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Carboxymethylation, Characterization and Potential Application of Sorghum (Bicolar) Starch in Pharmaceutical Formulations

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Abstract: The work presented herein discusses the carboxymethylation of sorghum starch which improved its physicochemical properties for a potential pharmaceutical application as an excipient in tablet formulations. Sorghum (*sorghum bicolor) starch* was extracted from sorghum cereal using 0.075% (w/v) sodium metabisulphite and it gave a yield of about 80.4% on dry weight basis. The starch was chemically modified via carboxymethylation and characterized. SEM of the native starch showed irregular shape while the modified starch has regular shape and fibrous long distort shape.The X-ray Diffractogram revealed that the native and modified starches are completely amorphous in nature.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 carboxymethylation there were introduction of new functional groups, 1800-1500cm^{-1} (-COO-) and 1606-1632cm^{-1} (OCH_2COONa) respectively.The physicochemical properties investigated includes:The moisture content was obtained for the Native Starch (NVS) (5.46±0.00), and Carboxymethyl Starch (CMS) (5.23±0.00). Overall the moisture content of the starch (unmodified and modified) compared favourably with the minimum standard ≤ 15% for good quality starch. The pH of NVS is (7.00±0.01), CMS (6.64±0.02). They are all similar to maize starch. Relative viscosity of NVS is (1.70±0.08), CMS (2.30±0.08). Water holding capacity was obtained for NVS (28.35±0.20), CMS (39.35±0.20). Modified starch improved in water holding capacity.These physicochemical analyses have shown that modification improved the physical nature of the native starch.The flow properties of the granules show low angles of repose, high flow rate due to lower cohesive forces, hence good flow and better tabletting properties. The tablets were evaluated for quality control such as weight, friability, crushing strength, diameter, thickness, disintegration, in vitro dissolution, and drug excipient interactions.

Keywords: Starch,carboxymethylation, SEM, XRD, FTIR, Excipient.

1 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 [1]. 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 and lubricant [2] . Unfortunately, it is not suitable for direct compression formulation due to its poor compressibility and flow characteristics. There is a need therefore to impart these properties requisite for direct compression by modifying the starch. Starches are used extensively in pharmaceutical industries as disintegrants, binders and lubricant in drug formulations.[3]. The use of cassava and yams starches as tablet disintegrant had been studied [4].They showed that all tablets made with the starches show a decrease in disintegration time with increasing concentration. However, this behavior could vary depending on type of other ingredients present in the formulation. [2]. Unmodified starches have limited usage due to their inherent weakness of hydration, swelling and structural organization[1]. Modified starches on the other

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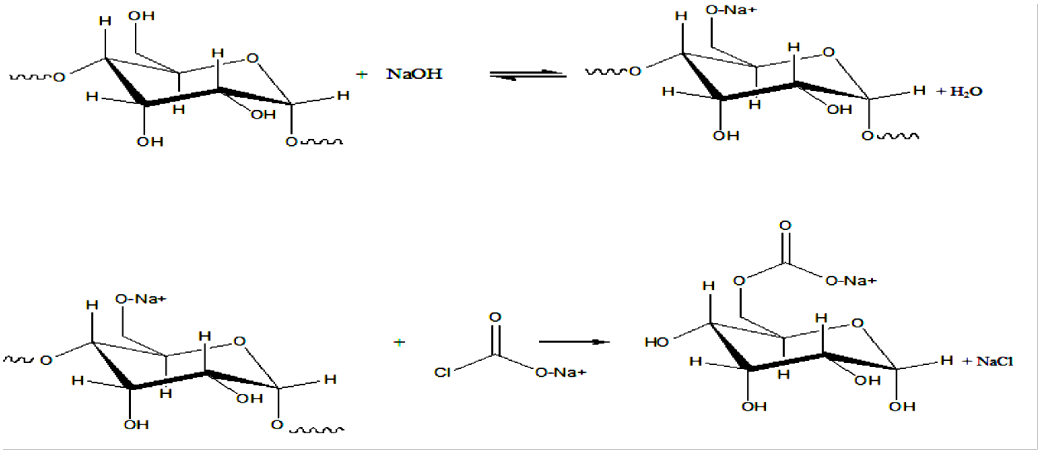
hand are native starches that undergo some changes by chemical, physical and or biotechnological means. Modifications on starches are carried out to enhance some physicochemical properties like viscosity, texture, stability, flow ability among many desired functional properties for many industrial applications.[1].Chemically Modified starches and Gums in various forms (cross-linked, hydroxypropylated, acid-thinned, carboxymethylated, and pre-gelatinized) have been used to give the tablets a range of properties. For example, hydroxypropylation and cross-linking of starch increased the compaction and tablet [5,6,7,8,]

carboxymethylation, the hydroxyl groups of linear amylose and branched amylopectin molecules of starch granules are derivatized to form carboxymethyl starch ethers. Since carboxymethylation occurs without degradation of starch molecules, they are excellent thickeners and have many applications in industries [6,7,8].



2 Materials and Methods

Extraction of Starch from Sorghum Cereal After inspection,sorghum cereal 2kg was thoroughly washed and all extraneous materials were removed 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 was then poured away while the sedimented starches was collected and a suspension of the starch in distilled water was 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 at40ºC. The dried starch lumps was size reduced to a fine powder using a blender. Crushing force and freeze-dried pre-gelatinized starch gave high crushing force and fast disintegration of the tablet. For example, compared to native starches, pre-gelatinized and carboxymethylated. (Adeyanju et al., 2018c). Carboxymethylation is used to improve aqueous dispersibility and cold storage stability of starch paste. In

Carboxymethylation of Starch

Carboxymethyl starch was prepared by dissolving chloroacetic acid (94.5g) in isopropyl alcohol (700ml), and neutralized with aqueous sodium hydroxide. The mixture was stirred vigorously. Subsequently air-dried starch (91.3g) and dry NaOH were added. The mixture was kept at 40 0C for 4h. After carboxymethylation, the mixture was neutralized with glacial acetic acid and was washed several times with 80% aqueous methanol, and was dried at 60^0C.

Determination of Physicochemical Properties of starch

Determination of Moisture

The moisture content of the starch was determined according to [9] method. 5g of the starch samples was accurately weighed into evaporating dish and dried in an oven at 105ºC for 3hours. The samples 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

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 [1] 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 [10]. A flow time (seconds) of distilled water was measured by filling the viscometer tube (held at 30ºC 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: $Relative\ viscosity\ (30oC) = \frac{[T-To]}{[To]}$

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

Samples were 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). FTIR of samples was determined using disc on a Nicolet 510 FTIR spectrophotometer. (California, USA). XRD of sorghum starch and the hydroxypropyl starch were studied using an X-ray diffraction pattern (XPERT pro, Netherlads). Thermal readings are based on the effects . UV Vis analysis was carried out using a spectrophotometer UV-1601 PC (Shimadzu Corperation, Japan).

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.

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

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).

3 Results and Discussions

Table 1: Identification of Sorghum Starch.

Identification Test	Native starch	Carboxymethyl 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
Carboxymethyl Starch	60	16.12 ± 0.10
	70	21.20 ± 0.20
	80	57.52 ± 0.02

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

Table 3: Physicochemical Properties of Sorghum Starch and its Derivative.

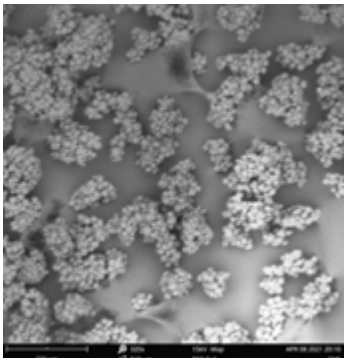
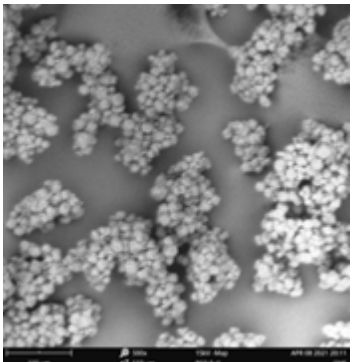
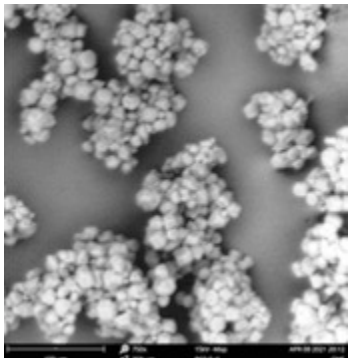
Type	Moisture	pH	Water Holding capacity	Relative viscosity	Emulsion capacity
Native Starch	5.46 ± 0.00	7.00 ± 0.01	28.35 ± 0.20	1.70 ± 0.08	25.86 ± 0.01
Carboxymethyl starch	5.23 ± 0.00	6.67 ± 0.02	39.35 ± 0.21	2.30 ± 0.08	31.32 ± 0.00

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

Table 4: Flow Properties of Paracetamol Formulations containing Sorghum Starch Granules.

Parameters	Native Starch	Carboxymethyl Starch	Maize Starch BP
Flow Rate (g/sec)	6.99 ± 0.15	7.50 ± 0.00	10.13
Tapped Density (g/ml)	0.49 ± 0.10	0.48 ± 0.19	0.48
Bulk Density (g/ml)	0.42 ± 1.10	0.42 ± 0.30	0.49
Carr's Index (%)	14.8 ± 0.04	12.50 ± 0.17	15.18
Hausner's Ratio	1.17 ± 0.19	1.14 ± 1.05	1.18
Angle of Repose (%)	37.00 ± 1.11	28.00 ± 0.01	32.00

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

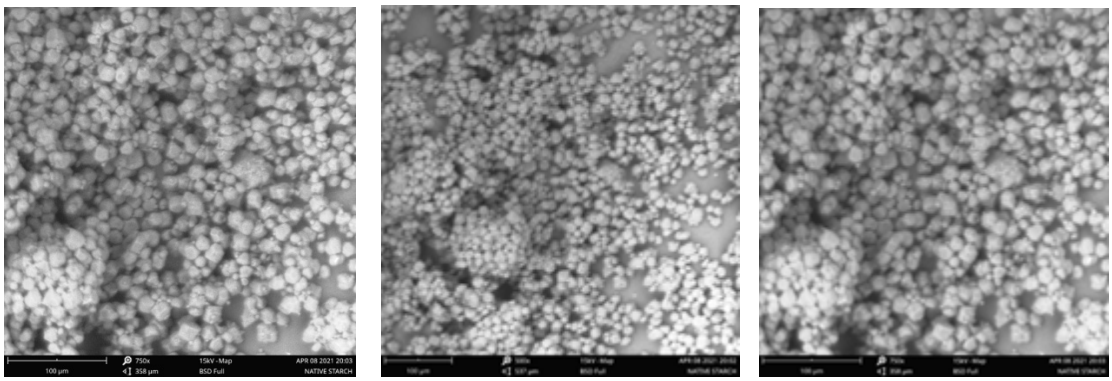


Plate 2: SEM for Native Starch (320x, 500x and 750x).

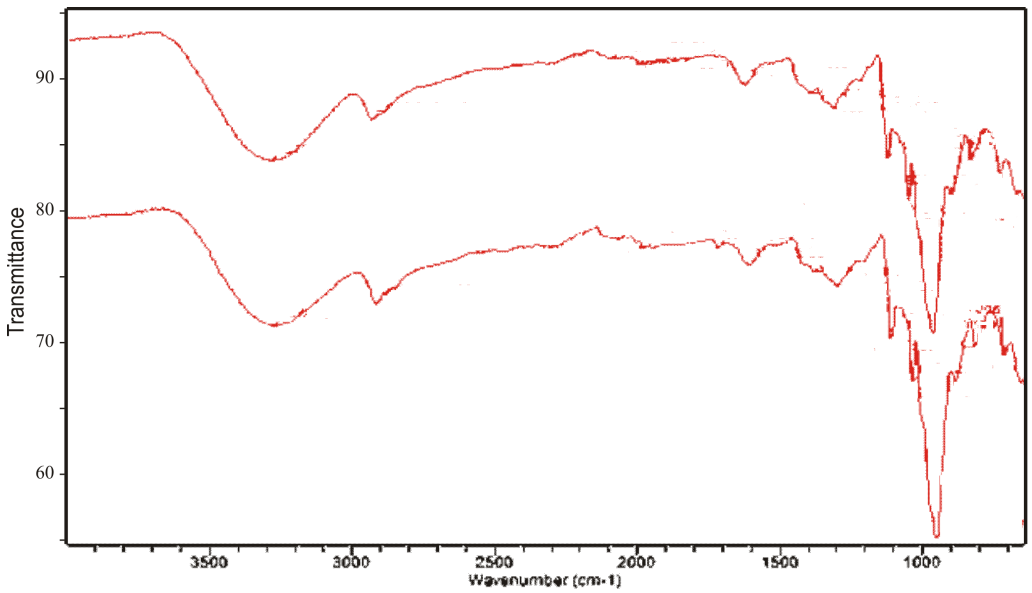
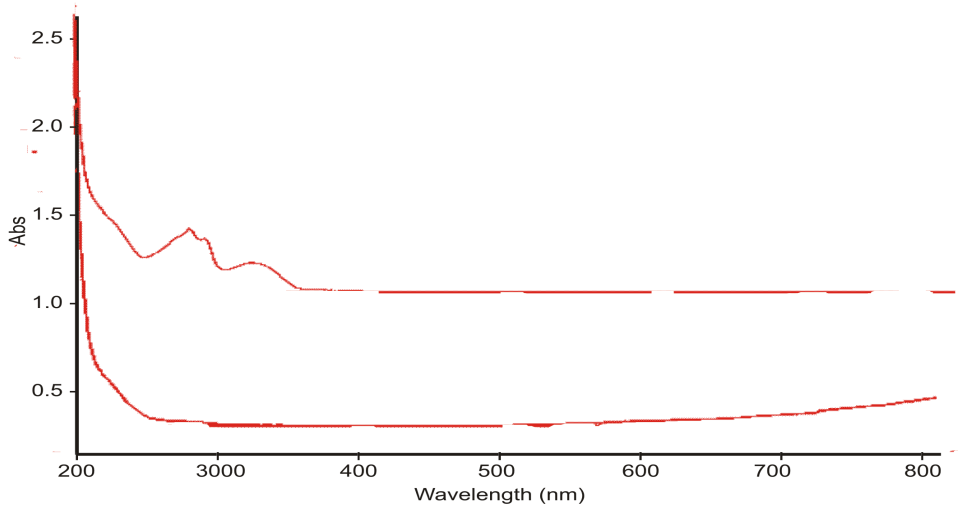


Fig. 1: FTIR for Carboxymethyl and Native Starch.



ranges from 28.35 ± 0.20 and 39.35 ± 0.20 for native, and caborxymeyhyl 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 [2] using similar technique [1] observed that hypochlorite oxidation is a mean for

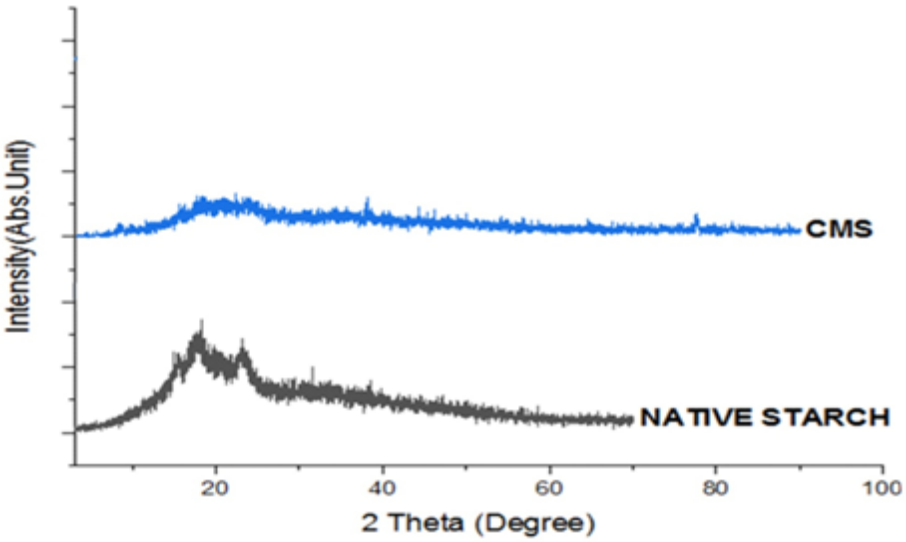


Fig.3: XRD for Carboxymethyl and Native Starch.

3 Discussions

Moisture content for all the materials must not exceed the 15% limit specified by the BP 2002 for starches. The moisture content of the starches varied from 5.46 ± 0.00 and 5.23 ± 0.00 for native and carboxymethyl starch respectively (Table 3). Overall, the moisture content of the starch (unmodified and modified) compared favourably with the minimum standard ≤ 15% for good quality starch according to European specification [10]. The starch modified starch moisture content decreased remarkably. The reduction in the moisture content might be due the chemical and heat treatment absorbed during the modification.High moisture contents of the granules which 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 important parameter in determing its suitability and physiological activity of most preparations depends on pH [11]. 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 carboxymeyhyl starch is of 6.64 ± 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 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) [15].

The relative viscosities of the starch are 1.70 ± 0.08 native and 2.30 ± 0.08 caborxymeyhyl starch (Table 3). Viscosity plays 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 [16], 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.[17]. Different types of starches have been reported to have different morphologies ranging from oval, spherical, polygonal to irregular shapes. [18,16]. 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 (Plate 2). While, carboxymethyl starch with 750x, 500x and 320x magnifications indicates that they also have 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[19].Carboxymethyl functional groups are introduced to the starch which contains free hydroxyl groups of starch. The insertion of these carboxymethyl 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 (Figure 1). The peak at 3300cm^{-1}-3400cm^{-1}caused by (-OH) stretching was also seen to decrease in carbonyl content. During carboxymethylation processes, the starch-starch interactions- in the granules are weakened by the introduction of carboxymethyl group's which are bulkier than hydroxyl. This facilitates the access of water to amorphous area enhancing the water holding capacity.UV-Vis spectroscopy was one of the first physical methods applied to quantitative analysis and the determination of molecular structures.The majority of the bands occurred between 250 and 1500cm-1 (Figure 2), which is consistent with the band information commonly reported for starch in the literature [18].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 [22,23].For the native starch(Fig 3) 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}.(Fig 3) 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 [13,2]. 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 granules [21]. 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[20]

4 Conclusions

Carboxymethyl starches obtained from sorghum cereal (Sorghum bicolor) were well compared with maize starch BP as a potential pharmaceutical excipient.Carboxymethylated starches have enhanced water solubility, aqueous dispersibility and cold storage stability of starch paste, thus giving tablets propensity to disintegrate fast. Chemically modified starch has improved physicochemical properties effectively.

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