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Influence of Some Starch Mucilages on Compression Behaviour and Quality Parameters of Paracetamol Tablets

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Authors' contributions

This work was carried out in collaboration between author MOA and OAI.Author MOA designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Author OAI managed the analyses of the study and the literature searches. Both authors read and approved the final manuscript.

Research Article

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ABSTRACT

Aims: To evaluate the effect of mucilages of natural and pregelatinized forms of trifoliate yams, rice and official corn starch binders on a paracetamol tablet formulation.
Methodology: Natural starches from two trifoliate yam varieties, and rice were isolated and pregelatinized. Both starch forms were then incorporated into a paracetamol tablet formulation as binders. The influence of the binders on compaction of granules and quality of tablets was assessed. Particle, bulk and tapped densities were measured for all the batches of the prepared paracetamol granules. The Heckel and Kawakita plots from which mean yield pressure, P_y and another pressure term P_k, which indicates the pressure required to reduce the volume of the granule bed by 50%, were derived respectively. Both were employed to assess the compaction behaviour of the granules. Quality of the compressed tablets was studied using tensile strength, friability, disintegration time and dissolution properties as evaluation parameters.
Results: Pregelatinized starch mucilages generally show lower values of both P_y and P_k than natural starch mucilages. Increased concentration of starch mucilage binder also yielded lower values of both P_y and P_k. Tablets containing natural starches exhibited

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higher Tensile strength and lower friability than those formulated with pregelatinized starch binders. Generally, Disintegration time (D_t) and the time taken for 80 % paracetamol to be released (t_{80}) were higher for formulations containing natural starch binders than those containing pregelatinized binders The drug dissolution rate constants k_1 and k_2, were higher for formulations containing pregelatinized binders.
Conclusion: The results obtained are suggestive of the fact that the use of mucilage of pregelatinized starch (rather than natural starch), as well as increase in concentration of the material, would yield formulations with faster onset of plastic deformation as well as higher total plastic deformation. The experimental starches compared well with the standard official corn starch and may thus be developed as substitutes in some tablet formulations.

Keywords: Pregelatinized starches; compaction behaviour; dissolution properties: friability; starch mucilages; tensile strength.

1. INTRODUCTION

Natural and modified starches are widely employed as multipurpose excipients in various solid dosage forms, especially as diluents, disintegrants and binding agents in tablet formulations [1,2,3]. The versatility of starches implies a need to continue to develop new starch excipients with suitable properties to meet the special needs of drug formulators and the demands of novel formulations. This is especially so because the cost of importation of starches, particularly, the official corn starch, is high.

Corn starch BP is the most widely employed official starch binder in tableting. Probably one of the factors that discourage commercial use of non-official starches in pharmaceutical industry is the non availability of detailed information on their fundamental and derived properties.

In this present investigation, starches from white and yellow trifoliate (T.) yam varieties (*Dioscorea dumetorum,* Pax) and rice (*Oryza sativa,* Linn) were isolated, fully pregelatinized and studied as binder in a paracetamol tablet formulation. A literature survey has shown that not much has been done to study relative effectiveness of natural and heat-treated starches from different varieties of trifoliate yam and rice vis- a- vis those of official corn starch. The compaction behavior was assessed using density measurements and Heckel and Kawakita equations [4,5]. Some tablet quality parameters such as friability, tensile strength, disintegration time and dissolution profile were also evaluated.

The Heckel equation is widely employed to relate the relative density, D of a bed of powder to the applied pressure, P during compression process and it is written as:

$$\ln \{1/ (1- D)\} KP + A \quad (1)$$

The mean yield pressure, P_y of the material is the reciprocal of the slope of the linear region, K. The relative density, D_a can be calculated from the value of the intercept A, using the following equation:

$$D_a = 1- e^{-A} \quad (2)$$

The relative density, D_0 of the powder when no pressure has been applied describes the initial phase of rearrangement of densification due to die filling. The relative density, D_b, which describes the phase of rearrangement at low pressures, is given by:

$$D_b = D_a - D_0 \quad (3)$$

The Kawakita expression was developed to assess the behaviour of powders during compression based on the degree of volume reduction and is expressed as follows [5]:

$$C = (V_0-V_p)/V_0 = abP/(1+bP) \quad (4)$$

The expression is used in the following form to obtain the degree of volume reduction, C, during compression [3].

$$P/C = P/a + 1/ab \quad (5)$$

Where V_0 is the initial bulk volume of the material and V_p is the bulk volume after compression. The constant *a* is the minimum porosity of the material while the constant *b* is related to the plasticity of the material. The reciprocal of *b* gives a pressure term P_k which provides an inverse measure of the deformability of the particles during compression, and has been identified as the pressure required to reduce the volume of the powder bed by 50% [6].

Friability describes the ease at which tablets can be reduced to tiny particles [7]. It is a measure of the resistance of tablets to surface abrasion and is assessed by determining the weight loss on subjecting the tablets to a standardized agitation procedure for a specified period of time. More specifically, a certain weight of de-dusted tablets (w_0) is subjected to a well defined level of agitation in a fixed geometry, closed container for a specific time. They are then re-weighed (w). The measure of abrasion resistance or friability, f, is usually expressed as [8,9]:

$$f = 100\ (1-w / w_0) \quad (6)$$

Values of f from 0.8 to 1.0% are usually quoted as upper limit of acceptability for pharmaceutical tablets [8]. Tensile strength, an index of the bond potential of compressed tablet, is usually computed from the determined load required to cause fracture (Hardness) and then applying an established equation [10]. A good tablet is expected to undergo disintegration process followed by dissolution of the drug constituent before the latter's absorption and eventual therapeutic effects at the site(s) of action. Determination of disintegration time usually involves some mechanical agitation. The dissolution properties of some tablets had been determined by Kitazawa et al. [11] by plotting $\ln [C_\infty/(C_\infty-C_t)]$ against time, t to obtain some multiple regression curves, intersecting at various times t.

The aim of this study is to determine the influence of mucilage of natural and pregelatinized forms of trifoliate yams, rice and official corn starch binders on the compression behaviour of a paracetamol tablet formulation. The possible use of these materials as alternative to official corn starch could thereafter be recommended. Paracetamol was employed for this investigation because of its poor tableting properties and hence requires a binder among other excipients to form satisfactory tablets.

2. MATERIALS AND METHODS

2.1 Materials

The materials used included paracetamol B.P. (BDH Chemicals Ltd, Poole, UK), Lactose B.P. (Aldrich Chemical Co. Ltd, Gillingham, Dorset, UK), Corn starch B.P.(BDH Chemicals Ltd, Poole, UK) and Polyvinylpyrrolidone, PVP (molecular weight 40,000; Aldrich Chemical Co. Ltd, Gillingham, Dorset, UK). Other materials used included the starches of white trifoliate yam, yellow trifoliate yam and rice prepared in the laboratory of the Department of Pharmaceutics and Industrial Pharmacy, University of Ibadan, Nigeria.

2.2 Methods

2.2.1 Preparation of natural and pregelatinized starches

Natural starches of white and yellow varieties of trifoliate yam *(Dioscorea dumetorum* Pax) and rice *(Oryza sativa)* were extracted using some established methods [12,13]. All the natural starches (including corn starch BP) were fully pregelatinized using the method described by The Pharmaceutical Codex, B.P.C [14] and Herman et al. [15]. A quantity (100 g) of each of the natural starches was dispersed in 100 ml of distilled water and then heated at 55ºC with constant stirring for 10 min to form a paste which was crisp-dried in an oven at 60ºC for 48 h. The resultant mass was pulverized in a laboratory mill (Christy and Norris Ltd., UK), screened through a number 120 mesh sieve (125 µm) and then stored in air-tight amber-coloured bottles.

2.2.2 Granulation for evaluation of starches as binders

280 g quantity of a basic formulation containing paracetamol (84 %w/w); corn starch (7 %w/w) and lactose (9 %w/w) were prepared to evaluate the starch samples as binding agents. The powders were dry-mixed in a Kenwood planetary mixer for 5 minutes, and then moistened with either 37 ml of distilled water (0.0 %w/v binder) or appropriate quantities of (0.5, 1.0, 2.0, 3.0 and 4.0 %w/v) hot mucilage of each starch sample to produce granules containing different concentrations of each starch binder. Massing was continued for 5 minutes and the masses were wet-screened, using a number 12 mesh sieve (1400 µm), dried at 60ºC for 6 hours in a hot air oven and then dry-screened using a number 16 mesh sieve (1000 µm).

2.2.3 Evaluation of the granules

2.2.3.1 Degree of mixing

About 180 mg of each type of paracetamol granules was dissolved in 50 ml of 0.1 M sodium hydroxide and then diluted with 100 ml of distilled water. The solution was then shaken for 15 minutes. More distilled water was added to produce 200 ml, shaken and then filtered. 10 ml of the filtrate was then diluted to 100 ml with distilled water. 10 ml of the resulting solution was mixed with 10ml of 0.1 M sodium hydroxide, and then diluted to 100 ml with water. The absorbance of the resulting solution was spectrophotometrically measured at 249 nm (UV Spectrometer, Pye, Unicam, UK) and the paracetamol content was determined from a previously prepared calibration curve [16].

The degree of mixing, M was calculated using the following expression [17,18]:

$$M = 1- \delta/ \delta_0 \quad (7)$$

Where δ is the standard deviation estimated from the analysed samples and δ_0 is the standard deviation of the completely unmixed system. δ_0 is a function of the proportion of paracetamol in the mixture (y) and is obtained thus:

$$\delta_0= [y (1-y)]^{1/2} \quad (8)$$

2.2.3.2 Determination of moisture content

The moisture content of each batch of the granules was determined on a wet-weight basis on an Ohaus moisture balance (Ohaus Scale Corporation, New Jersey, USA). A 10 g quantity of each sample was uniformly spread on the sample pan and then the heating cycle was started. The percentage moisture content which is the percent weight loss from the sample by heating was displayed on the equipment. The instrument was allowed to cool between tests.

2.2.3.3 Angle of repose

The static angle of repose was determined using the fixed base cone method [19,20]. A 30 g quantity of the sample was transferred into an open-ended cylinder placed on a static base cone on a horizontal surface. The cylinder was gradually withdrawn vertically and the sample formed a cone-shaped heap. The height of the sample (h) was determined using a cathetometer; the radius (r) was gotten by dividing the fixed diameter by two. Angle of repose (Θ) for each sample was gotten using the equation;

$$\Theta = \tan^{-1} h/r \quad (9)$$

2.2.3.4 Granule size distribution

The size distribution of each granule formulation was determined by sieve analysis (British Standard 1460). A stack of sieves of the following sizes: 12 mesh (1400 µm), 16 mesh (1000 µm), 22 mesh (710 µm) 30 mesh (500 µm) 44 mesh (355 µm), 60 mesh (250 µm), 120 mesh (125 µm) and the receiver, was arranged in descending order of aperture size with the receiver at the bottom. 100g of granules was put on the uppermost sieve, firmly covered and the stack of sieves was shaken for 10minutes on a sieve shaker (Pascal Engineering, Essex, England). The quantity of granules retained on each sieve was weighed and the cumulative weight percentage oversize curve was plotted and the mean granule size $\overline{g}$, which corresponds to the sieve size (µm) at 50% cumulative weight percentage oversize, was calculated. For each sample, the granules of size 500-1000 µm were collected and stored in an airtight container for subsequent experiments.

2.2.4 Measurement of densities

2.2.4.1 Particle density

The particle density (ρ_p) of each paracetamol formulation was determined by the pycnometer method using xylene as the displacement fluid. An empty 50ml pycnometer bottle was

weighed (w), then filled to overflowing with xylene and the excess wiped off. The bottle with the inert solvent was weighed again (w_1). The difference between the two weights was calculated (w_2). A 2 g quantity of each granule batch (w_3) was quantitatively transferred into the pycnometer bottle. The excess xylene was wiped off and the bottle re-weighed (w_4). The particle density, ρ_p was calculated using the following expression:

$$\rho_p = w_2 w_3 / 50(w_3-w_4+w_2+w) \quad (10)$$

2.2.4.2 Other density parameters

A 30 g quantity of each granule batch (M) was carefully poured at an angle of 45º through a glass funnel, into a 100 ml glass measuring cylinder of an internal diameter of 28 mm [21,22]. The height, h (cm) of the powder bed and the internal radius, r (cm) of the measuring cylinder were used to compute the loose bulk volume V_0, thus:

$$V_0 = \pi r^2 h \quad (11)$$

The value so obtained was in turn used to calculate the loose bulk density, ρ_0 (g/cm^3)

$$\rho_0 = M/V_0 \quad (12)$$

The relative density at zero pressure (that is, loose initial relative density or precompression density, D_0) of each granule sample was computed as the ratio of its loose bulk density, ρ_0, to its particle density, ρ_p.

$$D_0 = \rho_0/\rho_p \quad (13)$$

2.2.5 Compression behaviour of paracetamol formulated with starch mucilages

Quantities (500 mg) of each batch of granules of size 500-1000 µm were compressed for 1 minute into tablets with predetermined loads on a Carver hydraulic press (Model C, Carver Inc. Wisconsin, USA), using a 10.5 mm die and flat faced punches lubricated with a 2 % w/v dispersion of magnesium stearate in diethylether- ethanol (1:1) prior to each compression. Tablets of 3.68 $\pm$ 0.22 mm thickness at zero porosity as calculated from particle density values were obtained. The tablets were then stored over silica gel for 24 hours to allow for elastic recovery and prevent falsely low yield values. The weights (w) and dimensions of the tablets were then measured to within $\pm$1 mg and $\pm$ 0.01 mm, respectively, and their relative density, D was calculated using the equation:

$$D = w/V_t\rho_p \quad (14)$$

Where V_t is the volume of the tablets (cm^3). Plots were made of ln{(1/1-D)} against the applied pressure, P for each paracetamol formulation. Values of K and A were obtained from the slope and intercept on y-axis of the extrapolated linear portion of the plots, respectively. The mean yield pressure, P_y was obtained as the reciprocal of K (Eq. 1), and the total precompression density, D_a (that is, at both zero and low pressures) was obtained by applying Eq. 2.

Values of the relative density at low pressures, D_b, were obtained as the difference between D_a and D_0 (Eq. 3).

The degree of volume reduction, C was calculated using Eq. 4. Plots were then made of P/C against the applied pressure, P (Eq. 5) for each paracetamol formulation. Values of *a* and *ab* were obtained from the slope and intercept, respectively. A pressure term $P_{k,}$, which indicates the pressure required to reduce the volume of the granule bed by 50%, and D_i, the packed initial relative density, were obtained from the plots [6].

2.2.6 Tensile strength determination

Using diametral compression on a Monsanto hardness tester, the load, F (MN) required to break each tablet into two halves was determined for all the tablets. Each tablet was placed between the platens of the tester and the knob was screwed until contact was made and then further screwed until there was just enough pressure to cause fracture. The values displayed on the scale of the tester (Hardness) were used to calculate the tensile strength T at different relative densities, respectively [10].

2.2.7 Friability test

The friability (%) of the tablets was determined using an Erweka friabilator (Erweka, Apparatebau, Offenbauch / Main, Germany). Ten tablets were de-dusted, weighed and then placed inside the compartment on the instrument and caused to tumble at the rate of 25 rpm for 4 minutes. The tablets were then re-weighed and the loss in weight, expressed as a percentage of the original weight, was recorded as the friability (Eq. 6).

2.2.8 Disintegration time test

The disintegration time of the tablets was determined in distilled water at 37 $\pm$ 0.5 ºC using a B.P. Manesty disintegration test unit (Manesty Machines Ltd; Poole, UK). A tablet each was placed on the wire mesh just above the surface of the distilled water in the test tubes and the unit was switched on simultaneously with a stop clock. The time taken for the tablets to disintegrate and all particles to pass through the wire mesh was recorded as the disintegration time.

2.2.9 Dissolution rate test

The dissolution rates for the tablets at different relative densities were determined at 37$\pm$0.5ºC in 1 litre of phosphate buffer (Potassium dihydrogen orthophosphate buffer, pH of 7.4) using an Erweka dissolution rate apparatus (Erweka Apparatebau, G.M.B.H Hensenstamm Kr Offenbach/main, Germany). The stirring rate used was 50 rpm [23]. The tablets were placed in a rotating basket, and with the aid of a pipette, 5ml of the medium was taken at pre-selected time intervals. The same quantity of the medium was added at the same temperature immediately after each sampling to keep the volume of the dissolution medium constant. With the aid of a Unicam 8620UV/Visible spectrophotometer (UV spectrometer, Pye, Unicam, UK), the proportion of paracetamol that had dissolved in the medium at each sampling time was determined. Concentrations of paracetamol were calculated from a standard calibration curve of paracetamol in phosphate buffer (pH 7.4) without interferences of excipients.

All the parameters determined were made in quadruplicate and the values presented in all the Tables are simple average.

3. RESULTS

The degree of mixing of the paracetamol granules evaluated spectrophotometrically was found to be greater than 0.95. The values of percent moisture content, mean granule size $\overline{g}$ (*μm*) and particle density for paracetamol granules prepared for evaluation of starch binding agents are presented in Table 1. Moisture content was found to increase as concentration of binding agent increased. Granules containing pregelatinized starch binding agents generally possessed slightly higher moisture content than those formulated with natural ones. As the concentration of binding agent increased, $\overline{g}$ values increased. Formulations granulated with natural starches had larger granule size than those granulated with pregels. The ranking of $\overline{g}$ values for all the formulations was: white T. yam > corn > yellow T. yam >rice. As the concentration of binding agent increased, the particle density also increased. From Table 1, as binder concentration increased, Θ values decreased. Formulations granulated with natural starches had lower Θ values than those granulated with pregels implying higher flowability of the former. The ranking of Θ values for all the granule batches was: white T. yam < corn < yellow T. yam < rice.

The values of loose initial relative density, D_0, for the paracetamol formulations are presented in Table 2. The values of D_0, which describes the initial rearrangement phase of densification as a result of die filling, were found to decrease with increase in the concentration of starch binding agent. From the values of relative density obtained at various applied pressures, Heckel plots of ln{1/(1-D)} versus P were made for all the formulations. Representative Heckel plots for formulations containing 3 $\%^{w}/_{w}$ starch binding agents are presented in Fig. 1. The plots show two regions: a curvilinear initial region, followed by a more linear one. The latter region commenced generally at 84.9 MNm^{-2}, and extended up to 226.4 MNm^{-2}, with correlation coefficient of >0.970 for all formulations. The constants K and A were obtained from the slope and intercept of the linear region, respectively. Heckel parameters (derived from Heckel plots) - mean yield pressure, P_y, and relative densities D_a and D_b are presented in Table 2. P_y values for all the formulations decreased with increase in starch binder concentration. The ranking of P_y values for the formulations was: corn < white T. yam < yellow T. yam < rice. D_b values can be seen to decrease with increase in concentration of binding agent. The values are also observed to be higher than D_0 values probably due to extensive fragmentation of granules as pressure is increased to fill up void spaces between particles. The values of D_b were higher for granules formulated with pregelatinized starches than for those formulated with natural starches. The values of D_a are shown to decrease as binder concentration increased. Also, granules formulated with pregelatinized starch binders exhibited higher values of D_a than those formulated with natural starches. Granules containing white T. yam starch binder exhibited lower P_y and higher D_0 values as well as higher D_b and D_a values than those containing yellow T. yam starch.

Table 1. Properties of formulations containing different types and quantities of starch binders

Nature of Starch Binder	Conc. (% w/w)	Moisture content (%)		Mean granule size $(\bar{g})$ (μm)		Particle density, ρ_p (gcm^{-3})		Angle of repose (Θ)(°)	
		Natural	Pregel	Natural	Pregel	Natural	Pregel	Natural	Pregel
None	0.0	1.34	–	425	–	1.327	–	47	–
White T. yam	0.5	1.44	1.73	601	510	1.327	1.328	33	38
	1.0	1.47	1.77	632	522	1.328	1.330	31	37
	2.0	1.48	1.82	643	568	1.330	1.332	30	37
	3.0	1.52	1.84	670	586	1.334	1.336	31	35
	4.0	1.54	1.91	691	613	1.336	1.338	28	34
Yellow T. yam	0.5	1.35	1.58	559	471	1.328	1.329	37	42
	1.0	1.37	1.64	584	491	1.329	1.330	37	39
	2.0	1.39	1.75	618	525	1.332	1.333	35	38
	3.0	1.40	1.76	639	549	1.334	1.335	34	37
	4.0	1.43	1.78	657	572	1.336	1.338	33	36
Rice	0.5	1.48	1.62	529	450	1.327	1.328	39	41
	1.0	1.52	1.66	540	471	1.328	1.329	37	40
	2.0	1.54	1.68	589	500	1.329	1.331	36	39
	3.0	1.56	1.70	611	519	1.330	1.333	36	38
	4.0	1.59	1.75	633	542	1.331	1.336	34	37
Corn	0.5	1.43	1.53	590	489	1.327	1.328	35	40
	1.0	1.60	1.74	612	509	1.329	1.331	33	39
	2.0	1.64	1.83	633	538	1.330	1.334	32	38
	3.0	1.70	1.94	651	568	1.331	1.335	31	36
	4.0	1.76	2.01	672	600	1.333	1.337	31	35

Table 2. Parameters obtained from Heckel plots and density measurements for paracetamol tablets formulated with different starch binders

Nature of starch binder	Conc. ($\%^{w}/_{w}$)	Natural				Pregelatinized			
		P_y	D_0	D_a	D_b	P_y	D_0	D_a	D_b
None	0.0	205.6	0.271	0.516	0.245	–	–	–	–
White T. yam	0.5	524.9	0.241	0.542	0.301	275.9	0.254	0.652	0.398
	1.0	396.2	0.239	0.539	0.300	215.6	0.252	0.648	0.396
	2.0	351.0	0.237	0.535	0.298	189.7	0.248	0.642	0.394
	3.0	299.8	0.234	0.529	0.295	162.1	0.245	0.636	0.391
	4.0	266.1	0.232	0.523	0.291	150.5	0.243	0.608	0.365
Yellow T. yam	0.5	530.2	0.239	0.538	0.299	323.6	0.253	0.636	0.383
	1.0	491.2	0.238	0.535	0.297	288.2	0.249	0.622	0.373
	2.0	380.2	0.235	0.527	0.292	263.3	0.245	0.617	0.372
	3.0	301.8	0.233	0.526	0.293	252.9	0.242	0.613	0.371
	4.0	286.2	0.231	0.522	0.291	245.8	0.239	0.609	0.370
Rice	0.5	627.7	0.225	0.531	0.306	388.4	0.239	0.615	0.376
	1.0	505.8	0.224	0.529	0.305	313.0	0.236	0.614.	0.378
	2.0	458.7	0.222	0.527	0.305	261.0	0.233	0.607	0.374
	3.0	410.2	0.219	0.523	0.304	231.5	0.231	0.595	0.364
	4.0	380.8	0.218	0.520	0.302	205.5	0.229	0.581	0.352
Corn	0.5	452.1	0.253	0.543	0.290	264.1	0.270	0.751	0.481
	1.0	389.6	0.251	0.540	0.289	210.8	0.266	0.746	0.480
	2.0	308.9	0.250	0.538	0.288	179.1	0.261	0.740	0.479
	3.0	246.5	0.247	0.534	0.287	153.9	0.257	0.732	0.475
	4.0	227.4	0.241	0.524	0.283	120.6	0.251	0.696	0.445

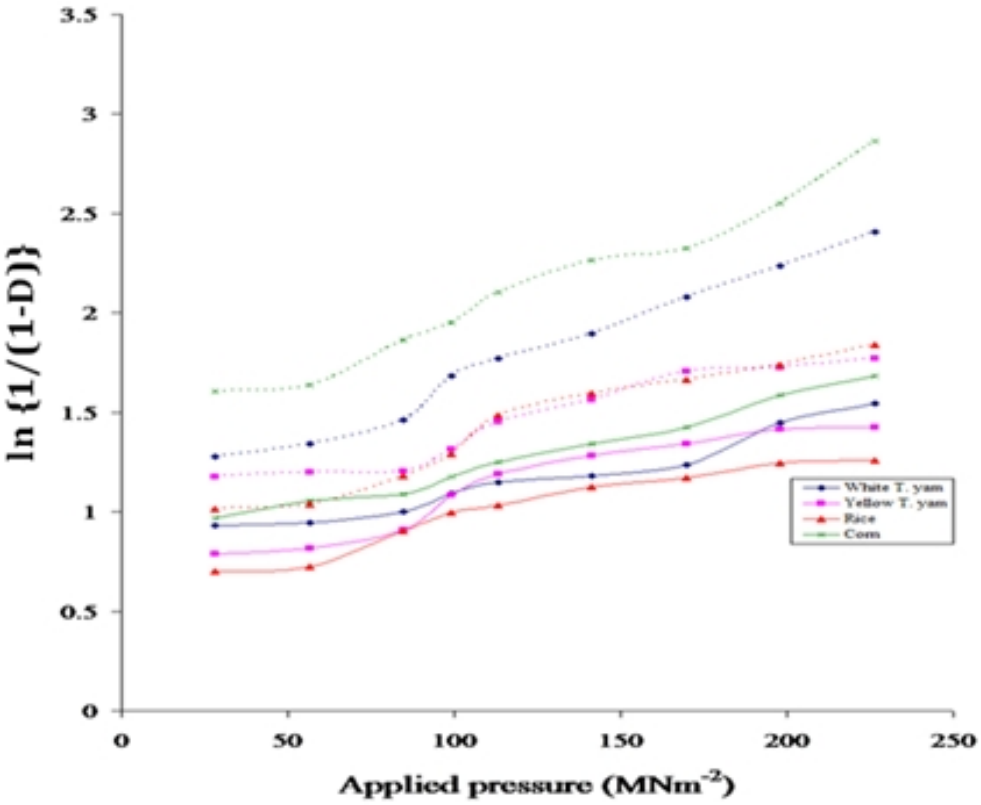

Fig. 1. Heckel plots for paracetamol tablet formulations containing 3% w/w natural (____) and pregelatinized (….) starch binders

From the values of V_0, V_p, and C obtained at various applied pressures, P, Kawakita plots of P/C versus P were made for all the formulations. Representative Kawakita plots for granules formulated with 3%$^{w}/_{w}$ starch binders are shown in Fig. 2. For all the formulations, a linear relationship was obtained at all applied pressures, with correlation coefficient > 0.999. From the slope and intercept of the plots respectively, the values of *a* and *b* were obtained. Values of (1–*a*) give the initial packed density of the granules, D_i, and P_k values were obtained from the reciprocal of the values of *b*. The values of D_i and P_k are presented in Table 3. P_k values decreased as the concentration of starch binding agents increased. Also, granules formulated with pregelatinized starches had lower values of P_k than those formulated with natural starches. The D_i values are shown to decrease as binder concentration increased. Also, granules produced with natural starch binders showed higher values of D_i than those produced with pregelatinized starches. Granules formulated with natural white T. yam starch binder exhibited lower P_k and higher D_i values than those formulated with natural yellow T. yam starch binder and vice-versa for their pregelatinized form.

The values of hardness obtained were used to calculate the tensile strength T for the tablets at different relative densities, respectively [10]. The values of T and Friability *f* are presented in Table 4. For all the formulations, the higher the concentration of binding agent, the higher

was the value of T and the lower was the value of *f*. At the same relative density, T values for tablets formulated with natural starch binders were higher than those for tablets formulated with pregelatinized starch binders and vice versa for the values of *f*. The values of disintegration time, D_t, at various relative densities were obtained and the values of D_t at relative density of 0.90 are presented in Table 5. From the Table, it can be seen that D_t values increased as binder concentration increased. Generally, for both natural and pregelatinized starch binders, tablets formulated with rice starch exhibited the least D_t values while those formulated with corn starch had the highest values. Tablets formulated with pregelatinized starch binders had lower D_t values than those formulated with natural starch binders. From the plots of percentage paracetamol released against time for all the tablets, the values of t_{50} and t_{80}, that is, the time required for 50% and 80% paracetamol to be released respectively, were obtained. Values of t_1, k_1 and k_2 were also obtained for all formulations. All the values at relative density of 0.90 were presented in Table 5.

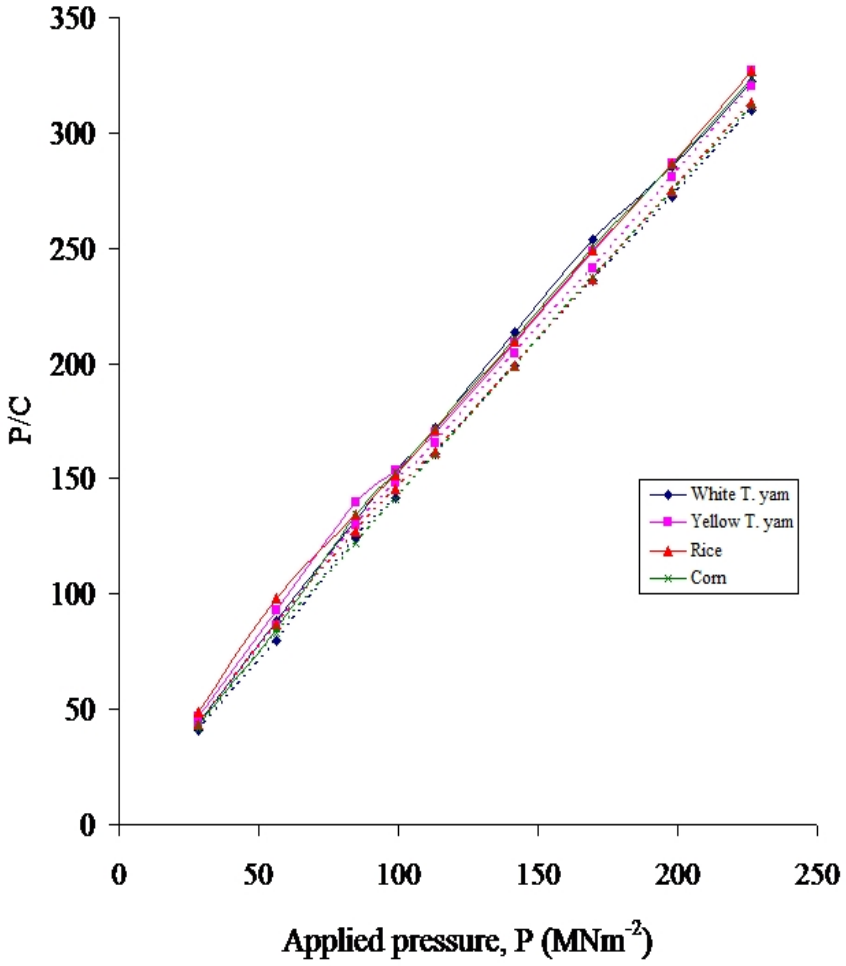

Fig. 2. Kawakita plots for paracetamol tablet formulations containing 3% w/w natural (___) and pregelatinized (….) starch binders

Table 3. Parameters obtained from Kawakita plots for paracetamol tablets formulated with different starch binders

Nature of starch binder	Conc. (% $^{w}/_{w}$)	Natural		Pregelatinized	
		P_k	D_i	P_k	D_i
None	0.0	18.09	0.273	–	–
White T. yam	0.5	9.73	0.323	5.95	0.288
	1.0	7.84	0.310	5.83	0.275
	2.0	7.68	0.301	4.32	0.271
	3.0	7.15	0.295	4.31	0.260
	4.0	7.11	0.280	4.28	0.260
Yellow T. yam	0.5	12.19	0.313	7.12	0.292
	1.0	11.51	0.309	7.02	0.289
	2.0	10.53	0.294	6.93	0.277
	3.0	10.33	0.277	6.50	0.274
	4.0	9.04	0.276	6.27	0.270
Rice	0.5	12.51	0.304	9.09	0.280
	1.0	12.00	0.290	8.63	0.268
	2.0	11.88	0.282	8.00	0.258
	3.0	11.28	0.273	7.59	0.254
	4.0	10.34	0.270	7.42	0.249
Corn	0.5	9.57	0.332	4.64	0.292
	1.0	9.52	0.319	4.61	0.278
	2.0	7.25	0.310	4.60	0.271
	3.0	6.80	0.289	4.33	0.263
	4.0	6.05	0.287	4.26	0.254

Table 4. Some derived properties of paracetamol tablets formulated with various starch binders at relative density of 0.90

Nature of Starch Binders	Conc. % w/w	Natural		Pregelatinized	
		Tensile strength, T MNm^{-2}	Friability *F (%)*	Tensile strength, T MNm^{-2}	Friability *F (%)*
None	0.0	0.331	3.88	–	–
White T. yam	0.5	0.411	1.22	0.364	1.32
	1.0	0.461	1.08	0.405	1.15
	2.0	0.537	0.98	0.459	1.02
	3.0	0.644	0.90	0.515	0.95
	4.0	0.690	0.88	0.543	0.95
Yellow T. yam	0.5	0.415	1.05	0.403	1.18
	1.0	0.515	1.11	0.447	1.16
	2.0	0.588	0.98	0.541	1.04
	3.0	0.711	0.89	0.566	1.00
	4.0	0.775	0.81	0.613	0.92
Rice	0.5	0.404	1.35	0.343	1.33
	1.0	0.451	1.18	0.379	1.21
	2.0	0.489	1.02	0.398	1.10
	3.0	0.495	0.94	0.424	0.95
	4.0	0.504	0.92	0.433	0.92
Corn	0.5	0.481	1.12	0.392	1.13
	1.0	0.534	1.02	0.436	1.07
	2.0	0.624	0/96	0.471	1.00
	3.0	0.734	0.82	0.517	0.88
	4.0	0.821	0.78	0.692	0.84

Table 5. Some release properties of paracetamol tablets formulated with various starch binders at relative density of 0.90

Nature of Starch Binder	Conc. (%w/w)	Natural						Pregelatinized					
		D_t (min)	t_{50}	t_{80}	t_1	k_1	k_2	D_t (min)	t_{50}	t_{80}	t_1	k_1	k_2
None	0.0	1.08	8.01	12.08	8.27	0.082	0.224	-	-	-	-	-	-
White T.	0.5	1.93	10.87	16.70	10.55	0.047	0.120	1.66	10.90	15.74	10.44	0.049	0.144
yam	1.0	1.99	12.99	18.88	12.97	0.041	0.116	1.78	12.50	17.53	12.35	0.045	0.141
	2.0	2.22	14.37	20.01	14.44	0.037	0.113	1.90	14.20	19.60	14.10	0.040	0.138
	3.0	2.36	15.40	22.19	15.43	0.030	0.111	2.00	15.22	21.05	14.56	0.036	0.134
	4.0	2.63	17.95	25.04	18.40	0.026	0.106	2.18	18.64	24.97	17.79	0.029	0.127
Yellow T.	0.5	2.00	12.70	18.68	12.98	0.042	0.118	1.75	12.55	17.52	12.04	0.040	0.139
yam	1.0	2.22	14.37	20.93	15.14	0.037	0.115	1.88	13.93	19.56	13.70	0.038	0.136
	2.0	2.66	15.27	22.17	16.22	0.035	0.112	2.05	14.94	21.00	14.58	0.036	0.130
	3.0	2.98	16.47	23.55	17.18	0.029	0.109	2.21	16.34	22.81	16.16	0.032	0.127
	4.0	3.37	18.31	26.08	19.59	0.023	0.103	2.28	18.06	23.77	17.14	0.028	0.124
Rice	0.5	1.75	10.78	15.16	10.36	0.051	0.139	1.56	9.79	13.17	10.02	0.048	0.156
	1.0	1.89	11.39	17.11	12.00	0.048	0.128	1.69	10.83	14.92	11.15	0.047	0.152
	2.0	2.05	12.45	18.92	13.62	0.041	0.121	1.84	11.75	16.27	12.00	0.043	0.146
	3.0	2.18	14.74	20.62	14.02	0.033	0.117	1.92	13.46	18.68	13.36	0.038	0.141
	4.0	2.29	16.91	24.45	18.08	0.029	0.112	2.06	15.32	20.86	15.14	0.034	0.138
Corn	0.5	2.01	13.33	19.57	14.12	0.037	0.114	1.83	13.23	18.65	12.35	0.039	0.130
	1.0	2.34	15.12	21.46	16.23	0.034	0.110	1.96	14.94	20.70	14.16	0.036	0.125
	2.0	3.12	18.61	23.97	17.33	0.030	0.104	2.10	18.28	23.85	17.25	0.028	0.117
	3.0	3.44	19.35	25.41	18.28	0.025	0.099	2.36	19.00	25.21	17.83	0.027	0.117
	4.0	4.01	20.46	28.33	20.53	0.021	0.074	2.49	20.43	27.01	19.13	0.025	0.112

4. DISCUSSION

The Heckel plots presented two regions: a curvilinear initial region, followed by a more linear one (Fig. 1). The latter region commenced generally from 84.9 MNm^{-2} to 226.4 MNm^{-2} and had correlation coefficient of >0.970 for all formulations containing starch binding agents. This indicates that while at high applied pressure, plastic deformation occurred [24], particle fracture and rearrangement predominated at the relatively non-linear region when the applied pressure was low [25].

P_y values for all the formulations decreased with increase in starch binder concentration, which indicates that the onset of plastic deformation occurred at lower pressures as the binder content increased. Granules formulated with rice starch generally exhibited the highest P_y values while those formulated with corn starch exhibited the lowest. This indicates that, of all the starch binders, corn starch would induce fastest onset of plastic flow while rice starch would induce the slowest. Also, products formulated with pregelatinized starches had lower P_y values than those formulated with natural starches. This means that pregelatinized starches would induce faster onset of plastic flow than natural starches. The plastic deformation process is time dependent [26,27] and, as such, the rate of plastic flow rather than total plastic flow, may be very important for the production of tablets free of capping and lamination problems, especially as most tablet presses have short compression cycle. D_b values decreased with increase in concentration of binding agents. The values are also observed to be higher than D_0 values, possibly due to fragmentation of granules at low pressures with eventual filling of interparticulate void spaces [28]. The values of D_b were higher for granules formulated with pregelatinized starches than for those formulated with natural starches. This implies that there were more fragmentation and rearrangement of the former granules than the latter at low pressures. For all the formulations, a linear relationship was obtained at all applied pressures (correlation coefficient > 0.999). P_k represents the pressure required to reduce the powder bed by 50 % and is related to the yield stress of the individual powder/granule particles [29,30]. Low values of P_k indicate materials that are soft and readily undergo plastic deformation under pressure. Granules formulated with pregelatinized starches had lower values of P_k than those formulated with natural starches. This implies that the former were softer and exhibited more plastic deformation than the latter in the granulated formulations. The finding here is at variance with results obtained for the pure starches where pregelatinized starches had higher P_k values than natural starches [3]. It is obvious therefore that the behaviour of the starches was modified by other materials included in the paracetamol tablet formulations and probably by the fact that the starches had been wetted by fluid during granulation. The D_i values are also seen to be higher than the D_0 values (compare Tables 2 and 3). This, in agreement with the findings of Odeku and Itiola [24] and Alebiowu and Itiola [2], implies that while D_i measures packed initial relative density with the application of small pressure, D_0 measures loose initial relative density due to die filling without any tapping or consolidation. Both the Heckel and Kawakita plots have their individual shortcomings. While P_y derived from the Heckel plots employs the elastic limit of materials to estimate the degree of plasticity, P_k (from the Kawakita plots) employs the degree of bulk volume reduction upon compression [24]. Thus, while the Kawakita plots may not detect some minor details in material behavior, Heckel plots may do so. Hence, both plots were complementary in the present investigation.

From Table 4, the higher the concentration of binding agent, the higher was the value of T. This occurred because the heat generated in the course of compression cause the asperities and the binding agents to melt and on cooling, solidified to form strong solid interparticulate bonds and as the binder concentration increases, the amount of bonds formed also

increased [31]. Because of their soft and plasto-elastic nature, binding agents would undergo plastoelasticity upon application of high compressional pressure and would be forced into interparticulate void spaces, thus, increasing interpaticulate contact area and, consequently more solid bonds would be formed. The value of friability (also in Table 4) reduced as binder concentration increased obviously for the same reason. Generally, for formulations containing natural and pregelatinized starch binders, the friability values obtained were acceptable at concentrations from 2% and 3% respectively.

In line with the results obtained by Upadrashta et al. [32], the D_t values as presented in Table 5, increased as R increased, probably because the presence of a binder in a formulation leads to formation of solid interparticulate bonds which increases in strength as R increases. An increase in disintegration time thus indicates a measure of difficulty in breaking those bonds. At relative density of 0.90, D_t values increased as binder concentration increased in agreement with observations made by various workers [32,33], not only as a result of capillarity and swelling of powder bed [34], but also due to the formation of thin film of the starch mucilage around the granules, which, in the presence of water, is converted to a mucilaginous viscous barrier between the granules and the water, thereby slowing down the disintegration of the granules. The thickness of this barrier depends on the quantity of the starch mucilage employed [33]. Tablets formulated with pregelatinized starch binders exhibited lower D_t values than those formulated with natural starch binders. This is probably because, during pregelatinization, the starch grains were disrupted causing the release of amylopectin which is partially responsible for the swelling of starch. Pregelatinized starches therefore, with higher amylopectin content as established in the preliminary investigation by Adedokun and Itiola [3] (lower amylose content) than the natural starches would exhibit higher swelling ability. The dissolution rate constants k_1 and k_2, were higher for formulations containing pregelatinized starch binders. Generally, the values of k_2 were higher than k_1 values, with the implication that the dissolution rate was faster after time t_1. Dissolution times t_{50}, t_{80} and t_1 generally increased as the relative density increased and also as binder concentration increased. The dissolution times were lower for tablets formulated with pregelatinized binders probably due to their higher swelling capacity and, consequently higher rate of water penetration into the tablets, resulting in faster fragmentation and, hence an increase in the surface area of tablet particles exposed to the dissolution medium.

All the tablets generally passed the official compendial disintegration tests for uncoated tablets (that is, not more than 15 minutes) and t_{80} was also less than one hour [16]. The dissolution profiles for the formulations showed that all the experimental starches exhibited lower disintegration and dissolution times than official corn starch, with rice starch having the least values.

5. CONCLUSION

In this study, the compaction behaviour of formulations is determined by the nature, form and concentration of starch mucilage binder. Also, in paracetamol formulations, pregelatinized starch mucilages induce both faster onset and total plastic deformation in tableting than natural starch mucilages. Thus, the use of pregelatinized starches as excipients could eliminate problems often encountered as a result of short dwelling time in high-speed tablet presses. All the natural and pregelatinized experimental starch mucilages produced creditably comparable effect as the official corn starch and its pregelatinized form with the implication that they can be developed as good substitutes.

CONSENT

Not applicable

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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