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SHORT COMMUNICATION

Effect of the mode of incorporation on the disintegrant properties of acid modified water and white yam starches

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Abstract Acid modified starches obtained from two species of yam tubers namely white yam – *Dioscorea rotundata* L. and water yam – *D. alata* L. DIAL2 have been investigated as intra- and extra-granular disintegrants in paracetamol tablet formulations. The native starches were modified by acid hydrolysis and employed as disintegrant at concentrations of 5 and 10% w/w and their disintegrant properties compared with those of corn starch BP. The tensile strength and drug release properties of the tablets, assessed using the disintegration and dissolution (t_{50} and t_{80} – time required for 50% and 80% of paracetamol to be released) times, were evaluated. The results showed that the tensile strength and the disintegration and dissolution times of the tablets decreased with increase in the concentration of the starch disintegrants. The acid modified yam starches showed better disintegrant efficiency than corn starch in the tablet formulations. Acid modification appeared to improve the disintegrant efficiency of the yam starches. Furthermore, tablets containing starches incorporated extragranularly showed faster disintegration but lower tensile strength than those containing starches incorporated intragranularly. This emphasizes the importance of the mode of incorporation of starch disintegrant.

1. Introduction

Disintegrants are essential components to tablet formulations since tablet disintegration is frequently a prerequisite for dissolution of the active drug from the tablet. While rapidly disintegrating tablets do not necessarily ensure fast bioavailability, slowly disintegrating tablets almost always assure slow bioavailability (Carter, 2002). Starch is one of the earliest known disintegrants although in recent times, super disintegrants such as sodium starch glycolate (Explotab, Primogel) and sodium carboxymethyl cellulose (Ac-Di-Sol) offer significant improvements over the native starches. Starches obtained locally from different botanical sources have also been evaluated as

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disintegrants in commercial tablets generally in the concentration range of 2–10%w/w (Adebayo and Itiola, 1998; Alebiowu and Itiola, 2003; Odeku and Alabi, 2007; Okunlola and Odeku, 2008; Odeku et al., 2009). Starch disintegrant may be incorporated to the powder mixture before granulation (internal, intra- or endo-disintegrant) or as a dry powder to the prepared granules (external, extra- or exo-disintegrant) or it may be added both internally and externally (Pilpel et al., 1978; Kamp et al., 1983).

Studies have shown that the properties of some starches have been improved by physical and chemical modifications (Osunsam et al., 1989; Visavarungroj and Remon, 1991; Kim and Ahn, 1996; Odeku and Alabi, 2007; Odeku et al., 2008; Odeku and Picker-Freyer, 2009a,b). The technique of acid hydrolysis has been used extensively in the food, textile and paper industries for many years to produce soluble thin-boiling starch (Wurzburg, 1986; Atichokudomchai and Varavinit, 2003). Acid modified starches are produced commercially by hydrolyzing the starches with hydrochloric or sulfuric acid at temperatures below the gelatinization temperatures of the starch for a period of time. The extent of hydrolysis depends on the starch consistency, acidity of the medium, hydrolysis temperature and duration of hydrolysis (Osunsam et al., 1989). Acid hydrolysis of starch involves the cleavage of the glucosidic bonds between the monomeric units which involves both protonation of the glycosidic oxygen and addition of water to yield the reducing sugar end group (D-glucose) of the starch (Yiu et al., 2008). This leads to an increase in the relative crystallinity of starch since acid preferentially attacks the amorphous regions, while the crystalline regions remain intact (French, 1984; Komiya and Nara, 1986; Chun et al., 1997). Acid modification changes the physicochemical properties of the starches without destroying its granule structure yielding starch with increased solubility and gel strength, and decreased viscosity (Osunsam et al., 1989; Kim and Ahn, 1996).

Recently, starches from four different Dioscorea species namely white (*D. rotundata*), bitter (*D. dumetorum*), Chinese (*D. oppositifolia*) and water yam (*D. alata*) have been modified by acid hydrolysis and the physicochemical, material and tablet formation properties of the starches have been investigated with the aim of determining their relative usefulness as a direct compression excipient in pharmaceutical tablets (Odeku and Picker-Freyer, 2009a). The results showed that the acid modified starches differed considerably in their physicocemical and material properties. Acid hydrolysis was found to increase the solubility but decrease the swelling capacity of the starches. Acid modification led to an increase in the crystallinity and compressibility of the starches when compared with the native forms of the starches. Furthermore, when the acid modified white and water yam starches were compressed directly into tablets, the starch tablets showed faster disintegration time indicating their potential usefulness as disintegrant in tablet formulations (Odeku and Picker-Freyer, 2009a). So far, these acid modified starches have not been evaluated as disintegrant in tablet formulations. Thus in the present study, acid modified white and water yam starches have been evaluated as disintegrants in paracetamol tablet formulations and the effects of the mode of incorporation of the disintegrant into the tablet formulation were also investigated. The mechanical strength of the tablets was assessed using the tensile strength which is a measure of bond strength, while the drug release properties of the tablets were assessed using the disintegration and dissolution (t_{50} and t_{80} – time required for 50% and 80% of paracetamol to be released) times of the tablets.

2. Materials and methods

2.1. Materials

The materials used were: paracetamol BP, corn starch BP and polyvinylpyrrolidone BP (all from BDH Chemicals Ltd., Poole, UK) and tubers of white yam – *Dioscorea rotundata* L. and water yam – *D. alata* L. DIAL2 were obtained from local farmers in Ibadan, Nigeria. The description of the preparation and purification of the starches has been given elsewhere (Odeku and Picker-Freyer, 2007).

2.2. Preparation of acid modified starch

Acid hydrolysis of the starch was carried out by suspending 300 g (dry basis) of native *Dioscorea* starch in 600 ml of 6%w/v HCl solution at 23 ± 1 °C for 192 h without stirring (Atichokudomchai and Varavinit, 2003). After hydrolysis, the suspension was neutralized with 10%w/v sodium hydroxide solution to terminate the reaction. The starch slurry was washed five times with distilled water, dried in a hot air oven for at 40 °C for 24 h and then powdered using a laboratory mill. All the starches were passed through a 125 μm mesh sieve. The physicochemical properties of the acid modified starches have been given elsewhere (Odeku and Picker-Freyer, 2009a).

2.3. Preparation of granules

Batches (300 g) of paracetamol granules containing 5 and 10%w/w of the starches were prepared by wet granulation method in a Kenwood planetary mixer (Erweka, Germany) using 2%w/w solution of PVP as binder. For the intragranular disintegrants, the starch was added to paracetamol powder prior to the addition of the binding agent. Massing was continued for 5 min and the wet masses were granulated by passing them manually through a number 12 mesh sieve (1400 μm), dried in a hot air oven for 18 h at 50 °C and then resieved through a number 16 mesh sieve (1000 μm). The granules were then stored in airtight containers. Particle densities were determined by the liquid pyconometer method with xylene as the displacement fluid.

For the evaluation of the extragranular disintegrants, the starch was added to the granules after drying and mixed in a cubic mixer for 5 min.

2.4. Preparation of tablets

Tablets (500 ± 10 mg) were prepared from the 500–1000 μm granules by compressing them for 1 min with predetermined loads on a Carver hydraulic hand press (Model C, Carver Inc., Menomonee Falls, Wisconsin, USA). Before each compression the 10.5 mm die and flat-faced punches were lubricated with a 2%w/v dispersion of magnesium stearate in ether:ethanol (1:1). After ejection, the tablets were stored over silica gel for 24 h 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 0.01 mm, respectively, and their relative density (D) was calculated using the equation:

$$D = w/V_t \cdot \rho_s \quad (1)$$

where V_t is the volume (cm^3) of the tablet and ρ_s is the particle density ($g\,cm^{-3}$) of the solid material.

2.5. Tensile strength

The tensile strength of the tablets was determined at room temperature by diametral compression (Fell and Newton, 1970) using a hardness tester (Katan Scientific and Chemicals, Ahmedabad, India) and by applying the equation:

$$T = 2F/\pi dt \quad (2)$$

where T is the tensile strength of the tablet ($MN\,m^{-2}$), F is the load (MN) needed to cause fracture, d is the tablet diameter (m) and t is the tablet thickness (m). All measurements were made in triplicate or more and the results given are the means of several determinations.

2.6. Disintegration and dissolution tests

The disintegration times, DT, of the tablets was determined in distilled water at 37 ± 0.5 °C using a Veego disintegration tester (Veego Scientific devices, Mumbai, Maharashtra, India). All measurements were made in quadruplicate and the results given are the means of four determinations.

The dissolution test was carried out on the tablets using the USP XXIII basket method (Erweka dissolution tester, GmbH, Hausenstamm Kr. Offenbach/Main, Germany) rotated at 100 rpm in 900 ml of 0.1 M HCl, maintained at 37 ± 0.5 °C. Samples (5 ml) were withdrawn at different time intervals and replaced with equal amounts of fresh medium. The sample was diluted and the amount of paracetamol released was determined using a UV spectrophotometer (UV spectrophotometer, Pye Unicam, UK) at the wavelength 249 nm. All measurements were made in quadruplicate and the results given are the means of four determinations.

2.7. Statistical analysis

Statistical analysis to compare the effects of the various starch disintegrants on the tensile strength and release properties of paracetamol tablets was done using the Analysis of Variance (ANOVA) on a computer software GraphPad Prism® 4 (GraphPad Software Inc., San Diego, USA). Tukey-Kramer multiple comparison tests were used to compare the individual differences between the starches. At 95% confidence interval, p values less than or equal to 0.05 were considered significant.

3. Results and discussions

The results of the tensile tests on the paracetamol tablets fit the general equation:

$$\log T = AD + B \quad (3)$$

with a correlation coefficient > 0.990. A and B were constants for each formulation. Representative plots of log tensile strength versus relative density for formulations containing 5%w/w of the starches as intragranular disintegrant are presented in Fig. 1 while the tensile strength at relative density of 0.80, which is representative of commercial paracetamol tablets, are presented in Table 1. The tensile strength of the paracetamol tablets decreased with increase in the concentration of the starches with tablets and the values were higher than those previously reported for the native forms of the starch disintegrants (Okunlola and Odeku, 2008). Acid hydrolysis has been shown to remove the amorphous regions of the starch resulting in the more crystalline acid modified starch granules being forced closer together during compression which will result in stronger packing of the granules and an increase in the tensile strength of the tablets (Atichokudomchai et al., 2001; Odeku and Picker-Freyer, 2009a). The ranking of T for the formulations containing the disintegrants was generally corn > white > water yam starches with formulations containing intragranular disintegrant showing higher values than those containing extragranular disintegrant. Previous studies have shown the need for careful selection of the type and concentration of starch disintegrants in tablet formulations since relatively high level of starch disintegrant often weakens the tablet structure (Odeku and Alabi, 2007).

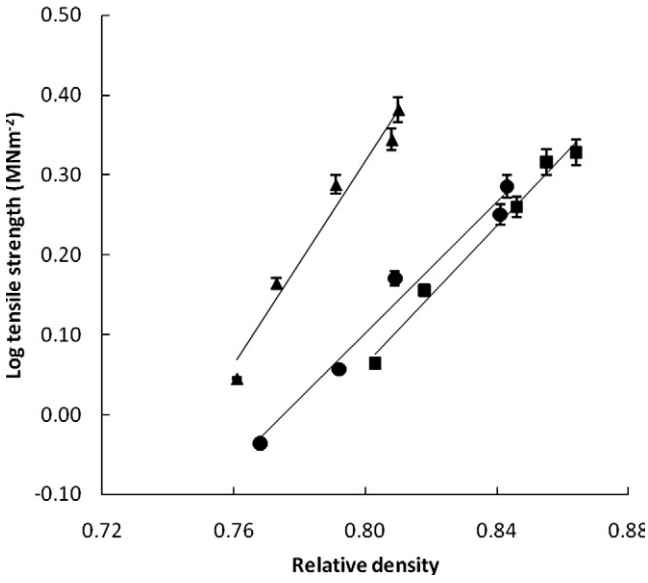

Figure 1 Log tensile strength versus relative density for paracetamol tablet formulations containing 5.0%w/w of the acid modified starches as intragranular disintegrant.■, water; ●, white; ▲, corn (mean ± SD, n = 4).

The disintegration time, DT, was plotted against the relative density of the tablet and representative plots for tablets containing 5%w/w of the starches as intragranular disintegrant are presented in Fig. 2, while the amount of paracetamol released was plotted against time and the values of the dissolution times, t_{50} and t_{80} (time required for 50% and 80% of paracetamol to be released) were calculated. Values of the disintegration and dissolution times of the tablet at relative density of 0.80 are presented in Table 1. The disintegration and dissolution times of paracetamol tablets decreased with increase in the concentration of starch disintegrant. It is believed that no single mechanism is responsible for the action of most disintegrants. A combination of swelling and/or wicking and/or deformation are the mechanisms that have been shown to be involved in disintegrant action (Lowenthal, 1973; Pilpel et al., 1978). Wicking is followed by the restoration of deformed starch particles on contact with aqueous fluid and the release of certain amount of stress which is responsible for disruption of hydrogen bonding formed during compression leading to disintegration of the tablets (Gordon et al.,

Table 1 Tensile strength and the disintegration (DT) and dissolution times of paracetamol tablets at relative density = 0.80 (mean ± SD, $n = 4$).

Mode of incorporation	Starch	Starch conc (%w/w)	Tensile strength (MN m^{-2})	DT (min)	t_{50} (min)	t_{80} (min)
		0.0	1.60 ± 0.20	32.00 ± 1.50	62.00 ± 5.00	100.00 ± 6.00
Intragranular	Water yam	5.0	1.66 ± 0.35	2.00 ± 0.02	20.00 ± 2.00	44.00 ± 2.00
		10.0	0.97 ± 0.02	0.60 ± 0.03	18.00 ± 1.00	41.00 ± 1.00
	White yam	5.0	1.96 ± 0.40	2.80 ± 0.02	29.00 ± 2.00	49.00 ± 4.00
		10.0	1.04 ± 0.40	1.40 ± 0.02	20.00 ± 3.00	42.00 ± 3.00
	Corn	5.0	2.18 ± 1.08	10.50 ± 0.05	36.00 ± 3.50	59.00 ± 3.00
		10.0	1.86 ± 0.75	5.00 ± 0.01	22.40 ± 2.00	47.00 ± 2.00
Extragranular	Water yam	5.0	1.36 ± 0.35	0.70 ± 0.02	19.70 ± 1.00	32.00 ± 1.00
		10.0	0.87 ± 0.10	0.50 ± 0.06	17.00 ± 2.00	30.00 ± 3.50
	White yam	5.0	1.81 ± 1.56	1.92 ± 0.04	27.00 ± 3.00	42.00 ± 4.00
		10.0	0.97 ± 0.34	1.20 ± 0.01	21.00 ± 1.50	36.00 ± 2.50
	Corn	5.0	2.06 ± 0.35	5.70 ± 0.04	33.00 ± 2.00	58.00 ± 2.00
		10.0	1.35 ± 1.74	3.00 ± 0.05	21.00 ± 4.00	45.00 ± 3.00

1993; Carter, 2002). Furthermore, tablet formulations containing extragranular disintegrants showed lower disintegration and dissolution times than those containing intragranular disintegrant. This is in agreement with previous studies that showed that disintegrants added intragranularly (in wet granulation processes) are usually not as effective as that added extragranularly due to the fact that it is exposed to wetting and drying (as part of the granulation process) which reduces the activity of the disintegrant and since a compaction process does not involve its exposure to wetting and drying, the disintegrant used extragranularly tends to retain good disintegration activity (Carter, 2002). The concentration of starch used as disintegrant is also a very crucial factor. If it is below the optimum concentration then there are insufficient channels for capillary action and if it is above optimum concentration then it will be difficult to compress the tablet (Kottke et al., 1992). The ranking for DT and dissolution times for the formulations containing the starch disintegrants was corn > white > water yam starches. Thus, acid modified water yam disintegrant appeared to facilitate the fastest disintegration of the tablets while corn starch facilitated the slowest disintegration and dissolution of the tablets. Statistical analysis showed that there were no significant ($p > 0.05$) differences in the disintegration time for tablets containing the various starch disintegrants. Futhermore, all the tablets conformed to official requirements for uncoated tablets on disintegration, i.e. disintegration within 15 min. Previous studies of the disintegrant properties of the native forms of these starches incorporated intragranularly at a concentration of 10%w/w in chloroquine tablet formulations have shown that the disintegration time of the tablets was 8.2 and 9.2 min for water and white yam starches, respectively (Okunlola and Odeku, 2008). Statistical analysis showed that the disintegration times of the acid modified starches were significantly ($p < 0.01$) lower than those of the native forms of the starches. This indicates that acid modification improved the disintegrant efficiency of the yam starches.

4. Conclusions

The results showed that the acid modified yam starches showed better disintegrant efficiency than corn starch BP in paracetamol tablet formulations. Acid modification appeared to improve the disintegrant efficiency of the yam starches. Furthermore, tablets containing starches incorporated extragranularly showed faster disintegration but lower tensile strength than those containing starches incorporated intragranularly. This emphasizes the importance of the mode of incorporation of starch disintegrant.

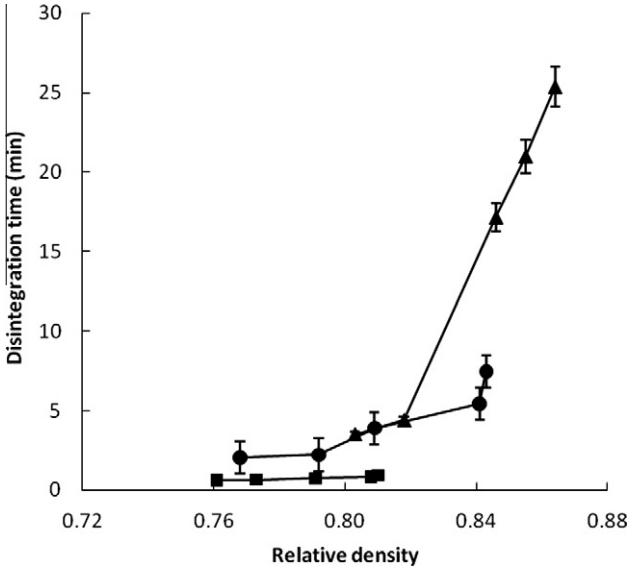

Figure 2 Disintegration time (min) versus relative density for paracetamol tablet formulations containing 5.0%w/w of the acid modified starches as intragranular disintegrant. ■, water; ●, white; ▲, corn (mean ± SD, $n = 4$).

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