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Asian Pacific Journal of Tropical Biomedicine

journal homepage: www.elsevier.com/locate/apjtb

Original article http://dx.doi.org/10.1016/j.apjtb.2015.05.003

Effect of thermal and chemical modifications on the mechanical and release properties of paracetamol tablet formulations containing corn, cassava and sweet potato starches as filler-binders

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ARTICLE INFO

Article history:
Received 19 Mar 2015
Received in revised form 6 Apr 2015
Accepted 1 May 2015
Available online 13 June 2015

Keywords:
Starch modification
Direct compression
Filler-binders
Mechanical and release properties

ABSTRACT

Objective: To investigate the effects of acetylation and pregelatinization of cassava and sweet potato starches on the mechanical and release properties of directly compressed paracetamol tablet formulations in comparison with official corn starch.
Methods: The native starches were modified by acetylation and pregelatinization. The tablets were assessed using friability (F_r), crushing strength (C_s), disintegration time (D_t) and dissolution parameters.
Results: Starch acetylation produced paracetamol tablets that were stronger and had the best balance of mechanical and disintegration properties, while pregelatinization produced tablets that were more friable but had a better overall strength in relation to disintegration than formulations made from natural starches. Correlations mainly existed between D_t and the dissolution parameters t_{80}, t_2 and k_1 in the formulations.
Conclusions: Modification of the experimental starches improved the mechanical and release properties of directly compressed paracetamol tablet formulations. Thus, they can be developed for use as pharmaceutical excipients in specific formulations.

1. Introduction

Tablets are the preferred dosage form for the presentation of many medicines [1]. They may be prepared by any of the methods of granulation or direct compression. The simplicity of direct compression, its cost effectiveness, suitability for moisture labile materials and capability for producing consistent dissolution profiles in tablets make it an attractive method of tablet production [2–5]. However, it requires the application of excipients with appropriate functionality to attain desired formulation goals. Starch is a widely used binder, filler-diluent, disintegrant and glidant in the manufacture of oral solid dosage forms especially tablets [6–8]. Natural starches from a variety of botanical origins have been characterised and noted for their limited functionality as excipients [9–11]. Their functionalities can, however, be improved through various modification methods [12–14].

Ideally, a tablet should be robust enough to withstand various post-compaction stress during handling and transportation [15]. Thus, mechanical strength of a tablet is frequently assessed as an in-process control during manufacturing [16]. Commonly used parameters for defining mechanical strength include friability (F_r) and crushing strength (C_s). Conversely, release properties of tablets have relevance in evaluating the bioavailability of the ingested drugs and are usually characterised by disintegration and dissolution parameters. The integrated parameter C_sF_r/D_t relates mechanical strength to disintegration time (D_t) and has been suggested as a better index for assessing tablet performance [17].

The mechanical and release properties of directly compressed paracetamol tablet formulations containing natural, acetylated and pregelatinized cassava and sweet potato starches as filler-binders in comparison with those containing corn starch BP grade were investigated in this study.

2. Materials and methods

2.1. Materials

Materials used included paracetamol powder (product of People's Republic of China), corn starch BP (BDH Chemicals

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Peer review under responsibility of Hainan Medical University.

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), phosphate buffer (derived from disodium hydrogen phosphate dihydrate and potassium dihydrogen phosphate-BDH Chemicals Limited, Poole, UK).

2.2. Methods

2.2.1. Collection of botanicals and preparation of natural and modified starches

Fresh tubers of cassava plant, *Manihot esculenta* Crantz, and sweet potato plant *Ipomoea batatas* (L.) Lam. were sourced in Ibadan, Nigeria. The natural forms were prepared in a laboratory in the University of Ibadan, Nigeria as described by Ayorinde *et al* [18].

Pregelatinized starches were prepared according to established procedures [19,20]. Acetylated starches were prepared as previous described by Odeniyi *et al* [21]. The recovered flakes of each modified form were blended in an Osterizer Dual range Pulse Matic Milling blender (Model 857, USA) and screened through a number 120 mesh (125 μm) sieve.

2.2.2. Microscopic analysis

The starch powders were analysed for particle size on approximately 400 particles per sample using a light microscope (Olympus, Tokyo, Japan).

2.2.3. Preparation of tablets

Five binary blends (labelled F1–F5) of paracetamol and the starch excipients were prepared per sample containing 10%, 20%, 25%, 50% and 80% (w/w) starch. A sixth formula (F6) contained pure starch only. The dry blends were prepared by gradual trituration with a mortar and pestle. Tablets (500 mg) were compressed on a Carver Hydraulic Hand Press (Model C, Fred S. Carver Inc., Menomonee Falls, Wisconsin, USA) using a 2% (w/v) magnesium stearate in acetone as lubricant. The compressional pressures applied ranged between 28.31 and 198.15 MNm^{-2} and the duration of compression was 1 min. After ejection, the tablets were stored over silica gel for 24 h to allow for elastic recovery and hardening.

2.2.4. Friability

Twenty tablets were lightly dusted and collectively weighed. They were transferred to a friability test apparatus (DBK Instruments, England) set to rotate at 25 r/min for 4 min. The tablets were removed from the friabilator, dusted and re-weighed. From the two weight values, the friability (%) of each batch of tablets was calculated by Equation (1):

$$\text{Friability (\%)} = \text{(Initial weight)} - \text{(Final weight)/Initial weight} \times 100 \quad (1)$$

2.2.5. Crushing strength

Ten tablets were individually held between a fixed anvil and a moving jaw of a tablet hardness tester (Model EH 01) fitted with a gauge calibrated in Newtons (N). The load was gradually increased by gently lowering the compression hand until the tablet just fractured. The value of the load on the gauge at this point gives a measure of the tablet crushing strength [22].

2.2.6. Crushing strength-friability ratio (C_sF_r)

Values of C_sF_r were calculated for each tablet by Equation (2) below:

$$C_sF_r = \text{Crushing strength (N)/Friability (\%)} \quad (2)$$

2.2.7. Disintegration test

Each tablet was placed in a separate tube in the basket-rack assembly of a tablet disintegration test apparatus (DBK Instruments, England). The medium was distilled water maintained at a temperature of (37.0 ± 0.5) °C. The tablets were carefully observed and disintegration was considered to be achieved at a time (min) when no residue remained on the mesh screen.

2.2.8. Correlations between C_sF_r and D_t for tablet formulations

Correlations between C_sF_r and D_t for the tablet formulations were determined by ANOVA and linear regression tests at $P = 0.05$, using the statistical software Graphpad Prism version 5.00 (Graphpad Software, San Diego, California, USA).

2.2.9. Dissolution test

The paddle (BP, 2010) dissolution test apparatus (DBK Instruments, England, UK) was employed. The dissolution medium was 900 mL of phosphate buffer pH 5.8 maintained at (37.0 ± 0.5) °C and stirring rate of 50 r/min. The test was performed for formulations F1, F2 and F3 only, containing 10%, 20% and 25% (w/w) of starch excipients respectively due to their higher paracetamol content. The absorbance A of the withdrawn solutions was determined at wavelength of 257 nm with the aid of a UV–visible spectrophotometer (Spectrumlab UV/Vis 752s), having a cell of path length of 1.0 cm.

2.3. Correlations between disintegration time (D_t) and dissolution rate

The dissolution data were assessed at an applied pressure of 198.15 MNm^{-2}. Correlations between disintegration time and dissolution rate were determined by means of a Two-way ANOVA on Graphpad Prism version 5.00 (Graphpad Software, San Diego, California, USA).

3. Results

Table 1 shows values of friability for the tablet formulations at a relative density of 0.9. The ranking of friability containing the native polymers was in the order of cassava > sweet potato > corn. Generally, formulations containing acetylated starch exhibited low values of friability compared to the other formulations, implying that acetylation produced tablets with fewer tendencies to abrasion. Conversely, pregelatinized starch containing formulations had higher friability values with the exception of paracetamol formulations containing sweet potato starch at

Table 1
Values of mechanical parameters for the paracetamol tablet formulations at relative density of 0.9.

Botanical source	Concentration of starch (%w/w)	Natural				Acetylated				Pregelatinized			
		F_r	C_s	D_t	C_sF_r/D_t	F_r	C_s	D_t	C_sF_r/D_t	F_r	C_s	D_t	C_sF_r/D_t
Corn	10	1.14	73.54	11.70	7.05	0.93	84.31	10.83	10.05	1.55	76.16	7.51	7.68
	20	1.00	75.41	12.31	6.90	0.74	83.39	10.84	11.25	1.21	75.70	9.24	7.00
	25	0.84	75.83	12.64	7.46	0.55	93.04	11.36	14.97	1.05	83.28	9.14	9.57
	50	0.71	76.04	13.61	7.65	0.51	95.93	12.36	14.58	0.95	83.89	9.89	8.41
	80	0.63	83.98	17.92	7.17	0.45	101.40	13.95	15.37	0.79	89.24	10.85	9.70
Cassava	10	2.12	74.61	10.13	5.04	1.39	83.94	9.62	8.83	3.02	82.77	8.29	4.33
	20	1.39	73.34	11.15	6.06	1.25	89.33	9.60	9.26	2.27	84.76	8.92	4.92
	25	1.01	73.07	11.75	7.08	0.96	92.56	10.05	10.43	1.19	88.82	9.38	8.32
	50	0.89	77.10	13.01	7.09	0.74	91.62	11.87	10.69	1.10	88.22	10.45	7.65
	80	0.75	82.37	15.04	7.53	0.66	98.04	12.09	12.28	0.93	92.79	11.48	8.51
Sweet potato	10	1.63	70.94	10.79	5.35	1.29	82.37	9.92	8.28	1.41	78.93	10.32	7.54
	20	1.21	76.53	11.36	6.76	1.03	88.22	10.29	9.59	1.07	84.68	9.61	9.13
	25	1.01	73.29	11.80	6.51	0.76	91.73	10.43	11.92	0.92	86.93	10.04	9.37
	50	0.82	77.89	13.28	7.34	0.60	93.69	12.00	12.69	0.83	88.08	11.21	9.09
	80	0.71	82.43	14.80	8.04	0.53	99.48	13.28	14.04	0.73	93.92	12.35	9.88

F_r: Friability; C_s: Crushing strength; D_t: Disintegration time; C_sF_r/D_t: Crushing strength-friability versus disintegration time ratio.

concentrations of 10%, 20% and 25% (w/w) starch, in which friability was the highest in the natural starch containing formulations. Also, presented in Table 1 are the values of crushing strength for the tablet formulations. The ranking was in the order of acetylated > pregelatinized > natural starch.

Table 1 shows values of disintegration time, D_t for the tablet formulations at a relative density of 0.9. Paracetamol tablet formulations containing natural starches exhibited higher D_t values than those containing the pregelatinized and acetylated starch counterparts. Values of correlations between C_sF_r and D_t for the starch-paracetamol tablet formulations and pure starches are presented in Table 2. The levels of significance were also determined and presented.

The plots of C_sF_r/D_t versus relative density are presented in Figure 1, while the dissolution plots at 25% filler-binder concentration are presented in Figure 2. The Kitazawa plots for the release kinetics at 25% filler-binder concentration are presented in Figure 3.

4. Discussion

Microscopic analysis showed increasing particle diameters with modification, most especially for the pregelatinized

Table 2
Correlations between C_sF_r and D_t for the Starch-paracetamol tablet formulations and pure starches.

Botanical source	Concentration (%w/w)	Starch form	Equation for line of best fit	Correlation coefficient (r)	Probability (P)
Corn	10	Natural	$D_t = 0.067\ 7\ C_sF_r + 5.832$	0.962	<0.0005
		Acetylated	$D_t = 0.074\ 8\ C_sF_r + 3.412$	0.964	<0.0001
		Pregelatinized	$D_t = 0.083\ 5\ C_sF_r + 2.887$	0.984	<0.0010
	50	Natural	$D_t = 0.051\ 4\ C_sF_r + 8.199$	0.983	<0.0005
		Acetylated	$D_t = 0.027\ 1\ C_sF_r + 7.679$	0.989	<0.0005
		Pregelatinized	$D_t = 0.052\ 6\ C_sF_r + 5.966$	0.938	<0.0050
	100	Natural	$D_t = 0.033\ 3\ C_sF_r + 15.946$	0.895	<0.0050
		Acetylated	$D_t = 0.036\ 9\ C_sF_r + 8.979$	0.974	<0.0010
		Pregelatinized	$D_t = 0.083\ 1\ C_sF_r + 5.959$	0.984	<0.0005
Cassava	10	Natural	$D_t = 0.123\ 0\ C_sF_r + 4.363$	0.917	<0.0050
		Acetylated	$D_t = 0.093\ 6\ C_sF_r + 2.441$	0.980	<0.0005
		Pregelatinized	$D_t = 0.177\ 3\ C_sF_r + 2.667$	0.953	<0.0005
	50	Natural	$D_t = 0.055\ 8\ C_sF_r + 8.143$	0.954	<0.0050
		Acetylated	$D_t = 0.045\ 7\ C_sF_r + 6.293$	0.976	<0.0005
		Pregelatinized	$D_t = 0.050\ 8\ C_sF_r + 6.929$	0.939	<0.0050
	100	Natural	$D_t = 0.044\ 0\ C_sF_r + 12.609$	0.950	<0.0010
		Acetylated	$D_t = 0.047\ 6\ C_sF_r + 8.633$	0.972	<0.0005
		Pregelatinized	$D_t = 0.052\ 6\ C_sF_r + 9.280$	0.927	<0.0050
Sweet potato	10	Natural	$D_t = 0.117\ 8\ C_sF_r + 4.754$	0.944	<0.0005
		Acetylated	$D_t = 0.010\ 9\ C_sF_r + 2.013$	0.962	<0.0001
		Pregelatinized	$D_t = 0.081\ 5\ C_sF_r + 4.169$	0.895	<0.0010
	50	Natural	$D_t = 0.050\ 7\ C_sF_r + 8.524$	0.970	<0.0010
		Acetylated	$D_t = 0.028\ 0\ C_sF_r + 7.873$	0.968	<0.0005
		Pregelatinized	$D_t = 0.046\ 6\ C_sF_r + 7.052$	0.927	<0.0010
	100	Natural	$D_t = 0.040\ 0\ C_sF_r + 13.783$	0.983	<0.0005
		Acetylated	$D_t = 0.034\ 9\ C_sF_r + 9.834$	0.946	<0.0005
		Pregelatinized	$D_t = 0.052\ 1\ C_sF_r + 9.406$	0.946	<0.0010

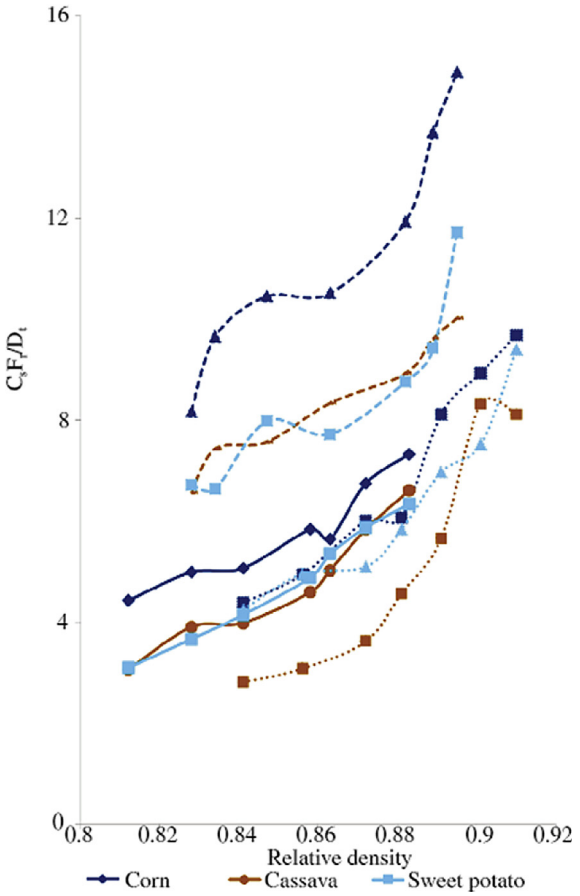

Figure 1. Plots of C_sF_r/D_t versus relative density for formulations containing 25% natural, acetylated and pregelatinized starches to paracetamol.
—: Natural; - - -: Acetylated; ...: Pregelatinized.

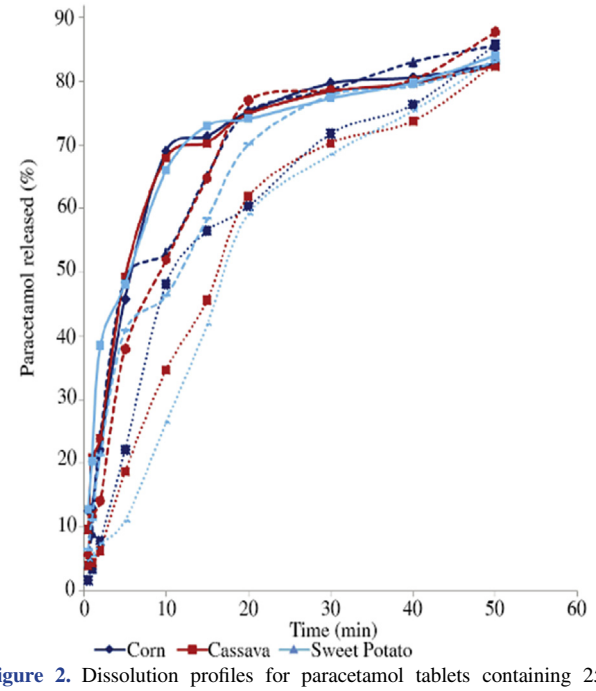

Figure 2. Dissolution profiles for paracetamol tablets containing 25% natural, acetylated and pregelatinized starches.
—: Natural; - - -: Acetylated; ...: Pregelatinized.

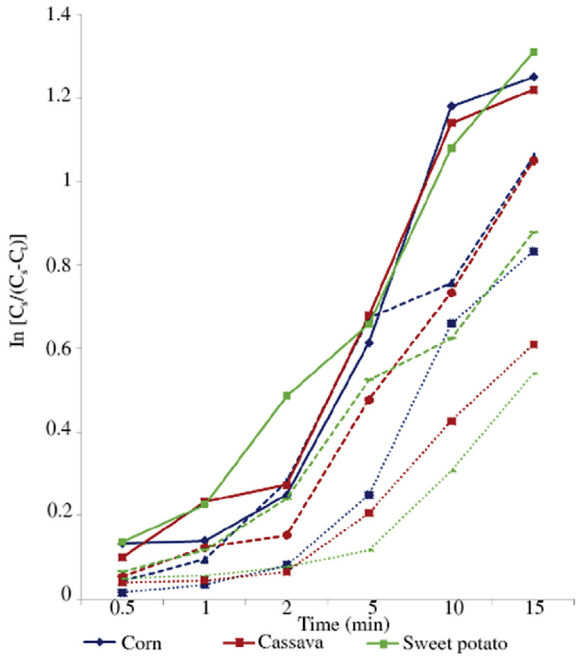

Figure 3. Kitazawa plots for paracetamol tablets containing 25% natural, acetylated and pregelatinized starches.
—: Natural; - - -: Acetylated; ...: Pregelatinized.

starches. Formulations containing corn starch generally had lower friability values than those incorporating sweet potato and cassava starches.

Increase in concentration of starch excipients in the formulations raised the crushing strength values suggesting that the starch excipients promoted tablet bonding. Thus, they acted effectively as filler-binders. Formulations containing acetylated starches had the highest crushing strength values, irrespective of the botanical source of starch, while those with natural starch had the lowest crushing strength values. Tablets containing pregelatinized cassava had higher crushing strength values than those of corn. However, the tablets of natural and acetylated corn exhibited greater strength than those of cassava and sweet potato.

The lower D_t values generally observed for formulations prepared with modified starches may be attributed to the increasing capacity of modified starches to absorb water which facilitated the wicking action associated with disintegration [7]. Increase in D_t as the concentration of starch in the formulations increased may be related to the formation of a mucilaginous viscous barrier in the presence of water, thus inhibiting disintegration. The thickness of the barrier is directly related to the concentration of the starch binder [23].

Tablets prepared with cassava and sweet potato starches disintegrated faster than those with corn starch and met monograph specification of D_t not to exceed 15 min for uncoated tablets [22]. A few of the formulations containing corn starch, mainly those containing natural corn at concentrations of $\geq$50% disintegrated later than 15 min. However, this is not likely to be of any consequence as such high starch concentrations will not normally be required in preparing standard 500 mg paracetamol tablets.

In the present study, C_sF_r/D_t values for natural starch containing formulations were generally the lowest due to their relatively high friability, low crushing strength and high D_t

values. Conversely, low friability, high crushing strength and lower D_t values for formulations containing acetylated starch accounted for their relatively high C_sF_r/D_t values. Although, formulations containing pregelatinized starch generally exhibited higher friability than their natural starch counterparts, their crushing strength and D_t values were intermediate. Correlations between C_sF_r and D_t were positive and significant ($P < 0.05$), indicating that the parameters were directly related.

The results of our study showed the dissolution profiles and Kitazawa plots for the paracetamol tablets containing 25% (w/w) starch. The dissolution rate constant k_1 derived from Kitazawa plots was generally lower than k_2 for all the formulation types suggesting that dissolution initially proceeded at a slower rate at time t_1, and thereafter increased as the time proceeded towards t_2.

The dissolution time constant, t_1 was constant (2 min) for most of the formulations, irrespective of botanical origin. Values of t_2 were higher and more variable than t_1. Formulations containing pregelatinized starch appeared to have the highest values of t_2, suggesting that dissolution was achieved later than for natural and acetylated starch formulations. Values of t_2 for acetylated starch formulations were generally the lowest suggesting faster rate of dissolution at the later stages, which conformed to the good swelling potential of acetylated starches [21]. The parameters t_{50} and t_{80}, representing the time for 50% and 80% of paracetamol to be released from the formulations, varied with botanical origins and forms of starch excipients.

Significant ($P < 0.05$) correlations were mainly observed between D_t and the dissolution rate parameters t_{80}, t_2 and k_1 in most of the paracetamol tablet formulations. However, insignificant ($P > 0.05$) correlations were predominantly observed between D_t and the dissolution rate parameters t_{50}, t_1 and k_2 in most of the formulations. The import of this is that there is interplay between disintegration and dissolution factors in the release of paracetamol from the directly compressed tablet formulations. This shows that tablet disintegration may not be the only factor influencing dissolution rate. The turbulent agitation maintained during the disintegration test tends to lower tablet disintegration time as compared to the streamlined flow of the dissolution apparatus [7]. Other factors that are independent of disintegration, such as solubility, particle size and crystalline structure come into play in drug dissolution [24].

Modification of the experimental starches by acetylation produced paracetamol tablets that were stronger and had the best balance of mechanical and disintegration properties. Starch pregelatinization produced tablets that were more friable but had a better overall strength in relation to disintegration, than formulations made from natural starches. Paracetamol tablets containing natural starch demonstrated the least balance of mechanical and disintegrant properties. Correlations mainly existed between D_t and the dissolution parameters t_{80}, t_2 and k_1 in the formulations. Paracetamol tablets formulations incorporating the modified starches compared favourably with corresponding formulations incorporating corn starch as filler-binder. They may consequently be developed commercially as substitutes to official starches.

Conflict of interest statement

We declare that we have no conflict of interest.

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