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Original Research Article

EXTRACTION AND CHARACTERIZATION OF CITRIC ACID MODIFIED POTATO STARCH AND ITS USE AS DISINTEGRANT IN METRONIDAZOLE TABLET FORMULATIONS

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ABSTRACT

Products of natural origin are used as active pharmaceutical ingredients and excipients in the production of medicines. Native starches are not effectively utilized in many applications oweing to their lack of ability to survive processing conditions like extreme temperature, variation in pH and its poor flow properties. To overcome these disadvantages, they are modified by physical, chemical, enzymatic, and genetic processes. Potato starch was altered with citric acid, and was used as disintegrant in formulation of metronidazole tablets in this study. Potato starch was separated from pulverized potato tubers using the distilled water method. It was transformed using citric acid (Modified potato starch, (MPS)). MPS was characterized based on flow and physicochemical properties. Microbial count and acute toxicity studies were also carried out. MPS was used and evaluated as disintegrant in metronidazole tablet formulations. The pH and gelatinization temperature of MPS was 4.9±0.0 and 67°C respectively. The bulk density was 0.55±0.01 g/ml, while the tapped density was 0.65±0.02 g/ml. It has a Carr's index of 15.75±4.34%, Hausner ratio of 1.19±0.06 and angle of repose value of 42.65±0.65°. These indicate poor flow property. The swelling index and loss on drying values of MPS were 86.19±2.34 and 4.17±0.58% respectively.The hardness value for the metronidazole tablets was from 4.08±0.02 to 7.97±0.05 Kgf, whereas the friability was from 0.32 to 6.83%. The disintegration time ranged from 13.09±2.40 to 41.05±3.65 min. The study showed that MPS has enhanced physicochemical properties and could be utilized as a disintegrant in metronidazole tablet formulation.

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INTRODUCTION

Products of natural origin are used as active pharmaceutical ingredients and excipients in the production of medicines. Natural products are deemed to be safer, easily available, more affordable and even more effective than synthetic products [1]. Excipients are aids included with active ingredients during the production of medicines to impart desirable properties such as better compressibility or fast disintegration to the prepared product [2]. Excipients such as binders, disintegrants, lubricants and diluents are utilized in tablet production, whereas, suspending agents, colourants and sweeteners are utilized in the preparation of suspensions [2]. Binders or adhesives include natural products like acacia gum, starch mucilage; semi-synthetic ones like methylcellulose and synthetic ones, like polyvinyl pyrollidone. Disintegrants include starch, crospovidone and

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croscamellose. Starch serves as a vital source of energy for human nutrition and forms a salient part of food. As a biodegradable natural polymer, it is also available in abundance. It is obtained chiefly from the tubers of potatoes, yam and cassava, and from grains or seeds of cereals [3,4]. Starch is made in granular form inside specialized organelles known as plastids, where it exists in two main types. Photosynthesis produces starch that is temporarily stored in the chloroplasts, while in amyloplasts, a long-term storage starch is produced [5]. Starch, a biopolymer, is consists of two main constituents: amylose and amylopectin. A predominantly linear polysaccharide, amylose has a -(1–4)-linked D-glucose units. In most plants, it forms 15–35% of the starch granules. Amylopectin, is mainly a branched molecule that has a -(1–4)-linked D-glucose backbones which have about 5% of a -(1–6)-linked branches and that has a huge influence on its biological and physical activities [5]. Amylose tends to retrograde, forming firm gels and durable films, while amylopectin, when mixed in water, is more durable and forms softer gels and weaker films. Starch's physical properties are determined by the interaction of amylose, amylopectin, phospholipids and lipids [5].

Native starches are not effectively utilized in many applications oweing to their lack of ability to survive processing conditions like extreme temperature, variation in pH and its poor flow properties, high retrogradation, its low solubility in common organic solvents, and freeze thaw variation [3, 6-8]. To overcome these disadvantages, they are often modified to improve or repress their inherent property and to introduce new properties that will enable them to be utilized for specific applications [3,7]. The role of modified starches as excipient with many functions in the pharmaceutical industry has been established [7]. Modification of starch can be done through processes that are genetic, chemical, physical or enzymatic [3, 8]. Factors like source of starch, type of reactants, time of reaction, and pH of the reacting medium influence the outcome of starch transformation [8]. The alteration of starch by chemical process can be attained by acid hydrolysis, etherification, esterification, crosslinking or oxidation. This can also occur through joint modification, such as a mixture of chemical, physical and enzymatic modifications [9].

Upon heating of citric acid, a reactive anhydride is formed and it reacts with starch to form

starch citrate by esterification reaction and crosslinking reactions [7, 9]. Starch citrate has higher swelling index in water when compared with native starch [7].

Ipomoea batatas (L.), commonly known as the sweet potato, is taxonomically placed within the Convolvulaceae family. Sweet potato is a vital but under-utilized tubers globally [10]. Its industrial usage is quite low, leading to decline in production. However, in developed countries, it has been utilized as a vital source of large scale extraction of starch [11]. Physical and chemical alteration of potato starch (PS) may render it more useful in traditional products where other type of starches are usually utilized [10]. Nigeria is ranked globally as the largest producer of sweet potato in Africa, and second only to China in the world in 2014 [12, 13]. The Sweet potato produced in Nigeria are largely utilized as food. This study is aimed at improving the physicochemical properties of native potato starch from Nigeria in order to generate interest in its usage as a pharmaceutical raw material in Nigeria.

MATERIALS AND METHODS

Materials

Reagents used include metronidazole (Central Drug House, New Delhi, India) citric acid (Tianjin Kermel, Tianjin, China), sodium hydroxide (Central Drug House, New Delhi, India), hydrochloric acid (Guangxing Guanghua Chemical, China), magnesium stearate (Loba Chemie, Mumbia, India), acacia gum (Central Drug House, New Delhi, India), talc (LobaChemie, Mumbia, India), lactose (BDH, Poole, England), and nutrients agar (Titan Biotech, India).

Collection and authentication of plant sample

Ipomoea batatas (sweet potato) tubers were bought from Ose market at Onitsha, Anambra State, Nigeria. Voucher number (UBH-I493) was given to the plant sample after authentication by a taxonomist, Dr Henry Adewale Akinnbosun of Plant Biology and Biotechnology Department, University of Benin, Benin City, Nigeria.

Extraction of starch from sweet potato tubers

Sweet potatotubers were peeled, washed, sliced and milled into a wet paste. It was mixed properly with distilled water to form slurry. It was kept for 8 h and filtered using a muslin cloth to isolate the starch from the fibers. The filtrate was filtered again using a 212 µm sieve and allowed to settle for 24 h. The supernatant was separated and removed, while the starch was re-suspended in distilled water, filtered using a 212 µm sieve, and kept to settle in the refrigerator (about 7°C). The supernatant was decanted and the starch sediment was dried overnight at 60°C using a hot air oven (KEMI, India). The dried starch was milled and sieved using 212 µm sieve. It was packed, and sealed in an airtight container [14].

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Modification of potato starch

Fifty milliliters (50 ml) of distilled water was utilized to dissolve 20 g of citric acid and 10 M sodium hydroxide was utilized to modify the pH to 3.85. Twenty grams (20 g) of potato starch (PS) was included in the solution and it was kept at 28ºC for 20 h. It was dried at 60°C using an oven. After drying, the modified starch was milled and distilled water was utilized to wash it several times. It was dried again at 60°C and sieved using a 212 µm sieve [15, 16].

Characterization of potato starch and modified potato starch

Angle of repose

The angle of repose for PS and MPS was assessed using the platform method. A cylinder having both ends opened was fixed on a base with known diameter (5.5 cm). The cylinder was filled with 20 g of the starch sample. The cylinder was slowly raised, allowing the starch powder to flow out to produce a cone-shaped heap. The heap's height was recorded. Three determinations were carried out and the mean angle of repose was determined. The angle of repose (θ) was determined using Equation 1 [17]:

$$\theta = Tan^{-1}\frac{h}{r} \quad . \quad . \quad . \quad \text{Eqn 1}$$

Where *h* is the height of the heap and *r* is the diameter of the base.

Bulk and Tapped Densities

Twenty grams of the sample was weighed. It was transferred into a 100 ml measuring cylinder and the volume (bulk volume) was noted. It was tapped 100 times to obtain a new volume (tapped volume). Bulk and tapped densities were determined using Equations 2 and 3 respectively [18, 19].

$$Bulk\ Density(g/ml) = \frac{weight\ of\ powder}{Bulk\ volume} \quad \text{Eqn 2}$$

$$Tapped\ Density\ (g/ml) = \frac{weight\ of\ powder}{Bulk\ volume} \quad \text{Eqn 3}$$

Hausner ratio

This was determined using Equation 4:

$$Hausner\ ratio = \frac{Tapped\ Density(g/ml)}{Bulk\ Density(g/ml)} \quad \text{Eqn 4}$$

Carr's index (Compressibility index)

Carr's index was determined using Equation 5:

$$Carr's\ index\ (\%) = \frac{Tapped\ Density\ \left(\frac{g}{ml}\right) - Bulk\ Density\ (g/ml)}{Tapped\ Density\ (g/ml)} \times 100\% \ . \quad \text{Eqn 5}$$

Evaluation of physicochemical properties of native and modified potato starches

Solubility

The solubility of PS and MPS was tested in water and organic solvents (methanol, chloroform, ethanol and petroleum ether) [16].

Gelatinization temperature

One gram of starch sample was dispersed in 10 ml of distilled water (10% w/v) in a 20 ml beaker. The suspension was heated and stirred with magnetic stirrer having hotplate until it formed gel. The gelatinization temperature was recorded [20].

Viscosity

The viscosity of 1% w/v starch sample in water was evaluated at 28ºC with spindle 3 of a Brookfield viscometer [21].

pH

The pH of 1% w/v starch sample in water was evaluated with a pH meter [22].

Swelling index

Two 0.2 g starch samples were taken in two different 10 ml measuring cylinders. Water (10 ml) and light liquid paraffin (10 ml) were poured into respective measuring cylinders and mixed properly. The dispersions were kept for 12 h to settle. The volumes of the sediments were noted and the respective swelling index was determined using Equation 6 [23];

$$Swelling\ index = \frac{(Vw - Vp)}{Vp} \times 100 \quad \text{Eqn 6}$$

Where *Vp* = sediment's volume in light liquid paraffin, *Vw* = sediment's volume in the water.

Swelling power

A 1 g of starch was dispersed in 20 ml of distilled water and shaken for 5 minutes prior to measurement of the sedimentation volume. The dispersion was then kept for 24 h, and the swelling capacity was determined using Equation 7:

$$Swelling\ Capacity = \frac{V2}{V1} \quad . \ . \ . \ . \quad \text{Eqn 7}$$

Where V_1 = initial starch volume, and V_2 = final starch volume after 24 h.

Loss on drying

Two grams of PS (W1) put in a pre-weighed crucible, was placed in an oven set at 105 °C to dry for 24 hours. The final weight (W2) was noted, and the percentage weight loss after drying was determined. This process was repeated for MPS. Weight loss on drying was determined using Equation 8 [24]:

$$Loss\ on\ drying = \frac{W_1 - W_2}{W_1} \times 100 \quad . \quad \text{Eqn 8}$$

X-ray diffraction

The XRD of the citric acid modified starch was established using the X-ray diffractometer (Rigaku miniflex 600, Rigaku Corporation, Japan).

Scanning electron microscopy

Images of the MPS surfaces were obtained at various magnifications with a Phenom ProX scanning electron microscope (Phenomworld, The Netherlands). Samples were prepared and placed on aluminum pin stubs under a vacuum for the SEM analysis.

Differential scanning Calorimetry (DSC)

DSC measurements of MPS was obtained using the Mettler Toledo DSC.

FTIR analysis

Agilent carry 360 Series FTIR spectrophotometer (Agilent Technologies, Malayasia) was utilized to obtain the FTIR spectra of PS, MPS, metronidazole alone and with MPS at 4000 - 650 cm^{-1} wavelength.

Microbial count

The microbial count of PS and MPS powder was performed by utilizing the plate count method.

Plate count: One gram of the MPS powder was dissolved in 9 ml of sterilized NaCl solution in a test tube, and was properly shaken. A serial dilution was made by putting 1 ml of the starch dispersion into another test tube and making it up to 10 ml with the sterilized NaCl solution. This dilution was used to make 10^{-5}, 10^{-4}, 10^{-3}, 10^{-2}, 10^{-1} dilutions of the MPS dispersions.

Nutrient agar was formed and poured into ten Petri dishes respectively. A 0.1 ml of 10^{-5} of MPS dispersion was transferred into 2 of the Petri dishes respectively. The procedure was repeated using 10^{-4}, 10^{-3}, 10^{-2}, 10^{-1} MPS dispersions respectively. The samples were evenly spread on solidified agar using a glass spreader, and the plates were left to solidify for 15 min. Afterward, the plates were inverted and incubated at 37°C for 24 h. The number of colonies produced were enumarated. This procedure was repeated using PS.

Acute toxicity studies of potato starch and modified potato starch in rats

Approval (RBC/FBMS/DELSU/24/640) was received from the Research, Ethics and Grants Committee of the Faculty of Basic Medical Sciences, Delta State University, Abraka before the acute toxicity studies was conducted. The lockes method [25, 26] was used. Twelve (12) male Wistar rats weighing (111–211 g) were used. These rats were procured from Department of Pharmacology and Therapeutics' animal house, Delta State University, Abraka. These animals were put in an animal cage under ideal laboratory environment.

Grouping of animals

Twelve (12) rats were used for this study. The rats were weighed and shared into 2 groups of 6 rats each.

Group 1: Those given PS.

Group 2: Those given the MPS.

Preparation and administration of the potato starch and the modified potato starch

PS and MPS were reconstituted and administered orally to different groups of animals at varying doses (10, 100, 1000, 1600, 2900, and 5000 mg/kg body weight). The animals were habited in a laboratory environment with normal feed for the following 10 days. They were closely monitored for any deviation in

behavior or physical activity after they received the doses.

Formulation of metronidazole tablets

Wet granulation technique was utilized to prepare granules following the formula in Table 1. Metronidazole was mixed with PS (or MPS) and lactose to form powder mix. The disintegrants (PS or MPS) were added intragranularly in all the formulations except for M6 where it was added intra-extragranularly. Slurry formed by the dispersion of acacia in distilled water was introduced into the powder mix. The mixture was properly mixed to produce a damp mass, which was then passed through a 1.18 mm sieve. Hot air oven was utilized to dry the granules at 60°C and subsequently they were sieved using 710 µm sieve to produce granules of relatively uniform size.

Table 1: Composition of metronidazole tablet formulations M1-M6

Ingredients	Formulations					
	M1	M2	M3	M4	M5	M6
Metronidazole (mg)	400	400	400	400	400	400
Acacia (mg)	30	30	30	30	30	30
Potato starch (mg)	-	120	-	-	-	-
Modified potato starch (mg)	-	-	60	90	120	120
Lactose (mg)	158	38	98	68	38	38
Talc (mg)	6	6	6	6	6	6
Magnesium stearate (mg)	6	6	6	6	6	6
Total (mg)	600	600	600	600	600	600

Granules' micromeritic evaluation

Preceding compression, the granules were assessed for bulk density, tapped density, Hausner ratio, Carr's index, and angle of repose, following the previously mentioned procedures.

Compression of metronidazole tablets

Talc (1%) and magnesium stearate (1%) were mixed lightly with the granules and compressed to tablets with a tableting machine (Clit Jemkay Engs., India) that has 13 mm punches.

Post compression evaluation of the metronidazole tablets

Weight variation

Twenty tablets selected randomly from all the formulations were weighed separately. The percentage deviation of each tablet's weight from that of the mean was ascertained.

Hardness

Monsanto hardness tester was utilized to ascertain the hardness of five tablets selected at random.

Friability

Ten tablets selected randomly were weighed together. They were put in the friabilator (Veego Friability Test Apparatus, India) and rotated at 25 rpm for 4 min. They were de-dusted and reweighed. Friability was evaluated as percentage weight loss using Equation 9:

$$Friability = \frac{initial\ weight - final\ weight}{initial\ weight} \times 100 \quad . \quad . \quad 9$$

Disintegration time

Six tablets selected randomly from a formulation were placed into the six tubes of a disintegration apparatus (Manesty, Liverpool, England). The

apparatus repeatedly immersed and raised the tablets in a disintegration medium of distilled water kept at 37±2°C until no tablet particle was left in the tubes. It was repeated for the other formulations.

***In vitro* dissolution studies**

A single tablet was weighed and placed in the basket of a Copley single-unit dissolution test apparatus (Erweka, Germany). The basket was engulfed in a dissolution chamber that contained 0.1 N HCl, kept at 37 ± 1°C as the dissolution medium, and rotated at 100 rpm. Periodically (5, 15, 30, 45, and 60 minutes), 6 ml of the dissolution medium was withdrawn and filtered while same volume of fresh, pre-heated medium was returned. The filtered and diluted samples' absorbance was measured at 277 nm using a Spectrumlab SPM-752 pro UV-spectrophotometer (Union Laboratories, England).

RESULTS

Organoleptic properties

The colour, odour, taste and texture of PS and MPS were as shown in Table 2.

Table 2: Organoleptic properties of potato starch (PS) and modified potato starch (MPS).

Starch sample	Appearance	Colour	Odour	Taste	Texture
Modified potato starch (MPS)	Powder	White	Slight odour	Tasteless	Smooth
Potato starch (PS)	Powder	White	Slight odour	Tasteless	Smooth

Micromeritic properties

The angle of repose

The values were 41.50 ± 0.67º for PS, and 42.65 ± 0.65º for MPS (Table 3).

Bulk and tapped densities

The mean bulk and tapped densities (g/ml) were 0.57 ± 0.01 g/ml and 0.66 ± 0.02 g/ml respectively for PS, and 0.55 ± 0.01 g/ml and 0.65 ± 0.02 g/ml respectively for MPS (Table 3).

Table 3: Micromeritic properties of potato starch and modified potato starch (mean ± SD., n = 3).

Flow properties	Potato starch (PS)	Modified potato starch (MPS)
Bulk density (g/mL)	0.57 ± 0.01	0.55 ± 0.01
Tapped density (g/mL)	0.66 ± 0.02	0.65 ± 0.02
Angle of repose (º)	41.50 ± 0.67	42.65 ± 0.65
Carr's index (%)	13.13 ± 2.80	15.75 ± 4.34
Hausnerratio	1.15 ± 0.04	1.19 ± 0.06

Carr's compressibility index

The mean compressibility index value for PS is 13.13 ± 2.80, and 15.75 ± 4.34 for MPS (Table 3).

Hausner ratio (HR)

PS and MPS have Hausner ratio of 1.15 ± 0.04 and 1.19 ± 0.06 respectively (Table 3).

Physicochemical properties

Solubility

Both the PS and MPS were insoluble in water, ethanol, chloroform, methanol, and petroleum ether.

pH

The mean pH of the 1% w/v suspension of PS and MPS was 4.9 ± 0.00.

Viscosity

The viscosity of PS was 1082.2, 603.9 and 498.7 mPas, while MPS was 1063.4, 603.1 and 427.6 mPas at 6, 12 and 30 rpm respectively.

Loss on drying

The result obtained for mean percentage loss on drying was 11.50 ± 2.00% and 4.17 ± 0.58% for PS and MPS respectively.

Moisture content

The result obtained for mean percentage moisture content was 13.03 ± 2.56 and 4.35 ± 0.63 for PS and MPS respectively.

Swelling index

The swelling Index of both PS and MPS were 74.56 ± 2.16 and 86.19 ± 2.34 respectively.

Swelling power

The swelling Power of both PS and MPS was 3.89 ± 1.06 and 2.94 ± 0.48 respectively.

Gelatinization temperature

The gelatinization temperature was from 65-70°C for PS and 67–70°C for MPS.

Table 4: Physicochemical properties of potato starch and modifies potato starch (mean ± SD., n = 3).

Physicochemical property	Potato starch	Modified potato starch
pH	4.9 ± 0.00	4.9 ± 0.00
Viscosity (mPas)[a]	1082.2	1063.4
Loss on drying (%)	11.50 ± 2.00	4.17 ± 0.58
Moisture content (%)	13.03 ± 2.56	4.35 ± 0.636
Swelling index	74.56 ± 2.16	86.19 ± 2.34
Swelling power	3.89 ± 1.06	2.94 ± 0.48
Gelatinization temperature	65 - 70°C	67 – 70°C

a: viscosity at 28°C using spindle 2 at 6 revolution per minute.

Microbial count

The nutrient agar plates containing 10^{-1} (which has many colonies) and 10^{-2} dilutions of PS (with 1 colony) can be analogized to the ones from the nutrient agar plates containing 10^{-1} dilution of MPS which contained 1 colony of bacteria.

Acute toxicity studies

By day 14 of observation, no signs of harm or death were recorded among the rats. The study revealed no physiological alterations in behaviour across all groups of rats up to a dose of 1000 mg/kg. However corner sitting was observed in rats administered a dose of 5000 mg/kg.

X-ray diffraction (XRD)

The X-ray diffractograms of PS and MPS shown in Figures 1 and 2 respectively, illustrated their semicrystalline nature. Both PS and MPS exhibited peaks at 2θ diffraction angles of approximately 15, 17, 18, and 23.

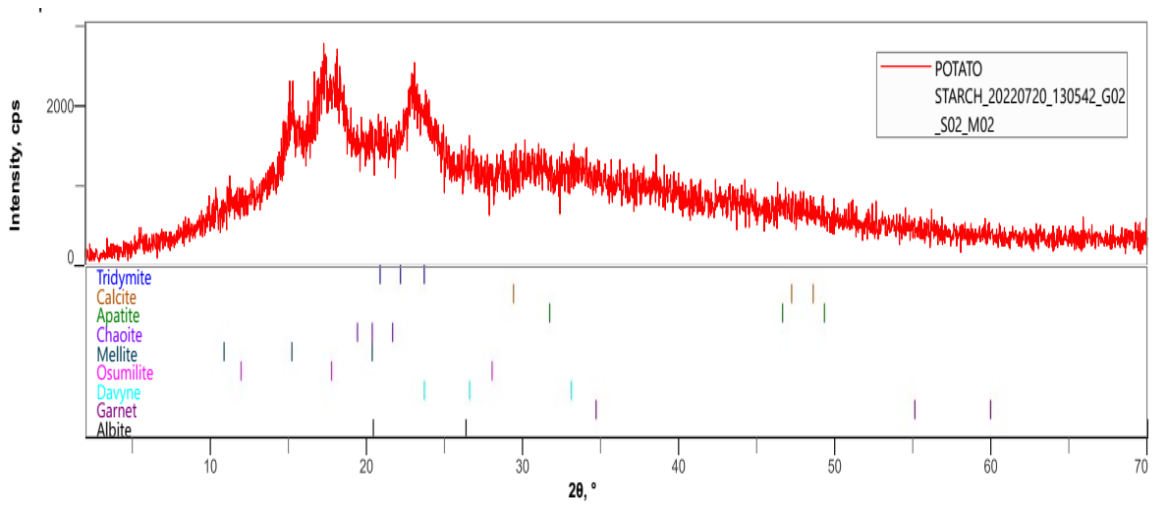


Figure 1: X-ray diffractogram for potato starch.

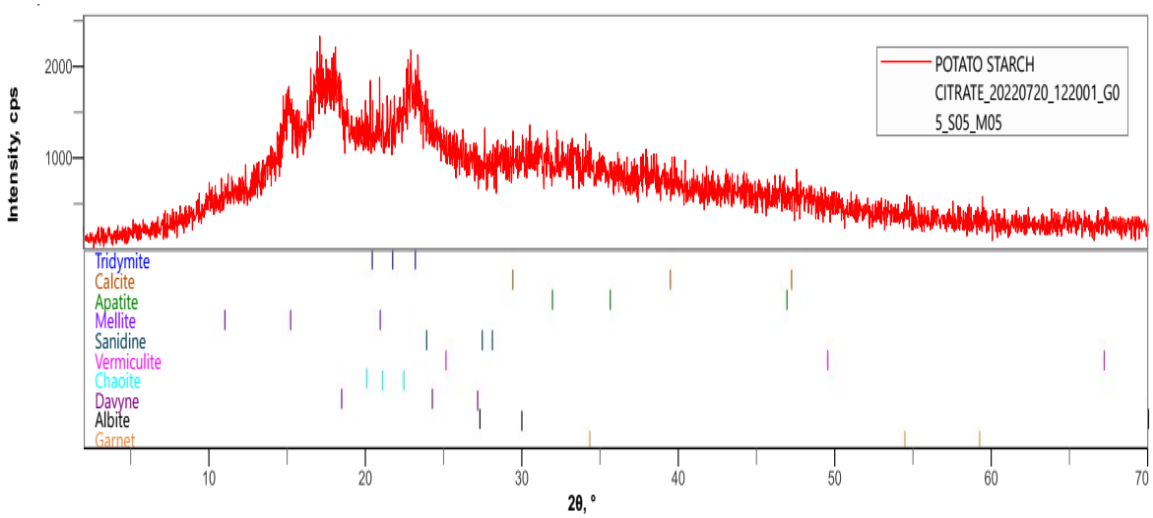
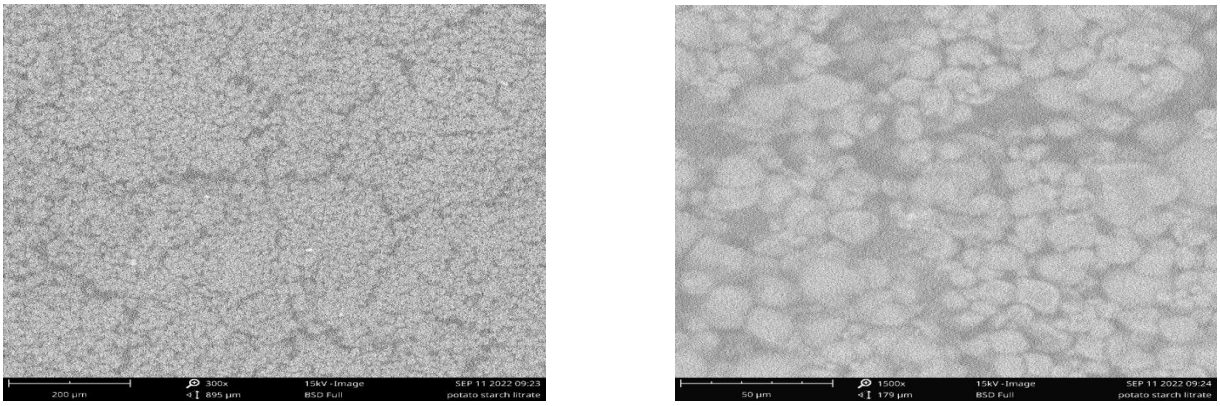


Figure 2: X-ray diffractogram for modified potato starch (potato starch citrate).

Scanning electron microscopy

The SEM images of MPS are shown in Figure 3.



(a) *(b)*

Figure 3: SEM image of MPS blend. (a) 300 x magnification (b) 1500 x magnification

Differential scanning calorimetry (DSC)

The DSC thermogram of MPS is displayed in Figure 4.

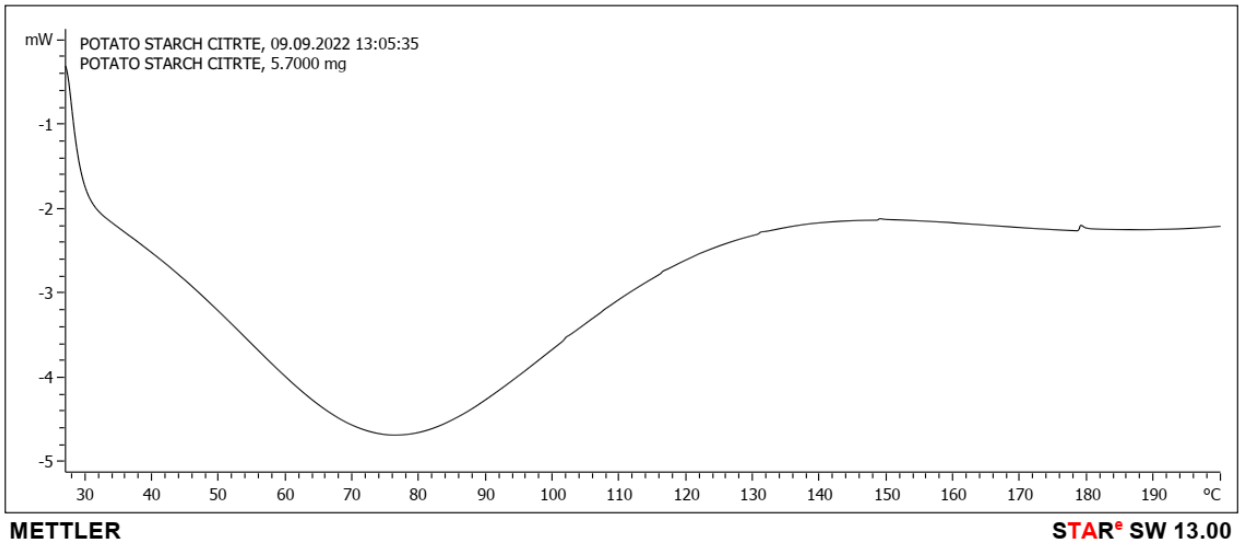


Figure 4: DSC thermograms of modified potato starch (potato starch citrate)

Drug-excipients compatibility studies

The FTIR spectra are shown in Figures 5-8.

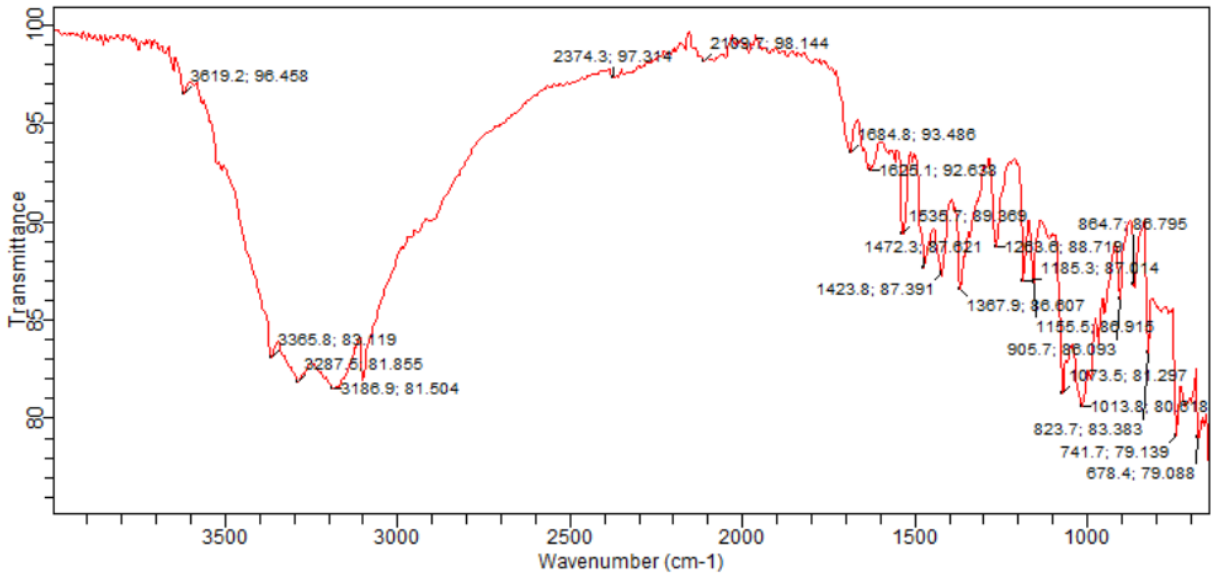


Figure 5: FTIR spectrum of metronidazole.

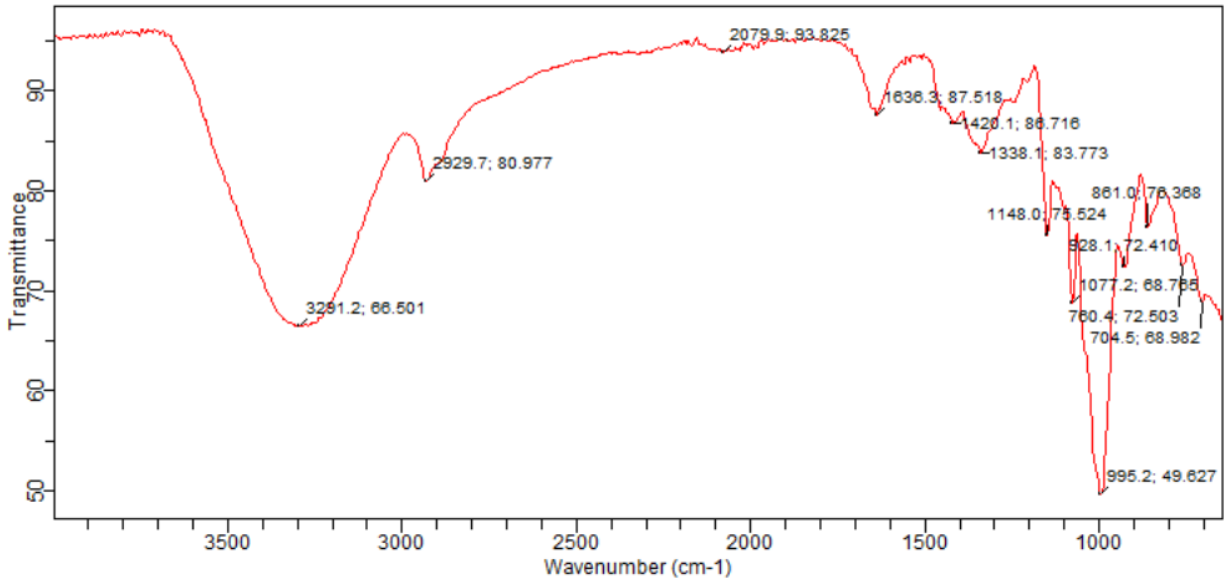


Figure 6: FTIR spectrum of the potato starch.

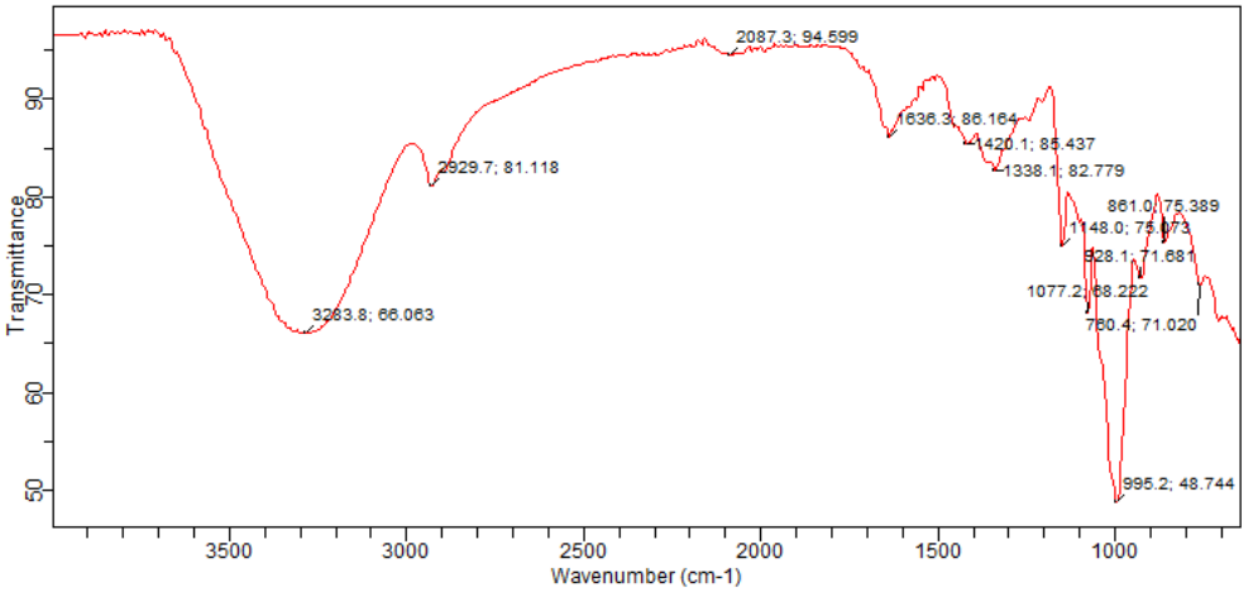


Figure 7: FTIR spectra of modified potato starch.

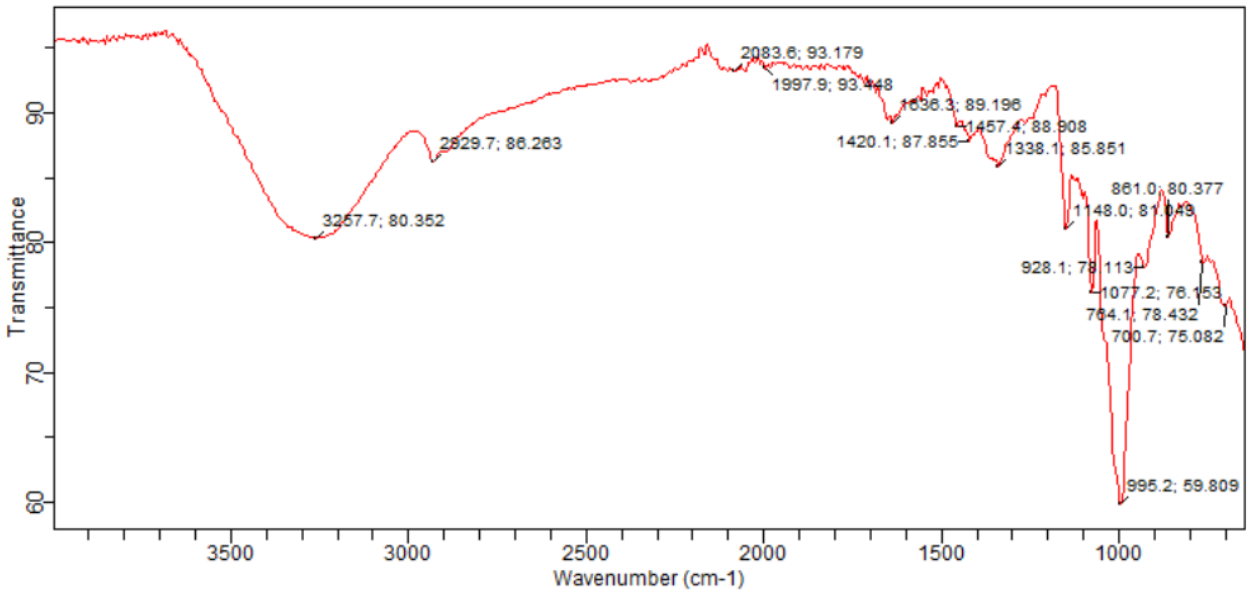


Figure 8: FTIR spectra of metronidazole + modified potato starch.

Characterization of metronidazole granules

The granules' flow properties are shown in Table 6.

Table 6: Pre-compression Parameters for prepared granules of tablet formulation (mean ± SD., n = 3).

Formulation	Bulk Density (g/mL)	Tapped Density (g/mL)	Flow rate (g/s) ± SD	Angle of Repose (°)	Carr's Index (%)	Hausner Ratio ± SD
M1	0.63 ± 0.0	0.73 ± 0.04	2.32 ± 0.16	23.10 ± 1.02	13.55 ± 4.77	1.16 ± 0.07
M2	0.45 ± 0.0	0.48 ± 0.01	1.67 ± 0.0	24.53 ± 1.59	5.93 ± 1.28	1.07 ± 0.01
M3	0.52 ± 0.0	0.57 ± 0.02	1.54 ± 0.0	24.36 ± 2.53	9.41 ± 2.96	1.11 ± 0.04
M4	0.47 ± 0.0	0.50 ± 0.01	1.37 ± 0.06	24.60 ± 0.42	6.15 ± 3.43	1.07 ± 0.04
M5	0.49 ± 0.0	0.54 ± 0.01	1.88 ± 0.11	26.77 ± 1.37	8.14 ± 1.41	1.09 ± 0.02
M6	0.52 ± 0.0	0.55 ± 0.01	1.82 ± 0.0	26.04 ± 1.11	5.99 ± 1.48	1.07 ± 0.02

Evaluation of metronidazole tablets

The thickness, diameter, uniformity of weight, hardness, friability, and disintegration time test of the metronidazole tablets are shown in Table 7, while the *in vitro* drug release is shown in Figure 9.

Table 7: Post-compression parameters of formulated granules (mean ± SD., n = 3).

Formulation	Thickness (mm) ± SD	Diameter (mm) ± SD	Friability (%)	Disintegration Time (min) ± SD	Weight Uniformity (g) ± SD	Hardness ± SD
M1	4.67 ± 0.38	13.13 ± 0.05	0.32	39.05 ± 1.79	0.61 ± 0.02	7.70 ± 0.45
M2	4.78 ± 0.32	13.27 ± 0.07	6.83	25.67 ± 4.45	0.59 ± 0.02	5.40 ± 0.90
M3	4.64 ± 0.42	13.31 ± 0.09	0.96	31.05 ± 3.65	0.61 ± 0.01	5.70 ± 0.67
M4	4.51 ± 0.46	13.25 ± 0.06	1.34	13.09 ± 2.40	0.60 ± 0.02	4.90 ± 0.55
M5	4.55 ± 0.49	13.37 ± 0.07	1.00	13.54 ± 1.69	0.59 ± 0.03	4.13 ± 0.25
M6	4.59 ± 0.51	13.20 ± 0.11	0.96	14.26 ± 1.33	0.61 ± 0.01	4.10 ± 0.74

Key: Disintegrant concentration of each formulation: M1 (0%); M2 (20% potato starch); M3 (10% modified potato starch); M4 (15% modified potato starch); M5 (20% modified potato starch, intragranularly); M6 (20% modified potato starch, intra-extragranularly)

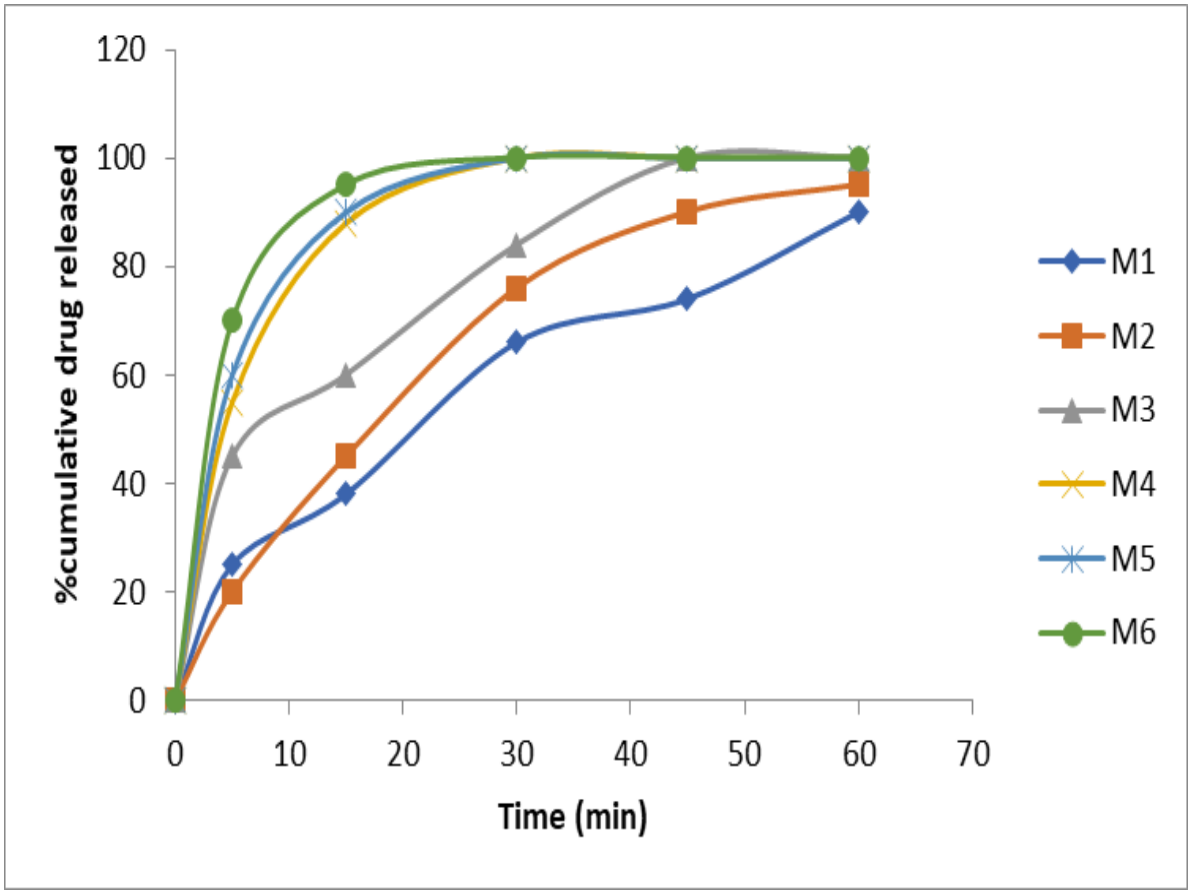


Figure 9: % Drug release of metronidazole tablet formulations

Key: Disintegrant concentration of each formulation: M1 (0%); M2 (20% potato starch); M3 (10% modified potato starch); M4 (15% modified potato starch); M5 (20% modified potato starch, intragranularly); M6 (20% modified potato starch, intra-extragranularly)

DISCUSSIONS

Both PS and MPS were white in colour, tasteless with slight odour and had smooth texture [5].

In the determination of angle of repose, the platform method was utilized instead of the funnel method because the starches were unable to flow pass the funnel. The minute size of the starch particles may have favoured cohesive forces over repulsive forces, leading to poor flow. The result corresponds to the findings of Okafo *et al*. [14], that *Pterocarpus santalinoides* and maize starches have very poor flow property (AOR of 43 ± 0.00º and 43.63 ± 0.40º respectively).

Powder material's flowability is estimated using the bulk density, whereas the tapped density shows how on repeated tapping, how efficiently the powder is packed within a closed space [27]. There was no much difference between the bulk and tapped densities of the native and modified potato starches.

The Carr's index value of 5–15 signifies excellent flow, 16–18, shows good flow, 19–21, indicates fair to passable flow, 22 to 35 shows poor flow whereas 36–40 shows very poor powder flowability [28, 29]. This signifies the excellent flow property of modified potato starch. This result is in disagreement with that of angle of repose, which shows that the starches have poor flow property. It also disagreed with work of Nwachukwu *et al*. [30] which showed that natural Pennisetum starch, and modified *Pennisetum glaucum* starch had Carr's index of 41.50 ± 1.69 and 33.33 ± 0.66 respectively.

The Hausner ratio, which reflects interparticle friction, serves as a predictor of powder flow [28]. Hausner ratio that is below 1.25 shows good flow, whereas values that are above 1.25 shows poor flow [27]. This indicates that PS and MPS has good flow property. However, this result is inconsistent with the angle of repose values for both PS and MPS. It is also inconsistent with the work of Nwachukwu *et al*. [30] which showed that natural Pennisetum starch, and modified *Pennisetum glaucum* starch had poor flow properties (HR of 1.71 ± 0.48 and 1.50 ± 0.23 respectively)

The solubility of PS and MPS agrees with the report of Dompo *et al.* [31], that the solubility of the acid modified GST starch was in the normal starches' solubility range. Starch is usually insoluble in water and most organic solvents, due to strong hydrogen bonds that exist in semicrystalline granules. [32].

The pH of both PS and MPS conformed to the acceptable limit for starch (4.5 - 7.0) [33].

The viscosity of potato starch decreased slightly after acid hydrolysis. This is in agreement with reports from previous research [34, 35], that acid hydrolysis of starch does not affect its granular structure but results in decrease in viscosity.

The limit for loss on drying for PS according to United States Pharmacopoeia is, not more than (NMT) 15% [36], therefore, the starches were within the accepted limits. However, MPS showed lower value when compared to unmodified potato starch, therefore, it will be less prone to microbial degradation.

The moisture content of PS was comparable to the value (14.40%) obtained by Julianti *et al.* [37]. Montoya-Anaya, *et al.* [38] obtained a moisture value of 10.60 ± 0.14 for potato starch. Dry starches often have moisture content that range from 6 to 16%. This difference is usually due to the environment and drying process used. Moisture content above 13% may cause microbial degradation and deterioration of the quality of the starch. [38].

There was reduction in the swelling power of MPS and this aligns with Golachowski *et al* [34] who reported of lowering of swelling power of PS due to modification by citric acid. The low swelling power of MPS shows its low amylose-amylopectin ratio. The amylose content has been immensely hydrolyzed by the acid leaving more branched amylopectin content, resulting in starch with more branched structure and lower swelling and expanding capabilities [31].

There was a slight increase in the gelatinization temperature of the modified starch. Some researchers claimed that acid hydrolysis of starch causes increase in gelatinization temperature [39, 40] while others claimed that it decreases it [41, 42]. However, Zhang *et al.* [35] reported that alteration of starch using citric acid causes increase in gelatinization temperature, a reduction in gelatinization enthalpy (ΔH), and a reduction in retrogradation. Babu *et al*. [10] reported that a greater level of hydrolysis may take place in starches within the amorphous regions due to acid modification, which might cause elevation in relative crystallinity and gelatinisation temperature elevation.

The C-type crystalline pattern is a characteristic feature of sweet potato starch, and it is consistent with the findings of Babu *et al*. [10], who reported 2θ values at 15.4°, 17.2°, 18.3°, and 23.4°. Acid modification did not alter the X-ray diffraction pattern of PS but resulted in a slight decrease in peak intensity.

The electromicrograph of MPS revealed that the granules have cylindrical as well as oval-shaped morphology. This compares to what was reported by Babu *et al.* [10] that sweet potato starch granules have such shapes as polygonal, round, and oval. Acid hydrolysis usually affect the physicochemical property of starch without affecting its granular structure [10].

The thermogram looked like a trough between 35^{o}C, onset (To) and 120^{o}C, conclusion (Tc) temperatures with a blunt endothermic peak between 70^{o}C and 80°C, peak temperature (Tp). The wide trough with a blunt endothermic peak shows the amorphous and semicrystalline nature of MPS while the blunt peak coincides roughly with the gelatinization temperature of MPS.

The functional groups in the chemical structure of analyte samples produce characteristic vibrational peaks (e.g., stretching and bending) on FTIR spectra, which are unique to

each specific functional group. These vibrational peaks are analyzed to aid in the structural characterization of the test compounds [43]. The FTIR spectra of metronidazole, PS, MPS, and Metronidazole + MPS are displayed in Figures 5-8 respectively. Figure 5 shows that metronidazole spectrum has characteristic peaks at 3287.6 cm^{-1} (vibrational peak for C-H), 1625.1 cm^{-1} (C=C stretching), 1472.3 cm^{-1} (N=O asymmetric stretching), 1423.8 cm^{-1} (C-C stretching), 1367.9 cm^{-1} (CH bending), 1155.6 cm^{-1} (C-O stretching), 1073.5 cm^{-1} (C-N stretching), 741.7 cm^{-1} (=C-H bending) [32]. Figure 4 shows that metronidazole + MPS spectrum has characteristic peaks at 3257.7 cm^{-1} (vibrational peak for C-H), 1630.6 cm^{-1} (C=C stretching), 1457.4 cm^{-1} (N=O asymmetric stretching), 1420.1 cm^{-1} (C-C stretching), 1338.1 cm^{-1} (CH bending), 1148.0 cm^{-1} (C-O stretching), 1077.2 cm^{-1} (C-N stretching), 764.1 cm^{-1} (=C-H bending). This shows that there was no incompatibility between metronidazole and MPS.

As shown in Figures 6 and 7, all the characteristics peaks in native potato starch were also present in MPS. The strong and wide peaks at 3291.2 cm^{-1} (PS) and 3283.8 cm^{-1} (MPS) were for O-H stretching vibration [44, 45]. The peaks at 2929.7 cm^{-1} (C-H stretching), 1636.3 cm^{-1} (C-O bending associated with OH group), 1420.1 cm^{-1} (CH2 symmetric deformation), 1338.1 cm^{-1} (C-H symmetric bending), 1148.0 cm^{-1} (C-O-C asymmetric stretching), 995.2 cm^{-1} (C-O stretching), 928.1 cm^{-1}, 861.0 cm^{-1}, and 760.4 cm^{-1} (C-O-C ring vibration of carbohydrate) [14, 44] were present in both PS and MPS.

The angle of repose of the granules was from 23.10 ± 1.02 to 26.77 ± 1.37, which indicates excellent flow. The Carr's compressibility index and Hausner ratio are within the range of 5.93 ± 1.28 to 13.55 ± 4.77 and 1.07 ± 0.01 to 1.16 ± 0.07 respectively, this signified good flow. The flow rate were from 2.46 ± 0.18 to 3.31 ± 0.30 g/s. Based on the different flow parameters results, the granules have good flowability.

The tablet thickness for the different formulation ranged from 4.51 ± 0.46 to 4.78 ± 0.32 mm, and the diameter ranged from 13.13 ± 0.05 to 13.37 ± 0.07 mm.

The metronidazole tablets hardness was from 4.08 to 7.97 Kgf, meeting the acceptable range. Tablet hardness ensures robustness during production, packaging, and distribution, with a minimum acceptable value of 4 kgf [46, 47]. Though Compendia recommends a crushing strength of 5–8 kg [36], a very hard tablet would elevate disintegration time significantly and in turn dissolution.

The friability values for the tablets were from 0.32 to 6.83%. Friability measures the extent to which a tablet can withstand mechanical stress, such as shocks and abrasion, without crumbling or fragmenting [48]. The friability value of tablets should be below 1% [47, 48] and as such, M2 and M4 were not within this limit, the outlier M2 being way off at 6.83%. Formulations M3-M5 prepared with 10%, 15% and 20% MPS were less friable than those formulated with 20% PS (M2).

The disintegration time limit as stated in BP for uncoated tablets is not be more than 15 min [49, 50]. The disintegration time for formulation M1 (zero disintegrant) was 39.05 ± 1.786, while M2 (20% PS) had a disintegration time of 25.67 ± 4.45 min. Formulations M3-M6 (10%, 15% and 20% MPS) had a disintegration time of 13.09 ± 2.40 to 31.05 ± 3.65 min. Formulations M1-M3 failed disintegration test while formulation M4-M6 passed the test. Among the formulations prepared with MPS as disintegrant (M3-M6), those prepared with greater quantity of the disintegrant, resulted in shorter disintegration time (31.05 ± 3.65 to 13.09 ± 2.40 min). Formulation M5 prepared with 20% of MPS intragranularly had a disintegration time of 13.54 ± 1.69 min compared to disintegration time of 25.67 ± 4.45 min by formulation M2, prepared with 20% of PS intragranularly. Disintegrants acts by swelling or capillary action (water channels) [51]. Ingram and Lowenthal [52] reported that potato showed outstanding swelling in distilled water and simulated gastric fluid U.S.P. The presence of citrate in MPS may produce greater water channels which may be the reason metronidazole tablets formulated with the MPS as disintegrants have decreased disintegration time when compared to those prepared with PS.

Uniformity of weight ranged from 0.59 ± 0.03 to 0.61 ± 0.01. None of the tablets varied by upto 5% from the mean tablet weight, therefore, they passed the uniformity of weight test. As shown in Figure 9, formulations M4-M6 that were prepared using MPS as disintegrant had percentage drug release of 100% at 30 min. M3 achieved 100% drug release at 45 min whereas, M1 and M2 achieved 90 and 95% drug release respectively at 60 min. This may be due to faster disintegration of tablets in formulations M4-M6 that were prepared using MPS as disintegrant. The amount of drug released at 45 minutes of dissolution, should not be below 70%. [36, 53] This shows that all the tablet formulations passed the in vitro drug release test.

CONCLUSION

The study showed that PS modified with citric acid have improved physicochemical properties. MPS (potato starch citrate) could be utilized as a disintegrant in formulation of tablets. MPS (M5 and M6) at the same concentration (20%), has better disintegrant activity than PS (M2).

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AUTHORS CONTRIBUTIONS

Concept – OSE; Design – OSE, ACO; Supervision – OSE, ACA; Resources – OSE, OPC; Materials – OSE, OPC; Data Collection and/or Processing – OSE, OPC; Analysis and/or Interpretation – OSE, ACA, ACO; Literature Search – OSE, OPC; Writing – OSE, OPC; Critical Reviews – OSE, ACA, ACO.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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