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# EVALUATION OF DISINTEGRANT PROPERTIES OF BREADFRUIT (*ARTOCARPUS ALTILIS*) STARCH IN METRONIDAZOLE TABLETS FORMULATIONS

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## ABSTRACT

Disintegrants are significantly important for tablet break up and release of the active drug for dissolution in conventional drug delivery. This study aimed at evaluating the disintegrant properties of *Artocarpus altilisi* (bread fruit*)* starch in metronidazole tablet formulations. The matured peeled fruits were soaked in 0.2 %w/v sodium metabisulphate, grated, and the slurry washed with distilled water through a muslin cloth. The bread fruit starch (BFS) obtained was dried at 60 °C, milled and sized (125 µm). The BFS was characterized using standard methods and applied as disintegrant in the formulation of metronidazole tablets respectively at 6, 12 and 18% using wet granulation method. Corn starch BP was used as comparing standard. The metronidazole granules were evaluated for their micromeritic properties and thereafter compressed into metronidazole tablets. Evaluation of the metronidazole tablets for their physical properties, assay and dissolution studies were done using British Pharmacopoeia methods. The metronidazole granules were flowable and compressible. Metronidazole tablets had good physical properties: minimal weight variation (0.526 ± 0.13 - 0.531 ± 0.10 g), hardness (5.00 ± 0.12 – 6.42 ± 0.10kg), disintegration time < 15 min and friability < 1 %. Dissolution of metronidazole from the tablets containing BFS complied with British Pharmacopoeia criteria. Breadfruit starch compared well with corn starch BP as disintegrant in metronidazole tablet formulation.

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## INTRODUCTION

The quest for improved health care has led pharmaceutical scientists and researchers to continue to search for new active pharmaceutical ingredients (API) and/or excipients, modification of the old excipients, invention of new machinery or modification of old machinery in order to achieve enhanced drug delivery that could lead to enhanced health response from sick people. The oral dosage forms are the most popular way of taking medication

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despite some setbacks such as slow absorption and onset of action of the API [1, 2].

Tablets have unarguably remained the most popular dosage form of commercial pharmaceutical products that are available for therapeutic purposes. Tablets are prepared by compressing a powder mixture consisting of API, filler, binders, disintegrants, lubricants, glidants, preservatives, flavoring agents, film formers, opacifiers and colors, etc. The role of excipients in the determination of the quality of a formulation especially the bioavailability of the API from tablets has received considerable attention [3, 4]. Amongst the excipients, the disintegrant plays a prominent role in making the API available for dissolution and absorption especially in conventional release tablets. Natural occurring materials such as polysaccharides are widely used in the pharmaceutical and food industries as excipients due to their low toxicity, biodegradability, abundance or availability and low cost [3, 5]. Starch is the major carbohydrate reserve in plant tubers and seed endosperm where it exists as granules. Starches from plant sources such as rice, maize, potato, wheat, millet, corn, yam, cocoyam etc. have been widely applied as disintegrants and binders in tablet formulations [6-11]. Disintegrants can be described as non-active pharmaceutical agents that are incorporated into tablet formulations with a major purpose of encouraging the break-up of the tablet into smaller fragments as it makes contact with an aqueous environment, resulting to a more rapid release of the API content of the tablet for dissolution and absorption [12, 13].

*Artocarpus altilis* (Breadfruit) is one of the highest-yielding food plants that exist. It belongs to the Moraceae family. A single breadfruit tree produces up to 200 or more grapefruit-sized fruits per season. According to DNA fingerprinting studies, the wild seeded ancestor of breadfruit is the breadnut (*Artocarpus camansi*) which is native to New Guinea, the Maluku Islands, and the Philippines. [14]. The most selectively bred cultivars of this plant have seedless fruits while some cultivars have fruits that contain seeds.

Breadfruit is rich in carbohydrates but has a low cholesterol and fat content and have served as a source of food and nutrition to mankind [15-20]. It also contains a lot of essential amino acids and could be a good source of supply of amino acids in poor and malnourished persons.

Metronidazole is a nitroimidazole compound known to be clinically effective in protozoan infections such as trichomoniasis, amoebiasis and giardiasis, as well as other variety of infections caused by obligate anaerobic bacteria including *Bacteroides, Clostridium* and *Helicobacteria* species. It is available commercially as tablets, suspensions, parenteral, creams and topical gels [21, 22].

The overdependence of pharmaceutical manufacturers on starch and other pharmaceutical excipients from abroad is a major concern to many poor countries of the world such as Nigeria, as it puts a major pressure on her foreign reserves. The need to lessen this burden and improve the local content in this sector has led to assessment of starch from locally grown crops. This study has its aim at determining the disintegrant properties of starch gotten from locally grown *Artocarpus altilisi* (bread fruit*)* and its application as a potential pharmaceutical grade disintegrant in the formulation of metronidazole tablets.

## MATERIALS AND METHODS

### Materials

Mature seedless fruits of *Artocarpus altilis* (locally sourced from Ahiazu Mbaise, Imo State, Nigeria), Corn starch BP (BDH, England), gelatin (J.T. Bayer, USA) , talc, metronidazole powder, magnesium stearate (Boai, Nky, China), lactose (Surechem, England), sodium metabisulphite, acetone, and ethanol. All reagents used were all of analytical grade and they were used as procured.

### Methods

#### Plant Collection and Identification

Mature seedless fruits of *Artocarpus altilis* (breadfruit) which were purchased from local farmers at Amaiyi Obohia in Ahiazu Mbaise Local Government Area of Imo State, Nigeria were identified by Dr. Maikalu S. and the sample (Voucher number UPHM0591) deposited in the herbarium of the Department of Pharmacognosy, Faculty of Pharmaceutical Sciences, University of Port Harcourt, Port Harcourt as *Artocarpus altilis.*

#### Starch Isolation

Breadfruit starch was isolated using the method described by Agboola *et al*., [23] with some slight modifications in the sifting and drying time. Peeled fruits were soaked in 0.2 % w/v aqueous solution of sodium metabisulphate to prevent enzymatic browning, and were later washed and grated. The grated pulp was suspended in 5 L of water for 24 h after which it was sieved using a muslin. The fiber which was retained in the muslin was washed severally with distilled water until the filtrate was no longer whitish. The filtrate which was collected in a container was allowed to sediment for 4 h, the supernatant was decanted off and the starch washed

with 5 L of distilled water twice to remove proteins and allowed to sediment for another 4 h. The supernatant was decanted again and the starch squeezed through a muslin to remove more water which it contained. The resulting wet starch was spread on stainless steel trays of a hot air oven drier (Memmert, England) at 60 °C and dried until properly dried. The dry starch (BFS) was milled to powder using a blender (Binatone, Japan) and passed through a 250 µm stainless steel sieve (Retsch, England), and packaged in glass jars for further analysis.

**Physicochemical Properties**

**Identification Test**

A 2 g quantity of BFS was dispersed in 10 ml of water in a beaker, 3 drops of iodine was added and boiled for 5 minutes with stirring on a water bath. This test was also done with Corn Starch BP (CSP). The presence of starch was determined by observation of any change in color [24].

**Organoleptic Properties**

Both BFS and (CSP) were evaluated to determine the organoleptic properties such as texture, color and odor.

**Gelation**

A 2 % w/v aqueous dispersion of BFS and CSP at room temperature was heated in a water bath up to 70 °C. It was observed for any physical change of the dispersion into a gel or paste.

**pH Determination**

A 2 % w/v aqueous dispersion of BFS and CSP starches were prepared and their pH determined by inserting a calibrated pH meter (Hannah, USA) into each of the starch dispersions and the digital readings recorded. Triplicate determinations were done.

**Solubility Test**

The solubility of the different starches was investigated by dispersing 2 g samples of these starches in 100 ml of water, ethanol and acetone. Their solubility in the different test media was visually observed with the naked eye and noted.

**Hydration Capacity Determination**

The hydration capacity of BFS and CSP powders was determined using the method of Kornblum and Stoopaks with slight modification [25]. A quantity of 1 g of each of BFS and CSP was put in a 15 ml plastic centrifuge tube and 10 ml of distilled water added to it. Each tube was shaken intermittently over a 2 h period and left to stand for 30 min. Centrifugation of the resultant starch mixture was done at 1000 revolutions per minute (rpm) for 10 min using a centrifuge model TX 150 (Thermo Fisher Scientific, UK). The supernatant or upper layer of the dispersion was carefully decanted and the wet sediment weighed. The hydration capacity was calculated using equation 1:

$$Hydration\ capacity = x/y \quad \ldots.1$$

where x = weight of wet sample/ powder sediment and y = weight of dry sample/powder.

**Swelling Index Determination**

The swelling capability of BFS and CSP was determined using a slight modification of the method of Bowen and Vadino [26]. A 3 g quantity of the starch sample was placed in a 50 ml graduated glass measuring cylinder and tapped to obtain the tapped volume, Vt. A dispersion of the powdered sample was prepared in 35 ml of water with thorough shaking and the volume was made up to 50 ml with water. The mixture was allowed to stand undisturbed for 24 h on the surface of a flat table and the volume of the sediment formed noted as Vv. Triplicate determinations were done for BFS and CSP and the swelling capacity (S.C.) calculated using equation 2.

$$S.C. = [(Vv - Vt)/Vt] \, x \, 100 \quad \ldots\ldots\ldots 2$$

**Scanning Electron Microscopy (SEM) Test**

This test was done independently with quantities ranging from 3-5 mg of BFS powder placed in an appropriate container in the sample chamber of the SEM equipment (Phenom Prox, Model no MVE016477830) and covered with a coating/sputter of gold. The equipment was switched on and the micrograph was taken to elucidate the morphology, particle shape and size of the BFS.

**X-ray Diffraction (XRD)**

A 150 mg quantity of the BFS powder tightly packed in the sample holder was exposed to the X-ray radiation using an X-ray diffractometer (D/MAX-1200, Rigaku, Japan). A diffractogram of BFS was made and the degree of crystallinity of each sample was calculated from Equation 3.

Crystallinity index (C.I) = $[(I_{002} - I_{am} / I_{am})] \times 100$ …… 3

where $I_{002}$ is the highest peak intensity of the crystalline fraction and $I_{am}$ is the low intensity peak of the amorphous region [27, 28].

**Fourier Transform Infra-Red (FTIR) Spectroscopy**

The FTIR of the BFS was investigated to establish the spectra of absorption which helps elucidate the possible functional groups that exist in the BFS using FTIR equipment (FTIR- 8001, Shimadzu, Japan) by the potassium bromide (KBR) pellet method.

**Particle Density**

The particle density of the BFS powder was determined by the liquid displacement method using n-hexane as the immersion fluid. An empty dry 25 ml pycnometer was weighed empty. It was filled with n-hexane, stoppered, and any excess fluid wiped and the pycnometer re-weighed. The pycnometer was emptied and 1 g mass of the BFS powder placed in it. It was refilled with n-hexane and stoppered. Excess fluid was wiped from its body and the weight also noted. The particle density was calculated using equation 4 [5].

$$Pd = (W2\ x\ W3) / V(W3 - W4 + W2 + W) \quad \text{..... 4}$$

where Pd is the particle density, W is the weight of empty pycnometer, W2 is the weight of the solvent, W3 is the weight of the powder, W4 is the weight of the pycnometer + solvent + powder and V is the volume of solvent. Triplicate determinations were conducted for each powder sample.

**Bulk and Tapped Densities**

A quantity of 10 g of the breadfruit starch and Corn starch BP was individually poured into a 100 ml graduated glass measuring cylinder. The poured or bulk volume of BFS and corn starch BP in the cylinder was measured after which it was tapped to constant volume (tapped volume). The bulk and tapped densities were calculated using equations 5 and 6 [29].

$$Db = M / Vb \quad \text{..... 5}$$

Where M = mass, Vb= bulk volume and Db = bulk density;

$$Dt = M / Vt \quad \text{..... 6}$$

Where Dt = tapped density, M = mass and Vt = tapped volume

**Preparation of Metronidazole Granules**

Metronidazole granules were prepared according to the formula shown in Table 1. A total granule quantity enough to produce 60 tablets was calculated for. The granules were prepared by wet granulation method. Each ingredient was weighed out according to their individual weights by the doubling up technique and triturated. Ten (10) ml of hot water was boiled and gelatin dissolved in it. The dissolved gelatin solution was added to the mortar containing the blended metronidazole (active pharmaceutical ingredient), and either breadfruit starch or corn starch BP and lactose and triturated to homogeneity. The damp mass was passed through a 2.0 mm stainless steel sieve (Retsch, England) and the granules dried in an oven at 60 °C. The dried granules were further screened through a 1.0 mm sieve.

**Evaluation of Metronidazole Granules**

**Bulk and Tapped Densities of Metronidazole Granules**

A quantity of 20 g of the respective granules of metronidazole containing breadfruit starch (BFS 1, BFS 2 and BFS 3) were individually poured into a 200 ml graduated glass measuring cylinder with the aid of a glass funnel. The poured or bulk volume of the granules was measured after which it was tapped to constant volume (tapped volume). The bulk and tapped densities were calculated using equations 5 and 6 [29]. The same procedure was employed in the determination of these parameters in CSP 1, CSP 2 and CSP 3 respectively) using equations 5 and 6.

**Flow Rate and Angle of Repose**

The flow rate and angle of repose of the metronidazole granules were determined by a slight modification of the Jones and Pipel method [30]. A quantity of 20 g of the metronidazole granules was poured into a funnel that was clamped with the orifice of the efflux tube at a height of 3 cm above a flat surfaced platform. The orifice was closed with a metric rule to prevent premature discharge of the granules. On removal of the metric rule, the time it took for the granules to be completely discharged from the funnel was noted. Replicate determinations were done for each of the powders. The flow rate was determined using equation 7.

Flow rate = Mass of powder / time of powder flow..... 7

The height and diameter of the base of the heap of granule formed on the platform was measured and the angle of repose calculated using equation 8:

Angle of repose θ = $\tan^{-1} \frac{2h}{d}$.....8

Where θ is the angle of repose, h is the heap of powder and d = diameter of heap.

**Hausner's Quotient and Carr's Index**

The Hausner's quotient (HR) was calculated as the ratio of tapped density to bulk density of the powder as shown in equation 9 while the Carr's Index (CI) was determined from equation 10 [31].

HR = tapped density / bulk density..... 9

$$Carr\ Index = \frac{Tapped\ Density - Bulk\ Density}{Tapped\ Density} \times 100 \ldots\ldots\ldots 10$$

**Compression of Metronidazole Tablets**

The metronidazole granules containing breadfruit and corn starch BP (Table 1) were compressed into metronidazole tablets. The talc and magnesium stearate were added immediately prior to compression. A single station Manesty tablet press, Model F-3 (Manesty, England) fitted with a set of flat faced punches (12.5 mm diameter) and dies at a compression pressure of 9.81 kN was used to compress 100 tablets per batch at a target tablet weight of 500 mg per tablet and dwell time of 20 sec.

**Characterization of Metronidazole Tablets**

The metronidazole tablets were characterized 24 h after they were tableted for their physical properties: uniformity of weight, hardness, disintegration, friability, thickness, assay and dissolution test using Pharmacopoeia methods [27].

**Physical Appearance**

The tablets were visually examined to determine their color, shape and whether defects such as staining, chipping or capping occurred.

**Uniformity of Weight**

The metronidazole tablets were checked for variation in tablet weight by randomly selecting and individually weighing 20 tablets from each batch of the formulation [27].

**Hardness**

Ten (10) tablets from each batch of the metronidazole formulation were collected randomly and a model TBH 100 hardness tester (Erweka, Germany) was used to determine pressure at which each tablet broke diametrically.

**Disintegration Time**

The disintegration time of the metronidazole tablets was determined by randomly selecting six tablets from each batch of the formulation and putting each tablet from any given batch into each of the six cylindrical holes of a model ZT-122 disintegration machine (Erweka, Germany). The disintegration medium was 800 ml of water held in a 1 L plain transparent glass beaker that was immersed in a water bath. The temperature of both the medium and bath were maintained at 37 ± 0.5 ˚C. The machine was switched on and disintegration was said to have taken place when the entire tablet has been broken down into small fragments which are not retained on the mesh at the bottom of the cylindrical hole. If any mass is retained, it must not be a firm palpable core of the tablet used for the test but could belong to insoluble materials used in the tablet formulation [27].

**Friability**

Ten tablets that were randomly selected from each batch of the metronidazole tablet formulations were freed of dust, collectively weighed (Wi) and put into one of the drums of the friability tester, model TAR 200 (Erweka, Germany). The machine was operated in a way that the drum rotated at 25 rotations per minute (rpm) for 4 min. The tablets were collected, de-dusted and reweighed (Wf) and the percentage friability (F) calculated using equation 11 [27]:

$$F = \left(\frac{Wi - Wf}{Wi}\right) \times 100 \ldots\ldots\ldots 11$$

**Thickness**

Ten tablets were picked at random from each batch of the metronidazole tablets. The thickness and diameter of the tablets were individually determined using a micrometer screw gauge. The mean and standard deviation for each determination was recorded.

**Dissolution Profile of Metronidazole Tablets**

The dissolution of metronidazole or its release profile from the tablets was carried out using a six station model DT 600 disintegration apparatus (Erweka, Germany). A tablet from each batch was individually put in 900 ml of 0.1N HCl (pH 1.3) solution contained in a 1 L flask kept in a water bath whose temperature was maintained at 37 ± 0.5 ˚C with a paddle speed set at 50 rpm . Five ml (5 ml) samples were withdrawn from the test media every 10 min and filtered through a filter paper. Five ml (5 ml) of fresh 0.1N HCl (pH 1.3) maintained at the bath temperature was used to replace the withdrawn sample after each sampling time [27]. The filtrates were scanned at wavelength of 264 nm in the

spectrophotometer and the absorbance readings obtained were converted to concentrations using the standard calibration equation earlier established.

**Statistical Analysis**

The statistical analysis of the data obtained was done using an IBM SPSS version 21 software (IBM, Chicago, USA). One way analysis of variance (ANOVA) and the student's t test were used and values were considered significant at 95 % confidence interval or $p < 0.05$.

## RESULTS

**Physicochemical Properties**

Results for the identification test, organoleptic properties, gel formation, pH, solubility, viscosity, hydration capacity and the swelling index of BFS and corn starch BP are shown in Table 2.

Results of the organoleptic evaluation of the starches show a similarity in their taste, color and texture. Generally, the dry starches were whitish, tasteless and had a soft fine texture when felt with the fingers. Breadfruit starch and Corn starch BP gelatinized when they were heated to temperatures above 70 °C.

The pH of the 2 % w/v aqueous dispersions of the BFS and CSP starches show that both starches were slightly acidic and there was no significant difference ($p > 0.05$) in their pH.

The starches were at room temperature (28 ± 2 °C) found to be insoluble in water, acetone and ethanol. Both BFS and CSP were found to be weakly viscous in cold water at 2 % w/v dispersion. This is also another characteristic of native starches.

**Scanning Electron Microscopy (SEM)**

The scanning electron micrograph of breadfruit starch is shown in Fiig. 1 at x1500 lens magnification. SEM enables quantitative extraction of information on the surface morphology or texture of any material [32]. Discrete pebble shaped grains with a hilum at the center was observed.

**X Ray Diffraction (XRD)**

The X ray diffractograph of bread fruit starch (BFS) is shown in Fig. 2. Prominent peaks were observed at between 16-22 ° of 2 theta.

**FTIR**

The FTIR spectra of the fruit bread starch, metronidazole, and fruit bread starch and metronidazole in equal proportions of 1:1 are shown in Figs. 3- 5.

**Some Micromeritic Properties of Bread Fruit and Corn Starch Powders**

The results of the densities and flow behavior of BFS and CSP powders are shown in Table 3.

**Micromeritics of Metronidazole Granules**

The result of some of the micromeritic properties of metronidazole granules such as the bulk and tapped density, Hausner's ratio, flow rate, angle of repose and Carr's index are shown in Table 4.

**Physical Parameters of Tablets**

Some of the physical parameters of the metronidazole tablets formulated with the starches such as weight variation, hardness, disintegration time, friability and thickness are shown in Table 5.

**Drug Release Profile**

Figure 6 show the dissolution profile of metronidazole from tablets containing bread fruit starch (BSF1-BSF3) and corn starch BP (CSP1-CSP3).

## DISCUSSION

The starches turned from their white color to a blue black color after exposure to some drops of iodine implying that the materials are actually starch [24, 33]. The gelation results show that the starches gelled which is one of the properties characteristic of starch [34]. From the results, since the pH of the starches was close to a neutral value, it implies that the starches will suit the formulation of both acidic and alkaline drugs. The solubility results show that the starches were insoluble in water, acetone and ethanol which is a characteristic that is peculiar to native starch irrespective of the source and the degree of solubility can be linked to the order of crystallinity [35]. The 2 % w/v of the starch dispersions had poor viscosity which is another characteristic of native starches. With regards to the hydration capacity and swelling index, both BFS and CSP absorbed water upon hydration and this would be dependent on the degree of amorphous

**Table 1: Formulation table for metronidazole**

| Batch/Ingredients | BFS 1 | BFS 2 | BFS 3 | CSP 1 | CSP 2 | CSP 3 |
|---|---|---|---|---|---|---|
| Metronidazole (mg) | 400 | 400 | 400 | 400 | 400 | 400 |
| Breadfruit starch (mg) | 30 | 60 | 90 | 0 | 0 | 0 |
| Corn starch BP (mg) | 0 | 0 | 0 | 30 | 60 | 90 |
| Gelatin (mg) | 25 | 25 | 25 | 25 | 25 | 25 |
| Talc (mg) | 5 | 5 | 5 | 5 | 5 | 5 |
| Magnesium stearate (mg) | 5 | 5 | 5 | 5 | 5 | 5 |
| Lactose (mg) | 35 | 35 | 35 | 35 | 35 | 35 |
| Total weight (mg) | 500 | 530 | 560 | 500 | 530 | 560 |

**Table 2: Some physicochemical properties of BFS and CSP starch**

| Parameter/material | | Bread fruit starch (BFS) | Corn starch BP (CSP) |
|---|---|---|---|
| Iodine test | | Blue black colour | Blue black colour |
| Color | | White | White |
| Taste | | Tasteless | Tasteless |
| Texture | | Fine powder | Fine powder |
| pH | | 6.90±0.10 | 6.85±0.01 |
| Gel formation | | Gelled/Pasty | Gelled/Pasty |
| Solubility | Water | Insoluble | Insoluble |
| | Acetone | Insoluble | Insoluble |
| | Ethanol | Insoluble | Insoluble |
| Viscosity (cP) | | 4.00 | 3.90 |
| Hydration capacity | | 2.64±0.42 | 2.53±0.15 |
| Swelling index (%) | | 281±0.61 | 273±0.22 |

Values are Mean ± SD

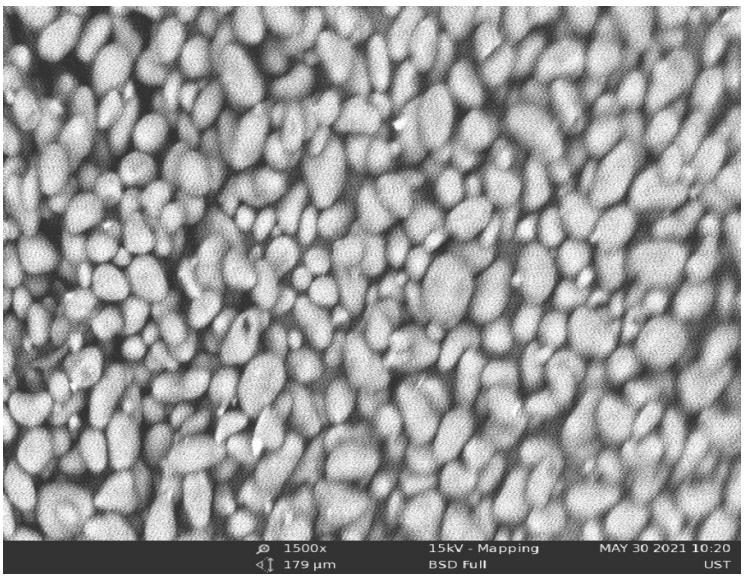


**Fig. 1: Scanning electron microscopy of breadfruit starch viewed at x1500 magnification**

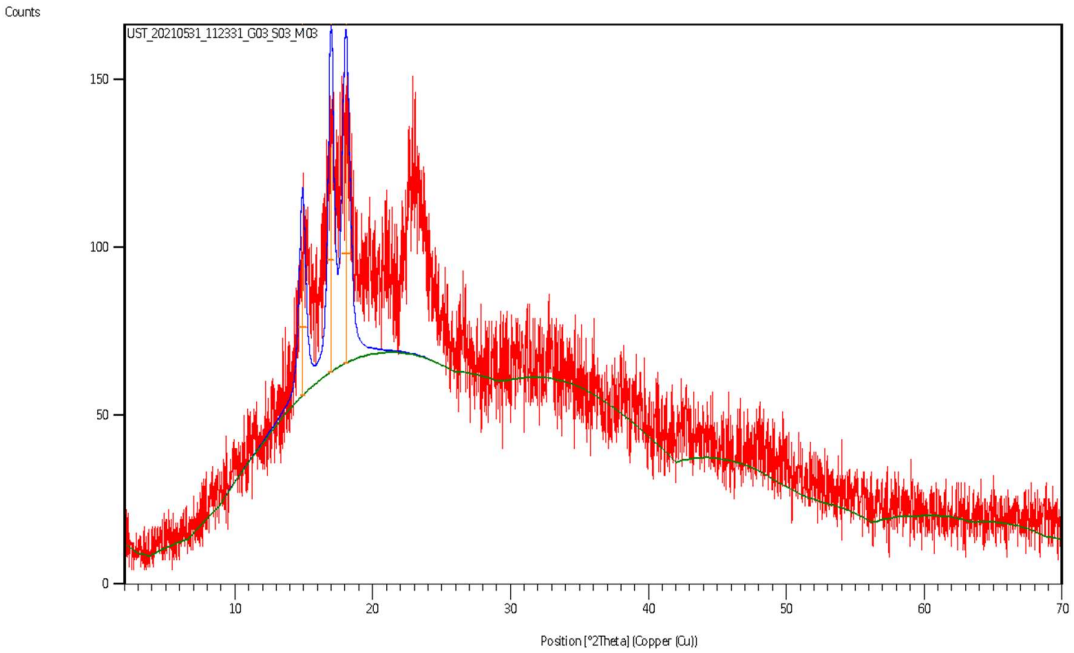


**Fig. 2: X ray diffractograph of bread fruit starch**

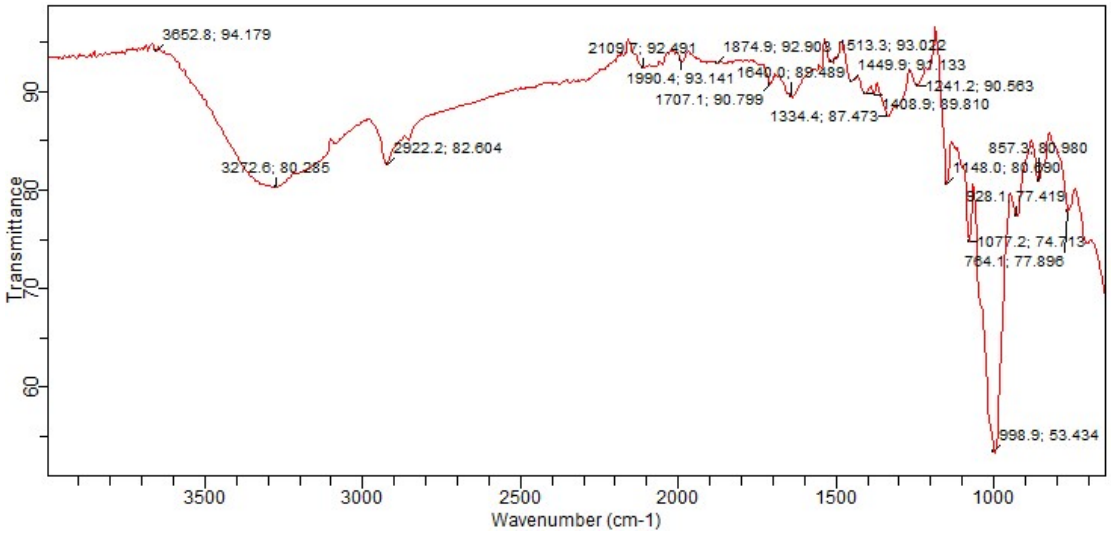


**Fig. 3: FTIR spectrum of bread fruit starch**

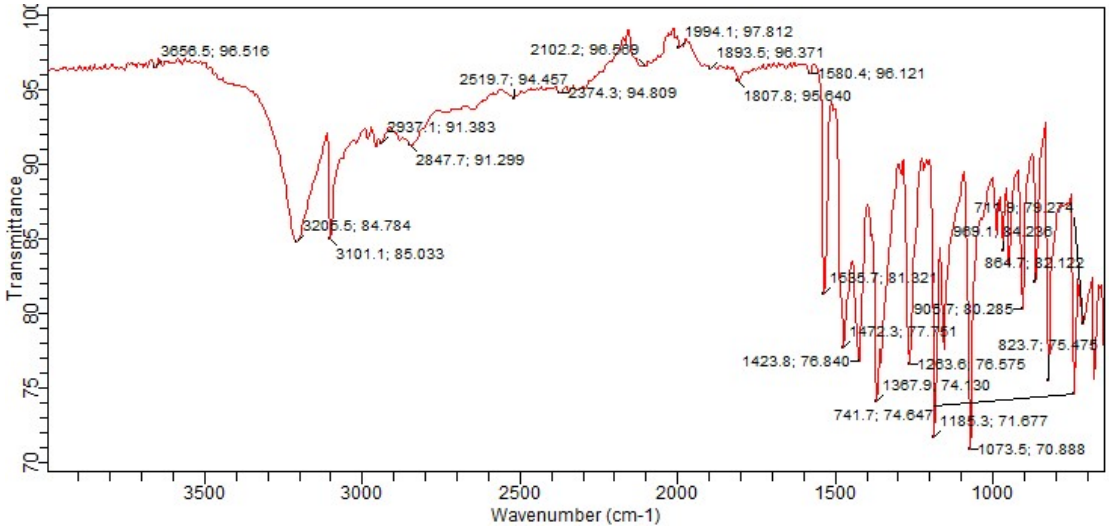


**Fig. 4: FTIR spectrum of metronidazole**

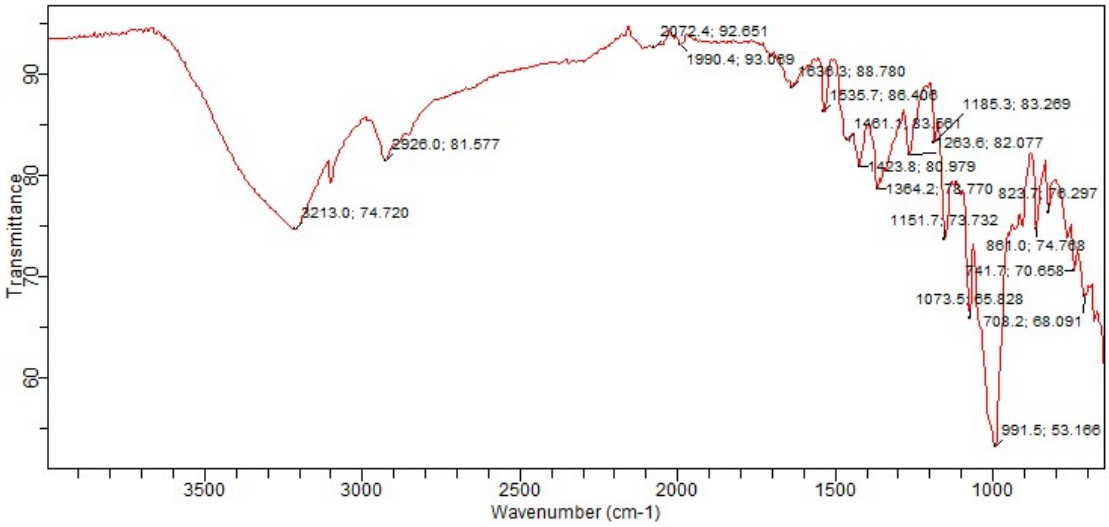


**Fig. 5: FTIR spectrum of breadfruit starch and metronidazole**

**Table 3: Some micromeritic parameters of Bread fruit and Corn starch powders**

| Parameter | Breadfruit starch (BFS) | Corn starch BP (CSP) |
|---|---|---|
| Bulk density (g/ml) | 0.52±0.02 | 0.50±0.10 |
| Tapped density (g/ml) | 0.77±0.11 | 0.68±0.10 |
| Hausner's ratio | 1.48±0.50 | 1.36±0.06 |
| Angle of repose (°) | 36.98±1.25 | 33.68±1.10 |
| Carr's index (%) | 32.46 ±0.24 | 26.47±1.00 |
| Flow rate (g/s) | Poor | 1.60±0.10 |
| Particle density (g/s) | 1.33 ± 0.05 | 1.68 ± 0.25 |

Values are Mean ± SD

**Table 4: Some micromeritic properties of metronidazole granules**

| Batch/parameters | BFS 1 | BFS 2 | BFS 3 | CSP 1 | CSP 2 | CSP 3 |
|---|---|---|---|---|---|---|
| Bulk density (g/ml) | 0.63±0.01 | 0.68±0.00 | 0.74±0.01 | 0.67±0.01 | 0.79±0.02 | 0.83±0.01 |
| Tapped density (g/ml) | 0.72±0.00 | 0.78±0.01 | 0.86±0.01 | 0.75±0.02 | 0.90±0.02 | 0.95±0.02 |
| Hausner's ratio | 1.14±0.01 | 1.15±0.01 | 1.16±0.01 | 1.12±0.01 | 1.14±0.01 | 1.14±0.01 |
| Flow rate (g/s) | 4.41±0.11 | 5.01±1.02 | 5.65±0.91 | 4.47±0.76 | 5.11±0.42 | 5.69±1.10 |
| Angle of repose (°) | 29.25±1.21 | 28.81±1.61 | 27.51±0.17 | 29.65±1.13 | 29.05±1.10 | 28.14±1.22 |
| Carr's index (%) | 12.50±0.14 | 12.82±0.32 | 13.95±0.25 | 10.67±0.82 | 12.22±0.17 | 12.63±0.55 |

Values are Mean ± SD

**Table 5: Some physical properties of metronidazole tablets**

| Batch/parameters | BFS 1 | BFS 2 | BFS 3 | CSP 1 | CSP 2 | CSP 3 |
|---|---|---|---|---|---|---|
| Uniformity of weight (g) | 0.531±0.12 | 0.548±0.14 | 0.537±0.90 | 0.521±0.10 | 0.533±0.73 | 0.526±0.13 |
| Friability test (%) | 0.70±0.23 | 0.68±0.10 | 0.73±0.13 | 0.71± 0.24 | 0.59±0.14 | 0.74±0.20 |
| Disintegration time (min) | 14.15±1.06 | 12.20±0.10 | 6.31±0.11 | 6.03±0.10* | 5.30±0.22* | 2.80±1.05* |
| Hardness test (kgF) | 6.42±0.10 | 5.76±0.24 | 5.06±0.10 | 5.54±0.32 | 5.00±0.12 | 6.12±0.15 |
| Thickness (mm) | 1.32±0.20 | 1.30±0.20 | 1.28±0.12 | 1.31±0.11 | 1.30±0.30 | 1.29±0.12 |

Values are Mean ± SD; *p < 0.05

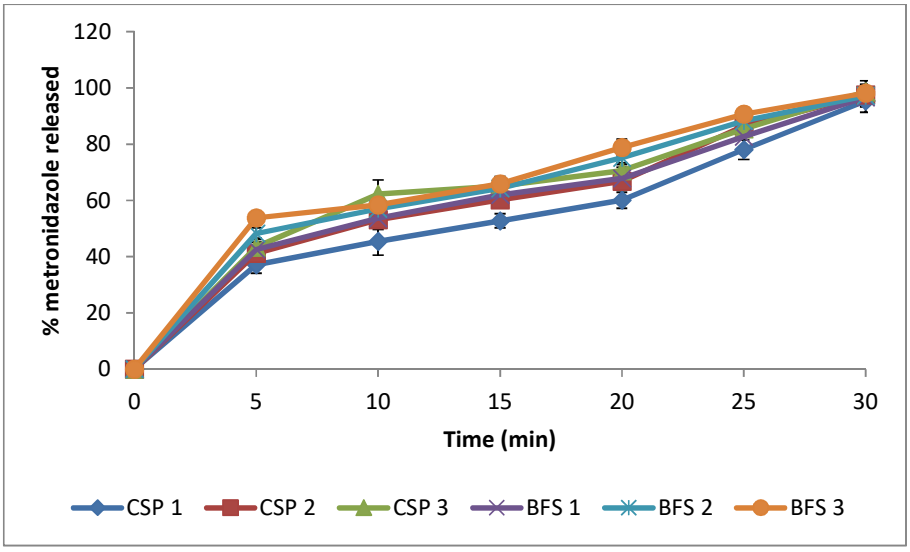


**Fig.6 : Dissolution profile of metronidazole from bread fruit starch and corn starch BP**

component of a material [35]. The quantity of water uptake when hydrated would affect the ability of the material to act as disintegrant in tablet formulation. The same applies to the swelling index. Starch granules absorb moisture very easily which is manifested as swelling and this causes a separation of the amylopectin-amylose and loss of crystallinity [35-38]. Swellability is a major property of starch. This factor aids in easy disintegration of tablets when hydrated or orally ingested.

Both features are responsible for the use of starch as disintegrant. Although the SEM of the starches showed discrete pebble-shaped grains with a hilum at the center of each grain, the presence of the hilum distinguishes starch from some other materials that may have a similar shape and texture. In the XRD spectra, the presence of prominent peaks at 16° of 2 theta depicts an amorphous property while peaks at 22° of 2 theta depict crystalline lattice and high degree of orderliness in packing. The amorphous

region permits solubility to solvents such as water while the crystalline region is responsible for the insoluble nature of the material. This property is similar to XRD of starch shown by some other workers in the past [36-38]. This pre-formulation study is used to elucidate whether the API and the excipient material are compatible. With regards to the FTIR results shown in Fig. 3, the peak seen at bands 2800-3800 $cm^{-1}$was sharp and broad which depicts an O-H stretching vibration. Also a sharp and prominent peak was observed at 2750 $cm^{-1}$ which depicts a $-CH_2$ vibration. Other peaks, although non prominent, were observed at 1800, 1060 and 1010 $cm^{-1}$ depicting C=O, C-O and O-C functional groups respectively. Deductions from Fig. 4 containing metronidazole show a sharp, non-broad peak at 3230 $cm^{-1}$ representing non aromatic vibrational mode of a hydroxyl (-OH) group. Non prominent peaks were observed at 2547 and 1536 $cm^{-1}$ bands which imply N=C and $NO_2$ vibrational mode. The formulation/product (Fig. 5) showed a prominent absorption peak at the region of 2547 $cm^{-1}$ depicting (C=N) vibrational mode which is characteristic of metronidazole. It was also observed that the metronidazole (-OH) side chain aliphatic vibration at the region of 3230 $cm^{-1}$ was still intact although this absorption band has been obliterated in the broad –OH vibration of the bread fruit starch. Since there was no major shift in the spectra peaks which depict the functional groups that exist in the compounds, it implies compatibility between the starch and the API. Thus, no untoward chemical reaction occurred and the products are expected to be stable after their formulation using such ingredients.

From the results of some of the micromeritic properties of the starches, the bulk densities showed a similarity in the manner the powders are packed in the measuring cylinder although BSF had an insignificantly higher value ($p>0.05$). On tapping, it was observed that there was a significant reduction in the powder bed implying densification ($p<0.05$).

The flow rate, Hausner's ratio and Carr's index (Table 3) depict a powder with poor flowing properties. This correlates with earlier reports by some other researcher's concerning the poor flowability of starch [32,33].The BP and USP describe Hausner's ratio of 1.35-1.45 and Carr's index of 26-31 % as poor flow indices for any given powdered material [27, 39].

The bulk and tapped density of the metronidazole granules show a similarity between both indices for formulations containing breadfruit starch and corn starch BP respectively. Granules of both formulations showed densification upon tapping. Both the bulk and tapped densities increased slightly as the quantity of both BFS and CSP used in the formulation increased. The flow properties of the granules were better than the flow properties of the individual starches that were employed in terms of flow rate, Hausner's quotient and Carr's index. Thus, improved die filling and compressibility shall be experienced. Expectedly, metronidazole tablets produced from these granules would have minimum weight variation, and enhanced mechanical properties.

The weight variation result of the different batches of the metronidazole tablets shows that none of the tablets of any given batch defected by more than 1 % (Table 5). The British Pharmacopoeia set limit is ± 5 % variation for tablets weighing not less than 250 mg [27, 39]. The metronidazole tablets passed the uniformity of weight test.

The hardness of the tablets were good (≥ 4 kg) which means that they would withstand the effects of handling and transportation which the tablets would be exposed to and still maintain their physical fitness [39].

All batches of the metronidazole tablets disintegrated within 15 min. There was a general decrease in the disintegration time of the tablets as the quantity of starch used in each batch formulation increased. Metronidazole tablets containing corn starch (CSP1-CSP3) had a significantly quicker disintegration time ($p<0.05$) than tablets containing bread fruit starch (BFS1-BFS3). However, all the batches of the metronidazole tablets complied with both the British and United States Pharmacopoeia standards for conventional release tablets which stipulates the upper limit of 15 and 30 min respectively [27, 39].

All the batches of metronidazole tablets had friability of less than 1.0 %. They passed the test as the upper limit of friability for uncoated tablets is given as ≤ 1.0 % [27, 39, 40].

The pattern of drug release was similar for both formulations. More than 80% of the metronidazole was released within 30 min from tablets containing both starches as disintegrant. There were statistically significant differences ($p<0.05$) in the quantities/amounts of metronidazole released from the tablets at all sampling times except at 10 min between BFS2 against CSP1, and at 30 min between BFS2 and CSP2 ($p>0.05$).The drug release pattern from the metronidazole tablets met with stipulations of the British and United States Pharmacopoeia regarding normal release tablet formulations [27, 39].

## CONCLUSION

Starch granules were successfully extracted from the fruit of *Artocarpus altilisi* (bread fruit). The starch had physico-chemical characteristics that compared well with corn starch BP and when used in the formulation of metronidazole tablets produced tablets that compared favourably in terms of uniformity of weight, hardness, disintegration time, friability and drug release. Thus, breadfruit starch can serve as a good substitute as disintegrant in the formulation of metronidazole tablets.

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