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Article *in* Pharmaceutica Analytica Acta · February 2018

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Khalid et al., Pharm Anal Acta 2018, 9:1
DOI: 10.4172/2153-2435.1000578

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Comparative FTIR, Compaction and *In vitro* Dissolution Studies of *Plectranthus esculentus* Modified Starches in Metronidazole Tablet Formulations by Direct Compression

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Abstract

Wet and dry granulation methods for tablet manufacturing tend to be problematic for thermolabile and moisture sensitive drugs, and few excipients are available for use in direct compression (DC) due to stringent requirements. This study aimed to evaluate the drug/excipients compatibility, compaction and *in vitro* dissolution properties of *Plectranthus esculentus* modified starches in tablets using metronidazole as a model drug by DC. Native starch extracted from *P. esculentus* was modified by three methods and we produced three modified starches namely; acid hydrolyzed *P. esculentus* starch (APS), pregelatinized *P. esculentus* starch (PPS), and ethanol dehydrated pregelatinized *P. esculentus* starch (PPE). For drug/excipient compatibility studies, Fourier Transform Infrared Spectroscopy (FTIR) was used. Powder compaction was evaluated using Heckel model, while *in vitro* dissolution studies were conducted using USP basket method. The starches were evaluated in comparison with microcrystalline cellulose (MCC PH 101). The FTIR peaks revealed no interaction of these excipients with the drug. Compaction studies indicate that the modifications yielded starches of comparable compact behaviors with MCC PH 101 especially APS and PPE, they both plastically deformed with PPE producing the hardest tablets. APS and PPS disintegrate faster 2.83 and 1.42 min respectively which were significantly different from the disintegration time of MCC PH 101 and PPE which are higher 35.34 and 45.53 min respectively. For the *in vitro* dissolution, APS and PPS, their T_{50} and T_{90} were achieved in less than 10 min, T_{50} and T_{90} for PPE were achieved at 38 and 58 min respectively, while for MCC PH 101 both T_{50} and T_{90} were not observed after 60 min. APS produced metronidazole tablets of better quality in terms crushing strength, friability and drug-release profile. Acid hydrolysis of *P. esculentus* starch produced good directly compressible excipient that can be use in DC for immediate release tablet formulations.

Keywords: *Plectranthus esculentus*; Modified starch; FTIR; Dissolution; Compaction; Tablet

Introduction

Solid dosage forms such as tablets and capsules are the most stable dosage form for drug delivery. They are more capable of maintaining the stability of an active pharmaceutical ingredient (API) over its shelf life when compared to liquid or semi-solid dosage forms. The solid dosage forms, in addition, permit the delivery of an accurate dose of an API to its active site in the body. Because of these properties, they are now economically mass produced and currently dominated the global drug market [1,2].

A tablet is a solid dosage form that is manufactured using Direct compression (DC) or wet granulation method. The DC method has been considered the simplest and most economical method of manufacturing tablets. It is thus, widely used because it requires less processing steps [3]. Despite its advantages, very few excipients are available for use in DC due to stringent requirements of compatibility, safety and stability. During the compaction process, the deformation mechanism of pharmaceutical powders used in formulating directly compressed tablets affects the physicomechanical characteristics of the tablets formed. The properties of the resulting compact can be influenced by the presence of a lubricant and binder since pharmaceutical materials normally consolidate by more than one mechanisms [4]. However, in pharmaceutical powder technology, the global models of Heckel and Kawakita have typically been the most frequently used [5].

In recent years, there is a rapid proliferation in the development of novel pharmaceutical excipients with enhanced functionality using particle engineering by processes such as physical or chemical modification and co-processing [6]. The versatility of native starch has made it the excipient of choice in many solid dosage forms. It has been successfully employed as tablet binder, disintegrant and filler in tablet formulations processed by wet granulation [6,7]. Native starches in their derivative forms open a wide scope in pharmaceutical applications. However, it has limited usage in DC due to its inherent weaknesses of poor flow and compressibility properties. The poor functionality of native starches could be attributed to its particle properties such as particle shape, size and particle size distribution that further constituted the bulk properties of the starch. Thus, this prompted researchers to embark on developing various methods of producing modified forms of starches that will enhance their functionality in tabletting technology. This study therefore serves to provide alternative sources for directly compressible excipients from locally available source for use in tableting.

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Received January 24, 2018; **Accepted** February 06, 2018; **Published** February 13, 2018

Citation: Khalid GM, Musa H, Olowosulu AK, Jatau AI, Ilyasu S, et al. (2018) Comparative FTIR, Compaction and *In vitro* Dissolution Studies of *Plectranthus esculentus* Modified Starches in Metronidazole Tablet Formulations by Direct Compression. Pharm Anal Acta 9: 578. doi: 10.4172/2153-2435.1000578

In the current study, we aimed to develop modified forms of starches from a local source of starch in Nigeria, *Plectranthus esculentus* popularly known as Livingstone potato, is an indigenous tuber cultivated locally in some parts of Nigeria and tropical Africa. It is cultivated in the Upper Niger valley of the Hausa land in Nigeria and in the Central African Republic [8]. The tuber is rich in carbohydrate, which forms more than 80% of its constituents used mostly as a staple food by locals. Metronidazole is a medium dose drug and poorly compressible due to its crystalline nature [9]. Furthermore, we use metronidazole as a model drug because of its inherent poor compressibility nature.

The objectives of this study were to (i) evaluate the compatibility of the modified starches developed from the *P. esculentus* with Metronidazole as an API using FTIR, (ii) conduct powder compaction studies using Heckel model and (iii) produce tablets using metronidazole as a model drug by DC.

Materials and Methods

Materials

Plectranthus esculentus starch powder was extracted from the tubers obtained from Vom, Plateau state, Nigeria. Metronidazole powder (BDH Chemicals Ltd Poole, England), microcrystalline cellulose PH 101 (ATOZ Pharmaceuticals Ltd, Ambattur, India), stearic acid (BDH Chemicals Ltd Poole, England), talc (BDH Chemicals Ltd Poole, England), absolute Ethanol (Emerck Darmstadt, Germany), Hydrochloric acid HCl (Emerck Darmstadt, Germany), xylene (Loba Chemic Laboratory Ltd, Mumbai India), sodium hydroxide pellets (Avondale Laboratories Ltd, Banbury, England) and glycerol (BDH Chemicals Ltd Poole, England).

Methods

Collection, identification and extraction of *Plectranthus esculentus* starch: Fresh tubers of *Plectranthus esculentus* were brought to the Process Laboratory of the Department of Pharmaceutics and Pharmaceutical Microbiology of Ahmadu Bello University, Zaria, washed, peeled and grated. The grates were washed, weighed, and then ground to a fine pulp using grinding machine. Calico cloth was used to sieve the starch from other impurities. The starch in the excess water was allowed to settle overnight. Little quantities of 0.1N NaOH solution were added and stirred for 10 minutes to dissolve the protein contents. The suspension was then centrifuged at 1000 rpm for 10 minutes. The starch obtained was spread on stainless steel trays and air-dried for 24 hours and then dried at 40^{0}C for one hour. The dried starch was size-reduced to a fine powder (90-250 µm) using mortar and pestle. It was weighed and percentage yield determined. This was then packed in a polyethylene bag, labelled and stored at room temperature until required.

Preparation of acid-hydrolyzed *Plectranthus esculentus* starch: Modified procedures of Wang et al., for acid hydrolysis of starch and the method in the Pharmaceutical Codex were adopted [10,11]. Three hundred grams (300 g) of the native starch powder was suspended in 800 mL of distilled water. The reaction was initiated by adding 28 mL of 6 N HCl into the suspension, stirred and placed on digital thermostatic water bath set at 52^{0}C. The reaction was allowed to proceed for 24 hours while stirring intermittently. An equal volume of distilled water was added at room temperature and centrifuged at 1000 rpm for 10 minutes. The pH was then adjusted with 1 N NaOH, sufficient quantity of distilled water was added again and then dehydrated with 95% ethanol. Hydrolyzed starch was spread on a stainless-steel tray and air dried for 24 hours, then dried in hot air oven (BS size 3 Gallenkamp, England) at 40^{0}C for 1 hour. The sample was then passed through 125 µm mech, packed in air-tied container and labelled as acid hydrolyzed *P. esculentus* starch (APS).

Preparation of pregelatinized *P. esculentus* starch/determination of gelatinization temperature: Pregelatinized starches were prepared according to method described by Adedokun and Itiola 2010 [12], with some modifications. Briefly, one hundred and fifty grams (150 g) of the native starch powder was suspended in 1 L of distilled water at room temperature. The suspension was placed in a water bath (Digital thermostatic water bath) set at 90^{0}C and stirred continuously until it begins to gelatinize at 66^{0}C. The mucilage was then thinly spread on stainless steel trays and dried in hot air oven (BS size 3 Gallenkamp, England) at 60^{0}C for 24 hours. The dried flakes were milled using laboratory blender. The pulverized powder was passed through 125 µm mech size, this was labelled pregelatinized *P. esculentus* starch (PPS) and packed in air-tied container until need. This procedure was repeated but instead of drying directly, absolute ethanol was used to dehydrate the starch, and then dried at 40^{0}C for 24 hours, milled and labelled as ethanol dehydrated pregelatinized *P. esculentus* starch (PPE).

Determination of bulk and tapped densities: Ten grams (10 g) of each starch powder was placed in a 50 mL measuring cylinder and the bulk volume noted. After several taps to a constant volume (rising to about 10 cm height), the volume was noted. The bulk density (BD) and tapped density (TD) were then calculated. The Carr's index (C.I) and Hausner's ratio (H.R) were also calculated using Wells and Aulton [13] equations:

$$\text{Carr's Index (C.I)} = \text{T.D} - \text{B.D}/\text{T.D} \times 100$$

$$\text{Hausner's ratio (H.R)} = \text{T.D}/\text{B.D}$$

Determination of true density: The true densities (Dt), of each starch samples were determined by the liquid displacement method using xylene as the immersion fluid and computed according to the following equation:

$$Dt = Wp\ [(a + Wp) - b] \times SG$$

Where, Wp is the weight of powder, SG is specific gravity of solvent (xylene, 0.86), a is weight of bottle + solvent and b is weight of bottle + solvent + powder.

Determination of packing fraction and porosity: The packing fraction (Pf) was expressed as the ratio between the bulk density (BD) and the true density (Dt):

$$Pf = B.D/Dt$$

$$\text{Porosity} = 1 - B.D/Dt \times 100$$

Determination of angle of repose: Twenty grams (20 g) of each starch sample was poured inside a glass funnel of orifice diameter 0.8 cm clamped at height 10 cm from the table surface and was allowed to flow freely. The angle of repose, Θ was calculated from the equation:

$$\Theta = \text{Tan}^{-1}\ h/r$$

Where h = height of heap and r is the radius formed by the heap. It was repeated thrice and the mean ± SEM determined.

Determination of flows rate: Twenty grams (20 g) each starch sample was placed in a flow rate machine (Type GD7, Erweka Apparatebau GMBH, Germany). The time of flow was note and the flow rate calculated in grams per second (g/s). The mean ± SEM of three determinations was calculated.

Flow Rate (Fr) = W/T

Where, W is the weight of the powder in grams (g) and T is the time taken for the powder to flow in seconds (s).

Determination of percentage moisture loss: Five grams (5 g) of each starch sample was heated in an oven (BS size 3 Gallenkamp, England) at 105^{0}C, examined every hour until a constant weight was obtained. Percentage moisture loss was calculated as a ratio of loss in weight to the initial weight of the sample.

Determination of pH: One gram (1 g) of each starch sample was dispersed in 100 mL of distilled water and shaken for 5 minutes and allowed to stand for 10 minutes. The pH of the supernatant liquid was determined using pH meter (Oaklon pH 1100 series).

Microscopy and mean particle size determination: Little quantity of powdered sample was suspended in glycerol as mounting reagent on a slide and covered with a thin slit. The optical microscope (Olympus Optical Co., Japan) was first calibrated using eye-piece and stage micrometer respectively, set at X250 magnification. The prepared slides were viewed under the electronic optical microscope, and 500 particles were counted in each case and the mean projected particle diameter were determined which reflect the mean particle size.

Compaction studies and determination of compressibility index: Compacts of each powder sample were made by weighing 500 mg individually and compressing at various compression loads ranging from 28.31 – 169.88 MNm^{-2} on Apex hydraulic hand press (Model 184, Apex Construction Ltd., London W.I and Dartford). The dwell time of 30 seconds was allowed for each compression. Before the compression, the 10.5 mm die and flat-faced punches were lubricated with 2% w/v dispersion of magnesium stearate in acetone solution. After ejection, the compacts were stored in a desiccator over silica gel for 24 h to allow for elastic recovery and hardening and to prevent low yield values. The tablet weights (*W*) and dimensions (thickness and diameter) were then determined to within ± 1 mg and 0.01 mm respectively and their relative densities (*D*) were calculated using the following equation adopted from Apeji et al., [14]:

$$D = W/V\rho s$$

Where *V* is the tablet volume (cm^3) and ρs is the particle density (g/cm^3) of the solid material. Heckel plots of ln (*1/1-D*) against the applied pressure *P* (MNm^{-2}). Compressibility index was determined using the plot of compact density (g/cm^3) versus log compaction load in mega Newton per meter square (MNm^{-2}).

Evaluation of dilution potential: 500 mg of the drug and excipients individually were mixed in the following proportions: 100:400, 150:350, 200:300, 250:250 and 300:200 (mg). The binary blends were then compressed at varying compression loads on the single punch tableting machine (Erweka-AR400, Germany) at 400-500 MNm^{-2}. The disintegration time of the tablets (n=6) was determined in distilled water at 37°C ± 1°C according to the method described by USP using disintegration test unit (Erweka ZT3, Germany). The crushing strength of the tablets (*n*=5) was determined using tablet hardness tester (Monsanto hardness tester, England) as the load required to cause diametral fracture of the tablet. The friability (F*r)* of the compacts (*n*=5) was tested in tablet friabilitor (Type TA3R Erweka, Germany) operated at 25 rpm for 4 min. The fractional weight loss was computed as:

$$Fr = [m_f - m_i m_i] \times 100$$

where m_i and m_f are the initial and final tablet weight, respectively.

The comparison was then made of these parameters for the different drug/excipients ratio to evaluate their dilution potentials using the method described by [6,9,14].

Tablet formulation: A batch size of 200 tablets was prepared, and four batches were made by direct compression using metronidazole as the active pharmaceutical ingredient (API). The target tablet weight was 550 mg as indicated in the formula for each batch in Table 1. The tablets were formulated by mixing the active drug and the filler/binder in a mortar using a pestle to achieve a uniform blend for 10 min. The calculated quantities of the glidant 0.75% w/w and lubricant 0.25% w/w were weighed on an electronic scale and incorporated into the powder and mix for additional 2 min. Tablets were produced by direct compression using a single punch tabletting machine (Erweka-AR400, Germany) fitted with 12 mm concave – faced punches and die set. Tablets were made at varying compression load between 3.5 – 9.5 metric tons.

Weight uniformity test of tablets: Twenty tablets from each batch were selected at random and weighed individually using an electronic balance (MSI-A, Singapore). Their mean weights ±SEM were determined based on BP method.

Tablet disintegration test: The disintegration time was determined on six tablets in distilled water at 37°C ± 1°C according to the method described by USP (25) [15] using disintegration test unit (Erweka ZT3, Germany). The time taken for each tablet (n=6) to disintegrate and pass through the mesh was noted. The data for an average of 6 ± SEM determinations were recorded.

***In vitro* dissolution studies:** The *in vitro* dissolution studies were conducted on the metronidazole tablet formulations using the USP basket apparatus [16] (DT, Erweka G.m.b.H. Germany) set at 100 rpm in 900 mL of dissolution medium (0.1 N HCl). The dissolution medium was maintained at 37 ± 0.5°C. Samples (5 mL) were withdrawn at different time intervals and replaced with the equivalent amount of fresh dissolution medium. The samples were diluted (1:9) with the dissolution medium prior to absorbance reading and the amount of metronidazole released was determined using UV spectrophotometer (Thermo-Biomate, England) at 277 nm. The percentage drug released was determined and plotted against time to generate dissolution profile data. A calibration curve was initially generated using standard metronidazole powder.

Assay of metronidazole (content uniformity): Five tablets were randomly selected from each batch, weighed and finely powdered using mortar and pestle. The weight of 550 mg equivalent to one tablet

Ingredients	Qty/tablet	Qty/tablet (mg)	Qty/Batch of 200 tablets (g)
Metronidazole (36.36%)	200 mg	200.00	40.00
Filler/binder: MCC PH 101, APS PPE, PPS (62.64%)	q.s	244.50	68.90
Lubricant: stearic acid (% w/w)	0.25	1.38	0.28
Glidant: talc (%w/w)	0.75	4.13	0.83
Total	*550 mg*	550.00	110.00

q.s means quantity sufficient, Qty – quantity, MCC PH 101 – Microcrystalline cellulose,
APS – Acid hydrolyzed *P. esculentus* starch, PPS – Pregelatinized *P. esculentus* starch, PPE – Ethanol dehydrated pregelatinized *P. esculentus* starch. *Batch size: 200 tablets*

Table 1: Tablet Formula for the formulation of modified starches of *P. esculentus* compared with MCC PH 101 in metronidazole tablet 200 mg.

was dissolved in 100 mL of 0.1 N HCl. Tenfold dilution of the aliquots was further made, filtered and analyzed using UV spectrophotometer (Thermo-Biomate, England) for the content of metronidazole at 277 nm. Three determinations were made for each batch as specified by BP [17].

Determination of tablet diameter and thickness: Tablet thickness and diameter was measured using digital screw gauge micrometre (Moore and Wright Sheffield, England). A mean ± SEM of five determinations was obtained and recorded.

Friability test: The friability of ten (10) tablets was determined for each batch using Roche Friabilator (Type TA3R Erweka, Germany) operated at a rotation speed of 25 rpm for 4 minutes. The tablets were removed, dusted and re-weighed. Percentage of weight loss was determined using the formula described above.

Determination of crushing strength: The crushing strength of tablets from each batch was determined using Monsanto hardness tester. The pressure was applied by turning the knob until the required pressure that crushed the tablet was read in terms of kilogram-force (kgf) on the scale, which was then converted to Newton (N). The results are presented as the mean of five (5) determinations.

Determination of tablet tensile strength: Tensile strength is the stress measured as force per unit area. It is the load required to fracture a tablet by diametrical compression. The load *P*, needed to fracture the five (5) tablets (n=5) were determined using the Monsanto hardness tester, the mean value was calculated and was used to calculate the tablet tensile strength (*TS*) from the equation:

$$TS = 2P/\pi dt$$

Where *P* is the load required to crush the tablet, d is the diameter and t is the thickness of the tablet.

Statistical Analysis

The statistical analysis was conducted using IBM SPSS version 20. The One-way Analysis of Variance (ANOVA) was used followed by Dunnett's test to compare the properties of modified starches of *P. esculentus* with MCC PH 101 in metronidazole tablet formulations. Significant differences among means were considered at 95% confidence level and $p \leq 0.05$.

Results and Discussion

Micromeritics and physicochemical characteristics

Angle of repose for the three modifications are presented in Table 2, the result revealed that they were all within theoretical limits for good flow of pharmaceutical powder [18]. On the other hand, the result for MCC PH 101 was 46.22 ± 0.25^0 indicating a poor flow. These results agree with the flow rates of these materials with MCC PH 101 having the lowest flow rate of 0.80 ± 0.02 g/s. From the results of angle of repose and flow rates, the flowability of these materials are ranked as follows; PPS > PPE > APS > MCC PH 101. The flow of powder during manufacturing predicts the quality of the final product in terms of weight and content uniformity [19]. Weight variation in tablets and ultimately content variation can be reduced to a minimum if the material possesses good flow property. For starch materials, such properties could be achieved by various modifications to affect the particle size and shapes [20].

Bulk and tapped densities are indirect measures of flow characteristics of powder, the values are also presented in Table 2. The values obtained were used to calculate the Hausner's ratio and Carr's index which also measure flowability of materials, and the values showed that for the modified starches, the Hausner's ratios are within theoretical limit for fair flow characteristics 1.19 - 1.25, and Carr's indices of PPE, PPS and APS respectively with all falling within range of 16-20% [13], indicating fair flow. For MCC PH 101, both the Carr's index and Hausner's ratio values indicated very poor flow [13]. This can be attributed to the inherent high cohesive nature of the MCC PH 101 which hindered its flowability. These could also be related to the particle size, shapes and particle size distribution of the materials because they all affect the flow of powder materials. Generally, as the values of these indices (Carr's index and Hausner's ratio) increases, the flow of powder decreases and this may lead to formulations problems like weight variation among others [13].

The bulk and tapped densities usually determine the die fill volume. Materials with higher bulk density require lower die fill volume than those having small bulk density [14]. From Table 2, it can be seen that MCC PH 101 has lower values both for bulk and tapped densities, indicating high die fill volume in comparison to those of the modified starches of *P. esculentus*. For the true density, the results are of the order APS>MCC PH 101>PPS>PPE. These results showed that true density is greater than the bulk density. Bulk density is always less than the true density of its component particles because the bulk powder contains interparticulate pores or interparticulate air-filled voids [13].

From the results of packing fraction and powder porosity in Table 2, it can be said that PPE and PPS showed the highest maximum volume reduction followed by APS and MCC PH 101 having the least. Similarly, the porosity was in the order PPE<PPS<APS<MCC PH 101. MCC PH 101 has the highest porosity, indicating that the particles

Parameter	PPE	PPS	APS	MCC PH101
Bulk Density (g/cm^3)	0.66 ± 0.01	0.73 ± 0.02	0.64 ± 0.01	0.34 ± 0.00
Tapped Density (g/cm^3)	0.78 ± 0.03	0.88 ± 0.03	0.78 ± 0.01	0.53 ± 0.01
True Density (g/cm^3)	1.42	1.71	1.91	1.82
Angle of repose (^{0})	15.65 ± 0.91	25.43 ± 1.33	30.05 ± 1.2	46.22 ± 0.25
Flow Rate (g/s)	8.13 ± 0.09	8.25 ± 0.19	2.85 ± 0.17	0.80 ± 0.02
Carr's Index (%)	15.63 ± 2.26	17.03 ±1.96	18.69 ± 2.03	35.38 ± 1.01
Hausner's Ratio	1.18 ± 0.03	1.2 ± 0.03	1.23 ± 0.03	1.54 ± 0.03
Moisture Content (%)	13.40	11.00	8.80	7.00
Packing Fraction	0.46	0.43	0.34	0.19
Porosity (%)	54.00	57.00	66.00	81.00
pH	7.40	7.05	6.81	6.89
Mean Particle Size (µm)	68.20 ± 3.02	102.53 ± 3.98	13.53 ± 11.45	118.67 ± 8.11

Table 2: Micromeritics and Physicochemical Properties of Modified Starches of *P. esculentus* compared with MCC PH 101 (Mean ± SEM).

are loosely packed, PPE on the other hand has the least porosity and therefore suggesting that its particles are more densely packed in comparison to PPS and APS.

For moisture contents, the BP 2009 [17] specifies that it should not exceed 15% for starch excipients. From the results obtained in Table 2, the values for all the materials are within the specified limit. Moisture level is also critical for solid dosage forms. Higher levels of moisture predict possible physical degradation and eventually it may lead to chemical decomposition as well as microbial contamination because moulds can easily grow in damp humid environment.

The pH values as shown in Table 2, for all the materials are within approximate neutral region, this finding indicate that when these materials are subjected to an aqueous medium, an acidic or alkaline medium will not result, which is particularly noteworthy when such products are to pass through the gastrointestinal tract.

The mean particle diameter from Table 2, are in the following rank APS<PPE<PPS<MCC PH 101. With the smaller mean particle diameter (size) of APS, it is expected to have improved packing in comparison to the rest with bigger particle size.

Dilution potential properties

Table 3 shows the dilution capacity of the various materials. Dilution potential measures the amount of an API that can be satisfactorily compressed into tablets with the given directly compressible excipient. The data obtained were generated from crushing strength, friability and disintegration time of the solid compact of the drug and excipients in varying ratios. The results showed the following ranking MCC PH 101>APS/PPE>PPS. The MCC PH 101 maintained superiority in terms of carrying capacity because it could accommodate up to 50% of the active drug, Apeji et al., made a similar finding [14]. From the modified starches, it was found that APS and PPE produced tablets with superior quality compared to PPS. But they are all within the range of 30-40% by weight, which is the range for a majority of directly compressible excipients [9,14].

Compaction and compressibility characteristics

Figure 1 shows the Heckel plots of modified starches of *P. esculentus* and MCC PH 101. The mean yield pressure P_y was calculated from the regions of the plots showing the highest correlation coefficient ($r^2 \geq 0.99$) for all the formulations. The intercept A was determined from the extrapolation of the linear line. The values for P_y, D_0, D_A, and D_B for the formulations are presented in Table 4. The mean yield pressure, P_y, is inversely related to the formulations ability to deform plastically under pressure [21,22]. The P_y values showed that MCC PH 101 has the lowest while APS exhibited the highest. This indicates plastic deformation of these materials in the following order MCC PH 101 >PPE>PPS>APS. This means that MCC PH 101 is still superior in terms of plastic deformation in comparison to the various starches used in this study. The D_0 value represents the degree of initial packing in the die because of die filling [23]. This result indicates that PPE exhibited a high degree of packing followed by PPS, with MCC PH 101 having the lowest initial packing. This could be related to the low bulk density of MCC PH 101. The D_A values, which represent the total degree of packing at zero and low pressures, PPE was shown to have the highest value while MCC PH 101 exhibited the lowest D_A value. The D_B value represents the particle rearrangement phase in the early compression stages and tends to indicate the extent of particle or granule fragmentation, although fragmentation can occur concurrently with plastic and elastic deformation of constituent particles [22,24]. The D_B values were PPS < MCC 101 <A PS < PPE. This indicates that PPE requires less pressure to undergo fragmentation and rearrangement while PPS may require higher pressure because it has the least D_B value.

Material	Drug/Excipient ratio (%)
MCC PH 101	50/50
APS	40/60
PPE	40/60
PPS	30/70

*Metronidazole was used as a model drug. Drug-carrying capacities (dilution potential) of modified starches of *P. esculentus* in comparison with MCC PH 101 after evaluation of their crushing strengths, friability and disintegrations.

Table 3: Dilution potential of Modified starches of *P. esculentus* and MCC PH 101.

Material	P_y	D_0	D_B	D_A
MCC PH 101	40.00	0.19	0.12	0.30
PPE	68.49	0.47	0.36	0.83
PPS	94.33	0.43	0.08	0.51
APS	133.33	0.34	0.18	0.52

*P_y is the mean yield pressure; D_0 is the relative density at zero pressure; D_A is the relative density from the value of intercept A; D_B describes the phase of rearrangement at low pressures ($D_A - D_0$).

Table 4: Parameters from Heckel plots used to evaluate the compaction and behaviours of modified starches of *P. esculentus* powders in comparison with MCC PH 101.

Compressibility simply means the ability of a material to reduce in volume when compression pressure is applied to it [23]. A linear relationship exists between the density of tablets and the log of compaction pressure. The rate of increase of tablet density with increasing compaction pressure could be considered as an expression of compressibility [5,25]. The value of the slope of the plot of tablet density versus log of compression pressure is considered to express the compressibility index of a material, the bigger the value the better the compressibility of the material as reported by Walker, 1923 [5]. These values are shown in Table 5 as obtained from Figure 2. This result shows a comparable increase in density of tablets with an increase in compression pressure of MCC PH 101 with APS and PPS, but PPE exhibited the lowest value, indicating lower compressibility.

FTIR analysis

Figure 3 presents the comparative FTRI results, it compared the peaks generated from pure metronidazole alone and subsequent peaks obtained from the binary mix of the metronidazole and each of the modified starch developed. Metronidazole shows characteristics FTIR

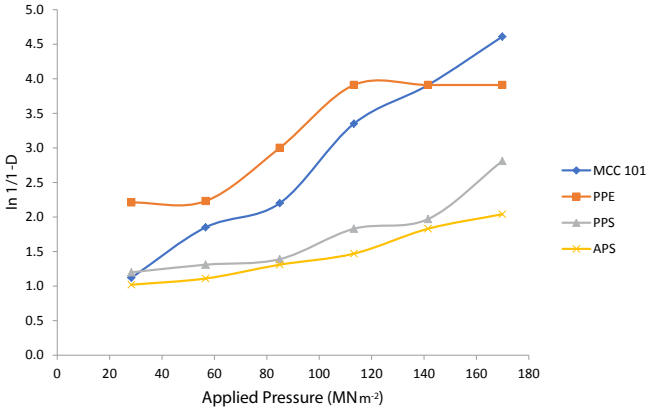

Figure 1: Heckel plots for modified starches of *P. esculentus* and MCC PH 101 of compact materials alone, the slope of which measure plastic deformation

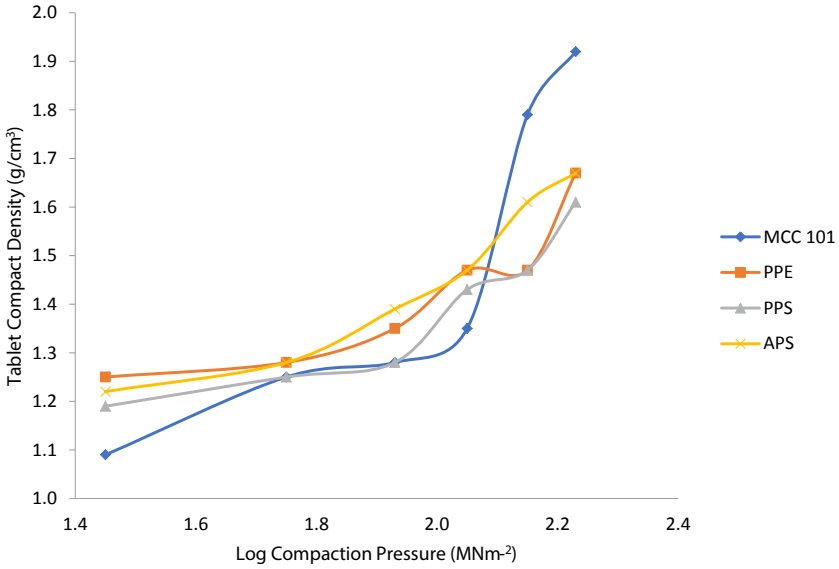

Figure 2: Plots of tablet compact densities of modified starches of *P. esculentus* and MCC PH 101 against log of compaction pressure

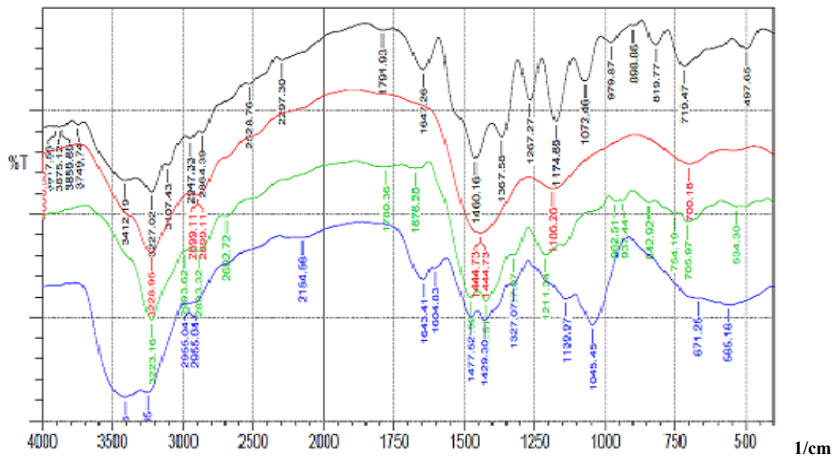

Figure 3: Overlay of comparative FTIR spectra of pure drug and physical mixture of drug and modified starches of *P. esculentus*.

peaks at 3223.16 cm^{-1} (N-H stretching vibration), 1676.20 cm^{-1} (C = N stretching vibration), 1477.52 cm^{-1} (C = C aromatic ring stretch vibration), 3223.16 cm^{-1} (O-H bonded vibration), 1423.51 cm^{-1} (-CH_3 bending vibration), 1327.07 cm^{-1} (C-N stretch vibration), 1211.34 cm^{-1} (C-O stretch vibration), 754.19 cm^{-1} (C-H bending vibration aromatic) and 1423.51 cm^{-1} (N = O stretching vibration). Furthermore, the spectra obtained from the physical mixture of the pure drug and the excipients Figure 3 showed mere superimpositions of that of the pure drug alone. This indicates that there was no chemical interaction between the drug and excipients used. FTIR spectroscopy is an important tool used to assess the interaction between excipients and guest molecules in the solid state which can be revealed as shifts disappearances or changes in the absorption spectrum of the API [2,21].

Physical evaluation of tablets

Crushing strength and tensile strength are indices used to measure the hardness of a tablet. Although there is no official limit for tablet hardness, values fall within the range of 40 - 78 N are generally acceptable for uncoated tablets [26]. From Table 5, it was shown that the hardness of metronidazole tablets formulated from PPE, APS and MCC PH 101 were high and are in the range of 64.30 - 79.43 N, these are within the acceptable limits. The values for PPS, however, was significantly low 28.44 N, this does not meet the required standard. It can also be noted from Table 6 that the values for tensile strengths for these formulations also followed a similar pattern. This implies that formulations with PPE, APS and MCC PH 101 are likely to withstand the harsh conditions of packaging, dispensing and transportation.

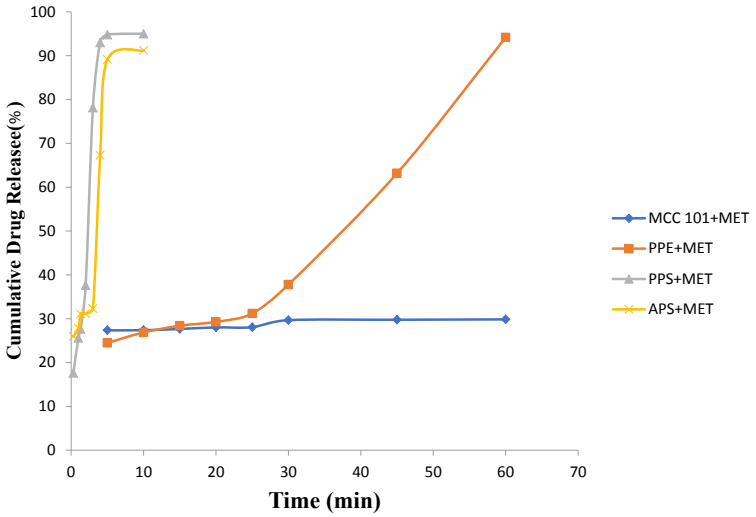

Figure 4: The cumulative *in-vitro* dissolution profile of metronidazole 200 mg tablets formulated with modified starches of *P. esculentus* and MCC PH 101 with T_{50} and T_{90} evaluated.

Material	Drug/Excipient ratio (%)
MCC PH 101	0.99
PPE	0.48
PPS	0.50
APS	0.60
slope generated from the plots of tablet compact densities against the log of compaction pressure which revealed the compressibility indices of modified starches of *P. esaculentus* in comparison with MCC PH 101.	

Table 5: Compressibility index of modified starches of *P. esculentus* and MCC PH 101.

Parameter	MCC PH 101	PPE	PPS	APS	*P value**
Mean tablet weight	553 ± 3.65	553.5 ± 1.86	532.5 ± 1.80	553.5 ± 3.18	
Thickness (mm)	4.67 ± 0.01	4.44 ± 0.02	4.41 ± 0.03	4.46 ± 0.03	
Diameter (mm)	12.09 ± 0.01	12.04 ± 0.01	12.17 ± 0.02	12.09 ± 0.01	
Friability (%)	0.72	0.54	8.74	0.90	
Crushing strength (N)	64.3 ± 0.41	79.43 ± 0.32	79.43 ± 0.32	70.41 ± 0.55	
Tensile strength (MNm^{-2})	0.73	0.95	0.03	0.83	
Disintegration time (min)	35.34 ± 4.33	45.53 ± 3.11	1.42 ± 0.19	2.83 ± 2.11	0.01
$T_{50\%}$ (min)	-	38.00	2.30	3.40	
$T_{90\%}$ (min)	-	58.00	3.40	5.15	
Content uniformity (%)	95.33 ± 3.04	102.12 ± 2.11	96.81 ± 3.12	104.05 ± 4.01	
*ANOVA, $T_{90\%}$ (min) is the time taken to release 90 % of the active drug from the tablet, $T_{50\%}$ (min) is the time taken to release 50% of the drug from the tablet					

Table 6: Physicochemical and quality control Properties of Tablets formulated from Modified Starches of *P. esculentus* compared with MCC PH 101 (Mean ± Standard Error of Mean).

On the other hand, a formulation with PPS fails to meet these requirements.

Friability is inversely related to tablets crushing strength and it measures the tablet softness to wear and tear. The lower the friability value the better the tablet withstands mechanical handling. Weight loss due to friability from formulations containing PPE, APS and MCC PH 101 all fell below 1% Table 5. MCC PH 101 and the two modified starches (PPE and APS) agrees with the findings of Apeji et al., [14]. Friability value for PPS, on the other hand, fails to meet the standard as the value was much higher 8.74%, this can be related to its low dilution potential observed.

Tablets thickness and diameter values are shown in Table 6, and the result revealed that there was no significant variation in their mean values. Addition of lubricant (stearic acid) and glidant (talc) must have prevented the die wall friction and enhanced the flow of powder blend respectively. This ensured uniform volume of the powder blend to be fed into the die cavity resulting in uniform tablets diameter and thickness.

Tablet disintegration test

From Table 6, APS and PPS disintegrate faster 2.83 and 1.42 min, respectively, which was significantly different p=0.01 from the disintegration time of tablets containing MCC PH 101 and PPE. Fast disintegration for starches and their use as tablets disintegrants have been documented [27]. On the other hand, the values for tablets containing MCC PH 101 and PPE were higher 35.34 and 45.53 min respectively. This could be attributed to the high hardness of both

materials (>60 N). However, for PPE, it was observed that it forms a sticky jelly in contact with water, this can prevent water penetration into the tablets during disintegration and hence could explain the reason why it disintegrates more slowly. MCC PH 101 and PPE, therefore, do not pass the official limit for disintegration (<15 minutes). Conversely, tablets containing APS and PPS both disintegrate within the official specification set by B.P. Rapid disintegration is one of the advantages of tablets produced by the direct compression method.

In vitro dissolution profiles

The dissolution profiles for metronidazole tablet formulations are shown in Figure 4 and data were generated are presented in Table 6. The T_{50} and T_{90} for MCC PH 101 and modified starches of *P. esculentus* formulations were evaluated from the profile. Tablets formulated with APS and PPS, both the T_{50} and T_{90} were achieved in less than 10 minutes, with a significant difference at, this directly revealed that 75% of the active drug was released from these two formulations in less than 45 minutes as specified by BP for immediate release tablets. Therefore, these formulations (4.8 minutes and 4.0 minutes respectively) are said to comply with the BP specification. On the other hand, the T_{50} and T_{90} for PPE were achieved at 38 and 58 minutes respectively, while for MCC PH 101 both T_{50} and T_{90} were not attained after 60 minutes. MCC PH 101 and PPE batches did not comply with the BP specification for dissolution. However, it can also be seen that the dissolution pattern for all the formulations relates to their respective disintegration scenario. *In vitro* dissolution rate affects the solubility of a drug molecule within the formulated tablet and consequently *in vivo* absorption and bioavailability of drugs. Thus, *in vitro* dissolution study plays an important role in the *in vivo* performance of tablets dosage form [28].

Tablet content uniformity

The official requirement for content uniformity of active ingredient is met if the percentage content of tablets with average weight above 250 mg falls within 95-105% (USP and BP). The mean average content of analyzed metronidazole tablets formulated from MCC PH 101 and modified starches of *P. esculentus* was found to be in the range of 95.33 - 104.05% (Table 6). All the tablets meet the pharmacopoeias limit for the content uniformity test.

Tablet weight uniformity

Weight uniformity test for tablets is required to ensure that the drug content in each tablet is distributed in a narrow range around the labelled strength because a slight variation in weight of tablet reflects variation in the content of active ingredient. The USP specified that for a drug product whose weight is above 324 mg, the allowed limit of ± 5% of the average is required to pass the weight uniformity test. From Table 6, the result shows that all the formulations passed the official acceptable limit for uniformity of weight (mean ± 5%).

Conclusion

The FTIR revealed no interaction of *Plecthantus esculentus* modified starches developed with the metronidazole, indicating their safety for use in pharmaceutical formulations. The compaction studies highlighted comparable plastic deformation behaviors of APS and PPE with MCC PH 101 indicating their ability to remain as solid compact after powder compression pressure withdrawal. Based on the *in vitro* dissolution profile and other quality control parameters obtained, metronidazole tablets formulated with APS were observed to have good quality characteristics. Therefore, acid hydrolysis of *P. esculentus* starch produced a good directly compressible excipient that can be substituted for MCC PH 101 in DC for immediate release tablet formulations.

Acknowledgement

The authors wish to acknowledge and appreciate the support received from the Bayero University, Kano-Nigeria as through the Academic Staff Training and Development (ASTD, 2014) of the Tertiary Education Trust Fund (TETFund) scholarship grant.

Declarations of conflict of Interest

none

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