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Article

Intra and Extra-granular Disintegrant Properties of Modified Underutilised Red Lima Bean Starch in Paracetamol Tablet Formulation

Mary Oluwaseun Okekunle[1], Olufunke Dorothy Akin-Ajani[2*], Bridget Lucy Ekpukpon[2], Oluwatoyin Adepeju Odeku[2], Bamidele Iromidayo Olu-Owolabi[1], Kayode Oyebode Adebowale[1]

[1]Department of Chemistry, Faculty of Science, University of Ibadan, Ibadan, Nigeria, [2]Department of Pharmaceutics & Industrial Pharmacy, Faculty of Pharmacy, University of Ibadan, Ibadan, Nigeria

Red lima bean (*Phaseolus lunatus* Linn) Family Fabaceae, has been modified by succinylation and annealing, and used as intra- and extra-granular disintegrants at concentrations of 5 and 10 $\%^{w}/_{w}$ in paracetamol tablet formulation in comparison with corn starch BP. The starches were characterised using FT-IR spectroscopy, SEM, proximate analysis, physicochemical and functional properties. FT-IR spectrometry revealed characteristic peaks at 1575.53 and 1713.99 cm^{-1} for the succinylated starch while the annealed showed no significant difference from the native starch. Modifications did not alter the ovoid shape of the native starch but reduced the particle size. Succinylation improved water absorption capacity, solubility and swelling of lima bean starch but annealing reduced the parameters. Tablets with disintegrants of lima bean starches generally had higher crushing strengths and lower friability than tablets with corn starch. Modifications reduced the disintegration time of the tablets when the starches were incorporated intra-granularly, which suggested particle-particle bond interruption and destruction of hydrogen bonds as mechanism of disintegration. Tablets containing 10 $\%^{w}/_{w}$ succinylated red lima bean starch incorporated intra-granularly had the highest disintegration efficiency ratio, DER, indicating a great balance between mechanical and disintegration properties. Modified red lima bean starches incorporated intra-granularly into paracetamol tablets led to faster disintegration and could efficiently substitute corn starch as disintegrant.

Keywords: Red lima bean. Succinylation. Annealed. Intra and extra-granular Disintegrants. Modified starches. Underutilised.

Abbreviation: DER – Disintegration Efficiency Ratio

INTRODUCTION

Underutilised plants have the capacity to contribute to food security, health, commerce and industry but have remained largely unexplored (Ogunwusi, Ibrahim, 2016). The global production and market value of these underutilised crops, also known as orphan crops, neglected crops, forgotten crops, and/ or minor crops, are not as significant as that of staple crops and other agricultural produce (Chivenge *et al.,* 2015). There is meagre scientific information about these plants and their potential economic value remains untapped (Osewa *et al*., 2013). Their potential to contribute to industrial development is however, high and expanding, as these underutilised plants can be employed as industrial raw materials in the pharmaceuticals, fruit juice, beverages and seasoning - producing industries (Ogunwusi, Ibrahim, 2016). Studies have shown that amongst the underutilised legumes, lima bean (*Phaseolus lunatus* Linn, Family Fabaceae) is one of the prominent minor grain grown on less than 10 % of total cultivated land area, attracting low level of income (Nwokolo, 1996; Saka *et al*., 2004; Osewa *et al*., 2013). Lima bean has the capacity to thrive in adverse tropical conditions.

***Correspondence:** O. D. Akin-Ajani. Department of Pharmaceutics & Industrial Pharmacy. Faculty of Pharmacy. University of Ibadan, Nigeria. Phone: +234 802 3007 412. Email: oakinajani@yahoo.com. ORCID iD: 0000-0002-8790-3653

Phaseolus lunatus is grown for its edible seed called lima bean (English) *Akidi-nwangwu* (Igbo) and *popondo* (Yoruba). It is eaten boiled, fried in oil or baked. In Senegal and Democratic Republic of Congo, the leaf extract is used in nasal instillations against headache and in eardrops against otitis; in Nigeria, the seeds are powdered and rubbed into cuts, tumours and abscesses to promote production of pus (Baudoin, 2006). In Asia, traditional medicine practitioners cherish the seeds and leaves for their astringent qualities and they are used for the treatment of fever (Ibeawuchi *et al*., 2007). It is a rich source of protein (24 %$^{w}/_{w}$) and starch (64 %$^{w}/_{w}$), though the presence of anti-nutritional factors and toxins have limited its consumption (Chel-Guerrero *et al*., 2002; Campechano *et al*., 2007). Hence, the need to optimise starch isolated from lima bean for other purposes aside from food.

Starch is commonly employed as disintegrant at concentrations of 2-10 % $^{w}/_{w}$ in commercial tablets to ensure tablet break-up on contact with fluid in the gastro-intestinal tract (Odeku, Akinwande, 2011). It could be added either as part of the powder mixture before granulation (endo-disintegrants) or as dry powder to prepared granules (exo-disintegrants), or before and after granulation (endo-exo-disintegrants). The position of disintegrants in tablet formulation has been shown to determine their effectiveness (Adebayo, Itiola, 1998). The mechanism of action of most disintegrants is the absorption of water and swelling to several times its size leading to a breakdown of the compressional forces that hold the tablet together, thus opposing the action of the binder. For starch disintegrants, the mechanism of disintegration is swelling and particle-particle bond interruption particularly for the non-swelling starch (Guyot-Hermann, Ringard, 1981; Desai *et al,* 2016). Disintegration depends on the degree of compression, porosity of the tablet and ability of the capillary system in the tablet to absorb water (Kanig, Rudnic, 1984). The nature of the disintegrants has been shown to play a role in the disintegrant activity.

Starch have been modified by physical and chemical methods to improve their physicochemical and functional properties and extend their use in pharmaceutical formulations (Rutenberg *et al*., 1984). Modification of starch is advantageous because it disrupts hydrogen bonding and overcomes the limitations of native starch leading to several benefits such as controlled hydration and water holding capacity; gel formation, clarity, and stability (Kalita *et al*., 2014). Succinylation is a method that chemically modifies starch using an esterification reaction. Esterification of starch with succinic anhydride imparts amphiphilic nature on the starch by the addition of a hydrophobic chain into the starch backbone, thus causing it to swell in cold water (Nur Farhana *et al*., 2016). Unlike succinylation, annealing is a physical method of modifying starch by heating at a temperature below the starch gelatinisation temperature with a large quantity of water without damaging the granules (Adebowale *et al*., 2005; Ariyantoro *et al*., 2018).

Previous studies have shown that native lima bean starch has capacity for hydrogel formation (Oladebeye *et al*., 2012) and lower binding ability but faster disintegrant property than corn starch in paracetamol tablets (Okhuelegbe *et al*., 2014a, b), indicating its potential as a disintegrant. However, the effect of the mode of incorporation of the disintegrants and the effects of starch modification, which have been shown to further enhance the activity of starch disintegrant, have not been evaluated. Therefore, the aim of this study was to evaluate the disintegrant activity of modified lima bean starch in paracetamol tablet formulation and the effects of mode of incorporation on disintegrant activity.

MATERIAL AND METHODS

Material

The materials used are paracetamol BP (gift from Fidson Healthcare Plc. Lagos, Nigeria), polyvinylpyrollidone (Gift from Bond Chemicals, Nig. Ltd.), red lima bean (*Phaseolus lunatus* L) was purchased from a local market (*Kasuwan Monday)* in Kurmin Gwari of Kaduna South Local government area of Kaduna state, Nigeria. All reagents used were of analytical grade.

Extraction of Starch

Starch was extracted from red lima bean seeds using the method described by Wang *et al*. (2011) with a slight

modification. One kilogram of lima bean was soaked in 4 L of distilled water and the pH adjusted to 8.0 using solution of 1 M NaOH for 12 h and the coats of the seeds were removed by manual abrasion. The de-hulled seeds were blended for 30 min using a grinder (Panasonic MX-AC400, India). The slurry obtained was re-suspended in 5 L of distilled water and the pH adjusted to 8.0 using 0.5 M NaOH solution. The mixture was stirred manually for 30 min while maintaining the pH at 8.0 – 8.5. The suspension obtained was screened using 75 µm sieve and centrifuged for 30 minutes at 10,000 rpm. The starch obtained was washed three times with distilled water, before air-drying for 48 h.

Annealing of Starch

The method of Jacobs and Delcour (1998) was employed in the preparation of annealed starch. Briefly, 20 g of starch was dispersed in distilled water at a starch to water ratio of 1:2 $^{w}/_{v}$ in a sealed container and heated over a water bath at 50 °C for 24 h. The suspension was then filtered through a Whatman (No. 1) filter paper and the solid air-dried for 72 h.

Succinylation of Starch

Starch (20 g) was dissolved in sodium carbonate solution (prepared by dissolving 1 g sodium carbonate in 30 ml distilled water), mixed with 1 g succinic anhydride and succinylation was carried out for 14 h at room temperature with stirring. The pH of the resultant solution was adjusted to 7.0 with 0.2 N HCl, filtered through a Whatman (No. 4) filter paper, washed with ethanol and the solid dried in an oven at 40 ± 1 ºC (Olayinka *et al*., 2011).

Characterization of native and modified red lima bean starches

Proximate analyses were performed according to the official methods of analysis described in the Association of Official Analytical Chemist (AOAC, 2005) for moisture content, crude protein, ash, fat and fibre. All analyses were carried out in triplicate.

The mean particle size of each starch was determined by optical microscopy using a Sony Digital Camera (14.1 megapixels) attached to an Olympus CH light microscope XSZ-107BN. The picture was transferred to a computer where a Motic Software (Motic MC2000 Image Capture Module; Motic China Group Co Ltd) was used in measuring the particle size at magnification of 40.

Scanning electron microscope (Hitachi model S-2460N, Tokyo, Japan) was used to study the surface morphology and capture the images of the native and modified red lima bean starches at an accelerating voltage of 20 - 25 kV.

The particle density (ρ_t) of the starches was determined by the liquid pycnometer method using xylene as the displacement fluid. A 50 ml pycnometer was weighed empty (W), filled with xylene (non-solvent) and the excess wiped off. The weight of the pycnometer with the non-solvent was determined (W_1). The difference in weight was calculated as W_2. A 2 g quantity of the sample was weighed (W_3) and quantitatively transferred into the pycnometer bottle. The pycnometer was weighed again (W_4) after excess non-solvent was wiped off. The particle density was calculated from the equation:

$$\rho t = {}^{W_2 W_3}/_{50\,(W3 - W4 + W2 + W)} \ g\ cm^{-3} \qquad (1)$$

Water absorption capacity (WAC) expressed, as the weight of water bound by 100 g of dry starch, was determined according to the method of Akin-Ajani *et al*. (2014). Starch (1 g) was suspended in 15 mL of distilled water in a 25 mL centrifuge tube. The tube was agitated on a vortex mixer for 2 min and centrifuged at 4000 rpm for 20 min. The clear supernatant was discarded and the residue was weighed (w1). The residue was dried to constant weight at 60 °C (w2) to remove adhering drops of water.

The method of Leach *et al*. (1959) was used to determine the solubility of the starches. Finely triturated and dried starch powder, 1 g, (w) was weighed into a 100 mL conical flask; 15 mL of distilled water was added to it and shaken for 5 min at low speed. This was then

transferred into a water bath and heated for 20 min at 60 °C with constant stirring after which it was then transferred into pre-weighed centrifuge tube (w_1); 7.5 mL of distilled water was added and it was centrifuge at 2200 rpm for 20 min. The supernatant was carefully decanted into a pre-weighed can (w_2) and dried at 100 °C to constant weight (w_3), then cooled in desiccators. The same procedure was repeated for all the starches.

$$\text{Solubility (\%)} = [(w_2 - w_3)/w] \times 100 \quad (2)$$

Starch (5 g) was transferred into a 100 mL cylinder (V_1) and distilled water (90 mL) was added and shaken for 5 min, then made up to 100 mL. It was allowed to stand for 24 h and the sedimentation volume (V_2) was determined. This was done in quadruplicates.

$$\text{Swelling Index} = V_2/V_1 \quad (3)$$

The FT-IR spectrometry of the starch prepared in potassium bromide (KBr) disks was carried out using an FT-IR system (Spectrum BX 273, Perkin–Elmer, USA). The scanning range was 350–4000 cm^{-1}.

Preparation of Granules

Batches of the basic formulation of paracetamol (80 $\%^w/_w$) and starch (5 and 10 $\%^w/_w$) were dry-mixed for 5 min in a rotomixer (VSF3843C Forster equipment Co. Ltd, Whetstone, Leicester, England) using polyvinylpyrrolidone (3 $\%^w/_w$, MW = 40,000) as binder. Mixing was continued for 5 min and the wet masses were granulated by passing them manually through a mesh sieve (1400 µm), dried in a hot air oven for 6 h at 60 °C and then screened through a mesh sieve (1000 µm). The granules were then stored in an airtight container.

Preparation of Tablets

Granule size fractions, 500-1000 µm was compressed using a carver hydraulic hand press (Model C, Carver Inc., Menomonee Falls, Wisconsin, U.S.A), fitted with a pressure gauge reading up to 2.5 metric tonnes was used. Tablet (500 ± 10 mg) was prepared using a 10.5 mm diameter die in combination with flat faced upper and lower punches with a dwell time of one minute. Before each compression, the punches and die were lubricated by brushing on 2 $\%^w/_v$ dispersion of magnesium stearate in ethanol-ether (1:1). The tablets were subsequently ejected and stored in an airtight container for 24 h to allow for elastic recovery.

Mechanical Properties of the Tablets

The crushing strength was determined using a DBK hardness tester (DBK Instruments, Mumbia, India). The tablet was placed between the anvil and axis and the screw was manually turned until the tablet fractured. The force applied to fracture the tablet was recorded.

Tablets (10) were weighed and placed in a DBK Friability Test Apparatus (Mumbia, India), which was then operated for 4 min at 25 rpm i.e. 100 revolutions. The tablets were then dusted to remove fragments and reweighed. The percentage loss was calculated using equation 4 and recorded as friability, F.

$$\text{Friability (\%)} = \frac{\text{Loss in weight (mg)}}{\text{Initial weight (mg)}} \times 100 \quad (4)$$

Disintegrant Properties

The disintegration times, DT, of the tablets were determined using a DBK disintegration test apparatus (Mumbia, India) in distilled water at 37 ± 0.5 °C. The tablets were placed on the wire mesh just above the surface of the water in the tube and the apparatus was started simultaneously with a stop clock. The time taken for the tablets to completely disintegrate and pass through the wire mesh into the water was recorded as the disintegration time (USP, 2016).

Disintegration efficiency ratio was obtained from equation 5:

$$DER = (Cs/Fr)/D_T \quad (5)$$

Where: Cs is crushing strength, Fr is friability and D_T is disintegration time.

RESULTS AND DISCUSSION

Proximate composition

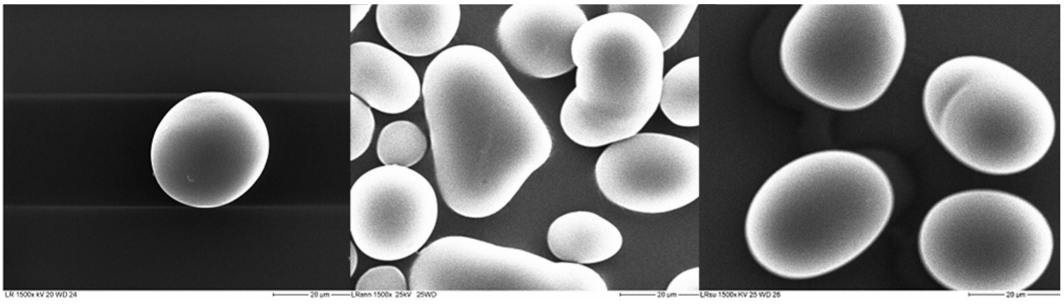
The proximate composition of starches has been shown to affect the functional performance such as pasting and gelling behaviour (Adebowale *et al*, 2012). The proximate composition of native and modified lima bean starches are presented in Table I. The results showed that the modified starches exhibited low levels of protein, fat and crude fibre (< 2 %) in comparison with the native starch indicating a high level of purity in the modified starches (98.1%). The moisture content of the starches was within the recommended moisture levels for safe storage of starches (Thomas, Atwell, 1999). Higher levels of moisture can lead to microbial spoilage and subsequent deterioration in quality (Odeku, Akinwande, 2011).

TABLE I - Proximate Composition of the starches

Starch	Modification	Moisture content (%)	Protein (%)	Ash (%)	Fibre (%)	Fat (%)
Lima bean	Native	7.80 ± 0.14	7.350 ± 0.132	3.000 ± 0.030	5.000 ± 0.090	2.000 ± 0.036
	Annealed	8.98 ± 0.45	0.010 ± 0.001	0.000 ± 0.000	0.010 ± 0.001	0.100 ± 0.005
	Succinylated	9.90 ± 0.17	1.750 ± 0.029	2.000 ± 0.034	0.010 ± 0.000	0.100 ± 0.002
Corn	Native	7.63 ± 0.37	0.458 ± 0.009	1.130 ± 0.056	0.686 ± 0.032	0.353 ± 0.011

Physicochemical and Functional properties of the starches

The SEM of the native and modified starches are presented in Figure 1. The results showed that native lima bean starch had an ovoid shape while corn starch granules were angular or polyhedral in shape (Akin-Ajani *et al*., 2014). There was no observable change in shape and morphology of the succinylated starch, although there was slight distortion of shape in the annealed starch. This is due to the transformation of amorphous amylose into a helical form in the annealed starch (Adebowale *et al*., 2005). Native lima bean starch had a mean granule size of 43.02 µm. Modification led to reduction in mean granule size of 21.0 and 40.5 µm for succinylated and annealed starches respectively.



Native Red Lima Bean Annealed Red Lima Bean Succinyl Red Lima Bean

FIGURE 1 - SEM of Succinyl, Annealed, and Native Red Lima Bean Starches (x1500).

The physicochemical and functional properties of the starches presented in Table II indicate that the ranking of mean projected diameter ($\bar{d}$) was native lima > annealed lima > succinylated lima > corn, indicating that native lima bean starch had the largest particle size while corn starch had the least.

TABLE II - Physicochemical properties of the starches

Starch	Modification	Mean projected diameter, $\bar{d}$ (μm)	Particle density, ρ_t (gcm^{-3})	WAC (%)	Solubility (%)	Swelling index (cm^3)
Lima bean	Native	43.0	1.470 ± 0.027	111.00 ± 2.00	23.61 ± 0.47	1.05 ± 0.02
	Annealed	40.5	1.450 ± 0.290	82.00 ± 10.00	19.98 ± 0.98	0.93 ± 0.05
	Succinylated	21.0	1.450 ± 0.025	116.00 ± 2.00	32.09 ± 0.53	1.04 ± 0.02
Corn	Native	15.0	1.479 ± 0.071	84.95 ± 2.97	53.43 ± 1.07	0.69 ± 0.03

Particle density refers to the number of particles per unit volume and has been shown to affect the packing behaviour of powdered materials. The modified starches had lower particle densities than the native starch, implying that the modified starches would readily form tablets at lower compression pressures (Akin-Ajani *et al*., 2014).

The ranking of the water absorption capacity (WAC) of the starches was succinylated lima > native lima > corn > annealed lima. The observed differences in WAC of the starches could be due to factors such as particle size and molecular structure (Wotton, Bammurachi, 1978). High water absorption capacity has been attributed to loose structure of starch polymers while low value indicates the compactness of the starch structure (Adebowale *et al*, 2012). The variations in WAC values indicate differences in the ability to form hydrogen and covalent bonds between starch chains and the degree of availability of water binding sites among the starches (Hoover, Sosulski, 1986).

Swelling index is a measure of the increase in volume and weight, which starches undergo when allowed to swell freely in water (Balagoplan *et al*., 1998). The rankings for solubility was corn > succinylated lima > native lima > annealed lima, and swelling index was native lima > succinylated lima > annealed lima > corn. The swelling index generally decreased with modification and annealed starch had the lowest values. The results are in line with other studies, which showed that annealing reduces swelling, while succinylation increases solubility (Ariyantoro *et al*., 2018). The swellability of starches is of great significance in tablet formulations because the disintegrant properties of starches have been shown to be affected by swelling and wicking action (Musa *et al*, 2008).

The FT-IR spectra indicating the molecular changes occurring in starches for native and modified lima starches are presented in Figure 2. Both the native and modified starches were seen to have certain discernible absorbance ranging from the O-H (3000-3600 cm^{-1}) stretch characteristic of starches, C-H (2800-3000 cm^{-1}) stretch characteristic of organic compounds, carbonyl group C=O conjugate (1641.91 – 1651.28 cm^{-1}), and 928 to 929 cm^{-1}, which are attributed to C = O bond stretching (Kizil *et al*, 2002; Kalita *et al*., 2014). Succinylation is a chemical modification, while annealing is a physical modification process. Succinylation is an esterification reaction of a hydroxyl group in the starch molecule with succinic anhydride (Lawal, 2012; Ariyantoro *et al*., 2018). The FTIR spectra of the succinylated starch showed two characteristic peaks at 1575.53 and 1713.99 cm^{-1}. The peak at 1575.53 cm^{-1} revealed the asymmetric stretching vibration of carboxylate RCOO- (Nur Farhana *et al*.,

2016; No, Mun, Shin, 2019) while the peak at 1713.99 cm^{-1} was attributable to the stretching vibration of C=O indicating existing ester carbonyl groups. Annealing modifies starch without damaging the granules, thus the spectra for the annealed lima bean starch was similar to that of the native starch (Ariyantoro *et al*., 2018).

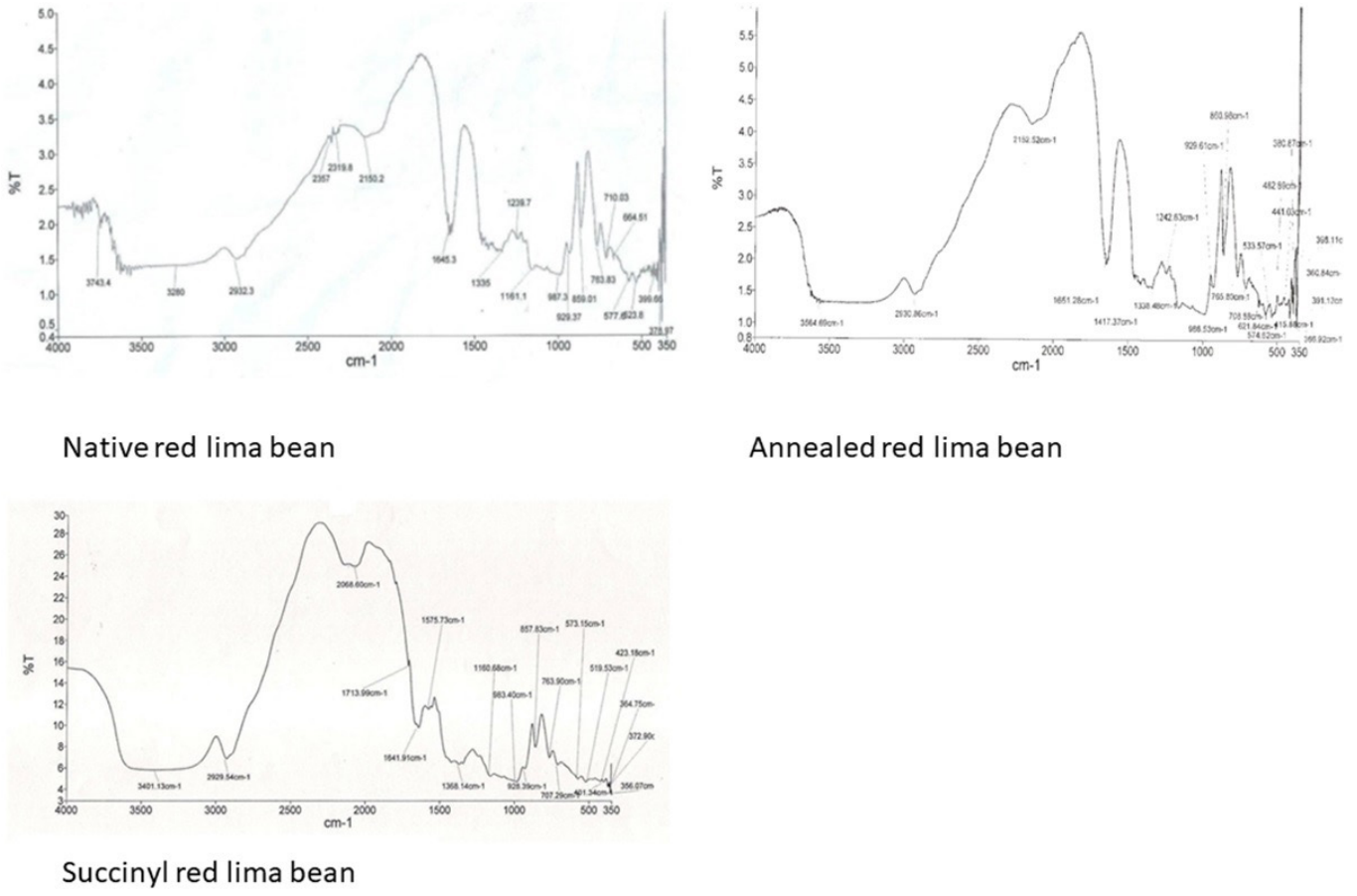


FIGURE 2 - FTIR Spectra of Succinyl, Annealed, and Native Lima Bean Starches.

Crushing Strength

Crushing strength is an important tablet property that demonstrates the mechanical strength of a tablet and the criteria for acceptance or rejection of crushing strength, is largely dependent on the intended use of the tablet (Alebiowu, Itiola, 2002; Odeku, Akinwande, 2011). Crushing strength of paracetamol tablets decreased with increase in concentration of starch disintegrant regardless of the mode of incorporation as shown in Table III. This result is in agreement with the findings of Odeku and Akinwande (2011) for water and white yam starches. The ranking for crushing strength of paracetamol tablets was native lima > succinyl annealed > corn, with the tablets containing exodisintegrants showing significantly ($p < 0.05$) lower values. This indicate that tablets containing native lima starch exhibited higher crushing strength than tablets containing modified lima and corn starches. This could be attributed to the particle size of the corn starch and modified starches, which were lower than that of the native lima bean starch. The crushing strength of tablets formulated with endo-disintegrants was generally higher than tablets formulated with exo-disintegrants. This suggests that the incorporation of the disintegrants intra-granularly led to increased intermolecular forces between the particles as a result of either aspartic melting on production of heat during

compression or due to decreased particle size leading to reduced porosity and increased strength (Yan *et al*., 2011). This is in agreement with previous studies on particle sizes of cement and ceramics (Yan *et al*., 2011; Olawuyi, Boshoff, 2013). Intra-granularly incorporated disintegrants have been shown to produce tablets with higher tensile strengths (Odeku, Akinwande, 2011). Tablets containing corn starch however, had lower crushing strength than the ones containing lima bean starches, regardless of the mode of integration.

TABLE III - Values of crushing strength C_s, friability F_r, and disintegration time D_T, at relative density of 0.85 of the paracetamol tablets

Mode of incorporation	Starch	Modification	Concentration (%)	C_s (N)	F_r (%)	D_T (min)
			0.0	77.80	2.01	47.05
Exo-granular	Lima bean	Native	5.0	141.00	1.21	1.80
			10.0	104.00	2.40	0.80
		Annealed	5.0	165.00	1.64	0.90
			10.0	59.00	3.25	1.70
		Succinylated	5.0	119.00	1.45	1.70
			10.0	105.00	1.55	2.20
	Corn	Native	5.0	113.40	1.39	0.95
			10.0	84.80	3.14	0.33
Endo-granular	Lima bean	Native	5.0	191.00	1.73	1.80
			10.0	148.00	1.49	0.84
		Annealed	5.0	103.00	2.20	0.90
			10.0	112.00	1.49	0.38
		Succinylated	5.0	161.00	1.77	1.75
			10.0	112.00	1.22	0.31
	Corn	Native	5.0	95.60	3.71	7.40
			10.0	107.50	2.83	3.52

Friability

Friability is a measure of tablet weakness; and friability at relative density of 0.85 are presented in Table III. For paracetamol tablets containing exo-disintegrants, friability increased with increase in concentration of disintegrants while friability decreased with increase in concentration of disintegrants for tablets containing endo-disintegrants. This further suggests that the incorporation of the disintegrants intra-granularly lead to greater distribution of the disintegrants within the tablet, thus causing faster disintegration. The rankings for friability of paracetamol tablets containing exo-disintegrants was annealed > corn > native lima > succinyl while those containing endo-disintegrants was corn > annealed > native lima > succinyl. Thus, succinylation improved mechanical properties yielding tablets with lower friability. Tablets containing cornstarch incorporated intra-granularly had the highest friability values.

Disintegration Time

The representative plots of disintegration time versus relative density for paracetamol tablets containing

10 % endo-disintegrants are shown in Figure 3 while disintegration times at relative density of 0.85 are presented in Table III. The disintegration times of the paracetamol tablets containing the native starches incorporated extra-granularly decreased with increase in the concentration of starch disintegrant while those containing modified starches increased with increase in concentration. The result showed that the optimum disintegrant concentration extra-granularly was less than 10 $\%^{w}/_{w}$. Furthermore, tablet formulations containing endo-disintegrants showed lower disintegration times than those containing exo-disintegrants. Studies have shown that no single mechanism is responsible for the action of most disintegrants (Odeku, Akinwande, 2011). Tablet porosity has been shown to play an important role than swelling as tablets containing disintegrants that do not swell performed similarly to tablets containing disintegrants that swell (Guyot-Hermann, Ringard, 1981). However, no linear relationship could be established between disintegration time, porosity and starch concentration. Particle diameter or size of starch if smaller than drug particle envelops the drug creating a continuous hydrophilic wall around the drug, thus enhancing disintegration (Guyot-Hermann, Ringard, 1981). This indicates that when compressive forces reduce porosity, fast disintegration will occur with this continuous network of starch particles around the drug. The ranking for disintegration time, DT, for the formulations containing exo-disintegrants was succinyl > annealed = native > corn while for formulations containing endo-disintegrants was corn > native > succinyl > annealed. All the tablets conformed to official requirements for uncoated tablet disintegration, i.e. disintegration within 15 min (USP, 2016). For modified lima bean starch, the disintegrant effect at 5 $\%^{w}/_{w}$ concentration appeared same irrespective of mode of incorporation. In a similar manner, native lima bean starch had the same disintegration time value irrespective of whether it was incorporated intra- or extra-granularly. On the other hand, corn starch was more efficient as a disintegrant when incorporated extra-granularly than intra-granularly. This is because; corn starch with a mean projected diameter of 15.0 µm is smaller than the drug particle (paracetamol with a mean projected diameter 63.3 µm). Corn starch will envelop the drug creating a continuous hydrophilic wall around the drug, thus enhancing disintegration more so when incorporated extra-granularly (Guyot-Hermann, Ringard, 1981).

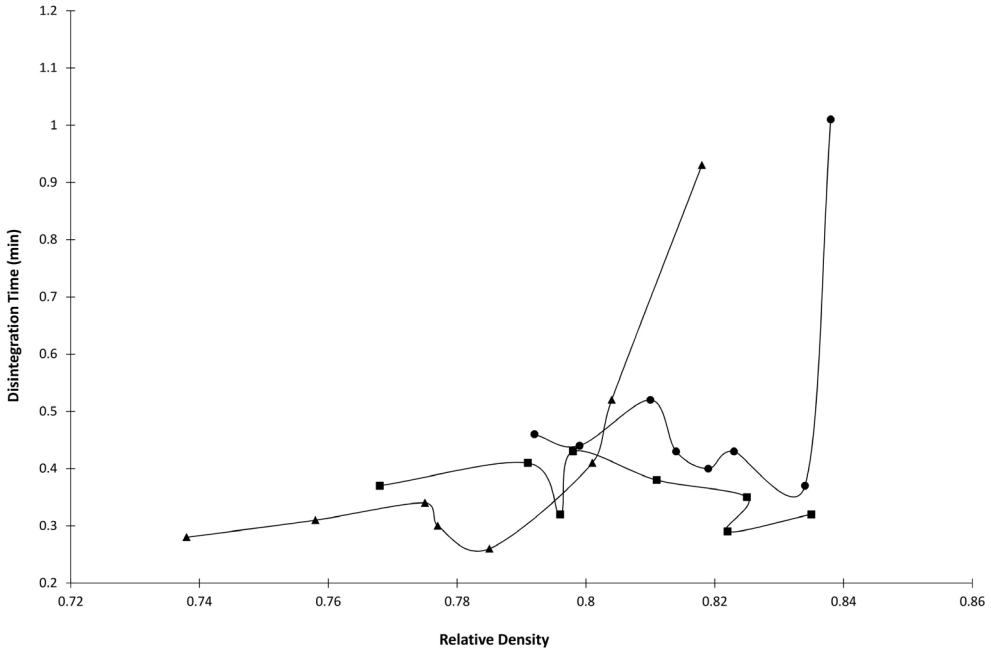


FIGURE 3 - Plots of Disintegration time against Relative density for paracetamol tablets containing 10% Endo Disintegrant of ▲ Native, ● Annealed, and ■ Succinylated Lima Bean Starches.

The WAC and swelling capacity of the disintegrants had no correlation with the disintegrant action. However, mechanism of loss of cohesion of tablet constituents when in contact with water (tablet disintegration) is known to be affected by not only the WAC/ swelling capacity of the disintegrants but also the porous network within the tablet structure. As fluid penetrates this structure, the cohesive force holding the particles together is quickly destroyed. Even though swelling has been adduced the basis for disintegration in starch disintegrants, other factors such as amylopectin content - amylopectin is known to increase solubility and swelling of starch granules; however, these results in reduced disintegrant activity as the increase in swelling leads to the formation of a viscous gel that slowly dissolves. Thus, starches with high amylopectin content are poor disintegrants (Nattapulwat *et al*., 2008; Kibar *et al*., 2010; Cornejo-Ramírez *et al*., 2018). Granule diameter and rate of fluid penetration i.e. through wicking also play an important role. Starch being hydrophilic introduces water into the tablet structure and the moisture influences cohesion either by adsorption, modification of conductivity, electrostatic changes or by condensation in capillars. The quantity of water has been shown to determine whether cohesion of particles occur or release of particle-particle force; as water brought into the tablet structure by starch increased, destruction of the cohesive forces that held the particles together occurred. The breaking up of hydrogen bonds in the presence of water further strengthens this phenomenon as the hydroxyls of water have affinity for those of starch (Guyot-Hermann, Ringard, 1981).

Disintegration also occurs as a result of the creation of repulsive forces, simple destruction of hydrogen bonds or the destruction of capillary cohesive forces (Desai *et al*., 2016). These repulsive forces come into play when tablet is exposed to water and the water seems to be sucked up. The edge where the fluid is sucked up forms clefts from which starch particles escape. As the clefts grow larger the agglomerates break. Thus, the disintegrant seems to present a real individualised power of its particles (Guyot-Hermann, Ringard, 1981).

Disintegration Efficiency Ratio

The disintegration efficiency ratio has been used as an index for assessing disintegrant quality. This is because, in addition to measuring tablet strength (crushing strength) and weakness (friability), it simultaneously evaluates any negative effects of these parameters on disintegration time. The disintegration efficiency ratio of the disintegrants shown in Figure 4 indicates that DER for formulations containing exo-disintegrants decreased with increase in concentration of starch disintegrant but DER significantly ($p < 0.05$) increased with increase in concentration of starch disintegrant for those incorporated intra-granularly. Tablets in which disintegrant was incorporated intra-granularly had greater DER than those in which disintegrant was incorporated extra-granularly. The ranking for DER, for the formulations containing exo-disintegrants was corn > annealed > native > succinyl, while the ranking for formulations containing endo-disintegrants was succinyl > annealed > native > corn. Tablets containing modified starch disintegrants incorporated intra-granularly generally had higher DER values than those containing native lima bean starch and corn starch. The modified starches did not swell as much as the native starches, thus particle-particle bond interruption mechanism may have come into play here along with the destruction of hydrogen bonds. Large variation was observed between the lowest and highest DER values. This suggests that a wide range of properties is obtainable with changes in concentration and mode of incorporation of disintegrants and perhaps other formulation materials. This also shows that changes in DER values are very important in predicting and establishing properties of desired formulations for particular purposes. High values of DER are generally desirable but lower values will generally be useful in the formulation of chewable and effervescent tablets.

Modification of the underutilized red lima bean starch did not alter the ovoid shape of the native starch but reduced the particle size. Tablets with native and modified lima bean starch as disintegrant had higher crushing strengths than tablets with corn starch disintegrant. The use of modified starches reduced the disintegration time of the paracetamol tablets formulated particularly when disintegrants were

incorporated intra-granularly. The modified starches compared well with corn starch 10 $\%^{w}/_{w}$ incorporated extra-granularly. The main mechanism of disintegration appeared to be by particle-particle bond interruption. Tablets containing 10 $\%^{w}/_{w}$ succinylated red lima bean starch incorporated intra-granularly had the highest DER, showing the greatest balance between mechanical and disintegration properties. Thus, modified red lima bean starches (10 $\%^{w}/_{w}$) intra-granularly incorporated will efficiently substitute corn starch disintegrant.

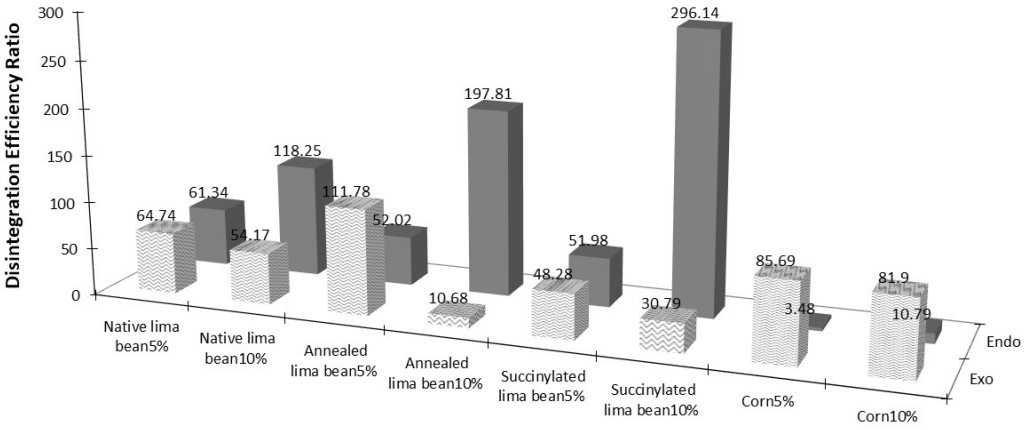


FIGURE 4 - Disintegration Efficiency Ratios of Disintegrants Incorporated Exo-granularly and Endo-granularly.

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CONFLICT OF INTEREST

The authors hereby declare no conflict of interest.

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