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RESEARCH

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Sucrose- and formaldehyde-modified native starches as possible pharmaceutical excipients in tableting

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Abstract

Background: Starches have been shown to be important across various disciplines such as the pharmaceutical industries, food industries and also paper industries. Starch is basically a mixture of polymers consisting of α-D-glucose as the monomeric unit. The goal of this study is to modify the native starches which were obtained from *Zea mays*, *Triticumestivum* and *Oriza sativa* through cross-linking (using sucrose and formaldehyde at different concentrations) and also to assess the utilizability of the modified starches as potential excipients [binder] for tableting of paracetamol.

Results: Maize and rice starches cross-linked with 2.5% sucrose gave the least percentage moisture content. The batches cross-linked with 40% formaldehyde showed the highest moisture content. The densities (bulk and tapped) of maize wheat and rice starches showed a reduction with the increasing concentration of the cross-linking agent for sucrose, which is the reverse case for formaldehyde. The different concentrations of sucrose and formaldehyde cross-maize, wheat and rice starches had pH values between 4.50 and 5.52. The onset and end set of the glass transition temperatures were varied for all the starches modified with formaldehyde. The melting peak temperatures obtained indicated that the formaldehyde-modified rice starch had significantly lower melting temperature than those of wheat and maize starches.

Conclusions: This study reveals that various concentrations of sucrose and formaldehyde had some influence on the properties of the native starches and resulted in the production of new starch motifs with improved or new functionalities suitable for use as drug excipients in tableting.

Keywords: Cross-link, Starch, Polymer, Sucrose, Formaldehyde

Background

Starches and their pharmaceutical uses have been studied extensively by many researchers. Starch is found in just about all green plants in the form of a carbohydrate reserve. It is a natural polymer which is generated from carbon dioxide and water by the photosynthesis in plants (Jankovi 2010). Starch is the chemical storage form of solar energy (Kolawole et al. 2013). It is basically a mixture of polymers which consists of α-D-glucose as the monomeric unit. Two types of starch polymers exist: a mixture of linear polymers (amylase) and a mixture of branched polymers (amylopectin). These polysaccharides exist in the plant as granules that are insoluble in cold water (Pérez and Bertoft 2010). The major intermolecular forces giving rise to the structure and integrity of the starch system are the hydrogen bonds between these units and water. Starch is highly present in staple foods, e.g., potatoes, maize, wheat, rice and cassava

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(Umida-Khodjaeva 2013), as it is the commonest carbohydrate form in human diet.

Starches (most especially modified starches) have widespread use in pharmaceutical, food and paper industries, and they contribute to the quality, appearance and structure of the food item (Hoover et al. 2010; Agyepong and Barimah 2018). Pharmaceutically, they are used as binders and diluents, in paper industries as binder for laminates and in the corrugating process, as surface sizing and coating agents (Garcia et al. 2020). Also, in food industries, starches and their modified forms have been used in canned, hot-filled, dry mix, baked or frozen foods, pet and infant foods, snacks and breakfast cereals, meats, dairy products, etc. ().

Cross-linking is a processing method in which small amounts of compounds, which have the ability to react with more than one hydroxyl group, are incorporated to starch polymers. Cross-linking of starch is a highly popular method employed in polysaccharide chemistry (Ayoub and Rizvi 2009; Ibrahim et al. 2018). Degradation of starch can be done by pre-gelatinization (Alabi et al. 2018). Gelatinization employs the application of heat and water to disrupt the granular and crystalline structures of starch (Adetunji 2019). A lot of biopolymers like starch are hydrophilic, and some are soluble in hot water. Native starch is incompatible with some hydrophobic polymers and hence cannot be used directly (Zhang et al. 2015).

Cross-linking has shown several effects on the physical properties of starch by varying its properties, and this is due to the fact that native starch does not usually possess the preferred properties (Shah et al. 2016; Ibezim and Andrade 2006; Thanh-Blicharz et al. 2021). The use of highly cross-linked starch amylose matrices has been described in the formulation of controlled release oral solid dosage forms (Elgaied-Lamouchi et al. 2020). Therefore, pharmaceutically, starch is a vital ingredient and no amount of study on its uses can be exhaustive. Changing starch so that it obtains the characteristics that deviate from the native starch is known as 'modification of starch' and the products are called 'derivatives.' There have been various modifications of starch granules, e.g., blending (Neelam et al. 2012; Sapsford et al. 2013). It does not matter whether or not change occurs in a physical or bio-chemical manner (Piriyaprasarth et al. 2010). The chemical modification of starch has proven to affect the digestion rate and level in the small intestine (Haub et al. 2010; Shen et al. 2019; Siroha and Sandhu 2018).

Excipients are defined as substances that are included in a drug delivery system (aside the active drug), and have been appropriately evaluated for safety. Pharmaceutical excipients are further explained as additives which are used in converting compounds which are pharmacologically active to pharmaceutical dosage forms which are appropriate for administration to patients (Persson and Alderborn 2018; Mohammed 2017). Pharmaceutical excipients should be stable physically and chemically, non-toxic, available commercially, feasible economically and possess pleasant organoleptic properties (Allamneni and Suresh 2014).

Starch is a commonly used excipient due to its relatively low cost and versatility (Muazu et al. 2012). Previously, native starches were used in solid dosage forms (as binders and disintegrants), but their utilization is restricted due to poor flowability. Nowadays, modified or cross-linked starches are mostly preferred, e.g., pregelatined starch (Mohammed 2017). Modification enhances the starch quality for use in pharmaceuticals as drug binders and disintegrants (Adjei et al. 2017). Modified rice starch, starch acetate, etc., are now established in pharmaceutical industries as multifunctional excipients (Lawal 2019). Different forms of modified starches have also been analyzed for maintaining the release of drug for improved compliances (Elgaied-Lamouchi et al. 2021). Acid-hydrolyzed modified starch of *Plectranthus esculentus* has been reported to produce fillers/binders that can be directly compressed and can serve as alternatives for MCC PH 101 (microcrystalline cellulose) in modern tablet formulations (Khalid et al. 2016). A study has shown that cross-linked *Cyperus esculentus* (tiger nut) starch and sodium alginate have the ability to sustain ibuprofen release making useful tool for targeted drug delivery, especially to the lower GIT (Olayemi et al. 2020).

The aim of this study is to modify the native starches which were obtained from *Zea mays*, *Triticumestivum* and *Oriza sativa* through cross-linking (using sucrose and formaldehyde at different concentrations) and also to assess the utilizability of the modified starches as potential excipients [binder] for tableting of paracetamol.

Methods

All the methods used were developed in-house except where indicated otherwise.

Extraction of starch

The maize [*Zea mays*], wheat [*Triticumestivum*] and rice [*Oriza sativa*] grains were procured from Nsukka Central Market, Enugu state, Nigeria. The grains were identified by Mrs. Onwunyili Amaka at the Department of Pharmacognosy and Traditional Medicine, Faculty of Pharmaceutical Sciences, Nnamdi Azikiwe University Awka, Anambra state, Nigeria, with the voucher number (PCG/474/A/052). The grains were then washed and soaked separately in distilled water for 24 h. After fermentation, they were grated (using an aluminum grater) and the resulting marsh was macerated for 24 h in distilled water and sieved with a fine nylon sieve, and the slurry allowed to stand undisturbed for ten hours [10 h]. The supernatant was then decanted and

further washed with purified water to remove any soluble impurities that may be present. The final slurry was kept to stand for another 10 h, and then, it was oven-dried at 60 °C for 2 hours and milled. This procedure was carried out on the three sources of starch.

Confirmatory test

This was done according to the British Pharmacopeia (Pharmacopoeia 2002) to confirm the starches. A 1-mg quantity of each starch was boiled with 50 ml of distilled water and then cooled. Mucilage was formed, to which 1 ml of iodine solution was added and observed.

Defatting of starches

This was carried out with aqueous methanol [85%] using a Soxhlet extractor. A 200-g quantity of *Z. mays* starch was extracted for 24 h in a Soxhlet extractor using 85% v/v aqueous methanol as solvent. The defatted starch was oven-dried and then pulverized to reduce its particle size with the aid of a pestle and mortar, and the resulting powder was stored in well-dried plastic containers. The same procedure was repeated for *T. aestivum* and *O. sativa* starches, respectively.

Cross-linking of maize starch

A 20-g dried maize starch was treated with 30 ml of ethanol to make it reactive. The slurry was then filtered to get back the starch residue. A slurry of the reactive starch was made in an alkaline medium using 0.5% NaOH and different concentrations of sucrose and formaldehyde used as the cross-linking agents [2.5, 5,10,20,40%]. The mixture was kept at a temperature of 40 °C for 30 min with continuous stirring. Subsequently, the pH of the mixture was further adjusted to about 5.0 with 0.1 N HCl after which it was washed and dried to recover the cross-linked maize starch. After drying, the particle size of the maize starch was reduced by passing through a 0.17-mm mesh. This procedure was repeated for both *T. aestivum* and *O. sativa* starches.

Starch powder characterization

Moisture content determination

One-gram quantity of the starch was heated in an oven at 100 °C for 3 h and the weight of the starch compared with the original weight, prior to heating. This process was continued until a constant weight was obtained. This final weight was noted and used to calculate the percentage moisture content.

The following equation (Onochie et al. 2020) was used to calculate the moisture content of the sample:

$$\text{Percentage of moisture in a sample} = \frac{100\left(\text{Wet sample weight} - \text{Dried sample weight}\right)}{\text{dried sample weight}}.$$

Bulk density determination

A 20-g starch powder was poured through a short glass funnel into a 100-ml graduated cylinder.

The volume occupied was then measured and the bulk density determined. The bulk density was taken for the average of three determinations. This was repeated with the two remaining starches.

Tapped density determination

A 20-g starch powder was poured into a graduated 100-ml measuring cylinder and then dropped 20 times from 2.5 cm height onto a wooden bench. The final volume after "tapping" was recorded and was used to calculate the tapped density. This was repeated for the other two starches.

Determination of the effect of electrolyte [NaCl] on swelling behavior

Ofner and Schott (1986) method was used with some modifications: About five different concentrations of NaCl [2.0 N, 1.0 N, 0.5 N and 0.1 N] were carefully added to the starch samples in a 10-ml measuring cylinder and the NaCl solution was allowed to get absorbed by the starch after which the unabsorbed solution was decanted. The product was left to stand at room temperature for 48 h. This was done for each of the cross-linked starches which were prepared with varying concentrations of cross-link agents [sucrose and formaldehyde]. The changes in volumes of the starches were recorded and the swelling extents calculated after 48 h.

pH determination

This was done on each formulated batch by inserting a pH meter into the slurry of the product and checking for the stabilization of the pH reading before taking the results.

Viscosity

A 1% gel was prepared by dispersing 1 g of starch in 20 ml of distilled water. The starch dispersion was heated using a water bath at a temperature of about 80–100 °C for 3 min while being continuously stirred to gelatinize. The gelatinized starch was raised up

to 100 ml with distilled water and further stirred to obtain complete homogeneous mixture. A part of the starch solution was then poured into a U-tube viscometer and its viscosity determined. This test was done in triplicates, and the results were recorded. The viscosity determination was carried out at room temperature.

Differential scanning calorimetry (DSC)

Method used by Adejumo et al. (2021) was used with some modifications. Investigations of the thermal transitions of the starch samples were done using a heat flux calorimeter (DSC-204 F1 Phoenix®, NETZSCH, 6.240.10 apparatus, Germany), which was calibrated using an indium of high-purity standard. A 1-mg starch sample was weighed into a high-temperature nimonic steel pan and a large quantity of water was added to yield a ratio of approximately 1:3. The pan was sealed, equilibrated (at 25 °C for 3 h) and also heated at a rate of 3 °C/min, from 25 to 220 °C. The transition temperatures were the onset gelatinization temperature (To), peak temperature (Tp) and also the conclusion temperature (Tc). The enthalpy of gelatinization was related to the dry mass of the sample.

Data analysis

The data were analyzed using GraphPad Prism software version 5.0. The inferential statistics used were analysis of variance (ANOVA), Bartlett's test for equal variances and Bonferroni's multiple comparison test. *P*-values < 0.05 (at 95% Confidence Interval) were taken to be significant.

Results

Yield of extractions

The percentage weight of starch extracted from *Zea mays* grain, *Triticumestivum* and *Oryza sativa* is 48.3% w/w, 27.5% w/w and 17.3% w/w, respectively. The result of the starch confirmatory test showed that product from *Zea mays, Triticumestivum* and*Oryza sativa* were positive to iodine solution.

Properties of cross-linked starches

Percentage moisture contents

From the result in Table 1, maize and rice starches cross-linked with 2.5% of sucrose gave the least percentage moisture content. Wheat starch, combined with 10%, 20%, 40% sucrose and 2.5% formaldehyde, also had 20% moisture content, while, in all the starches, the batches cross-linked with the 40% formaldehyde had the highest moisture content.

Bulk and tapped density

The bulk and tapped densities of maize, wheat and rice starches, as presented in Table 2, showed a decrease with a raise in the concentration of the cross-linking agent for sucrose, while in formaldehyde, reverse was the case in some cases. The bulk and tapped densities of maize decreased as concentration of the cross-linking agent for sucrose increases, while in formaldehyde, the reverse is the case. The sucrose cross-linked maize starch had greatest bulk and tapped density of 25 and 35 g/ml, respectively, while formaldehyde cross-linked also had highest bulk and tapped density of 27 and 40 g/ml. The 20% sucrose cross- linked maize starch has the highest Carr's index of 42.4 and Hausner's ratio of 1.74, while 40% formaldehyde cross-link had highest Carr's index of 32.5 and Hausner's ratio of 1.48 which showcase poor flowability of the starch powder.

Table 1 The moisture content determination

Cross-linking agent	Comparative % moisture content		
	Maize	Wheat	Rice
Native starch	30	35	25
2.5% sucrose	20	40	20
5% sucrose	40	40	40
10% sucrose	40	20	40
20% sucrose	40	20	40
40% sucrose	40	20	40
2.5% formaldehyde	40	20	40
5% formaldehyde	40	40	40
10% formaldehyde	40	40	40
20% formaldehyde	40	20	40
40% formaldehyde	50	40	40

The bulk and tapped densities of wheat starch reveal that 40% sucrose cross-linked wheat starch powder had the highest bulk and tapped density of 37 g/ml and 55 g/ml, respectively. Similarly, the 2.5% formaldehyde cross-linked wheat starch powder had the least bulk and tapped density of 9 g/ml and 13 g/ml. The bulk and tapped density of rice starch powder was significantly influenced (p value < 0.05) by the moisture content as the bulk density reduced greatly with a rise in moisture content. The result revealed that 40% sucrose rice cross-linked starch had the highest bulk density of 39.5 g/ml and 10% formaldehyde cross-linked rice starch powder had better Carr's index of 11.8 and Hausner's ratio of 1.13. Also 5%, 10%, 20% and 40% formaldehyde cross-linked rice starch powder with Carr's indices 12.2, 11.8, 12.8 and 12.5 and Hausner's ratio of 1.14, 1.13, 1.15 and 1.14, respectively, had good flowability.

From the results, further physicochemical profiles of the different cross-linked starches are shown in Table 3. The percentage swelling of the native starches of maize, wheat and rice is higher than the cross-linked derivatives. The highest swelling for the cross-linked starches was

Table 2 The bulk and tapped densities of the cross-linked three starches

Cross linked agent	Bulk density [g/ml]			Tapped density [g/ml]			Carr's compressibility index [%]			Hausner's ratio		
	Maize	Wheat	Rice	Maize	Wheat	Rice	Maize	Wheat	Rice	Maize	Wheat	Rice
Native Starch	38	47	28	44	52	43	13.6	9.6	34.9	1.16	1.12	1.54
2.5% sucrose	25	32	21.5	35	45	34	28.6	29	36.8	1.40	1.41	1.58
5% sucrose	21	19	27	30	23	35	30.0	17.4	22.9	1.43	1.21	1.30
10% sucrose	20	35	16	32	50	26	37.5	30	38.5	1.60	1.43	1.63
20% sucrose	23	24	29	40	32	35	42.5	25	17.1	1.74	1.33	1.21
40% sucrose	11	37	39.5	15	55	47	26.7	32.7	16	1.36	1.49	1.19
2.5% formaldehyde	18	9	19	22	13	24	18.2	30.8	20.8	1.22	1.44	1.26
5% formaldehyde	22	18	18	31	23	20.5	29.0	21.7	12.2	1.41	1.28	1.14
10% formaldehyde	20	20	15	24	25	17	16.7	20	11.8	1.20	1.25	1.13
20% formaldehyde	24	23	15	32	33	17.2	25.0	30.3	12.8	1.33	1.43	1.15
40% formaldehyde	27	25	14	40	37	16	32.5	32.4	12.5	1.48	1.48	1.14

Table 3 Further physicochemical profiles of the cross-linked maize, wheat and rice

Cross linking agent	% Swelling			pH			Viscosity [CP]		
	Maize powder	Wheat powder	Rice powder	Maize starch	Wheat starch	Rice starch	Maize starch	Wheat starch	Rice starch
Native starch	40	58.3	49.5	6.12	5.84	6.27	150.0	152.0	149.0
2.5% sucrose	42	44	71	5.47	5.40	5.01	143.2	145.3	150.0
5% sucrose	41	54	68	5.52	5.35	5.28	145.6	143.0	147.0
10% sucrose	47	44	72	5.12	5.41	5.23	146.0	146.0	148.0
20% sucrose	48	63	71	5.47	5.40	5.03	148.4	148.0	152.0
40% sucrose	42	42	72	5.50	5.47	5.13	152.0	149.0	149.7
2.5% formaldehyde	76	44	72	5.35	5.47	5.11	142.0	147.0	145.0
5% formaldehyde	66	62	72	5.05	5.53	5.10	146.5	147.5	147.0
10% formaldehyde	56	64	75	4.77	5.26	5.04	149.0	145.0	148.0
20% formaldehyde	48	43	70	5.18	5.50	4.50	151.0	150.0	146.5
40% formaldehyde	44	46	72	5.54	5.13	4.74	150.7	149.2	149.4

observed in both sucrose and formaldehyde cross-linked rice starch, while the least swelling was observed in 5% and 40% sucrose cross-linked maize and wheat starches.

Hydrogen ion index (pH)

The different concentrations of sucrose and formaldehyde cross-linked maize, wheat and rice starches had pH values between 4.50 and 5.52. The 5% formaldehyde cross-linked wheat starch had the highest pH of 5.53, while 20% formaldehyde sucrose cross-linked rice starch had the lowest pH of 4.5. The pH of almost all the concentrations of sucrose and formaldehyde cross-linked maize, wheat and rice starches with cross-linked maize and rice had pH above 5, while the exception of 10%, 20% and 40% formaldehyde cross-linked maize and rice starch had pH below 5, respectively. The sucrose and formaldehyde cross-linked maize, wheat and rice starches had acidic pH between 4.50 and 5.55.

Thermal properties of cross-linked starches

As observed in Tables 4 and 5, the onset and end set of the glass transition temperatures [Tg] were varied for all the starches which were modified with either sucrose or formaldehyde. The energy changes [ΔH] for the glass

Table 4 Thermal properties of starches modified with formaldehyde

Parameter	Thermal property (value) per % Wheat						Thermal property (value) per % Maize						Thermal property (value) per % Rice					
	2.5%	5%	10%	20%	25%	40%	2.5%	5%	10%	20%	25%	40%	2.5%	5%	10%	20%	25%	40%
Various concentrations of the cross-linking agent used																		
A	42.70	39.0	42.0	28.90	43.40	34.70	38.5	37.6	39.6	33.3	38.4	40.6	23.4	28.8	30.16	29.57	31.4	24.5
B	39.00	48.5	41.60	30.40	69.50	50.10	41.4	43.2	44.6	55.1	47.3	45.9	32.7	35.5	31.27	32.15	38.1	25.1
C	5.37	8.21	2.35	6.47	42.29	14.06	5.58	11.47	19.39	27.83	23.5	7.13	20.12	18.19	15.23	8.61	10.27	13.87
D	300.1	304.5	310.6	299.50	284.30	297.10	291.1	297.6	302.3	297.6	298.8	298.2	173.2	184.2	196.8	224.5	239.7	266.7
E	− 0.39	− 0.119	− 1.007	2.15	− 1.43	0.14	0.97	1.02	1.04	0.34	0.73	0.64	− 4.97	− 5.87	− 7.34	− 2.17	− 1.29	2.26

KEY: **A** = Tg Onset temp (°C); **B** = Tg Endset temp (°C); **C** = ΔH (Delta Cp) (J/ (gk)); **D** = *Melting/EndothermicPeak Temperature (°C); **E** = Peak intensity (m/N/mg); **Tg** = Glass Transition; **ΔH** = Energy change

Table 5 Thermal properties of starches modified with sucrose

Parameter	Thermal property (value) per % Maize						Thermal property (value) per % Rice					
	2.5%	5%	10%	20%	25%	40%	2.5%	5%	10%	20%	25%	40%
Various concentrations of the cross-linking agent used												
Tg Onset temp (°C)	37.3	33.7	62.9	3.9	ND	40.8	47.0	28.1	22.3	17.9	14.7	10.8
Tg Endset temp (°C)	13.1	55.5	73.8	65.4	ND	29.8	50.4	40.7	37.2	31.9	27.6	19.5
Δ*H* (Delta Cp) (J/(gk))	0.294	16.55	4.96	163.30	ND	3.642	14.77	18.88	20.54	23.82	29.63	32.28
Melting/Endothermic (Peak Temp) (°C)	297.4	281.7	294.7	273.4	ND	215.1	239.3	209.1	187.1	188.5	274.1	222.1
Peak intensity (m/N/mg)	− 0.25	− 0.90	− 0.52	− 2.65	ND	− 0.52	− 2.20	− 3.65	− 2.25	− 3.81	− 3.20	− 3.90

KEY: **Tg** = Glass Transition; **ΔH** = Energy change; ND = Not determined

transition were also varied at the various concentrations of cross-linking agent used. In the sucrose-modified maize and rice starches (Table 5), the onset of transition occurred at approximately similar temperature except at 10% sucrose concentration where it was significantly much higher. The results showed that the ΔHs for the Tg were generally higher for the formaldehyde than the sucrose-modified maize starches except at 20% chemical agent concentration where the latter had significantly higher value (p value < 0.05). The melting peaks generally occurred at higher temperatures for the formaldehyde-modified maize starch than the sucrose-modified except at 2.5% chemical agent concentration where the reverse was the case.

A two-way ANOVA of the data shows that the concentrations of the cross-linking agent accounted for 99.83% of the total variations seen in the thermal properties tested with a p value < 0.0001. The effect is considered extremely significant.

Table 6 shows the effect of the thermal [DSC] treatment of the defatted and undefatted wheat, maize and rice starches as analyzed. For the defatted starch, the onset temperatures of the Tg were of the order: wheat › rice › maize, while those of the end set were: wheat › maize › rice. However, there was no significant difference in the thermal properties of the defatted and undefatted starches (p value > 0.05). The ΔHs, obtained for the defatted starches, were of the order: maize › wheat › rice with significant differences between the values obtained. However, the melting peaks were recorded at 292.9 °C, 285.2 °C and 287.5 °C for the defatted wheat, maize and rice starches, respectively, showing only slight differences. Considering the maize starch, both the onset and end set temperatures of the glass [Tg] as well as the energy change [ΔH] recorded were higher for the undefatted than the defatted.

Discussion

Native starch has limited applications due to the fact that it cannot exhibit the desired properties such the inability to withstand some conditions for processing, packing and compressibility. However, these limitations can be corrected by the modification of native starch and

Table 6 Thermal properties of defatted and undefatted starches

Thermal properties	Defatted starches			Undefatted starches		
	Wheat	Maize	Rice	Wheat	Maize	Rice
Tg Onset temp [°C]	40.3	31.0	36.4	37.2	35.6	31.8
Tg Endset temp [°C]	49.7	48.8	41.3	28.5	56.6	49.4
Δ*H* [Delta Cp][J/[gk]]	13.226	22.604	10.125	32.42	29.6	16.865
*Peak Temperature	292.9	285.2	287.5	279.5	284.7	282.2
Peak intensity [m/N/mg]	0.8362	0.9534	0.1582	1.041	1.041	1.256

Melting/endothermic Peak temperature [°C]

*Key: Tg = Glass Transition, ΔH = Energy change

the most commonly used method is the chemical modification (Okeke et al. 2021). More so, the use of specific moisture and temperature conditions can lead to alterations in the physicochemical properties of starch since a lot of physical modifications involve the use of water and heat (Senanayake et al. 2013).

Cross-linked maize and rice starch had the highest pore sizes which trap a huge amount of water, resulting in the highest moisture content. At 40% formaldehyde concentration, the moisture content of maize when treated with 40% formaldehyde is the highest as compared to wheat and rice. This demonstrates that formaldehyde treatment has a direct proportionate impact on maize starch, i.e., the percentage moisture contents fluctuated but typically increased as the quantity of cross-linker rose (Oladunmoye et al. 2014; Belibi et al. 2014). However, the variation in the concentration of formaldehyde treatment on rice showed a constant effect on moisture content. In all the starches, the batches cross-linked with the 40% formaldehyde had the highest moisture content. On the other hand, 2.5% sucrose gave a decrease in the moisture content of maize and rice, while 10, 20 and 40% sucrose gave a reduced effect in wheat starch. This shows that increasing the sucrose concentration has an inversely proportional effect on the moisture content of wheat starch. Enzyme activation and microbial multiplication may occur when there is a high moisture level. Low moisture content generally demonstrates a high level of stability during storage, protecting starches from mould formation and providing a high dry weight yield (Jubril et al. 2012). A moisture content of 12% or more will provide enough moisture for drug breakdown and microbial activity (Odeku et al. 2003).

The flow properties of powders are crucial in the assessment of the adequacy of a material as a direct compression excipient. Hausner index and Carr's percent compressibility are regarded as indirect ways of measuring the flow property of powder. The Hausner index measures inter-particle friction, whereas the Carr's index measures a material's capacity to reduce in volume. Hausner ratio which is higher than 2.5% signifies poor flow, Carr's index less than 16% signifies good flowability, while values more than 35% signifies cohesiveness. As the value of these indexes increases, there is a reduction in the flow of the powder and this increases the likelihood of producing tablets with more weights variation (Okunlola and Odeku 2011). All starches obtained from all the three sources had an Hausner's ratio less than 2 and Carr's index greater than 16% (except for 10%, 20% and 40% formaldehyde-treated starches). Wheat cross-linked with 5% sucrose, with Carr's index of 17.4, which indicates low flowability and chances of producing tablets with weight variation (Jubril et al. 2012).

Bulk, tapped and true densities are usually the measured density values, which are also used to analyze the major properties of powders. Bulk density gives details on the volume occupied by the inter-granular spaces, inner and external pores of the solids. It indicates the overall degree of packing in a specific volume, or coarseness of starch sample. Tapped density is referred to as the density after tapping or vibration. From the observations in Table 2, the bulk densities of maize reduced with a raise in the concentration of sucrose but increased with an increase in the concentration of formaldehyde. Wheat and rice showed a slight irregularity at 10% and 40% sucrose and decreased with an increase in the concentration of formaldehyde. At various sucrose and formaldehyde concentrations, the tapped densities exhibited an irregular/wavy effect. This demonstrates that increasing the quantity of cross-linking agents increases the volume and tapped density of the starch powder (Awolu and Olofinlae 2016).

Swelling is widely accepted as an assessment of tablet disintegration ability. From the results obtained for swelling profile of different cross-linked starches in Table 3, the percentage swelling of native maize, wheat and rice starches is larger than that of cross-linked derivatives, which might be attributable to granule alteration that reduced hydration capacity in cross-linked starches. An increase in the concentration of the cross-linking agent resulted in an increase in the number of cross-links, conferring increased stability on the starch granule. As a result, the decrease in water absorption was more apparent at greater cross-linker concentrations. This suggests that cross-linking has an influence on the ease with which water may reach the starch. As a result, the swelling properties of the cross-linked polymer are reduced (Yu et al. 2016). Porosity determines the swelling ability of starch. The higher the porosity, the more the inter-particulate spaces where water could be absorbed (Carmona-Garcia et al. 2009).The increase in the ionic strength of the cross-linked starch decreased the osmotic pressure inside the charged paste and a reduction in its swelling. Cross-linking also caused a high elastic contraction of polymer network which counteracted the swelling process. Hydration leads to swelling, and it is dependent on the type and number of hydrophilic groups in the polymer structure. The highest swelling for the cross-linked starches was observed in both sucrose and formaldehyde cross-linked rice starch, while the least swelling was observed in 5% and 40% sucrose cross-linked maize and wheat starches. Swelling power is a parameter that is analyzed in theory of disintegration, which must be preceded by water penetration. Therefore, an increase in the percentage swelling of sucrose and formaldehyde cross-linked rice starches leads to the activation of the reactive

moieties, which enhances the disintegrating properties of formulated tablets (Tesfay et al. 2020).

The pH of any starch is an important factor in their applications in the pharmaceutical and other industries, due to the fact that it is an indication of the acidity or alkalinity of the liquid media (Ashogbon and Akintayo 2012). All cross-linked starches showed an overall slight reduction in their pH as compared with the native starch. The pH of almost all the concentrations of sucrose and formaldehyde cross-linked maize, wheat and rice starches was above 5 with the exception of 10%, 20% and 40% formaldehyde cross-linked maize and rice starch which had pH below 5, respectively. A slightly acidic pH will not pose a problem when the starch sample is employed as food additives (Awolu et al. 2020).

Swelling and viscosity of cross-linked starches are the very important and useful features of assessing the level of cross-linking. Table 3 also illustrates the dependence of viscosity of starch on the concentration and type of cross-linkers. It is observed that the viscosity of the cross-linked wheat and rice decreased as the concentration of the cross-linker increases for the two cross-linkers except for maize which showed a slight increase at 40% sucrose and formaldehyde. Also, the viscosities of the cross-linked starches were generally different from those of the non-cross-linked (Native) ones. In general, the viscosities of the native starches were more than those of the cross-linked starches. This is in conjunction with Shah et al. (2016) that the degree of peak viscosities of cross-linked starches is inversely proportional to the concentration of cross-linking agent. Starch with a greater cross-linking level will show a lesser peak viscosity as compared with starch with lesser cross-linking levels.

The thermal properties of the defatted and undefatted wheat, maize and rice starches were also analyzed as shown in Table 5. For maize starch, both the onset and end set temperatures of the glass (Tg) as well as the energy change (ΔH) recorded were higher for the undefatted than the defatted. This shows that the process of defatting probably lowered the intermolecular forces within the starch sample leading to the requirement of less energy for the Tg process. Except for the onset temperature, similar trend was observed for the rice starch. There were no significant differences between the melting peaks recorded for the undefatted and defatted starches.

Furthermore, considering the thermal parameters of the defatted and formaldehyde-modified wheat starches, it was shown that the Tg took place at lower temperatures for the samples treated with 2.5–20% formaldehyde. However, with increased formaldehyde concentrations up to 25–40%, the Tg occurred at much higher temperatures. Similar trend was observed for the ΔHs involved in the transitions. The melting peaks generally occurred at slightly elevated temperatures for the formaldehyde-modified wheat starch samples. These observations indicate that the chemical modification resulted to wheat starch of a more ordered (crystalline) molecular conformation than the natural moiety (Gonenc and Us 2019 Mar). In comparison with the sucrose-modified wheat starch, the end set temperature of the Tg as well as the ΔH was significantly higher than for the formaldehyde-modified sample. However, the melting endotherm was higher for the formaldehyde-modified wheat starch than for the sucrose-modified sample.

For the formaldehyde-modified maize starch, the onset temperatures of the Tg were obviously greater than that of the defatted maize starch for the various range of concentrations tested. The end set temperatures were, however, lower except at 20% formaldehyde concentration. Similarly, the ΔH for the Tg of the defatted maize starch was higher than those of the formaldehyde-modified except at 20% formaldehyde concentration. The melting peaks of the formaldehyde-modified maize starch were greater than for the untreated defatted sample (Šuput et al. 2016). In comparison with the sucrose-modified maize starch, the onset temperatures were also higher than for the untreated and defatted samples. The onset of transition occurred at approximately similar temperature except at 10% sucrose concentration where it was significantly much higher. The results showed that the ΔHs for the Tg were generally higher for the formaldehyde than the sucrose-modified maize starches except at 20% chemical agent concentration where the latter had significantly higher value. The melting peaks generally occurred at higher temperatures for the formaldehyde-modified maize starch than the sucrose-modified except at 2.5% chemical agent concentration where the reverse was the case.

Both the onset and end set temperatures of the Tg for the formaldehyde-modified rice starch were greater than for the untreated and defatted sample. However, the ΔHs for the Tg of the cross-linked rice starch samples were higher than for the untreated sample. On the other hand, the melting peaks of the formaldehyde-treated rice starch samples occurred at really lesser temperatures compared to the untreated sample. Cross-linking leads to an increase in the decomposition temperature, and this is a result of the formation of a stronger network of intra- and inter-molecular bonds, which were formed on the of the cross-linking agents (Dhull et al. 2021).

For the sucrose-modified rice starch, the onset and end set Tg occurred at higher temperatures, at 2.5% sucrose concentration than for the untreated but defatted sample. However, the onset and end set Tg occurred at lower temperatures when the sucrose concentration was increased to 5%. The ΔHs for the Tg were also higher for

the sucrose-modified rice starch than for the untreated sample. However, the melting peak of the untreated but defatted rice starch was significantly higher than for the sucrose-modified samples. In comparison with the formaldehyde-modified rice starch, the sucrose-modified had higher onset and end set temperatures for the Tgs. Varied results were obtained for the ΔHs and the melting peak temperatures. The overall results obtained for the various modified starches showed that the chemical (cross-linking) agents used had effects on their original molecular conformations of the native samples though the amorphous and crystalline structures were still present as indicated by the glass and melting transitions which has also been observed in other studies (Hassan et al. 2020; Franco-Bacca et al. 2021). The changes were due to the cross-linking of the starch moieties by the functional groups in the chemical agents used. The extent of changes might partly be attributed to the level of amorphosity and crystallinity of the original starch molecules. The resultant effect is that new starch motifs were produced with improved or new functionalities as pharmaceutical excipients.

Conclusions

This study reveals that various concentrations of sucrose and formaldehyde had some influence on the properties of the native starches. The cross-linking agents raised the surface activity of the starch molecules by generating a change in conformation of the molecules at the interface, resulting in an increase in viscosity and other physicochemical properties. In general, the cross-linking agents denatured the starches, leading to the formation of new starch motifs with improved or new functionalities, which may increase their appropriateness as pharmaceutical excipients in tableting.

Abbreviations

DSC: Differential scanning calorimetry; MCC: Microcrystalline cellulose.

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Authors' contributions

ECI conceived and designed the work. IJO participated in the design of the work and carried out laboratory work and data collection. ANO and CMO drafted the manuscript. JNO read the work for intellectual content. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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