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## Preparation and Evaluation of Gastroretentive Floating Pellets of Metronidazole Using Na-alginate and Hydroxyl Propyl Methyl Cellulose Polymers

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**Abstract:** Gastroretentive floating pellets of metronidazole were formulated to prolong the gastric residence time in order to obtain controlled release characteristics of the drug. Nine formulations of metronidazole floating pellets such as AX, BX, CX, AY, BY, CY, AZ, BZ and CZ were prepared by extrusion method using different quantities of hydroxyl propyl methyl cellulose (HPMC) polymers such as methocel K4M premium and methocel K100LV premium in the ratio of 2:1, 1:2 and 1.5:1.5 while the amount of Na-alginate used in the formulations was 3.50, 5.25 and 7.0 g, respectively. The *in vitro* dissolution studies were carried out in 900 mL of phosphate buffer (pH 1.2) at  $37 \pm 0.5^\circ\text{C}$  and 50 rpm for 6 h using USP XXIV paddle method and the content of drug release was done by UV spectrophotometer at 277 nm. It was found that the percent release of metronidazole from different formulations was different with passing of time. The drug release profile of the formulation (AX) having Na-alginate 3.50 g methocel K4M premium and methocel K100LV premium in the ratio of 2:1 showed best fit to Higuchi release kinetics with  $R^2$  value of 0.994. Finally, it might be concluded that the polymers had significant effect on drug release kinetics of metronidazole from floating pellets. The selection and use of suitable polymers in appropriate ratio might be very important in designing floating pellets and using the capabilities of these polymers, suitable floating pellets of metronidazole with desirable release rate could be formulated. Thus, *in vivo* research studies by the future researchers will confirm the appropriateness of these formulated metronidazole floating pellets.

**Key words:** Metronidazole, floating pellets, methocel, hydroxyl propyl methyl cellulose, Na-alginate, Higuchi release kinetics

### INTRODUCTION

The pharmacokinetics of drug can be pH-sensitive. Therefore, changes in a disease condition and in plasma concentration need to be considered for the development of drug delivery systems intended for the treatment of diseases with required dose (Balamuralidhara *et al.*, 2011). Due to inabilities and difficulties in controlling the release rate of drug to the targeted tissues and specific organs of the Gastrointestinal Tract (GIT), it has become a big challenge to the formulation scientists to prepare a controlled drug delivery system (Khan, 2001). Various technological approaches have been made for the development of sustained drug delivery systems (Hamdani *et al.*, 2006) in order to decrease unpredictable gastric emptying times. Several approaches have been investigated to increase the gastric residence time for overcoming these problems. The most viable technique to control the gastric residence time for attaining extended and expected drug delivery in GIT is gastroretentive drug delivery systems (Reddy *et al.*, 2011). A continuous release of drug from the gastroretentive drug delivery

systems before reaching to the systemic circulation is maintained and thus optimal bioavailability is ensured (Trivedi *et al.*, 2011). The main principle of the gastroretentive drug delivery system is to prolong the release of the drug at the site of absorption and one of the most recent approaches for the prolongation of gastric residence time is the floating drug delivery system. Due to low bulk density of the floating dosage forms, they can float in the gastric environment for a longer period of time which attributes to improve bioavailability of the drug (Natarajan *et al.*, 2011).

It is known that gastroretention time of a drug is affected by several factors, but the gastric emptying time in human is particularly influenced by the size of the orally administered object. Therefore, various approaches for prolonging drug gastroretention have been investigated and the floating system has been found to be promising because it prolongs gastroretention without influencing the size of the orally administered dosage form. Thus, metronidazole would be very effective for the eradication of *H. pylori* infection if it is delivered specifically at the site of infection of the stomach (Shah *et al.*, 1999). An

alternative method of controlling the release of drug substances is the polymer based drug delivery dosage form (Mownika and Srinivas, 2012). Hence, the present study was designed to develop floating pellets of metronidazole using Na-alginate and hydroxy propyl methyl cellulose blend (methocel K4M premium and K100LV premium) in different amounts as polymers.

## MATERIALS AND METHODS

**Chemicals and reagents:** Metronidazole, a poorly water soluble drug (Obitte *et al.*, 2008), was obtained as a gift sample from United Pharmaceuticals Ltd., Chittagong, Bangladesh. Na-alginate (LOBA Chemicals Pvt. Ltd., India), bioadhesive and hydrophilic polymers such as Hydroxy Propyl Methyl Cellulose (HPMC) (Shaheen *et al.*, 2006; Hossain *et al.*, 2004) were used in this study, two brands of HPMC i.e. methocel K4M premium and methocel K100LV premium were collected from BASF Bangladesh Ltd. Calcium chloride ( $\text{CaCl}_2$ ) (Merk, India), disodium hydrogen phosphate (Merk, India), potassium dihydrogen phosphate (Merk, India) were collected from GlaxoSmithKline, Chittagong, Bangladesh. All the chemicals and reagents used for the present research work were of analytical grade. The equipments used in the entire study were scanning electron microscopy (Hitachi S-3400N), Dissolution tester (Erweka-DT70), Digital pH meter, electronic balance and UV-Visible spectrophotometer (Shimadzu, Japan).

**Preparation of metronidazole floating pellets:** Drug, polymers (Na-alginate, methocel K4M premium and methocel K100LV premium) and other excipients were weighed separately according to the proposed formulations of floating pellets. The pellets were prepared by extrusion technique (Vani *et al.*, 2010) with slight modification. In the present study, nine formulations of metronidazole floating pellets coded as AX, BX, CX, AY, BY, CY, AZ, BZ and CZ were prepared using various quantities of polymers and other excipients. To prepare the metronidazole floating pellets, Na-alginate (1%w/w) gel was prepared by over night soaking with sufficient quantity of demineralized water which was homogenized by using electronic stirring (4000 rpm) for half an hour. Then required amount of methocel K4M premium and methocel K100LV premium for each formulation was added to form suspension and the resultant mixture was homogenized for half an h. A requisite quantity of metronidazole was also added to the obtained mixture which was further homogenized for another 45 min. The homogenized solution was sprayed on to cationic solution ( $\text{CaCl}_2$ , 0.1%) and 15 min reaction time was

provided for the formation of pellets which were collected and washed for four times with distilled water. Finally, they were dried at room temperature for approximately 12 h. During the entire experiments, all of the parameters such as stirring time, rpm, reaction time, drying time and temperature were optimized by error and trial method.

**Examination of metronidazole floating pellets by Scanning Electron Microscopy (SEM):** The morphology of metronidazole floating pellets was examined by SEM (Hitachi, S-3400N) at Bangladesh Centre of Scientific and Industrial Research (BCSIR), Dhaka, Bangladesh. The pictures of dried pellets were shown in (Fig. 1a) and the magnifications used for taking micrographs were 10-3500. SEM was performed on the metronidazole pellets which were performed randomly to get idea on the shape of pellets for formulation AY (Fig. 1b), drug distribution and polymer network for formulation AY (Fig. 1c), surface of metronidazole pellets for formulation BZ (Fig. 1d) and surface of polymer in dried pellets for formulation CZ (Fig. 1e). It was evident from the figures that magnifications provided the morphology of a single pellet which was roughly spherical in shape. Even, the idea of smooth pellet surface was provided by the magnifications which also showed the drug distribution though the drug particles were present on the surface and were scattered and amalgamated. In addition, the figures gave the idea of network among the polymers used for pelletization. This unique rearrangement satisfied the stability and strength of pellets.

**Preparation of buffer solution:** Phosphate buffer of pH 1.2 used in the entire experiment was prepared with disodium hydrogen phosphate and sodium dihydrogen phosphate. To prepare 1 L of phosphate buffer, 8.05 g of disodium hydrogen phosphate and 1.50 g of sodium dihydrogen phosphate were dissolved in distilled water initially and the volume was made up to 1000 mL by adding distilled water. The pH of the phosphate buffer solution was measured by digital pH meter.

**In vitro dissolution study:** The *in vitro* dissolution of metronidazole floating pellets was performed by Erweka-DT70 dissolution tester using United States Pharmacopoeia (USP) XXIV paddle method. Metronidazole floating pellets equivalent to 20 mg of metronidazole were poured in 900 mL of phosphate buffer (pH 1.2) at  $37 \pm 0.5^\circ\text{C}$  and 50 rpm using an automated sampling procedure. 10 mL samples were withdrawn with predetermined time intervals (0.25, 0.50, 1, 2, 3, 4, 5 and 6 h) and were replaced by fresh medium to maintain the total volume constant. Finally, the drug content was

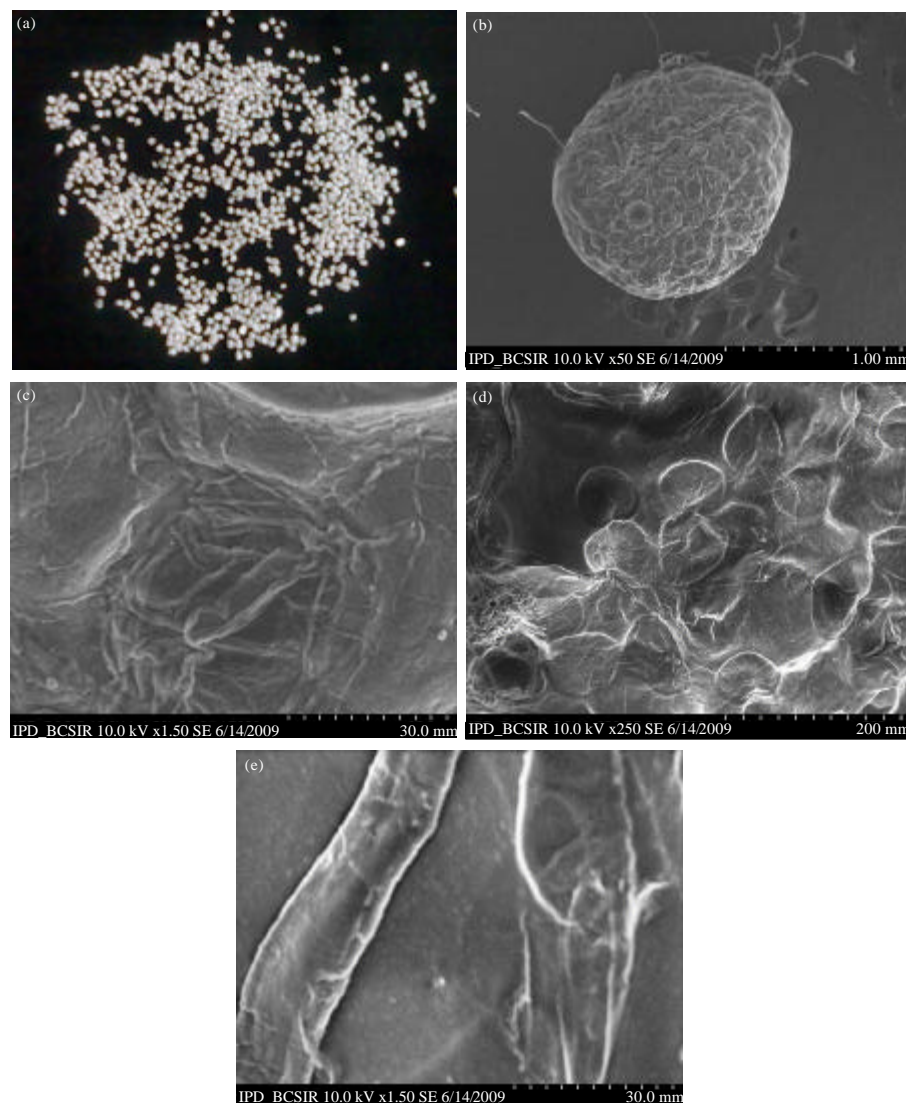


Fig. 1(a-e): (a) Photograph of floating pellets of metronidazole (dried), (b) SEM photograph showing shape of pellet for formulation of AY, (c) SEM photograph showing drug distribution and polymer network of formulation AY, (d) SEM photograph showing surface of metronidazole pellets formulation of BZ and (e) SEM photograph showing polymer surface in dried pellets formulation of CZ

determined spectrophotometrically at 277 nm using UV-visible spectrophotometer (Shimadzu, Japan).

**Drug release kinetics:** The effect of Na-alginate, methocel K4M premium and methocel K100LV premium in the release of metronidazole from floating pellets was investigated to understand the order and possible mechanism involved in the release pattern. To study the mechanism of drug release, the data obtained from *in vitro* dissolution profiles of all the prepared formulations were subjected to Higuchi release model and zero order release kinetics.

**Statistical analysis:** Statistical software such as SPSS 14 version was used for statistical analysis in the entire study and Pearson's SPSS was used to determine the regression co-efficient ( $R^2$ ).

## RESULTS

Table 1 showed the formulation codes such as AX, BX, CX, AY, BY, CY, AZ, BZ and CZ. The different quantities of Na-alginate and HPMC polymers were used in each formulation. The highest quantity of Na-alginate (7.0 g) was used for AZ, BZ and CZ formulations while

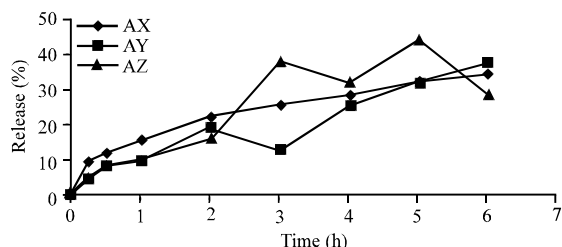


Fig. 2: Comparison of *in vitro* zero order release pattern of metronidazole from AX, AY and AZ formulations containing 3.5, 5.25, 7.0 g of Na-alginate, respectively, while methocel K4M premium and methocel K100LV premium used in 2:1 ratio in each formulation

Table 1: Codes and composition of various formulations of metronidazole floating pellets

Composition of formulations	Code of formulations								
	AX	BX	CX	AY	BY	CY	AZ	BZ	CZ
Metronidazole	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Sodium alginate	3.50	3.50	3.50	5.25	5.25	5.25	7.00	7.00	7.00
Methocel K4M	2.00	1.00	1.50	2.00	1.00	1.50	2.00	1.00	1.50
Methocel K100LV	1.00	2.00	1.50	1.00	2.00	1.50	1.00	2.00	1.50
Calcium chloride	1.11	1.11	1.11	1.11	1.11	1.11	1.11	1.11	1.11
Water up to	350	350	350	350	350	350	350	350	350

All figures are weights of each formulation expressed in g

AX, BX and CX contained lowest amount (3.5 g) of Na-alginate. On other hand, AX, BX, CX, AZ, BZ and CZ possessed methocel K4M premium and methocel K100LV premium in the ratio of 2:1, 1:2, 1.5:1.5, 2:1, 1:2 and 1.5:1.5, respectively as shown in Table 1. This research work was carried out to observe and compare the effect of polymers on the release patterns of metronidazole from all prepared formulations.

#### ***In vitro* dissolution studies of metronidazole floating pellets from AX, AY and AZ formulations:**

Figure 2 showed the comparison of *in vitro* zero order release of metronidazole from AX, AY and AZ formulations. The AX formulation which contained 3.5 g of Na-alginate and methocel K4M premium and methocel K100LV premium at 2:1 ratio showed drug release to the extent of 34.38% after 6 h. When the amount of Na-alginate was increased to 50% (AY) and 100% (AZ) keeping the ratio of methocel K4M premium and methocel K100LV premium at 2:1, 37.85 and 28.39% of drug release was achieved within 6 h. But the release of metronidazole from AX was found to be increased in gradual fashion with increase in time compared to other two formulations, AY and AZ.

#### ***In vitro* dissolution studies of metronidazole floating pellets from BX, BY and BZ formulations:**

In case of BX, BY and BZ formulations, K4M premium and methocel K100LV premium were used at 1:2 ratio with different

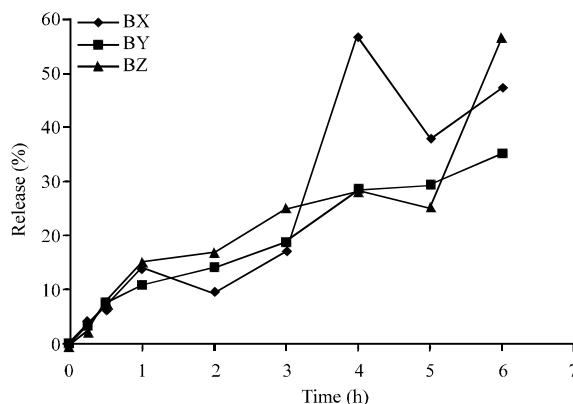


Fig. 3: Comparison of *in vitro* zero order release pattern of metronidazole from BX, BY and BZ formulations containing 3.5, 5.25, 7.0 g of Na-alginate, respectively, while methocel K4M premium and methocel K100LV premium used in 1:2 ratio in each formulation

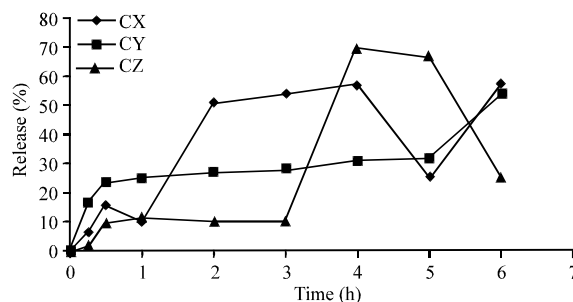


Fig. 4: Comparison of *in vitro* zero order release pattern of metronidazole from CX, CY and CZ formulations containing 3.5, 5.25, 7.0 g of Na-alginate, respectively, while methocel K4M premium and methocel K100LV premium used in same ratio in each formulation

quantities of Na-alginate. The *in vitro* zero order release profiles of metronidazole from BX, BY and BZ formulations were shown in Fig. 3. It was found that 47.31% release of metronidazole from BX was achieved after 6 h. But 35.33 and 56.78% release of metronidazole was obtained from BY and BZ after 6 h when the amount of Na-alginate was increased by 50 and 100%, respectively. In case of formulations BX and BZ, few fluctuations in drug release were found.

#### ***In vitro* dissolution studies of metronidazole floating pellets from CX, CY and CZ formulations:**

Even, the use of methocel K4M premium and methocel K100LV premium at 1.5:1.5 with different quantities of Na-alginate affected the drug release characteristics from floating pellets. Figure 4 showed that only the formulation CY, containing

Table 2: Kinetic release data of different model for all formulations of metronidazole floating pellets in phosphate buffer (pH 1.2)

Code of formulations	Zero order plot		Higuchi release plot	
	Regression equation	Regression coefficient ( $R^2$ )	Regression equation	Regression coefficient ( $R^2$ )
AX	$y = 4.947x + 7.833$	0.900	$y = 13.69x + 1.551$	0.994
BX	$y = 8.320x + 1.374$	0.790	$y = 21.19x - 6.866$	0.747
CX	$y = 8.039x + 11.06$	0.554	$y = 23.02x - 0.309$	0.662
AY	$y = 5.654x + 2.815$	0.931	$y = 14.51x - 2.928$	0.893
BY	$y = 5.543x + 3.074$	0.973	$y = 14.45x - 2.859$	0.963
CY	$y = 5.447x + 13.04$	0.722	$y = 14.91x + 6.269$	0.788
AZ	$y = 6.186x + 5.198$	0.750	$y = 16.87x - 2.423$	0.813
BZ	$y = 7.223x + 2.308$	0.851	$y = 18.40x - 4.858$	0.805
CZ	$y = 8.657x + 1.673$	0.512	$y = 22.52x - 7.533$	0.505

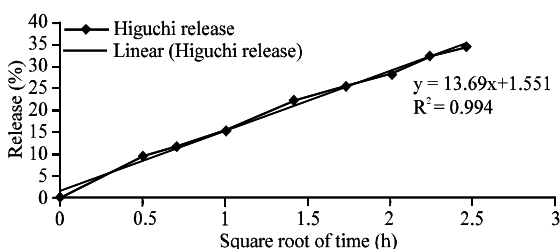


Fig. 5: Higuchi release curve of metronidazole from floating pellets of AX formulation

equal amount of methocel K4M premium and methocel K100LV premium with 5.25 g of Na-alginate, showed the better retarded release profiles compared to that of CX and CZ. After 4 h, 56.78, 30.59 and 69.39% metronidazole was released from CX, CY and CZ preparations, respectively and even after 6 h, the release pattern was also varied. It was found that 56.78, 53.63 and 25.23% of the drug was found to be released after 6 h of dissolution as shown in Fig. 4.

**Drug release kinetics:** The *in vitro* dissolution data of metronidazole floating pellets were fitted to zero order release and Higuchi release kinetics in order to analyze the release mechanisms. The regression analysis was done using the *in vitro* dissolution data and regression equation with regression coefficient values ( $R^2$ ) were shown in Table 2. In the present study, the release profile of AX formulation fitted best to Higuchi release kinetics showing good linearity with  $R^2$  value of 0.994. This indicated that the diffusion mechanism was predominantly found in respect of drug release with AX formulation. The Higuchi release curve of metronidazole from floating pellets of AX formulation was shown in Fig. 5. On the other hand, BY formulation fitted best to zero order release profile with  $R^2$  value of 0.973 while CZ formulation showed poor fit to zero order ( $R^2 = 0.512$ ) and Higuchi release profile ( $R^2 = 0.505$ ) as shown in Table 2.

## DISCUSSION

Gastroretentive floating drug delivery system such as pellets is a modern approach for delivering and controlling

the release profile of the target drug to a specific tissue or organ (Pahwa *et al.*, 2012). Due to several advantages of pellets such as freely dispersible in GIT fluids, less susceptible to dose dumping, low accumulation of drugs, reduction of peak plasma concentration variations and large surface area for drug absorption, they have gained more attention in order to formulate modified release dosage form (Supriya *et al.*, 2012). Floating pellets possess lower density than the stomach juice. As a result, they provide buoyancy in the gastric fluids without influencing the gastric emptying time for longer period of time (Vani *et al.*, 2010).

The development of an effective floating drug delivery system is dependent on the performance of the floating system. Generally, the swellable polymers would play important roles to obtain a suitable floating time (Adibkia *et al.*, 2011). Metronidazole sustained release and floating matrix tablets containing HPMC as filler showed prolonged lag times for buoyancy (Asnaashari *et al.*, 2011). It was found that out of nine prepared formulations of metronidazole floating pellets, only three formulations such as AX, BY and CY provided good retarded release characteristics. The formulation AX showed the best retarding capacity than the rest of the formulations. Thus, it indicated and proved the significant influence of Na-alginate and HPMC on different formulations of metronidazole floating pellets. The obtained results also showed similarity with the study performed by Babu *et al.* (2011). They found that the optimum quantities of Na-alginate and HPMC showed good retarded capacity of releasing metronidazole from floating tablets. Thus, it may be assumed that a retarded drug delivery system of metronidazole with desirable drug release may be prepared using suitable polymer combinations of Na-alginate and HPMC.

## CONCLUSION

This study discussed the preparation and evaluation of release pattern of metronidazole from floating pellets. In this study, the floating pellets were prepared by extrusion method and the release profiles of the pellets were investigated in simulated gastric fluid at pH 1.2. The release mechanism was explained with Zero order and

Higuchi release profiles. In this study, the variation of polymer ratio influenced the release rate of drug from the pellets. It was also found from the *in vitro* release profiles that high concentration of polymers used in preparing pellets showed less retarding capacity whereas low concentration of polymers gave more retarding effect in release of metronidazole from floating pellets. So, it might be possible to modify the release rate of metronidazole from floating pellets by choosing appropriate drug polymer ratio. Thus, oral administration of metronidazole floating pellets might be a better way of delivering antimicrobial agents into *Helicobacter pylori* infected mucosa. The study results suggested that the floating pellets prepared with the decrease in the polymer ratio resulted in better retarded release of metronidazole. Finally, it was recommended for the future researchers that *in vitro* and *in vivo* correlation should be performed to get the information about the efficacy of Na-alginate and HPMC based floating pellets of metronidazole.

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