Preparation and Evaluation of Metronidazole Sustained Release Floating Tablets

Laila H. Emara1*, Aya R. Abdou1, Ahmed A. El-Asshawy1, Nadia M. Mursi2

1Industrial Pharmacy Laboratory, Medical and Pharmaceutical Chemistry Department, Division of Pharmaceutical Industries, National Research Centre, El-Tahrir Street, Dokki, Giza 12622, Egypt, 2Department of Pharmaceutics, Faculty of Pharmacy, Cairo University, Cairo, 11562, Egypt. Email: lhemara@yahoo.com

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 Gube-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 caromers 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.
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 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 rapidly in acidic medium. Secondly, the drug must diffuse into the antibacterial agents, such as penicillin and erythromycin, degrade rapidly in acidic medium. Lastly, the contact time of antibacterial drugs with the gastric mucosa under mucous remains on the luminal surface of the gastric mucosa under mucous layer and gastric cancer due to \( H. pylori \) resides ensuring better microorganism eradication. 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 \((\text{NaHCO}_3)\). 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) and 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 F9/00/20, 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 \((\text{NaHCO}_3)\) was from Kahira Pharm. (Egypt). Methanol (HPLC grade) was from Prolabo (France). Distilled water was used for all experiments (MilliRO 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>
<thead>
<tr>
<th>Composition:% (w/w)/tablet</th>
<th>M1</th>
<th>M2</th>
<th>M3</th>
<th>M4</th>
<th>M5</th>
<th>M6</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPMC-K4M</td>
<td>20</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Na alginate (medium viscosity)</td>
<td>0</td>
<td>20</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Na alginate (low viscosity)</td>
<td>0</td>
<td>0</td>
<td>20</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Locust Gum</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>20</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Guar Gum</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Carbopol 974P</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>NaHCO₃</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>20</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Avicel</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>20</td>
<td>20</td>
<td>0</td>
</tr>
</tbody>
</table>

**Characterization of the prepared tablets**

**Physical parameters**

PTB (311E) 3 in 1 Hardness, Diameter and Thickness Tester (PTB 311E Tablet Testing Instrument, 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 λmax 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 1 L 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 0.1 N 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 λmax (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 (f2) as proposed by Moore and Flanner [55] was calculated from the mean release data and used to compare between the different release profiles. f2 is given by Eq. (1):

\[ f_2 = 50 \times \log \left( \frac{(1 + (1/n))}{(R_t - T_t)^2} \right) - 0.5 \times 100 \]

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 f2 value is a measure of the similarity between two dissolution curves and its value ranges from 0 and 100. A high f2 value indicates high similarity between two release rate profiles. FDA suggests that two dissolution profiles are considered similar if the similarity factor f2 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]:

\[ Q_t = k_s \times t \]

First-order Equation [57-60]:

\[ \ln(100 - Q_t) = ln100 - k \times t \]

Second-order Equation [58]:

\[ \frac{1}{(100 - Q_t^2)} = k_o \times t \]

Hixson–Crowell model Equation [57,59,60]:

\[ Q_t = k_s \times t^{1/3} \]

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 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

Emara et al.

Int J Pharm Pharm Sci, Vol 6, Issue 9, 198-204
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 formulations (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 24 h. 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>
<thead>
<tr>
<th>Formula code</th>
<th>Polymer used</th>
<th>FLT (s)</th>
<th>FD (h)</th>
<th>Matrix integrity</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1</td>
<td>HPMC-K4M</td>
<td>2</td>
<td>&gt; 24</td>
<td>+</td>
</tr>
<tr>
<td>M2</td>
<td>Na alginate, medium viscosity</td>
<td>1</td>
<td>&gt; 24</td>
<td>+</td>
</tr>
<tr>
<td>M3</td>
<td>Na alginate, low viscosity</td>
<td>1</td>
<td>&gt; 24</td>
<td>+</td>
</tr>
<tr>
<td>M4</td>
<td>Locust gum</td>
<td>1</td>
<td>&gt; 24</td>
<td>+</td>
</tr>
<tr>
<td>M5</td>
<td>Guar gum</td>
<td>1</td>
<td>&gt; 24</td>
<td>+</td>
</tr>
<tr>
<td>M6</td>
<td>Carbopol 974P</td>
<td>7200</td>
<td>&gt; 24</td>
<td></td>
</tr>
</tbody>
</table>

(+) 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 GFDDS 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 carpolbol (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 ($Q_6$) from different polymers as well as the release similarity between HPMC-K4M and the natural polymers studied [alginites (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 $f_1$ value between the tablets of the two grades of alginites (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 factor $f_1$ 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.](image)

Table 3: Percentage of MZ released after 6 h ($Q_{6\text{h}}$) and a comparison between release profiles of natural polymers and HPMC-K4M (set as reference) by the similarity factor method ($f_{2}$).

<table>
<thead>
<tr>
<th>Formula</th>
<th>$Q_{6\text{h}}$ (% ± SD)</th>
<th>$f_{2}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1 (HPMC-K4M)</td>
<td>61.26 ± 0.91</td>
<td>60</td>
</tr>
<tr>
<td>M2 (Na alginate - LV)</td>
<td>43.42 ± 2.52</td>
<td>39</td>
</tr>
<tr>
<td>M3 (Na alginate - MV)</td>
<td>75.11 ± 3.66</td>
<td>50</td>
</tr>
<tr>
<td>M4 (Locust gum)</td>
<td>54.25 ± 2.71</td>
<td>51</td>
</tr>
<tr>
<td>M5 (Gum guar)</td>
<td>54.56 ± 2.54</td>
<td>63</td>
</tr>
</tbody>
</table>

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 formulations 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 dissolve 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.

*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 °C. 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.](image)

**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 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.](image)
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 pharmacoclinical 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


