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Formulation of Mucoadhesive Tablets of Metronidazole using *Irvingia gabonensis* (Irvingiaceae) Gum

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ABSTRACT

***Background*:** The aim of this study was to formulate mucoadhesive tablets of metronidazole using admixtures of HPMC and irvingia gum (IG) which was extracted from the seeds of *Irvingia gabonensis (Irvingiaceae)*.

***Methods*:** Various batches of metronidazole granules were prepared by wet granulation technique with the extracted irvingia gum at varying concentrations of 25-50%w/w. The granules were then compressed to tablets at a compression pressure of 25 N/m^2. The tablets were evaluated for hardness, friability, bioadhesive strength, *in vitro* dissolution studies and release kinetics.

***Results*:** All the formulated granules were free flowing with angle of repose between 25.4 and 29.6º and Carr's index of ≤ 12.5%. The granules were compressible with hardness of 5.0 - 7.0 Kpa and friability of ≤ 0.67%, while the bioadhesive force was between 0.31 -1.31 N. The percent maximum release (m_∞) and time to achieve it (t_∞) for all the mucoadhesive tablets were ≤97.2% at 10 h respectively. All batches fitted well into the Higuchi model release. The release mechanism showed non-fickian diffusion with $0.45<n<0.89$.

***Conclusion*:** Irvingia gum exhibited good mucoadhesive property retarding the release of metronidazole with maximum release of 88.8% at maximum time of 10 h.

***Key words*: Irvingia gum, metronidazole, mucoadhesion, sustained release.**

1. INTRODUCTION

Mucoadhesion is a phenomenon that occurs when two materials are held together for a prolonged period of time by interfacial forces. Mucoadhesive drug delivery system (MDDS) is designed to enable prolonged residence time of the dosage form at the site of application or absorption and facilitate intimate contact of the dosage form with the underlying absorption surface thereby contributing to improved and better therapeutic performance of the drug [1]. This drug delivery system utilizes the property of bioadhesion of certain polymers which become adhesive on hydration and hence can be used for targeting a drug to a particular region of the body for extended period of time [2]. Some advantages of MDDS include: prolong residence time of the dosage form at the site of absorption, hence increases the bioavailability of the drug, good accessibility, rapid onset of action, rapid absorption because of increase blood supply, protection of the drug from degradation in the acidic environment of the gastrointestinal tract (GIT) and reduced dosing interval hence improved patient adherence to therapy [3], [4]. *Irvingia* gum is a hydrocolloid extracted from the defatted cotyledons of *Irvingia gabonensis* by the method previously described by Airemwen *et al*., [5] and was used as a natural polymer in this formulation. It is a natural gum hence, chemically inert, non-irritant, biodegradable, biocompatible eco-friendly and safe. Irvingia gum has been previously used as a matrix former in the formulation of floating drug delivery system [6], binder in tablet formulations [7], as an emulsifying and suspending agent. However, its use as a bioadhesive polymer in mucoadhesive drug delivery system has not been investigated. Metronidazole is an antimicrobial nitroimidazole derivative originally introduced in 1959 for the treatment of *Trichomonas vaginalis* and has since been evaluated for the treatment of

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infections caused by anaerobic bacteria. It has a molecular weight of 171.15 g/mol and a melting point ranging from 159-163˚C. Metronidazole appears as white to pale yellow crystals or crystalline powder that is sparingly soluble in water and alcohol and slightly soluble in ether and chloroform. It is used in the management of bacterial vaginosis, pelvic inflammatory disease (PID), pseudomembranous colitis, periodontitis, amoebiasis, oral infections, giardiasis, trichomoniasis and *Helicobacter pylori*-induced peptic ulcer disease. The objective of this study was to formulate mucoadhesive tablets of metronidazole which could be administered once daily in the management of diseases such as periodontitis, amoebiasis etc. thereby leading to adherence of patients to therapy.

2. MATERIALS AND METHODS

2.1 Materials

2.1.1 Chemicals and Reagents

The active ingredient used in the study as drug model was metronidazole powder (Aarti Pharmaceutical Co.Ltd, China), hydroxypropylmethylcellulose (HPMC) used was obtained from BDH Chemicals Ltd, England. All other chemicals were of analytical grades.

2.1.2 Biological Materials

Irivingia gabonensis (Ogbono) gum was extracted from the pulverized seeds of *Irvingia gabonensis.*

Methods

2.2.1 Extraction of Irvingia gabonensis gum

Blended *I. gabonensis* seeds (100 g) was weighed and placed in 200 mL of distilled water and heated at 78°C with the addition of 2.0 g of sodium chloride for 1 h using a hot plate. The mixture was then allowed to settle for 24 h in order to separate the lipids. Further separation was achieved by means of a separating funnel clamped on a retort stand. The supernatant portion containing the gum was removed and dried on a ceramic plate in a hot air oven at a temperature of 65°C. The dried gum was scraped off the ceramic plate and triturated [6].

2.2.2 Preparation of metronidazole granules

Mucoadhesive granules of metronidazole were prepared using the wet granulation method. Three (3) batches were prepared using *Irvingia gabonensis* gum and HPMC (100, 150 and 200 mg). In each formulation, lactose, metronidazole and HPMC were mixed in the dry state in a mortar using the geometric mixing method. Then the binder mixture of the gum was used to wet mass the powder in the mortar. The damp mass formed was forced through a sieve mesh of 710 µm and dried at 60 ºC for 30 min in a hot air oven. The granules formed were further passed through a sieve of mesh size 850 µm and evaluated for micromeritic properties. The composition formula is shown in Table 1.

2.2.3 Evaluation of prepared granules

The prepared granules were evaluated for micromeritic properties such as bulk and tapped densities [8], angle of repose [9], Carr's index and Hausner ratio using established procedures [10].

2.2.4 Bulk and tapped densities

A quantity of granules from each batch (20 g) was weighed and packed into a 50 mL graduated cylinder. The granules were carefully levelled without compacting and the unsettled apparent volume (V_0) was read and recorded as the bulk volume. Thereafter, the cylinder was tapped and the volume obtained after hundred taps (100 taps) was recorded as the final tapped volume (V_f). The process was done in triplicate and then the bulk density and tapped density in g/ml were calculated thus;

$$\text{Bulk density} = M/V_0 \quad \text{- - -Equation 1}$$

$$\text{Tapped density} = M/V_f \quad \text{- - -Equation 2}$$

Where, M = mass of the powder, V_0= bulk or unsettled apparent volume of the powder, V_f= final tapped volume of the powder.

2.2.5 Angle of repose

A sample of each set of granules (20 g) was allowed to fall freely from a funnel clamped to a retort stand at a height of 7.5 cm from a horizontal surface. The diameter of the base of the heap and the height of the pile formed by the granules were measured using a meter rule. The angle of repose was calculated as;

$$\text{Angle of repose } (\Theta) = \tan^{-1}(h/r) \quad \text{- - - Equation 3}$$

Where, h = height of the pile, r = radius of the pile and Θ = angle of repose.

Carr's compressibility index and Hausner ratio were calculated from the values of bulk and tapped densities using equation 4 and 5 respectively.

Carr's index (%) = (Tapped density-Bulk density)/ (Tapped density) x 100 - - - --Equation 4

Hausner ratio = (Tapped density)/ (Bulk density) - - - Equation 5

2.2.6 Formulation of metronidazole tablets

Metronidazole granules were compressed into tablets at a compression pressure of 25 N/m^2 after the addition of 1% w/w talc using a single punch compression machine (Manesty machines, UK).

2.2.7 Evaluation of the metronidazole tablets

Weight uniformity: In order to carry out this test, ten (10) tablets were randomly selected from each batch of tablets and weighed individually. The average weights as well as percentage deviation were computed. The tablets meet the USP test if not more than 2 tablets are outside the percentage limits and if no tablet differs by more than 2 times the percentage limit.

Hardness test: The hardness of each of five (5) tablets from each batch selected at random was determined using the Campbell electronic hardness tester (HT-30/50, India) and recorded.

Friability Test: Five (5) tablets were selected at random, dusted and weighed. The tablets were placed in the drum of a friabilator (Erweka friabilator) and subjected to cascading and free falling stress at 25 rpm for 4 min. The tablets were removed from the friabilator, dusted and reweighed. The difference between the initial weight and final weight expressed in percentage was taken as percentage weight loss (friability percentage).

$$\text{Friability (\% loss)} = (W_1 - W_2)/W_1 \times 100 \quad - - - \quad \text{Equation 6}$$

Where, w_1 = weight of five randomly selected tablets before friabilation, w_2 = weight of only the intact tablets after friabilation

2.2.8 In vitro dissolution studies

In vitro dissolution tests were performed in triplicate using dissolution tester (ST7, G.B. Caleva Ltd, England), USP dissolution apparatus 1 rotating at 50 rpm in 900 ml of 0.1 N HCl at 37 ± 0.5ºC. Aliquot of dissolution medium equal to 5 ml was withdrawn at specified time intervals and same volume of fresh dissolution medium was replaced. The withdrawn media were properly diluted and the concentration and percentage of metronidazole released at each time interval was determined using UV Spectrophotometer at a wave length of 276 nm by using the regression equation from the standard calibration curve.

2.2.9 Ex-vivo bioadhesion test

This test was carried out by a modified method of Attama *et al.*, [11]. A 50 mL burette was clamped on to a retort stand and a stage clamped at an angle of 30º below the burette. A freshly excised cow ileum of about 4 cm was tapped to the stage; one tablet was weighed and placed on the exposed mucus surface. Normal saline was allowed to flow at a rate of 100 mL/min. The weight of fluid that detached the tablet was recorded and used to compute the mucoadhesive force. The mucoadhesive force was calculated thus;

$$N = w/100 \times g \quad - - - 7$$

Where N= mucoadhesive force (Newton), w= weight of fluid that detached the tablet (g), g= acceleration due to gravity (m/s^2).

2.2.10 In vitro release kinetics

The data obtained from in vitro release studies were fitted into various release models, namely; zero order, first order, Higuchi square root [12] and Korsmeyer- Peppas model [13] to determine the kinetic and mechanism of release of the metronidazole tablets.

Zero order: $P = k_0 t$ - - - Equation 8

First Order: $\ln P_1 = \ln P_0 + k_1 t$ - - - Equation 9

Higuchi Model: $P = kH\, t^{1/2}$ - - - Equation 10

Korsmeyer-Peppas: $P = k\_KP\, t^{n}$ - - - Equation 11a

$\text{Log } P = \text{Logk\_KP} + n\text{Log}t$ - - -Equation 11b

2.2.11 Drug-Excipient compatibility (FTIR Analysis)

The potassium bromide (KBr) method was used for the analysis; 5 mg of the sample under test was ground to fine powder and mixed with dry KBr powder. The sample was then placed in an evacuable KBr die and a 13 mm clear disk was pressed in a hydraulic press to form a KBr pellet. The pelletized sample which was formed inside the evacuated chamber in the cell holder (Universal Demountable Cell) was inserted into the FTIR machine (FTIR SYSTEM, Spectrum BX, PerkinElmer, England) and scanned at a range of 350 – 4000 nm. After a few seconds the spectrum was displayed on the computer screen.

2.3 Statistical Analysis

All experiments were performed in triplicates for validity of statistical analysis and expressed as mean ± standard deviation (SD). The hardness, friability, and mucoadhesive strength data were analyzed using GraphPad instat at a level of significance of $P < 0.05$.

3. RESULTS

Table 1: Composition formulae of metronidazole mucoadhesive tablets

S/N	Ingredients	Quantity
1	Metronidazole	400 mg
2	*Irvingia gabonensis* gum	25-50 w/w
3	HPMC	100, 150 and 200 mg
4	Lactose	Qs
5	Talc	1%

Table 2: Micromeritic properties of metronidazole granules

Formulation	Bulk Density (g/ml)	Tapped Density (g/ml)	Angle of repose (°)	Carr's Index (%)	Hausner Ratio
IG1	0.536 ±0.1	0.590 ±0.1	25.4 ±0.2	09.2 ±0.1	1.10 ±0.01
IG2	0.529 ±0.2	0.582 ±0.1	25.3 ±0.1	09.1 ±0.1	1.10 ±0.01
IG3	0.492 ±0.1	0.565 ±0.1	29.7 ±0.1	12.1 ±0.1	1.15 ±0.01
IG4	0.413 ±0.1	0.472 ±0.2	29.6 ±0.1	12.5 ±0.2	1.14 ±0.01

where IG1, IG2, IG3 are metronidazole tablets formulated with 100, 150 and 200 mg IG respectively and IG4 contains 100 mg IG and 100 mg HPMC.

Table 3: Physicotechnical properties of metronidazole tablets

Formulation	Hardness (Kpa)	Friability (%)	Weight uniformity (g)
IG1	5.0 ± 0.2	0.67 ± 0.01	0.53 ± 0.01
IG2	6.0 ± 0.3	0.60 ± 0.01	0.56 ± 0.01
IG3	6.5 ± 0.1	0.53 ± 0.01	0.61 ± 0.01
IG4	7.0 ± 0.1	0.20 ± 0.01	0.60 ± 0.01

Table 4: Mucoadhesive strength of metronidazole tablets

Formulation	Mucoadhesive strength (N)
IG1	0.31 ± 0.02
IG2	0.95 ± 0.01
IG3	1.22 ± 0.01
IG4	1.31 ± 0.02

Table 5: Dissolution parameters of metronidazole mucoadhesive tablets

Batches	m_∞ (%)	t_∞ (h)	m_∞ / t_∞ ($\%h^{-1}$)
IG1	97.2	10	9.72
IG2	89.5	10	8.95
IG3	85.8	10	8.58
IG4	88.8	10	8.88

Table 6: Regression coefficient values for different release models

Formulations	Zero Order	First Order	Higuchi model	Korsmeyer - Peppas

	R^2	K0	R^2	K1	R^2	Kit	R^2	n
IG1	0.875	8.190	0.977	0.141	0.978	29.287	0.397	0.476
IG2	0.932	7.680	0.981	0.087	0.988	26.739	0.439	0.491
IG3	0.961	7.462	0.967	0.074	0.980	25.493	0.515	0.545
IG4	0.925	7.359	0.978	0.082	0.990	25.741	0.400	0.459

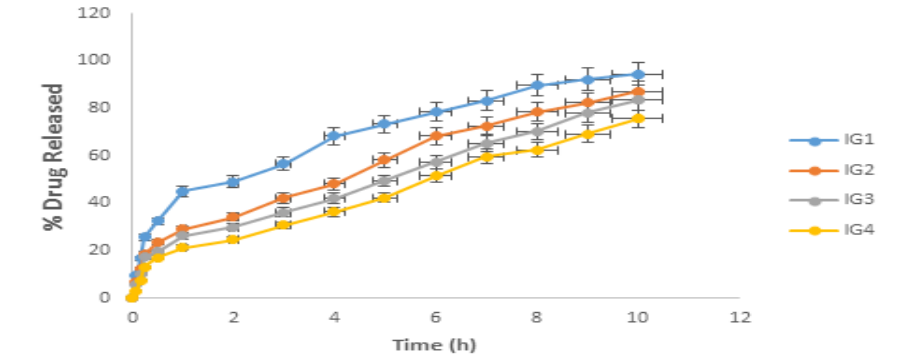

Figure 1: Drug release profile of metronidazole mucoadhesive tablets formulated with Irvingia gum.

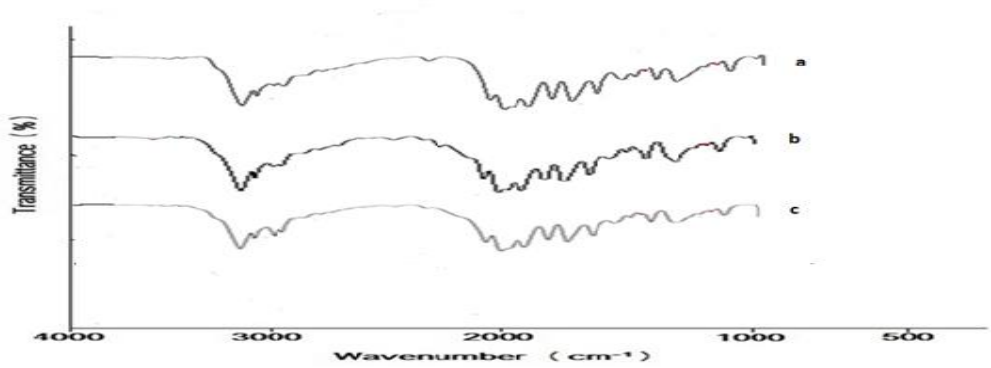

Figure 2: FTIR spectra of (a) pure metronidazole sample (b) metronidazole and irvingia gum (c) Metronidazole, irvingia gum and HPMC.

4. DISCUSSION

The results of the micromeritic properties of the formulated mucoadhesive tablets using IG are shown in Table 2. The bulk and tapped densities are a measure of the flow properties of the granules. Each of the batches showed relatively close bulk and tapped density values which indicates that the interparticulate interactions were less significant and granules were free flowing. Poor flowing materials frequently have greater interparticulate interactions and a greater difference between the bulk and tapped densities will be observed. It was observed that all the granules produced with IG had angle of repose ranging from 25.4 – 29.7º while Carr's index values ranged from 09.2 – 12.5 %. The Hausner ratio was between 1.10 - 1.15. The results of the weight uniformity, hardness and friability tests are presented in Table 3. The weight uniformity tests results showed that all the batches complied with the weight uniformity test because for each batch, no individual tablet deviated from their respective mean values by more than ± 5% (Table 3). This will help to ensure that uniformity of dosage form is achieved because the active ingredient, metronidazole forms a greater part of the tablet unlike in cases of potent drugs administered in low doses where the excipients form a major component of the tablet. The mechanical strength (hardness) of a tablet plays a very important role in the handling, transportation, packaging, shipping, disintegration and dissolution of the tablet. There are no official pharmacopoeial specifications for tablet hardness, but tablets should not be too hard or too soft. Some literatures have suggested a range of 4 – 10 Kpa as acceptable hardness limit for uncoated tablets [14]. The hardness values obtained from this study range from 5.0 to 7.0 Kpa indicative of tablets that are not too soft or hard but with adequate hardness. The tablets also showed an increase in hardness with a corresponding increase in gum concentration. This is because an increase in binder concentration

has been shown to increase particle-particle contact points resulting in the creation of more solid bonds. It also promotes a decrease in intra-granular and inter-granular voids with an increase in packing fraction causing breakage of granules and creating more contact points leading to an increase in the degree of bonding between particles, hence a higher hardness was obtained [5], [15]. The loss in total weight of the tablets due to friability was in the range of 0.2 ± 0.01 to 0.67 ± 0.01 % in all the formulations and the values were less than 1%. Friability determines the mechanical strength of a tablet when exposed to mechanical shock and attrition. Tablets that lose less than 1% of weight are considered acceptable by pharmacopoeial standard. All the batches had good percentage friability values falling below the pharmacopoeia limit of 1% [14]. There was a decrease in percentage friability with an increase in gum concentration [5]. The results of the mucoadhesive properties of the tablets formulated using IG are presented in Table 4. IG exhibited good mucoadhesive property with mucoadhesive strength ranging from 0.31-1.22 N, with batch IG3 giving the strongest mucoadhesive strength. Batch IG4 containing a combination of irvingia gum (100 mg) and HPMC 100 mg gave a synergistic mucoadhesive effect with a mucoadhesive strength of 1.31 N compared to the values obtained without the incorporation of HPMC. In this study, it was observed that an increase in the concentration of the gum resulted in a corresponding increase in the mucoadhesive strength of the tablet i.e. the gum concentration is directly proportional to the mucoadhesive strength of the tablet. This can be attributed to the increase in compaction and interparticulate forces of the gum with an increase in its concentration [16]. The *in vitro* drug release profiles of the mucoadhesive tablets of metronidazole formulated using IG are shown in Figure 1. The drug release from batch IG1 showed a faster release of drug content compared to the other batches (IG2-IG3). It was also observed that there was a decrease in the rate of release of the drug content as the concentration of the gum increased. For example, batch IG1 released about 58% of its drug content within 2 h while batches IG2 – IG3 released about 70 - 80% of the drug contents for up to 8 h. There was a more sustained release of drugs from batch IG4 – containing HPMC. This shows that the release profile of the tablet was concentration dependent. The higher the concentration of the gum, the more sustained the release of drug content from the tablet [5]. It was also observed that the time to attain maximum release in the mucoadhesive tablets also reduced as the concentration of the gum increased. 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 IG1 was 97.2%, 10 h and 9.72% h^{-1} respectively while the corresponding values for batch IG4 was 88%, 10 h and 8.8% h^{-1}. The higher the concentration of the gums, the slower the drug release from the formulations studied [5]. The results of the various release kinetics for mucoadhesive metronidazole tablets are presented in Table 6. The results obtained from the dissolution studies were fitted into zero order, first order, Higuchi, Korsmeyer and Peppas release models in order to determine the release kinetics of the different formulations. The in vitro release profiles of the mucoadhesive metronidazole tablets simulated the Higuchi release model as the plot showed the highest coefficient regression (r^2) values of 0.978-0.990 compared to the zero and first order release models which had r^2 values within the ranges of 0.875-0.925 and 0.967-0.978 respectively. This shows that the drug released from the tablets were mainly by Higuchi's model which states that the amount of drug released is dependent on the square root of time [12]. This is in line with studies conducted by Higuchi, 1963 who in analyzing the mechanism of drug release from matrices, postulated two mechanisms which are dissolution and diffusion controlled mechanisms. The natural gums in the mucoadhesive tablets studied controlled dissolution and gelation rate of the drug in the matrix being hydrophilic and the diffusion of the drug through the gel. The data obtained were fitted into Korsmeyer and Peppas equation in order to determine the mechanism of release. The formulation showed poor linearity with r^2 values ranging 0.397-0.515. Since the r^2 values were consistent with Higuchi's model, it was expected that the mechanism of drug release from matrix tablet was diffusion controlled. The release exponent (n) for the metronidazole tablets ranged from 0.46-0.55. All the formulations had their release exponent (n) > 0.45; hence their release mechanism was by Non-Fickian diffusion. This indicates that diffusion was the dominant mechanism of drug release. The FTIR spectra of pure metronidazole powder and admixture of metronidazole and the polymers are shown in the figures below. From the spectrum of formulated tablet, it shows that there were no interactions between metronidazole and the excipients used in the formulation.

5. CONCLUSION

IG and HPMC exhibited good mucoadhesive properties retarding the release of metronidazole from the formulated dosage form. From the study, formulation IG4 containing 100 mg IG and HPMC produced the optimum mucoadhesive effect could be exploited in the formulation of sustained drug delivery systems.

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Conflict of Interest

No conflict of interest associated with this work.

Contribution of the Authors

Michael U. Uhumwangho conceived and designed the study and supervised the laboratory works; Collins O. Airemwen and Johnull A. Obarisiagbon co-supervised the laboratory works, analyzed the data and prepared the manuscript; Catherine D. Soni-Osayande reviewed the manuscript while Opeyemi Ganiyat carried out the laboratory work.

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