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Formulation and Evaluation of Metronidazole Tablets Prepared from *Irvingia gabonensis* as Binder

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ABSTRACT

Background: Metronidazole tablets was formulated using Irvingia *gabonensis* (ogbono) as binder. The use of plants as excipients in drug formulation and development is quite desirable as they are generally regarded as safe (GRAS). In addition, Plants are cheap, biocompatible and readily available.

Methods: The tablets were produced by wet granulation method using corn starch as binder at concentrations of 5, 10, 15 and 20 % w/w, and as disintegrant (5% w/w). The micromeritic properties of the granules were determined using the direct and indirect methods. The official and non-official tests carried out on the tablets were; uniformity of tablets weight, content of active ingredient, disintegration test, hardness, friability tests and in vitro drug release.

Results: The results showed that the granules had good flow properties as the values obtained were within the specified limits for the production of good quality tablets. Deviations obtained from the tablet weight uniformity test were significantly ($p< 0.05$) below 5%. Tablets disintegration time ranged from 1.86 ± 0.2 min to 27.3 ± 2.20 for all the batches. The tablets hardness ranged from 6.25 ± 2.36 to 9.30 ± 1.58 kgf.

Conclusion: *In vitro* release showed that Metronidazole tablets produced from *Irvingia gabonensis* had T_{25}, T_{50} and T_{70} % at 3, 7 and 20 min respectively. The tablets formulated followed zero order kinetics via fickian diffusion.

***Key words*— Mineral elements; *Colocasia esculenta;* Soil; Construction site; Bayelsa State.**

1. INTRODUCTION

Metronidazole is an antiprotozoal in the class of nitroimidazoles [1]. It is mostly available in solid dosage forms and is well absorbed after oral administration [2]. Drug excipients are an integral part of pharmaceutical preparations. Excipients used in formulation solid forms like tablets include: lubricating agents, stabilizing agents, disintegrating agents, binding agent, bulking agent, coating agents, etc [3]. These excipients are either from natural, synthetic or semi-synthetic sources. The plant Irvingia is a genus of African and Southeast Asia trees in the family Irvingiaceae. Binders are excipients incorporated into tablet formulation to impact cohesiveness common names Wild mango, African mango, bush mango, dika or ogbono. It is an economic food tree with high economic fortune for rural farmers and whole sale traders [4]. Irvingia tree species have been earmarked for domestic purposes in various nations due to their potential for applications in the areas of biodiesel and cosmetics, among others [5] to powders, providing the necessary bond to form granules which when compresses to form tablet [6]. This research work aims to assess the effectiveness of *Irvingia gabonensis* (ogbono) as a binder in the formulation of Metronidazole tablets.

2. MATERIALS AND METHODS

2.1 Materials

Irvingia gabonensis seeds (ogbono), Corn starch, Metronidazole powder (BDH, Chemicals), Distilled Water, Tragacanth Powder, polivinylpyrollidone, and Acacia gum were of laboratory grade. Magnesium stearate (BDH Chemicals, England). All other chemicals and reagents were of laboratory grade.

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2.2 Methods

2.2.1 Extraction Process of Gum from Irvingia gabonensis Seeds (Ogbono)

0.72kg of Irvingia gabonensis seeds (ogbono) was size reduced and transferred into a clean transparent plastic bucket. Exactly 3 L of distilled water was added and stirred thoroughly using paste spatula. The mixture was allowed to stand for 30 minutes for proper dispersion in distilled water. The dispersion (mixture) was filtered through a clean muslin cloth after which the residue was discarded and the filtrate which contains biopolymer, fat and water was collected. A small amount of the filtrate was transferred into a 500ml beaker and sufficient amount of acetone added (all in batches) to precipitate the gum (Separate the biopolymer or gum and fat from water). The mixture was filtered using a clean muslin cloth. The filtrate (small amount of fat, acetone and water) was discarded while the residue (mixture of gum and fat) was collected. The residue was properly spread on a clean white tile and dried in an oven (to avoid environmental contamination) at room temperature (37^0C) for 24 hours.

2.2.2 Defatting of the Gum

The extracted gum (biopolymer) contains some proportion of fat. It was defatted by the use of n-hexane and a soxhlet apparatus (Gallanhamp magnetic stirrer with hot plate). 350 ml of n-hexane was measured into the distillation flask of the apparatus using 1000 ml measuring cylinder. The dried undefatted gum was divided into two (2) portions (A and B). A portion was introduced into the column chamber. Two holes were connected to the condenser, one of which was connected from the tap (water source) to the condenser while the other from the condenser (inlet) to the drain tank (outlet). The magnetic stirrer was connected to electricity source and when switched on, heat was applied to n-hexane at controlled temperatures between 40 -70^0c. N-hexane when heated, evaporated and circulated the column containing the gum and further condense and refluxed as fat in the form of condenser oil. This process was repeated with the B portion of undefatted gum. Finally, the defatted gum was spread on a clean white paper and air dried. It was triturated thoroughly using mortar and pestle and further passed through a 0.25 mm size sieve to obtain a fine powder. The fine powder obtained was weighed 30.2g and the percentage yield was determined to be 95.8%.

2.2.3 Method of Granulation (Wet Granulation)

Exactly 12g of metronidazole powder, 1.8g of com starch and 15.6g of lactose were weighed into a mortar and mixed thoroughly by trituration. 0.06g of the powdered gum (Ogbono) was weighted into a 100ml beaker. The dispersed gum was slowly added to the powder mix until a wet or damp mass was produced. The damp mass produced was passed through 2mm sieve and dried on a clean paper in an oven at 50^0C. The dried granules were again passed through 1.0mm sieve in order to have a uniform size of five granules. The granules were characterized (evaluated) for Tapped density, Bulk density, flow rate, Hausner's ratio, Carr's compressibility index and Angle of repose.

2.2.4 Mineral Elements Analysis in Plant Samples

Standard method was used in the analysis of mineral elements in plant materials as described by [17]. Leaf samples of *Colocasia esculenta* were washed several times with water and rinsed with distilled water. They were placed in polybags, and thereafter dried in an oven maintained at 60° C to a constant weight. The dried plant samples were macerated to powder, and stored in sample bottles for analysis. The powdered plant samples were oven dried at 105ºC for 2 hours, 1.0g weighed into a platinum crucible and placed in a muffle furnace maintained at 400ºC. The powdered plant materials were ashed for 5 hours and then dissolved with 10cm^3 of 1M HCL. The solution obtained was filtered through Whatman No. 1 filter paper into 50cm^3 volumetric flask and made up to the required mark with distilled deionized water. Standard reagents for analytical experiment were used, and contents of mineral elements in the solution were determined using Atomic Absorption Spectrophotometer (AAS) of Unicam Model.

2.2.5 Tableting (Compression)

1.3g of magnesium stearate was measured and added to granules produced using *Irvingia gabonensis*(ogbono) gum,and mixed thoroughly.The granules were introduced into the hopper of the tableting machine and compressed into tablets.Similarly,1.3g of magnesium stearate was measured and added to granules produced using tragacanth gum,acacia gum and polyvinyl pyrrolidone(pvp).The tablets formulated in four batches each using a different binder (ogbono,tragacanth,acacia and polyvinyl pyrollidone) were evaluated for weight uniformity, hardness, thickness,,diameter,,friability, dissolution and disintegration time.

2.2.6 Evaluation of metronidazole Granules

2.2.6.1 Flow Rate

A dry plastic funnel was supported by a retort stand at 5cm distance from the tip of the funnel to the table. A paper was placed below the funnel assembly. A sheet of fiber board was used to block the funnel outlet. Then 10g of

the powdered mix was introduced without compacting into the funnel. The fiber board sheet was withdrawn and the timer started simultaneously. The time was stopped when all the powder has passed through the funnel. The time needed for the entire powder to flow out of the funnel was recorded. The experiment was carried out in triplicates for each batch of granules and the mean was calculated.
Flow rate is calculated using this formula:

$$Flow\ rate = \frac{\text{Weight of powder}}{\text{Time of flow}} \text{ ----------Eqn1}$$

2.2.6.2 Angle of Repose
Angle of repose was determined using the fixed funnel method. A clean dry funnel was kept upright in a retort stand at a height 5cm above a paper placed in a flat horizontal surface. The aperture of the funnel was blocked and 10 gm of powder sample was poured into the funnel. Then the funnel was opened to release the powder onto the paper to form a conical heap. The height of the heap was measured by using two rulers. A pencil was used to trace the contour of the base of the powder on the paper and the diameter of the cone was also measured. The experiment was repeated three times for each batch of granules and the average was calculated. Angle of repose was calculated by using the equation below:

$$Tan\ \theta = h/r \text{ ---------- Eqn2}$$

Where,
h- height of heap and
r-radius of base of the powder.

2.2.6.3 Bulk Density
A 10 gm quantity of the granules was weighed and transferred into a 100 ml graduated cylinder. The initial volume Vo was noted. This determination was done in triplicate for each batch of granules and the average was calculated. The bulk density was calculated using the equation below.

$$BD = W/Vo \text{ ----------Eqn3}$$

Where BD is bulk density,
W is weight of granule and
Vo is bulk volume.

2.2.6.4 Tapped Density
A 10 gm quantity of the granules which was previously placed in the 100 mL graduated cylinder as described above was mechanically tapped by raising the cylinder and allowing it to drop under its own weight. The cylinder was tapped for 100 times on the towel placed on laboratory bench to a constant volume of the powder. The volume occupied by the powder was noted. This determination was done in triplicate for each batch of granule and the average calculated. The tapped density was then calculated using the equation below:

$$Tapped\ density(TD) = \frac{\text{Weight of powder}}{\text{Tapped volume}} \text{ ----------Eqn4}$$

2.2.6.5 Hausner's Ratio
This was calculated as the ratio of the tapped density to the bulk density for each batch of granules.

$$Hausner's\ ratio = \frac{\text{Tapped density}}{\text{Bulk Density}} \text{ ----------Eqn5}$$

2.2.6.6 Carr's Compressibility Index
This was calculated by using the equation below

$$Carr's\ index = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100 \text{ ----------Eqn6}$$

2.2.6.7 Compression of Metronidazole Tablets.
The prepared granules were lubricated with 0.5% stearic acid, and compressed into tablets using a single punch tableting press fitted with 12.5 mm flat faced punches (Cadmach, Ahmedabad, India) at a constant compression force of 15kN.

2.2.7 Evaluation of Physical Properties of Metronidazole Tablets
2.2.7.1 Weight Uniformity Test
Twenty tablets were randomly selected from each batch and individually weighed using an electronic balance (OHAUS, Galaxy). The mean, standard deviation, and coefficient of variation were calculated.

2.2.7.2 Crushing Strength
The crushing strength of the tablets was determined using the Monsanto hardness tester (Rolex, Chandigarh). Ten tablets from each batch were randomly selected and tested and the mean calculated.

2.2.7.3 Friability

The friability of 5 tablets was measured in a Roche friabilator (UNID 056830 Campbell Electronic, Mumbai, India). The tablets were dedusted and weighed (W_o) and then placed in the friabilator, which was then operated at a speed of 25 rpm for 4 minutes. Then the tablets were removed from the chamber dedusted and reweighed (W_1). The friability was then calculated using the equation below:

$$F = \frac{W0 - W1}{W0} \times 100 \quad \text{----------Eq}$$

Where, W_0 is the initial weight of tablets before friabilation,
W_1 is the final weight of tablets after friabilation.

2.2.7.4 Thickness

This was done using ten tablets randomly selected from each batch and the thickness measured using the micrometer screw guage (KFW Scientific Industries Ambala Cantt, India) and the average thickness was calculated.

2.2.7.5 Diameter

Ten tablets from each batch were randomly selected and their individual diameters was determined using the micrometer screw guage (KFW Scientific Industries Ambala Cantt, India) and the average diameter was calculated.

Disintegration study of direct compressed metronidazole tablet in distilled water.

Five tablets from each batch were randomly selected and added into a tablet disintegration testing machine (Digital disintegration testing machine). The average time required their disintegration was determined.

2.2.8 Standard Calibration Curve of metronidazole in 0.1N HCl

A 25 mg quantity of metronidazole powder was dissolved in 50 mL of 0.1N HCl. The resultant solution was transferred to 250 mL volumetric flask and made up to volume with 0.1NHCl. Serial dilutions of 1 µg/mL, 2 µg/mL, 3 µg/mL, 4 µg/mL, 5 µg/mL and 6 µg/mL were prepared, and their absorbances were read in a UV-spectrophotometer (UNICO-spectrophotometer, UV-2100 PC, Shanghai instrument Co., China) at a wavelength of 278 nm. Graphs of absorbance versus concentration were plotted to obtain the calibration curves of metronidazole in 0.1N HCl.

2.2.9 Dissolution study of metronidazole in 0.1N HCl

In vitro drug release of formulated eggshell powder tablets was determined using Digital Dissolution apparatus (DA-6D, India). The dissolution test was performed using 900ml 0.1N HCl at 37±0.5 degree celcius. The speed of rotation of paddle was set at 50 rpm.10 ml samples were withdrawn from at 5,10,15,20,30,40,50, and 60 minutes and the absorbance of the solution was measured by using UV Spectrophotometer (L7 double beam uv-vis spectrophotometer)
at wavelength of 278nm.The amount of drug release was determined from the standard curve.

2.3 Statistical analysis

Data was expressed as mean ± SD and analyzed using one-way ANOVA on spss software version 25

3. RESULTS

Micromeritic and Flow Properties of Metronidazole Granules

The result of the micromeritics and flow properties of granules is presented in Table 2

Table 2: Micromeritic and Flow Properties of Metronidazole granules

Formulations	Bulk Density (g/cm3) Mean ± SD	Tapped Density (g/cm^3) Mean ± SD	Carr's Index (%) Mean ± SD	Hausner's Ratio Mean ± SD	Flow Rate (g/s) Mean ± SD	Angle of Repose (°) Mean ± SD
Batch 1	0.57 ± 0.000	0.66 ± 0.009	14.06 ± 1.235	1.17 ± 0.019	12.01 ± 0.344	21.45 ± 0.976
Batch 2	0.55 ± 0.009	0.64 ± 0.009	15.02 ± 1.356	1.18 ± 0.017	11.14 ± 0.507	24.90 ± 0.316
Batch 3	0.58 ± 0.009	0.67 ± 0.000	13.93 ± 1.410	1.17 ± 0.019	10.94 ± 0.585	23.83 ± 1.048
Batch 4	0.59 ± 0.000	0.69 ± 0.000	14.49 ± 0.000	1.17 ± 0.000	13.33 ± 0.000	24.69 ± 0.482

Key: Batch 1: Metronidazole granules using Irvingia gabonensis(Ogbono) gum as polymer
Batch 2: Metronidazole granules using Tragacanth gum as polymer
Batch 3: Metronidazole granules using Acacia gum as polymer
Batch 4: Metronidazole granules using polyvinyl pyrrolidone(PVP) as polymer

Table 3: Physicochemical properties of Metronidazole Tablets(200mg)

Formulation	Weight variation (g) Mean ± SD n=20	Thickness (mm) Mean ± SD n=10	Diameter (mm) Mean ± SD n=10	Hardness (kg/f) Mean ± SD n=10	Friability (%) n=10	Disintegration Time (Min)
Batch 1	0.48 ± 0.028	3.82 ± 0.141	12.60 ± 0.021	6.25 ± 2.359	1.68	27.3 ± 2.2
Batch 2	0.51 ± 0.019	3.21 ± 0.127	12.60 ± 0.006	9.30 ± 1.584	1.57	7.66 ±0.28
Batch 3	0.53 ± 0.019	3.85 ± 0.062	12.60 ± 0.007	6.75 ± 1.401	1.85	3.28 ± 0.39
Batch 4	0.52 ± 0.011	3.85 ± 0.042	12.62 ± 0.005	7.40 ± 1.136	1.68	1.86 ± 0.20

Key:
Batch 1: Metronidazole tablets(200mg) using Irvingia gabonensis (Ogbono) gum as polymer
Batch 2: Metronidazole tablets(200mg) using Tragacanth gum as polymer
Batch 3: Metronidazole tablets(200mg) using Acacia gum as polymer
Batch 4: Metronidazole tablets(200mg) using polyvinyl pyrrolidone (PVP) as polymer

Table 4: Kinetics and Mechanism of Release of the Formulations

BATCH	ZERO ORDER	FIRST ORDER	HIGUCHI	KORSEMEYER/n-Value
OGBONO	0.9106	0.9796	0.9621	0.9801 (0.33)
TRAGACANTH	0.9165	0.7124	0.9642	0.9548 (0.17)
ACACIA	0.9938	0.9531	0.971	0.8956 (0.04)
PVP	0.9139	0.9339	0.9646	0.9647 (0.02)

Table 5: Release Profile of the Formulations

BATCH	T25 (Min)	T50 (Min)	T70 (Min)	Maximal release
OGBONO	3.0	7	20	99
TRAGACANTH	2.5	4	10	99
ACACIA	2.0	3.5	5	97.8
PVP	2.1	3.6	5.1	88.7

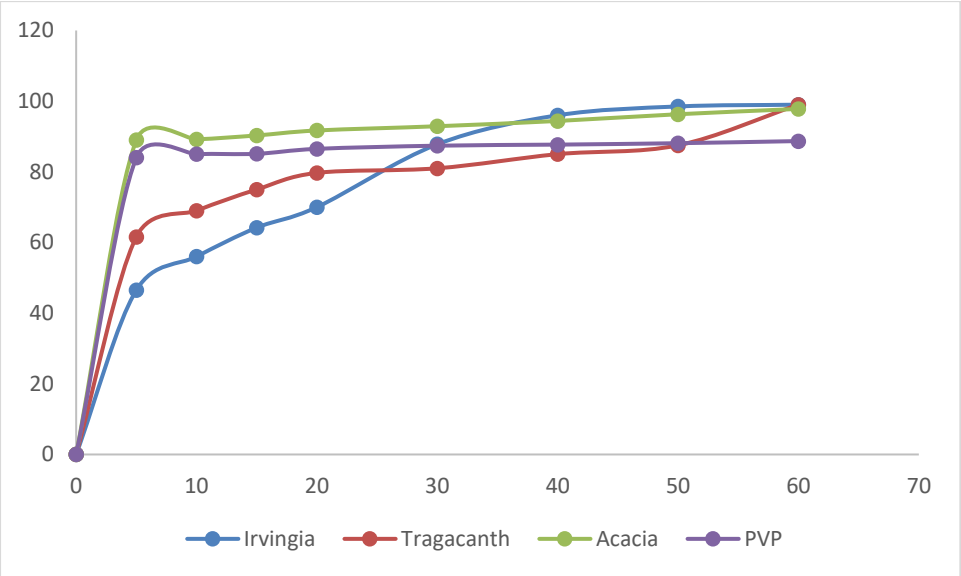

Figure 1: Release profile of the metronidazole formulations

4. DISCUSSION

Hausner's ratio and Carr's index are both indirect means of assessing the flow properties of granules. The batches of metronidazole tablets formulated had angle of repose less than 25^0 (table 2), which is an indication of excellent flow properties [6,7,8]

The formulated tablets in the four batches exhibited good compressibility properties with values Carr's indices of 14.06, 15.02, 13.93 and 14.49 for batches 1, 2, 3 and 4 respectively. All the values were between 12 and 16 [6,7]

4.1 Physicochemical Properties of Metronidazole Tablet

The result of the physical properties of tablets produced are presented in the Table 3. From the result, the crushing strength of the tablets was in the range of 6.25 to 9.30 kg/f, the weight variations of the tablets of all the formulation were less than 5%. The friability of all the formulations was in the range of 1.57 % to 1.85 %. Tablet thickness and diameter was in range of 3.21 mm to 3.85 mm and 12.60mm to 12.62 mm respectively.

4.1.1 Weight uniformity, hardness, thickness and diameter

Weight uniformity test is a pharmacopoeial or official test which ensures consistency of dosage units during compression (9). The weight uniformity test indicated no significant difference ($P>0.05$) in the weights of tablets from batch A to G and hence conformed to the British Pharmacopoeia specification which states that for tablets weighing greater than or equal to 250mg, not more than two of the individual weights should deviate from the average weight by more than ± 5 % and none should deviate by more than ± 10 % [10]. Although there was no significant difference ($p>0.05$) amongst the tablet dimensions (thickness and diameter), the slight variation in tablet thickness and diameter among the batches of tablets could be as a result of the varying density of the granulation. From the study, the tablet hardness ranged from 3.7kg/f to 9.0kg/f for all formulation. Tablet hardness affects parameters like tablet disintegration, dissolution as well as the buoyancy properties of the tablet [11]. There was significant difference ($p>0.05$) in the tablet hardness as the proportion of the eggshell powder is varied. The friability of all the formulations was in the range of 1.2% to 1.86%. The test of friability measures the ability of the tablet to withstand abrasion during packing, handling and shipping. The normal limits for tablet friability is less than or equal to 1% [10]. From the result of the study, the friability loss for all formulation was found not within this stipulated limit.

4.1.2 Disintegration Time

The statistical analysis of the disintegration time of the four batches of tablets showed an overall significant difference between them. From the results in table 3, the disintegration time for metronidazole from Irvingia gabonensis (27.3 min) was significantly ($P < 0.05$) higher than the other batches. This *irvingia gabonensis* batch can serve as an ideal formulation for sustained release.

The disintegration time for tablet formulated with tragacanth gum (7.66 min) was significantly ($P<0.05$) higher than those from acacia (3.28 min) and PVP (1.86 min)

4.2 Release Profile of Metronidazole Batches

From figure 1 and table 5, the T_{25}, T_{50} and T_{70} for the various batches are displayed. Metronidazole formulated from *Irvingia gabonensis* had a significantly ($P< 0.05$) higher release values than the other batches

4.2.1 Kinetics and Mechanism of Release

From the results in table 4, all the formulations release the active drug through Higuchi kinetics via fickian mechanism.

5. CONCLUSION

Metronidazole was successfully formulated with Irvingia gabonensis gum as binder. The tablet had good granules and tablet properties. The hardness, friability and disintegration times were within compendial limits.

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Conflict of Interest

Authors declared no conflict of interest.

Contribution of the Authors

Tenderwealth C. Jackson supervised the research work and carried out the statistical data analysis.
Ntiido Aniekan and Nkem Obiakor helped in manuscript editing.

Sifon Edem also contributed to the editing of manuscript.
Obo Ita and Adaeze Ucheokoro contributed in the write up of the introduction and literature review.
Sunday Okoi carried out the formulation of the tablet under the lead Author's supervision

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