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Research Article

Formulation And Evaluation of Gastroretentive Floating Matrix Tablets of Metronidazole Using *Khaya Ivorensis* Gum

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ABSTRACT

This study was carried out to design and evaluate gastro-retentive floating matrix tablets (GFMTs) of metronidazole formulated using *Khaya ivorensis* gum. Granules were prepared by wet granulation technique using the gum at varying concentrations (2, 4, 6 and 8% w/w). Sodium bicarbonate (30%) and tartaric acid (5%) were incorporated as the gas generating agent. Formulations were either prepared alone with the *Khaya ivorensis* or with the addition of 1.0% w/w of acrylatemethacrylate copolymer. All granules were evaluated for micromeritic properties and compressed at an optimized compression pressure of 30 arbitrary units on the tableting machine load scale. Tablets were evaluated for hardness, friability, floating lag time, *in vitro* buoyancy test and drug release profiles. Release data were subjected to analysis by zero order flux, first order, Higuchi square root of time relationship and Korsmeyer equations. Results revealed that all formulated gastroretentive floating matrix granules (GFMG) were free flowing with angle of repose and Carr's index ≤ 29.1° and ≤ 19% respectively. The floating lag time for GFMTs was ≤ 725 seconds. The *in vitro* buoyancy test of GFMTs formulations using the gum alone (i.e. without the incorporation of acrylatemethacrylate copolymer) were <12 h while those with acrylatemethacrylate copolymer were >12 h. All GFMG were compressible with tablet hardness between 14.1 – 45.7N while percentage friability was ≤ 0.97%. 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 KI - K3 have their exponent values <0.45, hence their release mechanism was by Fickian diffusion while for K4 and K5 their exponent values > 0.45, therefore the release mechanism for all these formulations was by non Fickian diffusion. The conclusion is that GFMTs of metronidazole have been developed using *Khaya ivorensis* gum which can sustain drug formulation for up to 10h.

Key-words: Khaya ivorensis gum, Higuchi square root of time, micromeritic properties, floating lag time and *in vitro* buoyancy test.

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INTRODUCTION

Drug absorption from the gastrointestinal tract is a complicated technique and is subject to many factors. Swift and irregular gastrointestinal transit could result in incomplete drug release from the device above the absorption zone leading to reduced efficacy of the administered dose[1]. It is well known that the amount of gastrointestinal tract drug absorption is related to contact time with the small intestinal mucosa[2]. However, different methods have been utilized to retain the dosage form in the stomach. These approaches include floating[3,4], mucoadhesion[5], sedimentation[6], expansion[7], modified shape systems[8,9]. Floating is the easiest way to enhance drug absorption in order to hold a drug delivery system above the absorption window. This is because most absorption windows are situated in the proximal small intestine (duodenum), hence, the most effective strategy will be to hold the formulation in the stomach[10].

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[11]. It is often used in combination with other drugs for the eradication of Helicobacter pyloric[12]. It is normally taken 400mg three times daily for 5 days, which is cumbersome to the patient. Its chemical name is 2-(2-methyl-5-nitro-1H-imidazole-1-yl) ethanol.

Khaya gum (KG) is a polysaccharide obtained from the incised trunk of the tree *Khaya ivorensis* (family Meliaceae). It has previously been investigated as a controlled release agent in comparison with hydroxypropylmethylcellulose (HPMC) using paracetamol (water soluble) and indomethacin (water insoluble) as model drugs[13]. Some researchers also evaluated the suspending properties of *khaya senegalensis* gum in comparison with those of *Acacia sieberiana* and *Acacia senegal* gums using paracetamol as drug model[14]. More recently, the influence of some channeling agents on the release profile of *Khaya Ivorensis*- ibuprofen matrix tablets was also investigated[15]. The use of *Khaya Ivorensis* as a matrix former in the formulation of gastro retentive floating formulation has not been investigated.

MATERIALS AND METHODS

Materials: The active ingredient used in the study as drug model was metronidazole (Cipla Ltd, Goa, India), acrylatemethacrylate copolymer was received from Rhoma Pharma, Darmstadt, Germany, *Khaya ivorensis* was used as a matrix former and was extracted by method described previously [15]. Sodium bicarbonate and tartaric acid were used as gas generating agents. All other chemicals were analytical grade.

Methods:

Granulation and Tableting technique: Gastroretentive floating matrix granules (GFMG) of metronidazole were formed by wet granulation technique. Composition of formulae is 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 GFMG equivalent to 400mg 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 granules. The packing properties of the GFMG were determined by measuring the bulk density (BD) and tap density (TD), using standard procedures[16] and values was determined using equations 1 and 2 respectively. From the data, compressibility index (CI) values of the GFMG was calculated as CI=TD-BD/TD x 100 [17]. The flowability of the GFMG was calculated by measuring the angle of repose formed when a sample of the granules (20g) was allowed to fall freely through the

stem of a funnel onto a horizontal bench surface[18]. The angle of repose was determined using equation 3.

Table 1: Formulae for preparing 50 GFMTs of metronidazole each containing 400mg of the drug.

Ingredients (g)	KI	K2	K3	K4	K5
Metronidazole	20	20	20	20	20
Khaya ivorensis	3.2	0.8	1.6	2.4	3.2
Acrylate methacrylate copolymer	-	0.4	0.4	0.4	0.4
Sodium bicarbonate	12	12	12	12	12
Tartaric acid	2.0	2.0	2.0	2.0	2.0
Talc	0.4	0.4	0.4	0.4	0.4

Bulk density (BD) = Weight of granules/Volume occupied by granules without tapping …….. Equ 1

Tap density (TD) = Weight of granules/Volume occupied by granules after 100 taps. …….. Equ 2

$\theta = \tan^{-1} h/r$ …….. Equ 3

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

Evaluation of gastroretentive floating matrix tablet (GFMT)

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 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 operated for 25 rpm after which the final weight of the tablets was recorded. These values were used to calculate the percentage friability using equation 4.

$\%\ \text{friability} = w_1 - w_2/w_1 x100$ ……..Equ 4.

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

Floating lag time and *in vitro* buoyancy test: The method described by Rosa *et al.*, was adopted[19]. A 1000ml beaker was filled with 900ml simulated gastric fluid (0.1 N HCl). A tablet was placed inside and the medium kept stagnant and maintained at 37 ± 2 ^{o}C. The time required for the tablet to rise to the surface and float was determined as the floating lag time. The time duration for which the tablet floats and remains afloat without breaking is determined as the floating lag time and *in vitro* buoyancy time respectively.

***In vitro* dissolution studies:** The basket method was used and dissolution studies were performed using 900ml of 0.1 N HCl as the dissolution medium maintained at 37 ± 2^{0}C. One tablet was placed in a cylindrical basket which was immersed in the dissolution medium. The dissolution fluid was stirred at 100 rpm with a single blade GallenKamp stirrer (Model APP No 4B 5784A). At predetermined time intervals (5min, 10min, 15min, 30min, 1hr, 2hrs, 3hrs, 4hrs, 5hrs, 6hrs, 7hrs, 8hrs, 9hrs, 10hrs) 5ml sample of the leaching fluid were withdrawn using a pipette fitted with a cotton wool plug. Equal amount of drug free fresh dissolution medium kept at the same temperature was used to replace the withdrawn fluid. The withdrawn samples were filtered, diluted and their absorbance determined with a UV/Visible spectrophotometer at λmax 277nm. The determination was carried out in triplicate and the mean results reported. The corresponding amount of metronidazole released at any time t, was determined.

***In vitro* drug release kinetics:** The data obtained from the dissolution studies of the GFMT of metronidazole were subjected to different models of drug release kinetics to determine the pattern of release kinetics. The models used are zero order, first order and Higuchi square root of time relationship [20-23]. The mechanism of drug release from the formulation was determined using the standard Korsmeyer and Peppas dissolution model. The linear regression coefficient (r^2) for each rate order was calculated. The dissolution profile was considered to have followed a particular release order if the r^2 value was >0.95 [24].

Statistical Analysis: The results of data obtained were expressed as mean ± standard deviation (SD). All the results obtained were subjected to Student t - test statistical analysis to test for significance of difference. $P < 0.05$ was considered to be significant.

RESULTS AND DISCUSSION

Micromeritic properties of the GFMG: The results of the micromeritic properties of the GFMG produced by different concentrations of *Khaya ivorensis* gum are presented in table 2. It was observed that all the granules produced with *Khaya ivorensis* gum displayed angle of repose ranging from 15.2 – 25.1^0 while Carr's index values ranged from 10 – 19%. These values were observed to increase with increase in the concentration of the gum, although the decrease was not significant. The indication is that all the GFMG exhibited good flow properties which are very essential in ensuring weight and content uniformities during tableting. Compressibility properties of granules are directly related to the particle size distribution and inter-particulate forces on the surface of the particles. Flow characteristics of pharmaceutical ingredients are of major concern especially during tablet production. Hence, the measurement of all these parameters can provide a means of monitoring batch to bath variation.

Table 2: Micromeritic properties of GFMG of metronidazole.

Formulations	B.D (g/cm^3)	T.D (g/cm^3)	Angle of repose (θ)	C.I (%)	H.R
K1	0.55±0.02	0.61±0.02	15.2±1.3	10±1.3	1.10
K2	0.55±0.03	0.62±0.01	25.1±1.1	11±1.2	1.13
K3	0.53±0.01	0.63±0.02	24.0±1.2	16±1.3	1.18
K4	0.57±0.02	0.69±0.03	21.4±1.1	17±1.6	1.21
K5	0.58±0.03	0.72±0.02	18.1±1.3	19±1.4	1.24

where B.D=bulk density, T.D=tap density, C.I=Carr's index and H.R=Hausner's ratio

Table 3: Floating lag time and In vitro buoyancy studies of GFMT.

Formulations	K1	K2	K3	K4	K5
Floating lag time (s)	120	484	608	606	725
Buoyancy time without rupture of tablet (h)	<12	>12	>12	>12	>12

Table 4: Physiochemical properties of GFMT.

Formulation	Hardness (N)	Friability (%)
K1	14.1±2.77	0.84±0.02
K2	17.5±2.32	0.80±0.04
K3	25.2± 4.05	0.79±0.03
K4	38.2±3.85	0.74±0.05
K5	45.7± 3.40	0.71±0.03

Table 5: Dissolution parameters of the GFMT.

Formulations	Dissolution parameters		
	m_∞	t_∞	m_∞/t_∞
K1	98	5	19.6
K2	95	10	9.5
K3	91	10	9.1
K4	89	10	8.9
K5	86	10	8.6

where m_∞ (%), maximum release, t_∞ (h), time to attain maximum release, m_∞/ t_∞ ($\%h^{-1}$) dissolution rate.

Influence of the gum concentration on tablet floating ability.

The results of floating lag time and *in vitro* buoyancy studies on GFMT of metronidazole produced using *Khaya ivorensis* gum are shown in table 3. The floating tablets produced using *Khaya ivorensis* displayed a floating lag time between 120 – 725 seconds. It was observed that as the concentration of the gum increased, there was a corresponding increase in the floating lag time. This could be attributed to an increase in the inter-particulate cohesive forces acting within the tablet matrix due to the increased binding properties of the gums. The floating tablets in batch K1 were found to have a very short floating lag time (120 seconds) compared to the other batches. One main reason for this significant time difference could be because the batch K1 contains only 8% $^w/_w$ of *Khaya ivorensis* without the addition of 1%$^w/_w$ acrylatemethacrylate copolymer which serves to maintain the integrity of the tablets. The polymer acrylatemethacrylate copolymer obviously improved the adhesion and compaction of the particles within the tablet matrix as shown by the increasing floating lag time of batches K2- K5. This indicates that the binding ability of the gum or polymer increased the floating lag time.

Effervescent floating drug delivery was used to achieve *in vitro* buoyancy by using sodium bicarbonate and tartaric acid. Sodium bicarbonate induced carbon dioxide generation in the presence of the dissolution medium (0.1N HCl). The carbon dioxide gas generated is entrapped and protected within the gel formed by hydration of the polymers within the tablet, thus decreasing the density of the tablet [25]. The *in vitro* buoyancy of floating tablets was induced by sodium bicarbonate and tartaric acid without compromising the matrix integrity with all the batches showing buoyancy duration of > 12 h except for batches K1. The batch K1 showed buoyancy duration without rupture of < 12 h. This was due to the reduced binder effect of *Khaya ivorensis* alone in comparison to the additive binder effect observed with the incorporation of acrylate methacrylate (batches K2 - K5). This however, indicates that the incorporation of the acrylate methacrylate helped to maintain the integrity of the tablet formulation hence showing buoyancy duration of > 12 h. The pictorial view of the *in vitro* buoyancy characteristic of GFMT formulated with *Khaya ivorensis* is shown in figure 1.

Influence of binder concentration on the GFMT physicochemical properties

The results of the influence of binder concentration on the physicochemical properties of GFMT of metronidazole produced by using *Khaya ivorensis* is presented in table 4. All tablets formed had no surface defects such as lamination or capping, so were adjudged good and acceptable in that regards. The usual standard for conventional tablets is that it disintegrates within 15 minutes, while some other tablets may fail to disintegrate even after hours irrespective of the polymer concentration. When this happens, it indicates the formation of a matrix tablets. Matrix tablets are non-disintegrating solid dosage forms which are usually employed in sustained release formulation[24]. Acrylate methacrylate copolymer is water insoluble but swells under hydration thus maintaining the integrity of the tablet formulation.

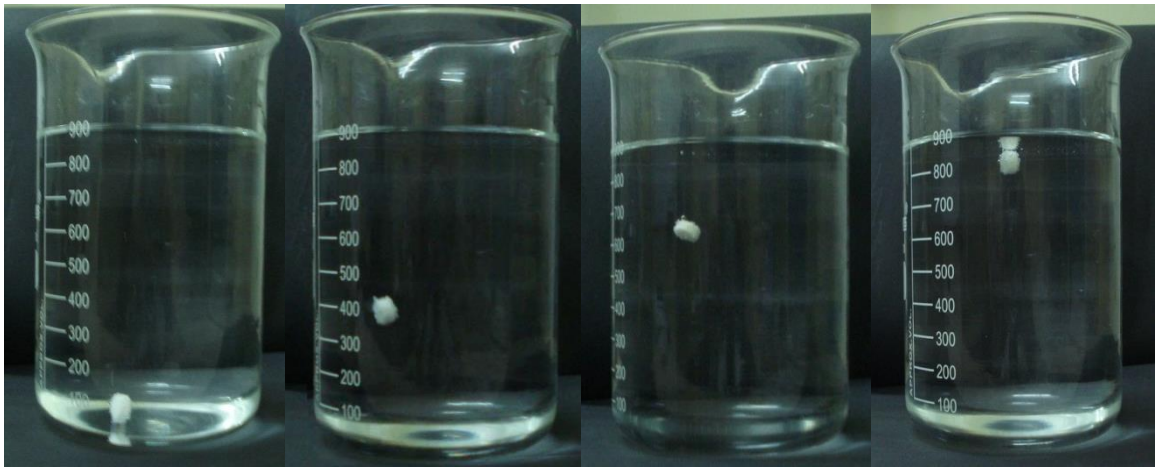

Figure 1: Photographs showing the in vitro buoyancy characteristics of GFMTs
(a) Photograph taken immediately after placing the tablet into the beaker;
(b) and (c) are the photographs taken during the intermediate stages of tablet floating;
(d) Photograph taken immediately after the tablet floated onto the surface indicating a floating lag time of 484 seconds.

The floating tablets prepared using *Khaya ivorensis* showed tablet hardness value between 14.1 – 45.7 N. Tablet hardness (crushing strength) gives a preview of the ability of the tablet to withstand pressure. All the floating tablets produced irrespective of the concentration applied formed hard compacts capable of withstanding any form of mechanical shock that may result from processing, shipping or handling. Binders are known to impart plasticity on granules, thus promoting the formation of a more cohesive inter-particulate bond [26]. It was also observed that for all the tablets produced using *Khaya ivorensis* gum, increase in the binder concentration of the gum resulted in a significant increase in the tablet hardness ($p<0.05$). This could be due to the fact that binders are added to provide cohesive binding of particles and to ensure that granules and tablets can be formed with the required mechanical strength. This is as a result of formation of plastic deformation of the particles during compaction [27].
The friability test values for the floating tablets produced with *Khaya ivorensis* ranged from 0.71 – 0.84% (see table 4). It was observed that the friability values decreased with increase in the gum concentration. This is as a result of inter-particulate bonding in the tablets just like hardness. The friability values for all the tablets produced were < 1% which is an indication of good mechanical resistance of the tablets.

Dissolution profile of GFMT of metronidazole produced with varying concentration of the gum: The results of the *in vitro* drug release profile studies of the GFMT of metronidazole prepared using *Khaya ivorensis* is presented in figure 2. The drug release from batch K1 tablet prepared using $8\%^{w}/_{w}$ of the gums alone displayed a faster release of drug content compared to the other batches containing acrylate methacrylate. For instance, batch K1 released 70% of the drug content within 2 h while batches K2 – K5 released about 70% of the drug contents for up to 5 h. There is thus a more sustained release of drugs from the batches K2 – K5. The drug release from batch K1 of the floating tablet prepared using $8\%^{w}/_{w}$ of the gums alone displayed a faster release of drug content compared to the other batches containing acrylate methacrylate. It was equally observed that there is a marked retardation (i.e. decrease in the amount of drug released) in the release profile of the floating tablets as the concentration of the gums increased. The results of the dissolution parameters are presented in table 5. For instance, maximum drug released (m_∞), time to attain maximum release (t_∞) and dissolution rate (m_∞/t_∞) for batch K1 are 98%, 5h and 19.6% h^{-1} respectively while the corresponding values for batch K5 are 86%, 10h and 8.6% h^{-1}. It shows clearly that the release profile in the tablets was concentration dependent.

The higher the concentration of the gums, the more retarded the release of the drug from the gastro-retentive floating matrix system studied.

Release kinetics of the GFMT of metronidazole: In order to determine the mechanism of drug release from the formulations, the data 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 various release kinetics for floating tablets prepared using *Khaya ivorensis* are presented in table 6. As clearly indicated in figure 2 the floating tablet formulations prepared with *Khaya ivorensis* did not follow a zero order release pattern as the plot showed poor linearity with regression value (r^2) ranging from 0.823 – 0.950.

Figure 2: Drug release profile from GFMT of metronidazole

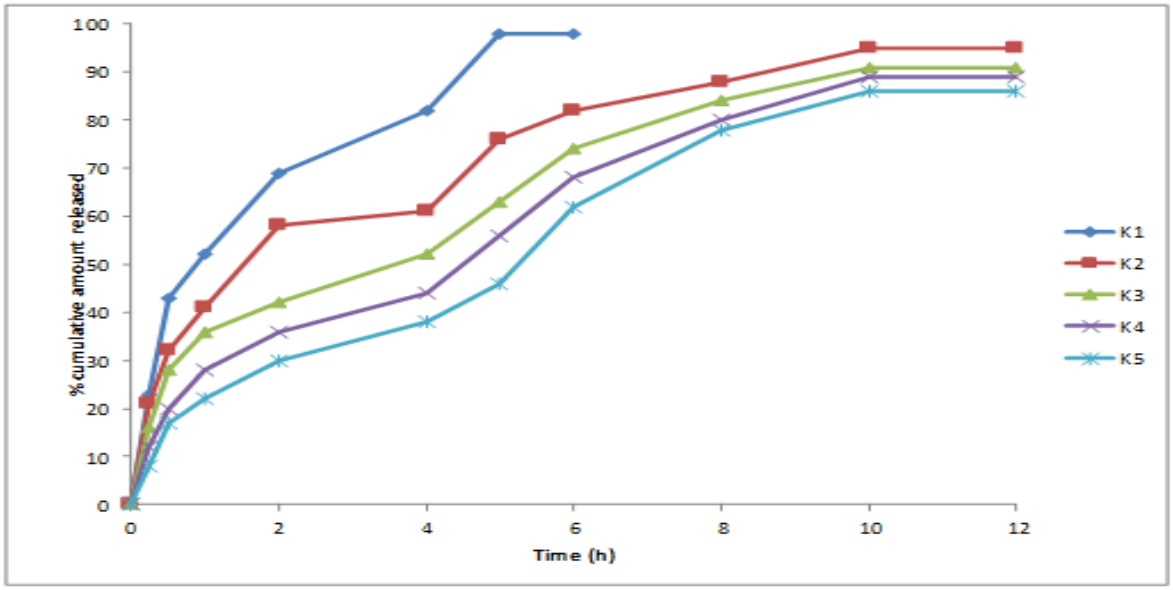

Table 6: Value of linear regression coefficient (r2) and release kinetics of GFMTs

	Zero		First		Higuchi		Korsmeyer and Peppas	
	r^2	K_0	r^2	K_1	r^2	K_H	r^2	n
K1	0.847	13.9	0.923	-0.28	0.971	39.4	0.957	0.42
K2	0.823	6.9	0.975	-0.11	0.963	27.3	0.980	0.38
K3	0.892	7.0	0.973	-0.09	0.981	26.7	0.975	0.43
K4	0.932	7.2	0.971	-0.08	0.983	26.9	0.984	0.50
K5	0.950	7.3	0.960	-0.07	0.965	26.6	0.972	0.58

This showed that the formulations did not obey zero order kinetic, where the amount of drug released is expected to be constant throughout the time of drug release irrespective of the concentration. Although, the desired release model for controlled drug delivery system is zero order, this was not attained. It was also observed that there was an increase in r^2 value for zero order kinetics as the gum concentration increased. Generally, the r^2 values were higher with first order kinetic compared to zero order kinetic. When data were plotted according to the first order equation, the formulations showed a fair linearity

with regression values r^2 ranging between 0.923 – 0.975. This implies that the amount of drug released was determined by the amount of drug left in the system. Release of drugs from a matrix tablets containing hydrophilic polymer generally involves factors of diffusion. Diffusion is related to transport of drugs from the dosage matrix into the *in vitro* study fluid depending on the concentration. The *in vitro* release profiles of all the formulations could best be expressed by Higuchi's equation as the plot showed a higher linearity with linear regression coefficient, r^2 for the formulations ranging between 0.963 – 0.983. The release kinetics was more consistent with this model since it gave a higher correlation when compared to the other models analyzed. It was therefore, the most likely kinetic order that controlled the release of drug from the floating matrix tablets. It was also observed that r^2 values for Higuchi model of release kinetic and the Korsmeyer and Peppas equation were close, although, Higuchi's model showed a higher correlation. This confirmed that the drug release from the matrix tablets were mainly by Higuchi model which states that the amount of drug released is dependent on the square root of time. Similar findings with matrix tablets of different polymers had been reported [28, 29].

In order to confirm the mechanism of release, the data were fitted into Korsmeyer and Peppas equation. The formulations showed good linearity with r^2 values for tablets prepared with *Khaya ivorensis* ranging from 0.957 – 0.984. Since the r^2 values were consistent with Higuchi release model, it was expected that the mechanism of drug release from matrix tablets will be diffusion controlled. This was confirmed from the values of the release exponent. The release exponent (n) for tablets prepared using *Khaya ivorensis* ranged from 0.38 – 0.58. This indicates that diffusion was the dominant mechanism of drug releases from these formulations. Formulations K1 to K3 have their release exponent (n) < 0.45, hence their release mechanism was by Fickian diffusion while K4 and K5 have their release exponent (n) > 0.45; hence their release mechanism was by Non Fickian diffusion.

Hydrophobic polymers have also been reported to release drug from their polymeric matrix by diffusion mechanism [30]. In a diffusion controlled model, the matrix systems are mainly characterized by an initial zone of depletion i.e. the surface layers are depleted of their drug content due to rapid leaching into the dissolution medium and this constitutes the diffusion layer. Eichie *et al*. [31] reported that the increase in time taken for the drug to be released is due to the fact that the depletion zone recedes inwards starting from the outer layer before the inner tablet core thereby causing an increase in the diffusion path length.

Conclusion: Conclusively, GFMTs of metronidazole have been developed using *Khaya ivorensis* gums which can sustain drug formulation for up to 10h. Batches K5 showed a better sustained release profile which can be taken as the optimized formulation.

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