Evaluation of the Binding Properties of a Polymer Obtained from Modification of *Triticum aestivum* Starch in Metronidazole Tablets Formulation

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**Authors’ contributions**

This work was carried out in collaboration among all authors. The study was designed by authors NN and KCU. Author AIA conducted the bench work. Author NN performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. All the authors managed the analysis of the study and the literature searches and approved the final manuscript.

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**ABSTRACT**

**Aim:** The binding properties of a polymer obtained from modification of *Triticum aestivum* (TA) starch in metronidazole tablets formulation were evaluated.

**Study Design:** Experimental design.

**Place and Duration of Study:** Department of Pharmaceutics and Pharmaceutical Technology, University of Port Harcourt, Choba, Rivers State, Nigeria from January to July, 2018.

**Methods:** TA seeds were steeped for 72 h, wet milled and the native *Triticum aestivum* starch (NTS) extracted. NTS (1kg) was oxidized by slurring in 4 L of 3.50% w/v sodium hypochlorite, washed to neutral pH with 95% v/v ethanol (MTS). MTS was dried at 60°C for 3 h, milled and classified (250 μm). The starches were characterized using standard methods and applied as binders at 1, 2 and 3% w/w in formulating metronidazole tablets using wet granulation. Methylcellulose and gelatin at similar concentrations were used as standards.

**Results:** The granules and tablets were evaluated using standard methods. NTS and MTS had...
similar properties with starch. The modification improved the densities, hydration capacity and flow properties of MTS. The granules flowed and compressed well. The tablets had minimal weight variation, hardness (≥ 4 kgF), friability (<1%) and disintegration (<15 min). Metronidazole release (≥ 85%) within 60 min existed in all the batches except batches containing 1% methylcellulose and 3% gelatine. **Conclusion:** The results met with United States Pharmacopoeia specifications for oral uncoated metronidazole tablets. MTS performed better than NTS and compared well with methylcellulose and gelatin as binder in metronidazole tablet formulation.

**Keywords:** Triticum aestivum; starch; binder; modification; metronidazole tablet.

### 1. INTRODUCTION

The Active Pharmaceutical Ingredient (API) which is the main ingredient of any drug formulation does not constitute a drug product alone because it lacks the physical and chemical properties to form a drug product on its own. As a result, excipients are added to the API to obtain a finished product [1,2]. They may be categorized based on the role they play in the formulation. The most common classes include binders, fillers/diluents, glidants, lubricants and disintegrants [3]. Excipients play a critical role in the performance of a drug product, roles that include (but are not limited to) provision of an acceptable dosage form, enhancing solubility, bioavailability, stability, maintaining pH, release profile etc. [4]. Amongst the different dosage forms through which drugs can be delivered, the oral pharmaceutical tablet is the most popular [5]. Its popularity stems from the fact that tablets are easy to prepare, contains the correct dose of API in unit doses, are stable and are easy to administer especially when compared with other dosage forms such as liquids, parenterals and suppositories [6]. Binders are often employed in tablet formulations because it enables the powder components of the formulation to stick or glue together to form granules. Aggregation of powders into granules helps to increase flow properties of powders as well as its compaction using a quantified pressure within a confined environment into a firm tablet. The post compression relaxation stress which tends to allow the particles to be released from the bond acquired during compression and return to their pre-compression state is prevented by the addition of a binder to the formulation. The strength of this inter particle bonds depend to a great extent on the type and concentration of polymer used and its method of addition in the formulation. Binders could be of natural origin such as those derived from plant parts such as okra fruits [7,8].

Starch is a frequently used excipient in pharmaceutical tablet formulation because it is easily sourced, cheap, biodegradable, renewable and ecofriendly [9]. It could be used as a binder, disintegrant or filler [10-12]. It is abundant in nature and is stored in different parts of green plants such as fruits, seeds, stem and root tubers, algae and some bacteria as carbohydrates [13]. The color of starch varies from white to slightly cream depending on the botanical source. The color of most cereal seeds are noticed in their starch. Starch in its natural or botanical state is referred to as native and in this state it is made up of two high molecular weight polymers, amylose and amylopectin. Besides amylopectin and amylose, native starch contains small amounts of proteins, lipids and minerals [14]. The ratio of amylose and amylopectin content of native starch defines their degree of crystallinity [15]. Most native starches are granular and have shapes which can be described as spherical, oval, flattened ovoid, elliptical, polygonal and lenticular [16]. The morphology of most starches when used as binder in the production of tablet formulations imparts cohesion on the mixture of powders [17,18] causing them to retain a firm shape and strength after compression. The application of binders during processing of powders could be either in the dry form or as a solution/paste and the degree of cohesion achieved is influenced by the quantity or concentration that is used [17]. Besides starch, materials that can be used as binder include acacia, natural gums, gelatin, microcrystalline cellulose, sugar, waxes, etc. The processing and pharmaceutical application of cellulose derived excipients have been reported [19-21]. Other non-pharmaceutical uses of starch include: as raw material in the production of ethanol, cyclodextrin and glucose, in the paint, glue and adhesive industry, textile and food industry [22,23]. The property of starch as a natural binder can be improved through chemical or physical modification methods [24] leading to an improved applicability [25].
modification of starch can be achieved through methods such as oxidation, esterification and etherification.

*Triticum aestivium* (wheat) is one of the cereals that its seed contains a large quantity of starch. It is a herbaceous annual plant with erect stems that grow up to 1.2 m in height and it is often cultivated for the grain/seed which is a rich source of carbohydrate. The seed is eaten whole by man and livestock or ground into flour for different uses. It is also a source of alcoholic beverages and industrial alcohol. Its straw is used to make mats, carpets, baskets, packing material, cattle bedding, and paper manufacturing [26,27].

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.

Studies on the use of *Triticum aestivum* (wheat) starch as a binder, disintegrant or/and filler in tablet manufacture for conventional release formulations has been reported [28]. However, the various limitations of native starch as a binder in tablet formulations such as poor pasting or gelatinization of its slurry at increased temperatures affects its viscosity and functionality as a glue/binder to pharmaceutical powders. The wet bridges formed between the particles during wet granulation become weak on drying resulting in granules with poor flow and compressibility [29,30]. The quest to improve or enhance the properties of native *T. aestivum* starch as a binder in the production of pharmaceutical tablet was the reason for this study.

### 2. MATERIALS AND METHODS

#### 2.1 Materials

*Matured Triticum aestivum* seeds (sourced from Rumuokoro market, Port Harcourt), 3.50% w/v sodium hypochlorite solution (Multipros Nig. Ltd., Lagos, Nigeria), ethanol, n-Hexane (JHD, China), and distilled water (Pharm. Tech. Laboratory. University of Port Harcourt, Nigeria).

#### 2.2 Methods

##### 2.2.1 Procurements of samples

Matured *Triticum aestivum* seeds were procured from Rumuokoro market, Port Harcourt, Rivers State, Nigeria.

##### 2.2.2 Processing of sample

A 4.50 kg quantity of matured *Triticum aestivum* seeds was steeped in water for 72 h. It was wet milled, and the starch extracted by washing and rinsing with water using a muslin cloth as sieve. The starch was allowed to settle and the water was decanted. The wet starch was put in the muslin cloth and pressed manually to remove more water. The damp starch clumps were spread thinly on stainless steel trays and dried at 55°C in an oven (Memmert, England) until completely dried. It was milled to fine powder using a blender (Binatone, Japan), was screened through a 250 µm stainless steel sieve (Retsch, Germany). The starch was coded as NTS.

##### 2.2.3 Modification of sample

A quantity of 1 kg of NTS was submerged in 4 L of 3.5% w/v sodium hypochlorite (Multipros Nig. Ltd., Lagos, Nigeria) and stirred intermittently for 30 min at temperature of 29 ± 3°C and relative humidity of 61%. The sodium hypochlorite was pressed out using a muslin cloth and the bleached starch washed severally with 95% v/v ethanol until it was neutral to litmus. The ethanol was drained off by squeezing through a muslin cloth. The damp starch material obtained was passed through a 250 µm stainless steel sieve, dried in an oven at 55°C (Memmert, England) until a consistent weight was attained. The dried powder which was coded MTS, was passed through 180 µm stainless steel sieve and appropriately labeled and stored.

##### 2.3 Characterization of Samples

#### 2.3.1 Organoleptic properties

The starch samples were observed for color, smell and texture.

#### 2.3.2 pH

The pH of 2% w/v aqueous dispersion of NTS and MTS was determined using a pH meter, model 10 (Corning, England).
2.3.3 Ash value determination

Ash determinations were done based on descriptions in the United States Pharmacopoeia, 2007 (USP, 2007) [31].

2.3.4 Scanning Electron Microscopy (SEM)

The scanning Electron Microscope (SEM) of the starches were analyzed with SEM equipment Phenom Prox, Model no MVE016477830 (Thermo Fisher Scientific, USA).

2.3.5 Fourier Transform Infrared Spectroscopy (FTIR)

The FTIR of the samples were analyzed using an FTIR equipment (FTIR- 8001, Shimadzu, Japan) using the potassium bromide (KBR) pellet method.

2.3.6 Bulk and tapped density

A 15 g quantity each of NTS and MTS powder was used. Each powder was separately poured into a Stampfvolumeter (STAV 2003JEF, Germany) which was switched on to determine the densities. The densities were calculated using equations 1 and 2.

\[
\text{Bulk density} = \frac{\text{mass}}{\text{bulk volume}} \quad (1)
\]

\[
\text{Tapped density} = \frac{\text{mass}}{\text{tapped volume}} \quad (2)
\]

2.3.7 Particle density

The particle density of the powder was determined by solvent displacement method using n-hexane. The n-hexane was poured into a tarred empty 25 ml (V) pycnometer and the weight recorded as (W). The pycnometer was filled with n-hexane and the weight recorded as W1. The weight of n-hexane used (W2) was derived by subtracting W from W1. A 0.5 g (W3) mass of either NTS or MTS was weighed into the pycnometer and the weight recorded as W4. Replicate determinations were done for each powder and the particle density determined using equation 3:

\[
Pt = \frac{W2 \times W3}{V(W3 - W4 + W2 + W)} \quad (3)
\]

2.3.8 Flow rate and angle of repose

The flow rate was determined using the funnel method [32]. A quantity of 20 g each of NTS and MTS was poured into a clamped funnel on a flat platform and the time taken for a complete and uninterrupted discharge of the powder from the funnel noted. Replicate determinations were done. The angle of repose was established by pouring 50 g of powder sample into a 13.5 cm long by 4 cm wide open ended plastic pipe that was placed on a clean white paper on a flat platform, after which the pipe was slowly pulled up vertically leaving a heap of the powder on the paper. The edges of the powder heap were gently marked without distortion to estimate the powder heap diameter. The height of the heap was also measured. The angle of repose was determined using equation 4:

\[
\text{Angle of repose,} \theta = \tan^{-1} \left( \frac{2h}{d} \right) \quad (4)
\]

2.3.9 Porosity

The porosity of the NTS and MTS powders were calculated using the bulk density and particle density values obtained from the evaluation of the powder. This was calculated using equation 5:

\[
\text{Porosity} = 1 - \frac{\text{bulk density}}{\text{Particle density}} \times 100 \quad (5)
\]

2.3.10 Hausner’s ratio

This is the ratio of the tapped density to the bulk density of the powder. This was calculated by using equation 6:

\[
\text{Hausner's ratio} = \frac{\text{tapped density}}{\text{bulk density}} \quad (6)
\]

2.3.11 Carr’s compressibility index

This was calculated using the bulk density and the tapped density values obtained from the evaluation of the powder earlier. This was calculated using equation 7:

\[
\text{Carr's Index} = \frac{\text{tapped density} - \text{bulk density}}{\text{tapped density}} \times 100 \quad (7)
\]

2.3.12 Moisture content

An empty crucible was weighed and the weight recorded. 1 g quantity of the sample was transferred to the crucible, labeled and weighed. The crucible was placed in the oven at 105°C until a constant weight was reached. This was carried out in triplicate and the mean and standard deviation determined.
2.3.13 Hydration capacity

The hydration capacity of the powder was determined using the method of Ring [33]. A 1 g quantity of each powder was placed in a 15 ml plastic centrifuge test tube of known weight and 10 ml of water was added. The test tube was shaken intermittently for 20 min and allowed to stand for 10 min and was centrifuged at 3000 rotations per minute (rpm) for 10 min using a table top centrifuge (PEC medicals, USA). The supernatant liquid was decanted and the weight was determined. This was carried out in triplicate and the mean was determined. The hydration capacity was calculated using equation 8:

\[ HC = \frac{\text{Weight of powder after centrifugation}}{\text{Weight of powder before centrifugation}} \] (8)

2.3.14 Swelling capacity

A 1 g quantity each of NTS and MTS was put in a 10 ml graduated measuring cylinder and tapped. The tapped volume (Vi) was read and water was added to fill up to the 10 ml mark, this was allowed to stand for 24 h and the volume of the sediment (Vf) read. The swelling capacity was calculated by using equation 9:

\[ \text{Swelling capacity} = \frac{V_f}{V_i} \] (9)

2.3.15 Moisture sorption

A 0.5 g quantity each of NTS and MTS were weighed into tarred porcelain crucibles. The crucibles were placed in large desiccators containing 50 ml saturated solutions of magnesium nitrate, sodium chloride, potassium chloride and potassium sulphate which simulated relative humidity of 52%, 75%, 84% and 96% respectively [34]. The weight gained by the exposed sample after 5 days was recorded and the amount absorbed was calculated from the weight difference. Replicate determinations were done.

2.4 Formulation of Metronidazole Tablet

Metronidazole granules were formulated by wet granulation using the ingredients in Table 1. The intra-granular excipients were weighed and triturated in a mortar using the doubling up technique. Aqueous pastes of NTS and MTS (1, 2 and 3% w/w), and hot aqueous dispersions of GLT and MCE at 1, 2, and 3% w/w respectively were prepared and used to wet mass powder blends containing metronidazole, corn starch and lactose in the quantities shown in Table 1. Actual quantities of ingredients used were targeted to produce 200 tablets per batch. The damp mass was screened through 2 mm stainless steel sieve (Retsch, Germany), dried at 60°C in an oven (Memmert, England) and rescreened through a 1 mm sieve. The metronidazole granules were stored.

2.5 Characterization of Metronidazole granules

2.5.1 Bulk and tapped density

A 20 g quantity of the different metronidazole formulations were each analyzed for the bulk and tapped densities using a Stampfvolumeter (STAV 2003JEF, Germany). The densities were calculated using equations 1 and 2.

\[ \text{Bulk density} = \frac{\text{mass}}{\text{bulk volume}} \] (1)

\[ \text{Tapped density} = \frac{\text{mass}}{\text{tapped volume}} \] (2)

2.5.2 Granule density

The granule density of the metronidazole granules was determined by solvent displacement method using n-hexane. The method has been described earlier in this work under particle density determination.

2.5.3 Flow rate and angle of repose

The flow rate and angle of repose of the metronidazole granules were measured using the funnel and free-standing cone method [35]. A quantity of 20 g of each of the samples was poured into a stoppered funnel which was clamped on a flat platform such that the orifice of the efflux tube length of the funnel was 3 cm above a flat surface. On removal of the stopper, the time taken for the granules to be completely discharged from the funnel, the diameter and height of the powder heap formed were measured and recorded. The flow rate and tangent of the powder heap were calculated. The angle of repose was determined by using equation 4:

\[ \text{Angle of repose}, \theta = \tan^{-1} \left( \frac{2h}{d} \right) \] (4)

2.5.4 Porosity

The porosity of the metronidazole granules was calculated using equation 5:

\[ \text{Porosity} = 1 - \frac{\text{bulk density}}{\text{Particle density}} \times 100 \] (5)
2.5.5 Hausner’s ratio

This parameter is determined based on the ratio of the tapped density to the bulk density of the powder. This was calculated by using equation 6:

\[
\text{Hausner’s ratio} = \frac{\text{tapped density}}{\text{bulk density}}
\]

2.5.6 Carr’s compressibility index

This was calculated using the bulk and tapped density values obtained from the evaluation of the metronidazole granules. This was calculated using equation 7:

\[
\text{Carr’s Index} = \frac{\text{tapped density} - \text{bulk density}}{\text{tapped density}} \times 100
\]

2.5.7 Moisture content

A quantity of 2 g each of the metronidazole granules was weighed on a moisture digital balance (Citizen, MB-50, China) after which the equipment was switched on with its temperature set to heat at 105°C.

2.6 Compression of Tablets

Talc and magnesium stearate were added extra granularly to the metronidazole granules prior to compression in the quantities shown in Table 1. The respective batches of the granules were compressed using single punch tableting machine (Manesty F-3, England). The granules were fed into the die and compressed with a set of 10 mm flat faced punches at a target tablet weight of 300 mg, compression pressure of 9.8 kN and dwell time of 25 ± 5 sec. A total of 200 tablets were compressed for each batch.

2.7 Determination of Tablet Properties

2.7.1 Weight uniformity

Twenty tablets were randomly selected from each batch of the metronidazole tablets and were weighed individually. The mean, standard deviation and coefficient of variance of the 20 tablets were calculated [36].

2.7.2 Tablet crushing strength

Ten (10) tablets from each batch were randomly selected and their crushing strength was determined using a hardness tester (Monsanto, Singla, India). The mean and standard deviation of the values were calculated.

2.7.3 Tablet disintegration time

Six tablets randomly selected from each batch of the metronidazole tablets were distributed singly into the six holes of the basket of the disintegration tester, model ZT-122 (Erweka, Germany). Each tablet was held in place with a glass disc and each beaker was filled with 500 ml of 0.1 N HCl heated up to 37 ± 1°C. The bath temperature was also kept at 37 ± 1°C. The time taken for each tablet to completely break up and pass through the mesh was noted. Three replicate determinations were done.

2.7.4 Friability test

Ten (10) tablets from each batch were randomly selected, weighed W1) and placed in the friabilator which was operated at 25 revolutions per minute (rpm) for 4 min. The tablets were removed, dusted and reweighed (W2). Friability (F) of the tablets was calculated using equation 9. Three replicate determinations were done.

\[
F = \left[ \frac{(w1 - w2)}{w1} \right] \times 100
\]

2.7.5 Thickness determination

Ten tablets were randomly selected from each of the batches of the metronidazole tablets. Each of the tablets was measured for its thickness and diameter using a micrometer screw gauge. The mean and standard deviation were calculated.

2.7.6 Crushing strength/friability ratio determination

This parameter is derived by the determination of the ratio between the crushing strength and friability of the each batch of the tablets.

2.7.7 Standard calibration plot of metronidazole

One hundred (100) mg of a pure sample of metronidazole was weighed into a 100 ml volumetric flask. It was dissolved with 0.1 N HCl and the volume of the metronidazole solution made up to the 100 ml mark [36]. Serial dilutions of the stock metronidazole solution were done to obtain 0.2, 0.4, 0.6, 0.8 and 1 mg %. These were scanned in the UV/Vis spectrophotometer, model 6405 (Jenway, UK) at 278 nm wavelength to obtain the absorbance readings of these readings against concentration was made and
| Batch                  | 1%NTS | 2%NTS | 3%NTS | 1% MTS | 2% MTS | 3% MTS | 1%MCE | 2% MCE | 3%MCE | 1%GLT | 2%GLT | 3% GLT |
|------------------------|-------|-------|-------|--------|--------|--------|-------|--------|-------|-------|-------|--------|
| Metronidazole (mg)     | 200.00| 200.00| 200.00| 200.00 | 200.00 | 200.00 | 200.00| 200.00 | 200.00| 200.00| 200.00| 200.00 |
| Corn starch BP (mg)    | 30.00 | 30.00 | 30.00 | 30.00  | 30.00  | 30.00  | 30.00 | 30.00  | 30.00 | 30.00 | 30.00 | 30.00  |
| NTS (mg)               | 3.00  | 6.00  | 9.00  | -      | -      | -      | -     | -      | -     | -     | -     | -      |
| MTS (mg)               | -     | -     | -     | 3.00   | 6.00   | 9.00   | -     | -      | -     | --    | -     | -      |
| Methylcellulose (mg)   | -     | -     | -     | -      | -      | -      | 3.00  | 6.00   | 9.00  | -     | --    | -      |
| Gelatin (mg)           | -     | -     | -     | -      | -      | -      | -     | -      | -     | 3.00  | 6.00  | 9.00   |
| Talc (mg)              | 0.75  | 0.75  | 0.75  | 0.75   | 0.75   | 0.75   | 0.75  | 0.75   | 0.75  | 0.75  | 0.75  | 0.75   |
| Mag. Stearate (mg)     | 0.75  | 0.75  | 0.75  | 0.75   | 0.75   | 0.75   | 0.75  | 0.75   | 0.75  | 0.75  | 0.75  | 0.75   |
| Lactose (mg)           | 65.50 | 62.50 | 59.50 | 65.50  | 62.50  | 59.50  | 65.50 | 62.50  | 59.50 | 65.50 | 62.50 | 59.50  |
| Total (mg)             | 300.00| 300.00| 300.00| 300.00 | 300.00 | 300.00 | 300.00| 300.00 | 300.00| 300.00| 300.00| 300.00 |
metronidazole solutions at the different concentrations. A plot of the absorbance slope, intercept and correlation value ($R^2$) of the straight line of the plot were established.

### 2.7.8 Content of active ingredient determination

Twenty tablets were randomly selected from each batch of the metronidazole tablets and weighed individually. The tablets were triturated to a fine powder and an amount equivalent to the weight of one tablet was weighed into a 100 ml volumetric flask where it was dispersed with 0.1 N HCl to obtain a 100 ml dispersion. This was filtered through a filter paper and the filtrate was scanned through the UV/Vis spectrophotometer at 278 nm wavelength. This procedure was used for all the batches of tablets. Replicate determinations were also done for each batch. The absorbance readings were fitted into the standard calibration plot equation to ascertain the concentrations of the metronidazole.

### 2.7.9 In vitro dissolution rate

The dissolution studies of the metronidazole tablets were conducted using the paddle method in a six station model DT 600 (Erweka®, Germany) dissolution equipment. Each of the six flasks was filled with 900 ml of 0.1 N HCl heated to a temperature of 37.0 ± 0.5°C and the paddle set to function at 100 rpm. One tablet was used in each flask for the test. Five (5 ml) samples were withdrawn at 10 min intervals up to 1 h with an equal replacement with dissolution medium maintained at the same temperature after each withdrawal. The filtrates obtained from the withdrawn samples were diluted and scanned using a model 6405 spectrophotometer (Jenway®, UK) at a wavelength of 278 nm. The absorbance results were converted to concentrations from the standard calibration plot equation.

### 2.8 Statistical Analysis

Analysis of data obtained was statistically done using one way Analysis of Variance (ANOVA) with SPSS version 21. All data were expressed as mean ± standard deviation except for uniformity of tablet weight which was expressed as mean ± coefficient of variance. The difference in value amongst each group was considered statistically significant when in the range of $P = .000$ to $.05$.

### 3. RESULTS AND DISCUSSION

The yield of starch from the dry TA seed was 40.10%. The NTS and MTS powders were white and odorless. The MTS had a granular texture while the NTS had a finer texture. The ash values (Table 2) showed that the starches were properly extracted and free of contaminants. The pH of the native starch was acidic (4.01 ± 0.10) while that of the modified starch was alkaline (9.02 ± 0.26) (Table 2). Modification using sodium hypochlorite had effect on the pH of the modified starches.

#### 3.1 Scanning Electron Microscopy

The Scanning Electron Micrographs of the starches are shown in Figs 1 and 2 respectively. There was a resemblance between the SEM obtained and those of earlier reports for starch [14,15]. However there were differences in the morphology of the two starches which shows that modification took place and this is expected to have an effect on the properties of both starches.

#### 3.2 FTIR

The FTIR spectra of NTS, MTS, metronidazole, metronidazole plus MTS are shown in Figs 3-6. It was observed that there was no major shift in the peaks of the spectra between the 1:1 ratio of metronidazole and MTS mixture, and the individual MTS and metronidazole samples. This implies that there was no change or alteration of the functional group of the samples which shows compatibility between the substances. This pre-formulation evaluation is necessary in order to ascertain the compatibility of the materials before the actual formulation is done.

#### 3.3 Densities

The bulk, tapped and particle densities of the starch powders are shown in Table 3. The difference between the bulk and tapped densities show that NTS powder was bulkier than MTS. Both were compressible and underwent densification upon agitation of the powder bed. The wide difference in the bulk and tapped densities suggest high interparticulate friction and cohesiveness amongst the powders [36,37]. Modification improved the densification as well as reduced the interparticulate friction that existed in the powder. Thus MTS would flow better than NTS. The higher particle density observed in the modified powder suggests an increased crystallinity and less amorphous region than in the natural starch powder.
Table 2. Ash content of natural and modified wheat starches

| Parameter                      | NTS   | MTS   |
|-------------------------------|-------|-------|
| Total ash (%)                 | 0.50  | 4.70  |
| Acid insoluble ash (%)        | 0.10  | 2.10  |
| Water insoluble ash (%)       | 0.50  | 0.80  |
| Sulphated ash (%)             | 1.00  | 6.00  |
| Ethanol extractive yield (%)  | 12.40 | 4.40  |

Fig. 1. Scanning electron micrograph of NTS

Fig. 2. Scanning electron micrograph of MTS
Fig. 3. FTIR spectrum of NTS

Fig. 4. FTIR spectrum of MTS
3.4 Flow Rate, Angle of Repose

The starch samples could not be completely discharged from the funnel without interruption which suggests that they have a poor flow which can be attributed to cohesiveness. The angle of repose of the NTS (Table 3) shows that it has a passable flow while MTS has a good flow [36].

3.5 Carr’s Index and Hausner’s Quotient

The Carr’s index and Hausner’s quotient values of the wheat starch powders are shown in Table 3. Carr’s compressibility index and Hausner’s ratio are measures of the propensity of a powder to flow. Based on these parameters, NTS can be described as having a very, very poor flow while MTS had a passable flow [31,36]. The modification enhanced these flow parameters of MTS ($P=.002$).

3.6 Moisture Content

The moisture content is shown in Table 3. NTS retained more moisture than MTS. The moisture content of both starches was above the official...
permitted upper limit of 8% stated in British Pharmacopoeia [36] implying that both starches would be unsuitable in the formulation of drugs that are easily degraded in the presence of moisture.

3.7 Hydration Capacity and Swelling Index

The hydration capacities were 173.72 ± 1.13 and 217.03 ± 1.42% for NTS and MTS respectively Table 3. These show that both starches can take up water upon hydration although modification enhanced this property ($P=0.002$). This property is desirable in tablets as it would aid disintegration. Regarding swelling, MTS swelled more than NTS. The hydration capacity is an index of the amount of water a material is able to absorb on hydration while swellability indicates increase in volume of water taken up after absorption [38]. Therefore, modification increased both the hydration and swelling capacities of MTS starch implying enhanced disintegrant effects when used in tablet formulation.

3.8 Moisture Sorption

The moisture sorption is shown in Table 3. Values of MTS were consistently higher than those of NTS at all humidity environments used for the evaluation. The moisture gained also increased with increase in the relative humidity. Moisture sorption capacity of a material measures the sensitivity of that material to moisture. Study of water sorption is of importance since it reflects the relative physical stability of tablets when stored under humid conditions. The extent of moisture sorbed could be as a result of interaction between the hexose group of the starch and hydroxyl groups [39,40]. Thus, the tablets containing MTS would be more liable to deterioration as a result of gain in moisture especially under humid environments.

3.9 Metronidazole Granule Properties

3.9.1 Densities

The bulk, tapped and granule densities of the metronidazole granules are shown in Table 4. Generally, the bulk and tapped densities were found to decrease as the concentration of the binder used in the formulation increased while the granule density increased with increase in the concentration of binder used. The granules were compressible and less cohesive. Granules containing methyl cellulose and gelatin had lower bulk and tapped densities than wheat starch.

3.9.2 Flow rate and angle of repose

Table 4 contains the flow rate and angle of repose of the metronidazole granules. The granules had uninterrupted flow from the funnel. The flow rate was generally found to increase as binder concentration increased. This suggests increased interparticulate bonding caused by the binder. Granules containing NTS had the least flow. The angle of repose also showed that the granules that contained NTS had good flow while those containing MTS and the standard polymers had excellent flow properties [31,36]. Modification improved the flow properties of wheat starch ($P=0.002$).

| Parameter                  | NTS     | MTS     |
|---------------------------|---------|---------|
| Bulk density (g/ml)       | 0.43 ± 0.01 | 0.63 ± 0.01 |
| Tapped density (g/ml)     | 0.81 ± 0.01 | 0.84 ± 0.01 |
| Particle density (g/ml)   | 1.42 ± 0.02 | 1.68 ± 0.01 |
| Angle of repose (deg.)    | 42.80 ± 1.31 | 27.73 ± 1.46 |
| Porosity (%)              | 69.89 ± 0.97 | 62.55 ± 0.89 |
| Carr's index (%)          | 46.38 ± 1.73 | 25.24 ± 0.98 |
| Hausner's quotient        | 1.86 ± 0.06 | 1.34 ± 0.01 |
| Loss on drying (%)        | 13.39 ± 0.08 | 9.96 ± 0.09 |
| Hydration capacity (%)    | 173.72 ± 1.13 | 217.03 ± 1.42 |
| index (%)                 | 106.66 ± 2.88 | 160 ± 2.10 |
| Moisture sorption (R.H. %)|         |         |
| 96.00%                    | 7.59 ± 0.11 | 13.07 ± 0.09 |
| 84.00%                    | 3.29 ± 0.72 | 6.98 ± 0.15 |
| 75.00%                    | 2.72 ± 0.15 | 6.82 ± 0.10 |
| 52.00%                    | 2.64 ± 0.07 | 6.51 ± 0.27 |
Table 4. Some micromeritic properties of metronidazole granules

| Batch/Parameter | Bulk density (g/ml) | Tapped density (g/ml) | Granule density (g/ml) | Flow rate (g/s) | Angle of repose (°) | Carr’s index (%) |
|-----------------|---------------------|-----------------------|------------------------|-----------------|---------------------|-----------------|
| 1%NTS           | 0.52±0.02           | 0.78±0.01             | 1.54                   | 4.53±0.31       | 35.15±1.15         | 26.92±1.00      |
| 2%NTS           | 0.56±0.10           | 0.71±0.01             | 1.60                   | 7.04±0.22       | 32.51±2.37         | 21.13±0.34      |
| 3%NTS           | 0.53±0.01           | 0.67±0.01             | 1.61                   | 7.98±0.14       | 29.03±1.31         | 20.90±0.50      |
| 1%MTS           | 0.59±0.01           | 0.76±0.03             | 1.52                   | 6.93±0.45       | 31.31±0.20         | 22.37±0.65      |
| 2%MTS           | 0.56±0.01           | 0.65±0.01             | 1.55                   | 11.93±1.34      | 27.35±0.35         | 13.85±0.62      |
| 3%MTS           | 0.48±0.00           | 0.56±0.01             | 1.63                   | 13.82±0.51      | 27.35±0.35         | 14.27±0.65      |
| 1%MCE           | 0.53±0.01           | 0.67±0.01             | 1.42                   | 14.07±2.05      | 26.84±0.28         | 20.89±1.00      |
| 2%MCE           | 0.50±0.02           | 0.61±0.02             | 1.46                   | 15.13±1.21      | 27.22±0.33         | 18.03±1.17      |
| 3%MCE           | 0.48±0.01           | 0.58±0.01             | 1.48                   | 15.30±1.21      | 29.00±0.29         | 17.24±2.37      |
| 1%GLT           | 0.56±0.02           | 0.70±0.02             | 1.42                   | 12.70±1.21      | 27.33±0.72         | 20.00±1.87      |
| 2%GLT           | 0.52±0.04           | 0.64±0.01             | 1.39                   | 13.30±0.87      | 27.25±0.46         | 18.75±0.96      |
| 3%GLT           | 0.50±0.01           | 0.59±0.02             | 1.48                   | 14.67±0.64      | 26.96±0.69         | 15.25±2.18      |

3.9.3 Carr’s index and Hausner’s quotient

The Carr’s Index and Hausner’s quotient are shown in Table 4. Besides the granule containing NTS at all strengths, MTS, MCE and GLT at 1% w/w had passable flow, while all other formulations containing the MTS, MCE and GLT had good flow [31,36]. Modification enhanced the Carr’s Index and Hausner’s quotient of wheat starch \( (P=.001) \). All these flow parameters that are improved would aid the overall quality of the tablets made from these granules when they are compressed into tablets.

3.10 Tablet Parameters

3.10.1 Appearance

The tablets were round, smooth, odorless and whitish. There were no stains, chipping or cracking or any physical defect on the tablets.

3.10.2 Weight uniformity

The uniformity of weight of the metronidazole tablets are shown in Table 5. The tablets weights were found to be within acceptable limits for uncoated tablets that weigh above 250 mg. The British Pharmacopoeia stipulates that a variance of 5% is permissible for tablets that weigh 250 mg and above [36]. This could be attributed to proper die filling of the granules which resulted from good flow properties of the granules.

3.10.3 Crushing strength

The crushing strength of the tablets is shown in Table 5. The metronidazole tablets containing NTS had the least strength while the tablets containing MTS were the strongest. The crushing strength results showed that in all the binders applied, there was an increase in the value obtained as the binder concentration increased. All the tablets had crushing strength of ≥ 4 kgF and values of 4-10 kgF is generally acceptable for uncoated tablets in order for the tablets to be able to overcome the stresses of handling, packaging and transportation [38]. Therefore, all the tablets passed the test.

3.10.4 Disintegration

The disintegration time results of the metronidazole tablets are shown in Table 5. The tablets containing NTS had the shortest disintegration time which implies that they were the first to have the tablets break up in an aqueous medium to release its API. The disintegration time increased as the binder concentration that was applied increased. All the tablets disintegrated within 10 min. The order of disintegration times were: NTS < MCE < MTS < GLT. The disintegration time upper limit is given as 15 min by the BP [36] or 30 min by the USP [31].

3.10.5 Friability

All the metronidazole tablets had friability below 1% (Table 5). The pharmacopoeia recommendation for the percentage friability permissible is ≤ 1% [31,36]. The metronidazole tablets passed the friability test and are expected to withstand abrasive forces especially on the surfaces of the tablets during packaging, transportation and handling.
3.10.6 Crushing strength friability ratio

The crushing strength friability ratio (CSFR) results of the metronidazole tablets are shown in Table 5. Based on the least minimum acceptable value of 4 kgF and 1% friability, CSFR value of ≥ 4 can be considered mechanically strong. The highest value was obtained at 3% w/w of MTS while the least was at 1% w/w.

3.10.7 Content of active ingredient

The content of metronidazole in the tablet formulations containing the different binders is shown in Table 5. All the batches passed the test as they contained metronidazole in the range of 97.88 – 99.87% in the tablets. The pharmacopoeia requirement is given as 95 - 105% [31,36].

3.10.8 In vitro dissolution

The in vitro dissolution profile of the metronidazole tablets containing 1% w/w is shown in Fig. 7. Up to 80% of metronidazole was released from the tablets containing the natural wheat starch, modified wheat starch, and methylcellulose within 10 min. At 20 min, all the batches had attained ≥ 95% drug release and there was a significant difference (P = .001) in the amount of metronidazole released from the tablets containing the different binders except between batches NTS and MTS, NTS and GLT, MTS and GLT (P = .163). The dissolution profile of the tablets met with pharmacopoeia requirements which stipulate that 80% or more of metronidazole must be released from the tablets within 30 min [31,36].

The release of metronidazole from the tablets at 2% w/w of binder concentrations is shown in Fig. 8. Generally, drug release within 10 min was high and batches NTS and MTS attained up to 80% release within this time. At 20 min, all the batches of tablets had attained more than 80% dissolution of their metronidazole content. Comparatively, drug release from metronidazole tablets containing gelatin was the least when compared with the other binders (P=.002). Similarly, there was a significant difference in the quantity of drug released from tablets containing the different binders except between NTS and MTS as well as MTS and MCE (P=.232). All the tablets met the pharmacopoeia dissolution requirements for metronidazole [31,36].

Fig. 9 shows the dissolution profiles of metronidazole tablets containing the natural wheat starch, modified wheat starch, methylcellulose and gelatin at 3% w/w concentrations. A similar pattern of release was observed except that the concentrations of metronidazole released was lower at the sampling time of 3% w/w binder compared to values obtained at similar times in 1 and 2% w/w of same binders as shown in Figs. 7 and 8 respectively. More than 80% of the metronidazole content of the tablets was released within 30 min. Comparing the release pattern at 30 min, there was no significant difference (P=.156) between NTS and MTS, NTS and GLT as well as MTS and GLT. The rest of the batches showed a significant difference (P=.000) in their release pattern when compared.
Table 5. Some physical parameters of metronidazole tablets

| Batch  | Uniformity of weight (mg) | Crushing strength (kgF) | Disintegration time (min) | Friability (%) | Thickness (mm) | CSFR | Content of active ingredient (%) |
|--------|---------------------------|-------------------------|---------------------------|---------------|---------------|------|---------------------------------|
| 1% NTS | 303.02±0.10               | 4.06±1.49               | 1.10±0.24                 | 0.95±0.01     | 3.20±0.10     | 3.54 | 99.57±2.41                     |
| 2% NTS | 305.15±0.20               | 4.84±1.06               | 1.45±0.13                 | 0.78±0.02     | 3.31±0.19     | 6.21 | 99.24±1.05                     |
| 3% NTS | 300.50±0.25               | 6.19±1.24               | 2.00±0.10                 | 0.55±0.01     | 3.27±0.11     | 11.25| 98.95±0.62                     |
| 1% MTS | 308.31±0.10               | 7.39±1.19               | 1.15±0.31                 | 0.33±0.05     | 3.25±0.73     | 22.36| 97.88±1.10                     |
| 2% MTS | 310.51±0.08               | 7.60±0.98               | 2.58±0.75                 | 0.31±0.02     | 3.49±0.17     | 24.48| 99.90±0.85                     |
| 3% MTS | 306.24±1.16               | 8.33±0.63               | 3.93±0.15                 | 0.09±0.02     | 3.42±0.90     | 92.55| 99.87±2.15                     |
| 1% MCE | 300.33±0.05               | 6.08±0.75               | 0.87±0.01                 | 0.32±0.02     | 3.85±0.08     | 19.00| 98.06±1.73                     |
| 2% MCE | 301.17±0.02               | 6.44±0.25               | 1.27±0.01                 | 0.26±0.02     | 3.10±0.14     | 20.13| 99.76±0.98                     |
| 3% MCE | 300.07±0.04               | 7.18±0.49               | 3.35±1.19                 | 0.20±0.10     | 3.17±0.13     | 35.90| 99.38±2.26                     |
| 1% GLT | 304.45±0.05               | 5.45±0.27               | 2.16±0.05                 | 0.68±0.08     | 3.63±0.06     | 8.01 | 99.71±1.56                     |
| 2% GLT | 291.37±0.03               | 6.71±0.15               | 1.71±0.39                 | 0.64±0.01     | 3.29±0.07     | 10.48| 98.90±0.85                     |
| 3% GLT | 305.13±0.05               | 6.91±0.21               | 9.73±1.14                 | 0.19±0.04     | 3.52±0.33     | 36.37| 99.00±2.01                     |
4. CONCLUSION

The starch extracted from matured dry TA seeds were characterized and chemically modified. The modified starch (MTS) had better micromeritic properties than the native starch (NTS). Its application as a binder using the wet granulation technology resulted in metronidazole granules with better flow, densification and compressibility. The metronidazole tablets had good mechanical strength, friability, disintegration time and dissolution. Some other physical properties of the tablets such as crushing strength and disintegration time increased as the concentration of the binder increased while in contrast, the friability decreased. All these good attributes were within the British Pharmacopoeia set limits. The metronidazole tablets formulated with the modified starch (MTS) had better attributes than the natural/native starch (NTS) and also compared well with the gelatin and methylcellulose which were the standard binders.

DISCLAIMER

The products used for this research are commonly and predominantly used products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement
of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable in this work.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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