a resolution of 4 cm^{-1}, from 4000 cm^{-1} to 400 cm^{-1}.

RESULTS AND DISCUSSION

Physical parameters of floating tablets

Weight variation

All the prepared floating tablets showed acceptable weight variation range. The average tablet weight for M1, M2, M3 and M6 ranged from 373.1 to 335.3 mg and from 654.3 to 590.6 mg for M4 and M5 (cf. Table 1 for tablet composition). Not more than two tablets deviated from the average weight by more than 5.0 % (which is the percentage deviation allowed according to the British pharmacopoeia for uncoated and film-coated tablets weighing more than 250 mg), and none of the tablets deviated by more than twice that percentage [63].

Thickness and diameter

The prepared tablets showed good uniformity of thickness and diameter. The values of tablet thickness were in the range of 2.25 to

2.43 mm for M1, M2, M3 and M6 and from 4.26 - 4.33 mm for M4 and M5. The average diameter ranged from 12.73 to 12.84 mm.

Hardness

Average tablet hardness was between 3.33 and 6.45 kP, except for Carbopol 974P based formula (M6) where the average tablet hardness was 24.6 kP.

Content uniformity

The drug concentration was not less than 92 % and did not exceed 100 % of the labeled claim. This result indicated that all the prepared formulations complied with the limits of pharmacopoeia for content uniformity, i.e., the average percentage of drug content of all formulas was found to be within the range of 85 % and 115 % of the label claim [64].

***In vitro* evaluation**

Floating lag time and floating duration

The investigated gastric floating tablets consisted of $NaHCO_3$ as a gas-forming agent dispersed in a hydrogel matrix. When the tablet reaches the stomach, carbon dioxide gas is liberated by the acidity of the gastric contents and is entrapped in the jellified hydrocolloid. A decrease in specific gravity causes the tablet to float on the test medium [54,65]. The extended residence time of drug in stomach could ensure more localized drug concentration which is useful for *H. pylori* eradication [25,66].

The preformulation optimization studies of tablets prepared with plain polymers showed that 10 % $NaHCO_3$ was required to achieve acceptable *in vitro* buoyancy. However, when avicel was added, to the tablets containing locust gum (M4) and guar gum (M5) in order to improve compression, $NaHCO_3$ percent had to be raised to 20 % to improve floating properties. In both cases, further increase in the concentration of $NaHCO_3$ did not show any remarkable improvement on floating behavior. Moreover, other researchers reported that when the amount of $NaHCO_3$ was increased, a large amount of effervescence occurred, which in turn resulted in pore formation, these pores led to rapid hydration of the polymer matrix and thereby to rapid drug release [67].

Table 2 showed the floating lag time (FLT), which is considered as one of the factors influencing the behavior of the effervescent systems as well as the floating duration (FD). All tablet formulas (except for formula M6) showed an almost instantaneous flotation with a floating lag time of 1-2 s (SD < 0.01), good matrix integrity, and a prolonged floating duration of more than 24h. This suggests that the gel layers, formed by the investigated polymers, enabled efficient entrapment of the generated gas bubbles. The possible increase in tablet gas entrapment made it float on the test medium (0.1 N HCl) for this extended period of time, without the loss of tablet integrity [31,68].

Table 2: Summary of the results of floating lag time (FLT) and floating duration (FD) for the prepared MZ tablets

Formula code	Polymer used	FLT (s)	FD (h)	Matrix integrity
M1	HPMC-K4M	2	> 24	+
M2	Na alginate, medium viscosity	1	> 24	+
M3	Na alginate, low viscosity	1	> 24	+
M4	Locust gum	1	> 24	+
M5	Guar gum	1	> 24	+
M6	Carbopol 974P	**7200**	**> 24**	-

(+) sign indicates good matrix integrity, (-) sign indicates loss of matrix integrity

Among all polymers, Carbopol 974P based tablets, M6, showed an extreme delay of floating lag time (2 h) and did not maintain good tablet integrity as well, where the polymer swelled and diffused resulting in a very weak texture. These results were unexpected from the preliminary studies, done in our laboratory, for tablets prepared with plain Carbopol 974P and 10 % $NaHCO_3$. These plain tablets were able to show acceptable *in vitro* buoyancy, with a mean FLT of 6 s and a FD of more than 24 h; meanwhile, good matrix integrity was maintained. Therefore, in this case carbopol might provide other gastroretentive mechanisms to maintain the GRDDS in the GIT but not a good candidate specifically, for incorporation of an amount of 250 mg MZ in GFDDS. Thus, this formula was excluded from further release studies.

This negative effect, with another grade of carpobol (CP934), on the floating behavior was also reported by other researchers [69]. Their results demonstrated that incorporation of CP934 had an undesirable effect on the floating behavior of gastric floating calcium capsules. This was explained by a moisture isotherm of CP934, illustrating that CP934 had a high moisture absorption curve. This resulted in a dramatic increase in the density of the GFDDS, which in turn showed a corresponding decrease in the floating capacity of GFDDS [69].

***In vitro* release studies**

Depending on the type of the investigated polymer in the current study, various drug release profiles were successfully tailored. Release profiles of the five selected tablet formulations, based on the results of the *in vitro* buoyancy studies, with acceptable floating properties were studied. Fig. 2 showed the influence of the polymer type on the release of MZ from the floating tablets in acidic medium. All tablet formulations were found to maintain good matrix integrity and MZ release retardation.

The percentages of MZ released after 6 h (Q_{6h}) from different polymers as well as the release similarity between HPMC-K4M and the natural polymers studied [alginates (MV & LV), gums (locust & guar)] are shown in Table 3. The results displayed showed that after 6 h, 43 % (lowest drug release), 54.25 %, 54.56 %, 61.26 %, and 75 % (highest drug release) of MZ were released from M2 (Na alginate - MV), M4 (locust gum), M5 (guar gum), M1 (HPMC-K4M) and M3 (Na alginate - LV), respectively. These polymers (except Na alginate - MV) could be used as an alternative to the widely used synthetic polymer HPMC - K4M for formulating floating tablets containing 250 mg MZ. This will be advantageous as natural polymers are safer, nontoxic, capable of chemical modification and have gel forming nature. Moreover, they are biocompatible, inexpensive and readily available compared to synthetic polymers. However, the long - term stability of the product will be the key factor for product selection.

Moreover, the similarity factor f_2 value between the tablets of the two grades of alginates (MV & LV) corresponding to formulas M2 and M3 release curves was found to be 40, indicating that these two release curves are not similar [56]. These results revealed that different formulation variables, specifically in this case Na alginate viscosity grade, were crucial for MZ release from the prepared floating tablets. On the contrary, when the two release profiles of the tablets of the two types of gums (locust & guar) corresponding to formulas M4 and M5 were compared, the similarity f_2 value was found to be 60, indicating that the two profiles were similar. Keeping in mind that these two gums gave similar floating properties as well, it can be predicted that these two gums can be alternatively used to prepare MZ floating tablets.

It is established that in controlled or sustained release formulations, diffusion, swelling and erosion are the three most important rate controlling mechanisms [25]. For formulas M1 (HPMC-K4M) and M4 (Locust gum) drug release rate gave a biphasic release rate pattern.

The rapid phase showed in the initial 15 min of the release study and followed by a slower one.

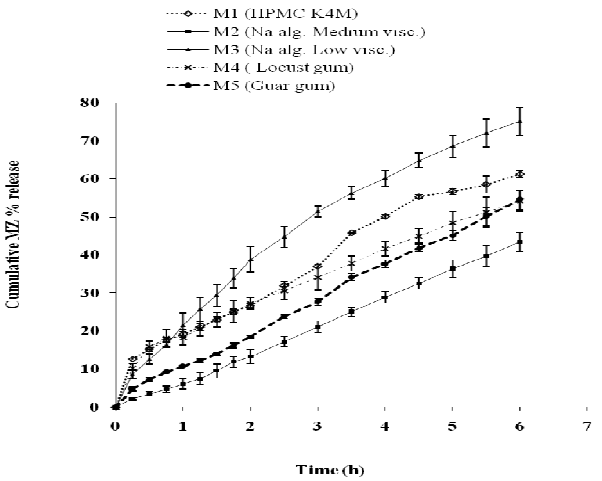

Fig. 2: Release profiles of MZ from different floating tablet formulas.

Table 3: Percentage of MZ released after 6 h (Q_{6h}) and a comparison between release profiles of natural polymers and HPMC-K4M (set as reference) by the similarity factor method (f_2).

Formula	Q_{6h} (% ± SD)	similarity factor (f_2)
M1 (HPMC-K4M)	61.26 ± 0.91	_
M2 (Na alginate - MV)	43.42 ± 2.52	39
M3 (Na alginate - LV)	75.11 ± 3.66	50
M4 (Locust gum)	54.25 ± 2.71	51
M5 (Guar gum)	54.56 ± 2.54	63

The release kinetics was computed by fitting the release rate data to zero-order, first-order, second-order, Higuchi, and Hixson & Crowell cube root models [Eqs. (2-6)]. The drug release rates from MZ formulas were found to follow either zero-order kinetics, Eq. (2) (M2, and M5), *i.e*. MZ release rate was independent of its concentration [59] or Hixson-Crowell cube root model, Eq. (6) (M1 and M4), explaining that the release of the drug from these systems depended on the change in surface area and diameter of the tablets with time which is a typical case of systems that dissolute or erode over time. Only formula M3 followed the first order release kinetics, Eq. (3), meaning that the release rate is concentration-dependent [59]. The $t_{1/2}$ values of the prepared floating tablets were in the range of 4.25 h - 6.76 h (Table 4). Formula M1 showed the lowest value of $t_{1/2}$, while formula M2 exhibited the highest value.

Table 4: The kinetic release models obtained from the release data and the corresponding $t_{1/2}$ values.

Formula Code	Release model	*$t_{1/2}$ (h)
M1	Hixson and Crowell Cube-Root	4.25
M2	Zero-Order	6.76
M3	First order	3.03
M4	Hixson and Crowell Cube-Root	5.29
M5	Zero-Order	5.70

*Where half-life ($t_{1/2}$) is the time required to reduce the drug concentration to one half its initial value [61,62].

DSC analysis results

The possibility of occurrence of any drug - excipients interactions in the tablets was predicted by conducting DSC studies [70]. Fig. 3 showed the DSC thermograms of MZ, polymers and MZ floating tablet formulations. A sharp endothermic peak corresponding to the melting point of pure drug MZ was found at 166 ºC. For drug sample and the proposed formulations, the thermograms did not show any significant shift in endothermic peaks. Based on the thermograms of DSC, there is no possibility of interactions between MZ and the proposed excipients. These systems will be subjected to a long-term stability study to give a full data about the feasibility of selecting the optimum formula.

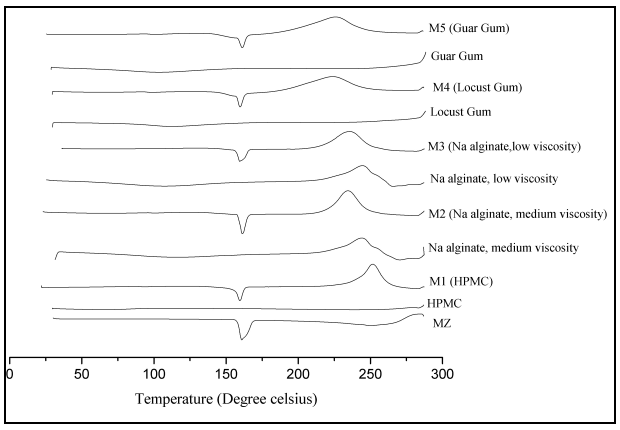

Fig. 3: DSC thermograms of MZ, polymers and MZ floating tablet formulations.

FT-IR analysis results

The FT-IR spectra analysis of MZ and the physical mixtures revealed that there was no significant interaction between drug and polymers as shown in Fig. 4. The characteristic band peaks acquired were taken from the prepared drug-polymer mixtures. The interaction study between drug and polymer was evaluated [71].

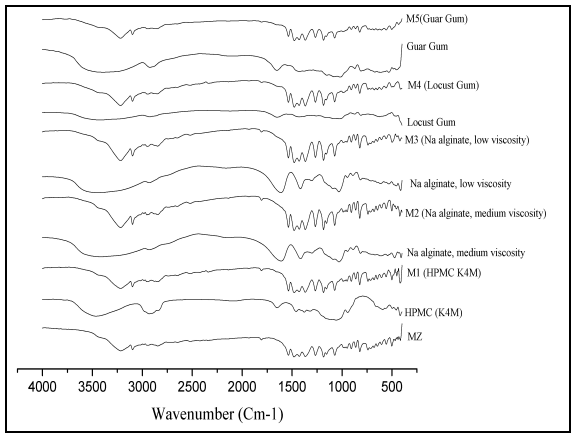

Fig. 4: FT-IR spectra of MZ, polymers and MZ floating tablet formulations.

The FT-IR spectra of the physical mixture of the drug with polymers exhibited all the characteristic bands as in the spectrum of the individual MZ, HPMC, Na alginates, Locust gum and Guar gum and other excipients excluding the possibility of any interaction. Also,

chemical and functional group changes during the processing of the formulation of floating tablets were excluded [72].

CONCLUSIONS

The present study demonstrates the feasibility of prolonging the gastric residence time of anti- *H. pylori* drugs via oral administration of the proposed floating tablets. Sustained release of metronidazole (MZ) from such floating tablets can be achieved over a period of at least 6 h. Additionally, the study proposed that Na alginate-LV and two gums (locust and guar) could be used as an alternative to the widely used synthetic polymer HPMC-K4M for formulating floating tablets containing 250 mg MZ. This would be an advantage as natural polymers are safe, nontoxic, capable of chemical modification and have gel forming nature. Also, they are biocompatible, inexpensive and readily available compared to synthetic polymers. These dosage forms need further phsicochemical stability studies as well as a clinical trial involving patients suffering from peptic ulcer. These stomach targeted dosage forms could maintain the minimum inhibitory concentration for sufficient time to allow for local eradication and thereby achieve better efficiency of therapy with improved patient compliance, reduced costs and minimized side effects caused by immediate release dosage forms.

CONFLICT OF INTEREST

There is no conflict of interest to disclose.

REFERENCES

1. Sathish D, Himabindu S, Shravan Kumar Y, Shayeda, Madhusudan Rao Y. Floating Drug Delivery Systems for Prolonging Gastric Residence Time: A Review. Curr Drug Deliv 2011;8(5):494-510.
2. Bardonnet PL, Faivre V, Pugh WJ, Piffaretti JC, Falson F. Gastroretentive Dosage Forms: Overview and Special Case of *Helicobacter Pylori*. J Cont Rel 2006;111(1-2):1-18.
3. Adibkia K, Hamedeyazdan S, Javadzadeh Y. Drug Release Kinetics and Physicochemical Characteristics of Floating Drug Delivery Systems. Expert Opin Drug Deliv 2011;8(7):891-903.
4. Chawla G, Gupta P, Koradia V, Bansal Ak. Gastroretention a Means to Address Regional Variability in Intestinal Drug Absorption. Pharm Technol 2003;7:52-68.
5. Pawar Vk, Kansal S, Garg G, Awasthi R, Singodia D, Kulkarni GT. Gastroretentive Dosage Forms: A Review With Special Emphasis on Floating Drug Delivery Systems. Drug Deliv 2011;18(2):97-110.
6. Ali J, Arora S, Ahuja A, Babbar Ak, Sharma Rk, Khar Rk, *et al*. Formulation and Development of Hydrodynamically Balanced System for Metformin: *In Vitro* and *In Vivo* Evaluation. Eur J Pharm Biopharm 2007;67(1):196-201.
7. Baki G, Bajdik J, Pintye-Hodi K. Evaluation of Powder Mixtures and Hydrophilic Gastroretentive Drug Delivery Systems Containing Zinc Acetate and Sodium Bicarbonate. J Pharm Biomed Anal 2011;54(4):711-6.
8. Yao H, Xu L, Han F, Che X, Dong Y, Wei M, *et al*. A Novel Riboflavin Gastro-Mucoadhesive Delivery System Based on Ion-Exchange Fiber. Int J Pharm 2008;364(1):21-6.
9. Rajinikanth PS, Mishra B. Floating In Situ Gelling System for Stomach Site-Specific Delivery of Clarithromycin to Eradicate *H. Pylori*. J Cont Rel 2008;125(1):33-41.
10. Gisbert JP, Torrado S, M De La Torre P, Mcnicholl AG, Torrado S. Amoxicillin Gastric Retention Systems for Helicobacter pylori Treatment. Gastroenterology 2011;140(5 Suppl 1):S-880.
11. Jang SW, Lee JW, Park SH, Kim JH, Yoo M, Na DH, *et al*. Gastroretentive Drug Delivery System of Da-6034, a new flavonoid derivative, for the Treatment of Gastritis. Int J Pharm 2008;356(1-2):88-94.
12. Guan J, Zhou L, Nie S, Yan T, Tang X, Pan W. A Novel Gastric-Resident Osmotic Pump Tablet: *In Vitro* and *In Vivo* Evaluation. Int J Pharm 2010;383(1-2):30-6.
13. Jimenez-Martinez I, Quirino-Barreda T, Villafuerte-Robles L. Sustained Delivery of Captopril from Floating Matrix Tablets. Int J Pharm 2008;362(1-2):37-43.
14. Kavimandan NJ, Lakshman JP, Matharu AS, Royce AE, Teelucksingh NR, Ogorka J. Extended Release Gastro-Retentive Oral Drug Delivery System for Valsartan. Ep2061438;2009.
15. Talukder R, Fassihi R. Gastroretentive Delivery Systems: A Mini Review. Drug Dev Ind Pharm 2004;30(10):1019-28.
16. Streubel A, Siepmann J, Bodmeier R. Drug Delivery to the Upper Small Intestine Window Using Gastroretentive Technologies. Curr Opin Pharmacol 2006;6(5):501-8.
17. Murphy CS, Pillay V, Choonara YE, Du Toit LC. Gastroretentive Drug Delivery Systems: Current Developments in Novel System Design and Evaluation. Curr Drug Deliv 2009;6(5):451-60.
18. Singh BN, Kim KH. Floating Drug Delivery Systems: An Approach to Oral Controlled Drug Delivery Via Gastric Retention. J Cont Rel 2000;63(3):235-59.
19. Arora S, Ali J, Ahuja A, Khar RK, Baboota S. Floating Drug Delivery Systems: A Review. AAPS Pharmscitech 2005;6(3):E372-E90.
20. Pawar Vk, Kansal S, Asthana S, Chourasia Mk. Industrial Perspective of Gastroretentive Drug Delivery Systems: Physicochemical, Biopharmaceutical, Technological and Regulatory Consideration. Expert Opin Drug Deliv 2012;9(5):551-65.
21. Khan GM, Jiabi Z. Formulation and *In Vitro* Evaluation of Ibuprofen-Carbopol® 974PNF Controlled Release Matrix Tablets III: Influence of Co-Excipients on Release Rate of the Drug. J Cont Rel 1998;54:185-90.
22. Gutiérrez-Sánchez PE, Hernández-León A, Villafuerte-Robles L. Effect of Sodium Bicarbonate on the Properties of Metronidazole Floating Matrix Tablets. Drug Dev Ind Pharm 2008;34(2):171–80.
23. Cedillo-Ramírez E, Villafuerte-Robles L, Hernández-León A. Effect of Added Pharmatose DCL11 on the Sustained-Release of Metronidazole from Methocel K4M and Carbopol 971P NF Floating Matrices. Drug Dev Ind Pharm 2006;32(8):955-65.
24. Lara-Hernández B, Hernández-León A, Villafuerte-Robles L. Effect of Stearic Acid on the Properties of Metronidazole/Methocel K4M Floating Matrices. Brazilian J Pharm Sci 2009;45:497-505.
25. Asnaashari S, Khoei NS, Zarrintan MH, Adibkia K, Javadzadeh Y. Preparation and Evaluation of Novel Metronidazole Sustained Release and Floating Matrix Tablets. Pharm Dev Technol 2011;16(4):400-7.
26. Murthy RSR. Biodegradable Polymers, Controlled and Novel Drug Delivery. 1st ed. New Delhi: CBS Publishers; 1997. p. 27-51.
27. Bechgaard H, Ladefoged K. Distribution of Pellets in the Gastrointestinal Tract. The Influence on Transit Time Exerted by the Density or Diameter of Pellets. J Pharm Pharmacol 1978;30:690-2.
28. Javadzadeh Y, Hamedeyazdan S, Adibkia K, Kiafar F, Zarrintan MH, Barzegar-Jalali M. Evaluation of Drug Release Kinetics and Physico-Chemical Characteristics of Metronidazole Floating Beads Based on Calcium Silicate and Gas-Forming Agents. Pharm Dev Technol 2009;15(4):329-38.
29. Eftaiha AF, Qinna N, Rashid IS, Al Remawi MM, Al Shami MR, Arafat TA, *et al*. Bioadhesive Controlled Metronidazole Release Matrix Based on Chitosan and Xanthan Gum. Mar Drugs 2010;8:1716-30.
30. Jagdale SC, Patil S, Kuchekar BS. Application of Design of Experiment for Floating Drug Delivery of Tapentadol Hydrochloride. Computational and Mathematical Methods in Medicine 2013:1-7.
31. Abdelbary A, El-Gazayerly ON, Nashwa A. El-Gendy NA, Ali AA. Floating Tablet of Trimetazidine Dihydrochloride: An Approach for Extended Release with Zero-Order Kinetics. AAPS Pharmscitech 2010;11(3):1058-67.
32. Garg R, Das Gupta G. Preparation and Evaluation of Gastroretentive Floating Tablets of Silymarin. Chem Pharm Bull 2009;57(6):545-9.
33. Jain GK. Gums and Mucilages: Versatile Excipients for Pharmaceutical Formulations Drug Delivery Systems. Asian J of Pharm Sci 2009;4:309-23.
34. Ganesh K, Archana D, Preeti K. Natural Polymers in the Development of Floating Drug Delivery Systems: A Review. J of Pharm and Life Sci 2013;2(4):165-78.

35. Marshall BJ. Unidentified Curved Bacilli in Gastric Epithelium in Active Chronic Gastritis. Lancet 1983;1:1273-5.
36. Marshall BJ, Warren JR. Unidentified Curved Bacilli in the Stomach of Patients with Gastritis and Peptic Ulceration. Lancet 1984;1:1311-5.
37. Vakil N, Cutler A. Ten-Day Triple Therapy with Ranitidine, Bismuthcitrate, Amoxicillin and Clarithromycin in Eradicating Helicobacter Pylori. Am J Gastroenterol 1999;94:1197–9.
38. Narkar M, Sher P, Pawar A. Stomach-Specific Controlled Release Gellan Beads of Acid-Soluble Drug Prepared by Ionotropic Gelation Method. AAPS Pharmscitech 2010;11(1):267-77.
39. Shah S, Qaqish R, Patel V, Amiji M. Evaluation of the Factors Influencing Stomach-Specific Delivery of Antibacterial Agents for Helicobacter pylori Infection. J Pharm Pharmacol 1999;51:667–72.
40. Emara LH, Abdou AR, El-Ashmawy AA, Badr RM, Mursi NM. *In Vitro* Evaluation of Floating Matrix Tablets of Amoxicillin and Metronidazole for the Eradication of Helicobacter pylori. Int J Pharm Pharm Sci 2012;4(3):671-81.
41. Amiji MM. Tetracycline-Containing Chitosan Microspheres for Local Treatment of Helicobacter pylori Infection. Cellulose 2007;14:3-14.
42. Umamaheshwari RB, Suman R, Jain Nk. Anti-Helicobacter pylori Effect of Mucoadhesive Nanoparticle Bearing Amoxicillin in Experimental Gerbils. AAPS Pharmscitech 2004;5:60-8.
43. Sung JJ, Chung SC, Ling Tk. Antibacterial Treatment of Gastric Ulcers Associated with *Helicobacter pylori*. N Engl J Med 1995;332 (3):139-42.
44. Dollery C. Therapeutic Drugs. 2nd Ed. Vol. 2, Edinburgh: Churchill Livingstone; 1999.
45. Yang L, Eshraghi J, Fassihi R. A New Intragastric Delivery System for the Treatment of *Helicobacter pylori* Associated Gastric Ulcer: *In Vitro* Evaluation. J Cont Rel 1999;57(3):215–22.
46. Sriamornsak P, Asavapichayont P, Nunthanid J, Luangtana-Anan M, Limmatvapirat S, Piriyaprasarth S. Wax-Incorporated Emulsion Gel Beads of Calcium Pectinate for Intragastric Floating Drug Delivery. AAPS Pharmscitech 2008;9(2):571-6.
47. Sriamornsak P, Sungthongjeen S, Puttipipatkhachorn S. Use of Pectin as a Carrier for Intragastric Floating Drug Delivery: Carbonate Salt Contained Beads. Carbohydr Polym 2007;67(3):436-45.
48. Ishak Ra, Awad Ga, Mortada Nd, Nour Sa. Preparation, *In Vitro* and *In Vivo* Evaluation Of Stomach-Specific Metronidazole Loaded Alginate Beads As Local Anti-Helicobacter Pylori Therapy. J Cont Rel 2007;119(2):207–14.
49. Murata Y, Sasaki N, Miyamoto E, Kawashima S. Use of Floating Alginate Gel Beads for Stomach-Specific Drug Delivery. Eur J Pharm Biopharm 2000;50(2):221–6.
50. Jeong B, Kim SW, Bae YH. Thermosensitive Sol-Gel Reversible Hydrogels. Adv Drug Deliv Rev 2002;54:37-51.
51. Nama M, Gonugunta CS, Reddy Veerareddy P. Formulation and Evaluation of Gastroretentive Dosage Forms of Clarithromycin. AAPS Pharmscitech 2008;9(1):231-7.
52. United States Pharmacopeia and National Formulary USP 30-NF 25;The United States Pharmacopeial Convention, Inc. :Rockville, MD; 2007. p. 2655.
53. Jiménez-Castellanos MR, Zia H, Rhodes CT. Design and Testing *In Vitro* of a Bioadhesive and Floating Drug Delivery System for Oral Application. Int J Pharm 1994;105(1):65-70.
54. Tadros MI. Controlled-Release Effervescent Floating Matrix Tablets of Ciprofloxacin Hydrochloride: Development, Optimization and *In Vitro-In Vivo* Evaluation in Healthy Human Volunteers. Eur J Pharm Biopharm 2010;74:332-9.
55. Moore JW, Flanner HH. Mathematical comparison of dissolution profiles. Pharm Tech 1996;20:64-74.
56. United States Food and Drug Administration. Guidance for industry, dissolution testing of immediate release solid oral dosage forms; 1997.
57. Sood A, Panchagnula R. Drug Release Evaluation of Diltiazem CR Preparations. Int J Pharm 1998;175(1):95–107.
58. Wright MR. The Kinetic Analysis of Experimental Data: An Introduction to Chemical Kinetics. The Atrium, Southern Gate, Chichester, West Suessex P019 8SQ, England: Wiley J and Sons Ltd; 2004. p. 43-95.
59. Philip Ak, Pathak K. Osmotic Flow Through Asymmetric Membrane: A Means for Controlled Delivery of Drugs with Varying Solubility. AAPS Pharmscitech 2006;7(3):E1–E11.
60. Karasulu E, Yesim Karasulu H, Ertan G, Kirilmaz L, Guneri T. Extended Release Lipophilic Indomethacin Microspheres: Formulation Factors and Mathematical Equations Fitted Drug Release Rates. Eur J Pharm Sci 2003;19(2-3):99-104.
61. Ostle B. Statistics in Research: The Iowa State University Press, Ames, Iowa, USA; 1960. p. 64.
62. Parab PV, Oh CK, Ritschel WA. Sustained Release from Precirol® (Glycerol Palmito-Stearate) Matrix. Effect of Mannitol and Hydroxypropyl Methylcellulose on the Release of Theophylline. Drug Dev Ind Pharm 1986;12(8):1309-27.
63. British Pharmacopoeia. London: The Pharmaceutical Press; 1998. p. 242.
64. United States Pharmacopeia and National Formulary USP 27–NF 22;The United States Pharmacopeial Convention, Inc. :Rockville, MD; 2004. p. 454–8.
65. Singh BM, Kim KH. Floating Drug Delivery Systems: An Approach to Oral Controlled Drug Delivery via Gastric Retention. J Cont Rel 2000;63:235-59.
66. Chavanpatil M, Jain P, Chaudhari S, Shear R, Vavia P. Development of Sustained Release Gastroretentive Drug Delivery System for Ofloxacin: *In Vitro* and *In Vivo* Evaluation. Int J Pharm 2005;304:178-84.
67. El Gamal SS, Naggar VE, Allam AN. Optimization of Acyclovir Oral Tablets Based on Gastroretention Technology: Factorial Design Analysis and Physicochemical Characterization Studies. Drug Dev Ind Pharm 2011;37(7):855-67.
68. Steingoetter A, Weishaupt D, Kunz P, Mader K, Lengsfeld H, Thumshirn M, et al. Magnetic Resonance Imaging for the *In Vivo* Evaluation of Gastric-Retentive Tablets. Pharm Res 2003;20(12):2001-7.
69. Li S, Lin S, Daggy BP, Mirchandani HL, Chien YW. Effect of HPMC and Carbopol on the Release and Floating Properties of Gastric Floating Drug Delivery System Using Factorial Design. Int J Pharm 2003;253:13–22.
70. Devraj, Bhatt DC. Studies on Enteric Coated Sustained Timed-Release Tablets of Metronidazole. J Chem Pharm Res 2010;2(2):226-32.
71. Choudhury PK, Murthy PN, Tripathy NK, Panigrahi R, Behera S. Investigation of Drug Polymer Compatibility: Formulation and Characterization of Metronidazole Microspheres for Colonic Delivery. Webmed Central Pharm Sci 2012;3(3):WMC003128.
72. Purushothaman M, Vijaya Ratna J. Formulation Optimization and Release Kinetics of Metronidazole Matrix, Compression and Spray Coated Tablets: Effect of Organic Acid on Colon Targeted Drug Delivery System. Int J Res Pharm Sci 2010;1(4):551-62.