

ASSESSMENT OF TAPIOCA STARCHES OBTAINED AFTER DIFFERENT STEEPING PERIODS AS BINDERS IN A PARACETAMOL TABLET FORMULATION

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Abstract

Starches obtained after steeping Tapioca tubers for different periods were each evaluated as a binding agent in paracetamol tablet formulations in comparison with corn starch British Pharmacopoeia (BP). Compression properties were analyzed using density measurements and the compression equations of Heckel and Kawakita as assessment parameters, while the mechanical properties of the tablets were assessed with the use of the tensile strength (TS) and the brittle fracture index (BFI) of the tablets. Formulations containing longer steeping period starches as binding agent showed a slower onset of plastic deformation - high value of P_Y , and a higher amount of deformation during compression-low value of P_K . Both P_Y and P_K were affected by the concentration of the starch binders. The TS of the paracetamol tablets increased with the increase in the binder concentration and with the subsequent increase in starch steeping period while the BFI of the tablets decreased accordingly. Starch obtained after 72 h steeping of Tapioca tubers showed a similar result with corn starch BP. The results generally suggest that the steeping period would influence the activity of a starch binder in a formulation.

Rezumat

Lucrarea prezintă studii efectuate asupra amidonului de Tapioca, utilizat ca și agent de aglutinare în formularea tabletelor cu paracetamol. Proprietățile de compresie au fost analizate cu ajutorul ecuațiilor Heckel și Kawakita. Proprietățile mecanice ale tabletelor au fost evaluate prin determinarea rezistenței la “tensile strength” și “brittle fracture index”.

Keywords: Tapioca starch, Steeping period, Heckel equation, Kawakita equation, Tensile Strength, Brittle Fracture Index.

Introduction

Tapioca starch is obtained from the rasped tubers of *Manihot utilisima*, a tropical root tuber commonly used as food in Nigeria and other tropical countries. The starch has been widely studied by many researchers as to its suitability as an excipient in pharmaceutical dosage forms particularly in tableting technology [1, 2, 3], even the effect of acid treatment on it has been studied [4]. Though, Alebiowu [5] carried out the

evaluation of the influence of the steeping period of the tubers on the quality of the pure starch i.e. physical, compressional and mechanical properties and Alebiowu and Adeyemi [6] also assessed the influence of the steeping period on the activity of the starch as a disintegrant, no published work is available in literature concerning the influence of the steeping period on the activity of the starch as an excipient - binder, disintegrant or diluent - in a tablet formulation.

Hence, the objective of this study was to investigate the influence of the steeping period on the activity of Tapioca starch as a binder in a paracetamol tablet formulation in a comparative study with corn starch BP as the standard binder. This investigation was carried out by evaluating the deformation mechanism of paracetamol granules and the mechanical properties of the tablets resulting from the formulations.

The Heckel analysis [7] has been widely applied to pharmaceutical solids for relating the change in the relative density, D , of a powder bed during compression to the applied pressure, P .

It is written as:

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

K and A in equation 1 are constants determined from the slope and the intercept respectively, of the extrapolated linear region of a plot of $\ln 1/(1-D)$ versus P , the constant K is inversely related to the ability of a material to deform plastically under pressure (i.e. $K = 1/P_Y$, where P_Y is called mean yield pressure). The value of K is dependent on the nature of the material e.g. pregelatinized starches have higher K values than native starches [8]. Also, ductile powders, such as microcrystalline cellulose, have higher K values than brittle powders such as lactose [9].

From the value of A the intercept, the relative density D_A can be calculated using the following derived equation [10]

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

The relative density D_B describes the phase of rearrangement at low pressure and is the difference between D_A and D_O :

$$D_B = D_A - D_O \quad (3)$$

The Kawakita equation [11] is used to study the powder compression using the degree of volume reduction C , and is written as:

$$C = V_O - V_P/V_O = abP/1+bP \quad (4)$$

The equation, in practice, can be rearranged to give

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

Where V_O is the initial bulk volume for powdered/granular materials, and V_P is the bulk volume after compression. The constant **a** is equal to the minimum porosity of the material before compression while the constant **b** gives a pressure term P_K which is the pressure required to reduce the powder bed by 50 % [12,13].

Both the Heckel and Kawakita plots have their limitations and are believed to generally exhibit linearity for materials at high and low pressures respectively [14]. Therefore, both were used in this study in order to obtain more accurate information on the compressional characteristics of the granulations obtained from different formulations.

Bond strength and lamination tendency are two important mechanical properties of tablets which are measurable by tensile strength and brittle fracture index (BFI) values respectively [12]. The BFI is claimed to measure the stress relief that occurs due to plastic flow of a powdered/granular material during compression and its value ranges between 0 and 1. Low values (tending to zero) indicate that the material is plastic while values approaching unity indicate that it is elastic with a tendency to cap or laminate.

Materials and methods

The materials used were paracetamol BP and corn starch BP (BDH Chemicals Ltd., Poole, UK), Lactose BP (AB Knight and Co., London, UK) and Tapioca starches – TS 24, TS 48 and TS 72 (Tapioca starches prepared after 24 h, 48 h and 72 h steeping periods respectively) - prepared in our laboratory. The Tapioca starches were prepared according to an established procedure [15] and as reported [5]. The Tapioca starches are spherical with a particle density and size range of 1.446 – 1.461 g/cm³ and 3.50 – 10.50 μm respectively. Their moisture content varies between 8.09 and 20.0 % and with poor flow properties. The steeping period had been found to influence the physical characteristics of the starches [5].

Preparation of starch mucilage

Starch mucilages were prepared by weighing amounts of starch powder that will produce various concentrations 1%w/w, 3%w/w and

5%w/w of the starch binders in the formulation. Each weighed quantity then was suspended in the required amount of distilled water in a beaker and heated with continuous stirring until the mucilage was formed. The mucilage was used while still hot for a more effective binding.

Preparation of granules

Batches (300 g) of a basic formulation of paracetamol (90 % w/w), lactose (6 %w/w) and corn starch (4 %w/w) were dry-mixed for 5 min in a Hobart planetary mixer (Hobart Canada Inc., Don Mills, ON). The batches were then mixed with either 35 mL of distilled water or the appropriate amounts of starch mucilages to produce samples containing various concentrations of the starch binders. Massing was continued for 5 min, and the wet masses were granulated by passing them manually through a number 12 mesh sieve (1400 μm). The granules were dried in hot air oven for 24 h at 60°C and then resieved through a number 16 mesh (1000 μm). The degree of mixing of the granules was determined by the spectrophotometric assay of paracetamol at 249 nm and was found to be > 0.95. The moisture content of the formulation as determined with an Ohaus moisture balance Ohaus scale corporation, Pine Brook, NJ, USA was between 1.0 and 2.0 %w/w. Particle densities were determined by the pycnometer method with acetone as the displacement fluid. The bulk density, ρ_{bd} and relative density D_0 of each formulation were determined as described [5, 8].

Preparation of tablets

Spherical, flat tablets giving a tablet thickness of $3.34 \pm 0.01\text{mm}$ at zero porosity as calculated from particle density values were produced from 500 mg quantities of 500-1000 μm size fractions of the granules of the different formulations. Compaction was done for 1 min with 10 predetermined loads (47.98, 63.96, 79.95, 95.94, 111.94, 127.93, 143.91, 159.90, 175.89, 191.90) on a Carver hydraulic hand press (Model C, Carver Inc., Menomonee Falls, WI, USA) using a 12.5 mm die and punches lubricated with a 2%w/v dispersion of magnesium stearate in acetone before each compression. Tablets with a hole (1.54 mm diameter) at their center were made using an upper punch fitted with a pin. After ejection the tablets were stored over silica gel for 24 h before tablet properties were determined, to allow for elastic recovery and hardening, and prevent falsely low yield values. Their weights, w , and dimensions were then determined to within ± 1 mg and 0.01mm respectively, and their relative densities D , were calculated using the equation 6.

$$D = W/V_t \rho_s \quad (6)$$

In which V_t is the volume (cm^3) of the tablet and ρ_s is the particle density (g cm^{-3}) of the material.

Determination of Mechanical Properties

The tensile strengths (T) of the normal tablets and apparent tensile strengths of those containing a hole were also determined at room temperature as described previously [5] and by applying the tensile strength equation 7 [16]:

$$T = 2F/Idt \quad (7)$$

where T (or T_o) is the tensile strength of the tablet (MNm^{-2}), F is the load (MN) needed to cause fracture, d, is the tablet diameter and t is the tablet thickness (M). The brittle fracture index (BFI) of the tablets was determined using the Hiestand [17] equation 8:

$$\text{BFI} = 0.5 [(T/T_o) - 1] \quad (8)$$

where T is the tensile strength of the tablet without a hole and T_o is the apparent tensile strength of the tablet when is present – both at the same relative density. Determinations were performed in triplicate and the results are expressed as mean values.

Results and discussion

Figure 1 shows representative Heckel plots for paracetamol formulations containing 3 %w/w starch binder. Two phases of compression are discernible, with the second phase beginning at between 111.94 and 191.90 MNm^{-2} approximately and showing higher correlation coefficient for linearity of > 0.983 for all formulations. Values of the mean yield pressure P_Y , of the formulations were calculated from the second compression region, and the intercept, A, was determined from the extrapolation of the region.

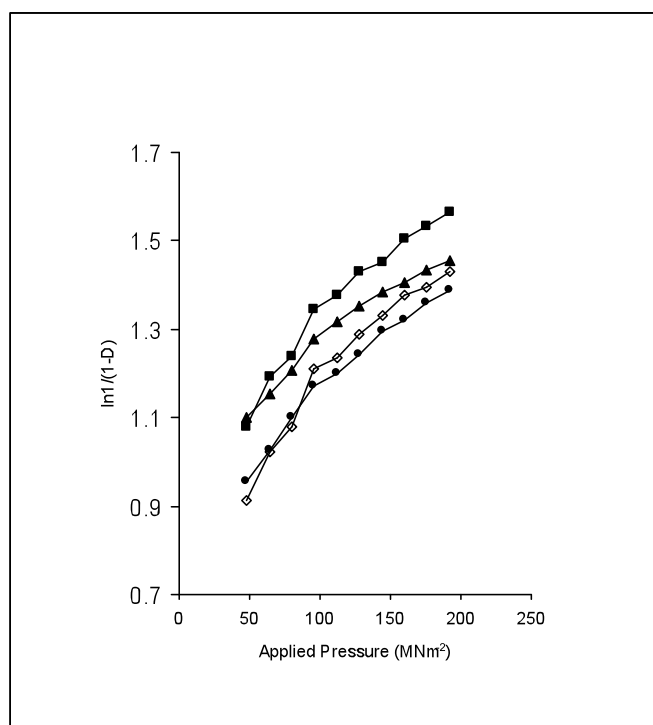


Figure 1

Heckel plots for paracetamol formulations containing 3 %w/w starch binder.

TS 24 ▲; TS 48 ■; TS 72 ●; CS □;

Where: D – relative density, TS – Tapioca starch, CS – Corn starch

The values of P_Y , D_O , D_A , and D_B for all the formulations are presented in table I. The values of D_O for the various formulations decreased with the increase in starch binder concentration, implying that the initial packing of the formulation as a result of die filling decreased with the increase in binder content. It is also seen from table I that the D_O values of the formulations decreases with the use of Tapioca starch obtained after a longer steeping period of Tapioca tuber (LSP starch). This implies that the LSP starch led to a decrease in the initial packing of the formulations in the die. This could be due to the bigger granular sizes with more intergranular spaces obtained (table I) for the formulations containing LSP starch. The D_B values, representing the degree of particle rearrangement at low pressures are also seen in table I. It is observed that the D_B values for the formulations containing the starches increase with subsequent increase in the steeping period. This suggests an advanced fragmentation at low pressures, of granules containing LSP starch, and could be due to bigger granular sizes which would lead to a decrease in the crushing strength of the granules [18].

It should also be noted that the D_B values for formulations containing Tapioca starch 72 (TS 72) and corn starch (CS) are similar to their D_O values.

Table I
Parameters derived from density measurements and from Heckel and Kawakita plots for paracetamol formulations

Binder	Concentration (% w/w)	Heckel plots				Mean granular (size μ_m) ($\pm$ SD)	Kawakita plots	
		D_O	P_Y	D_A	D_B		$D_I (1 - a)$	P_K
TS 24	1.00	0.298	703.1	0.712	0.414	590 (13.460)	0.485	9.239
	3.00	0.314	581.2	0.677	0.358	650 (10.110)	0.424	7.778
	5.00	0.321	544.9	0.640	0.319	670 (12.170)	0.384	7.308
TS 48	1.00	0.305	441.0	0.702	0.397	630 (8.500)	0.489	8.613
	3.00	0.332	433.2	0.664	0.344	685 (12.230)	0.422	7.285
	5.00	0.350	366.0	0.619	0.269	710 (12.640)	0.394	6.272
TS 72	1.00	0.327	462.2	0.655	0.328	680 (10.280)	0.445	7.729
	3.00	0.331	427.6	0.612	0.281	700 (10.650)	0.407	6.937
	5.00	0.340	353.3	0.548	0.208	720 (14.050)	0.390	5.963
CS	1.00	0.330	448.1	0.665	0.335	675 (12.100)	0.428	7.620
	3.00	0.336	413.9	0.623	0.287	710 (7.450)	0.417	6.826
	5.00	0.342	340.6	0.542	0.200	730 (10.300)	0.390	6.063

where: TS – Tapioca starch, CS – Corn starch

The D_A values representing the total degree of packing achieved at zero and low pressures (as implicit in equation 2) are seen to be higher in the formulations containing the LSP starches. It is also observed a decrease with subsequent increase in starch binder concentration. The higher D_A values obtained for formulations containing the LSP starches could be due to a higher amount of reduction in intergranular void spaces for the formulations, while the reduction obtained with increase in starch binder concentration could be caused by the increased strength of the granulations. It is generally known that a higher binder concentration leads to an increase in the granular strength [19].

The mean yield pressure, P_Y , is inversely related to the ability of a material to deform plastically under pressure. The values of P_Y for the formulations decreased with the increase in starch binder concentration implying that the onset of plastic deformation in the formulations occurred at lower pressures. Also, the P_Y values were observed to increase with the use of LSP starches. This suggests that increase in tuber steeping period facilitates the production of starch that will reduce the plasticity of a formulation. It is also notable that the formulations containing TS 72 and CS have the highest P_Y values.

Figure 2 shows representative Kawakita plots for paracetamol formulations containing 3.0% w/w starch binders. A linear relationship

obtained at all compression pressures used with a correlation coefficient of 0.999 for all formulations suggests that the equation may be used to predict the densification mechanism of the paracetamol formulations. Values of **a** and **ab** were obtained from the intercept of the plots, respectively. Values of $1-a$ give the initial relative density of the formulations, D_I , while P_K values were obtained from the reciprocal of the values of **b**.

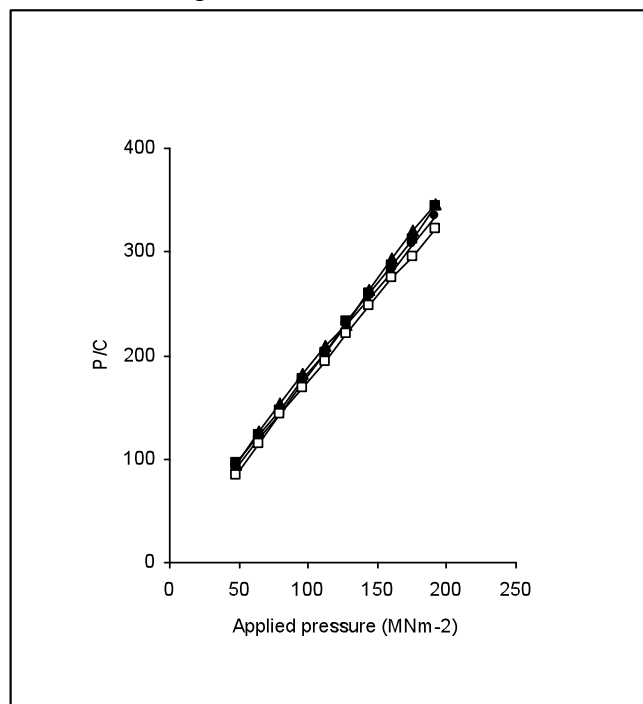


Figure 2

Kawakita plots for paracetamol formulations containing 3 %w/w starch binder.

TS 24 ▲; TS 48 ■; TS 72 ●; CS □;

Where: C – degree of volume reduction, P – the applied pressure, TS – Tapioca starch, CS – Corn starch

The values of D_I and P_K are included in table I. The values of D_I decrease with the increase in binder concentration. These values are also generally higher than D_O . The difference in the values of D_I and D_O are probably due to the fact that while D_O describes the loose initial relative density of the formulations due to die filling, D_I provides a measure of the packed initial relative density of the formulations with the application of small pressure or what may be referred to as tapping of the formulations [8, 20]. The D_I values of the formulations containing TS 72 and CS are generally lower than those of TS 24 and TS 48. Furthermore, lower values obtained with the increase in starch concentration could be due to the size

(Table I), and strength of the granules obtained [19]. From table I, it is seen that the values of P_K for the formulations decreased with the increase in starch binder concentration implying that the binders increased the softness of the formulation and its ability to deform plastically under pressure. The values of P_K of formulations containing the LSP starches are found to be lower than those containing starch obtained after a lower steeping period of the tuber. It is equally notable that the P_K values for formulations containing TS 72 and CS as starch binders are similar yet the lowest.

P_Y has been shown to be different from P_K [8, 12], while the P_Y values relate essentially to the onset of plastic deformation during compression; the P_K values appear to relate to the total amount of plastic deformation occurring during the compression process. With plastic deformation being a time dependent phenomenon [21], the present results i.e. P_Y and P_K values suggest that though starch binder obtained after a higher steeping period of Tapioca tubers will not enhance the onset of plastic flow, it would facilitate the total amount of plastic flow during compression in the paracetamol granule formulation when compared with paracetamol granule formulation containing starch binder obtained after a lower steeping period of Tapioca tuber.

The results of the tensile strength (T) tests on the paracetamol tablets were found to fit the general equation:

$$\log T \text{ (or } T_0) = AD + B \quad (8)$$

with a correlation coefficient > 0.970 . A and B are constants which depended on the nature and concentration of starch binder present in the formulation. Representative plots for tablets made from formulations containing 3.0 %w/w starch binders are presented in Figure 3. It can be seen that at all relative densities, the T of a tablet with a hole was smaller than that of the same tablet without a hole, the hole acted as a stress concentrator [17]. Values of T and BFI for all formulations at $D = 0.90$ which is representative for commercial paracetamol tablets are presented in Table II. It can be seen that the values of T increased with the increase in starch binder concentration while the BFI values decreased. The steeping period of the tuber is observed to affect the influence of the starch on the T and BFI, with paracetamol tablets containing starch obtained after a longer steeping period of tuber having a higher tensile strength and lower BFI. This may be due to T and BFI of the pure starches as reported previously [5]. The results indicate that the bond strength of the paracetamol tablets increase with the subsequent increase in the steeping period of the starch binders used, while the brittleness reduces.

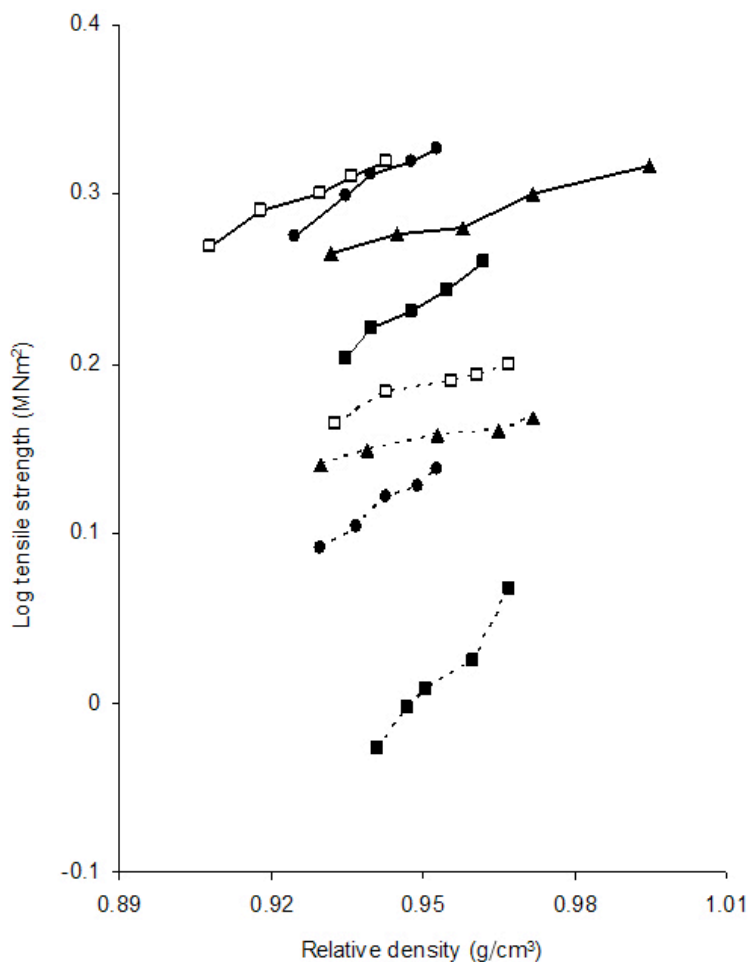


Figure 3

Log tensile strength *versus* relative density for paracetamol tablets containing 3 %w/w starch binder.

TS 24 ▲; TS 48 ■; TS 72 ●; CS □; with (....) and without a hole (___) at the center
Where: TS – Tapioca starch, CS – Corn starch

This suggests that starch binders obtained after a longer steeping period (LSP) of the tubers could be more useful binders than the starch binders obtained after a shorter steeping (SSP) period of the tuber when brittleness is an important issue in the tablets production process.

Table II
Tensile strength and brittle fracture index values for
paracetamol tablets at a relative density $D = 0.90$

Starch binder	Binder concentration (% w/w)	Tensile strength (MNm^2) ($\pm$ SD)	Brittle fracture index ($\pm$ SD)
TS 24	1.0	0.730 (0.13)	0.583 (0.09)
	3.0	1.372 (0.16)	0.383 (0.08)
	5.0	1.471 (0.11)	0.319 (0.10)
TS 48	1.0	1.324 (0.04)	0.321 (0.07)
	3.0	1.710 (0.09)	0.297 (0.14)
	5.0	1.737 (0.06)	0.282 (0.11)
TS 72	1.0	1.586 (0.15)	0.234 (0.05)
	3.0	1.740 (0.09)	0.164 (0.06)
	5.0	1.755 (0.11)	0.131 (0.10)
CS	1.0	1.489 (0.10)	0.231 (0.12)
	3.0	1.725 (0.08)	0.180 (0.14)
	5.0	1.860 (0.13)	0.119 (0.09)

where: TS – Tapioca starch, CS – Corn starch

Hence, LSP starches would facilitate the production of tablets with good bond strength yet with a reduced propensity for capping and lamination particularly in high speed tableting machines with a short dwell time. It is also notable that the tablets containing TS 72 and CS have higher tensile strengths, yet they have lower and similar brittle fracture index values. This suggests that when the process of lamination and capping is of great concern, TS 72 could be a substitute for CS binder.

Conclusion

The result of the present study shows that the steeping periods of Tapioca tuber influenced the binding activity of the starches obtained when used in a formulation and that the binding activity of TS 72 is comparable with that of the CS starch. It also shows that an increase in Tapioca tuber steeping period will produce starch binders that will:

- * facilitate an increase in the total degree of packing of granules in the die (i.e. D_A).
- * enhance an increase in the total amount of plastic deformation occurring during compression as reflected in the P_K values.
- * assist in producing tablets with high bond strength, yet with a lower brittleness.

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