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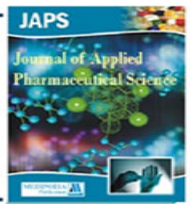

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Binding Effect of Cassava Starches on the Compression and Mechanical Properties of Ibuprofen Tablets

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ABSTRACT

Starch is the most common binder in tablet formulations and important sources include cassava tubers. Using cassava starches extracted from three different cultivars (Mbundumali, Mulola and Sauti), the effect of native cassava starches as binders on the compression and mechanical properties of ibuprofen tablets was studied. The starches were used as binders for 400 mg ibuprofen tablets produced by wet granulation at the various concentrations (2-8 %w/w) and compressed at different punch settings (23-27). The formed tablets were evaluated for hardness, friability and disintegration. Cassava starches, derived from the three cultivars can be used as binders in uncoated ibuprofen tablets under the following operating conditions: punch setting of 24 and binder concentration of 2% w/w. Under such conditions, less friable tablets were produced and reduced amounts of materials were used. Mulola starch is the most appropriate binder for ibuprofen tablets while Sauti starch could be useful when fast disintegration is more essential and a requirement.

Keywords: compression, tableting, excipients, mucilage, cassava starch, ibuprofen.

INTRODUCTION

Corn starch is the most widely used excipient in the production of tablets and hence is utilized as disintegrants, fillers or binders (Uhumwangho *et al.*, 2006; Musa *et al.*, 2011). Binders are pharmaceutical excipients that are commonly used in tablet formulation to impart cohesion on the powder mix (Musa *et al.*, 2010; Patil *et al.*, 2010). The resultant cohesiveness ensures that the tablet remains intact after compression (Oyi *et al.*, 2009). Binders are used either in solutions or dry form depending on the other ingredients in the formulations and the method of preparation especially in wet granulation (Chalapathi *et al.*, 2010; Patil, *et al.*, 2010). The quantity of binders used has a considerable influence on the characteristics of the compressed tablets (Musa *et al.*, 2010; Ibezim *et al.*, 2008). Increasing the binder concentration invariably raises the disintegration times (Mgbahurike and Igwilo, 1991).

Important materials commonly used as binders are starch, gelatin, natural gums, sugar, acacia sodium alginate, methyl-cellulose, microcrystalline cellulose, polyethylene glycol, waxes and water (Musa *et al.*, 2010). Uhumwangho and co-workers established that cassava starch is a more effective binder than the mucilage of maize starch BP in paracetamol tablets (Uhumwangho *et al.*, 2006). Chalapathi and co-researchers recently reported that the binding capacity of cassava starch in paracetamol tablets was much greater (in terms of friability, disintegration time and hardness) than that of industrial maize starch (Chalapathi *et al.*, 2010). Acid modification of cassava starch has also been found to show superior disintegration properties in metronidazole tablets than either the native cassava starch or maize starch (Achor *et al.*, 2010). Cassava (*Manihot esculenta* Crantz) is currently being exploited as an important source of starch to meet the increasing starch demand in the confectionery, adhesive and pharmaceutical industries in Malawi (Mweta, 2009). In Malawi, the corn starch remains the choice starch for tablet formulation. The corn starch being used in Malawi is imported from South Africa, Zimbabwe, Tanzania, Kenya, China, United Arab Emirates and India (NSO, 2010). Earlier studies on the chemistry of Malawi cassava starches indicated that an opportunity exists for using a wide range of cassava cultivars for various uses including tablet formulation (Mweta, 2009; Benesi, 2002). This study was therefore undertaken to establish the effect of Malawian native cassava starches as binders in ibuprofen tablets.

MATERIALS AND METHODS

Materials

Starch was isolated from three cassava varieties (Mbundumali, Sauti and Mulola) collected from Makoka Research Station, Malawi. Ibuprofen powder, Ac-Di-Sol, magnesium stearate and lactose monohydrate were purchased from Sandoz South Africa (PTY) Limited, Crest Chemicals (PTY) Limited, Warren Chem Specialities (PTY) Limited and Amchem (PTY) Limited (South Africa) respectively. Only analytical and pharmaceutical grade reagents and chemicals were used.

Starch extraction

Extraction of starch was done as described by Benesi (2002). Fresh tubers were washed with tap water, peeled, washed again, and chopped to about 1 cm^3 pieces. The cubes were mixed with water and pulverized using a high speed blender (Waring Commercial, model 8011ES) for 5 min. The pulp was suspended in 10x its volume of tap water, stirred for 5 min and filtered using a double muslin cloth. The filtrate was allowed to stand for 2 hrs to facilitate sedimentation and the top liquid decanted as a waste. The sediment was re-suspended in 10x its volume of tap water, stirred for 5 min and filtered using a double muslin cloth. The filtrate was allowed to stand for 2 hrs for the starch to sediment and the top liquid decanted. The sediment was washed and air dried at room temperature for 48 hrs, pulverized into fine powder and stored in polyethylene containers prior to use and analysis.

Solubility of the starches

The solubility of the extracted starches in water was carried out as done by Odeku and Picker-Freyer (2007). Starch suspensions (0.4 g in 20 ml) were prepared in flasks, in triplicate, and heated to 50, 65, 75 and 85 °C, respectively, for 30 min with shaking every 5 min and then left to cool at room temperature for 15 min. The suspensions were centrifuged for 15 min at 3000 × g to separate gel and supernatant. The supernatant was dried in an oven for 2 hrs at 130 °C and the residue (A) after drying represented the amount of starch solubilized in water. The solubility was calculated using equation 1, where S is the sample weight.

$$\text{Solubility}\,(\%) = \frac{100 \times \text{A}}{\text{S}} \qquad (1)$$

Moisture content of the starches

To determine the moisture content in the starch samples, the hot oven method was used (Mweta, 2009; AOAC, 1990). Porcelain dishes with covers were washed and dried in an oven at 105 °C overnight, cooled to room temperature in a dessicator for 1 hr and weighed to the nearest 1mg (W_0). Starch samples (3 g) in triplicates, were weighed in pre-heated, cooled and pre-weighed porcelain dishes to the nearest 1 mg (W_1). The dishes containing the samples were dried for 24 hrs at 105°C and then cooled in a dessicator for 1 hr and immediately weighed after removal from dessicator to the nearest 1 mg (W_2). The moisture content was determined using the equation 2:

$$\text{Moisture}\,(\%) = 100 - \left[100 \times \frac{(W_2 - W_0)}{(W_1 - W_0)}\right] \qquad (2)$$

Ash content of the starches

The ash content of the starches was determined out as done by Benesi (2002). Ashing crucibles were carefully cleaned and heated for 3 hrs in a furnace at 575 °C. The crucibles were cooled to room temperature in a desiccator for 1 hr and weighed to the nearest 0.1 mg (W_0). Approximately 1.0 g of the starch samples, to the nearest 0.1 mg was weighed in the pre-weighed crucibles (W_1). The crucibles with the samples were placed in a furnace at 300 °C overnight, removed from the furnace, cooled in a desiccator for 1 hr at room temperature and immediately weighed after removal from desiccator to the nearest 0.1 mg (W_2). The ash content was calculated using equation 3:

$$\text{Ash content}\,(\%) = 100 \times \frac{(W_2 - W_0)}{(W_1 - W_0)} \qquad (3)$$

pH of starches

Determination of the pH of the starches was done using the method used by Mweta (2009). Starch samples (5 g), in triplicates, were weighed into a beaker and mixed with 20 ml of distilled water. The resulting suspension was stirred for 5 min with

a magnetic stirrer and left to settle for 10 min. The pH of the mixture was measured using an 827 pH meter (Metrohn, Switzerland), which were previously calibrated using pH 4 and 7 buffers.

Formulation and compression of tablets

Batches (320 g) of basic formulations comprising ibuprofen, Ac-Di-Sol, magnesium stearate, starch and lactose were prepared. Granulation of the mixtures was done as described by Ibezim et al (2008) and Adentunji et al (2006). The granulation process was done as follows: accurately weighed quantities of ibuprofen, lactose and Ac-Di-Sol were dry-mixed for 10 min in a Turbula mixer (Model T2C, Willy A. Bachofen Maschinenfabrik, Switzerland), and moistened with appropriate quantities of starch mucilage to achieve various concentrations (2, 4, 6 and 8% w/w) of the starch as binders. The wet masses were granulated manually by passing them through a 10-mesh sieve, dried in a hot-air oven for 3 hrs at 50 ˚C, and passed through a 20-mesh sieve. The obtained granules, magnesium stearate and Ac Di-Sol were weighed and mixed for 10 min in a Turbula mixer. The resultant granules were stored in airtight containers for 2 days at room temperature and compressed into 400 mg tablets at different punch settings of 23-27 using a Cadmach single punch (Type SSF_3 Ahmedabad-India) tablet press using 10 mm flat-faced punches. The produced tablets were stored in airtight bottles for 24 hrs at room temperature.

Bulk and tapped densities of the granules

Granule samples (20 g), in duplicate, were weighed into a 50 ml measuring cylinder, and the volume occupied by the granules recorded as bulk volume. The cylinder was then tapped on the wooden platform height of 2.5 cm three times at 2 seconds intervals until the volume occupied by the granules remained constant. The data generated was used in computing the Hausner ratio (equation 4) and compressibility index (equation 5).

$$\text{Hausner ratio} = \frac{\rho_t}{\rho_b} \qquad (4)$$

$$\text{Compressibility Index} = \left[\rho_t - \frac{\rho_b}{\rho_t} \right] \times 100 \quad (5)$$

Analysis of compressed tablets

Weight and thickness of tablets

The weight and thickness of tablets were determined as described by Patil et al (2010) and Ibezim et al (2008). Twenty tablets from each batch were randomly selected and weighed individually using an electronic balance. Ten tablets from each batch were also selected at random and the thickness of the tablets measured accurately to 0.01 mm using a digital caliper (Mitutoyo, England).

Friability of tablets

The friability of tablets was determined as described by Ibezim et al (2008) and Patil et al (2010). Twenty tablets were selected at random, put in a sieve No. 10, dedusted using a vacuum and weighed together using the electronic balance in duplicate and placed in the Friabulator (Pharmatest, USA) for 4 min at 120 rev/mins. The tablets were dedusted again and reweighed. The percentage losses were calculated for each batch of the tablets. The friability of the tablets was calculated using equation 6:

$$\text{Friability}(\%) = 100 \times \frac{W_0 - W_f}{W_0} \qquad (6)$$

where W_o is the initial weight of the tablets, W_f is the final weight of the tablets after the tablets are put through the friabriator.

Disintegration of the tablets

The disintegration characteristics of the tablets were determined according to the BP, Adentunji et al (2006) and Ibezim et al (2008). The disintegration times of the tablets were obtained in distilled water at 37 °C ± 0.5 °C using the disintegration testing apparatus (Erweka ZT500) in triplicate. Six tablets were selected at random from each batch placed in a cylindrical tube basket and supported on the wire mesh just above the surface of the water and the apparatus was started. The tablets were kept in contact with distilled water in the tube and the time taken for all the tablets to disintegrate and go through the wire mesh was recorded.

Hardness of the tablets

The crushing strength was determined as described by Ibezim et al (2008). Ten tablets were selected at random from each batch in duplicate and a hardness tester (Pharma test PTB 301) was used. The tablet was placed between spindle and anvil of the tester and the calibrated length adjusted to zero. The knob was screwed to apply a diametric compression force on the tablet and the position on the calibrated length at which the tablet broke was recorded.

Statistical analysis

Analysis of variance (ANOVA) was performed using the Genstat Discovery 13th edition to establish the effect of cassava starches as binders on the properties of ibuprofen tablets. Significant differences among means were tested at 95 % confidence level.

RESULTS AND DISCUSSION

The results for moisture, ash, pH and solubilities of the starches are presented in Table 1.

Table. 1: Properties of the native starches.

Genotype	Functional property						
	Moisture content (%)	Ash content (%)	pH	Solubility (%)			
				50 °C	65 °C	75 °C	85 °C
Mbundumali	13.09±0.32	0.24± 0.02	5.34	0.91±0.06	4.20±0.42	11.30±3.15	14.5±0.69
Sauti	13.3±0.40	0.30± 0.01	5.85	0.30±0.72	6.40±0.23	12.70±1.38	18.0±1.75
Mulola	12.60±0.30	0.29±0.0.01	5.63	2.85±0.13	3.07±0.25	12.10±0.37	15.8±0.33
Corn	9.36±0.30	0.29±0.03	4.35	0.23±0.04	1.69±0.37	4.85±0.81	8.84±2.14

Table 2: Granule properties of starch based ibuprofen

Granule property	Bulk density (g/cm^3)				Tapped density (g/cm^3)				Hausner ratio				Carr's index (%)			
Binder conc. (%w/w)	2	4	6	8	2	4	6	8	2	4	6	8	2	4	6	8
Mbundumali	0.52	0.49	0.49	0.49	0.63	0.60	0.61	0.67	1.20	1.21	1.23	1.35	16.9	17.3	18.5	25.9
Sauti	0.49	0.46	0.45	0.43	0.66	0.64	0.66	0.65	1.33	1.39	1.45	1.51	24.7	28.2	31.5	33.9
Mulola	0.49	0.48	0.48	0.47	0.67	0.66	0.66	0.67	1.31	1.38	1.38	1.42	23.5	27.4	27.4	29.4

The moisture contents for the starches (9.4-13.3%) were within the acceptable limits of less than 15% (BP, 2009). The ash content for the starches varied from 0.24% - 0.30%; and these values were below the required maximum (0.6 %) (BP, 2009). The ash contents of the corn starch and that of Mulola starch (0.29%) were similar ($p \geq 0.05$). Generally, cassava starches exhibited higher pH (5.34-5.85) values than corn starch (4.35). The solubility of all the starches in water increased with rising temperature and significant differences amongst cultivars were observed ($p \leq 0.05$). Sauti starch exhibited the highest solubility values at temperatures greater than 65 °C. Corn starch exhibited the lowest solubility across the temperature range; this reflects the amylose-amylopectin content (Mweta, 2009).

The values for bulk and tapped densities, Hausner ratio and Carr's compressibility index of the different ibuprofen granule formulations are presented in Table 2. The results showed that the bulk and tapped densities were low indicating that the granules were not porous and are free flowing. For each binder concentration, the bulk and tapped densities were not different amongst the cultivars ($p \geq 0.05$). However, bulk densities generally decreased with concentration of the binder in all formulations. Granules prepared using Mbundumali (2-6% w/w), Mulola (2% w/w) and Sauti (2% w/w) exhibited fair and passable flow properties; the Carr's compressibility and Hausner ratio were below 25% and 1.34 respectively. The effect of binder concentration and pressure on the weights of cassava starch based ibuprofen tablets are presented in Table 3. The results showed that all the formed ibuprofen tablets gave acceptable uniformity of weight; no tablet afforded greater than 5 % deviation in weight. The weights of the tablets valued from 394 to 429 mg. The differences in weight variation were probably due to segregation of larger granules from the fines or non-uniform flow rate (Allagh *et al.*, 2008). The effect of binder concentration and pressure on the weights of cassava starch based ibuprofen tablets are presented in Table 3. The results showed that all the formed ibuprofen tablets gave acceptable uniformity of weight; no tablet afforded greater than 5 % deviation in weight.

The weights of the tablets valued from 394 to 429 mg. The differences in weight variation were probably due to segregation of larger granules from the fines or non-uniform flow rate (Allagh *et al.*, 2008). The disintegration results for the three cassava varieties are provided in Figure 1. The results indicate that all the tablets disintegrated within 15 min, consistent with the recommended maximum of the British Pharmacopoeia for uncoated tablets.

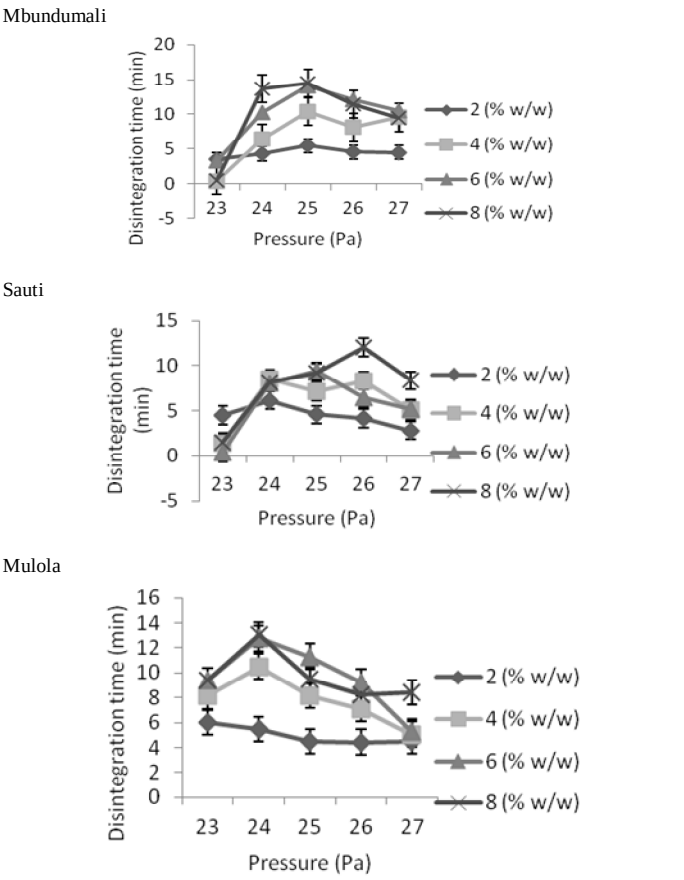

Fig. 1: Effect of pressure and concentration on the disintegration time of cassava starch based ibuprofen tablets.

Table 3: Weights (mg) of cassava based ibuprofen tablets.

Binder conc. (w/w)	2					4					6					8				
Upper punch setting	**23**	**24**	**25**	**26**	**27**	**23**	**24**	**25**	**26**	**27**	**23**	**24**	**25**	**26**	**27**	**23**	**24**	**25**	**26**	**27**
Mbundumali	406.45	405.55	402.25	404.90	401.35	406.52	403.35	400.10	396.10	406.00	418.45	403.95	406.85	397.20	401.60	429.00	400.95	400.60	401.75	394.85
Sauti	401.95	400.20	401.15	399.55	402.70	408.25	394.25	396.35	400.75	401.55	419.80	404.20	398.75	403.25	403.20	403.70	406.50	402.65	401.85	402.65
Mulola	404.00	401.20	402.30	403.70	404.70	406.75	399.70	400.65	404.05	410.80	407.00	398.15	400.90	403.45	406.15	407.15	396.30	397.05	399.85	403.55

Table. 4: Friability (%) of ibuprofen tablets.

Binder conc. (w/w)	2					4					6					8				
Upper punch setting	**23**	**24**	**25**	**26**	**27**	**23**	**24**	**25**	**26**	**27**	**23**	**24**	**25**	**26**	**27**	**23**	**24**	**25**	**26**	**27**
Mbundumali	0.52	0.35	0.47	4.88	4.93	1.52	0.29	0.38	4.84	5.16	0.32	0.29	0.26	0.33	5.04	8.70	0.36	0.40	0.48	5.01
Sauti	0.38	0.39	0.43	3.96	4.94	0.30	0.42	0.37	4.84	5.04	0.39	0.39	0.37	4.67	5.15	0.32	0.28	0.37	5.00	5.05
Mulola	0.30	0.33	1.81	2.34	2.62	0.31	0.40	1.18	1.56	1.73	0.23	0.39	0.34	2.40	3.51	0.26	0.32	3.77	5.02	5.10

Table. 5: Hardness, friability, disintegration time, hardness-friability ratio (HFR) and hardness-disintegration ratio (HDR) for cassava and corn based ibuprofen tablets.

Cultivar	Binder concentration (%w/w)	Hardness (N)	Friability (%)	Disintegration time (min)	HFR	HDR
Mbundumali	2	99.2	0.35	4.32	283.43	23.0
	4	86.4	0.29	6.50	279.93	13.3
	6	99.1	0.29	10.2	341.72	9.72
	8	115.4	0.36	13.7	320.56	11.2
		100.03	**0.32**	**8.68**	**306.4**	**14.3**
Sauti	2	117.6	0.39	6.14	301.54	19.2
	4	110.1	0.42	8.50	262.14	13.0
	6	120.2	0.39	8.09	308.21	8.09
	8	105.5	0.28	8.20	376.78	14.7
		113.35	**0.37**	**7.73**	**312.2**	**13.8**
Mulola	2	114.7	0.33	5.47	347.58	21.0
	4	123.4	0.40	10.5	308.50	11.8
	6	118.1	0.39	12.8	302.82	9.22
	8	122.9	0.32	13.1	384.06	9.38
		119.76	**0.36**	**10.47**	**335.7**	**12.9**
Corn		104.5	0.18	7.55	580.6	13.9

The Sauti based ibuprofen tablets disintegrated in less than 12 minutes; this is consistent with its highest solubility of the starch (Table 1). The disintegration time initially increased with increasing upper punch setting (23-25) and then decreased (26-27) for most of the binders. These results are understandable because increasing compaction pressure either increases or decreases disintegration time (Aulton, 2007). At the punch setting of 23, Mbundumali (4 and 8% w/w) and Sauti (4, 6 and 8% w/w) starches produced tablets which disintegrated in less than 1 min. The 2% w/w ibuprofen tablets disintegrated within 7 min at all the compression pressures and for all starch varieties. The binder concentration, 2% w/w, offers a unique opportunity for further exploitation since reduced amounts of materials are used.

The hardness of the starch based ibuprofen tablets are shown in Figure 2. It is evident that the hardness increased with binder concentration and punch setting (23-25) Pa for Mbundumali and Sauti formulations. This was the case because the greater the applied pressure, the harder the tablets (Ansel *et al.*, 2011). In order to achieve satisfactory mechanical strength of a tablet, the minimum requirement is 4 kg or ≥ 60 N (BP, 2009; Cirunary and Vercammen, 1997). At the punch setting of 23, Mbundumali (4 and 8 % w/w) and Sauti (6 and 8 % w/w) failed to comply with the specifications. However, Mulola starch at all the concentrations and punch settings, complied with the prescribed specifications. Thus, Mulola starch appears the best binder because it produced tablets with acceptable mechanical strength which should be able to withstand stress during packaging and transportation.

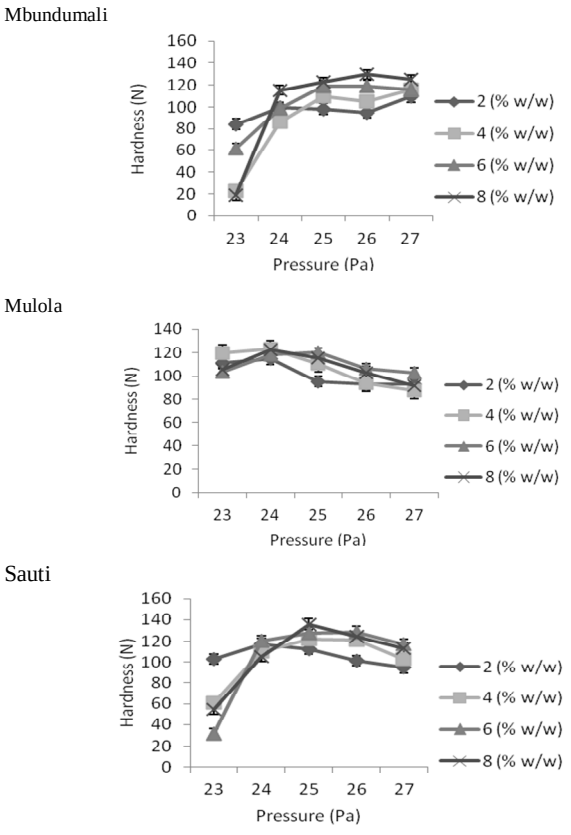

Fig. 2: Effect of pressure and concentration on the hardness of cassava starch based ibuprofen tablets.

The friability of the starch based ibuprofen tablets are given in Table 4. The results indicated that friability decreased with increasing punch setting for Mbundumali at all the concentrations. Friability values of greater than 1% were obtained at punch settings of 26 and 27 for all the starch varieties and at all the concentrations except for Mbundumali (6 and 8 % w/w). Less than 1% friability value is the required specification (BP, 2009; Ansel *et al.*, 2011). The punch setting of 24 provided less than 1% friability values for all the starch formulations and thus, the tablets had good mechanical strength to withstand stress during handling, packaging and transportation. Consequently, the best punch setting was 24.

A comparison of the produced tablets at the punch setting of 24 with 400 mg corn starch based ibuprofen tablets was undertaken (Table 5). The data revealed that the hardness of the tablets increased with binder concentration for most of the starches and were within the acceptable range of 4 kg or ≥ 60 N (BP, 2009; Cirunary and Vercammen, 1997). The tablet hardness was generally high with Mulola starch. Mbundumali (2 and 6% w/w) and Sauti (4 and 8% w/w) starches produced tablets which were comparable in hardness to the corn starch ($p \geq 0.05$).

The friability values of the tablets were less than 0.5% for all the formulations. Mbundumali (4% w/w) starch gave tablets which were comparable to the corn starch ($p \geq 0.05$). Although all the formulated batches disintegrated within 15 minutes as specified by the British Pharmacopeia for uncoated tablets, Sauti starch formulations disintegrated within 9 min for all the binder concentrations. This is despite that the Sauti based tablets exhibited higher average hardness values than that of Mbundumali. The 2% w/w formulation exhibited the shortest disintegration time 4.3-6.1 min of all concentrations used. At this binder concentration, the disintegration time was shorter that than of the corn starch. At higher binder concentrations, there is increased bonding and this prolongs disintegration time (Musa *et al.*, 2008).

The hardness-friability ratio (HFR) provides a parameter for measuring tablet strength (Odeku and Itiola, 2003). Generally, the higher the HFR value, the stronger is the tablet (Adentunji *et al.*, 2006). The HFR values indicate that Mulola starch formulation produced stronger tablets than Sauti and Mbundumali. When compared with the corn starch, the cassava based tablets are weaker. Alternatively, the hardness-disintegration ratio (HDR) can also be exploited to establish tablet strength. The HDR values of the corn starch (13.9) and Sauti starch (13.8) were almost similar ($p \geq 0.05$). However, Mulola starch would be more desirable if a lower HDR is required; this could indicate a possible lower disintegration time.

CONCLUSIONS

The results of this study show that the type of cassava variety affects the binding characteristics and hence the properties of formulated ibuprofen tablets. The choice of the cassava variety informs the final quality of the tablets. The conditions: punch setting of 24 and binder concentration of 2% w/w provide less friable tablets and the later ensures reduced amounts of materials

being required. Under such conditions, Sauti starch based tablets have the lowest disintegration time. Mulola based starch provided the best mechanical strengths of the tablets.

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