INTRODUCTION

In recent years, there has been increased interest in the search for polymers, which are biodegradable, biocompatible and show low or non-toxicity in the development of novel pharmaceutical drug carriers (Nep et al., 2017, 2018). Although synthetic polymers exhibit chemical stability and have been extensively used in drug delivery, their use is limited in some cases to unsatisfactory biocompatibility (Coviello et al., 2007) and high costs especially in the developing countries. Starch is a natural polymer from botanical sources such as maize, wheat, potato, tapioca, legumes, peas, or rice among others, and it can be extracted from plant tubers or seed endosperm (Rowe et al., 2004). It is relatively cheap, abundant, biocompatible and biodegradable in nature (Rowe et al., 2009) and is one of the most commonly used excipients in the pharmaceutical industry as a binder, diluent (Lawal et al., 2015) and disintegrant (Bolhuis et al., 2016). Starch consists of two main polysaccharides - water accessible (Ingram et al., 1966) amylose (mostly linear α-D-(1-4)-glucan) and water insoluble amyllopectin (mostly branched α-D-(1-4)-glucan, which has α-D-(1-6) linkages at the branch point) (Cheetham et al., 1998) and contains only glucose as monomer (Lawal et al., 2015; Manners 1989). The proportion of both components in a starch sample depends on their source with amylose contents ranging from 10 to 20% and the amyllopectin content varying from 80 to 90 %. It has been reported that the water absorption/swelling capacity of starch is inversely related to its amylose content (Hosenev 1986) and directly associated with the amyllopectin content (Singh et al., 2003). The use of native starches have been limited in pharmaceutical and food industries due to the fact that these starches produce tablets with low mechanical properties when used as binders, have poor processing stability (Choi et al., 1999), low thermal and shear resistance, poor solubility in cold water (Mukeriea et al., 2007),
tendency for decomposition and retrogradation on aging (Berski et al., 2011; Wang et al., 2015) and high viscosity once gelatinized (Shi et al., 2011). In addition, it has been reported that orally administered dosage forms prepared with native starches are susceptible to erosion by α-amylase in the gastrointestinal (GI) tract (Hong et al., 2016) due to their amylose content. Therefore, several methods have been used to modify starch in order to obtain desirable properties such as enhanced solubility and texture to broaden its commercial applications (Kittipongpatana et al., 2006; Odeniyi et al., 2011, 2017). Physical modification methods such as pregelatinisation/heat treatment (Thomas and Atwell, 1999) and chemical methods such as etherification (Misman et al., 2015), esterification (Winkler et al., 2013), cross-linking (Zhou et al., 2016), grafting (Setty et al., 2014) and hydrolysis (Roman et al., 2017) have been reported. These methods can be explored alone or in combination to modify the biopolymer structure. Pregelatinization imparts substantial irreversible changes such as loss of organized starch structure, polymer swelling, loss of birefringence and crystallinity and enhanced cold water dispersibility (Anastasiades et al., 2002) as a result of the re-arrangement of the intra- and intermolecular hydrogen bonding between the water and the starch molecules. Carboxymethylated starch, which is a starch ester derivative, is one of the most important commercial starch products. The modification reactions occur by reacting starch with sodium monochloroacetate in the presence of sodium hydroxide to produce starches that are soluble in cold water. Carboxymethylated starches produce pastes that have a smoother texture, greater flexibility and mechanical strength than pregelatinised starch (Mishra et al., 1991).

Further, inclusion of modified starches in some tablet formulations have produced sustained release of drugs (Omoteso et al., 2018). The mechanism of release has been adduced to retrogradation in heat modified starch (Yoon et al., 2009), degree of Substitution in carboxymethylated starch (Lemieux et al., 2009), or formation of a gel layer in cross-linked starch (Lenaerts et al., 1998).

African rice (Oryza glaberrima Steud) (AR) and Fonio (Digitalis exilis Stapf) (FR) are cereal crops native to sub-Saharan Africa and form a major part of the diet. AR is one of the two main types of domesticated rice that is cultivated around the world apart from Asian rice (Oryza sativa) (Ndjiondjop et al., 2010; Wambugu et al., 2013). The plants have generated interest due to the fact that they are tolerant and have developed adaptive and protective mechanisms for resisting major biotic and abiotic stresses and can grow in harsh environments with minimal human interference (Agnoun et al., 2012). AR starch has been reported to have a higher amount of amylose and a higher proportion of intermediate and long amylopectin chains length than white rice (O. sativa) (Wang et al., 2015). FR - a seasonal African grain is a member of the grass family Gramineae (Poaceae) and belongs to the same family as maize. The waxy starch obtained from this cereal has been reported to have amylose content similar to that of white rice and has a large proportion of branched type (British Pharmaceutical Codex, 1979).

Starches from different sources are known to possess different physicochemical properties and there is limited research on the properties of starch extracted from these species of cereal crops. To the best of our knowledge, pregelatinization and carboxymethylation of starches extracted from African rice and Fonio has not been studied extensively, therefore, this research was aimed at studying the differences between the two types of starches and determining the effects of modification on the properties of the starches which are in abundance in the developing world and how it impacts on drug release from a model poorly soluble active pharmaceutical ingredient (Ibuprofen).

MATERIALS AND METHODS

Good quality grains of AR and FR were sourced from Bodija market in Ibadan, Southwest Nigeria. Ibuprofen powder B.P. was purchased from BASF (Germany). Sodium chloride, acetic anhydride and hydrochloric acid were obtained from BDH (UK) and magnesium stearate was obtained from Sigma Aldrich (USA). All other chemicals were of analytical grade and were used as obtained.

Methods

Extraction of Starches

The native starch forms for both AR and FR were obtained by extraction in water. The grains were firstly washed with sodium metabisulphite solution (0.1 %w/v) to prevent discoloration and milled into a fine paste using a blender (Osterizer Dual range Pulse Matic Milling blender (John Oster Manufacturing Co., Racine, Wisconsin, USA)). The slurry was then sieved to remove the chaff and allowed to settle for 24 h after which the supernatant was decanted leaving the starch sediment. The sediment was washed with distilled water over a 4 day period and the wet mass was dried in a hot air oven at 50 °C for 18 h. The dried mass was ground using the Osterizer Dual range
Pulse Matic Milling blender for 15 min and then sieved using a number 120 mesh (125 µm mesh sieve).

Modification of Starches

Pregelatinization
The pregelatinized starches were prepared according to the British Pharmaceutical Codex, 1979; (Herman et al., 1989).

Carboxymethylation
Native starch powder (100 g) was added into 1-propanol solution (400 mL) containing 7.5 %w/v monochloroacetic acid. 10 mL solution of sodium hydroxide (30 % w/v) was added to the starch suspension and this mixture was then heated and maintained at 50 °C for 20 min under constant agitation (200 rpm) on a hot plate. The reaction was neutralized with glacial acetic acid and filtered using a filter paper with the remaining sediment washed initially with 80 % methanol and then finally with 100 % methanol. The starch obtained was dried in an oven maintained at 50 °C for 6 hours. The recovered flakes of each modified form were blended in an Osterizer Dual range Pulse Matic Milling blender (John Oster Manufacturing Co., Racine, Wisconsin, USA) for 15 min and screened through a number 120 mesh (125 µm) sieve. The degrees of substitution of the prepared carboxymethylated starch were determined as previously described (Stojanovic et al., 2005).

Particle size analysis
Particle size measurements were obtained using a Sympatec particle size analyser (Sympatec (Clausthal-Zellerfeld, Germany) to determine the average particle diameters (D10%, D50%, and D90%). In addition, the samples were examined using a light microscope (BH-2 BHS, Olympus, Tokyo, Japan) and particle sizes of approximately 200 particles per sample were viewed.

Scanning electron microscopy (SEM)
Samples were mounted on aluminium stubs using an adhesive double-sided carbon tape. The mounted samples were coated with a gold film under vacuum using a sputter coater and observed under magnification at x 1000 and x 5000) with a scanning electron microscope (Leica Cambridge S360, UK) operating at 10 kV.

Particle image analysis
A small amount of sample starch powder (~ 20 mg) was homogeneously dispersed on a microscope slide to form a thin layer and then viewed under a microscope (Nikon Eclipse, ME600, NY). Quantitative number-weighted particle shape analysis was conducted using computerized image software (Image pro plus 4.5.0.19). A minimum of 100 particles were detected randomly from various positions and measured. Particle shape was quantified using the elongation ratio (Eq. 1) and roughness (Eq. 2) (as the percentage of estimated particle perimeter (Perimeter) to circumscribed particle perimeter (ConvexPerim) (Kaialy et al., 2012).

\[
\text{Elongation ratio} = \frac{\text{Length}}{\text{Breadth}}
\]

\[
\text{Roughness} = \frac{\text{Perimeter}}{\text{Convex Perim}}
\]

Determination of true density and flow properties
The true density of each starches was determined by the pycnometer method using xylene as a displacement fluid as described previously (Ayorinde et al., 2013). The bulk volume of the powdered sample was determined by weighing a sample (30 g) (M) which was then transferred into a graduated measuring cylinder with the loose bulk volume, \( V_o \), determined by measuring the height, \( h_o \) (cm) of the bulk powder without any disturbance using Equation 3:

\[
V_o = \pi r^2 h_o
\]

where \( r \) is the radius of the graduated measuring cylinder.

The tapped volume of each sample was determined by mechanically tapping the loose powder in the graduated cylinder. Volume readings were taken for 38 taps, 100 taps and until there were no further changes in volume observed. The volume at this point is the tapped volume, \( V_t \), which may be determined from the final height \( h_t \) obtained after tapping using Equation 4:

\[
V_t = \pi r^2 h_t
\]

The loose bulk density, \( \rho_o \), and tapped density \( \rho_t \) were determined by dividing the mass of powder (M) used for the analysis by obtained volumes (mass per volume formed by each sample in g/cm³), that is \( V_o \) and \( V_t \), using Equations 5 and 6, respectively:

\[
\rho_o = \frac{M}{V_o}
\]

\[
\rho_t = \frac{M}{V_t}
\]

The compressibility index, also known as Carr’s index, \( C \), was determined for each sample using Equation 7:
\[
C = \frac{100 (V_o - V_t)}{V_o} \tag{7}
\]

The Hausner ratio, \( H \), of the starches was also determined from the ratio of loose bulk volume to tapped volume using Equation 8:

\[
H = \frac{V_o}{V_t} \tag{8}
\]

The angle of repose of the samples was determined using an open ended cylinder which was placed on a base of similar diameter. Starch powder (5g) was allowed to flow freely through a funnel under gravity, to form a conical heap. The angle of repose was calculated using Equation 9:

\[
\tan \theta = \frac{h}{r} \tag{9}
\]

where \( h \) is the height of the powder and \( r \) is the radius of the base of the cone. The angle of repose was obtained from the mean of three determinations.

**Determination of pH, solubility, swelling index (SI) and water absorption capacity**

Slurries of each sample were prepared at a concentration of 2 % w/v in water and the pH of the slurry was measured using a bench-top pH meter (pH-016, China). Starch powder (1 g) was accurately weighed (\( w \)) and transferred to a conical flask containing distilled water (15 mL). The slurry was shaken slowly for 5 min and transferred to a water bath maintained at 80 °C for 20 min under constant stirring at 100 rpm. The sample was transferred into a pre-weighed centrifuge tube and the new weight with the tube was determined (\( w_1 \)). Distilled water (7.5 mL) was added to the tube and the sample was centrifuged at 2220 rpm for 20 min. The supernatant was decanted carefully into a pre-weighed dish (\( w_2 \)) and dried at 100 °C to a constant weight (\( w_3 \)) and cooled for 30 min. The solubility was calculated using Equation 8:

\[
\% \text{ Solubility} = \frac{w_2 - w_3}{w} \times 100 \tag{8}
\]

The swelling index was determined using a modification of the method described by Bowen and Valdino (Bowen et al., 1984) Starch powder (5g) was placed into a measuring cylinder (100 mL) and the volume occupied was noted (\( V_o \)). Deionized water (90 mL) was added with the dispersion shaken for 2 min at room temperature (25 ± 2 °C) and then made up to volume with water. The slurry was allowed to stand for 24 h before the sedimentation volume was recorded (\( V_s \)). The SI was calculated using Equation 9:

\[
\text{SI} = \frac{V_s}{V_o} \tag{9}
\]

The water absorption capacity (WAC) was determined by adding starch (5 g) to distilled water (75 mL). This suspension was agitated at 200 rpm for 1 h at room temperature before centrifuging at 3000 rpm for 10 min. Excess water was removed from the moist starch by draining and the residual starch was weighed. WAC was then calculated using Equation 10:

\[
\text{Pasting properties of the starches}
\]

Pasting properties of the starch samples were assessed using the Rapid Visco Analyser (RVA-4) (Newport Scientific Pty. Ltd, Warriewood, Australia). The starch at a concentration of 30 % w/v in water was prepared and the slurry was held at 50 °C for up to 1 min, heated to 95 °C over 4 min, held at 95 °C for 3 min, cooled to 50 °C over 3 min and then finally held for 4 min in the instrument. Pasting peak temperature (the temperature where viscosity first increases by at least 25 cp over a 20 s period), peak time (the time at which peak viscosity occurred), peak viscosity (the maximum hot paste viscosity), holding strength or trough viscosity (the trough at the minimum hot paste viscosity), final viscosity (the viscosity at the end of test after cooling to 50 °C and holding at this temperature), breakdown (peak viscosity holding strength or trough viscosity) and setback (final viscosity holding strength) (Adebisi et al., 2016; Odeniyi et al., 2017) were calculated from the pasting curve, using Thermocline version 2.2 software (Newport Scientific Pty. Ltd., Warriewood, Australia).

**Fourier Tranform Infra-Red (FTIR)**

The FTIR spectra of the samples were recorded across a range of 4000 to 400 cm\(^{-1}\) using the ATR-FTIR spectrometer (Thermo Electron Corporation Nicolet 380). The spectra obtained were analysed with the OMNIC software and the result was an average of four scans at 1 cm\(^{-1}\) resolutions.

**X-ray diffraction**

The samples were characterised by X-ray powder diffraction using a D2 Phaser diffractometer (Bruker AXS GmbH, Germany), with a sealed microfocus generator operated at 30 kV and 10 mA, producing CuK\(_\alpha\) (\( \lambda = 0.1542 \text{ nm} \)) radiation and a Lynxeye ‘silicon strip’ multi-angle detector. The samples were scanned in Bragg-Brantano geometry, over a scattering (Bragg, 2\( \theta \)) angle range from 5 to 60°, in 0.02° steps at 1.5° min\(^{-1}\).

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Thermal Analysis
Thermogravimetric analysis (TGA) was performed by filling an open crucible with accurately weighed samples using Series 7 thermal systems (Perkin-Elmer, USA). Mass calibration was performed with a 100 mg calibration weight. Each sample was heated from room temperature to 600 °C at a heating rate of 10 °C/min. The internal atmosphere was maintained by purging nitrogen as a purge gas at a flow rate of 20 mL/min. The reduction in the weight of the samples was measured. The moisture content of the starch samples was also determined using this method.

Tablet compaction
Binary mixtures of IBU (25%) and each of the starch samples (75%) were made into flat tablets by direct compression with a final tablet weight of 400 mg. For each formulation, the specified quantities of each starch and IBU were carefully blended by gradual trituration using a mortar and pestle for 10 min and the tablets were compressed using a Carver Hydraulic Hand Press (Wisconsin, USA) at a force of 1 metric tonne for 1 minute using a die of diameter 10 mm. A 1% w/v dispersion of magnesium stearate in acetone was used as a lubricant.

In vitro drug release profile of the tablet formulations
Drug release profiles of tablet samples were studied using a USP Type 1 dissolution apparatus in 900 mL phosphate buffer (pH 6.8) maintained at a temperature of 37 ± 0.5 °C and agitated at 50 rpm for 2 h. Five millilitres of the dissolution medium was collected at intervals and replaced with fresh media maintained at the same temperature. Samples were analysed by UV spectroscopy at a wavelength of 222 nm. Drug release kinetics was assessed using various kinetic models (Najib and Suleiman, 1985; Desai et al., 1965; Higuchi, 1963; Hixson and Crowell, 1931) fit analysis (Moore and Flanner, 1996) was used to assess the similarities or differences between the different starches and the mean dissolution time (MDT), which is the most likely time for a molecule to be dissolved from a solid dosage form of IBU tablets, was also determined (Khan, 1975). The equations and information about these dissolution parameters have been detailed in previous papers (Odeniyi et al., 2015; Asare-Addo et al., 2015; Adebisi et al., 2016).

Statistical analysis
Statistical analysis was carried out using Graphpad Prism version 6.00 (GraphPad Software, California, USA). Various tests such as the Student’s t-test and ANOVA were carried out with significance criteria assumed a 95 % confidence level.

RESULTS AND DISCUSSION
Degree of substitution of Carboxymethylated starch
The total degree of substitution (DS) is the average number of functional groups introduced in the polymer and this mainly determines the properties of the carboxymethylated products (Spychaj et al., 2013). The DS obtained for these starches are shown in Table 1 with the FR starch (0.36) having a higher DS than the AR starch (0.13), which may due to the differences in the composition of both starches. The DS value determined for these starches was similar to the DS values of most commercially available carboxymethylated starches and the observations of other researchers from carboxymethylation of rice starch (Kittipongpatana et al., 2006, 2007). The DS can be controlled by varying the various parameters influencing the reaction such as the reaction time, temperature and the molar ratio of the monochloroacetate to the starch (Xie et al., 2005).

Morphology of starches
The native starches were granules that appeared polygonal in shape; although there were some ovoid shaped particles (Figure 1a and 2a). The sharp edged polygonal shape is as a result of vigorous starch biosynthesis, which leads to the tight packing of the granules in the kernel (Newman et al., 2007) and is typical of horny starches such as rice (Fujita and Nakamura, 2015). However, the ovoid shape is as a result of a reduction in the growth of starch granules in the endosperm at the early stage of development (Fujita and Nakamura, 2015). Different types of starches have been reported to have different shapes ranging from oval, spherical, polygonal to irregular shapes (Lawal 2004; Kunle et al., 2003; Manek et al., 2005; Lawal and Adebowale, 2005). The native FR starches demonstrated uniform sizes averaging less than 10 µm and the granules appeared smooth with very minimal surface damage, which appears to form aggregates (Figure 2b and c). The aggregation may be due to drying conditions as a result of exposure to heat and moisture, which makes the surface of the granules adhesive (Newman et al., 1996). Native starch granules exhibited some mild aggregation while the modification processes led to further aggregation of the granules. Carboxymethylation led to a significant disruption and rupture of the granular structure of the starch as a result of the strong alkaline
conditions (Lawal et al., 2008; Jiang et al., 2011). Cardoso et al., 2007, reported that rice starch treatment with NaOH resulted in a progressive loss of granular morphology. The carboxymethylated AR granules were generally larger than their native forms with a slight increase in aggregation observed. Pregelatinisation also produced significant alteration in the granular nature, shape and size of both starches (Anastasiade et al., 2002; Colonna et al., 1984; Kibbe 2000). This was due to the fact that starch pregelatinization is an order-disorder transition procedure that involves the disruption of the ordered semi-crystalline structure of starch granule (Cooke and Gidley 1992). In this study, it was observed that the pregelatinised AR starch had large distinct, irregularly shaped granules with little or no aggregation while pregelatinised FR starch produced significantly larger aggregates (Figure 1c; Figure 2c). Larger granular sizes of between 30 to 150 µm are normally characteristic of pregelatinised starches (Rowe et al., 2009).

**Particle size analysis**

The plots of cumulative number percent oversize versus particle size were made to determine the mean projected diameter, \(d\), of each sample (Table 1). Native starch from both sources had the lowest particles size (Table 2). The \(d\) values were in the general order, AR > FR for all forms of the starches. The modification processes caused an increase in the particle sizes of the starches and this increase may be attributed to swelling of the starch granules and resultant leaching of the amylose occurring during the process. The loss of amylose causes an increased action of amylopectin, which increases the swelling capacity of starches (Mohan et al., 2010; Nuwamanya et al., 2011). On introduction of the carboxymethyl (\(C_2H_3O_2\)) group to the starches, they become more hydrophilic thereby aiding water retention, hence increasing the particle diameter of the starches (Carr 1965). The decrease of particle diameter of CMS particles at higher degree of substitution (DS) could be as a result of higher compaction of the particles due to carboxyl-carboxyl or carboxyl-hydroxyl stabilization (Lemieux et al., 2009).

In addition to the particle size analysis, it is important to characterize the shape and surface roughness of particles as the shape has a major impact on the physical and chemical actions occurring on the particle surface and helps in the prediction of the behaviour of particles as a bulk or on their own (Ahmed 2010). Surface roughness is related to surface energy of the particle and the adhesion force between the particle and any other particle in contact with it (Wilson et al., 2017). It was observed that the surface roughness of the particles remained unchanged for the native and modified starches with the exception of C-AR, which showed a significantly lower roughness compared the other starches (Table 2). Shapes symmetrical in all axes such as circles and squares have an ER close to 0, smooth sphere/ needle shaped particles have ER values of 1 and smaller ER values indicate less elongation and /or more irregularity in shape (Mikli et al., 2001). The particles as observed in the SEM images and based on the results in Table 2, had ER greater than 1 with the closest sample to 1 (spherical shape) being N-FR which appeared the most spherical of all the samples in the SEM images (Figure 2a).
The physical properties of the various starches are shown in Table 1. The lower values of Hausner ratio, Carr’s index and Angle of repose for the modified starches suggested that pregelatinisation and carboxymethylation of the starches improved their flow properties. Flowability was greater for the pregelatinised than the carboxymethylated starches and may be related to the increased particle size of the modified starch granules (Table 2). Larger particles are generally known to flow better as a result of higher density and gravitational effects, while finer particles tend to be more cohesive due to surface effects (Neumann et al., 1967; Liu et al., 2008; Staniforth and Aulton, 2002). AR starch had better flowability than FR starch. The scale of flow all the test starches had Hausner ratio values greater than 1.11 and Carr’s indices of over 10. This is the usual characteristic of commercial starches (Rowe et al., 2009). Values of Hausner ratio and Carr’s index will guide the formulator on the rational choice of excipients in order to avoid hindering the flow of powder from the hopper into the die cavities especially when using high speed, multi-station compression machines on commercial scale. This could influence the uniformity of weight of the formed tablets.

**pH, solubility, swelling index (SI) and water absorption capacity**

The pH values for the starches ranged between 3.43 and 6.64 (Table 2), generally within the range specified for commercial starches (Rowe et al., 2009). With most drugs being either weakly acidic or basic, the addition of these starches as excipients in drug formulations will not produce any significant changes in pH or induce stability problems. The native starch forms from both sources had higher solubilities than their pregelatinised and carboxymethylated forms (p<0.05) (Table 2). However, the solubilities of all the different forms of each starch were similar to the corresponding form of the other starch (p>0.05). Carboxymethylated starch forms had the lowest solubility and this may be as a result of the addition of the bulky carboxyl group to the starches. This bulky functional group decreases the mobility of the starch therefore limiting water solubility. The solubility of carboxymethylated starches has been documented to be higher than native starches due to the higher hydrophilicity of the carboxyl group which takes up water. Starch granules contains both amorphous and crystalline regions (Buleon et al., 1998) and despite being highly hydrophilic exhibits low solubility even at high temperatures (Mweta et al., 2008). The SI and WAC of the starches appeared to be inversely related to their solubility values (Table 1). These values significantly increased with pregelatinisation and carboxymethylation. This can be rationalized as these two parameters are related to the water-holding capacity of starch molecules through hydrogen bonding. Gelatinization leads to the breakup of hydrogen bonds with water (Mweta et al., 2008) and due to the leaching of amylose that occurs during this carboxymethylation and pre-gelatinization processes the starch granules have a tendency to swell (Nuwamanya et al., 2011). The increases observed in SI on carboxymethylation might be due to the weakening of the intra-granular binding forces within the starch granule, thereby offering less restriction to swelling of the modified starches. The carboxymethylated forms of the starches were shown to absorb an amount of water 23 times their initial weights. This property of starches have also been shown to be mainly determined by their total degree of substitution (Heinz and Koschella, 2005). This can significantly impact on tablet disintegration and drug release as well as preventing the detrimental influence of hydrophobic lubricants on the disintegration time of tablets or capsules.

**Pasting properties of the starches**

The pasting properties and viscosograms of the starches are shown in Figure 3 and Table 3 to assess the effect of high temperature and shear stress on the starch samples. On exposure of aqueous starch suspensions to high temperatures, the starch granules swell and peak viscosity is observed when a larger portion of the intact starch granules are fully swollen. This gives an indication of the water binding capacity of the starch. The starch suspension then reaches a critical temperature where the swelling becomes irreversible and amylose leaches into the solvent resulting in increased viscosity known as pasting. The viscosity recorded at this point is known as the breakdown viscosity. All the starches demonstrated increases in viscosities with increase in temperature and it was observed that the carboxymethylated AR/FR starches had the highest peak, breakdown and final viscosity values (Table 3). A high value of breakdown viscosity is known to be directly related to high peak viscosity and SI of the starch on exposure to high temperatures (Ragae and Abdel-Aal, 2006) as the viscosity of a starch paste depends on the volume fraction occupied by swollen starch granules (Eliasson and Bohlin, 1982). Pregelatinised AR and native FR had the lowest peak and breakdown viscosity with the latter indicating paste stability. Therefore, they both demonstrate resistance to high temperatures and shear stress. Generally, AR produced starches that have lower peak viscosities than their corresponding
Table 1. Physical parameters of the Native and Modified starches (mean±s.d. n=3)

<table>
<thead>
<tr>
<th>Form of starch</th>
<th>Plant Source</th>
<th>True density (g/cm³)</th>
<th>H</th>
<th>C</th>
<th>A (°)</th>
<th>SI</th>
<th>WACa (%)</th>
<th>MCa (%)</th>
<th>Sa (%)</th>
<th>pHa</th>
<th>DS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Native</td>
<td>African rice</td>
<td>1.56(0.01)</td>
<td>1.23(0.05)</td>
<td>19.35(4.80)</td>
<td>50.67(0.78)</td>
<td>0.61(0.05)</td>
<td>329.65</td>
<td>6.24</td>
<td>58.32</td>
<td>3.88</td>
<td>-</td>
</tr>
<tr>
<td>Fonio</td>
<td>1.48(0.01)</td>
<td>1.25(0.06)</td>
<td>19.90(6.04)</td>
<td>70.27(0.37)</td>
<td>0.12(0.02)</td>
<td>241.11</td>
<td>9.11</td>
<td>58.57</td>
<td>5.88</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>PG</td>
<td>African rice</td>
<td>1.47(0.01)</td>
<td>1.18(0.02)</td>
<td>14.62(4.66)</td>
<td>45.92(1.08)</td>
<td>1.51(0.08)</td>
<td>359.80</td>
<td>5.63</td>
<td>52.05</td>
<td>5.62</td>
<td>-</td>
</tr>
<tr>
<td>Fonio</td>
<td>1.47(0.01)</td>
<td>1.19(0.04)</td>
<td>16.26(4.00)</td>
<td>42.87(1.51)</td>
<td>1.46(0.12)</td>
<td>324.40</td>
<td>6.31</td>
<td>51.02</td>
<td>6.36</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>CMS</td>
<td>African rice</td>
<td>1.53(0.02)</td>
<td>1.21(0.05)</td>
<td>17.50(4.97)</td>
<td>44.41(1.74)</td>
<td>5.15(0.18)</td>
<td>874.90</td>
<td>5.68</td>
<td>52.05</td>
<td>5.62</td>
<td>0.13</td>
</tr>
<tr>
<td>Fonio</td>
<td>1.52(0.01)</td>
<td>1.33(0.02)</td>
<td>23.55(1.42)</td>
<td>49.87(1.85)</td>
<td>1.51(0.08)</td>
<td>359.80</td>
<td>5.63</td>
<td>52.05</td>
<td>5.62</td>
<td>0.36</td>
<td></td>
</tr>
</tbody>
</table>

Values are the averages of triplicate analyses

PG, Pregelatinised starch; CMS, Carboxymethylated starch; d, Mean projected particle diameter; H, Hausner ratio; C, Carr’s Index; A, Angle of Repose; SI, Swelling Index; WAC, Water absorption capacity; MC, Moisture content and S, Solubility; DS, degree of substitution

Table 2. Micromeritic parameters of the native and modified starches of African rice and Fonio

<table>
<thead>
<tr>
<th>Starch</th>
<th>Form of starch</th>
<th>D10% (µm)</th>
<th>D50% (µm)</th>
<th>D90% (µm)</th>
<th>d (µm)</th>
<th>Elongation Ratio</th>
<th>Roughness</th>
</tr>
</thead>
<tbody>
<tr>
<td>African rice</td>
<td>Native</td>
<td>15.17(2.45)</td>
<td>74.83(3.48)</td>
<td>307.33(5.68)</td>
<td>7.24(3.78)</td>
<td>2.11(0.83)</td>
<td>0.84(0.05)</td>
</tr>
<tr>
<td></td>
<td>Carboxymethylated</td>
<td>26(0.43)</td>
<td>123(3)</td>
<td>306.33(3.21)</td>
<td>13.13(7.15)</td>
<td>1.35(0.89)</td>
<td>0.40(0.12)</td>
</tr>
<tr>
<td></td>
<td>Pregelatinised</td>
<td>70(7.67)</td>
<td>195.66(13.05)</td>
<td>335.33(9.61)</td>
<td>15.37(13.17)</td>
<td>2.13(1.07)</td>
<td>0.88(0.10)</td>
</tr>
<tr>
<td>Fonio</td>
<td>Native</td>
<td>5.01(0.02)</td>
<td>26.63(11.56)</td>
<td>220.33(4.51)</td>
<td>3.16(1.85)</td>
<td>1.17(0.24)</td>
<td>0.94(0.11)</td>
</tr>
<tr>
<td></td>
<td>Carboxymethylated</td>
<td>10.76(0.72)</td>
<td>124.33(12.09)</td>
<td>300.33(11.37)</td>
<td>7.69(3.99)</td>
<td>1.27(0.30)</td>
<td>0.93(0.07)</td>
</tr>
<tr>
<td></td>
<td>Pregelatinised</td>
<td>32.43(0.6)</td>
<td>180.33(3.21)</td>
<td>336(8.88)</td>
<td>4.98(3.02)</td>
<td>1.71(0.60)</td>
<td>0.91(0.12)</td>
</tr>
</tbody>
</table>

Table 3. Rheological parameters of Native, Pregelatinised and Carboxymethylated starches

<table>
<thead>
<tr>
<th>Botanical source</th>
<th>Form of starch</th>
<th>Pasting temperature (°C)</th>
<th>Peak time (min)</th>
<th>Peak viscosity (cP)</th>
<th>Trough viscosity (cP)</th>
<th>Breakdown viscosity (cP)</th>
<th>Final viscosity (cP)</th>
<th>Setback from trough viscosity (cP)</th>
<th>Setback from peak viscosity (cP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>African rice</td>
<td>Native</td>
<td>83.90</td>
<td>5.73</td>
<td>1632</td>
<td>1125</td>
<td>507</td>
<td>2283</td>
<td>1158</td>
<td>651</td>
</tr>
<tr>
<td></td>
<td>Pregelatinised</td>
<td>90.40</td>
<td>5.93</td>
<td>1417</td>
<td>1156</td>
<td>261</td>
<td>2188</td>
<td>1032</td>
<td>771</td>
</tr>
<tr>
<td></td>
<td>Carboxymethylated</td>
<td>50.20</td>
<td>4.27</td>
<td>3769</td>
<td>2896</td>
<td>873</td>
<td>4366</td>
<td>1470</td>
<td>597</td>
</tr>
<tr>
<td>Fonio</td>
<td>Native</td>
<td>89.60</td>
<td>6.33</td>
<td>2262</td>
<td>1837</td>
<td>425</td>
<td>2609</td>
<td>772</td>
<td>347</td>
</tr>
<tr>
<td></td>
<td>Pregelatinised</td>
<td>88.80</td>
<td>5.67</td>
<td>3376</td>
<td>2384</td>
<td>992</td>
<td>3566</td>
<td>1182</td>
<td>190</td>
</tr>
<tr>
<td></td>
<td>Carboxymethylated</td>
<td>64.30</td>
<td>5.87</td>
<td>4146</td>
<td>2035</td>
<td>2111</td>
<td>3649</td>
<td>1614</td>
<td>497</td>
</tr>
</tbody>
</table>

Values are the averages of triplicate analyses
FR starches. Carboxymethylated starch forms had the lowest peak times and pasting temperature which might be due to the faster rate of absorption and swelling of carboxymethylated starch granules correlating with the SI results. On cooling, the re-ordering and aggregation of amylose leads to the formation of a gel structure with the viscosity of the starch increasing to a final viscosity (Miles et al., 1985). This phase is related to the retrogradation of starch molecules observed from the setback values. Carboxymethylated starches exhibited higher setback from trough values than the native and pregelatinised starch forms which means an increased tendency to retrogradation than other starch forms. This could account for the sustained release of IBU observed in the tablet formulations.

FTIR characterization of the starches
The characteristic functional group peaks of the starch samples (Figure 4) such as the –OH group due to hydrogen bonding was observed by a broad stretching between 3300 and 3600 cm\(^{-1}\); C=O group in the range 1850-1540 cm\(^{-1}\); C=H group at ~3000 cm\(^{-1}\) due to \(\text{CH}_2\) asymmetric stretching \(^{[82]}\) and aromatic stretching around 1600-1500 cm\(^{-1}\). The carboxymethylation of the starch samples was confirmed by a sharp peak at around 1600 cm\(^{-1}\) which is typical for C=O stretching. A singlet peak at 1419.61 cm\(^{-1}\) and 1417.42 cm\(^{-1}\) observed for carboxymethylated AR and FR, respectively, is typical of the carbonyl group (Kittipongpatana and Kittipongpatana, 2013). This bands were similar to the observations reported for carboxymethylated potato starch, corn starch, and maize starches. The FTIR spectra of pregelatinised starches were similar to that of their corresponding native starches due to the fact that pregelatinisation did not significantly alter the internal structure of the starch.

PXRD analysis of the starches
The combined diffractograms for the native, carboxymethylated, and pregelatinised starch forms of the starches are shown in Figure 5. Starches are semi-crystalline (Hizukuri et al., 2006) in nature as confirmed by the few sharp peaks and the characteristic broad peaks. The crystalline peaks have been attributed to presence of amylopectin whereas the broader peaks are thought to be due to amylose. The native starches exhibited the typical A-type diffraction pattern of cereal starches with the crystalline peaks at around 15°, 17° and 23° (Wang et al., 2017). The diffractograms of the carboxymethylated starches showed the loss of the peaks at the lower 2θ; however carboxymethylated AR starch exhibited new peaks at higher 2θ - 31.76° and 45.43°. There was a slight loss of crystallinity in both pregelatinised starches as peaks were slightly less intense than those observed from the native starches. This minor loss of peak intensity suggests that pregelatinisation did not significantly alter the internal structure of the starch.

Thermal stability of the starches
TGA scans showed that both native starches and their pregelatinised forms were stable up to 310 °C before significant thermal degradation occurred. However, carboxymethylation of the starches led to a decrease in thermal stability with degradation beginning at
approximately 230 °C for both starch types. At higher temperatures, a greater portion of the carboxymethylated starches (25%) remained partially degraded whilst the native and pregelatinised starches were completely degraded (Figure 6a) at 600°C. The average moisture content of the starches varied from 5.6 - 9.1% with the native starches having the highest moisture content as observed in Figure 6b, 6c and Table 1, indicating an efficient drying process.

Fig. 4. FTIR Spectrum for of (A) Native, Pregelatinised and Carboxymethylated African rice starches and (B) Native, Pregelatinised and Carboxymethylated Fonio starches

Fig. 5. Combined diffractograms for A) Native and Modified African rice starches and B) Native and Modified Fonio starches
In vitro release profile of Ibuprofen-starch binary tablets

The drug release profiles of the different formulations were compared with that of the pure drug. Dissolution of pure IBU in phosphate buffer (pH 6.8) was slow with over ~ 2 % drug released within 5 min; ~ 8 % release after 10 min and ~ 20 % release after 30 min (Figure 7). This is due to the low solubility of IBU in aqueous medium (BCS class II).

IBU release from the binary tablets was rapid from all the starch samples than the pure drug with AR starch being relatively more rapid than FR starches. The time taken for 25% ($t_{25\%}$) and 50% ($t_{50\%}$) drug release from the tablets is shown in Table 4. N-AR starch ($f_2 = 25.9$), P-AR starch ($f_2 = 25.7$) and C-AR starch ($f_2 = 18.2$) all demonstrated significantly different dissolution profiles relative to the pure drug. Both N-AR and C-AR starch exhibited similar immediate IBU release ($f_2 = 57.5$) from their polymeric matrices in contact with the dissolution media with over 50 % drug released after 5 min (Figure 7). The P-AR starch however, released only ~16 % of IBU at 5 min and ~ 30 % release after 10 min with profiles significantly different from the native starch release profile ($f_2 = 39.3$).

Similarly, IBU release from C-AR and P-AR matrices were significantly different ($f_2 = 32.8$). IBU release from AR starches was in the order C-AR > P-AR > N-AR according to their DE values in Table 4. Similarly, N-FR starch ($f_2 = 20.5$), P-FR starch ($f_2 = 26.1$) and C-FR starch ($f_2 = 28.1$) all demonstrated significantly different dissolution profiles relative to the pure drug (Figure 8). Both P-FR and C-FR starches exhibited significantly different release profiles (relative to the native starch with $f_2$ values of 41.8 and 44.3, respectively). However, IBU release from C-AF and P-AF matrices were similar with $f_2 = 58.3$. IBU release

Fig. 6. TGA scans of A) all native and modified starches, (B) Native and Modified Fonio starches and C) Native and Modified African rice starches

Fig. 7. In vitro release profile of ibuprofen from its binary mixtures with native and modified African rice starches
from FR starches was in the order P-FR > C-FR > N-FR based on the DE values in Table 4. More than 70% of IBU was released from the compacts made from all AR starches and P-FR at 45 min, indicating that the compacts met the requirements for the dissolution of immediate release tablets (BP, 1998). However, drug release from N-FR and C-FR was more sustained relative to the other starches.

This leads to the enhancement of drug solubility and drug concentration at the diffusion layer surrounding the IBU particles and subsequently drug release into the dissolution medium. The source of the starch also had an effect on the release rate of the starch with the drug release from AR starches being in the order AR > FR for most of the samples.

The dissolution data were best fitted to the Korsmeyer-Peppas equation (Table 5). The release exponent, n < 0.5 indicates with Fickian diffusion as the main release mechanism. Although all tablets were within the range of Fickian diffusion, the manipulation of the starch bought about changes either toward greater Fickian diffusion or towards anomalous transport thereby giving a formulator the opportunity to select the polysaccharide with the desired outcome.

Table 4: Dissolution parameters of IBU-starch binary matrix tablets

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>t25% (h)</th>
<th>t50% (h)</th>
<th>DE2h (%)</th>
<th>MDT (h)</th>
<th>MDR (%h⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBU</td>
<td>0.533</td>
<td>2.333</td>
<td>53.933</td>
<td>2.237</td>
<td>0.006</td>
</tr>
<tr>
<td>N-AR</td>
<td>&lt; 0.083</td>
<td>&lt; 0.083</td>
<td>83.921</td>
<td>0.866</td>
<td>0.024</td>
</tr>
<tr>
<td>P-AR</td>
<td>0.131</td>
<td>0.666</td>
<td>84.361</td>
<td>0.805</td>
<td>0.017</td>
</tr>
<tr>
<td>C-AR</td>
<td>&lt; 0.083</td>
<td>&lt; 0.083</td>
<td>91.192</td>
<td>1.166</td>
<td>0.013</td>
</tr>
<tr>
<td>N-FR</td>
<td>0.222</td>
<td>0.621</td>
<td>71.523</td>
<td>1.166</td>
<td>0.013</td>
</tr>
<tr>
<td>P-FR</td>
<td>0.133</td>
<td>0.262</td>
<td>81.832</td>
<td>0.785</td>
<td>0.019</td>
</tr>
<tr>
<td>C-FR</td>
<td>&lt; 0.083</td>
<td>0.27</td>
<td>78.541</td>
<td>1.059</td>
<td>0.018</td>
</tr>
</tbody>
</table>

Overall, the use of the modified starches led to an increase in the DE of IBU relative to the native starches in majority of the starch matrices and the pure drug. The faster drug release from the binary mixtures is as a result of the fact that the starch particles are hydrated relatively faster when in contact with water leading to increased wettability of the IBU particles.

Table 5: In vitro release kinetics of IBU-starch binary tablets

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Zero-order</th>
<th>First-order</th>
<th>Higuchi</th>
<th>Hixson-Crowell</th>
<th>Korsmeyer-Peppas</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r²</td>
<td>k₀</td>
<td>r²</td>
<td>k₁</td>
<td>r²</td>
</tr>
<tr>
<td>N-AR</td>
<td>0.657</td>
<td>0.314</td>
<td>0.782</td>
<td>0.090</td>
<td>0.780</td>
</tr>
<tr>
<td>P-AR</td>
<td>0.768</td>
<td>0.320</td>
<td>0.960</td>
<td>0.037</td>
<td>0.887</td>
</tr>
<tr>
<td>C-AR</td>
<td>0.626</td>
<td>0.331</td>
<td>0.902</td>
<td>0.106</td>
<td>0.768</td>
</tr>
<tr>
<td>N-FO</td>
<td>0.859</td>
<td>0.283</td>
<td>0.886</td>
<td>0.013</td>
<td>0.952</td>
</tr>
<tr>
<td>P-FO</td>
<td>0.738</td>
<td>0.307</td>
<td>0.910</td>
<td>0.040</td>
<td>0.864</td>
</tr>
<tr>
<td>C-FO</td>
<td>0.816</td>
<td>0.305</td>
<td>0.813</td>
<td>0.035</td>
<td>0.918</td>
</tr>
</tbody>
</table>


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CONCLUSIONS

Starches isolated from AR and FR had typical irregular polygonal and spherical morphology synonymous to other starches. Pregelatinization and carboxymethylation caused significant changes in the physical, microscopic, pasting, and structural properties of native AR and FR starches. The modification processes led to a significant increase in the swelling and water absorption capacity of the starches. The modified FR starch was observed to be more heat stable compared to the native forms, which may make it a suitable excipient for use at high processing temperatures in formulation development. Drug release from the modified starches showed AR to have a quicker onset of drug release to that of FR. Modification of the starch either through pregelatinisation or carboxymethylation impacts on the starches varied physico-chemical properties thereby showing the potential of these natural materials in the developing world.

Conflict of Interest

The authors note no conflicts of interest.

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