Hydroxypropylation of Sorghum Starch: A Potential Excipient in Drug Formulation.

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DOI : https://doi.org/10.51584/IJRIAS.2024.907048

Received: 24 Jun 2024; Accepted: 11 July 2024; Published: 17 August 2024

ABSTRACT

Hydroxypropylation of sorghum starch for a potential pharmaceutical application as an excipient in tablet formulations was carried out. The starch was chemically modified via hydroxypropylation and characterized by SEM, XRD and FTIR. SEM showed irregular shape while the modified starch has regular shape and fibrous long distort shape. The XRD revealed the native and modified starches are completely amorphous in nature as there were no sharp peaks observed. The FTIR spectra showed broad band located within the region 3800-3500cm^{-1} which appeared in the native and modified starches indicating the free OH stretching vibration as well as intra-molecular hydrogen bonding in starch molecules. The major functional groups in the native starch were 1736cm^{-1} (C=O), 1625cm^{-1} (-COO-), 1427cm^{-1} (-COO-), 1227cm^{-1} (-C=O-), 1162cm^{-1} (C-O stretching and C-H stretching). During hydroxypropylation there were introduction of new functional groups observed at 1800-1500cm^{-1} (-COO-) and 1606-1632cm^{-1} (OCH_2COONa) respectively. The moisture content of the native starch was 5.46±0.00% and modified Starch was 4.82±0.01%. The pH of the native and hydroxypropyl starch were 7.00±0.01 and 7.29±0.02 respectively. Relative viscosity value of 1.70±0.08 and 2.76±0.00 were observed for the native and modified starches respectively. Water holding capacity of the native and modified starches were 28.35±0.20% and 33.25±0.01% respectively. The flow properties of the starch granules show low angles of repose, high flow rate which fall within hausner ratio and carr's index for tablet formulation. Hence, Modification of native sorghum starch by hydroxypropylation shows better physicochemical properties than the native which enhanced a better efficacy in the tablet granule and flow properties in drug formulation.

Keywords: Starch, modification, hydroxypropylation, SEM, XRD, FTIR, Excipient

INTRODUCTION

Starch is one of the most abundant natural carbohydrates store in plants. It is found in many different plant organs Including seeds, fruits, tubers and roots, functioned as a source of energy. (Adeyanju and Emesi,2019). Starch is a Versatile, cheap and readily available material obtained from renewable sources that has found wide application in tableting as a binder, disintegrant, diluents, lubricant and glidant. Unfortunately, it is not suitable for direct compression formulation due to its poor compressibility and flow characteristics. (Ibrahim *et al.*,2022). There is a need therefore to impart these properties requisite for direct compression by modifying starch. Starches are used extensively in pharmaceutical industries as disintegrants, binders and lubricant in tablets formulations. The use of cassava and yams starches as tablet disintegrant had been studied (Ibrahim et al.,2022). The effect of various starches on the physical standards of sulfa guanidine tablets were studied (Ibrahim *et al.*,2022). Starch molecule can be extracted and sold as such (native starch), but it can also undergo several processing operations in order to improve its properties and enlarge the range of its uses. Modified starch on the other hand is a native starch that undergoes some changes by chemical means. (Adeyanju and Emesi, 2019.). Hydroxy propylated starch products, i.e., starches that have been etherified by reaction with

ISSN No. 2454-6194 | DOI: 10.51584/IJRIAS |Volume IX Issue VII July 2024

propylene oxide (PO), are stable because they reduce the tendency of starch pastes and gels to retrograde.

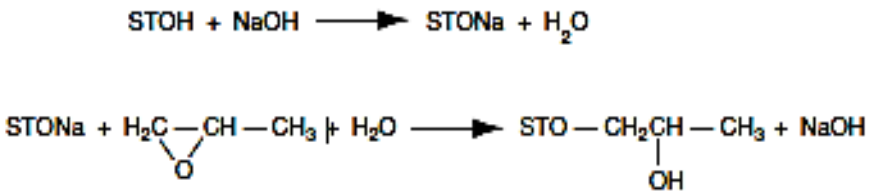


Fig1: Starch. hydroxypropylation

According to the international pharmaceutical excipient council, Excipient is defined as "Any Substance other than active drug or pro-drug that is included in the manufacturing process or is contained in Finished pharmaceutical dosage forms". Excipients are pharmaceutical additives, the inactive Ingredients used to make up a medication. They include Dyes, flavors, binders, emollients, fillers, lubricants, Preservatives and many more classifications. A joint conference on excipients identified starch as one of the top ten excipients. Starch is a multipurpose excipient in tablet formulation. It is used as a binder, disintegrant and lubricant. (Adeyanju and Emesi, 2019). The aim of this work is to chemically modify sorghum starch via hydroxypropylation and relate this to its potential efficacy in drug formulation.

MATERIALS AND METHODS

Extraction of Starch from Sorghum Cereal

After inspection, sorghum cereal 2kg was thoroughly washed and then soak in water for 24hrs. The steeped grains was taken to the mill and blended. The blended mass was mixed with enough water, and then pass through a filter cloth to remove the chaff and 100ml of 0.1N NaOH was added to separate the starch and proteineous materials and to neutralize the prevailing slight acidity. Excess sodium hydroxide was removed by washing several times with distilled water. The clear supernatant fluid will then be pour away while the sedimented starches was collected and a suspension of the starch in distilled water will then be centrifuged for 15minutes at 2800 revolutions per minute to separate the non-starch components from the starch. The starch retrieved was collected and spread to dry in an oven at 40^{o}C. The dried starch lumps was size reduced to a fine powder using a blender.

Hydroxypropylation

A starch sample of 50 g, 110mL of distilled water, and 10 g of Na_2SO_4 were mixed in a centrifuge tube. The pH was adjusted to 11.3 with 1M NaOH and 4.5mL of 3.0% propylene oxide was added for the substitution and capped the sample tube immediately and shaken vigorously for proper mixing, then incubated at 35^{0}C in shaking water bath for 24 h and the reaction were terminated by adjusting the pH to 5.3 with 1M HCl. The slurry was then centrifuged at 3000×g for 10 mins and the remaining residue after discarding the supernatant was washed with distilled water and dried at 35^{0}C.

Determination of Moisture

The moisture content of the starch was determined according to (AOAC 1999) method. Starch 5g was accurately weighed into evaporating dish and dried in an oven at 105^{o}C for 3hours. The sample was cooled in desiccators and weighed. The process of heating, cooling and weighing was repeated after every 30mins interval until a constant weight was obtained. The moisture content was then calculated as follows;

$$\% \text{ moisture} = \frac{W1-W2}{W1-W0} X \frac{100}{1}$$

Where:

W_0=Weight of Petri dish in grams

ISSN No. 2454-6194 | DOI: 10.51584/IJRIAS |Volume IX Issue VII July 2024

W_1=Weight of Petri dish in grams and sample before drying.

W_2=Weight of Petri dish in grams and sample after drying

pH

The method of Akpa and Dagde (2012) was adopted as follows: A measured volume, 10ml of distilled water was added to 1.5g of starch and was stirred properly. The pH meter was inserted into the solution and the reading recorded.

Water Absorption Capacity

A 1g of native and modified starch was weighed into test tubes. 10ml of distilled water and 10ml of groundnut oil in the second test tube was added, and then heated in a water bath at 60^0C for 30 minutes. The starch slurry was centrifuged at 1000rpm for 15 minutes and the supernatant carefully decanted and weighed and ratio was determined.

Solubility Test

The native starch and modified starch samples (2g each) was suspended in 20ml of distilled water and heated to 70^0C for 30 minutes with continuous shaking. The mixture was centrifuged at 4000rpm for15 minutes. An aliquot of supernatant (5ml) was evaporated at 105^0C and weighed. The solubility of starch is the ratio in mass (g) of the dried supernatant to the initial mass (g) of dried starch.

Relative Viscosity

Relative viscosity of starch samples was measured in filtered 1% aqueous solution using U-shaped viscometer (AOAC, 1990). A flow time (seconds) of distilled water was measured by filling the viscometer tube (held at 30^oC in water bath) with water and then drawn by suction to the upper mark of the viscometer. Initial and final times was recorded using stop watch while the water passing the upper and the lower marks of the U-shaped tube. The flow time of a carbon dioxide free aqueous starch solution (2%) was measured as before.

Calculations:$Relative\ viscosity\ = \frac{[T-To]}{[To]}$

Where:

T =flow time of starch solution in seconds;

To =flow time of distilled water in seconds.

Microstructure Studies by SEM, FTIR, UV Vis, and XRD

Isolated starch samples were mounted on a metal stubs and coated with gold palladium (≈20 nm thickness) using a Hummer sputter-coating system (Anatech Ltd., Union City, CA). Samples will then be observed using a scanning electron microscope (S- 3000N, Hitachi Science Systems, Tokyo) at an acceleration potential of 15 kV. Pictures were captured using automated image capturing software (Hitachi High-Technologies, Pleasanton, CA). Method described by (Kemas *et al.,* 2009) was adopted. Before mounting sample disc on a Nicolet 510 FTIR spectroscopes (California, USA), sample disc will first be prepared by mixing 2mg of the dry sample with 300mg of anhydrous finely powdered KBr. Then, the powder mixture was poured into a die and compressed in a KBr press (Specac, Germany) under high pressure and vacuum to form a suitable disc. XRD of sorghum starch and the hydroxypropyl starch were studied using an X-ray diffraction pattern test was carried out on extracted starch using the diffract meter –XRD analytical (X "PERT pro, Netherlads). UV Vis analysis was carried out using a spectrophotometer UV-1601 PC (Shimadzu Corperation, Japan). The spectral measurements was made over the region 200-600nm for various concentrations chemically pure starch is measured in terms of absorbance which directly proportional to the rate of hydrolysis of starch by the enzyme.

ISSN No. 2454-6194 | DOI: 10.51584/IJRIAS |Volume IX Issue VII July 2024

Evaluation of starch granules properties

Bulk Density: Bulk density of *sorghum* starches was determined by carefully pouring 30g powder into a graduated glass measuring cylinder. The cylinder will then be lightly tapped twice to collect all the Powder sticking on the wall of the cylinder. The volume will then be read directly from the cylinder and used to calculate the bulk density. The bulk density (g/ml) was calculated by using Eq. 2.3. Bulk Density was determined as a mean of three measurements.

$$Bulk\ density\ (\rho b)\ = \frac{m}{vb}$$

Where *m* is the weight of the powder and *vb* is bulk volume

Tapped density: For tapped density, 30g of powder was graduate measuring cylinder 50 times using tapped densitometer (ERWEKA, Germany) to attain a constant volume reading from the cylinder and the tapped density was calculated from the weight and tapped volume of the powder. Tapped density (g/ml) was determined as a mean of three measurements.

$$Tapped\ density\ (\rho t)\ = \frac{m}{Vt}$$

Where *m* is the weight of the powder and *Vt* is the tapped volume

Carr's Index: Carr's Index (% compressibility) was calculated from the difference between the tapped and bulk density and divided by the tapped density.

$$Carr's\ Index\ (CI)\ = \frac{([\rho t\ -\ \rho b])}{pt}\ x\ 100$$

Hausner ratio: Hausner ratio was obtained from the ratio of tapped density to bulk density of the starches.

$$Hausner\ ratio\ (HR)\ = \frac{\rho t}{\rho b}$$

True density: True density was determined by liquid displacement method using xylene as immersion fluid (Odeku *et al.,* 2008). Two grams of starch sample of *sorghum power* was placed in a pre weighed empty pycnometer, closed after xylene was added and weighed. Sufficient xylene was added to wash down and overlay the sample; all spilled over liquid (xylene) was wiped off with an absorbent cloth. After 10 min, the sediment starch was stirred with a glass-stirring rod to release entrapped air, the sample equilibrated for a few min and stirred again. When evolution of minute air bubbles through the supernatant xylene layer had stopped, the stirrer was removed and rinsed into the pycnometer with several milliliters of xylene. The sample was allowed to settle, the pycnometer filled with xylene and the meniscus was adjusted.

$$True\ density\ (g/ml)\ \ p\ =\ \frac{[(W1+W2)-W3]}{W1xSG}$$

Where:

P= true density of starch

W_1= weight (g) of starch

W_2= weight (g) of the pycnometer filled with xylene

W_3= weight (g) of pycnometer plus sample plus xylene, and

SG= specific gravity of xylene (g/ml) (~0.855).

ISSN No. 2454-6194 | DOI: 10.51584/IJRIAS |Volume IX Issue VII July 2024

RESULTS AND DISCUSSIONS

Table 1: Identification of Sorghum Starch

Identification Test	**Native starch**	**Hydroxypropyl starch**	**Maize BP**
Solubility (water) ml	Insoluble	Insoluble	insoluble
Solubility(alcohol) ml	Insoluble	Insoluble	insoluble
Iodine test	blue/black	blue/black	blue/black
Colour	off white	off white	off white

Table 2: Solubility of sorghum starch and its derivative

Type	**Temperature (°C)**	**Solubility (%)**
Native Starch	60	10.50 ± 0.20
	70	27.50 ± 0.01
	80	60.27 ± 0.20
Hydroxypropyl Starch	60	15.50 ± 0.01
	70	28.51 ± 0.01
	80	45.50 ± 0.02

Values expressed are mean ± standard deviation (n=3).

Table 3: Physicochemical Properties of sorghum starch and its derivative

Type	**Moisture**	**pH**	**Water Holding capacity**	**Relative viscosity**	**Emulsion capacity**
Native Starch	5.46 ± 0.00	7.00 ± 0.01	28.35 ± 0.20	1.70 ± 0.08	25.86 ± 0.01
Hydroxypropyl starch	4.82 ± 0.01	7.29 ± 0.02	33.21 ± 0.01	2.76 ± 0.00	30.06 ± 0.02

Values expressed are mean ± standard deviation (n=3).

Table 4: Flow Properties of Paracetamol Granules Prepared with the hydroxypropyl sorghum Starch

Parameters	**Native Starch**	**Hydroxypropyl Starch**	**Maize Starch BP**
Flow Rate (g/sec)	6.99 ± 0.15	8.86 ± 0.07	10.13
Tapped Density (g/ml)	0.49 ± 0.10	0.47 ± 0.18	0.48
Bulk Density (g/ml)	0.42 ± 0.10	0.42 ± 1.11	0.49
Carr's Index (%)	14.8 ± 0.04	11.57 ± 0.25	15.18

ISSN No. 2454-6194 | DOI: 10.51584/IJRIAS |Volume IX Issue VII July 2024

Hausner's Ratio	1.17 ± 0.19	1.13 ± 0.00	1.18
Angle of Repose (%)	37.00 ± 1.11	29.00 ± 0.15	32.00

Values expressed are mean ± standard deviation (n=3).

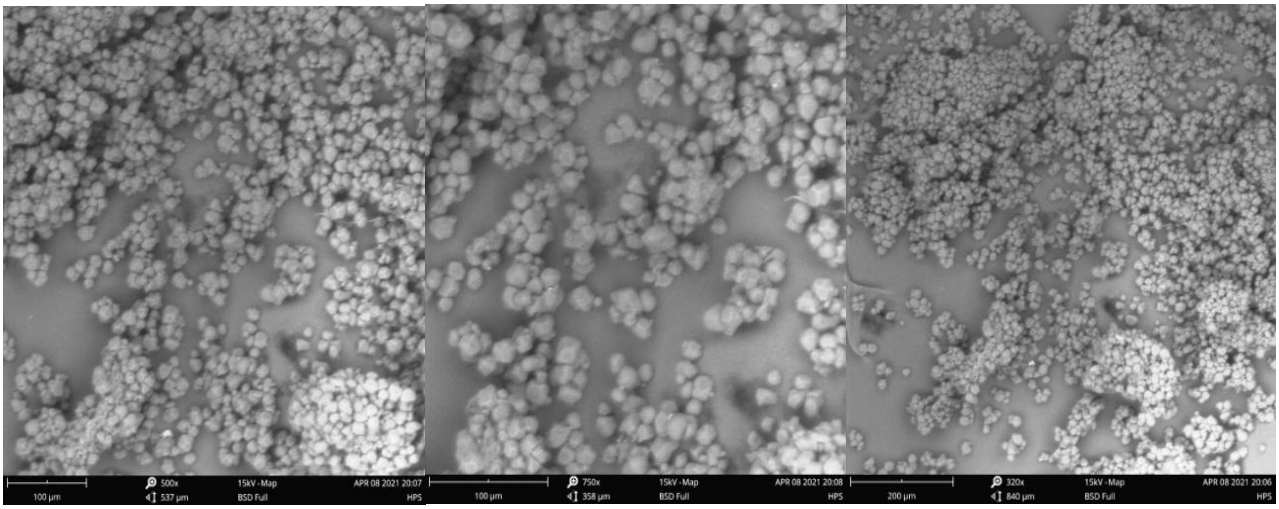


Plate 1: SEM for Hydroxypropyl sorghum starch (320x, 500x and 750x)

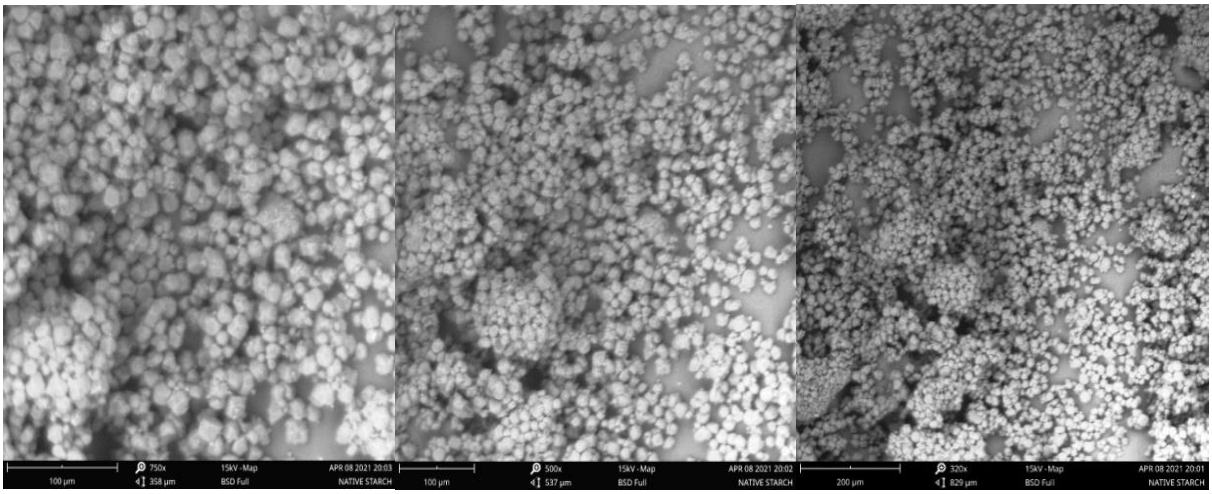


Plate 2: SEM for Native sorghum starch (320x, 500x and 750x)

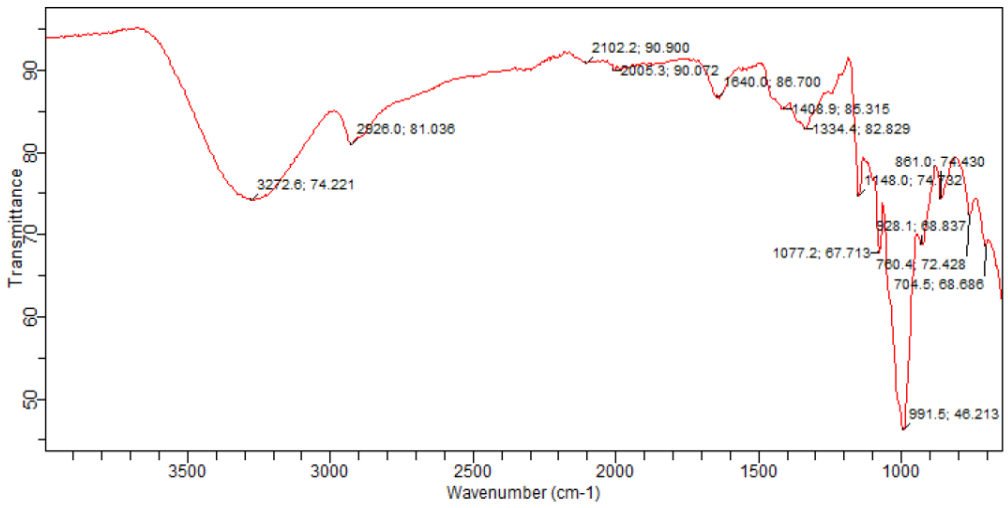


Figure 1: FTIR for Hydroxypropyl sorghum starch

ISSN No. 2454-6194 | DOI: 10.51584/IJRIAS |Volume IX Issue VII July 2024

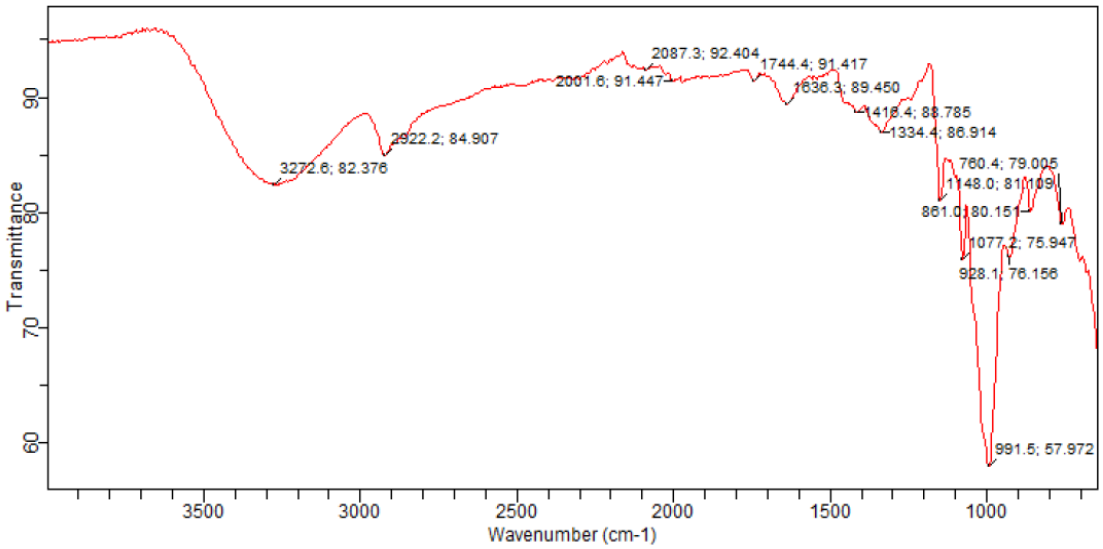


Figure 2: FTIR for Native Starch

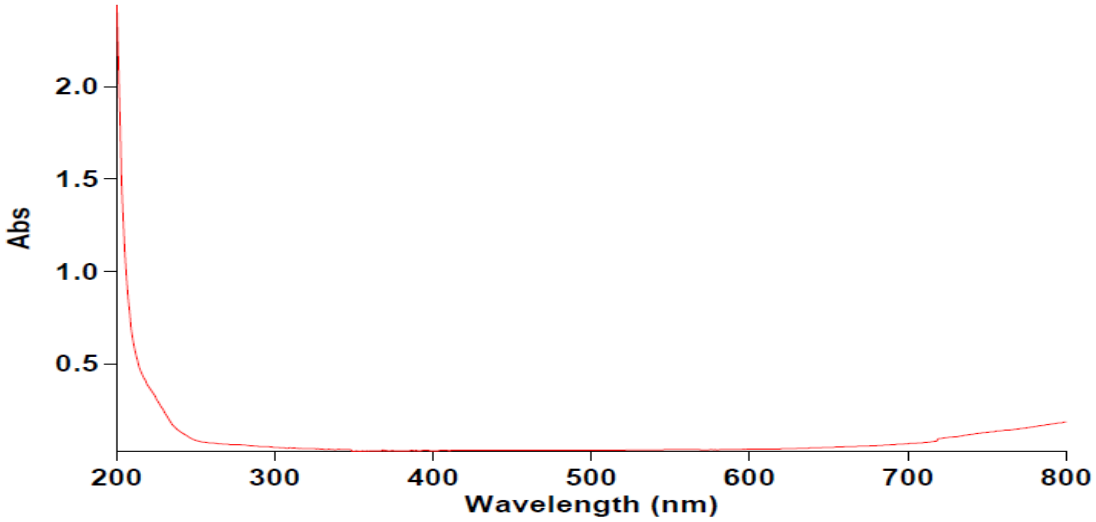


Figure 3: UV for Hydroxypropyl sorghum starch

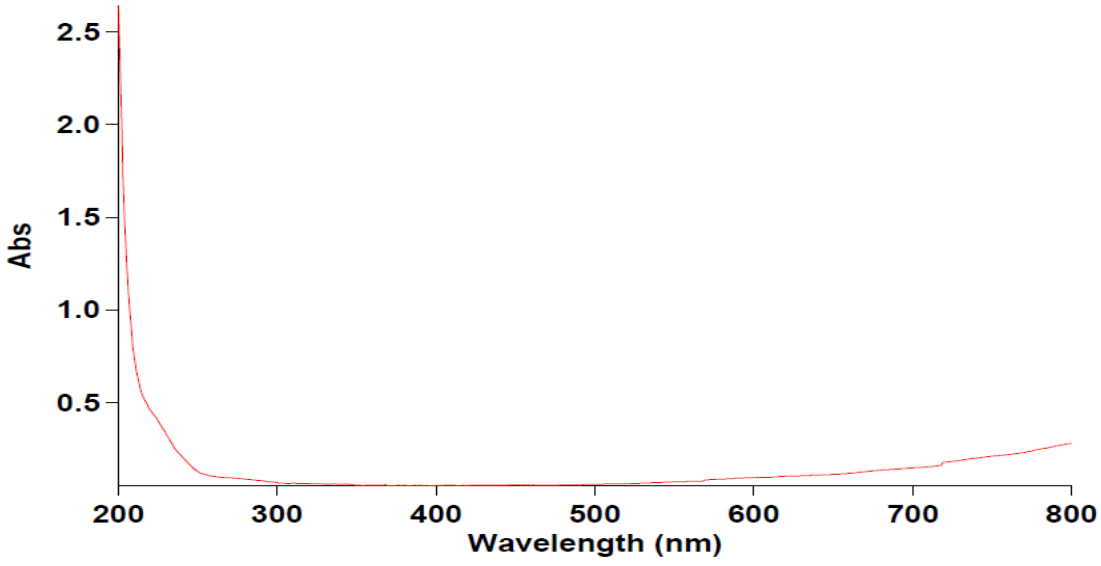
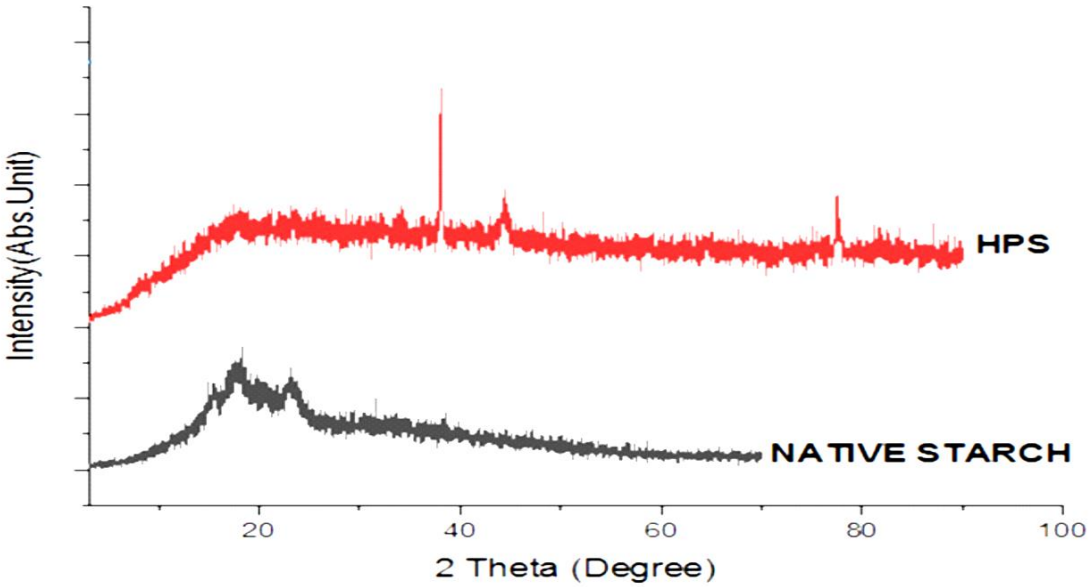


Figure 4: UV for Native soghum starch

ISSN No. 2454-6194 | DOI: 10.51584/IJRIAS |Volume IX Issue VII July 2024



Hps = Hydroxypropylated Starch

Figure 5: XRD for Hydroxypropyl and Native Starch.

The moisture content of the starches varied from 5.46 ± 0.00 to 4.82 ± 0.01 for native and hydroxypropyl starch respectively (Table 3). Overall of the moisture content of the starch (unmodified and modified) compared favourably with the minimum standard ≤ 15% for good quality starch according to European specification FAO (1995). The reduction in moisture content of the modified starch might be due to the chemical and heat treatment during the modification. High moisture contents of the granules could affect some parameters of the tablets like flow property, and the content uniformity. Low moisture content of the starch is suitable in formulations containing moisture sensitive drugs. The pH of an excipient is an important parameter for its suitability. Physiological activity of most preparations depends on pH (Gupta and Grasdalen 1989). The neutral pH of starches implies that when used in uncoated tablets, it may be less irritating to the gastrointestinal tract. The pH of native starch is of 7.00 ± 0.01, and hydroxypropyl starch is 7.29 ± 0.02 which is similar to maize starch (Table 3). The pH value is in good agreement with reported pH values for starch by several authors. (Samia *et al*, 2009 ; Seemal, 1997 ; Raquel *et al* ; 2002 ; Aspinall *et al*, 1995).

Water holding capacity of the starches ranges from 28.35 ± 0.20 and 33.25 ± 0.01 for native, and hydroxypropyl respectively (Table 3). The increase in water holding capacity for the modified starch could be as a result of alteration of the starch during chemical modifications. Consequently, the water holding capacity of starch samples studied agreed quite well with those of native and modified starches reported by medcalf and Giller (1965) using similar technique Leach *et al*., 1959) observed that hypochlorite oxidation is a mean for weakening the internal structure of the granules. This makes the starch to be more susceptible to water molecules. Water holding capacity can also be attributed to starch structure and the nature of the functional group present (hydrophilic and hydrophobic) (Kaur, *et al*., 2009).The relative viscosity of the native starch was 1.70 ± 0.08 and 2.76 ± 0.00 for hydroxypropyl starch. Viscosity play important role in food and pharmaceutical processing. The viscosity of the modified starch is higher than the unmodified starch; this suggests that modification altered the physical nature of the native starch. According to Pablyana *et al*. (2007), chemical modification by oxidation increases the uronic acid content 3.7% to 3.8% which further increases solubility, water holding capacity and viscosity. The presence of several –OH groups in starch creates an interaction with neighboring hydrocolloids which leads to higher viscosity of starch solution (Adeyanju and Lajide,2012).

Different types of starches have been reported to have different morphologies ranging from oval, spherical, polygonal to irregular shapes. (Lawal, 2004; Kunle *et al*; 2003, Lawal *et al*., 2003). The surface morphology of starch is characterized by using scanning electron microscope (SEM). The native starch with 750x, 500x and 320x magnifications shows that the granules have spherical shape and were mostly compacted together (Plate2). While, hydroxypropyl starch 750x, 500x and 320x magnifications indicates that they also have

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spherical shapes but the granules compacted in a clustering shape (Plate 1). This clustering process might have enlarged and disrupted starch granules occurring during modifications.

FTIR spectroscopy has been widely used in carbohydrate research as it provided a simple method of obtaining direct information on the chemical changes that occur during various chemical treatment (Adeyanju *et al*.,2016; Ristolainen *et al*; 2002). Hydroxypropyl functional groups are introduced to the starch which contains free hydroxyl groups of starch. The insertion of these hydroxypropyl groups to starch molecule structure was confirmed through FT-IR spectroscopy. The broad band located within the region of 3800-3200cm^{-1} (OH), 1427cm^{-1} (-COO-) 1227cm^{-1} (C-O). The bond at 1162cm^{-1} and 2942cm^{-1} represent C-O stretching as well as C-H stretching. The frequencies at 1625cm^{-1} indicates C-O stretching and amide [N-H] bonding peaks at 1162 and 1150cm^{-1} are due to C-O stretching frequency. The peak at 3300cm^{-1}-3400cm^{-1}caused by (-OH) stretching was also seen to decrease in carbonyl content (Figure 1). During hydroxypropylation processes, the starch-starch interactions- in the granules are weakened by the introduction of hydroxypropyl group's which are bulkier than hydroxyl. This facilitates the access of water to amorphous area enhancing the water holding capacity (Figure 2).

UV-Vis spectroscopy was one of the first physical methods applied to quantitative analysis and the determination of molecular structures (Figure 3 and 4). The majority of the bands occurred between 250 and 1500cm-1, which is consistent with the band information commonly reported for starch in the literature (Almeida *et al*., 2010). Random orientation of a crystal lattice in a powder sample causes the X-ray to scatter in a reproducible pattern of peak intensities at distinct angles (θ) relative to the incident beam (Leon *et al.*, 2009). For the native starch, the crystallinity is presented by diffraction peaks well-defined at $15^{0,}$ 19.3^{0}, 23^{0}, and at 17^{0} which were attributed to an A-type crystal polymorph structure for the modified starch, the crystallinity is presented by diffraction peaks well-defined at1 5^{0}, 18^{0}, 23^{0} 37^{0}, 43^{0}, and 77^{0}, 82^{0}. More crystal peaks were formed, and therefore, the modifications improved the crystal region more than the amorphous region of modified sorghum starch (Figure 5). The flow properties of the granules were all very good, they had low angles of repose, high flow rate due to lower cohesive forces, hence good flow and better tabletting properties (Musa, 2002; Martin *et al,* 1983; Musa, 1999). This might be due to increase in densities with increase in binder concentration, the lower the density of a material the poorer the flow properties. The flow properties of the granules also indicate that flowability decreases with increase in size of the angle of repose of granul. Both granules exhibited similar characteristics. Low bulk and tapped densities and therefore lower value of Carr's consolidating indices, these properties increased with increase in disintegrant concentration. The granules show that there was decrease in granule bulk and tapped densities with increase in concentration of binder (Table 4). Flow properties have been reported to increase as binder concentration increased from low to high (Zayic and Buckton, 1990).

CONCLUSION

Hydroxypropyl starch obtained from sorghum cereal (Sorghum bicolar) was compared with maize starch BP as a potential pharmaceutical excipient. Hydroxypropylated starch improved freeze-thaw stability, gel stability, storage stability, and digestivity and reduced gelatinization temperation, high levels of peak viscosity. Chemically modified starch improved physicochemical proterties effectively.

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