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Research Article

Effects of Chemical Modification of *Manihot esculenta* Starch on the Phyisco-Chemical, Binder and Disintegrant Properties in Metronidazole Tablet Formulation

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Abstract

The aim of the study was to evaluate the modification of starch from *Manihot esculenta* in metronidazole tablets as disintegrant and a binder. Wet granulation method was used to produce the metronidazole tablet. Starch was used as disintegrant at concentration 0%w/v (B0), 5%w/v (B1), 10%w/v (B2) and 15%w/v (B3) for native starch and 5%w/v (B4), 10%w/v (B5) and 15%w/v (B6) for modified starch. The starch was also evaluated for binder properties using concentration 0%w/v (C0), 5%w/v (C1), 7.5%w/v (C2) and 10%w/v (C3) for native starch and 5%w/v (C4), 7.5%w/v (C5) and 10%w/v (C6) for modified starch. The micromeritic properties of the starch powder were investigated. Some evaluative tests performed on the tablets include uniformity of tablet weight, disintegration test, hardness, friability test and *in vitro* drug release. For disintegrant studies, tablet disintegration time ranged from 11.40 ± 0.8 to 15.30 ± 0.3 sec for the NSCE batches and 13.30 ± 0.5 to 20.10 ± 0.7 sec for the MSCE batch. Tablet hardness ranged from 6.9 ± 0.8 to 7.08 ± 0.6 kgf for the native starch and 5.46 ± 0.6 to 6.54 ± 0.5 kgf for the modified starch. The dissolution profile of the tablet formulation was measured at time taken to release 25%, 50% and 90% for each of the batches. Only batch B2 passed the dissolution test and release up to 90% of the drug in 30 minutes, although B1, B3and C1 released ≤ 80% under 30 minutes. In conclusion, NSCE performed better than MSCE as both a disintegrant and binder and can be used in the formulation of metronidazole tablets. Using high concentration of the starch for these functions could be inhibitory to the drug release of metronidazole due to matrix formation on swelling.

Keywords: Binder; Disintegrant; Modified; Native; Starch

Abbreviation

MSCE: Modified Cassava Starch; NSCE: Native Cassava Starch; US-FDA: United State Food and Drug Agency; DSC: Differential Scanning Calorimeter; BP: British Pharmacopeia; BCS: Biopharmaceutical Classification System.

Introduction

In recent years, pharmaceutical scientists have been paying increasing attention to the extraction, development and use of starches from various natural sources in the formulation of dosage forms [1-4]. Starch a polysaccharide usually obtained from various plant parts, are excellent multipurpose excipient in tablet formulation. It combines binder, disintegrant and filler functions in tablets depending on the pharmaceutical use [5]. Cassava starch, an odourless, white, tasteless powder gotten from the tubers of *Manihot esculenta* (Euphorbiaceae) is a tropical wooden shrub famous for its edible tubers. It is also called tapioca in local parlance and is one of the world's cheapest and abundant staple foods in the tropics. The physico-chemical properties of cassava starch shows that the total amylopectin content in cassava starch shows that the total amylopectin content range from 13.6% to 23.8% [6] and the amylose content ranges from 16.8 to 21.5% [7]. Cassava starch has been shown to deform mainly by plastic flow during compression in a similar manner to official corn starch, suggesting that it can be an alternative in tablet formulation [8]. A study of the packing and cohesive properties of cassava starch has also shown that cassava

starch which has round and regular shape exhibited the lowest shape factor which could promote closer packing of particles and could be useful in the production of capsules [6]. When used as a binding agent in a paracetamol tablet formulation, cassava starch exhibited stronger binding properties than gelatin BP [8]. Cassava starch has also been shown to possess disintegrant functions when used in this capacity [9]. Hence with the versatility and low cost of this material, it is important that the optimized form should be investigated and commercialized.

Modification of starch arises from the limitation posed by its native form. Cassava starch when used in its native form has been shown to have high retrogadation, syneresis, low sheer resistance, easy gelatinization and high thermal decomposition [10]. There are various methods of modification which include the physical, thermal, enzymatic and genetic [11]. For the purpose of our study, we investigated of acid modification on native starch. Acid modification breaks the glycosidic bond linking the amylase sub- unit releasing the hydroxyl groups which interact with unbound water molecule and can thus swell more. Time of contact with the acid can be a determining factor as extended stay can impact not only the glycosidic bonds, but also the amylase subunit percentage.

Starch as a disintegrant was believed to function by swelling [12], but research has shown that starch act by deformation [13]. The mechanisms of disintegrant action include swelling, wicking or deformation [14]. Pressure can affect the conformation of a native starch grain. Usually under compaction pressure, starch undergoes permanent deformation. These deformed grain when exposed to water, exothermically absorb it resulting in disintegration action.

The addition of starch and other disintegrants in tablet formulations may be performed intragranularly (endo-disintegrants), extra-granularly (exo-disintegrants), or as a combination of intra-granular and extra-granular techniques (endo-exo-disintegrants) [15]. The mode of incorporation of a disintegrant influences its effectiveness. Starch exhibits faster disintegrant action when added extragranularly than intra-granularly [16]. However, disintegrants which are added to tablet formulations both intra- and extragranularly give the best performance [17]. Other factors which affect disintegrant effectiveness are particle size, moisture content, and the compression force applied [18].

In general, native starch lack ideal disintegrant properties and usually have poor compressibility and act as disintegrant only at high concentrations (10-15%). When used as a binder, the principle of sorption and swelling still holds but given the fact that there is no observable external pressure at the point of swelling, disintegration does not occur.

Metronidazole is a BCS class I, poorly compressible anti-protozoal, anti-helminthic agent, that is very effective against trichomoniasis, giardiasis among other parasitic diseases [19]. It is also poorly water soluble at 0.1g/100ml of water [20].

The aim of this study was to extract and chemically modify starch from *M. esculenta* and characterize or evaluate the physicochemical, binder and disintegrant properties in metronidazole tablet formulations.

Materials and Methods

Materials

Metronidazole was obtained as a gift from Evans Pharmaceutical Ltd., England, lactose (Merck, Germany and magnesium stearate (May and Baker, England). Starch was extracted from the tubers of *M. esculenta* purchased from Orba market in Nsukka, Nigeria. All other reagents and solvents were of analytical grade and were used as supplied.

Collection and authentication of plant material

Fresh tubers of *M. esculenta* were purchased from Oye Orba market in Nsukka, Enugu State, South-East Nigeria in October, 2017 and identified by Mr. Ifeanyi of the department of Botany, University of Nigeria, Nsukka.

Extraction and modification of *M. esculenta* starch

Cassava starch was extracted using wet milling process [21]. The *M. esculenta* starch was chemically modified by acidification with dilute hydrochloric acid [22]. A 40% w/w slurry of native *M. esculenta* starch in dilute hydrochloric acid was heated to 600^0C with constant stirring for 4 h. The reaction mixture was cooled and neutralized to pH of 7.0 with dilute sodium hydroxide (dil. NaOH) solution. The treated starch was recovered, washed and dried at 600^0C for 6 h.

Microscopy (particle size and morphology)

A 100 mg sample of the *M. esculenta* sample was mixed in a 500 µl of distilled water and observed under a compound light microscope (Shimadzu, Japan) at 100x magnification.

Moisture content and moisture sorption

A 1 g quantity of the starch powder was weighed out and put in the crucible. The weight of starch and crucible (T_o) was noted. The

crucibles with the starches were put in an oven at 50^0C for 4 h and the change in weight on each hour (T_1, T_2, T_3, T_4) was noted.

Moisture sorption was determined by weighing 2 g quantity of the starch powder out in two places and put in a desiccator of relative humidity 80% and temperature 250^0C. The weights of the samples were monitored at days 0, 2, 4, 7, 14 and 21 and the change in weight relative to the moisture absorbed was noted.

Analysis of Trace metal, ash value and protein content

Trace metal content

The model of Atomic Absorption Spectrophotometer (AAS) used was the graphite tube AAS (GTAAS) (AA-6200, Shimadzu Japan). All the glassware and plastic ware used dipped in a detergent overnight and washed thrice using distilled water, then dipped in 10% nitric acid solution overnight and then again washed with distilled water before drying. A 1 g starch sample is homogenized in 10 mL nitric acid and ran through a microwave program (Mars CEM XP-1500, closed vessel system), for 30 min. The digested sample was made up to 50 ml using de-ionized water. A 10 ml nitric acid was used as the blank and read against a 0.5 ml 1 ppm standard solution of the starch sample. Then the result of the GT-AAS was recorded.

Ash value and Protein content determination

The Association of Official Analytical Chemists (AOAC) method (1990) was used. A 10 g starch sample was burnt at 6000C in a VULCAN furnace model 3 – 1750 (Cole-Parmer, IL 60061, United States). The weight of residue after incineration was recorded. Protein content determination was determined using the Kjeldahl method using Kjeldahl model 2300 (FOSS, 2003). A 1 g sample was digested at 420ºC for 1 h to the nitrogen in the form of ammonium sulphate. This ammonium sulphate was then distilled into a boric acid solution and titrated with standard Hydrochloric acid. A 6.25 conversion factor was used to convert the recorded nitrogen to percentage crude protein.

Micromeritic properties

Bulk, tapped densities, flow rate, angle of repose (AR), Hausner's quotient (HQ) and Carr's index (CI)

A 25 g quantity of the starch powder/granule was poured into a 100 ml measuring cylinder. The measuring cylinder containing the starch was gently tapped three times on a flat surface to obtain the bulk volume. It was then firmly tapped continuously on the flat surface until maximum packed volume was achieved. The bulk and tapped density were calculated from the equation:

$$\text{Bulk density} = \frac{mass\ (g)}{Bulk\ volume\ (ml)} \quad \text{.....eqn 1}$$

$$\text{Tapped density} = \frac{mass\ (g)}{Tapped\ volume\ (ml)} \quad \text{.....eqn 2}$$

The flow rate of individual starch sample was determined simultaneously with the angle of repose using the fixed-height funnel method [23]. A plastic funnel with an orifice diameter of 1 cm fitted firmly by the means of a clamp and retort stand support with its tip 7.5 cm above a piece of white paper placed on a flat horizontal surface was used. A 25 g quantity of individual starch sample was transferred into the funnel and the time taken to exit completely was taken and calculated as,

$$\text{Flow rate} = \frac{Weight\ of\ starch\ sample\ (g)}{Time\ taken\ taken\ to\ flow\ (s)} \quad \text{.....eqn 3}$$

The mean height of the heap and the diameter of the base of the powder heap were determined from five evaluations. Using a meter rule, the tangent of the angle of repose was then calculated from the geometry of the powder heap as expressed below:

$$\Theta = \tan^{-1} \quad \text{.....eqn 4}$$

The bulk and tapped densities were estimated as mentioned above and the CI and HQ calculated as,

$$\text{C.I (\%)} = \frac{Tapped\ density - Bulk\ density}{Tapped\ density} \text{ x } 100 \quad \text{.....eqn 5}$$

$$\text{HQ} = \frac{Tapped\ density}{Bulk\ density} \quad \text{.....eqn6}$$

Determination of particle density (Dp)

The solvent displacement method was adopted [24]. N-hexane was used as non-solvent. The pycnometer empty and filled with the non-solvent was determined. Some volumes of the non-solvent were poured out and one gram of each starch was added.

$$\text{Dp} = \frac{dw.Ws}{Ws - [Wsw - Ww]} \quad \text{.....eqn 7}$$

dw= density of non-solvent (n-hexane = 0.692 g/ml)

Ws = weight of sample (1 g)

Wsw= Weight of pycnometer + sample + non-solvent

Ww = Weight of pycnometer + non-solvent.

p = Particle density

Differential Scanning Calorimetry analysis and gelation temperature

This was determined using a differential scanning calorimeter (DSC) (Mettle STAR SW-13.00, England). A 6 mg weight of the powder was placed in a crucible made of aluminum pan, covered with a pierced lid and then placed on the DSC heater after calibration with a reference metal, Indium at 156.8^{0}C. The temperature was set at a range of 0^{0}C to 300^{0}C and the nitrogen purge gas supply set at a constant rate of 20 ml/min and the test carried out at a heating rate of 20 K/min.

Preparation of granules

The granules were prepared by wet granulation method using MSCE and NSCE at concentrations of 0%, 5%, 10% and 15% w/w for disintegrants and 0%, 5%, 7.5% and 10% w/w for binder batch respectively. The general formulae given in table 1 were used in the formulation of metronidazole granules. Appropriate weights of the drug and excipients required to produce 100 tablets per batch were weighed. The metronidazole granules were produced by triturating the required amount of metronidazole powder, disintegrant (MSCE or NSCE) and lactose in a mortar with a pestle. The wet mass was passed through a 1.7 mm stainless steel sieve and dried in a hot air oven at 600^{0}C for 2 h. The dried granules were then passed through a 1.0 mm sieve. The granules were stored in air tight container.

Preparation of metronidazole tablet

The metronidazole granules were compressed into tablets using a single punch tableting machine (F3 No 181 174, Manesty, England), fitted with 9.5mm punches to a target weight of 400 mg at 2.5 kN.

Evaluation of Tablets

Tablet diameter and thickness and weight uniformity

Thickness and diameter of the tablets produced were measured using a vernier calipers (Shimadzu, Japan). The mean diameter and thickness were calculated for each batch. Twenty tablets were randomly selected from each batch. The tablets were weighed individually using an electronic weighing balance (Karl-kolb, Germany).

Tablet hardness (Crushing strength)

Monsnato hardness tester (Manesty, England) was used to determine the force required to diametrically break ten randomly selected tablets from each batch.

	Quantity (mg)						
Ingredients	**Batch**						
	B0	B1	B2	B3	B4	B5	B6
Metronidazole (mg)	200	200	200	200	200	200	200
NSCE (mg) (disintegrant)	0	20	40	60	-	-	-
MSCE (mg) (disintegrant)	0	-	-	-	20	40	60
Gelatin (mg)	20	20	20	20	20	20	20
Magnesium stearate (mg)	4	4	4	4	4	4	4
Lactose (mg)	176	156	136	116	176	156	116
Total tablet weight (mg)	400	400	400	400	400	400	400
	Quantity (mg)						
Ingredients	Batch						
	C0	C1	C2	C3	C4	C5	C6
Metronidazole (mg)	200	200	200	200	200	200	200
NSCE (mg) (binder)	0	20	30	40	-	-	-
MSCE (mg) (binder)	0	-	-	-	20	30	40
Ac-Di-Sol® (mg)	12	12	12	12	12	12	12
Magnesium stearate (mg)	4	4	4	4	4	4	4
Lactose (mg)	184	164	154	144	164	154	144
Total tablet weight (mg)	400	400	400	400	400	400	400

Table 1: Composition of metronidazole tablet using starch as disintegrant and binder.

Key: NSCE-Native Cassava starch MSCE- Acid-modified cassava starch

Tablet friability

Ten tablets randomly selected from each batch were de-dusted and weighed using an electronic weighing balance. The tablets were placed in an Erweka friabilator rotated for 4 minutes at 25 rpm, then de-dusted, re-weighed and the percentage friability calculated using the equation.

% Friability = $\frac{W1-W2 \times 100}{W1}$ .....eqn 8

where W1 is the original weight and W2 the final weight.

Tablet disintegration time and Disintegration Efficiency Ratio (DER)

The disintegration time of six randomly selected tablets from each batch were evaluated in 900 ml of 0.1 N hydrochloric acid (HCl) at 37 ± 10^0C using the Erweka disintegration apparatus. The disintergration efficiency ratio, a measure of mechanical and disintegrant property balance was calculated using the formular

DER = $\frac{Ca/Fr}{Dt}$ .....eqn (9)

Where Ca is crushing strength, Fr is friability (%) and Dt is the disintegration time (secs) of the tablet. The comparison is made using the dimensionless disintegrant quantity DERc given as

DERc = $\frac{DER\ test\ starch}{DER\ reference\ starch}$ ..... eqn (10)

When MSCE is used as the reference standard, a DERc value >1 means that NSCE performed better as a disintegrant.

Tablet dissolution test

The Erweka dissolution apparatus with paddle operated at 50 ± 5 rpm was used. The dissolution medium was 900 ml of freshly prepared 0.1N HCl in a `1.0 L beaker. The temperature was maintained at 37 ±10^0C and 10 ml volume of the sample of the dissolution medium was withdrawn at 5, 10, 20, 30, 40, 50, 60 min. For each withdrawal, 10 ml of fresh 0.1 N HCl maintained at the same temperature was added into the dissolution medium. Absorbance was taken at 250 nm using spectrophotometer. The concentrations were then calculated with reference to the calibration curve of metronidazole.

Statistical analysis

The data obtained were analyzed by one-way analysis of variance (ANOVA) using the SPSS version 14.0. Differences between means were assessed by a two-tailed student's t-test. $p < 0.05$ was considered statistically significant.

Results and Discussion

Physico-chemical properties of the starch powder

A representation of the physico-chemical and functional properties of NSCE and MSCE were characterized and given in table 3. The average particle diameter of NSCE and MSCE was determined microscopically to be 18.8 µm and 15.54 µm respectively (Table 2). They were equally rough surface and polygonal in shape (Figure 1). Acidification of NSCE resulted in a slight decrease in particle size usually as a result of the reduction of amylase sub-unit.

Test	MSCE	NSCE
Organoleptic	Odorless, white, tasteless, fine powder	Odorless, white, tasteless, fine powder
Particle size diameter	15.540 ± 18.800 µm	18.80 ± 4.700 µm
True density	3.138	5.069
Bulk Density	0.631 ± 0.017	0.535 ± 0.022
Tapped density	0.801 ± 0.019	0.698 ± 0.018
Angle of repose (^{0})	36.649 ± 0.37	31.840 ± 0.481
Mean flow rate (g/sec)	1.776 ± 0.562	0.857 ± 0.191
Hausner's Quotient	1.269	1.305
Compressibility index	21.223	23.352
Moisture content (%)	10.060	10.641
Crude protein (%)	1.750	2.192
Gelation temperature (^{0}c)	62.421	69.831
Ash value (%)	0.081	0.090

Table 2: Result of some physic-chemical properties of MSCE and NSCE powder.

Values shown are mean ± SD (n = 3)

Figure 1: Micrograph of MSCE (A) and NSCB (B).

Natural polymers like starches or gum usually have adsorbed water which may activate microbial enzymes that might lead to fermentation and degradation [25]. Owing to the hygroscopic nature of starch, knowledge of the water content is important as it would inform us on possible storage conditions challenges. Commercially produced corn starch contains 10 – 14% unbound water. Moisture control of the 10.6% and 10.0% was recorded for MSCE and NSCE respectively and can be said to be stable [26].

The study of moisture sorption capacity is particularly important as it shows the relative stability of tablets made from MSCE when in accelerated humid conditions. Moisture sorption at 8% RH (figure 2d) showed maximum values of 12.5% for MSCE and 13.0% for NSCE. This is a good index for stability as it shows that the excipient MSCE can confer better protection than the NSCE.

Proximate analysis

The supervision of the level of trace element is important in preformulation studies as may cause neurological impairment especially in children when they accumulate over time in the body. The results of the trace metal concentrations were below the BP specification [27] and also validate the level of purity during extraction. The ash value and protein content are also a representation of the purity of the extraction process. According to the European Pharmacopeia, the limit for ash content is ≤ 0.6% (for corn, potato and wheat starch) to ≤ 1.0% (rice starch). The ash content were 0.08% and 0.09% for NSCE and MSCE and the crude protein was 2.19% and 1.75% for NSCE and MSCE respectively, which falls in the acceptable pharmacopoeia limit and also shows the purity level. Both starch showed the same organoleptic properties. The tapped, true and bulk densities of the powders and granules provide an insight on the packing, flowability and densification behavior. Modification of the NSCE led to an increase in tapped density a possibly due to the smoother surface of MSCE. The particle density of 3.138 for MSCE was lower when compared to 5.069 for NSCE suggesting loss of amorphous content on acidification. The particle size and density affect tabletting, and tabletting properties like weight, disintegration time [28]. In summary, values of the AR, HQ and CI all show that both powders have passable flow. This can be improved by granulation, addition of lubricant or oven drying.

Viscosity, Paste Clarity, freeze thaw test and moisture sorption

Heating a starch in excess water exposes the free hydroxyl group of the amylase that was previously in the glycosidic bond [29]. This leads to swelling and it can be measure through viscosity, paste clarity or freeze thaw test. From figure 2a, the powders of NSCE showed increase viscosity in direct proportion with the concentration as opposed to MSCE starch granules. This observation has been reported when treatment with acids like hydrochloric acid are used to modify starch as they destroy the glycosidic linkage connecting the amylase sub-units of the polymer [30].

Paste clarity test is an important when food thickeners that can retain transparency and aesthetic appeal are required. Hence starch stands out using this advantage. Paste clarity can be measured by percentage light transfer. Figure 2b shows the light transmittance of MSCE and NSCE as a function of starch concentration. NSCE in this case outperformed MSCE at 8%w/v concentration. Similar reports have been made for cocoyam starch at the same concentration [26].

Retrogradation however, is usually a problem when starch is preserved in freezing temperature. Figure 2c shows the effect of cold storage on the retrogadation properties of NSCE and MSCE. Retrogradation can be measured by free-thaw cycle test. NSCE outperformed MSCE but subsequently lost more water over the subsequent days owing to rapid structural degradation. This, however, poorly compares to other starches. Tacca involucrata starches usually have < 5% into the second day [31]. It would not be advisable to use this NSCE and MSCE variants when better alternatives are available. If they are to be use, then refrigeration is not advised.

The moisture sorption is a measure of the stability of the powder on storage as a high sorption percentage could make available high water activity which might lead microbial contamination of the final product. the representation in figure 2d of the moisture sorption indicates that MSCE has a slightly lower moisture sorption after 5 days but ultimately had no difference after 20 days indicating that moisture sorption is a function of the individual amylose sub-unit and not in conjunction with the glycosidic bond. MSCE only slight performed better than NSCE but not significantly ($p > 0.05$).

DSC analysis and gelation temperature

DSC is the preferred thermal analytic method for the measurement of starch gelatinization and thermal stability. Gelatinization is an endothermic process. The DSC thermogram for NSCE and MSCE (figure 3a and 3b) NSCE gelatinized with onset gelation temperature (T_o) of 69.83^{0}C reaching a peak value (T_p) at 119.7^{0}3C and endset (T_c) at 192.32^{0}C. MSCE had a reduced T_o of 62.42^{0}C, T_p of 37.25^{0}C and T_c of 194.82^{0}C. Acid modification reduced the T_o by freeing up the individual amylase subunit. Thus, reduction of the gelation temperature in the case of MSCE is not a function of the crystalline subunit.

Figure 2: a) Representation of viscosity as a function of concentration b) Representation of pasta clarity as a function of transmittance and concentration c) Freeze thaw test represented by water release versus days observed d) The change in moisture sorption across days observed.

Figure 3: DSC thermogram of MSCE (A) and NSCE (B).

Evaluation of metronidazole tablets

The results of Tablets weight uniformity of metronidazole tablets are shown in Table 3. From the result, the tablets weight ranged from 400.30 ± 2.9mg to 402.60 ± 3.0 mg. The percentage deviation obtained from the tablet weight uniformity test were significantly ($p < 0.05$) below 5% stipulated for tablets weight greater than 250 mg [9]. Therefore, the tablets passed the weight uniformity test. Weight uniformity affects drug content and overall bioavailability of drug and is thus an important quality control test. The diameter and thickness of the tablet were ≤ 9 mm and ≤2.5 mm.

Disintegration test and Disintegration Efficiency Ratio

The tablets disintegration time results presented in Table 3 shows that the tablets complied with BP [9] specification for the disintegration time of normal release tablet. Tablet disintegration time ranged from 11.40 ± 0.8 to 15.30 ± 0.3 sec for the native starch and 13.30 ± 0.5 to 20.10 ± 0.7 sec for the modified starch. It is important to mention that the NSCE performed better than the batches prepared from MSCE when used as disintegrants. The possible mechanism of action for the native starch is deformation, while MSCE may act by swelling.

Compression forces, hydrophobicity of lubricants, cohesive force such as hydrogen bonds, Van der Waals, electrostatic forces, physical interlocking of powder owing to particle size can affect disintegration efficiency. The mechanism of disintegration of the tablet dosage form usually increases the surface area for potential drug release. When MSCE was used as a reference standard, the DER of the NSCE improved with increase in the concentration of NSCE (Table 3) proving that NSCE is a better disintegrant to MSCE. Despite the fact that the hydroxyl groups of the amylase subunit are free to affiliate with water it would seem that there are too few amylase subunit to actually swell and disintegrate.

Tablet code	Tablet Weight (mg ± CV)*	Drug content (mg ± SD)	Disintegration time (sec ± SD)	Hardness (KgF ± SD)	Fraibility (%)*	DER
B0	398.07 ± 1.26	198.32 ± 0.75	400.12 ± 0.10	6.75 ± 0.25	0.70 ± 0.20	0.23
B1	402.35 ± 2.87	201.34 ± 0.27	15.26 ± 0.63	7.08 ± 0.39	0.70 ± 0.61	0.97
B2	400.20 ± 2.90	195.12 ± 0.32	11.76 ± 2.11	6.98 ± 0.66	2.10 ± 0.92	1.21
B3	408.50 ± 2.73	194.74 ± 0.71	11.38 ± 2.09	7.08 ± 0.55	0.80 ± 0.78	1.42
B4	401.90 ± 3.24	192.12 ± 0.31	20.11 ± 0.72	6.16 ± 1.01	2.00 ± 0.37	0.83
B5	401.10 ± 2.95	191.76 ± 0.67	19.13 ± 1.58	6.54 ± 0.54	2.70 ± 0.81	0.78
B6	400.95 ± 2.80	194.40 ± 0.81	13.33 ± 1.39	5.46 ± 0.59	1.00 ± 0.72	0.64
C0	402.00 ± 11.52	194.30 ± 0.32	0.663 ± 0.10	6.10 ± 0.31	3.10 ± 0.45	-
C1	400.35 ± 10.34	198.71 ± 0.89	2.52 ± 0.60	6.80 ± 0.40	1.00 ± 0.34	-
C2	400.30 ± 11.60	204.23 ± 0.12	2.03 ± 0.42	6.00 ± 0.70	0.90 ± 0.33	-
C3	403.25 ± 11.47	201.23 ± 0.36	2.37 ± 1.05	5.90 ± 0.50	0.80 ± 0.12	-
C4	401.00 ± 14.83	197.45 ± 0.25	1.48 ± 0.21	5.00 ± 1.00	1.10 ± 0.81	-
C5	402.10 ± 11.00	198.75 ± 0.24	2.11 ± 0.70	5.90 ± 0.54	0.90 ± 0.57	-
C6	402.60 ± 12.16	198.34 ± 0.97	2.81 ± 0.10	7.00 ± 0.59	0.80 ± 0.62	-

Table 3: Properties of metronidazole tablets.

*Mean for 20 tablets

It would be advised that the relationship between the time of interaction with the dil. HCL and the amount of amylose sub unit be estimated to ensure that the benefits of the modification is seen as a disintegrant [32].

Tablet hardness and friability, drug dissolution profile

The result of tablet hardness also seen in Table 3 shows that metronidazole tablets had a good hardness profile and met the BP 2009 [33] specification for tablet hardness of 5 to 8 kgF. The tablet hardness for the native starch batches were between 6.98 ± 0.8 to 7.08 ± 0.6 kgF and there was no observable correlation between the concentration of the disintegrant and the tablet hardness. The batches from MSCE disintegrant were weaker, but still passed the test. The recorded values were between 5.46 ± 0.6 to 6.54 ± 0.5 kgF. Thus, the integrity of the tablets would not be compromised during packaging, transportation and use.

The result of tablets friability test presented in table 3 shows that the tablet friability test ranged from 0.7% to 2.1% for the

native starch batches and 1.0% to 2.70% for the modified starch batch. Friability is usually a function of the binder and the compression pressure, but batch B2, B4, B5, C0 And C4 did not meet the friability requirement of ≤ 1% [27]. These batches may have capping and chipping issue with the aesthetics of the tablet when exposed to shock and vibration during the packaging, transportation and use.

The results of the drug release profile of metronidazole tablet formulated with different concentrations of NSCE and MSCE as disintegrant and binders are shown from figures 4. According the US-FDA guidelines, immediate release drug product should release 85% (T_{85}) of labeled drug within 30 minutes of Study [20]. The time for the release of 25, 50 and 90% of metronidazole in all the formulation were obtained (T_{25}, T_{50}, T_{90}). The results as seen in figure 4c, d and e shows NSCE showed more promised as a disintegrant here than the modified variant. As the percentage disintegrant increase, the disintegration time reduced however the inability to release up to 90% in 30 minutes as seen in batch B3 can be attributed to a mechanism of drug release. It might be that the deformed starch granules did not have enough potential energy to swell on water absorption or that during swelling, a matrix was formed around some of the drug excipient preventing further drug release. There was no added advantage in the modification of the cassava as they performed poorly when compared to the native variant.

Figure 4: *In vitro* drug release of binder concentration a) b) c) and disintegrant concentration d) e) and f).

The effect of binder concentration on *in vitro* release of drug is of little significance as the disintegrant plays a bigger role. However, hydrogen or covalent bonding with the active principle ingredient might also have a depot effect on the release of the drugs. This was not the case however as the Ac-Di-Sol® disintegrant used, improved the dissolution profile of the formulation.

Conclusion

Natural polymers have advantages over the synthetic and semi-synthetic polymers in terms of cost, accessibility, reactivity (inert) and biocompatibility. NSCE and MSCE can be good disintegrant and binders [34].

The overall results indicate that the acid modification of the native starch of *M. esculenta* did not improve the micromeritic. The reasons for this have already been discussed. However, other forms of modification can be done. MSCE and NSCE can be used in the formulation of BCS class 1 drugs as seen in this case of metronidazole [6].

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