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Ultra-sonication aided synthesis of starch nano-particles from *D Bulbifera* and *D Esculanta* as potential pharmaceutical excipient.

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Abstract
This study reports the synthesizing starch nanoparticles from two yam varieties and their evaluation as excipients for drug tableting. Starch particles were extracted from the yams by cold maceration with methanol and characterized for their phytochemical constituents and their physicochemical parameters. FITIR analysis was also carried out to identify the functional groups. Alkaline hydrolysis with ultrasonication was used to synthesize starch nanoparticles from the characterized starch. The synthesized starch nanoparticles were then applied as excipient for the tableting of paracetamol and compared to a standard (maize starch). The results obtained from the tableting test showed a weight uniformity (mg ± cv) of 597.5±1.2 and 595.5±1.2 for *D. Bulbifera and D. Esculanta*, respectively, a hardness (KGF ± SD) of 5.20±0.67 and 5.18 ± 0.67 for *D. Bulbifera and D. Esculanta*, respectively, a thickness (mm ± SD) of 5.68±0.04 for *D. Bulbifera* and 5.65±0.04 for *D. Esculanta*, and a disintegration time of (min ± SD) 4.5±1.56 for *D. Bulbifera* and 4.2±1.56 for *D. Esculanta*. A friability of 0.99 and 0.97 % for *D. Bulbifera and D. Esculanta* was also recorded, as was a hardness-friability ratio of 5.25 and 5.24 for *D. Bulbifera and D. Esculanta*. On comparison with the values obtained for the standard (maize starch), the two fabricated starch nanoparticles present competitive substituents for the tableting of paracetamol.

Keywords: Starch, excipient, nano-particles, tableting, alkaline hydrolysis, ultrasonication

1. Introduction
Starch is a natural biopolymer found abundantly in nature, in plant roots, staple crops, and cereals [1] and also as a major component of our daily diet [2]. Starch is a renewable and biodegradable semi-crystalline natural polysaccharide polymer created by many plants, with the general molecular formula $[C_6H_{10}O_5]$ n. It comprises of two glycosidic macromolecules: 18–28 % linear amylose (α-D-glucose units, bonded together by α-1,4 glycosidic bonds) and branched 72–82 % amylopectin (short linear glucose units linked together by α-1,4 glycosidic bonds and branched by α-1,6 glycosidic bonds) assembled in the form of granules with a size ranging from 1 to 100 μm^2 [3].
The relatively low cost and availability, coupled with great physical and chemical functionalities that allow for vast applications, has led to the numerous uses of starch. It has traditionally been used in baked goods, confectioneries, pasta, soups and sauces, and mayonnaises as thickeners, gel formers, stabilizers, preservatives, and quality enhancers [4]. Recent advancements in technology have led to its continuous application in many other sectors, such as health and medicine [3, 5–6], textiles, paper, fine chemicals, petroleum engineering [7], agriculture [8–9], and construction engineering [10]. Starch has long been used in pharmaceutical manufacturing as a binder, disintegrate, and filler in tablet formulation [11–12]. It has also been reported that starch acts as both a reducing and a stabilising agent for silver nanoparticle preparation [13]. Furthermore, starch has also found extensive application in encapsulating and delivering a variety of food ingredients [14].
In recent decades, nanotechnology has become a vital part of humanity. Prior to the recent advancement in nanotechnology by scientists, native nanomaterials had already been in existence around us, be it in smoke emanating from a fire or as volcanic ashes from an eruption, or even in micelles in milk that help to stabilize milk fats [15]. With the development of tools and technology to envisage and manipulate these tiny structures, nanomaterials have unavoidably accessed all areas of human life, starting with fabrics (e.g., antibacterial socks) [16]

Applications of nanomaterials provide superior characteristics not observed in larger-sized materials. Recently, starch-based nano-systems have attracted focus due to their distinguishing properties that are different from their bulk ingredients. One enthralling feature of starch-based nano-systems is their ability to encapsulate varieties of biologically active compounds, like testosterone, caffeine, ciprofloxacin, 5-fluorouracil, and curcumin [17–18]. Starch-based nano-systems have higher surface area, lower viscosity, and better entrapment of active components [17, 19–21]. Numerous botanical sources of starch-based nano systems have been reported, including waxy maize [22], potato [23–24], cassava [19], tapioca [25], breadfruit [26], banana [18], wheat [27], Lotus seed [28], corn, and yam [29].

This study reports the synthesis and characterization of starch nanoparticles from two varieties of yam (*D. Esculanta* and *D. Bulbifera*) by alkali hydrolysis coupled with Nano precipitation via an ultra-sonication process and its application in pharmaceuticals as drug excipients.

2. Materials and Method

2.1 Reagents and Chemicals

All analytical chemicals used were purchased from Sigma Aldrich Analytical Grade, Ethanol, Sodium hydroxide, Methanol, hydrochloric acid, Iodine, Potassium hydroxide.

2.2 Sample collection and Preparation

The two yam species (*D. Esculanta* and *D. Bulbifera*) were sourced locally from the research farm of Joseph Sarwuan Tarka University, Makurdi. The yam samples were carefully peeled and washed with distilled water, then cut into smaller pieces and sun-dried at room temperature for days till a constant weight was obtained, after which they were milled into powder using a blender (Silver Crest, SL-2020).

2.3 Starch Extraction

The extraction method adopted is similar to that of Okoye and Onyekweli [6], with modifications. The pulverised yam powder was carefully emptied into a sample container and soaked in 2000 ml of methanol for 72 hours (1000g for *D. Esculanta* and *D. Bulbifera*). After that, the mixture was filtered and the filtrate was subjected to solvent recovery using a rotary evaporator set at 50 °C. The recovered starch was again soaked in acetone for another 72 hours to wash off any extracted product outside starch. The mixture was again filtered and the acetone was recovered using rotary evaporation at 40 °C. The final extract was then washed with distilled water and air-dried to a constant weight. The yields were determined at 98 % and 98.5 % respectively. The extracted starches were kept in an airtight container and stored at room temperature for further analysis.

2.4 Phytochemical analysis

Phytochemical screening of the extracted starch powder was carried out according to previously published protocols by Andriani *et al.* [30] and Shankar *et al.* [31].

2.5 Physicochemical Evaluation

pH test

The pH of the starch extract was determined using a digital pH meter (Hannah HI 7007L).

Moisture content

5.0 g of the starch powdered was weighed and placed in an Oven (Memmart, UN160plus, Western Germany) for 1 hour and then allowed to cool in a desiccator. After which it was weighed this was repeated until a constant weight was obtained and the moisture content thus estimated using equation 1.

$$Moisture\ content = W_i - W_f \quad (1)$$

Swelling capacity

The swelling capacity of the two starch samples was estimated using a method similar to the reports of Eraga *et al.* [32] and Okoye and Onyekweli [5] with slight modifications. 1.0 g of the starch powder was emptied into a calibrated test tube and soaked in 30 ml of distilled water, and the resulting mixture was allowed to stand for 24, 48, and 72 hours. The increase in the height of the starch was noted. The swelling capacity was thus calculated using equation 2.

$$Swelling\ capacity = \frac{h_t - h_i}{h_i} \times 100 \quad (2)$$

Where h_t is the height of the starch powder at time t and h_i is the initial height of the starch powder before swelling.

Gelatinization temperature test

0.5, 1.0, and 1.5 grams of the starch samples were emptied into test tubes, 5 ml of distilled water was added, and the resulting solution was placed in a water bath with constant stirring. The temperature at which gel starts to appear is recorded.

Amylose and Amylopectin content

20 mg of the starch powder was weighed and emptied into a 50 ml beaker, 10 ml of KOH solution was added, and the resulting mixture was stirred for 5 minutes. The stirred solution was then introduced into a 100 ml volumetric flask and filled to the mark with distilled water. The 10 ml of the resulting solution was pipetted into a 50 ml volumetric flask with 5 ml of HCl and 0.5 ml of Iodine. They were then introduced and a colour change (from white to blue-black) was observed. The solution was then filled with distilled water up to the 50 ml mark. The solution was then subjected to a UV spectrophotometry analysis using a UV spectrophotometer (Jenway 741501, Stone Staffs, UK). The amylose content was then calculated using equations 3 and 4.

$$\%\ Amylose = 105.32X + C \quad (3)$$

Where X is the absorbance from the UV spectrophotometer and C is the concentration of the starch analytic.

$$\%\ Amylopectin = 100 - \%\ Amylose \quad (4)$$

2.6 Synthesis of starch nanoparticles

The synthesis of starch nano-particles was accomplished by mild alkali hydrolysis aided by ultra-sonication as earlier reported by Ahmad *et al.* [1]. For 30 minutes, 1.5 % of the starch solution was preheated in 0.1M NaOH at 80 °C with constant stirring using a heater and magnetic stirrer (ROTILABO MH15, Germany). The starch slurry thus formed was then sonicated at 40 kHz for 30 minutes at intervals of 5 minutes to avoid damage due to excessive heating, using a sonicator (Powesonic 420, Telangana, India). The resulting nano-starch particles were precipitated using ethanol in a proportion of 1:2 by drop wise addition of the nano-starch solution to ethanol under continuous magnetic

stirring. The solution was kept in the refrigerator for 12 hours. The precipitated starch nanoparticles were recovered by centrifugation at 8000 rpm for 15 minutes using a centrifuge (MPW-260). The powdered starch nanoparticle was recovered when it was sent for analysis as a drug excipient.

2.7 Tableting Preparation

The pure paracetamol powder (API) and each of the ingredients were accurately weighed as seen in the formulae below. The API was weighed and put into a mortar. An appropriate quantity of lubricant and diluents were added into the mortar and it was mixed thoroughly. Mucilage of acacia (20 % w/w) was prepared by dissolving an appropriate quantity in water and then transferred into the mortar and triturated with a pestle until a damp mass was formed. The damp mass was forced through a 1.7 mm sieve using a spatula. The granules obtained were dried in an oven at 50 ^{o}C. The dry granules were passed through a 1.0 mm sieve to reduce the particle size of the granules. Moreover, the granules were sieved through a 0.25 mm sieve to separate the fine and coarse granules. Magnesium stearate was added to the fine in a mixing bottle and mixed for 2 minutes. Finally, the coarse granules were added and mixed for another 5 minutes. The weight of one tablet (600 mg) was weighed and set in the tableting machine. However, the compression force was adjusted to 40–50 psi and tablets were individually compressed using a Manesty F3 single-punch tabletting machine.

Formulae

Batch A

S/N	Ingredients	QTY 1 tablets (mg)	QTY in 100 tablets (mg)
1	Paracetamol (API)	500	50000 (50 g)
2	Acacia (2 %)	12	1200 (1.2g)
3	Disintegrate (Corn starch) (10%)	60	6000 (6g)
4	Lubricant (1 %)	6	600 (0.6g)
5	Diluent (lactose) QS	22	2200 (2.2g)
	Total weight	600 mg	

Batch B

S/N	Ingredients	QTY 1 tablets (mg)	QTY in 100 tablets (mg)
1	Paracetamol (API)	500	50000 (50 g)
2	Acacia (2 %)	12	1200 (1.2g)
3	Disintegrate (Yam starch) (10 %)	60	6000 (6g)
4	Lubricant (1%)	6	600 (0.6g)
5	Diluents (lactose) QS	22	2200 (2.2g)
	Total weight	600 mg	

**Maize starch in batch A was used as a standard disintegrate. While the disintegrates for batch B are the starch samples from *D. Bulbifera and D. Esculanta*.

2.7.1 Weight uniformity test

Twenty (20) tablets were randomly selected from each batch of drug sample, the individual and the total weight of each batch was determined using an electronic balance (Metller-HS-502N). The mean, standard deviation and the percentage deviation were determined.

2.7.2 Tablet friability test

Ten tablets were randomly selected from each batch of ibuprofen tablets. The ten tablets were de-dusted and accurately weighed together using an electronic balance and the initial weight was recorded. They were then placed into a friabilator set to rotate at 25 rpm for four (4) minutes. The tablets were removed, deducted and the final weight was determined. The percentage friability was therefore determined using equation (3):

$$Friability\ (\%) = \frac{initial\ weight - final\ weight}{initial\ weight}$$

2.7.3 Hardness test

Ten tablets were randomly selected from each batch of drug sample. Using the Monsanto hardness tester, the hardness (kg/f) of each tablet was determined and recorded. However, the mean, standard deviation and the coefficient of variation were determined.

2.7.2 Disintegration time test

Six (6) tablets were randomly selected from each batch of drug sample. Distilled water was used as disintegration medium. One tablet was placed into each of the six tubes contained in disintegration apparatus and the time taken for each tablet to completely breakdown to particles and pass through the wire mesh was determined. However, the mean, standard deviation and the coefficient of variation was determined.

2.7.3 Shape and dimension

Ten tablets were selected randomly from the tablet batch and the thickness of the tablets was determination using venier caliper. However, the mean, standard deviation and the coefficient of variation was determined.

3. Results and Discussion

Table 1: Phytochemical analysis of the extracted starch powders.

Test	Test Result	
	D. Esculanta	***D. Bulbifera***
Iodine test	++	++
Fehling's test	++	++
Borntrager's test	++	++
10% NaOH test		++

3.1 Phytochemical analysis

Phytochemical screening carried out on the extracted samples (Table 1) confirms the presence of starch from the blue-black colouration observed for the iodine test carried out. The presence of a reducing sugar was also confirmed by the appearance of a red precipitate from the Fehling's test carried out. Borntrager's test carried out showed the presence of glycosides, which was confirmed by the appearance of a pink colouration. The presence of glycosides was further confirmed by the 10 % NaOH test carried out.

Table 2: FITR analysis of the extracted starch powders.

		Wavenumber (cm^{-1})		
S/N	**Functional groups**	**Literature**	***D. Esculanta***	***D. Bulbifera***
1	O - H stretching	3600 – 3300	3288.9	3272.0
2	C - H stretching	2931	2929.7	2929.7
3	C-O bending associated with OH	1637	1640.0	1640.0
4	CH_2 symmetric vibration	1458-1415	1420.1	1420.1
5	C-H symmetric bending	1385-1375	1341.8	1341.8
6	C - O - C asymmetric stretching	1149	1148.0	1148.0
7	C-O stretching	1200 – 800	1077.2, 991.5	1077.2, 991.5
8	C-O-C ring vibration of carbohydrate	920, 856, 758	928.1, 861.0, 760.4, 704.5	928.1, 857.0, 760.4
9	O = C = O	2350	2087.3	2083.0

3.2 FTIR analysis

The result of the FTIR analysis (Table 2, Figure 1 and 2) showed a broadband of an OH stretching vibration at 3288.9 cm^{-1} (for *D. Esculanta*) and 3272.0 cm^{-1} (for *D. Bulbifera*) C - H stretching vibration, at 2929.7 cm^{-1}, C-O bending vibration band associated with OH at 1640.0 cm^{-1}, CH_2 symmetric scissoring of CH_2OH moiety at 1420.1 cm^{-1}, C-H symmetric bending vibration at 1341.8 cm^{-1}, C-O-C asymmetric stretching vibration at 1148.0 cm^{-1}, C-O stretching vibration band at 1077.2 cm^{-1} and 991.5 cm^{-1}, C-O-C ring vibration of carbohydrate at 928.1 cm^{-1}, 861.0 cm^{-1}, 760.4 cm^{-1}, 704.5 cm^{-1} and 928.1 cm^{-1}, 857.0 cm^{-1}, 760.4 cm^{-1} and the uncommon O=C=O stretch vibrations was observed at 2087.3 cm^{-1} and 2083.0 cm^{-1} for *D. Esculanta* and *D. Bulbifera* respectively. This result is similar to that previously reported by Abdullah *et al.* [33].

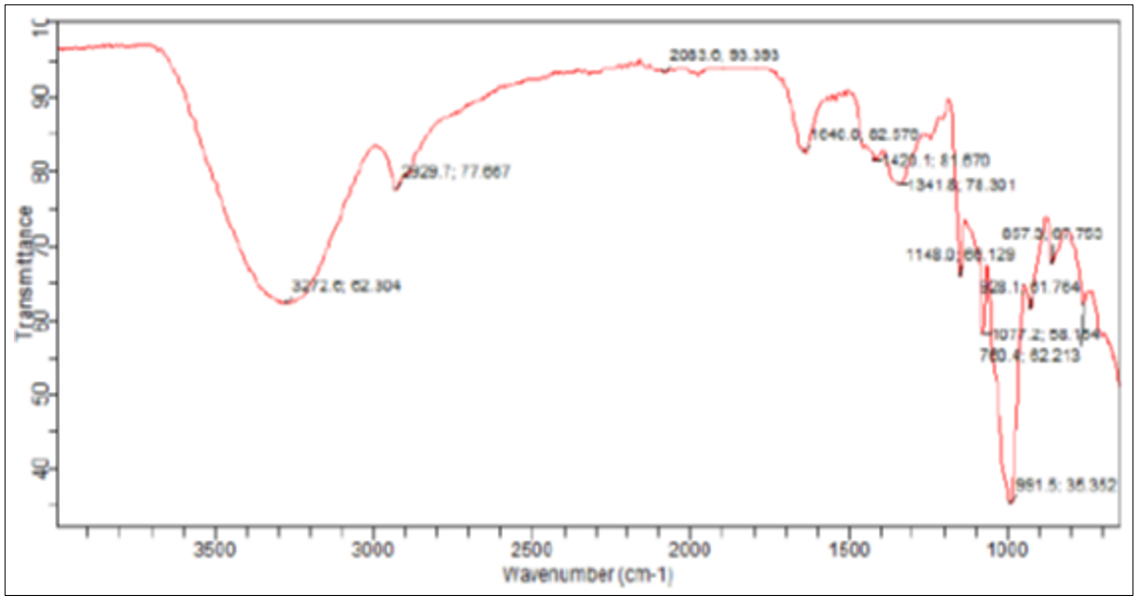

Fig 1: FTIR spectrum for *D. Esculanta*

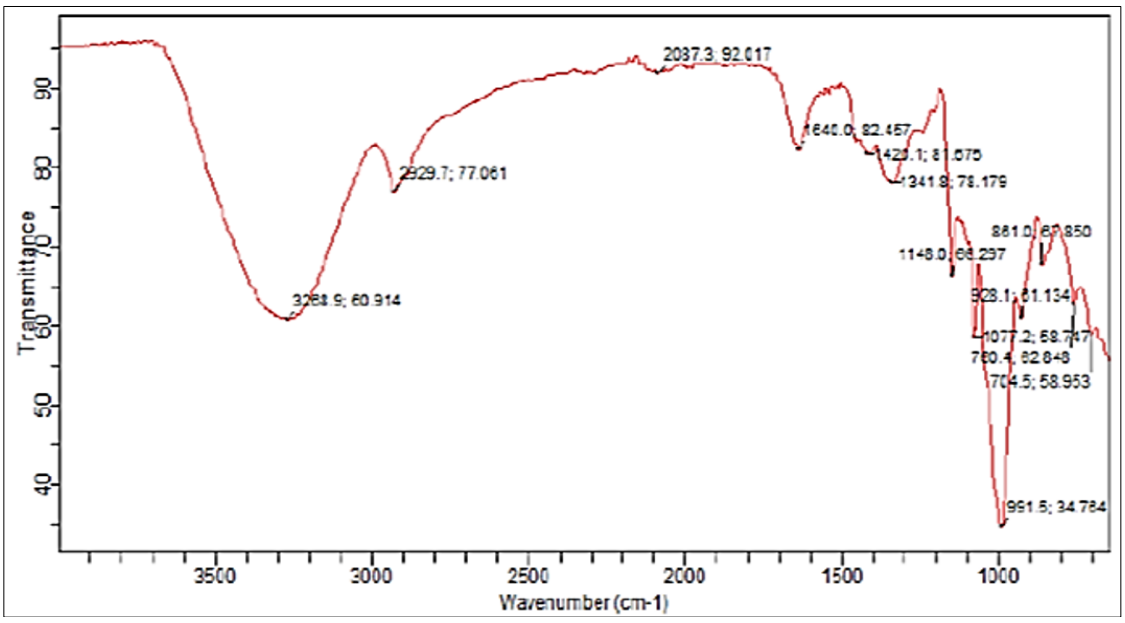

Fig 2: FTIR Spectrum for *D. Bulbifera*

Table 3: Physicochemical characterization of the extracted starch powders.

S/N		*D. Esculanta*	*D. Bulbifera*
1	pH	6.90	6.70
2	Swelling Capacity (%)	50.00	46.15
3	Moisture Content (%)	0.40	0.20
4	Gelatinization temperature (℃)	91 for 0.5 g 56 for 1.0 g 58 for 1.5 g	61 for 0.5 g 70 for 1.0 g 54 for 1.5 g
5	Bulk Density (gcm^{-3})	0.9266	0.8877
6	Amylose Content (%)	5.46	2.82
7	Amylopectin Content (%)	94.54	97.18

3.3 Physiochemical analysis

Physicochemical analysis (Table 3) carried out on the extracted starch powders reveals that the pH values of 6.9 and 6.7 for *D. Esculanta* and *D. Bulbifera*, respectively, and this significantly implies that little or no caution should be exercised when used as diluents in formulations of low-dose alkaline or acidic drugs. Starch is made up of two main components, namely; the amylose component and the amylopectin component. The higher the amylose content, the lower the amylopectin, and vice versa. The amylose part is responsible for complex formation with lipids to inhibit granule swelling and solubilisation, while the amylopectin supports granule swelling [34]. The amylose content of the two starch powders *(D. Esculanta* and *D. Bulbifera*) was found to be 5.46 and 2.82% respectively. This corresponds to an amylopectin content of 94.54 and 97.18% respectively. *D. Bulbifera*'s higher amylopectin ratio would exert a stronger disintegrate action compared to *D. Esculanta* Bayor *et al.* [34].

Table 4: Proximate analysis of the extracted starch powders.

S/N		*D. Esculanta*	*D. Bulbifera*
1	Ash content (%)	0.10	0.12
2	EE (%)	0.99	0.72
3	Crude Protein (%)	1.53	0.75
4	Crude Fiber (%)	0.06	0.08
5	Carbohydrates (%)	92.48	97.39
6	Energy (%)	384.95	399.04

3.4 Proximate analysis

From the proximate composition data obtained (Table 4), an ash content of 0.10 and 0.12% was recorded for *D. Esculanta* and *D. Bulbifera*, respectively. Ash content reveals the presence of all other contaminants or impurities (insoluble salts and complexes) other than starch in the sample. The low ash content values obtained indicate a low level of contamination with inorganic compounds, including heavy metals. High protein content affects starch gelatinization in diverse ways depending on the degree of polymerization, and also affects its ability to retain water and its interaction capacity with starch molecules and granule surface. Thus, starch protein content below 0.2% is best recommended. Crude protein content was estimated to be 1.53 and 0.75% for *D. Esculanta* and *D. Bulbifera*, respectively. Carbohydrate content was found to be 92.48 and 97.39% for *D. Esculanta* and *D. Bulbifera*, respectively, showing the high purity of the starch molecules. A good starch material for pharmaceutical purposes is expected to contain more than 96% (w/w) carbon hydrate content [35]. The crude fibre content obtained for *D. Esculanta* and *D. Bulbifera* was 0.06 and 0.08% respectively. The measured EE content was 0.99, and the measured energy content was 384.95 and 399.04%.

3.5 Results of SEM analysis

The statistical mean area of the nano particles is 518.518 while the statistical mean length of the particles is 34.114 for the *D. Bulbifera* starch material, while that for *D. Esculanta* is 127.092 for the length and 128.646 for the mean area of the particle. The particle shapes are oval with measurable length, breath, and thickness. This is consistent with other starch granules from other researchers (ref). The minimum area of individual particles is 222.258 and the maximum area of individual particles is 659.632 for the *D. Bulbifera* starch sample. The minimum area of individual particles for *D. Esculanta* is 2131.236, while the maximum area of individual particles is 5497.56. This simply means that the relative particle dimension of the *D. Bulbifera* starch is bigger than that of *D. Esculanta*, and consequently, in application areas where fineness of material is required, *D. Esculanta* will be the ideal candidate of choice.

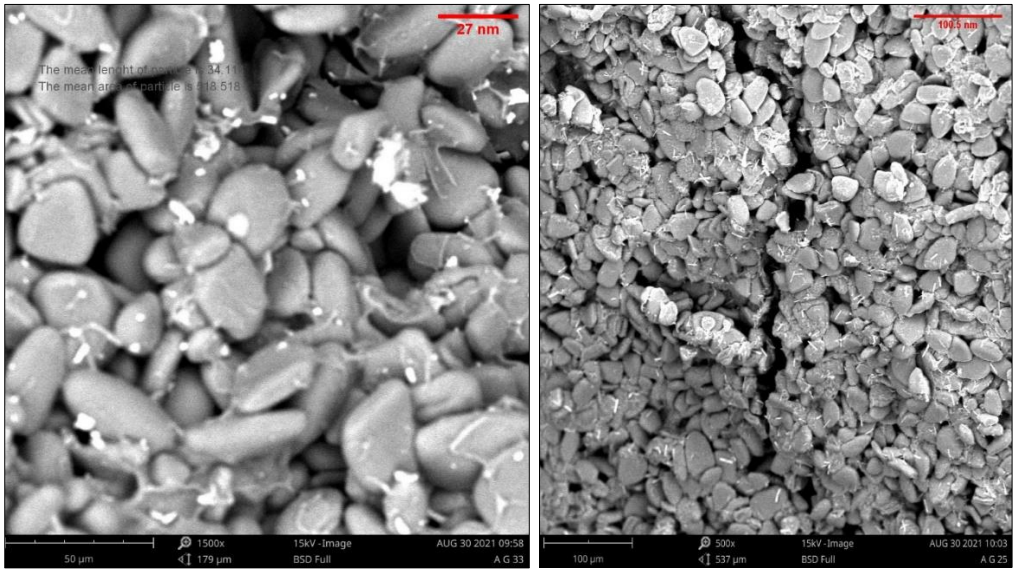

Fig 1: SEM micrograph of *D. Bulbifera* and *D. Esculanta* nano starch particles.

Table 5: Tablet properties

Properties	Control	Test sample	
	Maize	*D. Bulbifera*	*D. Esculanta*
Weight Uniformity (mg ± CV*)	598.5 ± 1.1	597.5 ± 1.2	595.5 ± 1.2
Hardness (KGF ± SD)	4.40 ± 0.37	5.20 ± 0.67	5.18 ± 0.67
Thickness (mm ± SD)	5.99 ± 0.03	5.68 ± 0.04	5.65 ± 0.04
Disintegration time (min ± SD)	17.9 ± 1.3	4.5 ± 1.56	4.2 ± 1.56
Friability (%)	1.15	0.99	0.97
Hardness-friability ratio (HFR)	3.83	5.25	5.24

**CV = Coefficient of variation*

3.6 Tableting Test

3.6.1 Weigh uniformity test

The tablets showed minimal weight variation across the two batches ($p < 0.05$) with low CVs. The tablet target weight was 600 mg. The tablets therefore, passed the weight uniformity test as stipulated by the British Pharmacopoeia [36].

3.6.2 Tablet disintegration time

The batches of tablets containing prepared with maize starch and yam starch disintegrated after 17.9 and 4.5 min respectively (Table 5). The value recorded for maize starch was higher than maximum limit of 15.00 min stipulated in the British Pharmacopoeia for uncoated tablets for immediate release [36], while yam starch tablets disintegrated after 4.5 min and thus passed the test. Disintegration time usually depends on the concentration of the starches and the inherent properties. The assessment of tablet disintegration serves as a useful tool in the checking and regulating of batch-to-batch discrepancies in distinct tablets in the course of production, though, sometimes it may not point to the certainty of the bioavailability of the API [37].

3.6.3 Tablet hardness

The hardness of tablets is a very important parameter to evaluate because it enables the manufacturers estimate the manner in which the tablets will withstand the shocks of packaging, transportation and use. The hardness values were generally above 4.00 KGF with yam starch tablets having higher value (Table 5). A minimum hardness of 4.00 KGF is considered adequate for uncoated oral tablets for immediate release, though, such tablets are expected to have a breaking force of 4.00-10.00 KGF [38].

3.6.4 Friability

The friability of the tablets (Table 5) did not significantly vary ($p < 0.05$). Friability depends on the moisture content of the compressed granules as well as the tablet shape [39]. It is a measure of the ability of the tablet to resist the abrasions during packaging and product handling [40]. For uncoated tablets, the British Pharmacopoeia [36] stipulated values less than 1.00% especially for tablets prepared by wet granulation. Considering the limits specified in the British Pharmacopoeia, maize starch failed the test while yam starch passed the test.

3.6.5 Hardness-friability ratio

The hardness friability ratio (HFR) is an estimation of the mechanical strength of tablets, being a ratio that compares the strength of the tablet to its weakness and it has been documented that the higher the HFR values, the stronger the tablet [41–42]. Yam starch possessed higher HFR and therefore give stronger tablets.

3.6.6 Shape and dimension

The thickness of the tablets was constant as shown in Table 5. All the tablets had very low SD values attesting further to the uniformity of weights of the tablets.

4. Conclusion

Two starch nano particles were fabricated from two yam varieties (*D. Bulbifera and D. Esculanta*) via an Ultrasonic aided alkaline hydrolysis. The fabricated starch nanoparticles were characterized using SEM and further applied as excipient for the tableting of paracetamol (acetaminophen) in comparison to a standard maize starch as control. From data obtained the two fabricated starch nano particles presents as good substitute excipient to maize starch (standard) for the tableting of paracetamol.

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Ethics Statement: None

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