

Development and *in vitro* analysis of floating matrix tablets of metronidazole using *Brachystegia eurycoma* gum.

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Abstract: Floating dosage forms aim to significantly increase the gastric residence time of drugs in the gastric region for several hours. Hence, this research was carried out to formulate and evaluate floating matrix tablets (FMT) of metronidazole using *Brachystegia eurycoma* (BE) gum as a matrix former. Floating matrix granules (FMG) were prepared by wet granulation method using the BE gum mucilage at different concentrations (2, 4, 6 and 8% w/w). Sodium bicarbonate (30%) and tartaric acid (5%) were added as the carbon (iv) oxide generating agents. Formulations were either prepared alone with the *Brachystegia eurycoma* or with the addition of 1.0% w/w of Eudragit RS₁₀₀. All FMG were evaluated for micromeritic properties and compressed at an optimized compression pressure of 30 arbitrary unit on the tableting machine load scale. FMT were analyzed for hardness, friability, floating lag time (FLT), *in vitro* buoyancy test and drug release profiles. Data from the release studies were subjected to analysis by zero order flux, first order, Higuchi square root of time relationship and Korsmeyer equations. From the results obtained, all formulated FMG were flowed freely with angle of repose and Carr's index between 15.2° to 29.1° and 10 to 18% respectively. FLT for FMT was ≤ 820 sec. The *in vitro* buoyancy test of FMT formulations using the BE gum mucilage alone (i.e. without the incorporation of Eudragit RS₁₀₀) were <12 h while those with Eudragit RS₁₀₀ were >12 h. All FMG were compressible with tablet hardness and percentage friability between 12.4-49.1 N and 0.77- 0.97% respectively. There was a significant difference in tablet hardness with increase in binder concentration (p<0.05). All formulations fitted well into Higuchi model release kinetics. Formulations BE1-BE4 have their exponent values < 0.45, hence their release mechanism was by Fickian diffusion while for BE5 the exponent value was > 0.45, therefore the release mechanism for this formulation was by non Fickian diffusion. The indication is that FMT of metronidazole have been developed using BE gum mucilage as a matrix former, this can be exploited in the formulation of controlled release systems.

Keywords: Floating matrix system, *Brachystegia eurycoma* gum, Higuchi model, floating lag time and *in vitro* buoyancy test.

INTRODUCTION

Floating systems are systems that have a bulk density less than gastric fluids and have adequate tendency to stay afloat over the gastric contents and remain buoyant in the stomach for a prolonged time interval without disturbing the gastric emptying rate (Yie, 1992). Floating of a drug in the stomach can be accomplished by integrating a floating chamber filled with vacuum, air or inert gas (Neha, 2011). However, different formulated floating formulations have been based on granules, powders, capsules, tablets, laminated films and hollow microspheres. Floating dosage form stays in the gastric region for some hours hence delays the gastric residence time of drugs (Uhumwangho *et al.*, 2010). Delayed gastric retention enhances drug targeting, bioavailability and solubility of drugs that are less soluble in a high pH milieu (Neha, 2011).

Over the years, different methods have been designed to increase the duration of tablets and capsules in the gastrointestinal tract. These methods include floating systems, bioadhesive systems, swelling systems, and high

density systems (Cremer, 1997; Chawla *et al.*, 2004). The floating systems have a bulk density below that of the gastric fluid and therefore, it remains afloat in the stomach for an extended time interval while releasing its active ingredient slowly at a desired rate from the system without interfering with gastric emptying rate (Sharma and Garg, 2003).

Metronidazole is used in the treatment of trichomoniasis, amoebiasis and anaerobic infections. Its half-life is 6h with a peak plasma concentration of 5 -7 g/ml attainable in 1-2h (BPC, 1988). It is frequently used in combination with other drugs for the eradication of *Helicobacter pyloric* (Meurer and Bower, 2002). It is taken 400mg three times daily for duration of five (5) days, which is cumbersome to the patient.

Brachystegia eurycoma (BE) gum is a polysaccharide obtained from Undehulled *Brachystegia eurycoma* seeds (Family Leguminosae-caesalpinioideae). It has been studied for the treatment of wound in combination with mucin and honey (Adikwu *et al.*, 2007). Previously, BE gum mucilage was explored as a binders in tablet formulations (Osazuwa and Uhumwangho, 2013; Uhumwangho *et al.*, 2014; Olubunmi *et al.*, 2011) and

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also as a suspending agent (Uhumwangho and Ileje, 2014). However, its use as a matrix former in the formulation of floating system has not been studied.

MATERIALS AND METHODS

The active constituent used in the research as drug model was metronidazole (Cipla Ltd., India), Eudragit RS₁₀₀ was received from Rhoma Pharma, Darmstadt, Germany, BE gum mucilage was used as a matrix former and was extracted by method described previously by Uhumwangho *et al.*, 2014. Sodium bicarbonate and tartaric acid were used as carbon (iv) oxide generating agents. All other chemicals were of analytical grades.

Methods

Granulation and Tableting technique

Floating matrix granules (FMG) of metronidazole were formed by wet granulation technique. Composition of formulae is shown in table 1. A Manesty Single Punch Tableting Machine (Type F3 Manesty Machine UK) was used to produce the tablets; talc was added as a lubricant. The FMG equivalent to 400 mg of metronidazole were placed in the die and compressed at a pressure of 30 arbitrary units on the tableting load scale. A constant pressure was maintained for all the batches of metronidazole produced. The resulting tablets were collected, dusted and stored in an air tight jar containing activated silica gel as a desiccant.

Micromeritic properties of the FMG

The packing properties of the FMG were obtained by measuring the bulk density (BD) and tap density (TD), using standard experimental procedures (Onyekweli, 2000) and values were determined using equations 1 and 2 respectively. From the obtained data, Carr's index (CI) values of the FMG was determined as $CI = TD - BD / TD \times 100$ (Carr, 1963). The flow property of the FMG was obtained by measuring the angle of repose formed when a sample of the granules (25 g) was allowed to descend freely through the stem of a funnel onto a plain bench surface (Travers, 1972). The angle of repose was determined using equation 3 (Uhumwangho *et al.*, 2011).

$$\text{Bulk density (BD)} = \frac{\text{Weight of granules}}{\text{Volume occupied by granules without tapping}} \quad \text{Eq. 1}$$

$$\text{Tap density (TD)} = \frac{\text{Weight of granules}}{\text{Volume occupied by granules after 100 taps}} \quad \text{Eq. 2}$$

$$\theta = \tan^{-1} h/r \quad \text{Eq. 3}$$

Where θ the angle of repose, h is the height and r is the radius of the heap.

Evaluation of floating matrix tablet (FMT)

Tablet hardness and friability

The tablet hardness was determined by diametrical compression using the Campbell Electronics Hardness tester machine (HT-30/50, India). The pressure required to break a tablet placed in the anvil of the hardness tester was recorded. Ten (10) tablets were used for the determination. The mean value and standard deviation were recorded. Ten tablets randomly selected were used in the friability test using the Roche Friabilator (Erweka Germany). The initial weight of the tablets was recorded before they were placed in the friabilator. The friabilator was allowed to operate at 25 rpm after which the final weight of the tablets was determined. These values were used to calculate the percentage friability using equation 4.

$$\% \text{ friability} = \frac{w_1 - w_2}{w_1} \times 100 \quad \text{Eq. 4}$$

Where w_1 and w_2 are initial weight and final weight of the tablets respectively.

Floating lag time (FLT) and in vitro buoyancy test.

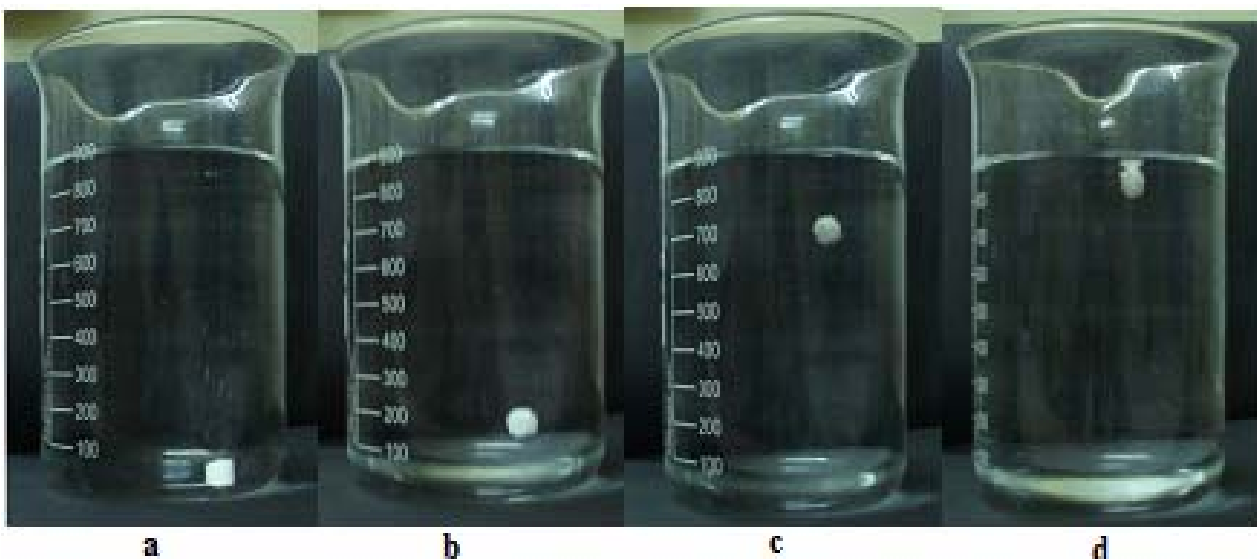
The procedure described previously by Rosa *et al.*, 1994 was implemented. A 1000 ml beaker was filled with 900 ml simulated gastric fluid (0.1 N HCl). A tablet was placed inside and the medium kept stagnant and maintained at $37 \pm 2^\circ\text{C}$. The time taken for the tablet to rise to the surface and float was recorded as the FLT. The time duration for which the tablet floats and remains afloat without breaking is determined as the FLT and *in vitro* buoyancy time respectively.

Table 1: Formulae of FMT of metronidazole

S.No.	Ingredients	Quantity
1	Metronidazole powder	400mg
2	<i>Brachystegia eurycoma</i> (BE) gum	2, 4, 6, 8% w/w
3	Eudragit RS ₁₀₀	1% w/w
4	Sodium bicarbonate	30% w/w
5	Tartaric acid	5% w/w
6	Talc	1% w/w

In vitro dissolution studies and drug release kinetics

The basket technique was adopted and dissolution studies were performed using 900 ml of 0.1 N HCl as the dissolution medium maintained at $37 \pm 2^\circ\text{C}$. One tablet was kept in a cylindrical basket which was immersed in the dissolution medium. The dissolution fluid was agitated at 100 rpm with a single blade Gallen Kamp stirrer (Model APP No 4B 5784A). At predetermined time intervals (5, 10, 15 and 30 min, 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 h) 5 ml sample of the leaching fluid was withdrawn using a pipette fitted with a cotton wool plug. Equal amount of fresh dissolution medium without the drug kept at the



(a) Photograph taken immediately after placing the tablet into the beaker; (b) and (c) are the photographs taken during the intermediate stages of tablet floating; (d) Photograph taken immediately after the tablet floated onto the surface indicating a FLT of 564 seconds.

Fig. 1: Photographs showing the *in vitro* buoyancy characteristics of FMT

same temperature was used to replace the withdrawn fluid. The withdrawn samples were filtered, diluted and their absorbance determined with a UV/Visible spectrophotometer (Model Spectronic 21D, Bausch and Lomb, USA) at λ_{max} 277 nm. The determination was done in triplicate and the mean results reported. The corresponding amount of metronidazole released at any time t , was determined.

The data gotten from the dissolution studies of the FMT of metronidazole were subjected to various drug release kinetics to determine the pattern of release kinetics. The models include: zero order, first order and Higuchi square root of time relationship (Higuchi, 1963; Korsmeyer *et al.*, 1983; Peppas, 1985; Harland *et al.*, 1988). The mechanism of drug release from the formulation was determined using Korsmeyer and Peppas model. The linear regression coefficient (r^2) for each rate order was computed. The dissolution profile was considered to have followed a specific release order if the r^2 value was >0.95 (Uhumwangho and Okor, 2006).

STATISTICAL ANALYSIS

The data obtained were documented as mean $\pm$ standard deviation (SD). All the data were subjected to Student t -test statistical analysis to test for significance of difference. $P < 0.05$ was considered to be significant.

RESULTS

Micromeritic properties of the FMG

The results of the micromeritic properties of the FMG produced by different concentrations of BE gum mucilage

are shown in table 2. It was observed that all the granules produced with BE gum displayed angle of repose ranging from 15.2-29.1° while compressibility index values ranged from 10-18%. The Hausner's ratio was between 1.10 - 1.22.

Effect of the gum concentration on floating lag time (FLT) and *in vitro* buoyancy studies

The results of FLT and *in vitro* buoyancy studies on FMT of metronidazole produced using BE gum mucilage are presented in table 3. The floating tablets produced using BE gum displayed a FLT between 195-820 sec.

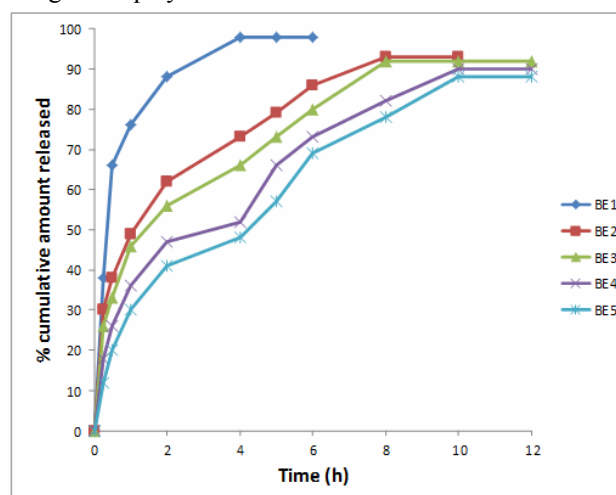


Fig. 2: *In vitro* drug release profile from FMT of metronidazole prepared using different concentrations of BE gum, where BE1 (BE gum alone), BE2 (2:1), BE3 (4:1), BE4 (6:1), BE5 (8:1).

Table 2: Micromeritics properties of FMG of metronidazole

Formulation concentration of BE: Eudragit RS ₁₀₀ (w/w)	Bulk Density (g/cm ³)	Tap Density (g/cm ³)	Angle of repose (°)	Carr's index (%)	Hausner's ratio
BE1	0.55	0.61	15.2	10	1.10
BE2	0.56	0.65	29.1	14	1.16
BE3	0.58	0.68	27.3	15	1.17
BE4	0.59	0.71	24.5	17	1.20
BE5	0.60	0.73	22.1	18	1.22

Where BE1=2%^{w/w} BE gum, BE2 = 2%^{w/w} BE gum + 1%^{w/w} Eudragit, BE3 = 4%^{w/w} BE gum + 1%^{w/w} Eudragit, BE4 = 6%^{w/w} BE gum + 1%^{w/w} Eudragit, BE5= 8%^{w/w} BE gum+1%^{w/w} Eudragit.

Table 3: FLT and *In vitro* buoyancy studies of FMT

Formulation concentration of BEG: Eudragit RS ₁₀₀	BE1	BE2	BE3	BE4	BE5
Floating lag time (s)	195	564	641	685	820
Buoyancy time without rupture of tablets (h)	<12	>12	>12	>12	>12

Table 4: Physicochemical Properties of FMT

Formulation concentration of BE: Eudragit RS ₁₀₀ (%w/w)	Hardness (N)	Friability (%)
BE1	12.4±1.52	0.97
BE2	15.2± 2.30	0.86
BE3	20.7±3.13	0.82
BE4	31.2±2.78	0.80
BE5	40.1±2.72	0.77

Table 5: Effect of different concentration of binder on the dissolution parameters of FMTs

Concentration /type of binder (%w/w)	m _∞ (%)	t _∞ (h)	m _∞ / t _∞ (%h ⁻¹)
BEG: Eudragit RS ₁₀₀			
BE1	98	4	24.5
BE2	93	8	11.6
BE3	92	8	11.5
BE4	90	9	10
BE5	88	10	8.8

Where m_∞ (%), maximum release, t_∞ (h), time to attain maximum release, m_∞/ t_∞ (%h⁻¹) dissolution rate.

Effect of binder concentration on the physicochemical properties of FMT.

The results of the effect of varying binder concentration on the physicochemical properties of FMT of metronidazole produced by using BE gum is shown in table 4. The FMT prepared using BE gum showed tablet hardness value between 12.4-40.1 N. The friability test values for the floating tablets formulated with BE gum mucilage was ≤ 0.97% (see table 4).

Release profile of FMT of metronidazole

The results of the *in vitro* drug release profile studies of the FMT of metronidazole formulated using BE gum mucilage is shown in fig. 2. The *in vitro* drug release from batch BE1 tablet formulated using 2%^{w/w} of the BE gum mucilage alone exhibited a faster release of drug content compared to the other batches containing Eudragit RS₁₀₀. For example, batch BE1 released about 90% of its drug

content within 2 h while batches BE2-BE5 released about 70% of the drug contents for up to 5 h. Thus, there was a more sustained release of drugs from batches BE2-BE5.

Release kinetics and mechanism of drug release from the FMT

The data gotten from the *in vitro* release studies were subjected to zero order (cumulative percentage of drug released vs. time), first order (log cumulative percentage of drug remaining vs. time), Higuchi's (cumulative percentage of drug released vs. square root of time), and Korsmeyer and Peppas (log cumulative percentage of drug released vs. log time) equations. The results of the release kinetics obtained from FMT are shown in table 6. It was noticed that all the formulations did not follow a zero order release behavior since the plot exhibited poor linearity with regression values (r²) ranging from 0.602-0.914. When data were plotted as per first order equation, the formulations showed a fair linearity with regression

values r^2 ranging between 0.924-0.976. The indication is that the amount of drug released was influenced by the extent of drug left in the system. The *in vitro* release profiles of all the floating matrix tablets were also subjected to Higuchi's equation. The plot presented higher linearity with regression values, r^2 ranging between 0.947-0.988. This shows that release kinetics was in line with this model since it gave higher correlation values when compared to the other models analysed.

The mechanism of drug release was obtained by fitting the data into Korsmeyer and Peppas equation. Their r^2 values ranged between 0.856-0.994 while their release exponent (n) was between 0.26-0.50. The indication was that diffusion was the main mechanism of drug release from these dosage forms. Formulations BE1 to BE4 have their release exponent (n) <0.45; hence their release mechanism was by Fickian diffusion. On the other hand, BE5 formulations have their release exponent (n) >0.45; therefore their release mechanism was by Non Fickian diffusion.

DISCUSSION

The results of the micromeritics properties show that all the FMG exhibited good flow which are very essential in ensuring weight and content uniformities during tableting. Hence, the measurement of all these parameters can provide a means of monitoring batch to batch variation.

It was equally noted that an increase in the concentration of the BE gum caused a corresponding increase in the floating lag time. This could be attributed to an increase in the inter-particulate cohesive forces acting within the floating tablet matrix due to enhance binding properties of the BE gums. The floating tablets in batch BE1 were found to have a very short FLT (195 sec) compared to the other batches. One main reason for this significant time difference could be because the batch BE1 contains only 2% w/w of BE gum mucilage without the incorporation of 1% w/w Eudragit RS₁₀₀ which serves to sustain the integrity of the tablets. The polymer Eudragit RS₁₀₀ enhanced the adhesion and compaction of the particles within the tablet matrix as shown by the increasing FLT of batches BE2-BE5. The indication is that the binding ability of the BE gum increased the FLT.

Sodium bicarbonate and tartaric acid were used to achieve effervescent. Sodium bicarbonate generated carbon (iv) oxide in the presence of the dissolution medium (0.1 N HCl). The carbon (iv) oxide gas released is trapped inside the gel formed by hydration of the polymers within the tablet, hence lowering the density of the tablet (Eyjolfsson *et al.*, 2000).

The *in vitro* buoyancy of floating tablets was induced by the gas generating agents without compromising the matrix integrity. Batch BE1 showed buoyancy duration without rupture of <12 h while the other batches showed

buoyancy duration of >12 h. This may have been attributed to the reduced binder effect of BE gum alone in comparison to the additive binder effect observed with the addition of Eudragit RS₁₀₀ (batches BE2 - BE5). The indication is that the addition of Eudragit RS₁₀₀ helped to enhance the integrity of the tablet formulation therefore showing buoyancy duration of >12 h. The illustrative view of the *in vitro* buoyancy characteristic of FMT formulated with BE gum mucilage is presented in fig. 1.

Tablet hardness is an indication of the capability of the tablet to resist pressure. It was observed that with increase in the binder concentration of the BE gum there was a noticeable increase in the hardness of the tablet (p<0.05). This could be attributed to the fact that binders when incorporated provide cohesive binding of particles and hence making sure that granules and tablets can be produced with the desired mechanical strength. It might also be due to the aggregative nature of the gum leading to an increased bond formation between the granules as the concentration increased. This may ensure plastic deformation of the particles during compaction (Musa *et al.*, 2008).

The friability values decreased with increase in the BE gum concentration and there were within the official standard limit < 1% which is a sign of good mechanical strength of the tablets. This friability result also shows the ability of the tablet to resist mechanical stress during transportation, storage and packaging.

The indication is that drug release from batch BE1 of the FMT prepared using 2% w/w of the BE gums alone displayed a faster release of drug content compared to the other batches containing BE gum and 1% w/w Eudragit RS₁₀₀. It was equally observed that there was a marked retardation (i.e. reduction in the rate of drug release) in the release profile of the FMT as concentration of the gums increased. The results of the dissolution parameters are presented in table 5. For instance, maximum drug released (m_{∞}), time to achieve maximum release (t_{∞}) and dissolution rate (m_{∞}/t_{∞}) for batch BE1 was 98%, 4 h and 24.5% h⁻¹ respectively while the corresponding values for batch BE5 was 88%, 10 h and 8.8% h⁻¹. The higher the concentration of the gums, the more retarded the drug release from the matrix system studied. This reveals that the release profile from the FMT depended on the concentration of the gum.

From the results, drug release from the FMT was predominantly by Higuchi model which states that the quantity of drug released is dependent on the square root of time. Previous researchers have reported similar findings with matrix tablets using different polymers (Uhumwangho and Okor, 2007; Uhumwangho and Okor, 2008; Uhumwangho *et al.*, 2010).

Table 6: Regression coefficient (r^2) and release kinetics of FMT of metronidazole (n=3).

Models	Zero		First		Higuchi		Korsmeyer and Peppas	
Formulations	r^2	K_0	r^2	K_1	r^2	K_H	r^2	n
BE1	0.602	11.7	0.924	-0.29	0.822	36.1	0.856	0.26
BE2	0.783	7.73	0.965	-0.11	0.947	28.1	0.994	0.31
BE3	0.799	6.6	0.942	-0.09	0.953	26.0	0.989	0.34
BE4	0.878	6.8	0.967	-0.08	0.981	26.2	0.987	0.41
BE5	0.914	7.0	0.976	-0.08	0.988	26.4	0.986	0.50

It was also previously reported by Darunkiasorn *et al.*, (2011) that the release of drug from polymeric matrix systems was by diffusion mechanism. In diffusion controlled mechanism, the matrix systems are mainly characterized by an initial zone of depletion. This is as a result of rapid leaching into the dissolution medium and this constitutes the diffusion layer.

CONCLUSION

FMT of metronidazole has been formulated using BE gum mucilage. This can control drug formulations for up to 10 h. Batch BE5 showed a better sustained release profile which can be taken as the optimized formulation because its maximum drug released (m_∞), time to achieve maximum release (t_∞) and dissolution rate (m_∞/t_∞) were 88%, 10 h and $8.8\% \text{ h}^{-1}$ respectively. Hence, BE gum mucilage can be exploited in the design of other matrix formulations for controlled release and enhanced bioavailability.

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