The effect of thermal and chemical modifications of excipients on the compressional properties of paracetamol tablet formulations including maize, cassava and sweet potato starches as filler-binders.

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Received: April 6, 2015; *Accepted:* August 6, 2015

Original Article

ABSTRACT

The effects of thermal and chemical modifications on the properties of directly compressed paracetamol tablets containing cassava and sweet potato starches were compared with official maize starch. Fresh tubers of the cassava plant, *Manihot esculenta* Crantz (family *Euphorbiaceae*) and the sweet potato plant *Ipomoea batatas* L. Lam (family *Convolvulaceae*) were obtained and the acetylated and pregelatinized forms of these were prepared using Maize Starch BP as the standard. Paracetamol tablet formulations (500mg) were prepared by direct compression including the starches at various amounts. The compressional properties of the tablets were evaluated using the Heckel, Kawakita and Gurnham equations. Modifications of the starches decreased the P_k (an inverse measure of plasticity) values in the paracetamol formulations at low starch concentrations (10.0% to 25.0%), indicating an increase in the total amount of plastic flow. The P_k values increased at higher starch concentrations (≥ 50.0%). Tablets containing maize starch showed higher *c* values when using the Gurnham equation suggesting greater densification. The thermal and chemical modification of the experimental starches improved the compressional properties of the directly compressed paracetamol tablet suggesting that they could be developed for use as pharmaceutical excipients.

KEY WORDS: Starch, excipients, acetylation, pregelatinization, direct compression, compressional properties

INTRODUCTION

Tablets are the preferred dosage form for medicinal products because they are simple and convenient to use as they provide an accurately measured dosage of an active pharmaceutical ingredient (API) in a convenient portable package (1). Direct compression is considered an attractive method for making tablets due to its simplicity, cost effectiveness, suitability for moisture labile materials and capability for producing consistent dissolution profiles in tablets (2-5). To achieve the desired drug release the process requires the inclusion of excipients possessing the appropriate functionalites.

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Starch is one of the most versatile excipients used in pharmaceutical formulations. Its use is particularly common in the manufacture of oral solid dosage forms (6, 7). In tablet formulations, it may provide different actions e.g., as a binder, filler-diluent, disintegrant or glidant (7-9). Native starches have been characterized previously and noted for their limited functionality (10, 11). Modifying these starches through could provide desirable functional properties required in pharmaceutical excipients (12-15).

The compaction properties of pharmaceutical formulations can be studied experimentally using a variety of techniques, ranging from instrumented tablet presses to compaction simulators (16). A compaction equation, however, can establish a relation between some measures of the state of consolidation of a powder as a function of the compaction pressure. A comparison between different sets of data is made easier by fitting the experimental data to linear plots (17). The relationship between the volume and applied pressure during compression is the main approach used in deriving a mathematical representation of the compression process (18). Basically, during the compression of powders, volume reduction occurs as a function of the compression force. Therefore, a widely used method in describing the compaction processes of powders involves the measurement of the porosity changes as a function of the compression pressure (19).

A literature review shows that most mathematical expressions describing the compaction process are based on the transformation of a classical stress strain or force displacement relationship (20), where either the compaction pressure or volume is transformed. Normalization of volume is achieved, either based on the initial bulk volume, or on the true density of the powder (19, 21). Many of these hypothetical equations have been criticized because it would appear that some of the constants lack physical significance (18).

The Heckel equation (22) is the best known and probably the most useful of the existing compression equations. It is similar to the equation of a first order chemical reaction, where the concentration is substituted with porosity and time with pressure. The pores are analogous to the reactant while densification is the product (18). The Heckel equation is shown in Equation 1:

$$\frac{dD}{dP} = K(1-D) \qquad \text{Eq. 1}$$

Where, D is the relative density or packing fraction of the compact at applied pressure P, and the constant K is a measure of the plasticity of the compressed material and represents the reciprocal of the mean yield pressure, that is $K = 1/P_y$, where P_y is the mean yield pressure. The yield pressure is the stress at which particle deformation is initiated reflecting the deformation of the particles during compression (6).

Integration of Equation 1 gives Equation 2:

$$\frac{\ln(1)}{(1-D)} = KP + A \qquad \text{Eq. 2}$$

The constant A is a function of the original compact volume and it is suggested that it represents the rearrangement and fragmentation of the particles.

A linear plot can be derived from this relationship where K is the slope of the straight line portion, while A is the intercept of the extrapolated linear portion. These Heckel plots, can be used to characterize the compaction properties of different materials.

The calculation of D_a was derived from the value of the intercept A where D_a is the total

precompression density at zero and low pressures (23) as shown in Equation 3:

$$D_a = 1 - e^{-A} \quad \text{Eq. 3}$$

The relative density D_o of the powder bed at zero pressure, that is, when no pressure has been applied describing the initial phase of densification and rearrangement due to die filling. The relative density at low pressures, D_b describes the phase of rearrangement at low pressures. Equation 4 was similarly derived to represent the relationship between the different density values:

$$D_b = D_a - D_0 \quad \text{Eq. 4}$$

The significance of the Heckel plots arises from their ability to identify the predominant form of deformation in a material. They have been used to distinguish between substances which consolidate by fragmentation and those which consolidate by elastic or plastic deformation. They are also applied to assess the plasticity of materials.

However, the usefulness of the plots may be limited as various researchers have obtained different Heckel parameters. These differences can be attributed to experimental variables (24) such as the method of measuring the compact density, dynamic in-die or quasi-static out-of-die method (25), method of measuring true density (helium or air pycnometry or mercury porosimeter), compaction speed, type of compression (uniaxial, rotary press or compaction simulator), total contact time at maximum load and the dwell time (26, 27). Other factors include the effect of compressional loads used (28), punch displacement during compaction and the type and proportion of lubricant used. Significant mathematical errors could also result when using the Heckel equation as it is based on a three-step transformation i.e., volume to density, density to porosity, reciprocal and logarithmic transformation.

Similar to the the Heckel equation, the Kawakita equation was developed to study the compressional behavior of powders (29). The degree of volume reduction, C, equivalent to the strain of the particle bed was used as a basis for the expression. Kawakita equation is shown in Equation 5:

$$C = \frac{V_0 - V_p}{V_0} = \frac{abP}{(1 + bP)} \quad \text{Eq. 5}$$

The expression can therefore be used to derive a linear plot known as the Kawakita plot. The Kawakita equation can further be rearranged giving Equation 6:

$$\frac{P}{C} = \frac{P}{a} + \frac{1}{ab} \quad \text{Eq. 6}$$

Where, C is the degree of volume reduction, P is applied pressure, V_o is the initial volume of the powder bed and V_p is the powder volume after compression, *a* and *b* are constants which are obtained from the slope and intercept respectively of the P/C versus P plots. The constant *a* is equal to the minimum porosity of the bed prior to compression while *b* is called the coefficient of compression, which is related to the plasticity of the material. Values of 1 – *a* yield the initial relative density of the material, D_i which have been shown to provide a measure of the packed initial relative density of tablets with the application of small pressure or what may be referred to as tapping (30).

The reciprocal of *b* yields P_k, which is the pressure required to reduce the powder bed by 50%. The value of P_k provides an inverse measurement of plastic deformation during the compression process. A lower value of P_k indicates that a higher degree of plastic deformation occurred during compression (31). However, Adams *et al.* (32) suggested that the

compression parameter $1/b$, that is P_k, corresponds to the strength of the granules in terms of compression strength.

A limitation of the Kawakita equation is that it is basically only applicable to powdered materials (20). Kawakita and Ludde (29) stated that the equation holds best for soft, fluffy pharmaceutical powders, with particular attention paid to the measurement of the initial volume V_o, and that deviation from this equation is sometimes due to the measured value of V_o. However, various researchers (6, 7, 33) have successfully applied the Kawakita equation to granules which cannot be described as light and fluffy. The Kawakita equation is now generally best applied for low compression pressures and high porosities (17), in contrast to the Heckel equation which shows linearity at high pressures.

The Gurnham equation was first used in the discipline of chemical engineering by Gurnham and Mason (34) to describe the expression of liquids from fibrous materials. Due to the limitations of the Heckel and Kawakita equations, the Gurnham equation has now been adapted for use as an alternative method for evaluating the compressibility of pharmaceutical powders. It is designed to produce more reliable and reproducible characterization of material compressibility (30, 33, 35).

The Gurnham equation proposes that an increase in pressure, expressed as a fractional increase over the existing pressure, results in a proportional increase in the apparent density of the mass. The relationship can thus be expressed as shown in Equation 7:

$$\frac{dP}{P} = A\, dD \qquad \text{Eq. 7}$$

Where, P is pressure, D is apparent density and A is a constant.

Integration of Equation 7 gives Equation 8:

$$D = a \ln(P) + b \qquad \text{Eq. 8}$$

Where a and b are constants.

Applied to pharmaceutical powder compaction, volume reduction may be expressed as porosity (ε) as shown in Equation 9:

$$\varepsilon = 1 - \frac{D}{\rho_t} \qquad \text{Eq. 9}$$

Where, D is the apparent density and ρ_t is the particle or true density of the material.

By replacing density with porosity in Equation 8, a relationship can be derived as shown in Equation 10:

$$\varepsilon = -c \ln(P) + d \qquad \text{Eq. 10}$$

Where, c and d are constants.

Equation 10 describes a linear relationship between lnP and porosity ε for powder compression, which if plotted gives c as the slope and d as the intercept on the regression line.

In its differential form, Equation 10 may be expressed as shown in Equation 11:

$$d\varepsilon = \frac{-c\, dP}{P} \qquad \text{Eq. 11}$$

The constant c represents the effect of pressure change on compact porosity. Large values of c suggest greater volume reduction ability of the compacted material and *vice versa*.

The functionality of excipients can be determined by characterizing their compressional properties in drug formulations. In the present study, three compressional

equations, namely the Heckel, Kawakita and Gurnham equations have been chosen for the evaluation of paracetamol tablets prepared by direct compression using native, acetylated and pregelatinized starches from cassava (*Manihot esculenta*) and sweet potato (*Ipomoea batatas*) in comparison with Maize Starch BP. The aim of the study was to determine the compressional properties of directly compressed paracetamol tablet formulations using the native and modified forms of the selected botanical starches as filler-binders in the formulations.

MATERIALS AND METHODS

Materials

Materials used were paracetamol powder (soured from the People's Republic of China), Maize Starch B.P. (BDH Chemicals Limited, Poole, UK), sodium chloride (BDH Chemicals Limited, Poole, UK), acetic anhydride (BDH Chemicals Limited, Poole, UK), hydrochloric acid (BDH Chemicals Limited, Poole, UK), magnesium stearate (Aldrich Chemical Company Inc., USA) and acetone (Merck Limited, Germany). Distilled water and starches of cassava (*Manihot esculenta* Crantz) and sweet potato (*Ipomoea batatas* L. Lam) were prepared in the laboratory of the Department of Pharmaceutics and Industrial Pharmacy, University of Ibadan, Nigeria.

Collection and preparation of the plant material

Fresh tubers of cassava plant, *Manihot esculenta* Crantz and sweet potato plant, *Ipomoea batatas* L. Lam sourced from local farms in Ibadan were purchased from the Bodija market in Ibadan, Nigeria. Maize Starch BP was used as the standard in this study. The native starch forms were prepared in the laboratory through extraction with water using the method described by Young (36).

Preparation of the pregelatinized starches

Pregelatinized forms of the three starches (including Maize Starch BP) were prepared in the laboratory using the method described in the British Pharmaceutical Codex (37) and Herman *et al.* (38). The products were stored in air tight, amber colored containers.

Preparation of the starch acetates

Acetylated forms of the starches, also known as starch acetates, were prepared using a method modified from Wurzburg (39). The dried flakes of the starches recovered were ground into powder using a mortar and pestle and screened through a number 120 mesh (125 μm) British standard sieve. Each dry product was weighed and stored in air tight containers.

Particle size analysis

Particle size analysis was carried out using a light microscope (BH-2 BHS, Olympus, Tokyo, Japan) to analyze approximately four hundred particles for each powdered sample. Plots of cumulative number percent oversize versus particle size were made to determine the mean projected diameter, $\underline{d}$ of each starch type.

Determination of moisture content

A 10 g starch sample was weighed into a tared weighing dish with an easily removable lid. The dish, without the lid, was placed in a Gallenkamp moisture extraction oven (Model BS 250, Gallenkamp Company, UK) maintained at a temperature of 100°C $\pm$ 2°C for 16 hours. The lid was then replaced and the dish transferred into a dessicator at room temperature and allowed to cool. After cooling, the dish and its content was weighed as quickly as possible. The dish without its lid was again placed in the oven for a further 2 hours. The lid was then replaced while it was allowed to cool in a dessicator and then reweighed.

The last two steps were repeated until the decrease in weight between succeeding weighing did not exceed 0.05 mg per gram of sample. The loss in weight was reported as moisture content. The percentage moisture content was calculated using Equation 12:

$$\%\,\text{moisture content} = \frac{(w_1 - w_2)}{(w_1 - w_o)} \text{x}\,100 \qquad \text{Eq. 12}$$

Where, w_o = weight (grams) of dish and lid; w_1 = weight (grams) of dish, lid and sample before drying and w_2 = weight (grams) of dish, lid and sample after drying.

Determination of particle density

The particle density of paracetamol powder, also known as the true density, was determined using the pycnometer method as described by Ayorinde *et al.* (40).

Determination of loose bulk and tapped bulk densities

The loose bulk and tapped densities of each powder sample were determined using standard methods.

The Hausner's ratio H values of the starches were determined from the ratio of loose bulk volume to tapped volume (Equation 13). The compressibility index, also known as Carr's index C, was determined for each starch powder sample (Equation 14).

$$H = \frac{V_0}{V_t} \qquad \text{Eq. 13}$$

$$C = \frac{100(V_0 - V_t)}{V_0} \qquad \text{Eq. 14}$$

Where, V_o is the loose bulk volume and V_t is the tapped volume.

Preparation of the tablets

Binary mixtures were prepared for direct compression of tablets containing paracetamol and the starches. The composition of the various tablet formulations are presented in Table 1.

Table 1 Composition of paracetamol and starch diluents in the tablet formulations

FORMULATION	PARACETAMOL CONTENT		STARCH CONTENT		TOTAL
	%	Weight (mg)	%	Weight (mg)	Tablet Weight (mg)
F1	90.00	450	10.00	50	500
F2	80.00	400	20.00	100	500
F3	75.00	375	25.00	125	500
F4	50.00	250	50.00	250	500
F5	20.00	100	80.00	400	500
F6	0.00	0	100.00	500	500

The different compositions of the formulations were designed to test the effect on the properties of the prepared tablets of a decreasing, equal or an increasing percentage of starch in the paracetamol concentration.

For each formulation, the specified quantities of each starch and paracetamol were carefully blended by gradual trituration using a mortar and pestle. Using the prepared dry granulation for each formula, tablets (500 mg) were compressed using a Carver Hydraulic Hand Press (Model C, Fred S. Carver Inc., Menomonee Falls, Wisconsin, USA) fitted with a pressure gauge calibrated in metric tonnes (0 to 2.5) using a 2% w/v dispersion of magnesium stearate in acetone as a lubricant. The compressional pressures applied ranged from 28.31 to 198.15 MNm^{-2} and the duration of compression was 1 minute. The prepared tablets were carefully ejected from the assembly and stored in labelled air tight containers kept over silica gel for 24 hours.

Determination of the Heckel relationships

Plots of ln (1/1-D) *versus* applied pressure P were drawn for each botanical starch at the various starch concentrations in the formulations. The values of K and A were obtained from the slope and the intercept on the y-axis of the extrapolated linear portion of the plots respectively as described previously. Mean pressure P_y was obtained as a reciprocal of K while the total pre-compression density D_a (that is, at both zero and low pressures) was obtained using Equation 3. The difference between D_a and D_o (relative density of the powder bed at zero pressure) gave the value of the relative density at low pressures, D_b (Equation 4).

Determination of the Kawakita relationships

The degree of volume reduction, C was calculated using Equation 5. Plots of P/C versus the applied pressure P were made for each botanical starch at the various starch concentrations in the formulations. Values of *a* and *ab* (Equation 6) were obtained from the slope and intercept, respectively, of the straight line obtained as described earlier. Values of P_k, a pressure term indicating the pressure required to reduce the volume of the powder bed by 50% and D_i, the packed initial relative density were derived from the regression plots by applying Equation 6.

Determination of the Gurnham relationships

Plots of percent porosity (% ε) versus lnP (natural logarithm of applied pressure) were drawn for each botanical starch at the various starch concentrations in the formulation. As explained previously, values of *c*, a compressibility term which represents the effect of pressure change on porosity were obtained as the slope of the regression line obtained from each plot.

Statistical analysis

A statistical analysis was carried out using Students' *t*-test and ANOVA, $p \leq 0.05$ was considered the limit of significance (GraphPad Software Inc., San Diego, USA).

RESULTS

Physical characterization of the starches

The percentage yields of the isolated natural starches from their peeled raw sources were 60.67% and 76.67% for cassava and sweet potato starches respectively. The yields of the acetylated starches produced from the weighed quantity of their native forms were 98%, 103.6% and 102.7% for maize, cassava and sweet potato starch acetates respectively. The percentage yields of the pregelatinised starches prepared from the weighed quantity of natural starch were 75.28%, 84.42% and 74.53% respectively for pregelatinized maize, cassava and sweet potato.

Microscopic analysis showed increased particle diameter after modification, especially for the pregelatinized starches. The physical parameters of the starches, including their particle density values, Hausner's ratios and Carr's indices are presented in Table 2. A summary of the relevant physical parameters of the paracetamol powder is shown in Table 3.

Table 2 shows that the paracetamol powder had very low particle density (1.293 gcm^{-1}) and was highly cohesive as indicated by its high Hausner's ratio (2.094) and Carr's index (52.26). Among the starches, native starch forms from all the experimental botanical sources had lower particle density values than the modified forms. Particle density values were higher for the pregelatinized starches than their acetylated counterparts.

The Heckel relationships

Heckel plots for tablet formulations containing 10% w/w starch excipients are shown in Figure

1, while parameters derived from the Heckel plots for all the tablet formulations are presented in Table 4. The linear region of the plots had correlation coefficients of > 0.970 for the tablet formulations.

The P_y values were observed to be generally lowest for the pregelatinized starch formulations, while the formulations including the acetylated starch also exhibited generally lower P_y values than those containing native starches, irrespective of botanical source. The ranking of P_y values by source was generally in the order Maize < sweet potato < cassava. The P_y values generally increased as the concentration ration of starch in the formulations decreased. Values of D_o (relative density of the powder bed at zero pressure), D_a (total precompression density at zero and low pressures) and D_b (degree of densification at low pressures) were generally highest for the formulations containing pregelatinized starch and lowest for formulations containing native starch (Table 4). The acetylated starch formulations had intermediate values of D_o, D_a and D_b at these concentrations.

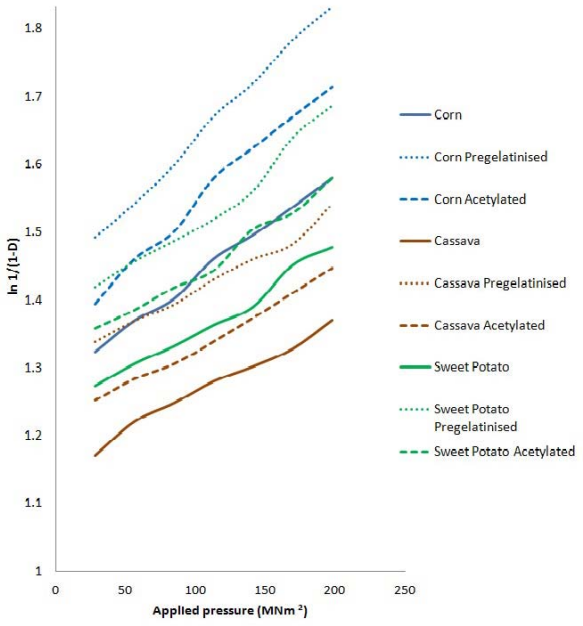

Figure 1 Heckel plots for formulations containing natural, acetylated and pregelatinised starches containing 10% starch to paracetamol.

Table 2 Physical parameters of the native, acetylated and pregelatinized starches (n =3, mean ± s.d)

BOTANICAL SOURCE	STARCH FORM	MEAN PROJECTED DIAMETER, d (μm)	PARTICLE DENSITY D (gcm^{-3})	HAUSNER'S RATIO	CARR'S INDEX	MOISTURE CONTENT (%)
Maize	Native	21.0 ± 0.01	1.49 ± 0.04	1.56 ± 0.01	35.87 ±1.22	5.71 ±2.01
	Acetylated	23.1 ± 1.04	1.52 ± 0.27	1.53 ±0.01	34.78 ±1.25	11.07±1.02
	Pregelatinized	42.9 ± 2.01	1.55 ± 0.41	1.48 ±0.02	32.54 ±2.571	6.45±1.71
Cassava	Native	16.2 ± 0.14	1.43 ± 0.12	1.67 ± 0.00	40.00 ±2.21	5.82±1.42
	Acetylated	10.5 ± 2.15	1.46 ± 0.08	1.61 ±0.05	37.78 ±3.01	10.85±3.47
	Pregelatinized	96.3 ± 1.44	1.50 ± 0.01	1.57 ±0.01	36.43 ±0.68	5.42±1.20
Sweet potato	Native	23.0 ± 0.17	1.48 ± 0.11	1.57 ±0.02	36.47 ±2.52	5.18±0.28
	Acetylated	27.7 ± 1.13	1.51 ± 0.11	1.56 ±0.01	35.71 ±1.24	9.92±2.72
	Pregelatinized	66.2 ± 0.14	1.54 ± 0.12	1.53 ±0.07	34.57 ±2.11	6.54±1.29

Table 3 Physical parameters for Paracetamol powder (n =3, mean ± s.d.)

Particle density (gcm^{-3})	1.293 ± 0.012
Mean projected particle diameter (μm)	3.501 ± 0.45
Hausner's ratio	2.094 ± 0.94
Carr's compressibility index	52.26 ± 3.27

A decrease in the values of D_b for formulations containing acetylated and pregelatinized starch was observed as the concentration of starch in the formulations increased beyond 50%. Without exception, D_o values increased as the concentration of starch in the paracetamol and pure starch formulations increased. These

observations were the same for all the botanical starches.

The Kawakita relationships

Kawakita plots for tablet formulations containing, 10% w/w starch are shown in Figure 2 while parameters derived from the Kawakita plots for the tablet formulations are presented in Table 5. A linear relationship with a correlation coefficient of $\geq$ 0.999 was obtained for the formulations at all applied pressures. For each of the three botanical sources, P_k values generally decreased as the concentration of starch in the paracetamol formulations increased up to the point of about 50% starch in the tablets.At higher concentrations of starch ($\geq$ 50%), P_k values tended to increase as the starch concentration inceased, although there were a few exceptions mainly in native maize and cassava starches where the P_k values maintained their descent with increasing starch concentration above 50%.

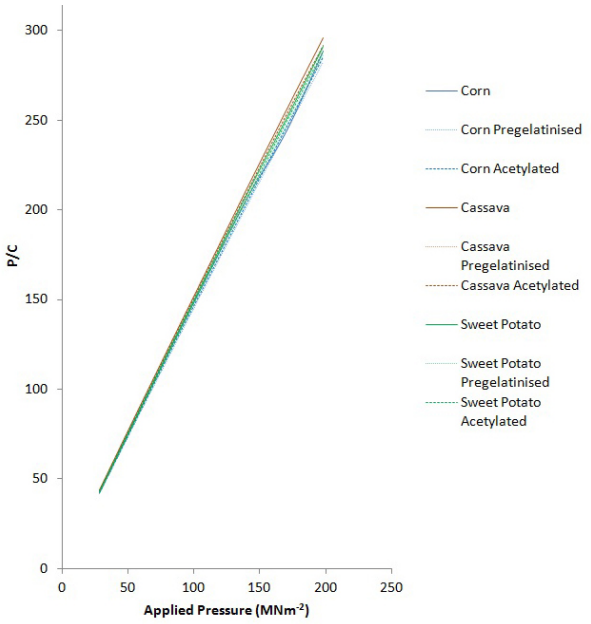

Figure 2 Kawakita plots for formulations containing natural, acetylated and pregelatinised formulations containing 10% starch to paracetamol.

Table 4 Parameters derived from the Heckel plots and density measurements for the starch-paracetamol formulations and pure starches

BOTANICAL SOURCE OF STARCH	CONC. (% w/w)	Native				ACETYLATED				PREGLATINISED			
		P_y	D_o	D_a	D_b	P_y	D_o	D_a	D_b	P_y	D_o	D_a	D_b
Maize	10	662.69	0.248	0.723	0.475	526.04	0.250	0.740	0.490	486.85	0.252	0.761	0.509
	20	580.72	0.255	0.753	0.498	461.04	0.259	0.791	0.532	433.65	0.263	0.814	0.551
	25	446.23	0.259	0.800	0.541	349.53	0.264	0.810	0.546	303.12	0.267	0.827	0.560
	50	309.41	0.280	0.830	0.550	288.85	0.293	0.846	0.553	282.49	0.305	0.865	0.560
	80	299.85	0.315	0.850	0.535	288.18	0.345	0.863	0.518	280.19	0.375	0.878	0.503
	100	282.81	0.346	0.869	0.523	274.73	0.397	0.876	0.479	262.47	0.451	0.889	0.438
Cassava	10	981.35	0.246	0.684	0.438	871.08	0.248	0.703	0.455	861.33	0.25	0.728	0.478
	20	669.79	0.251	0.720	0.469	582.41	0.254	0.736	0.482	558.66	0.259	0.758	0.499
	25	517.60	0.253	0.750	0.497	475.29	0.257	0.759	0.502	448.23	0.263	0.778	0.515
	50	444.25	0.265	0.799	0.534	395.26	0.276	0.806	0.530	388.95	0.291	0.815	0.524
	80	423.37	0.284	0.814	0.530	392.00	0.306	0.823	0.517	366.03	0.339	0.835	0.496
	100	406.67	0.299	0.837	0.538	368.87	0.332	0.841	0.509	334.11	0.385	0.856	0.471
Sweet Potato	10	821.02	0.247	0.708	0.461	767.46	0.249	0.731	0.482	636.94	0.251	0.744	0.493
	20	665.78	0.251	0.752	0.501	544.66	0.256	0.769	0.513	537.35	0.26	0.790	0.530
	25	476.87	0.253	0.792	0.539	411.18	0.259	0.796	0.537	369.82	0.265	0.804	0.539
	50	411.02	0.267	0.811	0.544	365.90	0.281	0.829	0.548	326.48	0.298	0.838	0.540
	80	366.57	0.288	0.829	0.541	360.75	0.317	0.842	0.525	317.16	0.357	0.860	0.503
	100	353.11	0.306	0.843	0.537	324.99	0.351	0.860	0.509	297.71	0.418	0.874	0.456

Table 5 Parameters derived from Kawakita plots for the starch-paracetamol formulations and pure starches (n =3, mean)

BOTANICAL SOURCE OF STARCH	STARCH CONCENTRATION (% w/w)	Native		ACETYLATED		PREGELATINIZED	
		P_k (MNm^{-2})	D_i	P_k (MNm^{-2})	D_i	P_k (MNm^{-2})	D_i
Maize	10	2.671 ± 0.12	0.302 ± 0.01	2.192 ± 0.06	0.299 ± 0.02	2.045 ± 0.92	0.294 ± 0.03
	20	1.984 ± 0.08	0.305 ± 0.02	1.918 ± 0.14	0.295 ± 0.03	1.649 ± 0.04	0.294 ± 0.01
	25	1.757 ± 0.14	0.292 ± 0.17	1.928 ± 0.18	0.291 ± 0.07	1.798 ± 0.85	0.290 ± 0.11
	50	1.970 ± 0.01	0.303 ± 0.07	1.800 ± 0.37	0.314 ± 0.12	1.573 ± 0.32	0.323 ± 0.07
	80	1.933 ± 0.08	0.337 ± 0.08	2.246 ± 0.92	0.375 ± 0.01	2.329 ± 0.14	0.400 ± 0.02
	100	1.975 ± 0.04	0.366 ± 0.09	2.280 ± 0.63	0.418 ± 0.11	2.738 ± 0.27	0.471 ± 0.14
Cassava	10	1.995 ± 0.14	0.327 ± 0.11	2.304 ± 0.14	0.318 ± 0.04	1.737 ± 0.08	0.315 ± 0.11
	20	2.242 ± 0.56	0.311 ± 0.02	2.651 ± 0.29	0.307 ± 0.01	1.970 ± 0.14	0.307 ± 0.08
	25	2.200 ± 0.04	0.299 ± 0.01	2.085 ± 0.32	0.302 ± 0.10	2.059 ± 0.05	0.302 ± 0.14
	50	1.803 ± 0.08	0.301 ± 0.06	1.927 ± 0.09	0.309 ± 0.06	2.048 ± 0.11	0.322 ± 0.03
	80	1.445 ± 0.36	0.300 ± 0.17	1.532 ± 0.18	0.322 ± 0.01	1.605 ± 0.06	0.353 ± 0.07
	100	1.730 ± 0.11	0.328 ± 0.08	2.136 ± 0.43	0.361 ± 0.05	2.488 ± 0.07	0.413 ± 0.16
Sweet potato	10	1.951 ± 0.01	0.316 ± 0.04	1.884 ± 0.12	0.309 ± 0.01	2.057 ± 0.16	0.304 ± 0.12
	20	1.957 ± 0.24	0.302 ± 0.02	1.951 ± 0.18	0.300 ± 0.12	1.763 ± 0.03	0.300 ± 0.06
	25	1.737 ± 0.11	0.290 ± 0.05	1.973 ± 0.52	0.291 ± 0.06	2.033 ± 0.11	0.294 ± 0.11
	50	1.781 ± 0.34	0.298 ± 0.01	1.732 ± 0.08	0.308 ± 0.05	2.513 ± 0.14	0.316 ± 0.07
	80	1.840 ± 0.17	0.316 ± 0.08	1.928 ± 0.67	0.345 ± 0.07	1.986 ± 0.13	0.382 ± 0.02
	100	2.010 ± 0.14	0.331 ± 0.05	2.136 ± 0.23	0.375 ± 0.01	2.704 ± 0.09	0.442 ± 0.13

With the exception of native maize (10% and 20% starch) and starch from native cassava (10%, 20%, 25% and 50% starch), the P_k values for the paracetamol tablet formulations containing between 10% and 80% of starch appeared generally lower than the corresponding values for the pure starches (100% starch). Paracetamol tablets prepared from lower concentrations (10%, 20% and 25%) of native starches from the three botanical sources exhibited generally higher P_k values than those from acetylated and pregelatinized starches. P_k values for paracetamol formulations containing pregelatinized starches at these concentrations were lower than those containing the starch acetates. The P_k values were more variable as the concentration of starch in the formulations was increased to 50% and above.

There was an apparent general increase in P_k values at higher starch concentrations (≥ 50%). Exceptions to this were observed in paracetamol tablets formulated with acetylated cassava starch at 50% and 80% of starch and pregelatinized cassava and sweet potato starches at 80% starch. The P_k values followed a reverse pattern of increase with modification of the starches by acetylation and pregelatinization at the higher starch concentrations. In this case also, formulations containing pregelatinized starches tended to have higher P_k values than those prepared with acetylated starches.

P_k values for the pure starch (100% starch) tablet formulations containing native starch of various botanical sources were generally higher than for their counterparts prepared with the modified starches. The values for those containing pregelatinized starches at this maximum concentration of starch were higher than for the formulations containing acetylated starches of each of the botanical sources. By origin, P_k values for the pure native starches were in the order sweet potato > maize >

cassava. P_k values for the pure acetylated starch tablets were equal for cassava and sweet potato starches but higher for Maize starch. Values for the pure pregelatinized starch tablets were in the order maize > sweet potato > cassava ($p>0.05$).

D_i (packed initial relative density) values generally decreased with the increasing concentration of starch in the paracetamol tablet formulations containing the various botanical starches at the lower starch concentrations between 10% and 25% starch. Formulations containing modified starches generally had lower D_i values than those containing native starches at these lower concentrations. Values for the pregelatinized starch containing formulations were lower than those containing acetylated starches. However, at the higher starch concentrations (50% starch and above), there appeared to be a general increase in D_i values with further increases in starch concentration in the formulations. The ranking order of D_i values at the higher starch concentrations in the formulations was pregelatinized > acetylated > native. Thus, modification of starches at these higher concentrations increased the packed initial relative density values of the paracetamol formulations. Irrespective of botanical origin of the starch, this pattern subsisted.

A comparison of the D_i and D_o (loose initial relative density) values derived from calculations using the Kawakita and Heckel equations respectively (Tables 4 and 5) showed that the D_i values at various starch concentrations in all the formulations were higher than their corresponding D_o values.

The Gurnham relationships

Gurnham plots for tablet formulations containing, 10% w/w starch excipients are shown in Figure 3 while parameters derived from the Kawakita plots for tablet formulations are presented in Table 6. Porosity decreased as applied pressure increased and, as the concentration of starch in the paracetamol formulations increased. Plots of porosity **ε** versus lnP showed linear relationships with negative correlation coefficients $r > 0.920$, an indication of inverse relationship between porosity and applied pressure.

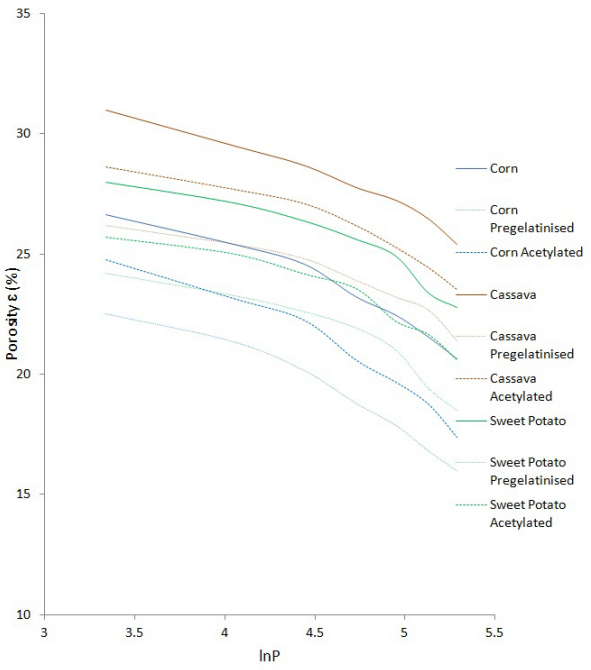

Figure 3 Gurnham plots for formulations containing natural, acetylated and pregelatinised starches containing 10% starch to paracetamol.

Maize starch containing formulations exhibited generally higher values of the slope constant *c* than the formulations containing sweet potato and cassava starch. Conversely, there were generally no significant differences ($p > 0.05$) between the *c* values of the formulations containing sweet potato or cassava starch. There were also no significant differences ($p > 0.05$) between the *c* values for the native starch and modified starch containing formulations. Values for *d* were highest for native starch formulations and lowest for pregelatinized starch formulations, while acetylated starch formulations had intermediate values of *d*. The *d* value also decreased with increase in starch concentration in the formulations.

Table 6 Parameters derived from Gurnham plots for the starch-paracetamol formulations and pure starches (n =3, mean ± s.d.)

STARCH SOURCE	CONCENTRATION (% w/w)	Native		ACETYLATED		PREGELATINIZED	
		c	*d*	*c*	*d*	*c*	*d*
Maize	10	3.072 ± 0.21	37.501 ± 2.15	3.692 ± 0.96	37.783 ± 1.55	3.402 ± 0.14	34.597 ± 2.01
	20	3.025 ± 0.14	34.209 ± 1.78	2.940 ± 0.17	29.890 ± 2.23	2.824 ± 0.52	27.303 ± 1.07
	25	3.037 ± 0.36	29.506 ± 2.11	3.391 ± 1.01	29.420 ± 1.08	3.532 ± 0.27	28.223 ± 1.22
	50	3.330 ± 0.11	27.157 ± 1.42	3.300 ± 0.89	25.695 ± 1.21	2.989 ± 0.96	22.836 ± 3.01
	80	3.032 ± 0.47	24.313 ± 3.01	2.735 ± 1.07	24.184 ± 0.88	2.781 ± 0.44	22.622 ± 1.08
	100	2.962 ± 0.10	22.530 ± 1.86	2.622 ± 0.89	20.323 ± 1.85	2.398 ± 0.32	18.318 ± 2.14
Cassava	10	2.714 ± 0.11	40.389 ± 1.04	2.559 ± 0.17	37.789 ± 1.68	2.304 ± 0.21	34.446 ± 1.98
	20	3.090 ± 0.17	37.762 ± 0.88	3.136 ± 0.54	36.180 ± 1.24	3.034 ± 0.44	33.666 ± 0.54
	25	3.375 ± 0.25	35.567 ± 1.11	3.523 ± 0.17	35.243 ± 1.16	3.421 ± 0.17	32.984 ± 1.23
	50	3.106 ± 0.85	29.882 ± 0.17	3.219 ± 0.32	29.290 ± 0.99	3.014 ± 0.91	27.742 ± 0.89
	80	2.959 ± 0.31	27.524 ± 0.28	2.597 ± 0.16	20.233 ± 0.48	2.373 ± 0.23	18.193 ± 1.02
	100	2.657 ± 0.22	24.589 ± 1.07	2.680 ± 0.41	24.030 ± 1.17	2.676 ± 0.12	22.656 ± 2.22
Sweet potato	10	2.613 ± 0.52	37.372 ± 0.87	2.561 ± 0.17	34.956 ± 1.18	2.786 ± 0.19	34.275 ± 1.02
	20	2.811 ± 0.14	33.700 ± 1.07	2.965 ± 0.63	32.337 ± 2.01	2.674 ± 0.22	29.282 ± 0.58
	25	2.950 ± 0.74	29.947 ± 1.08	3.207 ± 0.41	30.300 ± 1.17	3.389 ± 0.85	30.067 ± 1.07
	50	3.028 ± 0.22	28.288 ± 0.29	2.997 ± 0.54	26.403 ± 1.03	3.038 ± 1.03	25.501 ± 1.02
	80	2.955 ± 0.63	26.145 ± 2.01	2.737 ± 0.49	24.191 ± 0.87	2.768 ± 0.99	22.560 ± 0.58
	100	2.744 ± 0.17	24.029 ± 1.06	2.612 ± 0.28	21.916 ± 1.07	2.540 ± 0.14	20.354 ± 1.01

DISCUSSION

Physical characterisation of the starches

The high yields of the starches from the native sources of cassava and sweet potato suggested that it could be economical to extract them in commercial quantities. The yields of starch acetates were as expected also high, since the replacing hydroxyl groups with the acetate moiety, naturally results in an increased molecular mass. The high percentage yields of the pregelatinized starches also suggested that the modification process was efficient.

Particle size analysis showed that the native starches exhibited the lowest values of mean projected particle diameter, d for all the botanical starches, with the exception of cassava starch (Table 2). The acetylated starches generally had higher d values than their native counterparts. However, pregelatinization was observed to markedly increase the d values of the starches. The ranking order of d for the pregelatinized starches was cassava > sweet potato > maize. The increased particle sizes of the pregelatinized starches may be attributed to swelling of the starch granules due to gelatinisation and resultant leaching of amylose. Loss of amylose has been associated with the increased swelling capacity of starches (41, 42). Larger particle sizes aid powder flow, which is expected to enhance compressibility (43).

The low particle density (1.293 gcm^{-1}) of paracetamol powder and its high Hausner's ratio (2.094) and Carr's index (52.26) values, as seen in Table 2, indicates that it has poor flowability and is highly cohesive in nature, which explains its poor compressional properties. Therefore, paracetamol powder on its own cannot be easily compacted and requires the use of excipients with good flow and densification properties.

The higher particle density values observed for the modified starches, particularly the pregelatinized forms compared with their native forms, reflect the increased particle sizes and

suggest better flow properties as stated by Neumann (43). The Hausner's ratios and Carr's indices of the pregelatinized and acetylated starches were also lower than for native starches. This also suggests better flowability after the modification of the starches. Improved flowability will facilitate better movement of the powder material from the hopper to the die and, thus enhance the uniformity of weight of tablets (44).

The percentage moisture content of the experimental starches ranged between 5.18 and 11.07% (Table 2). These ranges all fell within the typical values expected at 50% relative humidity (45). The native starch forms from the different botanical sources were observed to exhibit lower moisture content than their modified forms. The acetylated starch forms exhibited the highest content of moisture compared with the other forms. The moisture content of the pregelatinized forms were moderately higher than for the native forms, with the exception of pregelatinized cassava which recorded a slightly lower moisture value (5.42%) than native cassava (5.82%). Starch is generally hygroscopic and absorbs atmospheric moisture to reach equilibrium humidity (45). Processing the starches by acetylation and pregelatinization exposes the starch to more humidity which may explain the higher moisture content values for the acetylated starches, pregelatinized maize and pregelatinized sweet potato starches. The slightly lower value obtained for pregelatinized cassava starch is not significant. Generally, increased moisture content hinders flow of materials. However, very low moisture content may also impair flowability since they are more likely to develop electrostatic charging (44). It is possible that moisture content of the starches, impacted on the compressional properties of the powders in the formulation. Nonetheless, the interplay of many other factors makes the magnitude of this influence difficult to quantify.

The Heckel relationships

The linearity of the Heckel plots obtained from plots of ln (1/1-D) versus applied pressure for the formulations, are suggestive of type A Heckel relationships. This is typical of materials that deform plastically. The generally lower P_y values observed for the pregelatinized and acetylated starches suggested that the starch modification induced faster onset of plastic flow. The P_y values generally increased as the concentration of starch excipients in the formulations decreased (Table 4), indicating that plasticity apparently decreased with decreasing concentration of starch in the formulations.

The parameters D_o, D_a and D_b were generally highest for the pregelatinized starch formulations and lowest for native starch formulations, while acetylated starch formulations had intermediate values. Higher values of these parameters imply a greater degree of initial packing in the die, a greater total degree of densification and a greater rearrangement of particles in the early stages of compression, respectively. The observed decrease in values of D_b for acetylated and pregelatinized starch formulations at higher concentrations of starch in the formulation (above 50% starch) may suggest that a rearrangement of the powder particles in the early stages of compression decreased at these concentrations for formulations containing acetylated and pregelatinized starches.

The increasing values of D_o at increasing concentrations of starch in the formulations indicated that initial packing of the powder particles in the formulations as a result of die filling increased with increasing starch content. Since the starches acted as binders with diluent properties (filler-binders), this may be attributed to increasing granular size due to increased bonding of the particles together with increasing starch concentration. This accounted for the increased values of D_o in the formulations containing modified starches, the

highest values being observed for the pregelatinized starch containing formulations. The larger particle size of the pregelatinized and acetylated starches caused higher D_o values in the formulations containing them (9). Thus, pregelatinization of the starches produced the best initial packing of the particles of the formulation in the die. To a lesser degree, acetylation also facilitated the process of initial packing of particles in the die.

The values of D_b, which describes the phase of rearrangement of the particles at the initial stage of compression were generally higher than their D_o counterparts in all classes of the starch and paracetamol tablet formulations. This could be attributed to the breakdown of the agglomerates of the starch particles following the application of low pressures, leading to the filling of interparticulate void spaces initially present at zero pressure thus facilitating densification (46).

The Kawakita relationships

The Kawakita parameter P_k is different from P_y derived from the Heckel equation, in that while the latter relates essentially to the onset of plastic deformation during compression, the former appears to relate to the total amount of plastic deformation occurring during the compression process. As P_k is an inverse measure of plastic deformation during the compression process, a lower P_k value is associated with improved or increased total plastic deformation (6, 33).

Higher P_k values were observed for formulations containing modified pure starches (100% starch) than for those containing their native starch counterparts suggesting that the modification caused a decrease in the total plastic deformation in the formulation of pure starch particles of the three botanical sources.

Based on their botanical origin, the P_k values for the pure native starches were in the order sweet potato > maize > cassava, sugges-ting that the cassava starch produced the highest total plasticity among the unmodified botanical sources. Acetylated maize had the highest P_k values among the acetylated pure starch formulations indicating that it caused the lowest total plastic deformation. Values for the pure acetylated starches were equal for cassava and sweet potato starches, suggesting that the acetylation of cassava and sweet potato resulted in approximately the same degree of plastic deformation. The P_k values for the pure pre-gelatinized starches were in the order maize > sweet potato > cassava. The higher P_k value for pregelatinized maize suggested lower total plasticity, while the lower value for cassava starch suggest increased total plasticity.

Unlike the pure starch formulations, the P_k values for the paracetamol tablet formulations followed a different trend. Paracetamol tablet formulations prepared with lower concentrations (10%, 20% and 25%) of native starches exhibited generally higher P_k values than those formulated with acetylated or pregelatinized starches. The P_k values for the paracetamol formulations containing pregela-tinized starches at these concentrations were lower than those containing the starch acetates. Thus, the incorporation of the modified starches at lower concentrations resulted in an increased total plastic deformation of the particles. Paracetamol formulations containing pregelatinized starches showed greater total plasticity than those containing acetylated starches at lower starch concentrations. The unmodified starch formulations had the lowest degree of plasticity.

The P_k values followed a reverse pattern of increase with modification of the starches by acetylation and pregelatinization at the higher starch concentrations (≥ 50%), indicating a decreased total plastic deformation at higher starch concentrations in the paracetamol tablet formulations. Here again the formulations containing pregelatinized starches tended to have higher P_k values than those prepared with acetylated starches. Therefore, high

concentrations of pregelatinized or acetylated starch resulted in a decrease in total plastic deformation of the particles in the paracetamol tablet formulations. On the other hand, high concentrations of the native starches resulted in an increased total plasticity in the formulations.

The differences observed between the P_k values for the pure starch formulations and those for the paracetamol tablet formulations may be attributed to possible changes in properties during the formulation process because the paracetamol formulations are multi-component systems, unlike the pure starch formulations. The deformation ability in a single-component system, such as the pure starch, is independent of any other component, whereas, in a multicomponent system, such as the paracetamol tablet formulation, plastic deformation begins once the yield point of any of the components is exceeded.

The D_i (packed initial relative density) values generally decreased with an increasing concentration of starch in the paracetamol tablet formulated with different botanical starches at lower starch concentrations (between 10% and 25% starch), suggesting that increasing the concentration of the starch up to about 25% decreased initial packing when applying some pressure. Additionally at these lower concentrations, formulations containing modified starches generally had lower D_i values than those containing native starches. The values for the pregelatinized starch formulations were lower than those containing acetylated starches. Thus, modification by pregelatinization and acetylation resulted in a decrease in the initial packing of particles in the paracetamol formulations.

The increasing values of in D_i at the higher starch concentrations (50% starch and above), suggested that increasing starch concentrations in the paracetamol formulations beyond 50% caused increasing packed initial relative density in the formulations on the application of small pressure. The order of the D_i values at the higher starch concentrations in the formulations was pregelatinized > acetylated > native, implying that modification of the starches by acetylation and pregelatinization led to increased initial packing on application of small pressure.

A comparison of the values of D_i and D_o (loose initial relative density) derived from the Kawakita and Heckel parameters respectively (Tables 4 and 5) showed that the D_i values were higher than D_o values in all the formulations. This is because D_i values provide a measure of the packed initial relative density of the formulations on the application of small pressure or tapping while D_o values provide a measure of loose initial relative density due solely to die filling (6). Similarily, the Heckel parameter D_b, which relates to densification at low pressures, had higher values than D_i in the respective formulations. The two parameters are significantly influenced by the packing geometry of the powder particles in the formulation, which is also influenced by particle size and morphology.

The Gurnham relationships

The porosity of the tablet formulations decreases with increasing pressure, and also as the concentration of starch in the starch-paracetamol formulations increased. This is attributable to the increase in densification of the powders as more pressure is applied, leading to closing up of pores, and consequently decreasing porosity. This has been confirmed by previous researchers (46, 47). Plots of porosity ε versus lnP showed a linear relationship with negative correlation coefficients, $r > 0.920$. This suggests an inverse relationship between porosity and pressure.

Higher values of the slope constant *c* were generally observed for maize than for sweet potato or cassava starch containing formulations, indicating greater densification in the maize starch formulations. However, the differences in *c* values for sweet potato and cassava starch formulations were not generally

significant ($p > 0.05$), suggesting that the two botanical starches had similar compressional properties. There were no significant differences ($p > 0.05$) between the *c* values of the native, acetylated and pregelatinized formulations of the experimental botanical starches.

The intercept constant *d,* appeared generally highest for native starch formulations and lowest for pregelatinized starch formulations. Values for acetylated starch formulations were intermediate. The *d* value also increased with increase in the concentration of starch in the formulations. The effect of *d* on the compressibility of materials has not been previously clearly defined. However, a comparison of data obtained from the Heckel and Kawakita plots relating to densification suggest that lower *d* values correspond to improved compressibility properties.

CONCLUSION

Acetylation and pregelatinization of the starches studied here resulted in a faster onset of plastic deformation but reduced the total amount of plastic deformation in the formulations containing the pure starches, as well as, paracetamol formulations prepared with higher concentrations (50% w/w and above) of the starches. The modification also improved densification in all the starches. Paracetamol tablet formulations containing maize starch exhibited higher densification than those containing cassava and sweet potato starches, irrespective of the type of modification employed. Cassava and sweet potato starches imparted closely related compressibility properties on the paracetamol formulations. A compressibility function was suggested for the *d* value in Gurnham equation.

Improved compressional properties of formulations prepared with the modified starches were obtained. Therefore, they could be developed commercially as direct compression excipients and thus provide alternatives to Maize Starch BP in tablet formulations.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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