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Evaluation of binder and disintegrant properties of starch derived from *Xanthosoma sagittifolium* in metronidazole tablets

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The aim of the study was to formulate metronidazole tablets using starch from *Xanthosoma sagittifolium* as binder and disintegrant in metronidazole tablets. Metronidazole tablets were produced by wet granulation method using *X. sagittifolium* starch as binder at concentrations of 5, 10, 15 and 20% w/w, and as disintegrant (5% w/w). The micromeritic properties of the granules were determined using the direct and indirect methods. The necessary official and non official tests were performed on the tablets to include uniformity of tablets weight, content of active ingredient, disintegration test, hardness, friability tests and *in vitro* drug release. Also, the phytochemical constituents of the starch were determined. The results show that the granules had a good flow and values obtained were within the specified limits for the production of good quality tablets. Deviations obtained from the tablet weight uniformity test were significantly ($p< 0.05$) below 5%. Tablets disintegration time ranged from 3.00 ± 0.08 min to 14.00 ± 0.10 min for M1 and M4 tablets formulated with 5 and 20% of *X. sagittifolium* starch respectively. The tablets hardness ranged from 7.20 ± 1.25 to 8.55 ± 1.17 kgf. *In vitro* release showed that M1 tablets had T_{25}, T_{50} and T_{90} % at 5, 13 and 23 min respectively, while M4 tablets had T_{25}, T_{50} and T_{90} % at 8, 18 min and were unable to release 90% of metronidazole at 30 min. Phytochemical analysis showed that the starch contained alkaloids, glycosides, carbohydrate and steroids. Therefore, starch from *X. sagittifolium* could be used to formulate metronidazole tablets for improved oral bioavailability of metronidazole.

Key words: *Xanthosoma sagittifolium* starch, tablets binder and disintegrant, metronidazole.

INTRODUCTION

In recent years, pharmaceutical scientists have been paying increasing attention to the extraction, development and use of starches in the formulation of dosage forms (Singh and Nath, 2012; Ogaji, 2011; Builders et al., 2011; Narkhede et al 2011; Peerapattana et al., 2010; Gangwarm et al, 2010). Natural polymers have advantages over the synthetic and semi-synthetic polymers which include better biocompatibility, relatively cheap, non toxic, less expensive, easily accessible and physiologically inert. The danger of use of synthetic polymer matrix materials which often goes along with detrimental effects on incorporated drug during manufacturing of formulations or after application are completely avoided (Reithmeier et al., 2001).

Starch is a multipurpose excipient in tablet formulation, and it is used as a binder, disintegrant and filler (Adebayo and Itiola, 2003). Disintegrants are essential components in tablet formulations. Disintegrants may exert its action by swelling, wicking or deformation (Isah et al., 2009). Starch is the commonest disintegrant in tablet formulation

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and is believed to act by swelling (Rubinstein, 1988), however, current research has shown that most starches exert their disintegrant actions by deformation (Ofoefule, 2002). Starch grains are generally elastic and at certain compression pressure, starch may undergo permanent deformation. These permanently deformed grains are rich in energy and when exposed to water, the energy is released causing disintegration of tablets (Ofoefule, 2002). Starches are widely available and have been very useful in tablet production due to their inertness, cheapness and utilization as fillers, binders, disintegrants and glidants and a lot of effort has been expended on the development of new starches from local sources as pharmaceutical excipients (Esezobo and Ambujam, 1982; Weirik et al., 1996; Alebiowu and Itiola, 2001; Olayemi et al., 2008).

Binders are polymeric materials which possess both cohesive and adhesive properties (Ofoefule, 2002; Momoh et al., 2012). Binding agents are incorporated into tablets during granulation in order to improve formation of agglomerates and the flowability of the drug and to enhance compressibility. These agents coat the drug particles and therefore the rate of solution of the binder in water can determine the release rate of drug from the tablet (Momoh et al., 2012). Excessive binder concentration yield slow disintegrating and hard tablets while insufficient binder concentration gives poor adhesive, soft tablets which tend to cap (Momoh et al., 2012). Binders confer structural strength required by tablets during processing, handling, packaging and transportation (Emeje et al., 2008). Binders ameliorate capping and lamination by decreasing the plastoelasticity of pharmaceutical powders. Materials used as binders predominantly display plastic compaction characteristics. Hence, when incorporated into elastic or fragmenting natured powders, they impart plasticity to them, thereby reducing their plastoelasticity (Uhumwangho and Okor, 2004).

Metronidazole is a poorly compressible antiprotozoal and anti parasitic agent that is very effective in the treatment of amoebiasis, trichomoniasis, giardiasis and many other parasitic diseases (Chukwu and Udeala, 2005; Phillips and Samuel, 2006). It also has poor water solubility (Obitte et al., 2008). Cocoyam starch, in a previous research work was found to possess superior moisture sorption capacities when it was compared with corn starch BP (Adebayo and Itiola, 1998). Natural, synthetic and semi-synthetic binders and disintegrants including mucilages, gums or starch from cashew, plantain, maize, okra, *Irvinga gabonensis* in addition to gelatin and acacia have been applied in the formulation of metronidazole tablets (Abdulsamad et al., 2008; Odeku and Patani, 2005; Chukwu and Udeala 2005; Momoh et al., 2009; Itiola and Pipel, 1986 and Shittu et al., 2010).

The economic importance of starch from cocoyam (*Xanthosoma sagittifolium*) stem ranges from both its high yield of starch as well as the functionality of starches derived from them. The granules are highly digestible and their sizes are in a range lower than 5 µm (Car et al., 1995; Aboubakar et al., 2008). Several reports has shown that cocoyam starch exhibit visco-elastic properties characterized by force of adhesion and relaxation, ability to absorb water and swell etc (Njintang et al., 2007; Rodriguez-Miranda et al., 2011; Ahromrit and Nema, 2010; Ammar et al., 2009). This makes *X. sagittifolium* starch a candidate material for use in the formulation of poorly compressible metronidazole powder. The aim of the study therefore, was to evaluate the binder and exo-disintegrant properties of starch from *X. sagittifolium* in metronidazole tablet.

MATERIALS AND METHODS

Metronidazole was from Evans Pharmaceutical Ltd., England, lactose was from Merck, Germany, (BDH, England), and magnesium stearate was from May and Baker, England. *S*tarch was extracted from the tubers of *X. sagittifolium* purchased from the market of Nsukka, Nigeria. All other reagents and solvents were of analytical grade and were used as supplied.

Extraction and purification of *X. sagittifolium*

X. sagittifolium was purchased from Orba market in Nsukka in Enugu state, Nigeria in February, 2011. The tubers were cleaned by removing the soil and washed with water. The bark were properly peeled and rewashed with clean water containing 1% sodium metabisulphite. After washing, the *X. sagittifolium* tubers were reduced to a fine pulp in a hammer mill. The pulp was separated from the rasped *X. sagittifolium* by means of a muslin cloth and agitation was provided using hands. During screening, the water used contained 1% sodium metabisulphite in order to avoid discolouration of the starch by oxidative enzymes. The obtained starch suspension was allowed to settle under gravity and the supernatant was decanted. The starch suspension was washed severally using three times its volume of water for three days with intermittent shaking and changing of water (Ajali, 2004). Dewatering was done using a bag with pores of about 100 mm and pressure was applied using hand. The starch was dried in a tray dryer (Manesty Ltd, Liverpool, England) at 40°C. The dried starch was finally passed through 55 mm sieve (Turgens & Co., Germany).

Phytochemical screening

Phytochemical tests were carried out on the starch for the presence of alkaloids, steroids, glycosides, carbohydrates. The tests were carried out using standard procedures of analysis (Harborne, 1993; Sofowora, 1993; Trease and Evans, 2002).

Preparation of granules

Granules were prepared by wet granulation method using *X. sagittifolium* starch as the binder at concentrations of 5, 10, 15 and 20% (w/w). Details of granulation are given in Table 1. Lactose was used as the diluents and 5% (w/w) *X. sagittifolium* starch, added extra granularly, served as the disintegrant. The powder samples were dried and mixed for 10 min in a tumbler mixer. The mixtures were moistened with the appropriate amount of binder solution prepared in distilled water. The homogeneous wet mass was then screened through a 1.7 mm sieve and the wet granules dried in a

Table 1. Composition of metronidazole tablets.

Ingredient	Quantity/tablet (mg)			
	M1	M2	M3	M4
Metronidazole	200.0	200.0	200.0	200.0
X. sagittifolium starch (paste)	15.0	30.0	45.0	60.0
X. sagittifolium starch	15.0	15.0	15.0	15.0
Magnesium stearate	3.0	3.0	3.0	3.0
Lactose	300.0	300.0	300.0	300.0

M1, M2, M3 and M4 are various batches of metronidazole tablets containing 5, 10, 15 and 20 % *Xanthosoma sagittifolium* starch as binder.

hot air oven at 60°C for 1 h. Thereafter, the dried granules were screened through a 1.0 mm sieve.

Characterisation of granules

Bulk and tapped densities

A 50 g quantity of the granules was placed in a 100 ml measuring cylinder and the volume occupied by the granules was recorded as the bulk volume. The bulk density was obtained using Equation 1:

$$\text{Bulk density} = \frac{\text{Mass of powder (M)}}{\text{Bulk volume of powder } (V_B)} \quad (1)$$

The cylinder was tapped on a wooden platform by dropping the cylinder from a height of one inch at 2 s interval until there was no significant change in volume reduction. The volume occupied by the sample was then recorded as the tapped volume. The tapped density was calculated using the formula:

$$\text{Tapped density} = \frac{\text{Massof sample (M)}}{\text{Tappedvolume } (V_T)} \quad (2)$$

Flow rate and angle of repose

A funnel was properly clamped onto a retort stand. A funnel of known efflux tube length, orifice and base diameter was used for the study. A 50 g quantity of the granules was weighed out and gradually transferred into the funnel with the funnel orifice closed with a shutter. The time taken for the entire granules to flow through the orifice was recorded. The flow rate was obtained by dividing the mass of the sample by the time of flow in seconds (Aulton, 2007; Chime et al., 2012).

The dynamic angle of repose was determined by measuring the height of heap of powder formed using a cathetometer; the radius was obtained by dividing the diameter by two. Angle of repose (Θ) for each granule was calculated using Equation 3:

$$\Theta = \tan^{-1}\frac{h}{r} \quad (3)$$

Compressibility index and Hausner's quotient

Carr's compressibility indices (%) of the granules were obtained using the formula:

$$\text{Carr's Index (\%)} = \frac{\text{Tapped density- Bulk density}}{\text{Tapped density}} \times 100 \quad (4)$$

Hausner's quotient (HQ) was obtained using the formula:

$$\text{HQ} = \frac{\text{Tapped density}}{\text{Bulk density}} \quad (5)$$

Preparation of tablets

The granules were treated with magnesium stearate and then compressed at 46 to 48 kgf using a 9.0 mm punch and die set fitted into an automated F3 Manesty Single Punch tabletting machine.

Evaluation of tablets

Disintegration time test

The disintegration time test was performed using an Erweka ZT 120 basket and rack assembly and 0.I N Hydrochloric acid maintained at 37.0 ± 1.0°C as the disintegration medium. Ten (10) tablets from each batch were used for the test and the procedure being as stipulated in the BP (2009).

Uniformity of weight

Twenty (20) tablets were randomly selected from each batch of the metronidazole tablets. The tablets were weighed twice, individually, using an electronic balance (Ohaus Adventurer, China) and the mean individual weights recorded. The mean weight, standard deviation and percentage deviation were calculated (BP, 2009).

Tablet friability test

Twenty (20) tablets randomly selected from each batch of the tablets were used for this study. The tablets were dedusted and weighed. The tablets were placed into the drum of the friabilator (Erweka GmbH, Germany) and rotated at 25 rpm for 4 min. The tablets were removed from the friabilator, dedusted and reweighed. The friability result was calculated from the formula:

$$Friability\ (\%) = 100\left[\frac{W_o - W}{W_o}\right] \quad (6)$$

Table 2. Micromeritic properties of metronidazole granules.

Batch	ℓ_B (g/ml ± SD)*	ℓ_T (g/ml ± SD)*	A.R (^{o} ± SD)*	C.I (%)	HQ	Flow rate (g/sec ± SD)*
M1	0.50 ± 0.07	0.64 ± 0.05	24.94 ± 0.23	21.88	1.28	13.73 ± 0.27
M2	0.51 ± 0.03	0.62 ± 0.12	18.43 ± 0.11	18.51	1.23	13.68 ± 0.10
M3	0.56 ± 0.10	0.71 ± 0.04	17.43 ± 0.10	21.74	1.28	12.79 ± 0.11
M4	0.57 ± 0.07	0.71 ± 0.05	25.77 ± 0.10	19.14	1.24	13.51 ± 0.17

Values shown are mean ± SD (*n = 3). M1, M2, M3 and M4, metronidazole granules prepared with 5, 10, 15 and 20% *Xanthosoma sagittifolium* starch as binder respectively; ℓ_B and ℓ_T = Bulk and tapped densities; AR = angle of repose; HQ = Hausner's quotient; CI = Carr's compressibility index.

Where, W_o and W are the initial and final weights of the tablets respectively.

Hardness/crushing strength test

This test was carried out using Monsanto-Stokes hardness tester (Manesty, England). Ten (10) tablets from each batch were randomly selected. Each tablet was placed between the jaws of the hardness tester and force was applied by adjusting the knob of tester until the tablet integrity failed. The results were recorded in kgf.

Content of active ingredient

Beer's calibration curve for metronidazole was obtained at a concentration range of 0.1 to 0.9 mg% in 0.1 N HCl at a predetermined wavelength of 277 nm. Twenty (20) tablets were randomly selected from each batch of the tablets. The tablets were weighed together and crushed in a mortar with a pestle. An amount equivalent to the average weight of the crushed tablet was weighed out, dispersed in the medium and filtered with a non adsorbent filter paper (Whatman No. 1). An aliquot of the filtrate was assayed using spectrophotometer (Jenway 6305, UK). The absorbance readings were recorded and the concentration of metronidazole in each tablet was calculated with reference to Beer's plot.

***In vitro* release studies**

The *in vitro* dissolution profile for each batch of tablet was determined using the paddle method with an Erweka DT 600 dissolution apparatus. The dissolution medium consisted of 900 ml of freshly prepared 0.1 N HCl maintained at 37 ±1°C. A tablet from each batch was placed inside a tightly secured basket and the basket was placed in the bottom of the beaker. The paddle was rotated at 100 rpm. At various intervals, 5 ml sample was withdrawn from the dissolution medium, filtered (Whatman No. 1) and an aliquot of the filtrate was assayed using spectrophotometer (Jenway 6305, UK) at 277 nm. An equal volume of the withdrawn sample was replaced with a fresh medium to maintain sink condition. The amount of drug released at each time interval was determined with reference to Beer's plot for the drug.

Statistical analysis

Data were analysed by one-way analysis of variance (ANOVA). Differences between means were assessed by a two-tailed student's T-test. $P< 0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

Micromeritic properties

The results of the micromeritic properties of metronidazole granules prepared with *X. sagittifolium* starch as binder and disintegrant are presented in Table 2. The results show that the granules had a good flow and values obtained were within the specified limits for the production of good quality tablets. From the results, the granules had angle of repose that ranged from 17.43 ± 0.10 to 25.77 ± 0.10°. These results show that the granules had low interparticulate friction and hence good flow. The results of compressibility index indicate that the prepared granules had good flowability and consolidation properties. When the CI and HR are adequate, the powder flows at minimum bulk density. A high bulk density, that is a low porosity, will result in a low deformation potential, a lack of space for deformation during compression will cause less intimate contact between the particles within the tablets, resulting in weaker tablets (Yüksel et al., 2007; Momoh et al., 2012). Carr's index in the range of 5 to 16% indicates good flow, 18 to 21% shows fair flow, while values above 38% show very poor flow (Chime et al., 2012) and from the results of Carr's compressibility index shown in Table 2, the granules had a fair flow. Hausner's ratio ≤ 1.25 indicates good flow, while values > 1.25 indicates poor flow (Aulton, 2007; Yüksel et al., 2007); from the results in Table 2, batches M2 and M4 had HQ below 1.25 and hence exhibited good flowability. However, batches M1 and M3 had HQ of 1.28. The results show that the granules had good flow rate and could be used to produce standard tablets.

Properties of metronidazole tablets

The results of tablets weight uniformity of metronidazole tablets are shown in Table 3. From the results, the tablets weight ranged from 300.00 ± 1.10 to 302.00 ± 1.03 mg. The percentage deviations obtained from the tablet weight uniformity test were significantly ($p< 0.05$) below 5% stipulated for tablets weight greater than 250 mg (BP, 2009). Therefore, the tablets passed the weight uniformity

Table 3. Properties of metronidazole tablets.

Tablet code	Tablet weight (mg ± CV)*	Drug content (mg ± SD)*	Disintegration time (min ± SD)[a]	Hardness (kgf ± SD)[a]	Friability (%)*
M1	300.95 ± 1.17	203.00 ± 0.27	3.00 ± 0.08	8.50 ± 1.00	1.29
M2	300.00 ± 1.10	201.00 ± 0.32	4.73 ± 0.11	7.20 ± 1.25	0.90
M3	302.00 ± 1.03	205.00 ± 0.71	12.00 ± 0.03	8.55 ± 1.08	0.56
M4	301.00 ± 0.83	203.00 ± 0.12	14.00 ± 0.10	8.55 ± 1.17	0.77

*Mean for 20 tablets; [a]Mean for 10 tablets; CV, coefficient of variation; SD, standard deviation; M1, M2, M3 and M4, metronidazole granules prepared with 5, 10, 15 and 20% *X. sagittifolium* starch as binder respectively.

test. Tablet weight uniformity test is a very important quality control test because variation in tablets weight will lead to variation in drug content and the overall bioavailability of the drug will be affected.

The results of assay of active ingredient shown in Table 3 indicate that the tablets passed the test for the assay of active ingredient. The low standard deviation seen in the results confirmed that the formulation method adopted was reliable. The results also confirmed that there was no form of interactions between the *X. sagittifolium* starch and the metronidazole, therefore, *X. sagittifolium* starch may be inert and hence a good excipient for the formulation of metronidazole tablets.

The tablets disintegration time results presented in Table 3 show that the tablets all complied with BP (2009) specifications for the disintegration time of normal release tablets. Tablets disintegration time ranged from 3.00 ± 0.08 to 14.00 ± 0.10 min for M1 and M4 tablets formulated with 5 and 20% of *X. sagittifolium* starch respectively. From the results, increase in the concentration of the binder significantly increased the disintegration time of the metronidazole tablets ($p < 0.05$). The mechanism of disintegration may be by deformation (Ofoefule, 2002). Starch grains are generally elastic and at certain compression pressure, starch may undergo permanent deformation. These permanently deformed grains are rich in energy and when exposed to water, the energy is released causing disintegration of tablets (Ofoefule, 2002).

The results of tablet hardness also shown in Table 3 show that metronidazole tablets formulated showed a good hardness profile and conformed to BP (2009) specifications for tablets hardness of between 5 to 8 kgf. The tablets hardness ranged from 7.20 ± 1.25 to 8.55 ± 1.17 kgf. The results of this study showthat the mechanical properties of the tablets would not be compromised during packaging, transportation and use.

The results of tablets friability test presented in Table 2 show that the tablets friability test ranged from 0.56 to 1.29%. The tablets therefore, passed the test for friability. According to BP (2009) specifications, values of friability ≤ 1% are acceptable for tablets formulated by wet granulation method but, for tablets prepared by direct compression, values of friability of up to 2% are acceptable. The results show that the tablets could be able to withstand shock and vibrations during the packaging, transportation and use.

The results of the drug release profile of metronidazole tablets formulated with different concentrations of *X. sagittifolium* starch as binder and disintegrant are shown in Figure 1. From the results, all the tablet batches had good drug release. The time for the release of 25, 50 and 90% of metronidazole in all the formulations were obtained (T_{25}, T_{50} and T_{90}). M1 tablets containing 5% of *X. sagittifolium* starch had T_{25}, T_{50} and T_{90} at 5, 13 and 23 min respectively, M2 containing 10% of *X. sagittifolium* starch had T_{25}, T_{50} and T_{90} % at 7, 13 and 27 min respectively, M3 containing 15% of *X. sagittifolium* starch had T_{25}, T_{50} and T_{90} at 10, 19 and 28 min respectively, while the batch M4 tablets containing 20% of *X. sagittifolium* starch had T_{25}, T_{50} and T_{90} at 8, 18 min and was unable to release 90% of metronidazole at 30 min. According to US-FDA guideline, immediate release drug products should release 85% ($T_{85\ \%}$) of labeled amount of drug within 30 min of study (Obitte et al., 2008). Therefore, the tablets exhibited good drug release properties as normal release tablets.

Phytochemical constituents of *X. sagittifolium* starch

The results of the phytochemical constituents of *X. sagittifolium* starch presented in Table 4 showthat the starch contained high concentrations of alkaloids, glycosides and carbohydrate, and low concentrations of steroids. Phytochemicals are non-nutritive plant chemicals that have protective or disease preventive properties. Plants produce these chemicals substances to protect themselves, and they are also believed to protect humans against certain diseases (Edeoga et al., 2005).

Conclusion

Natural polymers have advantages over the synthetic and semi-synthetic polymers which include biocompatibility, relatively cheap, easily accessible and physiologically inert. Starch obtained from *X. sagittifolium* could be used

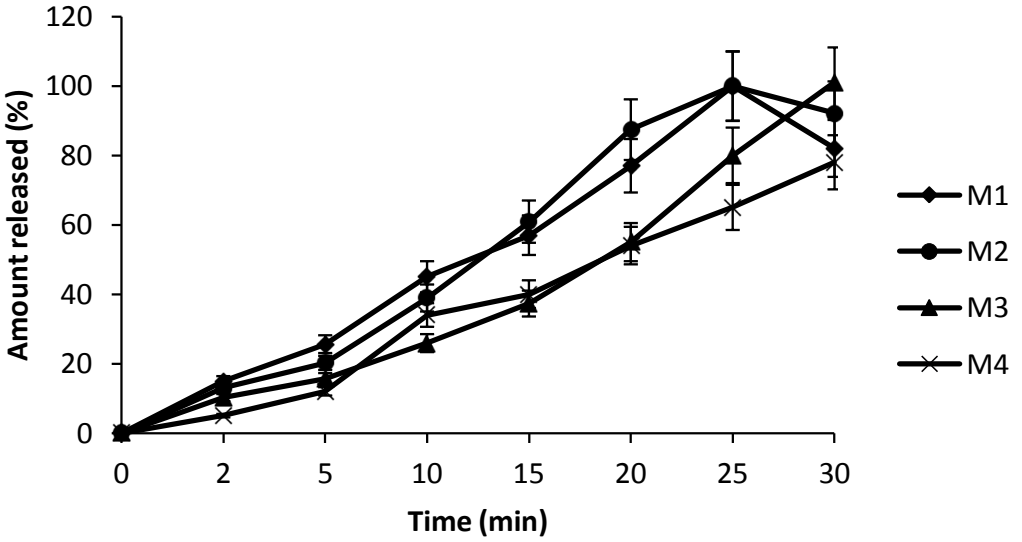

Figure 1. The drug release profile of metronidazole tablets formulated with *X. sagittifolium* starch as binder and disintegrant in 0.1 N HCl. M1, M2, M3 and M4, metronidazole granules prepared with 5, 10, 15 and 20% *X. sagittifolium* starch as binder respectively.

Table 4. Phytochemical constituent of *X. sagittifolium* starch.

Phytochemical constituent	Remark
Glycosides	++++
Alkaloid	++++
Carbohydrates	++++
Steroids	+

++++, High concentration; + low concentration.

to formulate metronidazole tablets giving optimum disintegration time and the dissolution profile of this drug. The physicochemical properties of the tablets showed that the tablets exhibited good quality as normal release tablets. However, further studies on the use of *X. sagittifolium* starch as tablet excipients are encouraged in order to scale up the production and finally make the starch available in the market.

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