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Chemical Modifications and their effects on Binding/Disintegrating properties of *Plectranthus esculentus* starch in Chloroquine Phosphate tablets.

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ABSTRACT

Starch from *P.esculentus* tubers was extracted and chemically modified using four different methods. Dextrinization of the native starch was done by heating in a hot air oven at 200^{o}C, while hydrolysis was achieved by HCl/ethanol hydrolysis. Gelatinization of the native starch was achieved at 90^{o}C while the starch xerogel was obtained by precipitation with 95% ethanol. Physicochemical characterization of these chemical forms was carried out in comparison with the native starch. These modified forms were then employed as binder/disintegrant (at 5% use level) in chloroquine phosphate tablets. The results showed that the modified forms of the starch possessed better flow properties compared with the native starch. All batches of tablets gave maximum release of the Active Pharmaceutical Ingredient (API) within 45 min of study except tablets containing the starch xerogel or starch dextrin (200^{o}C). The present study indicated that the starch xerogel or dextrin may be suitable as binders in conventional tablet formulations at low concentrations and may find application as hydrophilic polymer matrices in sustained release tablet formulation.

Keywords: *P. esculentus* starch, disintegrant property, binder property, tablet formulation, modification, xerogelized derivative.

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INTRODUCTION

Previous research on starches from tubers as sources of pharmaceutical excipients have yielded interesting results mainly due to their adhesive, thickening, gelling, swelling and film forming properties. Native starches irrespective of their source are not desirable for many applications [1], because of their inability to withstand processing conditions such as high temperature, high shear rate, freeze-thaw variation, and different pH conditions. The native starches are therefore limited in their use due to their large molecular size, insolubility in water, instability in viscous solutions and susceptibility to microorganisms [2]. In order to improve the desirable functional properties, modifications are often desired. Chemical modifications like acid hydrolysis, oxidation, gelatinization, dextrinization and starch xerogel formation has been used to overcome this problem.

P. esculentus also known in English as Livingstone potatoes belongs to the mint family Lamiaceae. The tubers are edible and cultivated as source of food in some countries of Africa. In Nigeria, the plant is cultivated for the edible tubers on the highlands of Plateau state. The starch from this plant has been characterized [3]. However, no work has been reported on the pharmaceutical application of the starch in solid dosage formulation. The present study was aimed at evaluating the effects of chemical modifications on the binding/disintegrant properties of the starch of *P. esculentus*.

MATERIALS AND METHOD

Materials

The materials used included: Chloroquine phosphate from BDH chemicals, England. Lactose and magnesium stearate from May & Baker Ltd, Dagenham England. *P. esculentus* starch was extracted in our laboratory. All other materials and equipments used were as cited in the text.

Extraction of *P. esculentus* Starch

The tubers of *P. esculentus* were purchased from a market (Heipang, Plateau state). The skin was peeled off to expose the white part which was then cut into several smaller pieces and washed in 0.1 % sodium metabisulphite before wet milling using a wet mill. The paste was sieved using muslin bag and allowed to settle overnight. Thereafter, the supernatant was decanted leaving the paste that has settled at the bottom of the container. The paste collected at the bottom was then washed thoroughly with 0.1% sodium metabisulphite which served as a preservative/antioxidant until the paste became whitish. The washed paste was then air-dried for 72 hours. When properly dried, it was reduced using a mortar and pestle to break up the dried powder mass into smaller

particles which was passed through a sieve size 250 µm and stored in an air-tight container.

HCl/ethanol hydrolysis of *P. esculentus* starch

The procedure described by [4]was adopted. Briefly, 150 g of starch was suspended in a 600 mL ethanol in a 1000 mL conical flask. The hydrolysis reaction was initiated by adding 50 mL of concentrated HCl into the conical flask and allowed to proceed for 1 hour at 50^{o}C in a water bath. The reaction was stopped by neutralizing with 3 M NaOH. The sample was then filtered with a muslin bag. The supernatant was collected and the precipitate washed with 50% ethanol until neutral to litmus. The starch samples were then filtered and dried in an oven (Gallenkamp, England) at 40^{o}C.

Gelatinization of *P.esculentus* starch

A 150 g quantity of *P.esculentus* starch was suspended in a beaker and about 1.0 L of distilled water was added at room temperature. The suspension was heated at about 90^{o}C in a water bath with continuous stirring until the starch gelatinized. The paste obtained was thinly spread on stainless steel trays and dried in a hot air oven at about 60^{o}C for 48 hours. The flakes were powdered using a blender and then sieved.

Preparation of xerogels of *P.esculentus* starch

A 150 g quantity of *P.esculentus* starch was suspended in a beaker and about 1.0 L of distilled water was added at room temperature. The suspension was then heated in a water bath at 90^{o}C with continuous stirring until the starch gelatinized. The paste obtained was then allowed to cool for 1 hr then 600 mL of 95% ethanol was poured into the paste stirred continuously and allowed to settle. The supernatant was decanted and sieved using a muslin bag. The precipitate obtained was then dried in a hot air oven at 50^{o}C for 45 min.

Heat modification of *P.esculentus* starch

A 150 g quantity of *P.esculentus* starch was weighed and heated in a hot air oven at 200 ^{o}C for 5 hr and allowed to cool.

Powder and Granule Evaluation

The powder and granule properties were evaluated. The bulk and tapped densities of 30 g of the powder or granules was weighed in triplicate into a 100 ml measuring cylinder, and the volume occupied by the granules recorded as the bulk volume. The cylinder was then tapped on the wooden platform height of 2.5 cm three times at 2 seconds intervals until the volume occupied by the granules remained constant. The data generated was used in computing the Hausner ratio and compressibility index. Moisture content was determined using the hot oven method. The particle size distribution of each granulated drug powder was characterized by sieve analysis.

Preparation of Chloroquine Granules and Tablet

The Chloroquine phosphate granules were formulated by wet granulation using *P. esculentus* starch or its derivative as a binder/disintegrant at concentration of 5 % w/w. The composition of tablet formulation containing Chloroquine phosphate using *P. esculentus* starch or its derivatives as binder is given in Table 1A. The required amount of the active ingredient (Chloroquine phosphate B.P), the diluent (lactose) and the disintegrant (maize starch) were weighed and blended for 10 min in a mortar using a pestle. Thereupon, 5 % w/w mucilage of the binder was added to the blended powders in the mortar to make a wet granulate. Screening of the wet mass was done using a suitable sieve size 10 and dried in a hot air oven at 60° C for 1 hour. Dry screening of the granule was done using sieve size number 16. A lubricant (magnesium Stearate) was added prior to compression. This procedure was followed to produce the granules of each starch binder.

Table 1A: Per Tablet Formula for Chloroquine Tablets Using *P.esculentus* Starch or its Derivative as Binder.

Ingredients	Quantity
Chloroquine (mg)	250
Disintegrant: maize mg)	40
*Binder (mg)	20
Lactose (mg)	86
Magnesium stearate (mg)	4

***Test binders:** Native starch, gelatinized starch, starch xerogel, starch dextrins and HCl/ethanol modified starch

Table 1B: Per Tablet Formula for Chloroquine Tablets Using *P.esculentus* Starch or its Derivative as Disintegrant.

Ingredients	Quantity
Chloroquine (mg)	250
*Disintegrant: (mg)	20
Binder: maize (mg)	40
Lactose (mg)	86
Magnesium stearate (mg)	4

***Disintegrants:** Native starch, gelatinized starch, starch xerogel, starch dextrins and HCl/ethanol modified starch.

The composition of a 400 mg tablet containing chloroquine phosphate with *P. esculentus* starch or its derivatives as a disintegrant is given in Table 1B. Briefly, the required amount of the active ingredient (Chloroquine phosphate B.P), the diluents (lactose) and the disintegrant (5% *P. esculentus* starch or its derivative) was weighed and blended in a mortar using a pestle for about

10 minutes. A binder solution or mucilage containing 5% maize starch was prepared. Wet granulate was then prepared by adding the binder mucilage to the blended powders in the mortar. Coarse screening of the wet mass was done using a suitable sieve size 10 and dried in a hot air oven at 60° C for 1 hour. Dry screening of the granule was done using sieve size number 16. The lubricant (magnesium Stearate) was added prior to compression.

Tablet Compression

A single punch tabletting machine (Erweka, Germany) fitted with 12 mm punch and die set was used to compress the tablets. The required tablets weight was 400 mg and the compressed pressure used was 4.5 MT. The tablets were stored in a desiccator for 24 hr before evaluation.

Tablet Evaluation

The mechanical properties of the tablets were evaluated. Weight uniformity test was carried out according to the B.P 1988 [5], procedure and the percentage coefficient of variation (% C.V) calculated. Tablet thickness and diameter were determined using a vernier caliper. The hardness of the tablets was determined using the Monsanto hardness tester while friability test was carried out using the Roche friabilitor. The percent losses were calculated for each batch of tablets. Disintegration time test was determined according to the B.P 1988[5], using Eagle Scientific disintegration apparatus and 0.1 N hydrochloric acid was the dissolution medium maintained at 37.5 ± 0.1°C.

TLC Analysis of Tablets

A modification of the TLC test developed by USP/USAID for the assessment of chloroquine phosphate tablets in Africa was used[6]. One tablet from each batch was crushed in aluminium foil using a pestle. It was then extracted with 10 mL methanol and filtered. Then 2 µl of the extract was spotted on the chromatoplate along with the reference chloroquine phosphate using micro capillaries. The plates were developed in a chamber containing 20 mL methanol, 5 mL ethyl acetate and 0.5 mL of concentrated ammonia solution. The spots were detected under UV light at 254 nm.

***In Vitro* Drug Release Studies**

The release of drug from the chloroquine phosphate tablets was studied in 1000 mL of 0.1 N HCl using the USP II (paddle method) at 100 rpm and 37 ± 1°C equipped with a 40 mesh sinker. A 5 ml sample was withdrawn at time intervals of 5 minutes up to thirty minutes and thereafter every 10 minutes for the next thirty minutes. The withdrawn samples were filtered through syringe filters (pore size = 0.45 µm) before assaying for drug content using the UV-spectrophotometer at 344 nm. After withdrawal of sample, it was replaced with an equal volume (5 mL) of fresh 0.1 N HCl at same temperature.

Statistical Analysis

The data was analyzed using two-way ANOVA (Instat software, Graph Pad, San Diego, CA).

RESULTS AND DISCUSSION

Physico-Chemical Properties of Powders and Granules

Percentage yield of P. *esculentus* starch

The percentage *of P. esculentus* starch obtained after extraction was 36.6% w/w which was good for tubers that grow and mature within a year [7]. The recovery yield after acid alcohol hydrolysis was 87 %w/w. Alcohol with shorter carbon chains like methanol and ethanol exhibit more yield than those with longer carbon chains.

Powder and granule flow properties

The flow properties of the powders and the formulated granules were evaluated and the results were as presented in Tables 2 and 3A & B. The powder flow properties suggest that native *P.esculentus* starch powder had poor flow characteristics and may require granulation or modification to improve the flow of the powder. The tapped density which is indicative of the powder packing properties was higher than the bulk density for all the powders used. *P. esculentus* starch powder gave the lowest bulk and tapped densities compared to the derivatives.

Table 2: Physicochemical Properties of Powder of *P.esculentus* Starch and its Derivatives Used as Binder/Disintegrant (Mean ± s.d)

	P. esculentus starch and derivatives				
	Native starch	**Gelatinized starch**	**Starch xerogel**	**HCl/Ethanol hydrolysed starch**	**Starch dextrin**
Bulk Density (g/cm^3)	0.44±0.01	0.74±0.01	0.66±0.01	0.72±0.00	0.56±0.00
Tapped Density (g/cm^3)	0.73±0.01	0.78±0.01	0.76±0.01	0.87±0.01	0.78±0.01
Carr's Compressibility (%)	40.1±5.36	4.96±0.06	13.2±1.68	17.1±1.42	27.9±2.26
Angle of Repose (^{0})	39.9±0.89	34.4±1.51	30.4±0.98	31.6±0.97	24.5±2.58
Hausner's Ratio	1.68±0.15	1.05±0.00	1.15±0.02	1.21±0.02	1.39±0.04
Moisture Content (%)	11.1±0.77	9.54±0.36	8.85±049	9.41±0.27	1.51±0.53

Table 3A: Physicochemical Properties of Granules of *P.esculentus* Starch and its Derivatives Used as Binder (Mean ± s.d)

	***P. esculentus* starch and derivatives**				
	Native starch	**Gelatinized starch**	**Starch xerogel**	**HCl/Ethanol hydrolysed starch**	**Starch dextrin**
Bulk Density (g/cm^3)	0.47±0.01	0.51±0.01	0.55±0.0	0.49±0.01	0.55±0.01
Tapped Density (g/cm^3)	0.52±0.01	0.56±0.0	0.64±0.02	0.52±0.01	0.59±0.01
Carr's Compressibility (%)	9.1±1.52	8.1±1.43	14.6±2.3	6.51±1.16	6.85±1.9
Angle of Repose (^{0})	29.78±0.33	29.6±0.16	30.1±0.36	29.2±0.13	29.6±0.57

Hausner's Ratio	1.10±0.02	1.09±0.02	1.17±0.03	1.07±0.01	1.07±0.02
Moisture Content (%)	1.89±1.44	1.50±0.4	1.22±0.77	1.75±0.64	1.68±0.47

Table 3B: Physicochemical Properties of Granules of *P.esculentus* Starch and its Derivatives Used as Disintegrant (Mean ± s.d)

	***P. esculentus* starch and derivatives**				
	Native starch	**Gelatinized starch**	**Starch xerogel**	**HCl/Ethanol hydrolysed starch**	**Starch dextrin**
Bulk Density (g/cm^3)	0.47±0.01	0.49±0.01	0.46±0.01	0.52±0.01	0.53±0.01
Tapped Density (g/cm^3)	0.51±0.01	0.53±0.02	0.49±0.02	0.58±0.02	0.59±0.02
Carr's Compressibility (%)	8.53±1.11	7.63±4.61	6.91±1.98	10.3±3.56	11.0±0.62
Angle of Repose (^{0})	29.1±0.82	28.9±0.37	29.7±0.59	29.8±0.47	30.0±0.78
Hausner's Ratio	1.09±0.01	1.09±0.05	1.08±0.02	1.12±0.04	1.12±0.01
Moisture Content (%)	0.06±0.01	0.07±0.01	0.05±0.01	0.07±0.01	0.06±0.01

The starch derivatives exhibited better powder flow than the native *P. esculentus* starch. On wet granulation of the powder blends using the native starch or derivatives as binder or disintegrant (Table 3A & B) the bulk and tapped densities of the resultant chloroquine phosphate granules formed was observed to decrease. The introduction of binder solution during wet granulation to form larger granules resulted in larger void spaces in between the granules [8] and this can improve the flow of the granules compared to the powders. The recorded value's for angle of repose, Carr's compressibility and Hausner's ratio decreases for the granules, indicating an improvement in the flow properties of the granules over the powders.

The starch derivatives had lower moisture content as compared with the native starch. Tablet granules have been reported to have superior compaction properties with a small amount (1-2%) of residual moisture [9].

Particle Size Analysis of granules

All the granules made using *P.esculentus* and its derivatives as binder or disintegrant had what could be described as fairly uniform particle size distribution across all the batches. In this study, the fines (particles of < 180 µm) were discarded and percentage weight of the discarded granules was ranging from 18-32% with maize starch having the highest percentage of fines.

Physicochemical Properties of Chloroquine Tablets

The properties of the compressed tablets of chloroquine phosphate are shown in Table 4A & B. The formulated tablets passed the tests of uniform weight, diameter and thickness of the tablets for all the batches. The tablet hardness varied according to the nature and quantity of the binder or disintegrant used in the formulation. Hard tablets were produced when the starch derivatives were used as binders (Table 4A) in contrast to when they were used as disintegrants. This is

expected because hardness is the direct effect of the type and quantity of binder used in the formulation while disintegrant effect is related to the intrinsic properties of the disintegrant used. All the tablets had a weight loss of less than 1% across all the batches (Tables 4A and B). Chemical modification caused increase in disintegration time of tablets. This was obvious in tablets containing the starch dextrin and starch xerogel with disintegration time of 27.00±1.6 min and 21.00±1.3 min respectively, which was significantly different (P<0.001) from the disintegration time of the other starch derivatives. This is indicative of good binding properties. The result in table 4A indicates that chemical modification of *P. esculentus* starch did not result in shortened disintegration time of tablets.

Table 4A: Physicochemical Properties of Tablet Using *P.esculentus* Starch and its Derivatives as Binder (Mean ± s.d)

	***P. esculentus* starch and derivatives**				
	Native starch	**Gelatinized starch**	**Starch xerogel**	**HCl/Ethanol hydrolysed starch**	**Starch dextrin**
Diameter	11.95±0.0	11.96±0.1	11.97±0.1	11.98±0.0	11.97±0.0
Thickness (cm)	3.40±0.1	3.38±0.1	3.37±0.1	3.37±0.1	3.35±0.1
Weight variation (% C.V)	399±10.44 (0.026)	400±4.47 (0.011)	399±7.00 (0.018)	402±7.48 (0.019)	402±6.00 (0.015)
Hardness (KgF)	7.33±0.5	12.00±0.5	11.67±0.5	8.67±0.2	11.90±0.3
Friability (%)	0.82±0.2	0.83±0.2	0.81±0.5	0.95±0.4	0.80±0.2
Disintegration time min	5.00±0.0	12.00±2.1	21.00±1.3	9.00±0.9	27.00±0.5

Table 4B: Physicochemical Properties of Tablet Using *P.esculentus* Starch and its Derivatives as Disintegrant (Mean ± s.d)

	***P. esculentus* starch and derivatives**				
	Native starch	**Gelatinized starch**	**Starch xerogel**	**HCl/Ethanol hydrolysed starch**	**Starch dextrin**
Diameter	11.98-±0.0	11.97±0.0	11.95±0.1	11.92±0.1	11.95±0.0
Thickness (cm)	3.37±0.0	3.36±0.0	3.37±0.0	3.35±0.0	3.36±0.0
Weight variation (% C.V)	402±8.7 (0.022)	399±12.2 (0.031)	400±7.8 (0.019)	398±4.0 (0.010)	402±7.5 (0.019)
Hardness (KgF)	9.67±0.5	9.33±0.5	9.50±0.4	11.67±0.5	10.20±0.4
Friability (%)	0.65±0.2	0.80±0.2	0.49±0.4	0.63±0.2	0.32±0.2
Disintegration time min	4.67±0.5	10.33±0.5	11.00±0.8	12.33±0.5	28.00±1.6

TLC Analysis of Tablets

TLC analysis (Figure 1) shows that all the tablets had no extra spot and by implication likely no impurities arising from the API, excipients and interactions between the two.

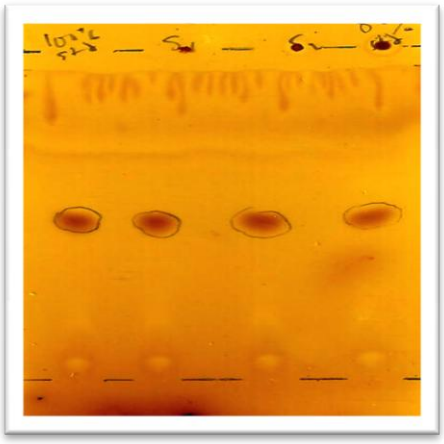

Figure. 1: TLC of Reference Chloroquine and formulated samples (RF=0.423)

***In Vitro* Drug Release Studies**

Release studies were carried out on the chloroquine phosphate tablets containing *P.esculentus* starch or its derivatives as binder at 5% w/w and all batches gave maximum release of the API within 45 min (Figure 2A) except tablets containing *P. esculentus* starch xerogel & *P. esculentus* starch dextrin. The t_{50} (Figure. 2B) of the tablets containing gelatinized starch, starch dextrin and starch xerogel were significantly higher ($P<0.001$) than the t_{50} of the native *P.esculentus* starch. The starch xerogel displayed remarkable delay in the release of chloroquine phosphate from the tablets even after 1 hour and may therefore not be suitably qualified as a binder in conventional tablet formulation at this concentration since it prolonged drug dissolution rate.

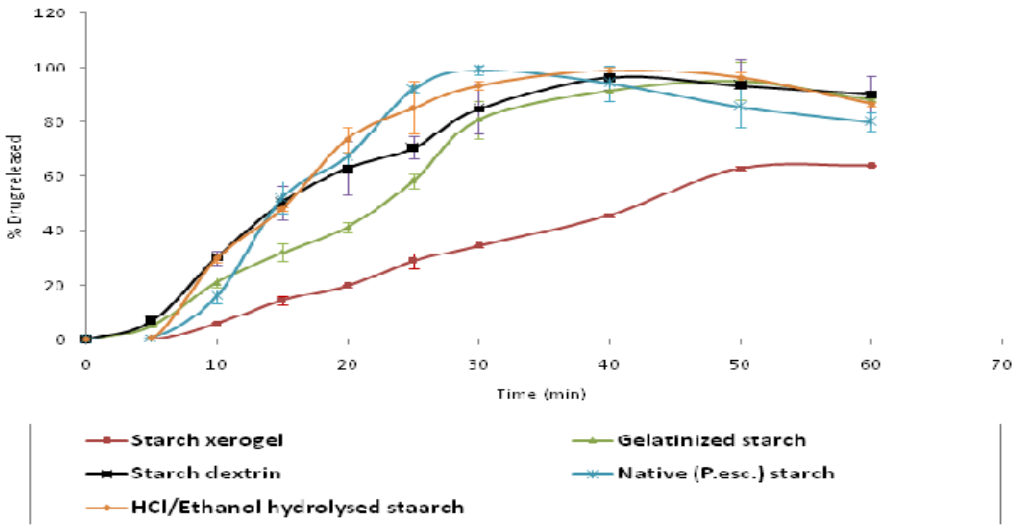

Figure 2A: Release profiles of chloroquine phosphate from tablets containing 5% w/w of native *P.esculentus* starch, Gelatinized starch, starch xerogel, starch dextrin or HCl/Ethanol hydrolyzed *P.esculentus* starch as binder in 0.1 N HCl (pH 1.0) solution at 37±1 ^{o}C (n=3, mean ± s.d).

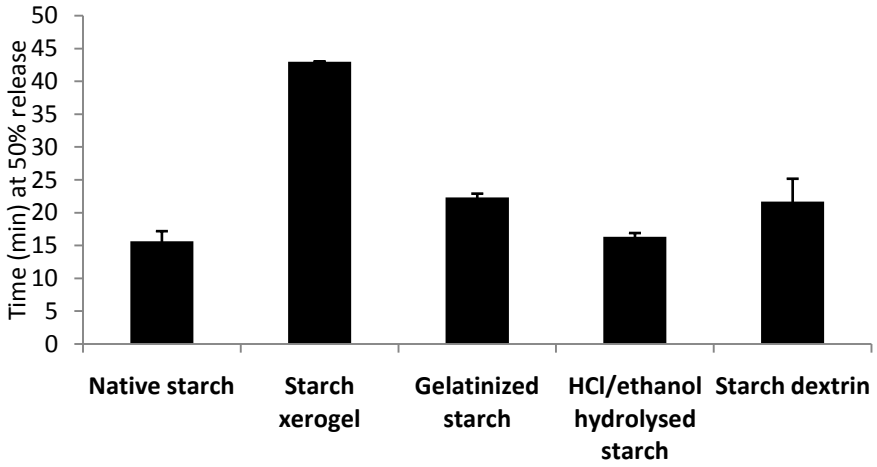

Figure. 2B: Time taken to release 50% (t_{50}) of API when native *P. esculentus* starch, gelatinized, xerogelized, dextrinized or HCl/Ethanol hydrolyzed starch was used as binder (mean ± s.d)

CONCLUSION

The results from the present study suggest that the chemical modification of native *P.esculentus* starch produced derivatives with improved binding properties. This effect was more pronounced in the starch xerogel, starch dextrin and the gelatinized derivatives than the HCl/ethanol hydrolyzed derivative. It would be therefore necessary to evaluate these modified derivatives as binder in sustained release tablets. Production of starch xerogel of *P. esculentus* starch may be a viable option when improvement in the binding property of native *P. esculentus* starch is indicated.

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