

IN VITRO EVALUATION OF FLOATING MATRIX TABLETS OF AMOXICILLIN AND METRONIDAZOLE FOR THE ERADICATION OF HELICOBACTER PYLORI

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ABSTRACT

The aim of this study was to develop floating tablets for amoxicillin trihydrate (AmoxTH) and metronidazole, for the treatment of *Helicobacter pylori* (*H.pylori*) mediated peptic ulcer. Tablets were developed based on gas-formation technique to prolong gastric-residence time with the desired in vitro release profile. Poly(ethylene oxide) (PEO) and hydroxypropylmethylcellulose (HPMC) of various grades were used as swellable polymers, while NaHCO₃ and CaCO₃ were used as the gas generating agents. Tablets were evaluated for physical parameters, floating characteristics and in vitro release rate studies using a well controlled open-loop system of the flow-through cell apparatus. Results showed that the shortest floating lag-time values recorded were 0.40 and 1.00 min, corresponding to AmoxTH tablets containing 150 mg HPMC-K4M and metronidazole tablets containing 240 mg PEO of M_w 8,000,000, respectively. The relation between floating lag time and M_w of PEO was directly proportional with AmoxTH tablets, and inversely proportional with metronidazole tablets. Tablets of both drugs were able to remain floating, without disintegration, for more than 6.0 hours in 0.1N HCl (pH 1.2), except in case of AmoxTH/PEO of M_w 100,000 and metronidazole/PEO of M_w 100,000, 300,000 and 900,000. The highest percentage of AmoxTH released (82.1%) was obtained from the double-layer tablet prepared with PEO of M_w 8,000,000, in the gas-generating layer and PEO of M_w 900,000 in the drug-releasing layer. While, the highest percentage of metronidazole released (75.3%) was obtained from the single-layer floating tablet containing PEO of M_w 100,000. Under the same storage conditions, AmoxTH double-layer tablet was found to show similar release profiles before and after storage, while metronidazole showed higher release rate profile.

Keywords: Gas formation technique, Amoxicillin trihydrate, Metronidazole, Flow-through cell apparatus, Floating tablets, Storage.

INTRODUCTION

Drug release from new drug delivery systems can be sustained for up to 24 h for many drugs using current release technologies. However, the real challenge in the development of oral controlled release dosage forms is to prolong the residence time of dosage forms in the stomach or upper gastrointestinal (GI) tract until the drug is completely released¹. Rapid GI transit could result in incomplete drug release from the drug delivery system in the absorption zone leading to diminished efficacy of the administered dose². Several approaches are currently used to retain the dosage form in stomach. These include different systems e.g.: floating^{3,4}, bioadhesive⁵, swelling and expanding systems^{6,7} as well as other delayed gastric emptying devices^{8,9}. The principle of floating preparations offers a simple and practical approach to achieve increased residence time for the dosage form in stomach and sustained drug release^{10,11}.

H.pylori is one of the major causative agents of peptic ulcer¹². According to the guidelines presented by the European Helicobacter Study Group (EHS¹³⁻¹⁷), ulcer patients who are *H.pylori* positive require treatment with antimicrobial agents, in addition to antisecretory drugs. Although many antibacterial agents have very low minimum inhibitory concentration (MIC) against *H.pylori* in vitro¹⁸, no single agent is effective in the eradication of the infection in vivo when administered alone¹⁹. The MIC₅₀ values (concentrations resulting in 50% inhibition) of amoxicillin and metronidazole, for instance, are as low as 0.008 µg/ml and 2 µg/ml, respectively¹⁸. In addition, single antibiotic therapy is strongly discouraged to prevent the development of resistant strains²⁰. There could be one or several reasons for the failure of single-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 mucosa²¹, which can be achieved through a gastroretentive dosage form.

Amoxicillin is the 4-hydroxy analogue of ampicillin, and is used in a similar variety of susceptible infections. It is given as part of treatment regimens to eradicate *H.pylori* infection in patients with peptic ulcer disease²². Metronidazole is a 5-nitroimidazole derivative with activity against anaerobic bacteria and protozoa. It is also used to eradicate *H.pylori* in peptic ulcer disease, in combination with antimicrobials, and either bismuth compounds or proton pump inhibitors²³.

Therefore, certain amoxicillin or metronidazole floating systems were developed for better eradication of *H.pylori*, including: amoxicillin floating minimatrices²⁴, gellan based amoxicillin floating in situ gelling systems²⁵, amoxicillin floating tablets²⁶⁻²⁸, amoxicillin floating alginate beads²⁹, floating metronidazole tablets³⁰⁻³⁵ and beads³⁶⁻³⁹.

Poly(ethylene oxide) (PEO) is among various hydrophilic polymers that, in the presence of water, form a hydrogel that could control the release of the active moiety either by swelling or by swelling/erosion. PEOs have been proposed as alternatives to cellulose or other ethylene glycol derivatives in the production of controlled release drug delivery systems⁴⁰. The rate and kinetics of drug release from hydrophilic matrix is dependant on various factors such as types of polymer, solubility of drug, polymer content, particle size of drug and polymer as well as types and amounts of excipients used in the formulation^{41,42}.

Hydroxypropylmethylcellulose (HPMC), a semi-synthetic cellulose derivative, is widely used as a matrix in oral controlled release tablet formulations^{43,44}. Its widespread use is mainly due to its generally regarded as safe (GRAS) status and biodegradable nature. Furthermore, it is compatible with numerous drugs, accommodates high levels of drug loading and can be easily incorporated to form matrix tablets by direct blending or granulation^{44,45}. The availability of a wide range of viscosity grades also allows the formulator to modify the release of drugs from HPMC matrix tablets according to the therapeutic need. Drug release from HPMC matrix tablet involves complex mechanisms⁴⁶. In contact with water, HPMC swells

to form a gel, which serves as a barrier to drug diffusion. Drug release from the HPMC-drug matrix involves solvent penetration into the dry matrix, gelatinization of the polymer, dissolution of the drug and diffusion of the solubilized drug through the gel layer. Concomitantly, outer layers of the tablet become fully hydrated and dissolve, a process generally referred to as erosion⁴⁷.

The objective of this study was to develop floating tablets of amoxicillin and metronidazole for treatment of peptic ulcers caused by *Helicobacter pylori*. PEO and HPMC were used as swellable polymers for their floating and drug release retardant properties⁴⁸. An effervescent mixture, for tablet floating, was used to release carbon dioxide in presence of acidic medium. Tablets were prepared by direct compression as a low cost method with no drug exposure to harsh conditions such as high temperature⁴⁹. The effect of different formulation variables on the tablet floating characteristics as well as the *in vitro* release rate profile was investigated.

MATERIALS AND METHODS

Materials

Amoxicillin Trihydrate (AmoxTH) and metronidazole were gifted from ELPICO (Egypt). Poly(ethylene oxide) (PEO) [molecular weights (M_w) 100,000, 300,000, 900,000, 4,000,000, and 8,000,000] and hydroxypropylmethylcellulose (HPMC): K4M, K15M and K100M, were purchased from Aldrich (Germany). Sodium bicarbonate (NaHCO_3) was from Kahira Pharm. (Egypt). Calcium carbonate (CaCO_3) and lactose were from BDH Laboratory Supplies (England). Magnesium stearate was obtained from Peter Greven (Nederland, Germany) and 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.

Tablet Preparation

Formulation of AmoxTH (375 mg/tablet) or metronidazole (250 mg/tablet) in swellable effervescent floating tablets was carried out as single and double layer tablets. These tablets were formulated with the use of swellable polymers (PEO or HPMC) and an effervescent mixture composed of sodium bicarbonate and calcium carbonate in the ratio of (1:2)³⁵, respectively. The final weight of the tablet was adjusted to 0.7 gm by adding lactose as filler.

All ingredients (for each formula) in their specified ratios (Tables 1, 2 and 3), were sieved through 710 μm sieve (mesh number 25) except for magnesium stearate which was sieved through 425 μm sieve (mesh number 40). Blending of all ingredients was carried out simultaneously using polyethylene bag⁵⁰, 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 formulae, a round die (13 mm internal diameter) with flat-faced punches were employed to give round flat-surface tablets.

Characterization of the prepared tablets

Physical parameters

Auto-Test4 (automatic tablet-testing system, Dr. Schleuniger Pharmatron, 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 100 ml glass-stoppered volumetric flask. The volume was then completed to the mark with either 0.1 N HCl (pH 1.2) or dilute HCl (1 in 100) for AmoxTH²⁴ and metronidazole⁵¹ tablets, respectively. The volumetric flasks were shaken using "temperature-controlled shaking water-bath (Lab-Line, USA)" for 30 min in 37°C water bath. The solution was then filtered, and the absorbance was measured spectrophotometrically at the predetermined λ_{max} at 272 and 277 for AmoxTH and metronidazole, respectively^{24,51}.

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 1.2⁵², at 37±0.5°C⁵³. The results were registered as an average of three repetitions.

Table 1: Composition of AmoxTH floating tablets (375 mg/tablet)

Tablet Code	Tablet Composition (mg) ^a										
	PEO Molecular Weight					HPMC Grade			Calcium Carbonate	Sodium Bicarbonate	
	8,000,000	4,000,000	900,000	300,000	100,000	K4M	K15M	K100M			
A1	240	0	0	0	0	0	0	0	0	40	20
A2	0	240	0	0	0	0	0	0	0	40	20
A3	0	0	240	0	0	0	0	0	0	40	20
A4	0	0	0	240	0	0	0	0	0	40	20
A5	0	0	0	0	240	0	0	0	0	40	20
A6	0	0	0	0	0	150	0	0	0	40	20
A7	0	0	0	0	0	225	0	0	0	40	20
A8	0	0	0	0	0	0	150	0	0	40	20
A9	0	0	0	0	0	0	0	150	0	40	20

^a 1% magnesium stearate was used as lubricant.

Table 2: Composition of metronidazole floating tablets (250 mg/tablet)

Tablet Code	Tablet Composition (mg) ^a					Calcium Carbonate	Sodium Bicarbonate
	PEO Molecular Weight						
	8,000,000	4,000,000	900,000	300,000	100,000		
M1	240	0	0	0	0	40	20
M2	0	240	0	0	0	40	20
M3	0	0	240	0	0	40	20
M4	0	0	0	240	0	40	20
M5	0	0	0	0	240	40	20
M6	120	0	120	0	0	40	20

^a 1% magnesium stearate was used as lubricant.

Table 3: Composition of the double layer floating tablets

Layer	Function	Total Weight of Each Layer (mg)	Composition ^a (mg)
1	Swellable gas- generating layer	200	PEO of M_w 8,000,000
2	Swellable / sustainable Drug containing layer	500	Calcium carbonate
			Sodium bicarbonate
			PEO of M_w 900,000
			AmoxTH ^b
			Lactose
			Or
			PEO of M_w 900,000
			Metronidazole ^c
			Lactose

^a1% magnesium stearate was used as lubricant; ^bTablet A.d.; ^cTablet M.d.

In vitro release studies

These studies were carried out using the open-loop 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 Figure (1), as this design allowed for floating observations while studying the release profile. Built - in filtration system (0.7 μ m Whatmann GF/F and GF/D glass micro-fiber filters, and glass wool) was used throughout the study. The dissolution medium was 0.1N HCL (pH 1.2), which was filtered (on 0.45 μ m filter), degassed, and then pumped at a laminar flow rate of 8.0 ± 0.2 ml/min. Temperature of the

dissolution medium was kept constant at 37 ± 0.5 °C. At predetermined time intervals, volume fractions were collected and then analyzed spectrophotometrically for AmoxTH or metronidazole content by measuring the absorbance at the corresponding λ_{max} (272 nm for AmoxTH and 277 nm for metronidazole) against 0.1N HCL (pH 1.2) as blank. Each formula was tested in triplicate for up to 6.0 h and the mean value was calculated.

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. The criteria for selecting the most appropriate model were based on the best goodness of fit and the smallest sum of squared residuals (SSR)⁵⁴⁻⁵⁷.

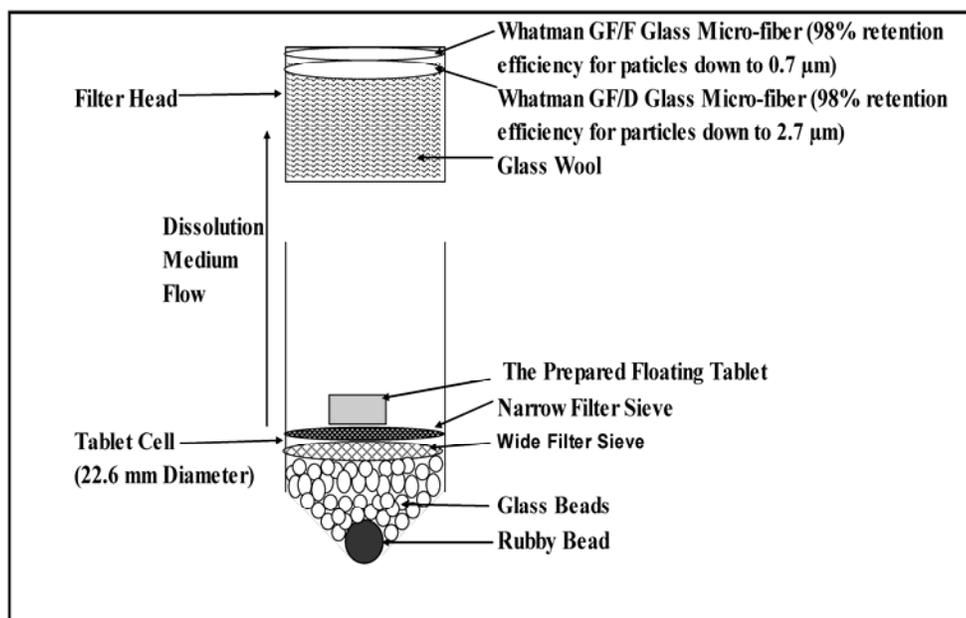


Fig. 1: Dissolution cell design used for the prepared floating tablets: laminar flow with free tablet position (glass beads filling the entry cone)

Effect of storage on drug release

The double layer floating tablet for each drug (A.d and M.d, cf. Table 3) was stored at ambient conditions for 12 months, in amber tightly closed glass containers away from direct light. After 12 months the tablets were re-evaluated for their appearance, floating properties, and *in vitro* release profile. The similarity factor (f_2), as proposed by Moore and Flanner⁵⁸ was calculated from the mean release data and used to evaluate the effect of storage on the release profile. f_2 is defined as:

$$f_2 = 50 \times \log \left\{ \left[1 + \left(\frac{1}{n} \right) \sum_{i=1}^n (R_i - T_i)^2 \right]^{-0.5} \times 100 \right\}$$

Where, n is number of data time points collected during the *in vitro* release test, R_i and T_i are the cumulative release percentages released at the selected (n) time point of the fresh and stored tablets, respectively.

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^{59,60}.

RESULTS AND DISCUSSION

Physical parameters of floating tablets

Weight variation

All the prepared floating tablets showed acceptable weight variation range. The average tablet weight ranged from 668.0 to 734.0 mg for AmoxTH formulations and from 666.6 to 729.6 mg for metronidazole formulations. Not more than two tablets deviated from the average weight by more than 5.0% (percentage deviation for uncoated and film-coated tablets weighing more than 250 mg), and none deviated by more than twice that percentage⁶¹.

Thickness and diameter

The prepared tablets showed good uniformity of thickness and diameter. The values of tablet thickness were in the range of 4.70 - 5.35 mm for AmoxTH formulations and from 4.31 to 4.83 mm for metronidazole formulations. The average diameter ranged from

12.66 to 12.76 mm for AmoxTH formulations and from 12.65 to 12.69 mm for metronidazole formulations.

Hardness

AmoxTH formulae average tablet hardness was between 9.90 and 12.30 kP, while that of metronidazole formulae was between 4.80 and 6.70 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 formulae was found to be within the range of 85% and 115% of the label claim⁶².

In vitro evaluation

Tables (4 and 5) summarize the results of floating lag time, floating duration as well as release characteristics for the prepared AmoxTH and metronidazole tablets.

Table 4: In vitro release data mean and floating behavior of AmoxTH floating tablets (375 mg/tablet)

Tablet Code	Floating Lag Time (min)	Floating Duration (min)	Release%	Release Model
A1	4.2	>360	12.89	Zero-order
A2	2.3	>360	15.03	Zero-order
A3	1.6	>360	30.76	Zero-order
A4	1.4	>360	38.71	Zero-order
A5 ^a	-----	-----	53.40	Hixson and Crowell Cube-Root
A6	0.40	>360	23.87	First-order
A7	0.88	>360	18.19	First-order
A8	2	>360	26.95	Zero-order
A9	5.25	>360	18.87	Zero-order

^a Failed to float and disintegrated.

Table 5: In vitro release data mean and floating behavior of metronidazole floating tablets (250 mg/tablet)

Tablet Code	Floating Lag Time (min)	Floating Duration (min)	Release %	Release Model
M1	1	> 360	14.93	First-order
M2	3.5	> 360	14.88	First-order
M3	8	120	33.86	Zero-order
M4 ^a	-----	-----	49.59	Zero-order
M5 ^a	-----	-----	75.29	Hixson and Crowell Cube-Root
M6	7.5	> 360	16.09	Second-Order

^a Failed to float and disintegrated.

Floating lag time and floating duration

When designing gastric floating drug delivery system, the two mechanisms most frequently used are low density of tablet ingredients and the use of gas generating agents⁶³. A low-density drug delivery system could be achieved by using PEO and/or HPMC in a polymeric delivery system. Upon contact with water, a hydrogel layer will be formed to act as a gel boundary for the delivery system. The other mechanism of floatation, gas generation, was also incorporated into these tablets. This was achieved by incorporating sodium bicarbonate and calcium carbonate into the delivery system. When water penetrates into the tablet, generation of carbon dioxide occurs, which becomes trapped in the polymeric system and helps the floatation of the delivery system⁶³.

Single layer tablets

Figure (2) shows the floating lag time values of AmoxTH and metronidazole tablets based on PEO. In case of AmoxTH/PEO based tablets, there was a direct relationship between PEO molecular weight and floating lag time values, where decreasing PEO molecular weight from 8,000,000 to 300,000 (Tablets A1-A4) decreased floating lag time from 4.2 to 1.4 min, while with further decrease of PEO molecular weight (i.e. 100,000), tablets (A5) failed to float (cf. table 4).

On the other hand, in case of metronidazole tablets, the relation between the PEO molecular weight and floating lag time was inversely proportional (cf. Figure 2). Also, tablets prepared with lower M_w PEO

of 300,000 (M4) & 100,000 (M5) failed to float. These results might be due to the different physicochemical properties of the two drugs.

It is worthy to mention that the tablets (A5, M4 and M5) disintegrated rather than swelled and hence failed to float. This means that all the produced carbon dioxide escaped into the test medium rather than being entrapped within the tablet. These results might be considered if it will be required to prepare a combined floating dosage form of these two drugs for improved patient compliance.

Metronidazole tablets containing (1:1) blend of PEO of M_w 900,000 and 8000,000 was prepared (M6). It was found that the floating lag time was governed by the lower PEO molecular weight (cf. Table 5). As the floating lag time values were 8.0 min versus 7.5 min for tablet made with pure PEO of M_w 900,000 (M3) and the 1:1 PEO blend (M6), respectively, while floating lag time of PEO of M_w 8,000,000 (M1) was 1.0 min (cf. Table 5).

In case of AmoxTH/HPMC based tablets (cf. Table 4), it was found that an increase in HPMC (K4M) from 150 mg/tablet (A6) to 225 mg/tablet (A7), increased the floating lag time by more than 50% (i.e. from 0.40 min to 0.88 min). Therefore, 150 mg/tablet HPMC was selected to study the effect of different HPMC viscosity grades on the floating lag time. **Figure 3**, shows that there was a direct relation between increasing HPMC viscosity and floating lag time. The floating lag time values were 0.40, 2.00 and 5.25 min for tablets A6 (K4M), A8 (K15M) and A9 (K100M), respectively.

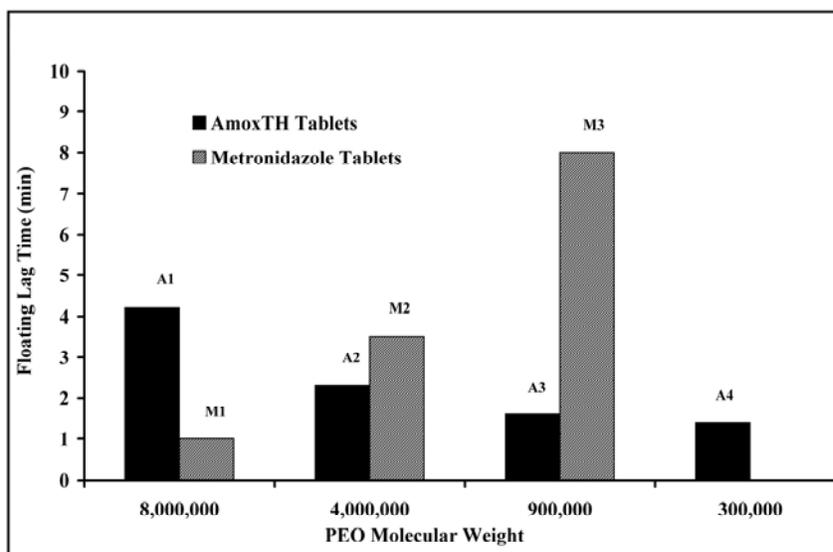


Fig. 2: Chart of floating lag time values of AmoxTH and metronidazole tablets

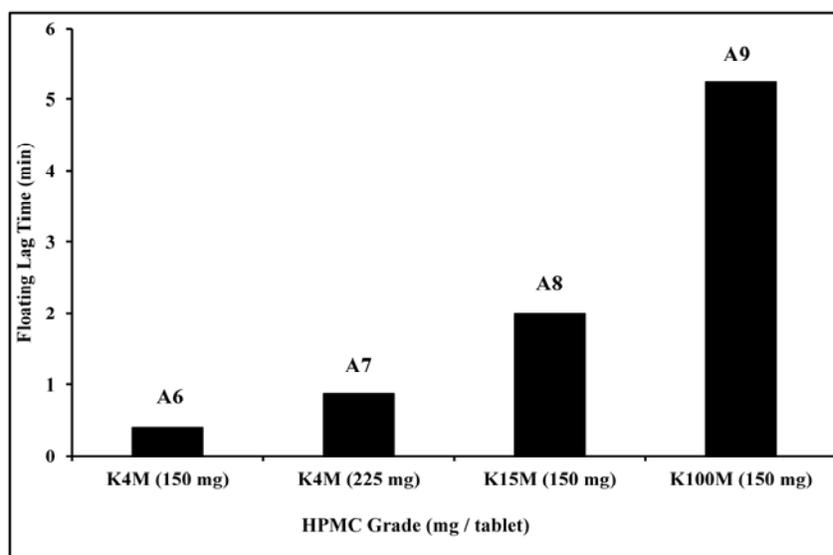


Fig. 3: Chart of floating lag time values of AmoxTH tablets based on different HPMC grades

Double layer tablets

A double layer tablet for each drug was prepared to study this system and its impact on both floating and drug release properties. The gas-generating layer was prepared with PEO of M_w 8,000,000, calcium carbonate and sodium bicarbonate. The drug releasing layer, containing either AmoxTH or metronidazole, was prepared with PEO of M_w 900,000 and lactose (c.f. table 3).

The results revealed that the floating lag time values, which corresponds to PEO of M_w 8,000,000, were increased in case of the double layer tablets compared to the single layer tablets for both drugs. It was found that the floating lag time values were extended to be 15.0 min versus 4.2 min in case of AmoxTH double (A.d) and single layer (A1) tablets, respectively. While in case of metronidazole, the floating lag time values were 20.0 versus 1.0 min for the double (M.d) and single layer (M1) tablets, respectively (c.f. Table 4 and 5). The prolongation of floating lag time values,

observed in double layer tablets of both drugs, might be due to the less amount of PEO of M_w 8000,000 used in the double layer tablet which was 140 mg compared to 240 mg in single layer tablet (cf. Tables 1-3). However, these floating lag time values were still less than the gastric emptying time⁶⁴.

The floating duration was more than 6.0 h for the double layer tablets of both drugs. This study could be extended to lessen the floating lag time to prevent premature emptying from the stomach.

It was interesting to point out that all tablets floated in less than 0.50 min in the dissolution cell during the in vitro flow-through cell dissolution study (dynamic test), compared to the previously described floating behavior study⁵² (static test). Also, this observation had been pointed out by Rosa et al.⁵² where sotalol HCl tablets floated after 27.7 min in the beaker method under static conditions and after 10.3 min during the dissolution test using USP basket method.

In vitro drug release

A specific in vitro release method for evaluation of gastro-retentive AmoxTH formulations in acidic test medium was adopted based on a previous study using an open-loop system of the flow-through cell⁶⁵, which provides a continuous flow of fresh dissolution medium during the study (i.e. perfect sink condition). This method was designed to overcome the errors in the calculation of the amount of AmoxTH released without the interference of AmoxTH degradation product. The study suggested that for evaluation of gastro-retentive AmoxTH products, the beaker method as well as USP paddle and basket are not recommended if the analysis of AmoxTH will be carried out by UV/spectrophotometer. The open-loop system of the flow-through cell was safely applied to evaluate such products, where AmoxTH was accurately analyzed by UV/spectrophotometric. On the other hand, the USP paddle and basket methods are not recommended if the analysis of AmoxTH will be carried out by UV/spectrophotometer, where in such cases samples should be analyzed by HPLC⁶⁵.

Single layer tablets

PEO based tablets

Figures (4 and 5) show the drug release rate profiles of AmoxTH and metronidazole from tablets containing PEO of different molecular weight, respectively. The drug release rate studies revealed that PEO of the highest molecular weight (M_w 8,000,000) gave the lowest drug release percentage after 6.0 h (12.89% and 14.93% for AmoxTH and metronidazole tablets, respectively) which might be due to its low erosion property. The highest drug release was obtained from the lower molecular weight (PEO M_w 100,000) which gave 50.94% and 75.29% for AmoxTH and metronidazole tablets, respectively. Therefore, it is obvious that the release rate from PEO matrices was inversely proportional to PEO's molecular weight. Similar results were reported in another study by Ali et al.⁴⁸, on Celecoxib floating formulations containing PEO of M_w 2,000,000 and 4,000,000.

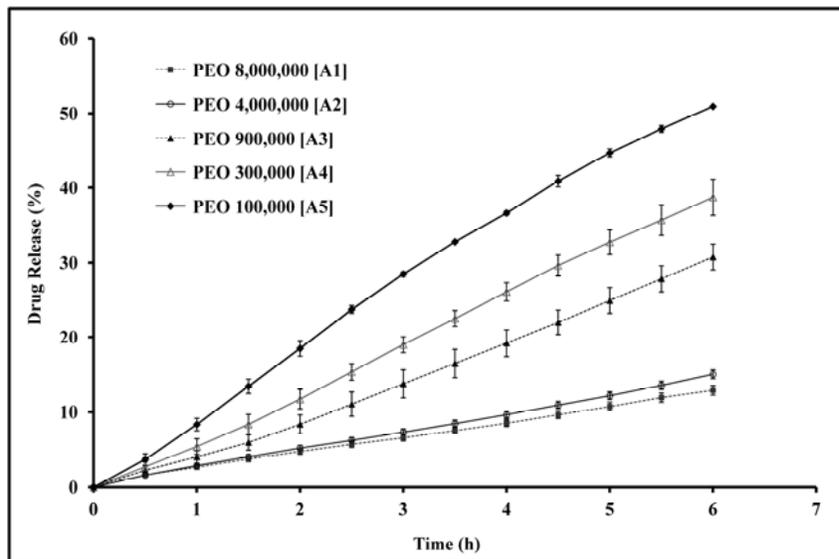


Fig. 4: AmoxTH release rate profiles from the single layer floating tablets containing PEO of different molecular weights

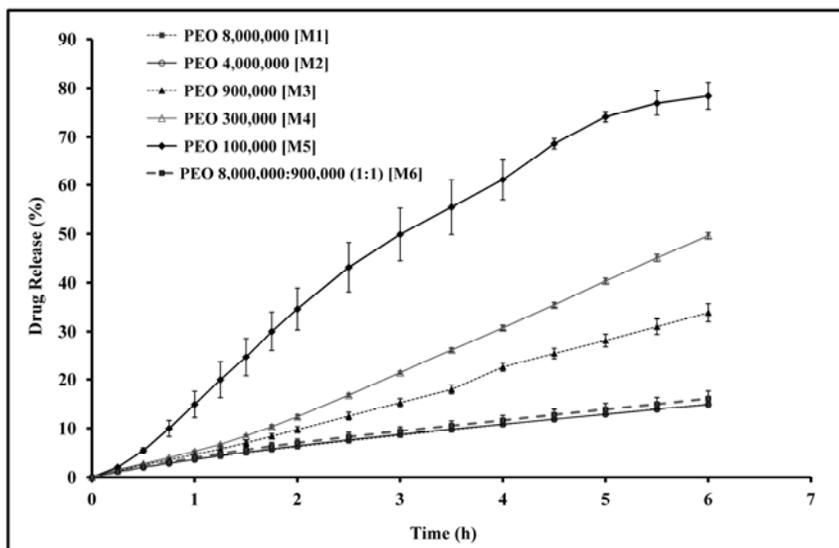


Fig. 5: Metronidazole release rate profiles from the single layer floating tablets containing PEO of different molecular weights

In a trial to obtain a reasonable release rate with minimum floating lag time, tablets containing (1:1) blend of PEO of M_w 900,000 and 8000,000 were prepared (M6) (cf. table 2). Results revealed that the release rate was governed by the high molecular weight polymer, where metronidazole release percentages after 6.0 h were 14.93% versus 16.09% for tablets made with pure PEO of M_w 8000,000 (M1) and the 1:1 PEO blend (M6), respectively (cf. Figure 5). On the other hand, the floating lag time was governed by the lower molecular weight polymer as shown in Table 5. Therefore, this might be a challenge for the formulator scientist.

Also, metronidazole release rate could be tuned by further changes in the polymer blend ratio. In a study carried-out by Korner et al.⁶⁶, hydrophilic matrix tablets were made by mixing PEO of M_w 100,000 and 2,000,000 in different ratios (10:90, 30:70, 50:50, 70:30 and 90:10). They reported that the polymer (PEO) dissolution rate decreased with increasing the fraction of the long polymer (2,000,000) in the tablet.

HPMC/AmoxTH based tablets

Figure 6 shows AmoxTH release rate profiles from A6, A7, A8 and A9 tablets containing 150 (HPMC K4M), 225 mg (HPMC K4M), 150 mg

(HPMC K15M) and 150 mg (HPMC K100M), respectively. It was found that when the polymer content increased from 150 mg (A6) to 225 mg (A7), the percentage of AmoxTH released after 6.0 h decreased slightly from 23.87 to 18.19%. This might be due to an increase in tortuosity and length of the diffusion path through the matrix⁶⁷. Tablets A6 and A8 containing 150 mg HPMC K4M and K15M, respectively, showed almost the same release rate profiles (23.87% and 26.95% released after 6.0 h, respectively), while the tablet containing K100M (A9) showed the least AmoxTH percentage released after 6.0 h (18.87%). This might be due to the fact that HPMC K4M has relatively low gel strength, least entanglement and smallest diffusion path length compared to HPMC K100M⁶⁸. In addition, as described by Siepmann and Peppas⁶⁹, the overall drug release mechanism of HPMC matrices is sequentially governed as follows: (i) At the beginning, steep water concentration gradients are formed at the polymer/water interface resulting in water imbibition into the matrix. (ii) Due to the imbibition of water, HPMC swells resulting in dramatic changes of polymer and drug concentrations and increasing dimensions of the system. (iii) Upon contact with water, the drug dissolves and diffuses out of the device due to concentration gradients. (iv) With increasing water content, the diffusion coefficient of the drug increases substantially⁶⁹.

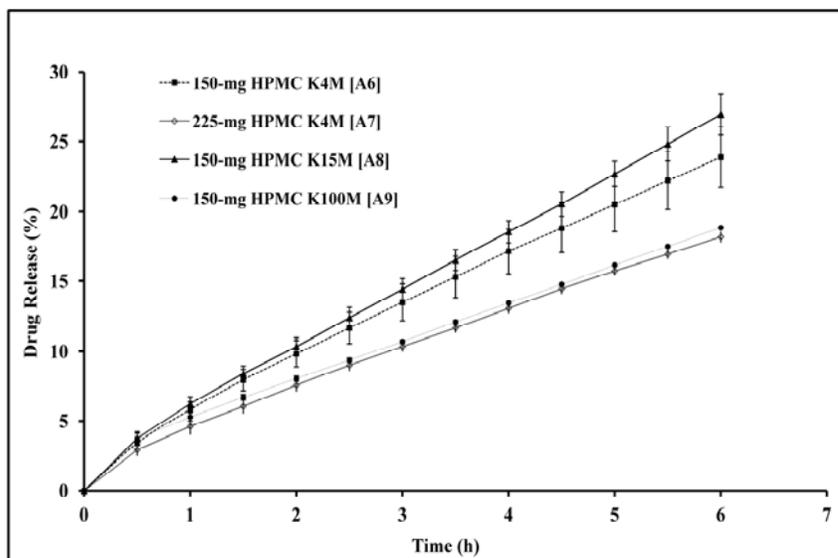


Fig. 6: AmoxTH release rate profiles from the single layer floating tablets containing HPMC of different grades

Double layer tablets

In vitro release study

Figure (7) shows the photograph of the double layer tablet in the flow-through cell. Figure 7 (B) shows that the two layers swelled as a result of fluid ingress, and as a result of the gradual and continuous generation of gas in the first layer, the tablet gradually floated. The drug release rate was controlled by polymer swelling, matrix erosion, drug diffusion and the gel thickness dynamics⁶⁹. Thus both floating and drug release could be optimized independently.

Figure (8) shows the release rate profiles for AmoxTH and metronidazole double layer tablets against their corresponding single layer tablets containing PEO of M_w 900,000. The results revealed that the percentages of drug released after 6.0 h were 82.13% and 57.64% for AmoxTH (A.d) and metronidazole (M.d) double layer tablets, respectively. While in case of single layer tablets containing PEO of M_w 900,000, the percentages of drug released after 6.0 h were 30.76% and 33.86% for AmoxTH (A3) and metronidazole (M3), respectively. It is worthy to mention that the higher release percentages of both drugs in case of the double layer tablets might be due to the effect of drug/polymer ratio that have been increased in case of the double layer tablets (cf. Tables 1-3).

Effect of storage on the release rate

Figures (9 and 10) show the release rate profiles of double layer floating tablets of AmoxTH (A.d) and metronidazole (M.d) before and after storage for one year at room temperature. After storage, floating lag time and duration as well as the physical appearance of AmoxTH and metronidazole tablets were not affected.

AmoxTH tablets exhibited similar release rate profiles after 1 year storage (" f_2 " values > 50), which might indicate good stability. On the other hand, metronidazole tablets showed a pronounced increase in the drug release rate after 1 year storage. The similarity factor " f_2 " value for the metronidazole tablets was 25.0, which was out of the FDA limit of acceptance⁶⁹. Therefore, metronidazole tablets (M.d) was not considered stable under these storage conditions as indicated by the f_2 value of the release rate data.

This different behavior observed for AmoxTH and metronidazole tablets may be due to the variation between type and degree of drug-polymer interaction, changes of degree of crystallinity or amorphous phases of the drug and drug molecular weight in each case, which could lead to the instability of the stored tablets.

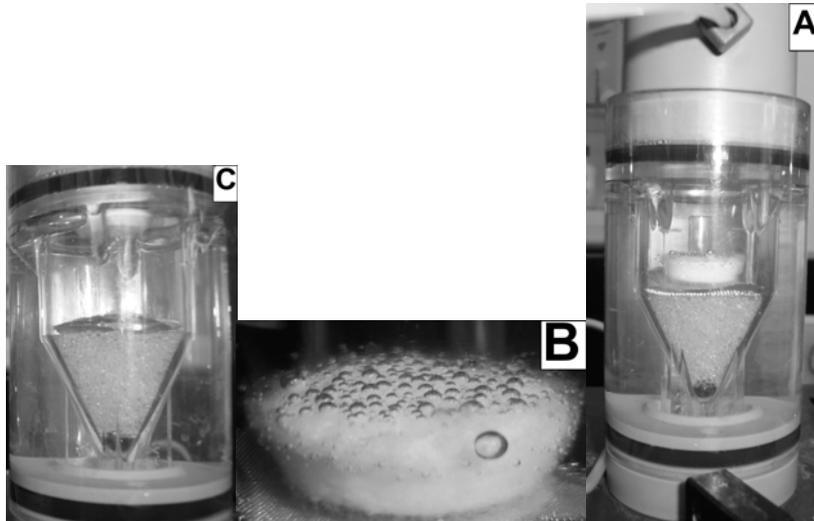


Fig. 7: Photographs of AmoxTH double layer tablet (A.d) in the flow-through cell.

Key: A: Cell filling, gas-generation and swelling of the tablet; B: Magnified photograph of the swelled tablet; C: Floated tablet

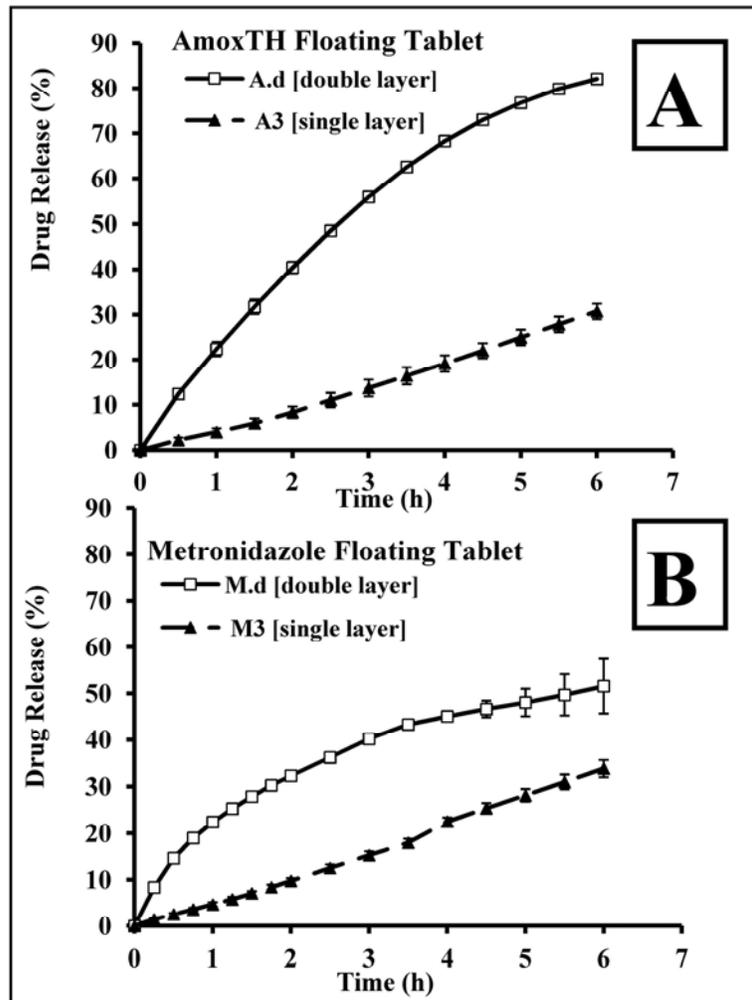


Fig. 8: Release rate profiles for PEO of M_w 900,000 based floating tablets (double versus single layer). Key: A: AmoxTH tablets; B: Metronidazole tablets

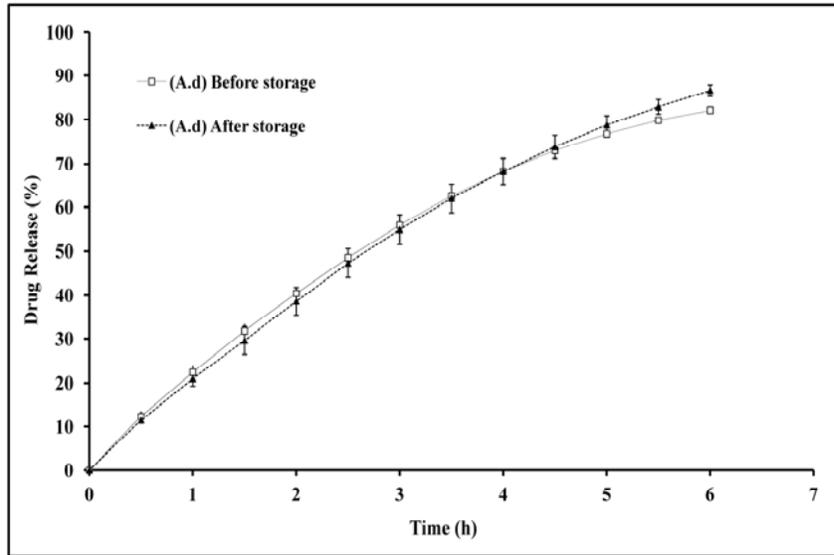


Fig. 9: AmoxTH release rate profiles from the double layer floating tablets before and after one year storage at ambient conditions

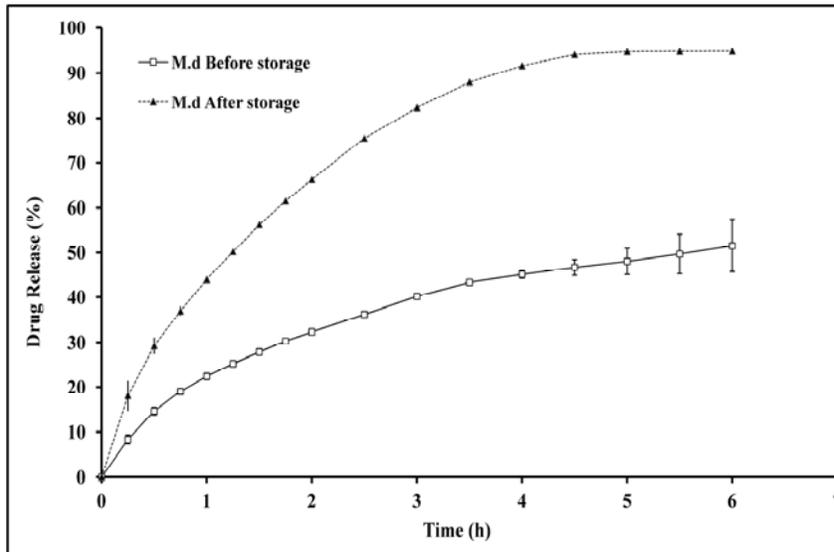


Fig. 10: Metronidazole release rate profiles from the double layer floating tablets before and after one year storage at ambient conditions

Other researchers had similar results of instability of metronidazole/PEO formulae of M_w 1,000,000 and 7,000,000 by storage⁷⁰. In case of lower molecular weight polymer (1,000,000), a significant increase in metronidazole release ($f_2 < 50$) was observed after storing the samples under stress conditions. The reason behind this phenomenon was reported to be the result of structural changes of PEO, which lead to stronger polymer-polymer interaction, resulting in the decrease of the strength of the secondary bonds formed between the polymer chains and the active ingredient molecules. On the other hand, no such changes were seen in the case of the higher molecular weight form, although earlier studies by these group of researchers confirmed structural alterations similar to those of the low molecular weight polymer⁷⁰. This suggested that not only the modified physical properties of the polymer matrix determine the behavior of the dosage form in the course of storage but also the characteristics of the molecules. Also, the authors reported that, in the case of theophylline, drug release of high molecular weight matrices increased to an even greater extent⁷⁰. In addition, it was reported that metronidazole release is higher than

that of theophylline, which can partly be attributed to the greater density of metronidazole molecules in the polymer matrix. This could lead to the higher concentration gradient of metronidazole, resulting in the faster diffusion of this drug. Another contributing factor was found to be that the interaction between theophylline and PEO was stronger, the energy gain of the H-bond between these two molecules was greater than in case of metronidazole⁷⁰.

Kinetic study of drug release data

By applying the linear regression method and subjecting the release rate data to different release kinetics and mechanisms (zero-order, first-order, second-order, Higuchi diffusion and Hixson-Crowell), most of AmoxTH tablets were found to follow mainly the zero-order release model, except for the tablets containing HPMC: 150 mg/tablet and 225 mg/tablet K4M (A6 and A7, respectively) which followed first-order model. Meanwhile, tablets (A5) which contained PEO of M_w 100,000 and AmoxTH double layer tablets (A.d) followed Hixson and Crowell cube-root model (cf. Table 4).

While for Metronidazole floating tablets, results revealed that tablets (M1) and (M2) containing PEO of M_w 8,000,000 and 4,000,000, respectively, followed the first-order release model, while tablets (M3) and (M4) containing PEO of M_w 900,000 and 300,000 respectively, followed the zero-order release model. Tablets (M5) containing PEO of M_w 100,000 followed Hixson and Crowell Cube-Root model. Tablets (M6) that contained (1:1) blend PEO of M_w 8,000,000 and 900,000, as well as metronidazole double layer tablets (M.d) followed the second-order release model (cf. Table 5).

CONCLUSIONS

This study demonstrates the feasibility of prolonging the gastric residence time of anti-*H.pylori* drugs via oral administration of the proposed floating tablets. Furthermore, sustained release of the model drugs (metronidazole and AmoxTH) from such floating tablets can be achieved over a period of at least 6.0 h. These dosage forms need further in vitro optimization, to shorten the floating lag time as well as a clinical trial involving patients suffering from peptic ulcer.

This stomach targeted dosage form 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.

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