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Original Research Article

Investigation into the use of acid modified millet (*Pennisetum glaucum*) starch mucilage as tablet binder

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Abstract

Purpose: To investigate the binding properties of the modified (acid treated) millet *(Pennisetum glaucum)* starch mucilage in comparison with maize starch BP on some physical characteristics of paracetamol tablets.
Method: *Pennisetum glaucum*starch was extracted and subjected to acid modification. Mucilages of the modified starch and maize starch BP was used to prepare paracetamol granules and tablets by wet granulation method at various concentrations. The granules were characterized for their flow properties while the tablets were characterized for their tablet parameters. *In vitro* drug release and FTIR compatibility studies was carried out on the tablet formulation.

Result: The starch extraction and modification processes gave a percentage yield of 53.65 and 58.74 % respectively. Prepared granules were free flowing with Carr's indices, Hausner's ratios and angles of repose of ≤15%, ≤1.2 and <31°, respectively. At all binder concentrations, the tablets showed satisfactory hardness(5.15-7.75 kp), friability values (< 1.0 %) and disintegration times(<15 min).The dissolution studies showed that all batches achieved over 70 % drug release in 30 min while the compatibility study revealed no interaction between paracetamol and the modified starch.

Conclusion: The results from the study shows that modified millet starch when used as a binder in paracetamol tablets exhibited comparable granule and tablet properties with maize starch BP.

Keywords: Pennisetum glaucum, modification, starch, binder, paracetamol tablets

Indexing: Index Copernicus, African Index Medicus

Introduction

Starch is a polymeric carbohydrate consisting of a large number of glucose units joined by glycosidic bonds. It is a white powder that is tasteless, odourless and insoluble in water. It is a natural polymerutilized in the pharmaceutical industry because of its cost effectiveness, availability and biodegradability. It is the most commonly used excipient in tablet formulation as a binder or disintegrant. A binding agent helps to maintain the cohesiveness and mechanical strength of granules to be used for tablet manufacture. This ensures that the compressed tablet from the granules is not compromised during transportation, handling and usage**.** Most commonly used binders are starch mucilages such as those from maize (corn), rice and potato starches with maize starch BP being the most popular and used as a binder or disintegrant [1]. Other pharmaceutical uses of starch are been investigated and with emphasis on the search for newer and local sources of the polymer [2-5].

Pearl millet (*Pennisetum glaucum*) is an important staple food throughout large parts of Asia and western Africa. Millet has been used in Africa and India as a staple food for thousands of

years. Today millet ranks as the sixth most important grain in the world, sustains one third of the world's population and is a significant part of the diet in northern China, India and Nigeria [6]. The dry grain of pearl millet contains about 70 % of carbohydrate which consists almost exclusively of starch [7].

Modified starch, also called starch derivatives are prepared by physically, enzymatically, or chemically treating native starch to enhance its properties[8]. The chemical modification of starch by acid hydrolysis involves suspending starch in an aqueous acid solution at certain temperatures for a period of time causing the glycosidic bonds between the monomer units of the starch polymer to cleave [9]. This leads to an increase in the relative crystallinity of starch since acid preferentially attacks the amorphous regions, while the crystalline regions remain intact [10,11]. The modification changes the physiochemical properties of the starch without destroying its granule structure and yielding starch with increased solubility, gel strength, and decreased viscosity [12,13].

Some studies involving the acid hydrolysis of various native starches have revealed a modified starch product imparting a range of enhanced properties on their tablet formulations. Such properties includes high bond strength, fast disintegration and better dissolution properties [4,14]. Therefore, this study aims at investigating the binding properties of modified (acid treated) millet *(Pennisetum glaucum)* starch mucilage on some physical characteristics of paracetamol tablets in comparison with maize starch BP mucilage.

Materials and Methods

Materials

Paracetamol and croscarmellose sodium powders were a gift samples from Edo Pharmaceuticals Ltd, Benin City, Nigeria. Maize starch BP and concentrated hydrochloric acid (BDH Chemicals Ltd, Poole, England), sodium hydroxide (CDH Ltd, New Delhi, India), concentrated sulphuric acid (Loba Chemie Pvt. Ltd, Mumbai, India), α-lactose monohydrate (Fluka, Netherlands), magnesium stearate and talc (International Co. Ltd, Anhui, China), Pearl millet (*Pennisetum glaucum*) was purchased from Lagos street market in Benin City and starch extracted in the Production Laboratory, Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, University of Benin, Benin City, Edo State, Nigeria

Extraction of millet starch

The extraction was carried out following an earlier reported method [14]. Briefly, about 2 kg of the dry millet grain was washed and soaked in water for 24 h. The steeped grains were milled into a paste and mixed with sufficient water and then strained through a muslin cloth to remove the grain chaff. About 100 ml of 0.1 N 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 starch was collected. The collected starch was spread to dry in an oven at 40 ºC. The dried starch lumps were size-reduced to powder using a blender and weighed. The percentage yield of the extraction process was calculated.

Acid treatment of millet starch

Using an earlier reported method with some modification [15], about 1.46 kg of the extracted millet starch was treated with 3 L of 1.0 N H_2SO_4 for 120 h. Thereafter, 0.2 ml of 0.5 %v/v ammonia was added to the solution to quench the reaction as well as mop up the sulphate groups on the surface of individual starch particles.The starch was washed several times with distilled water, allowed to sediment and the supernatant poured away until the clear supernatant tested neutral to litmus. The sedimented starch was collected and dried in a hot air oven at 40 ºC for 24 h. The starch was powdered with a laboratory ball mill, passed through a 125 μm mesh sieveand weighed. The percentage yield of the modification process was calculated.

Preparation of binder solutions

Various concentrations of the modified *Pennisetum glaucum* (2.5-15 %w/v) and maize starch BP (7.5 %w/v) mucilages were prepared by dispersing the required quantities of the starch in 20 ml of distilled water contained in a 500 ml beaker and then making up to 100 ml. The beaker was transferred to a water bath thermostated at 60 °C. The dispersion was heated with continuous stirring until a gel of uniform consistency was formed.

Preparation of paracetamol granules and tablets

The wet granulation method was used for the preparation of the granules. Five batches were prepared, consisting of one batch of the standard binder (Maize starch BP) and four batches of the test binder (modified *Pennisetum glaucum* starch) as shown in Table 1. Calculations were made for the preparation of 100 tablets. The required amounts of paracetamol powder, lactose and half of that of croscarmellose sodium were dry mixed in a mixer for 5min. Sufficient quantity of the various binder mucilages (*Pennisetum glaucum* starch and maize starch BP) were added to the mix with continuous mixing to produce an evenly damp mass which was then passed through a 1.7 mm aperture sieve and then oven dried at 60 ºC for 15 min. The dried granules were then passed again through a sieve of 710 µm aperture size. The remaining half quantity of croscarmellose sodium was then added extra-granularly as well as talc and magnesium stearate and mixed to obtain the final granules.

The granules was compressed into tablets using a manually operated single punch machine (Type F3 Manesty Machines, UK) at a load of 27KN. The pressure was maintained for all batches of paracetamol tablets. The tablets were collected, dedusted and stored in an air tight container for further evaluation.

Table 1: Formula of prepared paracetamol granules and tablets

Ingredients	A	B	C	D	E
Paracetamol powder (mg)	500	500	500	500	500
Lactose (mg)	50	50	50	50	50
Croscarmellose sodium (mg)	50	50	50	50	50
Maize starch BP mucilage (%w/v)	7.5	-	3	6	-
Modified millet starch mucilage (%w/v)	-	15	10	5.0	2.5
Magnesium stearate (mg)	3	3	3	3	3
Talc (mg)	3	3	3	3	3

Granules characterization (micromeritic properties)

Bulk and tapped densities: A 30 g quantity of the granules was poured gently into a graduated measure. The volume of the granules was read and the bulk density calculated. The measure containing the 30 g of the granules was tapped 100 times on a wooden platform. The volume was noted and used in calculating the tapped density.

Carr's index and Hausner's ratio: The difference between the tapped and bulk density of the granules divided by the tapped density was calculated and the ratio expressed as percentage to give the Carr's index. The ratio of the tapped density to the bulk density of the granules was calculated as the Hausner's quotient.

Angle of repose: The fixed funnel and free standing cone method was used. A transparent glass funnel was clamped at 2.7 cm above a flat horizontal surface. Granules were carefully poured through the funnel onto the horizontal surface until the apex of the cone made by the heap of granules touched the tip of the funnel. The height of the heap and the diameter of the cone base were measured. The angle of repose, θ, was calculated using Equation 1.

$$\theta = \tan^{-1}(h/r) \quad \ldots . \quad (1)$$

Where h is the height of the heap of granules and r is the radius of the circular base

Flow rate: The funnel method was employed. A glass funnel was clamped to a retort stand at a certain distance from a horizontal surface. Fifty grams of granules was poured into the funnel with its orifice blocked with a glass sheet. The glass sheet was withdrawn and the granules allowed to fall freely under the influence of gravity. The time taken for the entire granules to pass through the orifice was recorded. This was carried out in triplicate and the mean values recorded.

Drug-excipient interaction studies

FTIR compatibility study was carried out on the native and modified millet starch powders as well as the formulated granules to investigate any interaction between the drug and the starch. Analysis of the sample was done using FTIR-4100 Spectrophotometer (Shimadzu Co. Japan). The potassium bromide (KBr) tablet method was used; five milligrams of the sample was blended with KBr to 200 mg. The powder was compressed using a Sigma KBr press into a tablet shape. The tablet was placed in the sample compartment and scanned at a range of 4000 - 750 cm^{-1}.

Tablets characterization

Dimensions: The thickness and diameter of each of ten tablets per batch were measured using a micrometre screw gauge and their mean and standard deviation values recorded.

Weight uniformity: The weight of each of 20 tablets was determined from each batch using an electronic balance (College B154, Mettler Toledo, Switzerland) and the mean weight and standard deviation were computed.

Friability: Ten pre-weighed tablets were placed in the drum of a friabilator (Erweka GmbH, Germany) revolving at 25 rpm. After 4 min, the tablets were brought out, de-dusted and reweighed. Their percentage loss in weight value was calculated. Triplicate determination was carried out and the mean and standard deviation were reported.

Crushing strength: Using a motorized tablet hardness tester (Campbell Electronics, Model HT-30/50, India), the crushing strength of ten individual tablets per batch was determined by diametric compression. The mean and standard deviation values were calculated.

Disintegration time: The time taken for six tablets per batch to disintegrate in distilled water at 37 ± 0.5 °C were determined using the BP disintegration tester (MK IV, Manesty Machines, UK). The mean or average time and standard deviation were calculated.

Dissolution profiles: The dissolution profiles of the paracetamol tablets were determined using the USP (Type II) dissolution test apparatus for the various batches of the tablets (Caleva ST7, UK). A dissolution medium of 900 ml of 0.1 N HCl solution maintained at 37 ± 0.5 °C with a paddle revolution of 50 rpm was used. A 5 ml volume of dissolution medium was withdrawn at various intervals over a period of 60 min and replaced with an equivalent volume of fresh dissolution medium maintained at same temperature (37 ± 0.5 °C). The samples withdrawn were filtered and suitably diluted with 0.1 N HCl solution. The absorbances of the resulting solutions were measured at λmax of 245 nm (T70, PG Instruments Ltd, USA). The concentration and the percentage of drug released at each time interval was determined using the equation from the standard calibration plot obtained from the pure drug.

Statistical analysis

Descriptive statistics was done for all data using Microsoft Excel (2007). Mean and standard deviations of triplicate determinations was computed and reported. Differences between mean was determined using one-way ANOVA while $p < 0.05$ was considered significant.

Results and Discussion

Percentage yields

The percentage yield of the millet starch extraction and modification processes were 53.65 and 58.74%, respectively. Though some studies have reported lower values for the extraction process [16], the value obtained from the study is in line with that reported by Hoover *et al*., 1996who reported a percentage extraction yield of 53-56 % on whole grain basis [17]. Also, the modification yield was found to be higher than previously reported [15], an observation that may be the result of the type of starch used.

Granule properties

The results of the packing properties of the granules are shown in Table 2. The particle density of *Pennisetum glaucum* starch and maize starch BP showed no variation. Satisfactory values for Hausner ratio and Carr's index were obtained for all the batches of granules except for batch E. Hence, while values indicating good flow properties were obtained for granules prepared using batches A, B, C and D, a value indicating fair flow was obtained for the granules prepared using E. This observation with batch Emay be due to the significant loss of mass granules during the granulation process. All the batches of granules exhibited variable but satisfactory flow rates and angles of repose (<31°) values. The flow rate increased with increasing binder concentration while the angles of repose is the reverse. This observation may be attributable to increase formation of larger particles with the smaller particle filling the spaces in-between the large particles.

Compatibility studies

FTIR analysis: Figure 1 (a), (b), (c) and (d) shows the FTIR spectra of native millet starch, modified millet starch, pure paracetamol powder and the prepared paracetamol granules. The spectrum of pure paracetamol powder showed characteristic peaks at 1227.00 cm^{-1}, 1636.42 cm^{-1} and 3171.00 cm^{-1} (Figure 1(c)). These peaks

observed for paracetamol remained unchanged when compared with the spectral data of the granules (Figure 1(d)). This observation ruled out the possibility of chemical interaction and complex formation between paracetamol and the modified starch during the mixing processes.

Tablet properties

Results from the evaluations carried out on the different batches of the formulated paracetamol tablets are shown in Table 3.

Table 2: The micromeritic properties of the prepared granules

Mucilage type	Batch	Binder concentration (%w/v)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Hausner's ratio	Carr's index (%)	Flow rate (g/s)	Angle of repose (°)
Maize starch BP	A	7.5	0.48(0.10)	0.56(0.10)	1.17 (0.11)	14.90(0.10)	2.25 (0.12)	25.20 (0.40)
Modified millet starch	B	15	0.48(0.10)	0.57(0.10)	1.18(0.10)	15.01 (0.30)	2.30 (0.11)	26.91(0.10)
	C	10	0.47 (0.30)	0.52 (0.20)	1.11(0.21)	11.35 (0.11)	2.30 (0.14)	28.25(0.12)
	D	5.0	0.51(0.10)	0.56(0.10)	1.13(0.10)	11.20(0.10)	2.24(0.12)	28.84 (0.13)
	E	2.5	0.51 (0.40)	0.60(0.10)	1.19 (0.11)	16.25 (0.13)	1.84(0.10)	30.84 (0.21)

Standard deviation in parenthesis

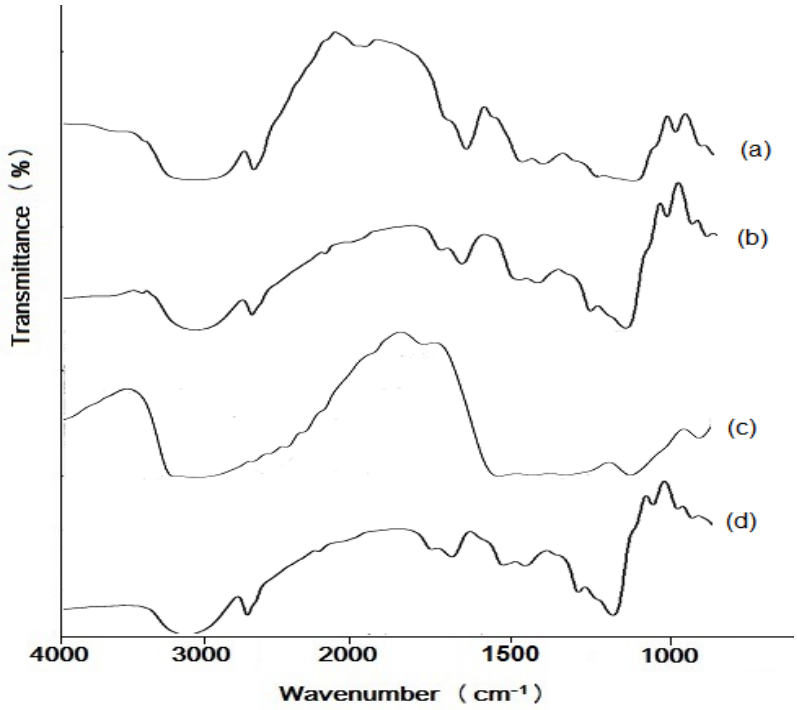

Figure 1: FTIR spectra of native (a) and modified (b) millet starches, pure paracetamol powder (c) and the tablet granules prepared with the modified starch

Table 3: Some physicochemical parameters of the formulated paracetamol tablets

Batch	Weight (g)	Dimension (mm)		Crushing strength (kp)	Friability (%)	Disintegration time (min)
		Thickness	Diameter			
A	0.596 (0.003)	4.31 (0.03)	12.93 (0.01)	7.13 (0.01)	0.68 (0.03)	5.37 (0.07)
B	0.610 (0.001)	4.40 (0.01)	12.97 (0.03)	7.75 (0.04)	0.69 (0.07)	8.28 (0.05)
C	0.600 (0.004)	4.33 (0.03)	12.94 (0.01)	7.25 (0.05)	0.69 (0.02)	7.57 (0.01)
D	0.593 (0.001)	4.32 (0.01)	12.94 (0.01)	6.12 (0.01)	0.70 (0.04)	6.35 (0.02)
E	0.597 (0.002)	4.33 (0.02)	12.93 (0.01)	5.15 (0.02)	0.71 (0.05)	4.40 (0.04)

Standard deviation values are listed in parenthesis

The results of the tablet parameters are presented in Tables 3.

Dimensions

The mean diameter and thickness for all the batches of tablets were not significantly affected by the concentration and type of binder used in the tablet formulation ($p > 0.05$). Tablet diameter depends basically on the diameter of the die wall while the thickness depends on the density of the tablet, compression pressure and speed of compression. All the values obtained were similar irrespective of the binder concentration used. This may be attributed to their comparable particle densities compression pressure and speed and die wall diameter.

Uniformity of weight

The weights of the tablets were not significantly affected by the concentration or type of the binders used. Therefore, was no significant difference ($p>0.05$) within and among the batches. Hence, the tablets passed the weight uniformity test which states that not more than two tablets should deviate from the average weight by 5% and none should deviate by more than 10% [18].

Crushing strength and friability

The formulated tablets exhibited satisfactory hardness with crushing strength values ranging from 5.15-7.75 kp. With increasing binder concentration, there was a corresponding increase in tablet hardness as seen with batches B to E. Also, the tablet gave acceptable friability values below 1.0 %. As specified in the official book, without the tablet capping, or breaking up in the course of the test, a range of 0.8 - 1.0 % loss in weight of the tested tablets is acceptable [18]. As observed, the friability values increased as the binder concentration decreased. As binders promote plastic deformation of particles thereby increasing the area of contact for inter-particulate bonding and subsequently leading to the formation of more solid bonds in the tablet [19], this may be responsible for the increased hardness and decreased friability with increase in the concentration of the binder. Although the hardness and friability values of the tablets formulated with the modified millet starch were comparable with those of maize starch BP, they were however superior to those tablets made with native millet starch in a similar study [14], however, this could be attributable to the wet granulation involving a mucilage binder used in this study as against the direct compression of the previous study.

Disintegration time

All the batches of tablets exhibited variable disintegration times but they disintegrated within 15 min (Table 3) as specified in the British Pharmacopeia for uncoated tablets [18]. The batch B tablets formulated with the highest concentration of the modified millet starch had the longest times. The disintegration times decreased with decrease in the concentration of the modified millet starch. As all the tablets were prepared with the same amount of disintegrant (croscarmellose sodium), it is expected that the differences in their disintegration times should be negligible. The differences in the tablet's hardness could be responsible for the variation in the disintegration times observed among the batches of tablets.

Dissolution profiles

The *in vitro* drug release profiles of the paracetamol tablet formulations are presented in Figure 2. Irrespective of the disintegration times of the tablets, all the tablets exhibited rapid drug release with over 70 % of drug released within 30 min [18].Since the rate of a tablet disintegrating influences drug release from the tablet, it is expected that the batches of tablets (E and A) with shorter disintegration times should exhibit faster and greater extent of drug dissolution, but this was not the case. The comparable drug release of batch B tablet may be the result of a higher water penetration or uptake by the modified millet starch binder resulting in increased swelling of the whole tablet and drug release. A similar study on acid treated Dioscorea starch showed that the treated starch exhibited a higher swelling power and greater water-binding capacity [4].The type and mode of incorporation of the disintegrant may also account for the rapid release of the drug. The portion of the disintegrant incorporated extra-granularly must have facilitated the break-up of the entire tablet into its primary particles, though at varying times which accounts for the different disintegration times. After this initial break-up, the primary particles which are now wholely in contact with the dissolution fluid, would not delay in further break-up due to the intra-granularly

incorporated disintegrant, leading to rapid release of the drug.

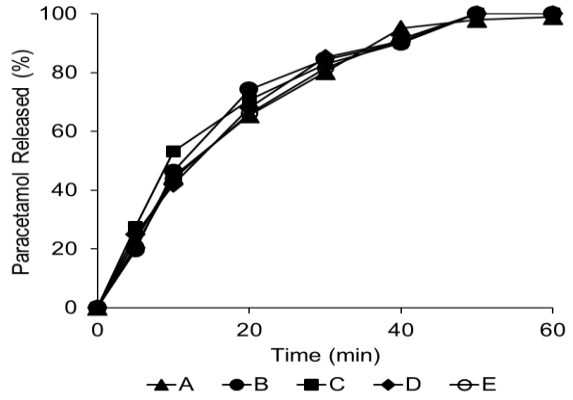

Figure 2: Dissolution profiles of the batches of paracetamol tablets

Conclusion

The results from the study show that modified millet starch when used as a binder in paracetamol tablets exhibited comparable granule and tablet properties with maize starch BP. Tablets formulated with the acid-modified millet starch showed superior disintegration times over maize starch BP at 2.5 %w/v. The acid-modified millet starch can also be used as an alternative to maize starch BP because of their comparable dissolution profiles at all test concentrations.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the author(s) named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. OAM collected and analyzed the data and prepared the manuscript, BOM contributed to the analysis of data and preparation of the manuscript, CPU carried out the laboratory works, SOE supervised the laboratory work and revised the manuscript while MAI conceived and designed the study.

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