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Evaluation of xerogels of cassava and cocoyam starches as dry granulation binders and disintegrants in directly compressed paracetamol tablet formulations

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ABSTRACT

The physicochemical properties of excipients play vital roles in the process of tablet manufacture. A comparative evaluation of the binding and disintegrant properties of xerogels of cassava and cocoyam starches with microcrystalline cellulose (MCC) in paracetamol tablet formulations was investigated. Cassava and cocoyam starches were extracted from their tubers following standard procedures. Xerogels of both starches were prepared and used to prepare batches of paracetamol granules for direct compression into tablets at concentrations of 3.8, 7.6 and 11.4 %w/w and with 7.6 %w/w MCC for comparison. Granules were analysed for their flow properties and drug-excipient compatibility and the tablets were evaluated for their tablets properties. The paracetamol granules prepared with the xerogel powders were comparable in flow properties with those made with MCC. Differential Scanning Calorimetry and Fourier Transform Infrared analyses revealed no interaction between the xerogel powders and paracetamol. Increase in concentrations of the xerogel powders led to an increase in hardness, wetting time, water sorption, disintegration time, drug release and a decrease in friability of the tablets. Tablets formulated with the starch xerogel powders met compendial requirements at 7.6 %w/w concentration. The study confirms the potentials of xerogels of cassava and cocoyam starches as dry granulation binders/disintegrants. Tablets made with the xerogel powders are superior to those made with MCC in terms of disintegration time but MCC produces harder and less friable tablets, as a superior binder.

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Introduction

Excipients are vital components in the direct compression process of tablet manufacture as they must not only possess those properties which are necessary for satisfactory tablet formulation but retain them when mixed together especially with the active ingredients (1). A wide variety of functionalities are met by excipients, these include ease of processing different active pharmaceutical ingredient (API) into dosage forms, better tablet binding, better tablet disintegration, better API bioavailability and also good flowability, compressibility, particle size distribution, hardness and taste masking that improve the manufacture and performance of tablets and capsules (2-4).

The performance of a pharmaceutical excipient is influenced by its physicochemical properties. There is need to predetermine the specifications of excipients in order to control their physical properties of size, shape, texture, density and moisture content. These physical properties can be manipulated during the production of excipients (3). Starch is one of the most commonly used excipients in the manufacture of solid dosage forms. Starches are modified by physically, enzymatically or chemically treating the native form of the starch (5). Starches from different sources have been evaluated and used as excellent binders in either mucilage (gel) or the dry powdered form (6,7). The removal of the fluid component of mucilages of starch by evaporation or freeze drying results in a solid mass termed xerogel which will swell and reform the gel on contact with fresh fluid component. The gel network within xerogels are usually highly porous (15-50 %) with very small pore size (1-10 nm) and a large surface area (150-900 m^2/g). The high porosity of the xerogel network may facilitate tablet disintegration by enhancing fluid penetration into the tablet mass, thereby promoting tablet swelling and disintegration, and consequently enhancing drug release (dissolution) from the tablet. Although reports have shown the pharmaceutical applications of other types of gels i.e. hydrogels and organogels (8-11), little work appears to have been reported on the use of xerogels in the pharmaceutical or food industries either as excipient for dosage forms or as food substitute or supplement. This study was designed to evaluate the xerogels of cassava and cocoyam starches as dry granulation inders/disintegrants in paracetamol tablet formulations.

Materials and methods

Materials

Paracetamol powder (Nomagbon Pharmaceuticals, Nigeria), microcrystalline cellulose (Avicel®) (FMC BioPolymer, USA), sorbitol (Sigma-Aldrich, Germany), maize starch BP (Roquette Freres, France), ethanol and talc (BDH Chemicals, Poole, England), 3.5 %w/v sodium hypochlorite (Reckitt and Coleman Nig. Ltd) and magnesium stearate (Hopkin and Williams, UK). All other chemicals used were of analytical grade. The cassava (*Manihot esculenta*) and cocoyam (*Colocasia esculenta*) tubers were purchased from a local market in Benin City, Edo State, Nigeria. Water was double distilled and all sieves were British Standard Sieves (Endecotts Ltd. London, England).

Extraction of starch

Using the method of Eraga *et al*. (12), tubers of cassava and cocoyam weighing about 5.0 kg each were washed, peeled and sliced into small pieces. The pieces were soaked in water for 3 h to soften the tissues and milled into a paste using an electric grinder (Moulinex, France). The paste was mixed with sufficient water and then strained through a muslin cloth. The suspension obtained was allowed to settle overnight in 1.0 L of water containing 30 m1 of 3.5 %w/v sodium hypochlorite solution for the bleaching of the starch material to take place. Thereafter, the supernatant layer was decanted and the starch sediment washed several times to remove any traces of the sodium hypochlorite and water soluble impurities. This process was repeated several times until a clear supernatant was obtained. The wet starch sediment was sun-dried for 24 h and further dried in an oven (Gallenkamp, UK) at 60 °C for 6 h and the percentage yield of the extraction process calculated. The dried sediment was micronized into fine powder using a ball mill and the powders passed through a 250 µm sieve (Gallenkamp, UK) and stored in an airtight plastic container.

Preparation of starch xerogels

A 15 %w/v starch mucilage was prepared of the cassava and cocoyam starches by dispersing 75 g of the starch powder in distilled water at 32 °C, to make a 100 ml slurry in a 1.0 L beaker. The slurry was well stirred to ensure that all the powder was properly wetted. Freshly boiled water at 100 °C was then added to the slurry to make up to 500 ml and stirred properly till a paste of uniform consistency was formed (13). The paste was then allowed to cool for about 1.0 h and 500 ml of 95 % ethanol was added with continuous stirring and allowed to settle. The supernatant was decanted and the sediment transferred into a transparent heat resistant plastic container, spread thinly and dried in the hot air oven at 50 °C for 48 h. The resulting dried xerogels were pulverized using a dry blender (Moulinex, France) and stored in an air tight container over silica gel until use.

Preparation of paracetamol granules and tablets

Batches of the paracetamol granules and tablets were prepared according to the formula in Table 1. The ingredients were weighed and passed through a 250 nm mesh sieve prior to mixing. The screened quantities were triturated in a mortar and then double compressed, first, by slugging in a heavy-duty tableting machine (Kilian and Co, GmbH, Köln, Germany) and breaking down the resultant slugs into granules with a mortar and pestle. The granules were evaluated for pre-compression parameters and then compressed into tablets using single punch tableting machine (Manesty Machines, UK) at a pressure of 30 arbitrary units (AU). Tablets from the various batches were evaluated for post-compression parameters.

Table 1: Formula of prepared paracetamol powder mixes and tablets

Ingredients	Quantities/tablet (mg)						
	I	II	III	IV	V	VI	VII
Paracetamol	500	500	500	500	500	500	500
Sorbitol	50	75	50	25	75	50	25
Maize starch BP	50	50	50	50	50	50	50
Microcrystalline cellulose	50	-	-	-	-	-	-
Cassava starch xerogel	-	25	50	75	-	-	-
Cocoyam starch xerogel	-	-	-	-	25	50	75
Magnesium stearate	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5

Pre-compression evaluations

Bulk density

Paracetamol granules (30 g) was weighed and poured gently into a 100 ml measuring cylinder. The volume occupied by the granules was recorded as the bulk volume and the bulk density was calculated using Equation 1. Determinations were made in triplicate

$$\text{Bulk density} = \frac{\text{Weight of powder}}{\text{Volume of powder}} \quad (1)$$

Tapped density

The measuring cylinder containing the 30 g granules was tapped mechanically on a flat surface for about a 100 times to a constant volume which was recorded as the tapped volume and the tapped density was calculated using Equation 2. Determinations were made in triplicate.

$$\text{Tapped density} = \frac{\text{Weight of powder}}{\text{Tapped volume of powder}} \quad (2)$$

Carr's (Compressibility) 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. While the ratio of the tapped density to the bulk density of the granules was calculated as the Hausner's ratio or quotient.

Flow rate

The time taken for 50 g of the paracetamol granules to pass through the orifice of an Erweka flow tester was recorded. This was carried out in triplicates and the mean value recorded.

Angle of repose

A short hollow tube of 3 cm in internal diameter sitting on a circular horizontal surface of same diameter was filled with granules. The tube was withdrawn vertically and excess granules allowed to fall off the edge of the circular horizontal surface. The height of the heap was measured. The angle of repose, θ, was calculated using Equation 3.

$$\theta = \tan^{-1}\frac{h}{r} \quad (3)$$

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

Drug-excipient interaction studies

DSC and FTIR compatibility studies were carried out on the paracetamol granules and pure paracetamol powder. The DSC analysis was carried out using a Netzsch DSC 204F1 Phoenix apparatus (Netzsch, Germany). Four milligrams of the sample was weighed into an aluminium pan. The seal was pierced and calibration of the calorimeter was carried out with indium. Heating of the sample was carried out at the rate of 10 °C per min from 30 to 350 °C under nitrogen at a flow rate of 70 ml/min. The FTIR analysis of the sample was done using a Fourier transform infrared spectrophotometer (Spectrum BX, Perkin Elmer, England). 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 the IR scan was carried out over a range of 4000 - 750 cm^{-1}.

Uniformity of weight and tablet dimension

The weight of each of 20 tablets was determined from each batch using an electronic balance and the mean weights calculated while the thickness and diameter of 10 tablets from each of the batches were determined using a Gallenkamp micrometre screw gauge and their mean values recorded.

Crushing strength

The crushing strength was determined by diametric compression of each of ten tablets using a motorized tablet hardness tester (Campbell Electronics, Model HT-30/50, India). Ten (10) tablets were randomly selected per batch and the mean value was calculated.

Friability test

Ten (10) tablets were weighed and 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. The percentage loss in weight value was calculated. Triplicate determination was carried out and the mean and standard deviation were reported.

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.

Wetting time and water sorption ratio

A weighed tablet was placed on a soaked mass of cotton wool in a petri dish and a small amount of amaranth powder was placed on the upper surface of the tablet. The time taken for the development of a red colour on the upper surface of the tablet was taken as the wetting time (14). The wetted tablet was then reweighed and the water sorption ratio of the tablet was calculated as the difference between the final and initial weights with respect to the initial weight and expressed as a percentage. Triplicate determinations were carried out and the average wetting time and water sorption ratio with their standard deviations were calculated.

In vitro drug release

The *in vitro* drug release profiles of the various batches of the paracetamol tablets were determined using the BP paddle method. A dissolution apparatus (Caleva ST7, UK) containing 900 ml of 0.1 N HCl solution maintained at 37 ± 0.5 °C with a revolution speed of 50 rpm was used. Samples (5 ml) were withdrawn from the dissolution fluid at specific time intervals over a period of 60 min and replaced with an equivalent volume maintained at same temperature (37 ± 0.5 °C). The withdrawn samples were filtered and diluted appropriately with 0.1 N HCl solution. The resulting solutions were subjected to spectrophotometric analysis at λmax of 245 nm (T70, PG Instruments Ltd, USA). The amount and the percentage of drug released at each time interval was calculated using the equation from the standard calibration plot obtained from pure paracetamol powder.

Statistical analysis

All the determinations were made in triplicates and data obtained were computed and analyzed using GraphPad InStat software version 3.10. The statistical difference among batches parameters were obtained using student's t-test at 5 % level of significance.

Results

Granule properties

The results from the flow properties analysis of the paracetamol granules are shown in Table 2. The bulk and tapped densities of the granules ranged between 0.61 - 0.71 and 0.70 - 0.79 g/cm^3, respectively, while the flow rate of the granules was within the range of 3.45 - 4.25 g/sec. The angle of repose of all the batches were below 30.85º while the Hausner's ratios and Carr's indices of the granules ranged from 1.17 - 1.25 and 14.10 - 20.61 %, respectively.

Table 2 The micromeritic properties of paracetamol granules

Granule samples	Batch	Sample concentration (% w/w)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Hausner's ratio	Carr's index (%)	Flow rate (g/sec)	Angle of repose (°)
Microcrystalline cellulose	I	7.6	0.63	0.70	1.17	14.10	4.25	22.05
Cassava starch xerogel	II	3.8	0.62	0.74	1.25	20.61	3.45	30.85
	III	7.6	0.63	0.71	1.22	18.75	3.56	30.18
	IV	11.4	0.61	0.70	1.20	16.35	3.56	29.25
Cocoyam starch xerogel	V	3.8	0.65	0.73	1.21	18.64	3.56	30.30
	VI	7.6	0.68	0.77	1.20	16.87	3.67	29.23
	VII	11.4	0.71	0.79	1.19	15.66	3.92	28.45

Compatibility studies

Thermal analysis: Figure 1 (a), (b) and (c) show the DSC thermograms of pure paracetamol powder and the granules prepared with xerogels of cassava and cocoyam starches, respectively. Paracetamol thermogram showed a sharp endothermic peak, corresponding to its melting point (196 °C).

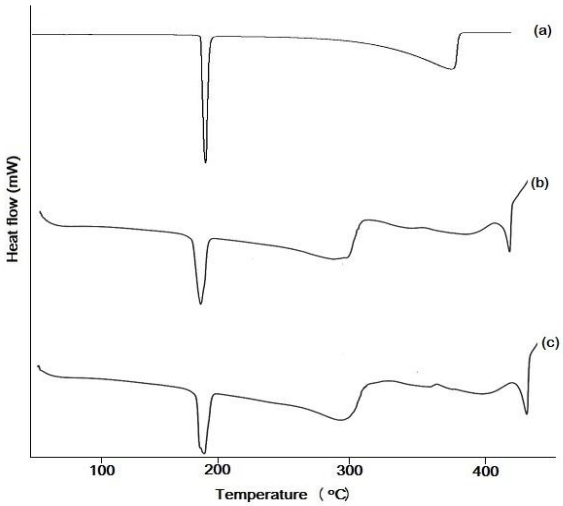

Figure 1 DSC of paracetamol powder (a), and paracetamol granules prepared with xerogels of cassava (b) and cocoyam (c) starches.

FTIR: The FTIR spectrum of pure paracetamol (Figure 2 (a)) powder showed characteristic peaks at 3750.00, 2136.42 and 751.00 cm^{-1}. These peaks observed for pure paracetamol remained unchanged when compared with the spectral data of the granules containing the xerogels of cassava (Figure 2 (b)) and cocoyam (Figure 2 (c)) starches.

Tablet properties

Weight and dimensions

The results from the evaluations of the formulated paracetamol tablets are presented in Table 3. The mean weight of the tablets was between 0.658 - 0.663 g, while the mean diameter and thickness ranged between 3.83 - 3.86 mm and 12.58 - 12.60 mm, respectively.

Hardness and friability

The mean crushing strength values of the tablets was between 3.45 - 5.25 kp with the highest values observed in Batch I tablets. The percentage friability of the tablets was between 0.62 - 1.25 % with the highest values observed in Batch II tablets. The friability of the tablets was observed to decrease with increased concentrations of the xerogels in the formulations.

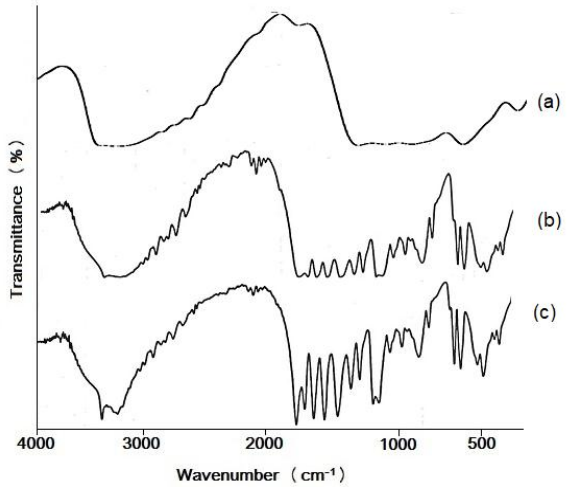

Figure 2 FTIR of paracetamol powder (a), and paracetamol granules prepared with xerogels of cassava (b) and cocoyam (c) starches.

Wetting time and moisture sorption

The Batch I tablets exhibited the highest wetting time of 5.54 min with a fairly good moisture sorption capacity of 50.9 %. Batches II - VII showed wetting times ranging

Table 3: Some physicochemical characteristics of the paracetamol tablet

Batch	Mean weight (g)	Dimensions (mm)		Crushing strength (kp)	Friability (%)	Wetting time (min)	Water sorption (%)	Disintegration time (min)
		Diameter	Thickness					
I	0.660 (0.009)	12.59 (0.016)	3.85 (0.017)	5.25 (0.23)	0.62	5.54 (0.66)	50.85 (0.65)	6.55 (0.81)
II	0.662 (0.025)	12.60 (0.009)	3.83 (0.032)	3.45 (0.55)	1.25	5.04 (0.54)	42.44 (0.18)	3.66 (1.00)
III	0.661 (0.011)	12.59 (0.015)	3.85 (0.097)	4.16 (0.05)	1.10	3.97 (0.42)	46.22 (0.71)	2.66 (1.17)
IV	0.663 (0.024)	12.60 (0.006)	3.86 (0.056)	4.55 (0.84)	0.95	3.35 (0.17)	66.43 (1.01)	2.50 (0.70)
V	0.659 (0.008)	12.59 (0.024)	3.84 (0.057)	4.05 (0.53)	1.05	3.47 (0.76)	52.49 (0.87)	2.83 (0.45)
VI	0.660 (0.011)	12.58 (0.020)	3.85 (0.055)	4.25 (0.79)	0.98	3.05 (0.56)	85.32 (0.54)	1.50 (1.91)
VII	0.658 (0.011)	12.59 (0.014)	3.85 (0.035)	4.75 (0.01)	0.83	2.65 (0.52)	91.60 (1.67)	1.33 (0.68)

Standard deviation values are listed in parenthesis

from 5.04 - 2.65 min while their water sorption ratios was between 42.44 - 91.60 %.

Disintegration time and in vitro drug release

The disintegration times of the various batches of tablets were from 6.55 to 1.58 min. Decrease in disintegration time occurred with increase in xerogel concentrations.

The dissolution of drug from the tablet indicated more than 70 % of the drug was released within 45 min (Figure 3) for Batches I, III, IV, VI and VII. In all the batches, it was observed that as the concentration of the xerogel powders increased, the amount of drug release also increased. The percentage of drug released was highest from Batch VII and lowest from Batch II. The starch xerogel powders increased the dissolution rate of the drug from the tablet compacts.

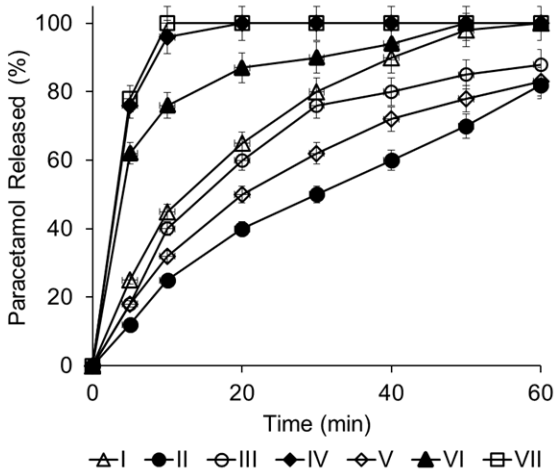

Figure 3 Dissolution profile of paracetamol tablets using varying amounts (w/w) of cassava and cocoyam starch xerogels and microcrystalline cellulose (MCC) (n=3) MCC: 7.6 % (Δ); Cassava starch: 3.8 % (●), 7.6 % (O), 11.4 % (◆); Cocoyam starch: 3.8 % (◊), 7.6 % (▲), and 11.4 % (□)

Discussion

The binding and disintegrant ability of the xerogels of cassava and cocoyam starches in comparison with microcrystalline cellulose was evaluated. The paracetamol granules prepared with the xerogels by dry granulation exhibited good flow properties. The increase in flow with increased concentrations of the xerogels may be due to the formation of larger granules. This increase in particle sizes would also lead to decrease in surface free energy of the granule particles and decrease in frictional forces between the granules leading to faster flow (7).

The compatibility studies showed the characteristic melting point peak of paracetamol appearing as a spike, indicative of its purity and crystallinity. On the other hand, the thermogram of the granules containing the starch xerogels as excipients and paracetamol together showed the same characteristic peak of pure paracetamol at the middle. This observation ruled out any chemical interaction and complex formation between paracetamol and the xerogels during the mixing process and there is no potential interaction between the constituents of the granules.

The properties of the tablets prepared met official compendial specifications with regard to tablet weight and hardness except Batch II that contained 3.8 %w/w of the cassava starch xerogel with crushing strength value lower than 4.0 kp since crushing strength values above 4.0 kp are considered satisfactory for tablets (15). The higher crushing strength values of tablets containing cocoyam starch xerogel suggest that it forms harder tablets hence it may be a superior binder to its cassava starch counterpart since the hardness of a tablet is attributable to the strength conferred on it by its binder (13). The increase in the hardness of the tablets and a decrease in friability in Batches II-VII would suggest that increasing the concentration of the starch xerogels, increases the tensile and mechanical strength of the tablets. This observation implies that the starch xerogels have significant compressibility. However, the Batch I tablets with crushing strength of 5.25 kp clearly show that microcrystalline cellulose (MCC) is a much more superior binding agent compared to the starch xerogels.

Nevertheless, the wetting times, moisture sorption ratios and disintegration times of the tablets from the xerogels reveal their superior nature over MCC in these regards. According to the European Pharmacopoeia (16), a disintegration time of less than 3 min is indicative of a fast disintegrating tablet (FDT). This study has revealed that the xerogels of cassava and cocoyam starches at the

concentrations tested except at 3.8 %w/w for cassava starch, are potential super-disintegrants or dry granulation excipient in the formulation of FDTs. The tablet's superior wetting times are indications of increased water uptake with increased amounts of the xerogels thus suggesting that wicking and swelling may be the mechanisms of their disintegrant action. Wetting time gives an idea of how fast the tablet will disintegrate. The shorter the wetting time, the faster the disintegration of the tablets (17,18).

The *in vitro* drug release studies revealed that tablets formulated with 3.8 %w/w of the xerogels did not release up to 70 % of drug within 45 min (19). This does not agree with the disintegration-dissolution theory, which maintains that disintegration usually plays a vital role in the dissolution process since it determines, to a large extent, the area of contact between the solid and liquid (20). Although these tablets were fast disintegrating, they may have actually disintegrated into coarse particles from which dissolution may be slow, a position maintained by some authors (21,22). At 60 min, the tablets formulated with 7.6 and 11.4 %w/w of the cocoyam and cassava starch xerogels respectively, released 100 % of the drug, which supports that these concentrations are optimum for disintegration and dissolution for the respective starches.

Conclusion

This study has shown the potentials of cassava and cocoyam starch xerogels as binding/disintegrant excipient. The study has also revealed the superiority of the xerogels over MCC as a disintegrant at all the concentrations studied but inferior to MCC as a binder, as MCC produced harder and less friable tablets at the 7.6 %w/w concentration studied.

Conflict of interest

The authors declares no competing interests.

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