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Disintegrant Properties of Native and Modified Polymers in Metronidazole Tablet Formulations

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ABSTRACT

Natural polymers may be modified in order to improve desired properties in tablet formulations. Granule incorporation techniques have different effects on the disintegrant properties of tablets. Disintegrant properties of two new plant polymers, extracted from Pigeon pea (*Cajanus cajan*) and *Khaya senegalensis* tree, were investigated in metronidazole tablet formulations. Native and microwave irradiated forms of the starch and gum were incorporated into the tablet formulations using a 3-factor general full factorial design. Type of disintegrants (X_1) was at two levels (Starch or Gum), effect of modification (X_2) was also investigated at two levels (Native or Irradiated), while the mode of incorporation (X_3) of the disintegrants was at three levels (Intragranular (IG), Extragranular (EG) or Intra-extragranular (IG/EG). Sodium starch glycolate was the standard. Tablets were evaluated for disintegration, dissolution and physical qualities using British Pharmacopoeia methods. The native and modified gum showed higher hydration capacity than the starches. The rank order of the disintegrant properties of the polymers was MG (modified gum)>NG (native gum)>MS (modified starch)>NS (native starch) ($p<0.05$). The crushing strength for tablets from both native and modified polymers was similar but differs with the mode of incorporation. In starch, the rank orders were IG/EG > IG > EG; and EG > IG/EG > IG for the gums. However, IG/EG incorporation of native and modified starches and gums gave a longer t_{80} (time taken for 80% of the drug to dissolve) than both IG and EG ($p<0.05$). The effect of the variables on the disintegrant properties of the polymers was in the order: $X_3 > X_1 > X_2$ and the effect on t_{80} was $X_1 > X_3 > X_2$. The gums and starches were better disintegrants than sodium starch glycolate, with the gums exhibiting better properties than the starches. Microwave irradiation had no significant effect on the disintegrant properties of both polymers but increased the crushing strength of the tablets. Intragranular incorporation proved to be the best method for optimum disintegrant property.

Key words: *Pigeon pea starch; Khaya gum; Polymer modification; Disintegrant properties; Factorial design*

INTRODUCTION

One of the desirable qualities of a tablet is the ability to release the contained medicinal agent(s) into the body system in a predictable and reproducible manner. Disintegrants are critical and essential excipients which facilitate the breakdown of the tablets into particles when in contact with aqueous environment of the gastrointestinal tract, thereby increasing surface area and promoting rapid release of the drug substance (Uddhav *et al*., 2006). Bakre and Jaiyeoba (2009) reported that since a tablet is not useful until its active component is

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made available for absorption, disintegrants are arguably the most important tablet excipients.

The four major mechanisms involved in tablet disintegration are swelling, porosity and capillary action (wicking), particle-particle repulsive force, and deformation (Pahwa and Gupta, 2011). Disintegrants can be added into formulations intragranularly, before the granulation process or extragranularly, after the granulation process. It can also be incorporated intra-extragranularly; in which case incorporation of part of the disintegrant is done intragranularly and the remaining part, extragranularly (Adebayo *et al*., 2008).

Materials used as disintegrants include starches, gums and celluloses. A gum is water-soluble or water-swellable polymer of a monosaccharide or mixed monosaccharide extractable from marine or land plants. It possesses the ability to contribute viscosity or gelling ability to their dispersions (Abu baker *et al*., 2007). The hydrophilic property and ability to swell in water enable gums to be used as disintegrants in pharmaceutical dosage forms (Malik *et al* 2011). Other properties include biodegradability, biocompatibility, non-toxicity, and naturally available. Starch is a ubiquitous material in the plant world and extremely useful to human as food, thickener, tablet binder and disintegrant. Starches are the most common disintegrating agents and they have great affinity for water through capillary action. Starches from different plant sources have been evaluated for use as pharmaceutical excipients (Esezobo and Ambujam, 1982; Muazu *et al*., 2009; Ayorinde *et al*., 2013a).

Gums and starches in their native forms have certain limitations in their usage; they could be modified to enhance their performance in different applications. Starches and gums may be modified to increase their stability against excessive heat, acid, shear, time, cooling or freezing, to change their texture, to decrease or increase their viscosity, to lengthen or shorten gelatinization time; or to increase their visco-stability (Collet and Moreton, 2000). Physical modification is achieved through inducing a molecular interaction between polymers via exposure to dry heat, saturated steam, microwave technology, ultraviolet radiation (Vatanasuchart *et al*., 2005; Khan *et al*., 2006) and gamma radiation (Desai and Park, 2006), while in chemical modification; the polymers are treated with chemicals to yield the desired change. Chemicals commonly used for modification include: aldehydes, epichlorhydrin, borax and glutaraldehyde.

Metronidazole was chosen as the model drug because commercial metronidazole tablets contain between 40 to 60 % excipients (Itiola and Pilpel, 1986); thus the nature and mode of incorporation of excipients in the formulation is capable of modifying the mechanical properties and release profile of the tablet.

This present work is therefore aimed at comparing the disintegrant properties of both native and physically modified forms of Khaya gum (obtained from the tree of *Khaya senegalensis*) and pigeon pea starch (obtained from the legumes of *Cajanus cajan*) in tablet formulations. The properties of metronidazole tablet formulations produced when the polymers are incorporated either as intragranular (IG), extragranular (EG) or intra-extragranular (IG/EG) disintegrants will also be assessed. Formulations incorporating sodium starch glycolate, a super-disintegrant, were used as standard.

MATERIALS AND METHODS

The materials used were metronidazole powder (Vision Pharmaceutical Co. Ltd. China), Lactose (DVM Veghel, Holland), Gelatin BP (Hopkins and Williams, Chadwell Health, Essex, UK), Sodium starch glycolate (JRS Pharma, Germany), Pigeon pea (*Cajanus cajan*), Khaya gum from *Khaya senegalensis*. The plant extracts were authenticated at the Department of Botany, University of Ibadan. All other reagents were of analytical grade.

Extraction of Khaya gum

Khaya gum was obtained from the incised trunk of *Khaya senegalensis* tree located along Ijeoma Road, University of Ibadan, Ibadan. The gum was extracted following established procedures by Odeniyi *et al*., (2013).

Extraction of starch

Pigeon pea grains were washed and milled into a fine paste using a laboratory blender. The slurry was strained through a fine muslin cloth and the filtrate was allowed to settle. The supernatant was decanted at 12 hours intervals and the starch sediment was washed with distilled water for 14 days. The starch sediment was spread on trays and placed in a hot air oven at 60 °C for 2 days. The dried mass pulverized using a mortar and pestle and a laboratory blender and the fine powder obtained was sieved using a sieve with mesh size of 0.500mm. The starch obtained was weighed and stored in an air-tight container.

Modification of Khaya Gum by Microwave Drying:

Quantity of 45g of the native gum was made into slurry with distilled water. 193ml of water was used, owing to the appreciable swelling capacity of the gum. The slurry

was dried in divided quantities with the aid of microwave unit (model R-218L, Sharp, 2450MHz) at 60 ^{o}C for 20seconds on square ceramic tiles; and subsequently dried in an oven set at 60 ^{o}C for 24hours. The dried gums were scraped off the tiles, milled using mortar and pestle. The powders obtained were sieved through a sieve of mesh size 0.250.

Modification of Starch

Preparation of pregelatinized starch

An amount (50g) of pigeon pea starch was weighed and 10mls of water added and placed over a boiling water-bath. The mixture was continuously stirred over the water-bath and 30mls of water was added again with continuous stirring. This process was continued until the starch was well prepared using 73mls of water in all.

Modification by microwave irradiation

A 45g quantity of starch was weighed and made into a slurry with 47mls of distilled water. The prepared slurry was evenly spread on tiles and each dried in a microwave oven for 20seconds. After placing the tiles in the microwave oven, they were put in an oven and dried for 24 hours at 60^{o}C. They were then scraped off the tiles and milled using a mortar and pestle and a laboratory blender. The powder obtained was sieved using a sieve with mesh size of 0.500mm.

Characterization of gum and starch

Swelling Capacity

A 5g quantity of the Khaya gum or pigeon pea starch was weighed and put in a 100ml cylinder. The tapped volume (V_x) occupied by the powders was determined and recorded. About 20ml of distilled water was used to form a dispersion of the gum or starch. The dispersion was thereafter made up to the 100ml volume with more water; and allowed to settle. The dispersion was allowed to stand for 24 hours before the sedimentation volume (V_v) was measured and the swelling capacity was calculated using the relation:

$$Swelling\ Capacity = V_x/V_v \quad (1)$$

Measurement of Angle of Repose

Quantities of 10g of the gum or starch was poured through a funnel clamped on a retort stand, into a cylinder that is open at both ends; the lower end of which rests on a round cork of equivalent radius (r). On raising the cylinder vertically, the granules flowed out and formed a conical heap on the cork; attributable to a balancing effect between gravitational forces and the interparticulate forces. The height (h) of the cone was measured using a pair of dividers and a ruler. The angle of repose (θ) was calculated thus:

$$Tan\ \theta = h/r \quad (2)$$

Determinations were done in triplicates.

Determination of Particle Size

The particle sizes of the native and microwave-modified Khaya gums and starches were determined by optical microscopy on 300 particles for each gum and starch samples. A constant eyepiece which had previously been calibrated with a stage micrometer was used throughout the determination. The mean particle size for each sample was calculated.

Determination of Loose and Tapped Bulk Densities

An amount (20g) of the gum (or starch) powder was weighed and transferred into a 100ml measuring cylinder. The cylinder was gently twisted to obtain a leveled surface of the powder. The initial volume occupied in the cylinder was noted as the Loose Bulk Density (LBD). The powder in the cylinder was then tapped 10 times at a time and the new volume occupied after each round of taps, noted as the Tapped Bulk Density (TBD). The tapping was continued until no further change in volume was noted.

LBD and TBD were calculated using the following formulas:

LBD (Loose Bulk Density)

= weight of powder/volume of the packing (3)

TBD (Tapped Bulk Density)

= weight of powder/tapped volume of packing (4)

Compressibility Index

The Carr's Compressibility index was used for the determination with the following equation:

Carr's index (%) = [(TBD-LBD) x 100]/ TBD (5)

Determination of Particle Density

The particle densities of the native and modified forms of the gum and starch were determined using established procedures (Odeniyi *et al*., 2013).

Determination of Relative Density

Relative density was determined from the ratio of bulk density to particle density according to the equation:

Relative density (Dr) = bulk density/particle density (7)

Preparation of Granules

The granules were prepared using the formula below:

Metronidazole (API)	200mg
Gelatin (Binder)	16mg
Khaya Gum or Pigeon pea starch or Sodium starch glycolate (Disintegrant)	16mg (4%)
Lactose (Bulking agent) to	400mg

Wet granulation method was used to prepare granules sufficient for 50 tablets for each of the Khaya gum and pigeon pea starch samples. Three sets of granules were prepared for each sample; intragranular (I.G), extragranular (E.G) and intragranular/extragranular (I.G/E.G) methods of disintegrant incorporation. For the intragranular method, the disintegrant was entirely mixed with other ingredients prior to wetting and granulation; while for the extragranular method, the disintegrant was added after granulation. Half the total quantity of disintegrant was added before and after granulation for the intragranular/extragranular incorporation method. Gelatin was used as aqueous slurry made with hot distilled water.

The wet masses, after being thoroughly mixed in a mortar, were forced through mesh 12 (1400 um), spread on appropriately labeled square ceramic tiles and dried for 24 hours in an oven set at 60 ^{o}C. The dried granules were thereafter stored in appropriately labeled air-tight plastic containers.

Granule Size Distribution

Standard sieves of the following sizes were used: 12 mesh (1400 um), 16 mesh (1000 um), 30 mesh (500 um), 44 mesh (335 um) and the receiver. These were stacked in decreasing order of aperture size (as above). The approximately 20g of each set of granules was weighed and placed on the topmost sieve (mesh 12), covered and manually shaken for 2 minutes. Thereafter, the granules retained on each sieve were carefully removed and weighed; including the weight of the fines retained by the receiver.

Preparation of Tablets

Tablets were compressed from each set of the granules (I.G, E.G, I.G/E.G) on Carver hydraulic hand press (Model C, Carver Inc., Menomonee Falls, Wisconsin, U.S.A) fitted with pressure gauge. The tablets were stored to allow for elastic recovery and subsequently evaluated.

Evaluation of Tablets

Weight Uniformity

All tablets from every batch were weighed using a weighing balance (Mettler PC 440 Delta Range®, CH-8606 GRIEFENNSEE-ZURICH, Switzerland); and the mean weight was determined.

Crushing Strength

The crushing strength of the tablets were determined at room temperature by diametral compression (Fell and Newton, 1970) using a hardness tester (DKB Instrument, 400065 Model EH 01; Mumbai). The results were taken only from tablets which split cleanly into two halves without any sign of lamination. The determinations were done in triplicates and the mean was calculated as the crushing strength.

Disintegration Time Test

The disintegration time of the tablets were determined in distilled water at 37^{o}C using a disintegration tester (DBK Tablet Disintegration Test Apparatus, England). Five tablets were used for each batch.

Dissolution Test

Dissolution test was carried out on the tablets using the USPXX III Basket Method (DBK- Dissolution Rate Test Apparatus, England); rotated at 50rpm in 900ml of 0.1M HCL buffer solution maintained at 37^{o}C. Samples (5ml) were withdrawn and replaced with equal volume of fresh medium. The sample was diluted appropriately and the amount of metronidazole released was determined at wavelength of 265nm, using a UV/Visible Spectrophotometer. Determinations were made in triplicate.

Factorial Experimental Design

A 3-factor general full factorial experimental design (Minitab ®) was used to study the effects type of disintegrants, effect of modification of disintegrants and mode of incorporation of disintegrants into tablet formulations on crushing strength, disintegration and dissolution times of the tablets. The experimental design of the independent process parameters, the levels used and the quantitative effect of the variables are presented in Table 3. Type of disintegrants (X_1) was at two levels (Starch or Gum), effect of modification (X_2) was also investigated at two levels (Native or Irradiated), while the mode of incorporation (X_3) of the disintegrants was at three levels (Intragranular, Extragranular or Intra-extragranular).

The summary of the individual and interaction coefficients are given in Table 4. For the independent variables, a positive coefficient value indicates that changing from one variable to the order caused an increase in the parameter being measured while a negative value implies the opposite. While for the interacting variables, a positive value for the coefficient

obtained indicates that the variables were interdependent and a negative coefficient value indicate that the effects of the variables were independent of each other.

Statistical Analysis

Statistical analysis was carried out using Students' t-test and ANOVA, p value lower or equal to 0.05 was considered the limit of significance.

RESULTS AND DISCUSSION

The physicochemical properties of the polymers are given in Table 1. The starch particles were of larger sizes than the gum particles ($p< 0.05$). Microwave irradiation led to significant ($p< 0.05$) increase in particle size of both the starches and gums. It has been reported that even small differences in particle size can have great effect on flow properties of materials (Byrne *et al*., 2002; Ayorinde *et al*., 2013b).

The values of bulk and particle densities were found to be higher in the starches than the gums. This suggests a higher degree of packing in the starches than the gums, which is attributable to the small sizes of starch particles filling up the void spaces in the materials (Ayorinde *et al*., 2013a). Modification was found not to affect the densities of the polymers especially the gums.

The angle of repose is a measure of the functional forces between the particles of a powder (Emeryl *et al*., 2009). It indicates powder flow properties. Other parameters indicating a material's flow properties include Carr's index and Hausner's ratio. They give indication of the flow characteristics of powders when subjected to compression force. The higher the Hausner's ratio, the greater the propensity to form a compact mass (Olayemi and Saida, 2011). It was observed that both the gums and the starches had poor flow properties as shown by high values of angle of repose and low values of Hausner's ratio (Table 1). Microwave irradiation did not impart appreciable improvement to the flow properties.

The disintegrant properties of the starch and gum polymers and swelling index are also presented in Table 1. The rank order was MG > NG > MS > NS ($p < 0.05$). Tablet disintegration has been described as the net result of both adhesion and breaking forces between the particles of a material, and the disintegrating forces are activated when tablets are wetted (Adebayo and Itiola, 1998; Alebiowu and Itiola, 2001). The results showed that the gum possesses a higher hydration capacity than the starch, and microwave irradiation further improved the swelling index in the polymers.

Values of tablet parameters at relative density of 0.90 (used for commercial tablets) are shown in Table 2. The crushing strength of tablets containing starch incorporated as IG/EG was highest ($p< 0.05$). The rank order was IG/EG > IG > EG. This trend was similar for both native and modified starches. Crushing strength is a useful parameter in evaluating the resistance of tablets to chipping, abrasion or breakage during storage, transportation and handling by the patient. It is not however always essential to seek to have high crushing strength for tablets because excessively high crushing strength is an indicator to poor tablet disintegration. For the gums, the rank order was EG > IG/EG > IG for native and IG > IG/EG > EG for modified gum. The crushing strength of sodium starch glycolate (SSG) was found to be higher than the official specification (British Pharmacopoeia, 2000) when incorporated as IG. These results suggest that the choice to modify the gum for disintegrant purpose should be determined by the intended mode of incorporation. Modification of the starch does not affect disintegrant property irrespective of the incorporation method. Furthermore, IG incorporation of SSG might result in excessively hard tablets. However, the values of crushing strength for tablets containing the starches and gums compare well with that of SSG when used as EG and IG/EG

Table 1:
Physicochemical properties of the native and modified polymers

Polymer Samples	Particle size (µm)	Particle density (g/cm^3)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's Index (%)	Hausner's Ratio	Angle of Repose (θ^o)	Swelling Index
Starch:								
Native	0.29±0.01	1.16±0.02	1.53±0.00	1.56±0.01	1.92±0.02	1.02±0.00	60.70±0.01	1.02±0.42
Microwave	0.52±0.00	0.58±0.01	1.34±0.01	1.50±0.00	10.67±0.00	1.12±0.01	61.93±0.01	1.70±0.12
Gum:								
Native	0.63±0.00	1.23±0.01	0.71±0.01	0.83±0.02	14.29±0.12	1.17±0.03	58.40±0.13	10.50±1.01
Microwave	1.88±0.01	1.27±0.01	0.71±0.02	0.77±0.03	7.14±0.03	1.08±0.02	55.40±0.12	13.70±2.53

Table 2:
Mechanical and release properties of metronidazole tablets incorporating disintegrants at different stages of formulation

Disintegrant	Modification	Disintegrant Incorporation Method	Crushing Strength (N)	Disintegration Time (min)	Dissolution Time (t_{80}) (min)	CS/DT
Starch:	None (Native)	IG	65.90±0.02	1.43±0.01	8.00±0.50	46.08
		EG	47.40±0.04	6.010±0.02	8.50±1.00	7.88
		IG/EG	77.20±3.10	5.87±0.15	22.40±0.01	14.49
Starch	Microwave irradiation	IG	69.30±0.04	1.96±0.00	11.00±0.02	35.56
		EG	73.70±0.02	6.01±0.04	10.00±2.01	12.26
		IG/EG	102.70±0.01	10.26±0.01	16.20±1.00	10.00
Gum	None (Native)	IG	62.45±0.01	1.81±0.01	22.00±2.00	34.50
		EG	68.10±0.02	2.27±0.04	32.30±2.01	30.00
		IG/EG	63.85±0.03	2.29±0.03	20.00±3.15	27.89
Gum	Microwave irradiation	IG	55.600±0.01	1.31±0.01	14.50±2.01	42.43
		EG	50.550±0.01	3.50±0.02	24.70±3.20	14.44
		IG/EG	51.000±0.02	3.33±0.01	12.40±1.70	15.32
Sodium starch glycolate	-	IG	108.500±0.00	4.61±0.01	13.30±1.40	23.54
		EG	75.150±0.00	10.99±0.02	12.05±2.01	6.84
		IG/EG	92.250±0.01	7.94±0.01	14.00±0.02	11.62

Table 3:
Independent process parameters and associated results

Run Order	Disintegrant type	Modification type	Mode of incorporation	Crushing Strength (N)	Disintegration time (min)	Dissolution time (t_{80}) (min)
1	Starch	Native	Intragranular	65.9	1.43	8
2	Starch	Native	Extragranular	47.4	6.01	8
3	Starch	Native	Intra-Extra	77.2	5.87	22
4	Starch	Microwave irradiated	Intragranular	69.7	1.96	11
5	Starch	Microwave irradiated	Extragranular	73.7	6.01	10
6	Starch	Microwave irradiated	Intra-Extra	102.7	10.26	16
7	Gum	Native	Intragranular	62.45	1.81	22
8	Gum	Native	Extragranular	68.1	2.27	32
9	Gum	Native	Intra-Extra	63.85	2.29	20
10	Gum	Microwave irradiated	Intragranular	55.6	1.31	14
11	Gum	Microwave irradiated	Extragranular	50.55	3.5	24
12	Gum	Microwave irradiated	Intra-Extra	51	3.33	12

The disintegration time of native and modified starches were not significantly different when incorporated as IG and EG, significant difference was however observed when used as IG/EG, with the modified starch having a longer disintegration time (Table 2, Fig. 1). Native gum had longer disintegration time than the modified gum when used as IG while in both EG and IG/EG incorporation, native gum had shorter disintegration time ($p<0.05$). This suggests that microwave irradiation could improve the IG disintegrant properties of the gum whereas, this might not be applicable for IG/EG incorporation methods.

Generally, the disintegration times of the gums were shorter than the starches and SSG, while both SSG and the starches had comparable disintegration time. Disintegration is a necessary condition for dissolution and subsequently the rate-limiting step in absorption process (Bamiro *et al*., 2007) and previous studies have shown that the type of excipients and process parameters affect drug disintegration (Tabandeh *et al*., 2003; Ayorinde and Itiola, 2010).

Table 4:
Summary of the individual and interaction coefficients of the variables on the Crushing strength, Disintegration time and Dissolution time (t_{80}) of tablets

Factor	Coefficient	Crushing Strength (N)	Disintegration time (min)	Dissolution time (t_{80})
Disintegrant type (X_1)	Effect	7.088	1.419	-4.083
	p-value	0.131	0.024	0.071
Mode of modification (X_2)	Effect	-1.529	-0.558	2.083
	p-value	0.723	0.298	0.315
Mode of incorporation of Disintegrant (X_3)	Effect	-5.742	-2.210	-2.833
	p-value	0.418	0.040	0.592
X_1X_2	Effect	-7.738	-0.263	-1.917
	p-value	0.095	0.510	0.115
X_1X_3	Effect	-2.700	-1.352	-0.167
	p-value	0.535	0.102	0.884
X_2X_3	Effect	2.292	0.550	-0.833
	p-value	0.593	0.360	0.495
$X_1X_2X_3$	Effect	5.075	0.005	-0.833

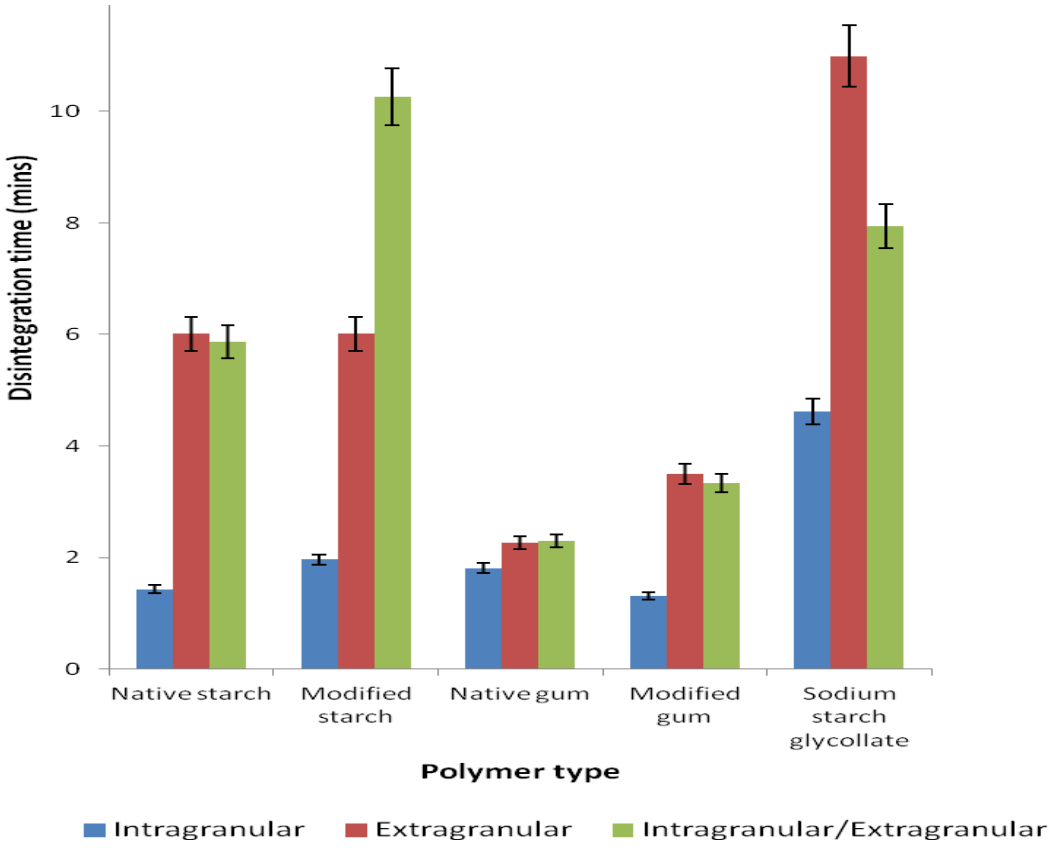

Figure 1:
Plots of disintegration times of the native and modified polymers in metronidazole tablet formulations

Hence, the incorporation mode is a process parameter that needs to be critically considered in achieving a satisfactory disintegration in tablets containing starch or gum polymers.

The effectiveness of oral dosage forms relies on the drug dissolving in the fluids of gastrointestinal tract prior to absorption into the systemic circulation. The rate of dissolution of tablets is therefore crucial and is affected by factors such as tablet hardness and porosity (Tabandeh *et al*., 2003). There was no significant difference ($p > 0.05$) in the dissolution time of the starches and gums when incorporated as IG and EG;

however, IG/EG incorporation of both native and modified polymers gave a longer t_{80} than both IG and EG ($p< 0.05$), (Table 2). Among the starches, native starch showed longer t_{80}. This suggests IG and EG incorporation methods to be better than IG/EG in the use of the polymers as disintegrant. However, when the starch is to be incorporated as IG/EG, microwave irradiation could be used as modification technique. The dissolution of formulations containing gums as disintegrants generally took longer time than for formulations containing starches.

Another parameter that was used to assess the tablet quality is the Crushing strength Disintegration (CS/DT) ratio. This ratio measures the tablet strength in relation to the disintegration time. High ratio is an indication of better balance of binding and disintegration properties (Adebayo and Itiola, 1998; Bamiro *et al*., 2007). Table 2 shows higher values of the ratio for IG incorporation of both the starches and gums. This suggests that IG incorporation method imparts best overall disintegrant properties.

The factorial experimental design has been found useful in previous studies in determining the quantitative contribution of each variable in the evaluation of pharmaceutical formulations (Ayorinde and Itiola, 2010; Odeniyi *et al*., 2008). It has also proven valuable in determining the optimum formulation and with the use of mathematical modeling, limits the number of trial runs in an experiment (Odeniyi and Jaiyeoba, 2009; Singh *et al*., 2005). The interaction term (X_1X_2 or $X_1X_2X_3$) shows how the response values change when two or more factors are simultaneously changed. A high positive or negative coefficient value indicate that by making a minor change in the setting of that factor, a significant change in the dependent variable will be obtained.

The effects of the variables on the crushing strength of the tablets were in the order $X_1>X_3>X_2$ ($p>0.05$). The highest effect was observed when the disintegrant was changed from the gum to the starch and lowest effect was due to modification of the disintegrants (Fig. 2). The effects of the variables on the disintegrants properties of the experimental polymers were in the order $X_3> X_1>X_2$. Disintegrant type and mode of incorporation contributed more to the disintegration time than modification. While change in disintegrants from gum to starch caused a decrease in disintegration time, incorporation of disintegrants intra-extragranularly caused an increase in disintegration time ($p<0.05$) (Fig. 3).

The time for 80% of drug to dissolve (t_{80}) was taken as dissolution parameter. The effect of the variables on t_{80} was in the order $X_1>X_3>X_2$ (Fig. 4). The type of disintegrant was observed to be the only significant factor ($p<0.05$) on dissolution time. Changing from starch to gum led to an increase in dissolution time while changing from the native to the modified disintegrant caused a decrease in t_{80}. Also, modification of the native polymers led to a decrease in dissolution time for the tablet formulations.

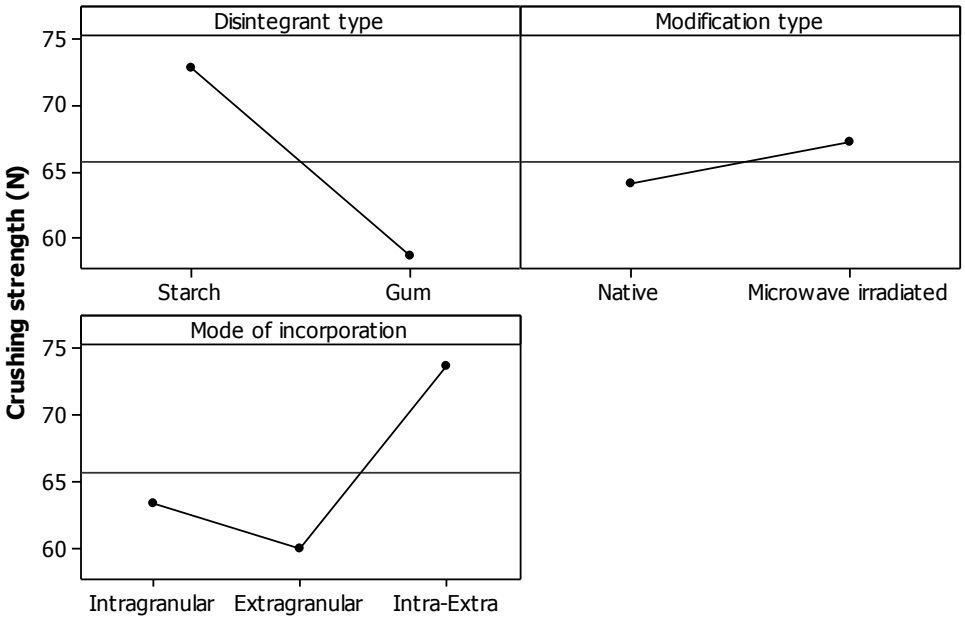

Figure 2:
Main effects plot of change in formulation variables on the crushing strength of tablets

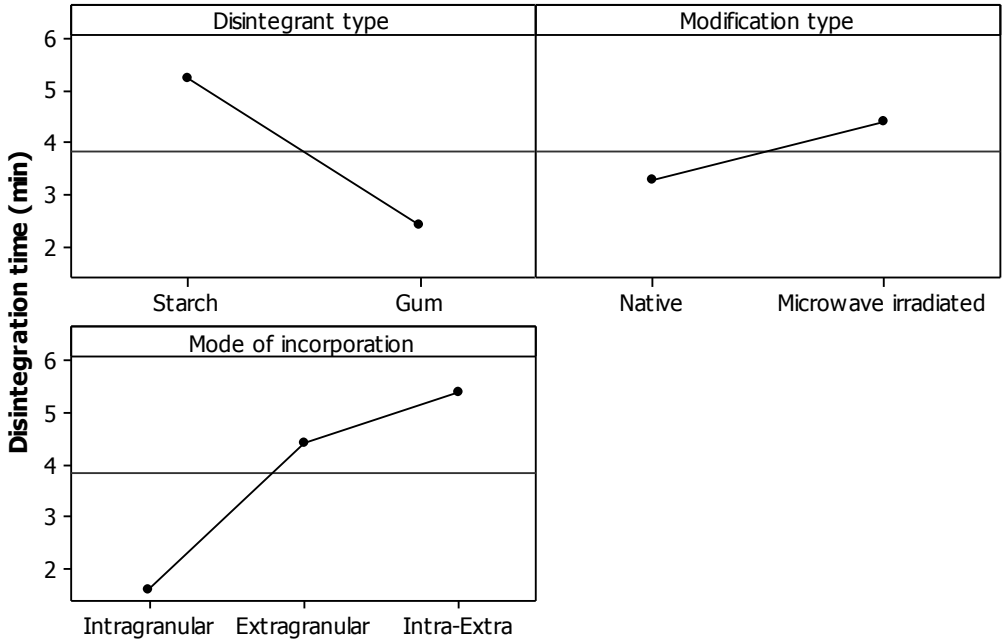

Figure 3:
Main effect plots of change in formulation variables on the disintegration time of tablets

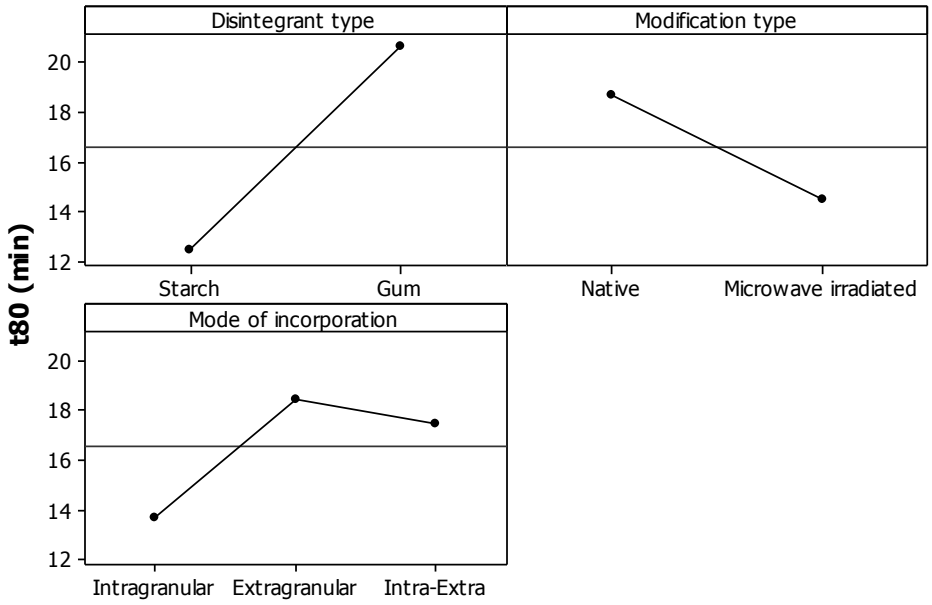

Figure 4:
Main effect plots of change in formulation variables on the dissolution time (t_{80}) of tablets

Conclusions

The native and modified forms of Pigeon pea starch and Khaya gum had superior disintegrant properties to Sodium starch glycolate, a superdisintegrant, in metronidazole tablet formulations. The mode of incorporation and disintegrant type had significant effect on disintegration time. The gum had better disintegrant property than the starch, which is attributable to better swelling indices of the gum. Infra-red irradiation of the microwave had no significant effect on tablet release properties but caused an increase in tablet crushing strength. The results indicate that Pigeon pea starch and Khaya gum could be used as intra-granular disintegrants in tablet formulations for which rapid release is desired as a substitute for sodium starch glycolate.

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