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EVALUATING THE FUNCTIONAL PROPERTIES OF MODIFIED MANIHOT ESCULENTA AND MANIHOT TRISTIS STARCHES FOR PHARMACEUTICAL APPLICATION

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ABSTRACT

Modification of starch is more effective in pronouncing inherent functional property of natural starch. The aim of this work is to determine the comparative susceptibility of *Manihot esculenta* and *Manihot tristis* cassava starches to modifications. The study was designed as 3 x 4 involving these cassava varieties and standard corn starches at four modification levels of physical gelatinization and pregelatinization, and chemical oxidation and acid hydrolysis. Corn starch was used as the control. The natural starches and their modified forms were subjected to morphometric, gelatinization, pasting, swelling and moisture uptake, and micromeritic tests. The results were subjected to statistical analysis and compared with dosage excipient properties. In comparison to *Manihot tristis* starch, *Manihot esculenta* starch had bigger granules, better thickening, swelling power and paste clarity, and lower gelatinization temperature. The functional properties of the cassava varieties were significantly different at $p < 0.5$. Binding and disintegration functionality of oxidized and gelatinized starches respectively were more pronounced with *Manihot esculenta*. Filling and direct-compression functionalities of hydrolysed and pregelatinized starches respectively were more pronounced with *Manihot tristis*.

KEYWORDS: Pregelatinization, Gelatinization, Hydrolysis, Oxidation.

INTRODUCTION

Starch is one of the commonly used excipient in pharmaceutical solid dosage formulation for diverse applications. Starches from different sources have different desirable-functional and undesirable-limiting properties.[1] Depending on the source, functional property, modification or preparation, starch can be used as diluent, self-lubricating diluent, lubricant, antiadherent, binder, and disintegrant at different concentrations.[2,3,4,5,6] The most widely used pharmaceutical grade starch is corn starch, from corn plant, because of its unique properties that include blandness, amorphous, odourless, and pure white appearance.[7] Local starch preparation are done by grasping plant starch source in water, decanting in open bagged basket and sun-drying, an action that brings about oxidative modification of the starch molecules by depolymerisation through the joint action of fermentation and sun-drying.[8] Pharmaceutical and food grades starch are prepared using different advanced processing and modification methods that improve or develop functional starch properties to meet specific dosage design requirement, and limit many drawback effects.[9,10,11] In comparison with native starches, modified starches have altered granule size, shape, structure, composition, nature, solubility and permeability, stability against heat, acid, shear, cooling time, freezing, texture, viscosity, gelatinization time, flow and swelling properties. Modification of starch can be done by genetic, enzymatic, physical and chemical modification methods.[6,12,13,14,15] Physical modification of starch is by thermal (heat, heat-moisture, hydrothermal, and radiation treatment) and non-thermal (mechanical, pH, pressure, ultrasonic, sonification, pulsed electric, deep freezing, cold plasma and other treatment) means.[1,16] Chemical modification is by depolymerisation, cross-linking or substitution of the gylcosidic unit of starch.[6,13,16,17,18] Depolymerisation breaks down (degrades) starch polymer structure through chemical (example through acid hydrolysis or oxidation), physical (dextrinization), biochemical, or enzymatic action leading to reduced viscosity. Crosslinking combines starch polymers and increases its gelatinization temperature, molecular weight and binding strength. Substitution by esterification or etherification blocks the hydroxyl unit along the polymer chain, and improves water affinity, clarity, swelling and stability.[19]

It is easier to modify starch by improving a pre-existing functional property than creating a completely new or foreign property. Starches with high amylopectin like waxy corn and tuber starches are easily and more effective to modify to swell-able and digestible starches. Starches with high amylose, such as from seeds, are much easier and effective to modify to smaller sized, resistant and non-swell-able starches.[20]

There is a huge store of low cost starch in cassava plant tuber. Cassava plant is abundant in nature, easily cultivated, and can survive extreme environmental conditions.[21] Cassava starch has unique properties of purity (low amount of secondary products), neutral bland taste, high paste clarity, and remoistening ability.[22,23] Unlike conventional corn starch, cassava starch application is limited by the high concentration of cyanide in cassava tuber, post-harvest deterioration of harvested tubers, need for thorough processing to eliminate cyanide content, and the nature and character of the starch such as thermal decomposition, low resistance to shear stress and retrogradation.[23,24,25] There are two main types of cassava, called the sweet and bitter cassava with varied properties.[26] Sweet cassava (*Manihot dulcis, Manihot tristis, Manihot aipi* and *Manihot palmata* Phol) tuber contains about 20 mg/kg of hydrocyanic acid (HCN) in its fresh root, and these cyanide is mainly concentrated on the surface of the outer peel. After peeling and washing, sweet cassava can be consumed either raw, sun-dried or cooked, without any special detoxification process. Bitter cassava tuber contains as much as 1000 mg/kg HCN that is evenly spread all through the tuber.[27] Bitter cassava (*Manihot esculenta* Phol) plant is cultivated for its starch commercial value, resistance to disease and deterrence to theft due to their poisonous nature, but can only be consumed after grasping and detoxification to remove this poison.[28,29,30]

We intend to modify starches from the two varieties of cassava using physical and chemical methods, determine their suitability and susceptibility to these methods, evaluate and compare the micromeritic qualities of their resultant modified starches for pharmaceutical dosage design application.

MATERIALS AND METHODS

Extraction of cassava starch

Taxonomical identification of one-year old *Manihot esculenta* and *Manihot tristis*,, referred to as bitter and sweet cassava plants respectively, were identified by Mr Amodu Emmanuel, The Curator, Paxherbal Clinic and Research Laboratories Herbarium, Ewu, Edo State, and the voucher specimen prepared as Herbarium numbers PAX/H/1933 and PAX/H/1934 for the sweet cassava, *Manihot esculenta* (Crantz), and bitter cassava, *Manihot tristis* (Mull. Arg.) respectively, and preserved for future references. The tuber of the one-year old bitter and sweet cassava plants were freshly harvested, separately sorted out, washed in cold water, peeled and washed again, weighed, cut and grated into mesh, screened through muslin cloth, and extracted of starch adopting the method of Nnamani and Okonkwo (2017).[31] The starch

suspension obtained through the muslin cloth was allowed to sediment for 2 h, and the supernatant was drained off. The starch sediment was dispersed again with fresh water to wash it, allowed to sediment for 2 h, and collected after decanting the supernatant. The thick slurry obtained was placed in a cloth bag, and then pressed to dryness using hydraulic pressure. The cake obtained was dried for 24 h at 40 ℃ using a hot oven (Kottermanns Company, Germany). The dried starch was milled using a vibro screening machine, screened through a 36 mm sieve, labelled and stored.

Modification of starch

Physical modification: Preparation of gelatinized cassava starch and dry-gel

The method of Morris *et al.*, (2002) was adopted in gelatinizing 2 kg of dried fine starch.[16] The starch was prepared as 50 % $^{w}/_{w}$ aqueous starch slurry, and heated to 80 ℃ with constant stirring at 1500 revolution per minute shear rate in an electronic heat stirrer (Adept, India) to obtain gelatinized slurry. The method of Nnamani *et al*. (2020) was adopted in obtaining dry-gel from the gelatinized slurry by pouring 15 L of 96 % ethanol 55 ºC for with constant stirring to obtain coacervate. The clear coarcervate was drained of fluid, and dried. The dried gel were screened, sieved, labelled and stored.

Chemical Conversion / Substitution: Preparation of hypochlorite oxidized cassava starch

Using the method of Attama, Obi & Nzekwe (2010), a 400 g quantity of starch was mixed with 1L of freshly prepared 0.1 N sodium hydroxide solution.[33] In another container, 20 g calcium hypochlorite was mixed in 50 ml of sodium hydroxide, and the mixture was allowed to stand, while being stirred every 15 min, for 1 h, and filtered. The filtrate of calcium hypochlorite was added to the mixed sodium hydroxide starch solution and left to stand for 1 h with intermittent stirring every 10 min. The supernatant was decanted and the product dried in the hot air oven (Kottermanns Company, Germany) at 115 ℃ for 12 h. The dried starch was then milled in the Kenwood miller with its grater attachment, and then screened through a 1 mm sieve.

Chemical depolymerization: Preparation of acid hydrolyzed cassava starch

The method of Zilli, Feng and Xiaogou (2012) was used as a guide.[34] A 350 g dried starch powder was passed through a 0.35 mm sieve, and made to 1 L with water in a 2 L volumetric flask. Then 10 ml of 0.3 M hydrochloric acid was added to the flask mix, kept at 40 ℃ in a hot air oven (Kottermanns Company, Germany). The flask was removed every 6 h, stirred for

2 min and replaced three times during 24 h period, and then filtered. The wet mass was then washed with 10 ml of 0.1 M sodium hydroxide three times, and with 500 ml water three times to obtain a neutral starch with litmus paper. The wet starch was pressed to a solid mass by squeezing in a muslin cloth, and dried at 70 ℃ in a hot air oven (Kottermanns Company, Germany) for 36 h.

Physical modification: Preparation of pregelatinized cassava starch

The method reported by Yanjuan, et al. (2013) was adopted.[35] A 500 g fresh cassava starch was placed in a 5 L volumetric flask, and made up to volume with water. The slurry was heated in an oven (Kottermanns Company, Germany) at 55 ºC for 12 h, followed by heating at 85 ºC for 24 h. The slurry was filtered using doubled muslin cloth, and the starch obtained was spread out on a stainless steel tray and dried at 70 ºC for 24 h in hot air oven (Kottermanns Company, Germany). The dried mass was grated and passed through sieve size of 0.45 mm.

Characterisation of modified starch

The method of Nnamani and Okonkwo (2017) was used to test for starch and to determine and analyse particle size and starch microscopy.[31] The methods of Daramola and Osanyinlusi (2006) and Oyewole and Afolabi (2001) were used in determining the gelatinization temperature, paste clarity, swelling ratio, moisture content, and moisture absorption of the starches.[36,37] All the tests were done in triplicate. The method of Persson *et al*. (2022) was adopted in determining the particle density of the powders using acetone in displacement pycnometry.[38] The bulk density of the samples were determined from measures of bulk volume of samples obtained from manually pouring 10 g powder at 45 ˚ through a funnel into a 50 ml measuring cylinder. The cylinder was tapped on a padded wooden base from a height of 2.5 cm until a fixed tap volume is reached to obtain the tapped volume. All test was done in triplicates. The bulk and tapped densities were calculated from their respective volumes, and used to determine the Hausner ratio and Carr's index (Equation 1 & 2), and powders' porosity (Equation 3).

$$\text{Carr's index} = \frac{Tapped\ density - Bulk\ density}{Tapped\ density} \quad \ldots\ldots 1$$

$$\text{Hausner ratio} = \frac{Bulk\ density}{Tapped\ density} \quad \ldots\ldots 2$$

$$\text{Porosity} = 1 - \frac{Bulk\ density}{Particle\ density} \quad \ldots\ldots 3$$

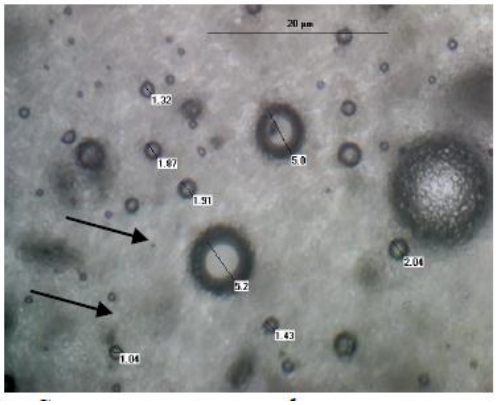
Statistical analysis of results

A 3 x 4 contingency table computation of the bitter and sweet cassava, and corn starches and the four modification process form in a one-way ANOVA of Kothari and Gaurav (2014) was used to statistically analysis the results.[39]

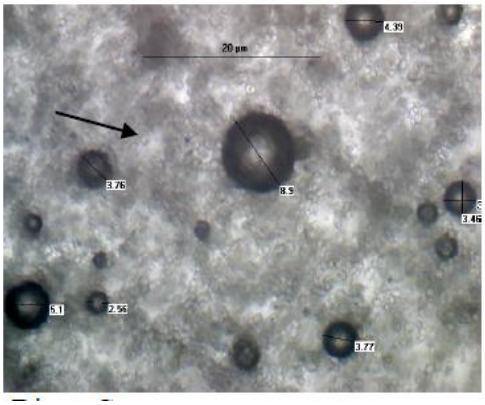
RESULTS

Microscopic properties of Modified and Unmodified starches

Photomicrographs of the starches are presented in Plates 1 – 4. Oxidized cassava starch granules appeared spherical, radially oriented and less tightly packed than the unmodified forms, with small meshed or sprayed granules as seen in Plate 2. Oxidized bitter cassava starch granules appeared to have less density than the sweet derivative (Plate 2b) and its unmodified form (Plate 1). Cassava starch xerogel granules appeared to have lost the spherical and radial structure of unmodified starch. The sweet cassava xerogel granules appeared crystalline, sharp and more densely packed (Plate 3a). While the bitter cassava xerogel granules appeared more crystalline, sharp and irregular (Plate 3b). Acid hydrolysed cassava starch granules appeared to have lost the spherical nature, but retained the radial orientation (Plate 4) of unmodified starch. They also appear to have uniform sized granules that are more tightly packed in sub lumps, especially the sweet derivative, than the unmodified cassava starches. Pregelatinized cassava starch granules in Plate 5 appeared to have retained the spherical nature of unmodified starch. The granule size of the pregelatinized bitter cassava starch appeared bigger and more spaced out than that of the pregelatinized sweet cassava starch.



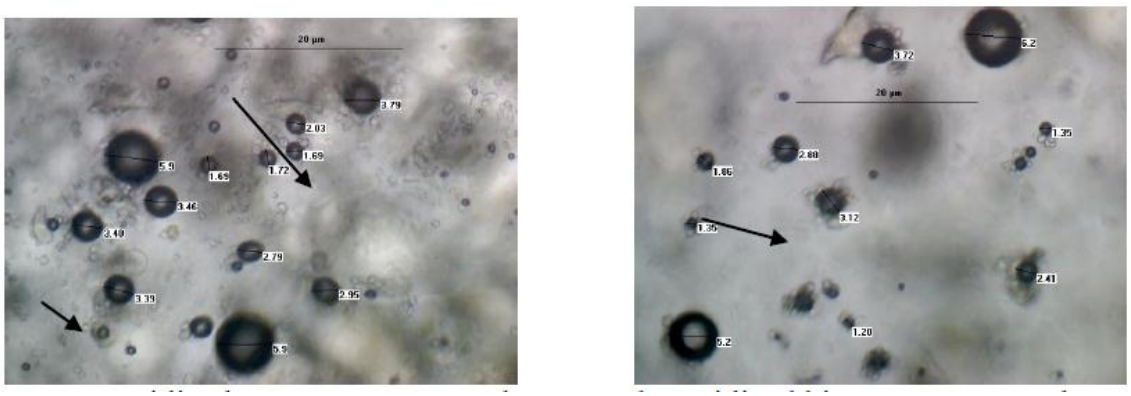
a. Sweet cassava starch



b. Bitter Cassava

Plate I: Photomicrograph of Native Cassava Starch Granules (x800 magnification).

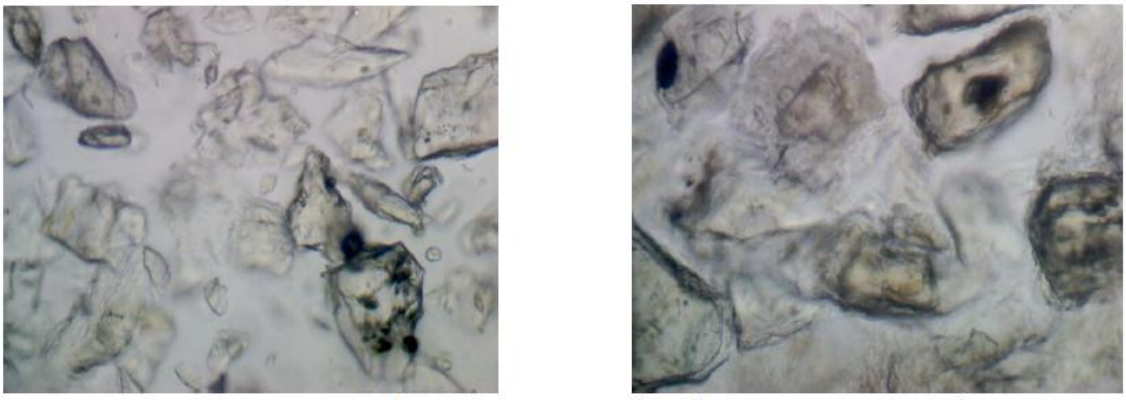
Key: → = Sizes of starch molecules in μm



a. Oxidized sweet cassava starch **b. Oxidized bitter cassava starch**

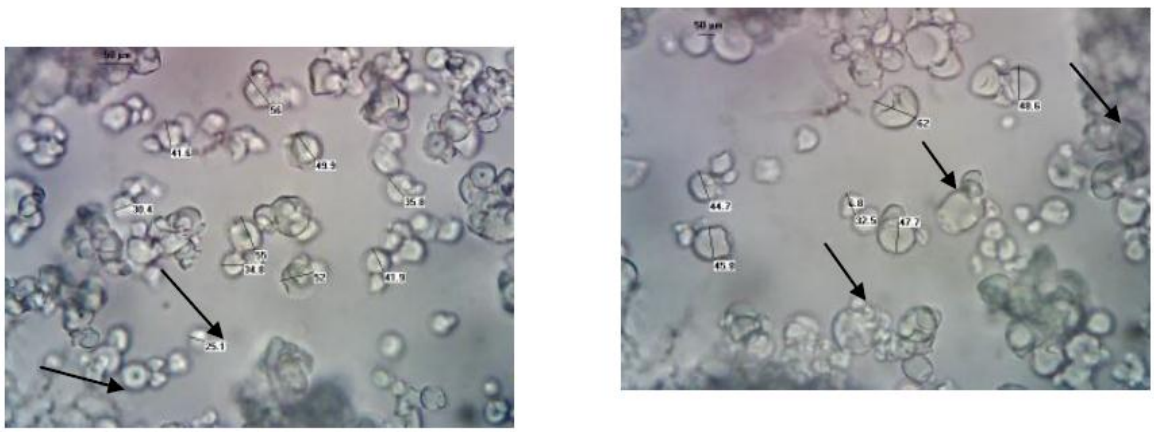
Plate 2: Photomicrograph of Oxidized Cassava Starch Granules (X800 magnification).

Key: → = Sizes of starch molecules in μm



a. Sweet cassava xerogel **b. Bitter cassava xerogel**

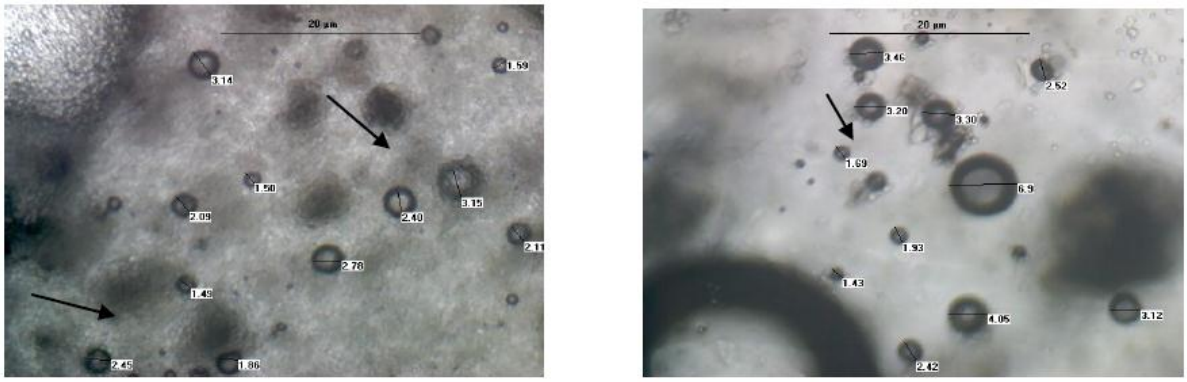
Plate 3: Photomicrograph of Cassava Starch Xerogel Granules (x800 magnification)



a. Acid hydrolyzed sweet cassava starch **b. Acid hydrolyzed bitter cassava starch**

Plate 4: Photomicrograph of Acid Hydrolyzed Cassava Starch Granules (x800 magnification).

Key: → = Sizes of starch molecules in μm



a. Pregelatinized sweet cassava starch **b. Pregelatinized bitter cassava starch**

Plate 5: Photomicrograph of Pregelatinized Cassava Starch Granules (x800 magnification)

Key: → = Sizes of starch molecules in µm

Physical (Micromeritic) properties of starches

Micromeritic properties of the starches are presented in Table 1. The unmodified sweet cassava starch granules appeared to be more tightly packed than the bitter cassava starch (Table 1). This can be attributed to the spherical nature of the sweet cassava starch granule in comparison to the bitter cassava starch granule as seen in Plate 1. Modification enhanced the spherical appearances of starches (Plates 2, 3 & 4), and increased their density (Table 1). These changes are more pronounced with the sweet cassava than with the bitter cassava starch. The flow and compressive properties of the starches from both species improved on modification (Table 1). This is related to the improved geometric form and spherical shape, and the blunting of surface roughness as observed in the Plates 2 and 4 after modification. The pregelatinized and oxidized cassava starches gave the least improved flow and compressive ability. The xerogel and acid hydrolyzed cassava starches were more crystalline in appearance, and showed better flow and compressive ability. This transformation is slightly more noticeable with the sweet cassava than the bitter cassava starch.

Micrometric properties of starches

Density and Flow properties

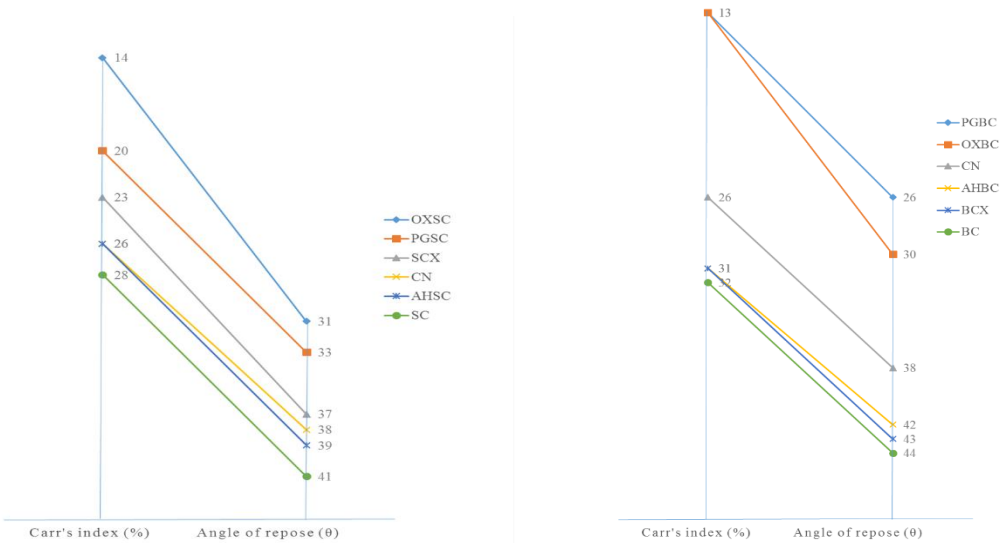
Table 1 and Figures 1 show some physical properties of the starches. Modified cassava starch showed better compression and flow properties (Table 1) than their unmodified starches. Modified bitter cassava starch gave better flow properties than their sweet cassava starch counterpart. The flow is in this order: pregelatinized > oxidized > acid hydrolyzed > xerogel starches. Modified starches showed denser, more compressible, flowable and less porous

characters. Acid hydrolysed starch had the highest porosity (which is still lower than unmodified starches), while hypochlorite oxidation of sweet and bitter cassava starches gave the lowest porosity respectively.

Table 1: Some Physical Properties of the Modified and Unmodified starches.

Starch	True D (g/ml)	Bulk D (g/ml)	Tapped D (g/ml)	Total porosity	Hausner's ratio	Carr's Index (%)	Angle of repose (θ)
SC	1.60	0.36	0.50	0.78	1.39	28.00	41.12
OXSC	0.99	0.71	0.83	0.28	1.17	14.00	31.08
AHSC	0.89	0.53	0.71	0.40	1.36	26.00	38.82
SCX	0.88	0.53	0.68	0.40	1.29	23.00	37.00
PGSC	1.21	0.72	0.90	0.40	1.25	20.00	33.23
BC	1.68	0.33	0.49	0.80	1.48	32.00	44.00
OXBC	1.07	0.71	0.82	0.34	1.16	13.00	30.29
ACHBC	1.33	0.65	0.95	0.51	1.46	31.00	41.78
BCX	1.16	0.65	0.95	0.44	1.45	31.00	42.62
PGBC	1.24	0.75	0.86	0.40	1.14	13.00	25.92
CN	2.20	0.40	0.54	0.82	1.35	26.00	37.71

Key: D = density, SC = sweet cassava starch, SCX = sweet cassava starch xerogel, AHSC =acid hydrolysed sweet cassava starch, OXBC = oxidized bitter cassava starch, PGSC = pregelatinized sweet cassava starch, BC = bitter cassava starch, BCX = bitter cassava starch xerogel, AHBC =acid hydrolysed bitter cassava starch, OXSC = oxidized sweet cassava starch, PGBC = pregelatinized bitter cassava starch, CN =corn starch



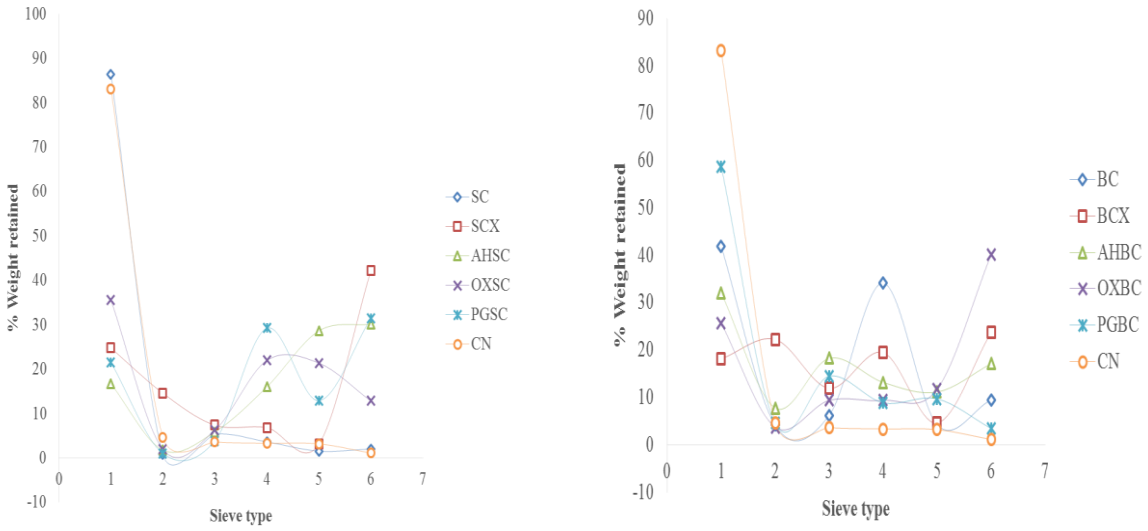
a. Sweet Cassava **b. Bitter Cassava**

Figure 2: The relationship between Angle of Repose and Carr's Index in Flow of Cassava Starches.

Key: CN= corn starch, SC= sweet cassava, OXSC= oxidized sweet cassava, AHSC= acid hydrolysed sweet cassava, SCX= sweet cassava starch xerogel, PGSC= pregelatinized sweet cassava, BC= bitter cassava, OXBC= oxidized bitter cassava, AHBC= acid hydrolyzed bitter cassava, BCX= bitter cassava starch xerogel, PGBC= prgelatinized bitter cassava.

Particle size distribution

Figure 2 show the particle size distribution of powdered starches. Corn starch showed more even fines and coarse particle distribution. The modified cassava starches show more proportionate size distribution, similar torn starch, than the unmodified cassava starches.



a. Sweet cassava **b. Bitter cassava**

Figure 2: Particle Size Distribution of Cassava Starches.

Key: CN= corn starch, SC= sweet cassava, OXSC= oxidized sweet cassava, AHSC= acid hydrolysed sweet cassava, SCX= sweet cassava starch xerogel, PGSC= pregelatinized sweet cassava. BC= bitter cassava, OXBC= oxidized bitter cassava, AHBC= acid hydrolyzed bitter cassava, BCX= bitter cassava starch xerogel, PGBC= pregelatinized bitter cassava.

Sieve type 1 = 0.0 mm, 2 = 0.2 mm, 3 = 0.55 mm, 4 = 0.7 mm, 5 = 0.85 mm, 6 = 1.2 mm mesh pore sizes.

Gelatinization temperature

Gelatinization temperature of the starches are presented in Table 2. The onset temperature of gelatinization for corn was higher than that of sweet and bitter cassava starches in that order. This follows the explanation by Napaporn and Saiyavit (2006) that corn starch, as a cereal contains more amylose, which is strongly bound and requires higher energy to dissociate from their inner embedded core than the low amylose starches.[41] Bitter cassava starch is

more viscous in water, and gels at a lower temperature than sweet cassava and corn starch. This imply that bitter cassava starch has less tightly bound amylose than sweet cassava starch, and on heating releases this less bound amylose out of its inner core structure more easily, faster and with less energy. This is consistent with reports that high amylose or smaller and more tightly starches require high temperature to completely gelatinize.[14,42,43] The oxidized and acid hydrolyzed starches had high gelatinization temperatures (Table 2) which is in conformity with the works of Kuakpetoon and Wang (2001) that chemical conversion by oxidation or hydrolysis occur by chemically depolymerising and collapsing the starch frame structure, entrapping the leached amylose against subsequent leaching, thereby requiring higher temperature to gelatinize, with consequent high peak viscosity.[45] This implied that the tightly packed small granular nature of sweet cassava starch correlates with its photomicrograph image in Plates 2 and 4 of acid hydrolyzed and oxidized starches.

Table 2: The relationship between percent Moisture, Swelling Ratio, Viscosity and Gelatinization Temperature of Native and Modified starches.

Starch	% MC	SR	RVU	G.T.	PC % T_{650}
Sweet cassava starch	12.46	1.32 ± 0.17	225.00	64.26	3.10 ± 0.20
Bitter cassava starch	12.38	1.52 ± 0.17	269.00	62.44	2.83 ± 0.10
Pregelatinized sweet cassava starch	11.41	4.10 ± 0.79	213.00	61.32	2.91 ± 0.30
Pregelatinized bitter cassava starch	11.16	4.30 ± 1.31	231.00	60.10	2.65 ± 0.10
Acid hydrolyzed sweet cassava starch	10.31	1.37 ± 1.19	151.00	68.70	6.64 ± 0.80
Acid hydrolyzed bitter cassava starch	11.06	1.51 ± 0.38	168.00	67.40	5.76 ± 0.70
Oxidized sweet cassava starch	12.94	2.37 ± 0.64	360.00	66.77	18.4 ± 3.10
Oxidized bitter cassava starch	13.04	1.80 ± 0.56	355.00	64.42	17.7 ± 2.50
Sweet cassava starch xerogel	11.60	5.20 ± 0.00	68.00	62.22	1.85 ± 0.10
Bitter cassava starch xerogel	12.22	8.50 ± 0.00	58.00	59.12	1.64 ± 0.30
Corn starch	12.78	1.15 ± 0.39	156.00	66.26	3.91 ± 0.20

Key: G.T. = Gelatinization temperature in ℃

% MC = Percent moisture content

SR= Swelling ratio

RVU = Rapid viscosity unit

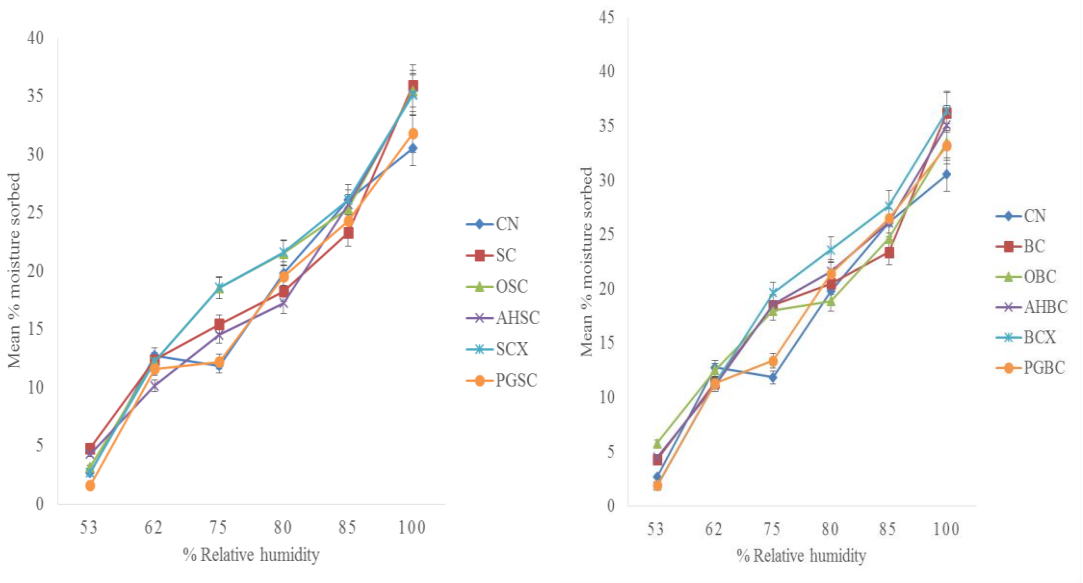
PC % T_{650} = Paste clarity percent absorbance at 650 nm wavelength

Water Absorption and Moisture content

Water absorption and moisture properties of the starches are presented in Table 2 and Figure 2. As seen in Table 2, corn starch contains slightly higher percent moisture than sweet and bitter cassava starches in that order. This can be related to the large surface area of corn

starch. On storage, corn starch absorbed less percent atmospheric moisture than sweet and bitter cassava starches (Figure 3a and 3b). This can be attributed to its already saturated surface, and less inter-particulate space for water lodging.[44] Corn starch also has lower swelling index than sweet and bitter respectively (Table 2). This can be related to the presence of fines and with low porosity for incorporating water on absorption for corn than the sweet and bitter cassava starches in that order. Sweet cassava starch granules gel at a higher temperature indicative of more densely packed amylose influence in starch. Bitter cassava starch gel at a slight lower temperature, indicative of influence of amylopectin portion.

The starches all showed type II adsorption isotherms, indicating formation of saturated monolayer in the first inflection, and subsequent saturated multilayer with increased vapour pressure.[43,44] This is consistent with results of non-porous monolayer drugs, textiles and other adsorbent materials in which a limiting moisture sorption value is not reached before saturation vapour pressure.[44] This implies that the starches are non-porous.



a. Sweet cassava **b. Bitter cassava**

Figure 3: Moisture Sorption Isotherm of Cassava Starches at Room Temperature of 27 °C.

Key: CN= Corn starch SC= sweet cassava starch, OXSC= oxidized sweet cassava starch, AHSC= acid hydrolysed sweet cassava starch, SCX= sweet cassava starch xerogel, PGSC= Pregelatinized sweet cassava. BC= bitter cassava starch, OXBC= oxidized bitter cassava starch, AHBC= acid hydrolyzed bitter cassava starch, BCX= bitter cassava starch xerogel, PGBC= Pregalatinized bitter cassava.

Statistical analysis

The F-ratios of the test results for sweet and bitter cassava and corn starches and their modified forms (at $p< 0.5$) were greater than the critical value of F-table and follows Snedico's F-distribution with (k-1), (n-k) degree of freedom as a right tailed test, indicative of significant difference between the qualities of the starches.

CONCLUSION

Sweet cassava (*Manihot tristis*) starch and its derivatives had comparative lower water affinity, smaller size, swelling ratio and better reactiveness of its exposed amylose content. The bitter cassava (*Manihot esculenta)* starch had slightly larger granule size that are loosely packed. Modification of the cassava starches improved their densities, compressibilities, and flow-abilities. The gelatinization temperatures of modified sweet cassava starches were higher than gelatinization temperatures of modified bitter cassava starches. The acid hydrolyzed and pregelatinized sweet cassava starches gave comparatively better diluent and direct compression characters respectively, than corresponding modified bitter cassava starches. The sweet cassava (*Manihot tristis*) were more appropriate for physical pregenalitization, and acid hydrolyzed chemical modifications. The oxidized bitter cassava starch exhibited better binder functionality of good cohesiveness, lower paste and gelatinization temperature, better water retaining capacity, high viscosity, paste clarity and thickening properties, and easy of spread. Gelatinized modified bitter cassava starch gave better water affinity and stronger swelling power. The properties of bitter cassava starch can be attributed to the comparative reactiveness of its outer amylopectin content. Bitter cassava starch are more appropriate for depolymerization of chemical oxidation and modification by wet gelatinization, and for application as binders and disintegrants respectively.

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