

Yellow *Mangifera indica* Linn. and *Artocarpus heterophyllus* Lam. seed starch as binder and disintegrant in paracetamol tablet formulation

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ABSTRACT

Utilization of fruit by-products offers a potential solution in minimizing the economic and environmental problems posed by these wastes. In this study, the seeds of yellow *Mangifera indica* Linn. and *Artocarpus heterophyllus* Lam. were used as sources of starch as binder and disintegrant in the formulation of paracetamol tablets. Physicochemical, binder and disintegrant properties of the isolated starches were measured and evaluated based on the United States Pharmacopeia (USP) specifications. The *M. indica* and *A. heterophyllus* seed starches were white to off-white in color, odorless, and fine in texture, with starch yields of 25.64% and 44.85%, respectively. The *M. indica* has elongated shape while *A. heterophyllus* has smaller round granules, resulting in passable to poor flowability. The lower solubility ($p < 0.001$), and higher swelling power ($p = 0.017$) and viscosity ($p < 0.001$) of *M. indica* may also be due to its larger, rod-shaped granules relative to *A. heterophyllus*. The isolated starches conformed to the USP specifications of identification, loss on drying, pH and limit of iron of official starches. Furthermore, both displayed acceptable average tablet weight, thickness, hardness, friability, disintegration time, dissolution and potency when used as binder and disintegrant in tablet formulation based on the USP acetaminophen (paracetamol) monograph. In conclusion, the starch isolated from yellow *M. indica* and *A. heterophyllus* seeds met the acceptance criteria of the physicochemical tests for starch and quality control tests for the USP acetaminophen (paracetamol) tablets. Hence, they can be used as economical and alternative sources of starch for pharmaceutical use.

INTRODUCTION

Philippines is within the top 10 fruit-producing countries in the world in 2010–2011, contributing to 2.70% of the total world fruit production (Pathak *et al.*, 2015). *Mangifera indica* Linn. (Anacardiaceae) or mango, and *Artocarpus heterophyllus* Lam. (Moraceae) or jackfruit, are major fruit crops in the country, with 885,000 and 44,605 metric ton production in 2014, respectively (Philippine Statistics Authority, 2015). These fruits have been used mainly in food industry and their pulp can be eaten raw, preserved or dried. Exportation of these fruits has also increased, as observed in the proliferation of dried products, candies and purees in the market. The huge utilization

of these fruits resulted in waste generation of approximately 6.0% their total production in 2014 (Philippine Statistics Office, 2015). These wastes were generated from the seeds during food processing and consumption. Thus, utilization of these seeds will significantly reduce the pollution load and may result in increased commercial value of the wastes.

Previous studies have reported the appreciable quantities of starch in the seeds of *M. indica* (El Saadany *et al.*, 1980) and *A. heterophyllus* (Tulyathan *et al.*, 2002). Starch is known to be one of the utilized excipients in tablet formulation because it is readily obtained from natural sources. It acts as binder, lubricant, disintegrant and diluent in various solid dosage forms (Hartesi *et al.*, 2016; Ohubiojo and Rodrigues, 2012). Starch has also been explored in several pharmaceutical applications such as in nasal (Illum *et al.*, 2001), periodontal (Bromberg *et al.*, 2001), nanoparticles (Ahmad *et al.*, 2012) and film-based (Krogars *et al.*, 2002) drug delivery systems. Common sources of starch in Asia include potato, corn, cassava, wheat and tapioca (Fuglie, 1998).

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However, these produce are also used as food, which compete with their pharmaceutical applications. Hence, interests on the search of novel sources of starch have been increasing.

In this study, the physicochemical, binder and disintegrant properties of starch from yellow *M. indica* and *A. heterophyllus* seeds were assessed to determine their potential as sources of pharmaceutical starch in the formulation of paracetamol tablets.

MATERIALS AND METHODS

Sample collection

Yellow *M. indica* and *A. heterophyllus* were collected from the local wet markets in the Manila, Philippines. The fruits were submitted to the Botany Division of the National Museum Philippines, and were given voucher specimen numbers 16-04-391-07 and 01, respectively.

Starch extraction

The method was based on Rajeevkumar *et al.* (2010) with some modifications. The seeds were washed thoroughly with water followed by removal of extraneous parts. The collected seeds were dried, cut into small pieces, weighed and soaked in 0.1% sodium metabisulfite solution for 24 h. The solutions were filtered with cheesecloth and the residues were soaked in hot 80% ethanol solution overnight. The soaked residues were homogenized by grinding in a regular blender at low speed to produce a smooth paste. The pastes were stirred, allowed to settle and decanted to remove the supernatant liquid. The residues were treated with 0.1 M NaOH with volume equivalent to five times the weight of the sample and left for 18 h at room temperature, with intermittent shaking. The supernatants and any brown surface layers were removed, and the residues were first washed with 0.1 M HCl and then repeatedly using distilled water until they become white. The residues were filtered under vacuum to remove residual water and dried in an oven at 60°C until completely dried. The dried powders were crushed, passed through a 100-mm sieve mesh and stored in airtight plastic containers at 4°C until analyzed.

Organoleptic characteristics

Six assessors were selected to evaluate the organoleptic characteristics using sensory evaluations of the following parameters: texture, odor, and color.

Density measurements

The procedure for bulk density was based on the United States Pharmacopeia (USP) (2017). A 25-g sample was placed in a dry 100-mL graduated cylinder and the initial volume was noted. The graduated cylinder was tapped to a constant volume. The bulk and tapped densities were calculated using the formulas below:

$$\text{Bulk density, g/mL} = \frac{\text{Weight of sample}}{\text{Initial volume}}$$

$$\text{Tapped density, g/mL} = \frac{\text{Weight of starch}}{\text{Tapped volume}}$$

The compressibility index (CI) and Hausner ratio (HR) were also computed using the results of bulk and tapped densities.

$$\text{CI} = \frac{(\text{Tapped density} - \text{bulk density})}{\text{Tapped density}} \times 100$$

$$\text{HR} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Angle of Repose

The angle of repose was measured using the method of the USP (2017) with some modifications. A powder funnel was clamped with its tip 2 cm above a clean white paper. The sample was allowed to flow through the funnel until the apex of the powder cone just touched the tip of the funnel. The angle of repose was determined by measuring the height and base of the powder cone using the formula below:

$$\tan \alpha = \frac{\text{height of the cone of powder}}{0.5 \times \text{base}}$$

Morphology

The morphology was investigated using scanning electron microscope (Jeol JSM 5120, USA). The samples were plated with gold using sputter coater and examined under the microscope, with an accelerating voltage of 15 kW and magnification of 1000, 3500 and 5000x. The size of the granules was determined by random selection of granule diameters in the micrographs.

Amylose-amylopectin ratio

Amylose and amylopectin were determined using the method of Wang *et al.* (2010) with slight modifications. The samples were defatted for 7 h using hexane prior to the conduct of analysis. A 10-mg sample was weighed and added with 3 mL 1 M NaOH. The solution was mixed, placed in a water bath set at 60°C for 5 min, and sonicated for 25 min. The sample was then neutralized with 1 M HCl and diluted to 10 mL with distilled water. An aliquot of 200 µL sample was transferred to a glass tube, added with 200 µL distilled water and 1600 µL iodine solution. The solution was mixed and then left in the dark for 30 min for color development. The absorbance was read at 535, 620 and 730 nm for amylose, and 466, 535 and 650 nm for amylopectin using UV-Vis spectrophotometer (Hitachi UH5300, Japan).

Swelling power and solubility

Swelling power and solubility characteristics were determined using the method of Walter *et al.* (2000) with some modifications. A 0.1-g sample was weighed in a tube, and the sum of the weight of tube and sample was recorded. One percent starch solution was prepared and heated from 50 to 95°C, at every 5 min interval, in a waterbath for 30 min with constant agitation. The slurry was centrifuged at 3200 rpm for 10 min. The supernatant was removed, transferred to a pre-weighed aluminum dish and dried to constant weight in oven at 100°C for 4 h. Solubility was calculated using the formula below. The weight of the wet sediment in tube was recorded and the swelling power was also calculated.

$$\% \text{ Solubility} = \frac{\text{Weight}_{\text{solid content of supernatant}}}{\text{Weight}_{\text{starch sample}}} \times 100$$

$$\text{Swelling power, g/g} = \frac{\text{Weight}_{\text{wet sediment in tube}} - \text{Weight}_{\text{starch sample in tube}}}{\text{Weight}_{\text{starch sample}}}$$

Viscosity of the samples was also evaluated using Brookfield digital viscometer (LVT Brookfield viscometer, USA) following the method of *de Oliveira et al.* (2011). Starch slurries were made by preparing 5% w/v with distilled water, heated to 80°C, maintained for 10 min and cooled for 30 min. The final viscosities were measured using spindle 2 at 60 rpm and reported as centipoise, cP (1 mPa·s) at room temperature.

USP Specifications

Identification test for starch was based on the USP (2017). A 0.2-mg sample was diluted in 10 mL water. The solution was boiled for 1 min and cooled. A 1-mL mucilage was transferred to another tube and added with 0.5 mL of iodine and potassium iodide solution. The presence of orange-red to dark blue color, which disappears upon heating, is indicative of a positive result.

The procedure for loss on drying (LOD) was based on the USP (2017) with some modifications. One-gram sample was placed in a weighing dish previously dried under the conditions prescribed for the sample to be examined. The starch was dried at 130°C ± 2°C for 1.5 h. The weighing dish with sample was placed in a desiccator for 30 min to cool and weighed. LOD was calculated based on the formula below:

$$\% \text{ LOD} = \frac{\text{Weight}_{\text{initial (dish+sample)}} - \text{Weight}_{\text{final (dish+sample)}}}{\text{Weight}_{\text{sample}}} \times 100$$

The pH measurement was conducted following the method of the USP (2017). A slurry was prepared by weighing 5 g starch sample and adding 25 mL of freshly boiled water. The solution was agitated continuously at a moderate rate for 1 min. The solution was allowed to stand for 15 min and the pH was determined using a pH meter (Trans BP3001, Singapore).

The determination of limit of iron was based on the procedure of USP (2017) under the corn starch monograph. A 1.5-g starch sample was mixed with 15 mL 2 N HCl and filtered. A 10-mL filtrate was transferred to a test tube followed by the addition of 2 mL citric acid solution (2:10) and 0.1 mL thioglycolic acid. The solution was made alkaline by the addition of 10 N ammonium hydroxide followed by dilution with water to 20 mL. The sample solution was observed for the intensity of pink color change after 5 min.

Paracetamol tablet preparation

Wet granulation method was employed in preparing 500 mg paracetamol tablet batches. The percentage composition of the tablet batch is shown in Table 1. Paracetamol and starch were screened separately through sieve no. 40. The starch binder paste was prepared by dispersing starch in 9 mL water followed by addition of 24 mL boiling water. The solution was stirred until a paste was formed. The weighed paracetamol and starch were mixed, and the starch paste was incorporated thoroughly. The moistened mass, formed into balls, were passed through mesh screen no. 4. The granules were spread on trays and placed

in drying oven set at 65°C for 50 min. The granules were then passed through sieve nos. 20 and 40. The good granules and fine granules (10% of the weights of good granules) were combined. Magnesium stearate, which was previously passed through sieve no. 8, was used as lubricant and added to the combined granules and mixed. The granules were compressed into tablets using 7/16" concave punches (Stokes, Pennsylvania).

Table 1: Composition of 500 mg Paracetamol tablet batch.

Ingredient	Percentage, %w/w
Paracetamol	81.08
Starch ^a	2.58
Starch ^b	15.11
Magnesium stearate	1.23

^aStarch as disintegrant. ^bStarch as paste binder.

Evaluation of paracetamol tablet batches

In order to assess the quality and performance of the paracetamol tablet batches, quality control tests were conducted based on the USP (2017) for paracetamol tablets. These tests include uniformity of weight, thickness, hardness, friability, disintegration, dissolution and assay.

Statistical analysis

All the physicochemical and quality control tests were performed in triplicate, except for uniformity of weight, thickness, and hardness, and dissolution, which were conducted in 10 and 6 trials, respectively. The data generated were reported as mean ± standard deviation (SD) and analyzed by independent t-test to compare the differences between starch samples using Statistical Package for Social Sciences (SPSS) 23.0 software. Probabilities, *p*, were considered statistically significant when *p* < 0.05.

RESULTS AND DISCUSSION

The starch from yellow *M. indica* yielded 25.64 g per 100 g seeds, which is similar to the yield obtained from earlier literature (*El Saadany et al.*, 1980). The starch from *A. heterophyllus* had a lower yield of 44.85 g per 100 g seeds compared to previous study (*Tulyathan et al.*, 2002) due to differences in the extraction method. The isolated starches displayed comparable organoleptic characteristics with official starches, which were white to off-white in color, odorless and fine in texture. This demonstrates that the isolated starches were acceptable in terms of organoleptic characteristics.

The physicochemical properties of the starch obtained from yellow *M. indica* and *A. heterophyllus* seeds are shown in Table 2.

Powder flow is an important criterion in the manufacture of solid dosage forms, particularly in the functionality of excipient for direct compression, and in the determination of weight, hardness, and content uniformity of tablets (*Achor et al.*, 2015; *Shah et al.*, 2008). CI, HR and angle of repose are indirect methods used to determine the flow properties of powders. Particularly, CI is a measure of powder bridge strength and stability, HR is related to interparticulate friction (*Shah et al.*, 2008) and angle of repose measures interparticulate cohesion. CI of 1-10% or HR

of 1.00-1.11 can be described as excellent, 11-15% or 1.12-1.18 as good, 16-20% or 1.19-1.25 as fair, 21-25% or 1.26-1.34 as passable, 26-31% or 1.35-1.45 as poor and >32% or 1.46-1.59 as very poor, in terms of flow properties (Aulton, 2017). For angle of repose, a 25-30° is indicative of excellent flow properties, 31-35° as good, 36-40° as fair, 41-45° as passable, 46-55° as poor and >56° as very poor (USP, 2017). Based on these criteria, the starch from yellow *M. indica* and *A. heterophyllum* seeds showed poor and very poor flow properties, respectively, on both CI and HR ($p < 0.001$). However, they displayed passable flow property and comparable results on angle of repose ($p = 0.103$). Disparity in the flow property results between CI and HR, and angle of repose may be caused by the qualitiveness of the measurements and their scaling (Shah *et al.*, 2008).

Table 2: Physicochemical properties of the starch from yellow *M. indica* and *A. heterophyllum* seeds.

Parameter	Yellow <i>M. indica</i> seed starch	<i>A. heterophyllum</i> seed starch
Bulk density, g/mL	0.28 ± 0.016	0.35 ± 0.002
Tapped density, g/mL	0.40 ± 0.017	0.56 ± 0.01
CI, %	29.54 ± 1.14*	37.90 ± 0.79
HR	1.42 ± 0.023*	1.61 ± 0.020
Angle of repose, °	45.24 ± 2.02	42.50 ± 1.00
Amylose/amylopectin ratio, %	15.59 ± 1.49*/76.39 ± 3.34	23.36 ± 3.96/69.16 ± 4.01
Swelling power, g/g	15.71 ± 0.84*	12.02 ± 1.40
Solubility, %	7.19 ± 0.44*	13.96 ± 0.77
Final viscosity, cP	1590.00 ± 151.33*	428.33 ± 65.21

*Significant difference ($p < 0.05$) between starch samples. CI – Compressibility index, HR – Hausner ratio.

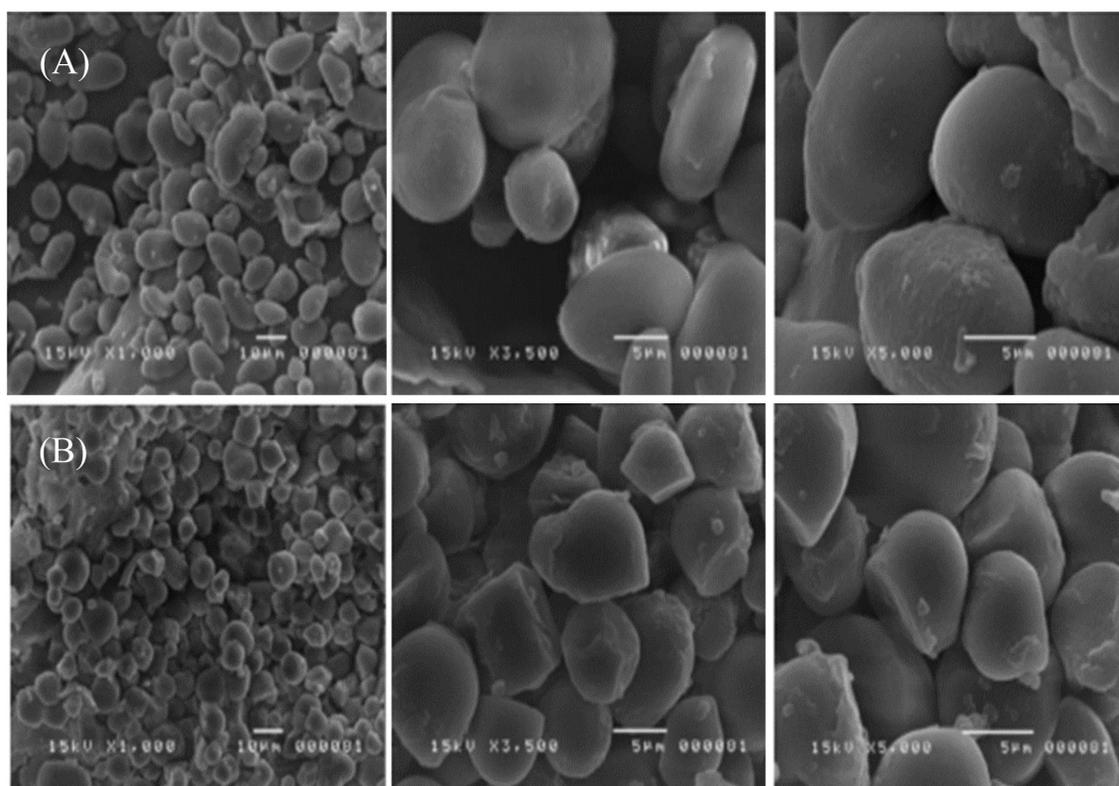


Fig. 1: Scanning electron micrographs of starch isolated from (A) yellow *M. indica* seeds and (B) jackfruit seeds.

The poor powder flowability of the starch isolated from yellow *M. indica* and *A. heterophyllum* seeds may be attributed to their distinct morphological features, with regards to size and shape. Both the granules of yellow *M. indica* (Figure 1A) and *A. heterophyllum* (Figure 1B) seed starches have slightly smooth surface, with sizes ranging from 7-20 µm classified under small to medium granules (Builders and Arhewoh, 2016). The yellow *M. indica* seed starch has elongated granules while *A. heterophyllum* has smaller round granules. Irregular, rod-shaped granules and small particle size have been reported to decrease bulk

density, leading to poorer flowability (Lahdenpää *et al.*, 1996). This is caused by strong interparticle interaction that results to interlocking. In turn, this leads to formation of arches, cakes and ratholes (Seville *et al.*, 1997).

Two important constituents of starch are amylose and amylopectin. Both of these polymers are composed of D-glucose units, with the straight-chain amylose exhibiting $\alpha(1\rightarrow4)$ linkages and the branched amylopectin containing $\alpha(1\rightarrow4)$ and $\alpha(1\rightarrow6)$ linkages. Determination of both polysaccharides is important as they affect the functionality of starch as excipients (Builders

and Arhewoh, 2016). The starch from yellow *M. indica* seeds demonstrated significantly lower amylose content ($p = 0.033$) relative to *A. heterophyllum* seed starch. The value of amylose obtained from both starches were similar to those reported on previous literatures (Hassan *et al.*, 2013; Tulyathan *et al.*, 2002). However, amylopectin content of both starches displayed comparable results ($p = 0.074$). It is noted that the sum of amylose and amylopectin contents of the starch samples was not equal to 100%. This observation is in accordance with the study of Wang *et al.* (2010) that the commonly used formula for amylopectin content, which is 100% less % amylose content, corresponds to the theoretical but not the actual amylopectin content.

Solubility, swelling power and viscosity are parameters that contribute to disintegrant and paste characteristics of starch. Starch granules start to absorb water and swell upon application of heat. Further increase in temperature leads to swelling and solubility. As maximum swelling is achieved, disintegration of swollen granules occurs, resulting to changes in viscosity (Builders *et al.*, 2010). The starch obtained from the yellow *M. indica* seeds displayed significantly lower solubility ($p < 0.001$) but significantly higher swelling power ($p = 0.017$) and final viscosity ($p < 0.001$) compared to *A. heterophyllum* seeds. This corroborated with earlier studies that higher swelling power and lower solubility may be due to irregular shape and large granule size of starches (Singh *et al.*, 2003). The larger, irregular, rod-shaped granules of yellow *M. indica* seed starch relative to *A. heterophyllum* seed starch aid in reducing the mobility of the starch, even at high swelling capacity, leading to lower solubility values. Previous studies have also reported the direct association of amylopectin content with swelling capacity. Amylopectin, due to its highly branched structure, takes up water easily resulting to increased swelling, while amylose has been reported to restrict initial swelling (Lin *et al.*, 2015; Singh *et al.*, 2003). The negative correlation between the amylose content and final viscosity has been attributed to the strong molecular interaction of amylose molecules and their ability to complex with lipids (Singh *et al.*, 2003), which inhibits the development of viscosity (Tziotis *et al.*, 2005).

Table 3: Physicochemical properties of the starch from yellow *M. indica* seeds and *A. heterophyllum* based on the USP specifications for potato, wheat, tapioca, rice and corn starch.

Parameter	Yellow <i>M. indica</i> seed starch	<i>A. heterophyllum</i> seed starch	USP specifications
Identification	Conforms	Conforms	Orange-red to dark blue color
Loss on drying (LOD), %	7.33 ± 0.68	8.05 ± 0.14	< 15
pH (as 20% starch)	4.59 ± 0.072*	6.08 ± 0.01	4.5-8.0
Limit of iron, ppm	< 10	< 10	< 10

*Significant difference ($p < 0.05$) between starch samples.

The starch obtained from the yellow *M. indica* and *A. heterophyllum* seeds conformed with the criteria set by the USP for potato, wheat, tapioca, rice and corn starch, as presented in Table 3. The starch samples turned dark blue in color due to the amylose-iodine complex formed after the addition of iodine-potassium iodide solution. LOD is a measure of the amount of water and

volatile matter present in the sample at specified drying conditions, which affects the physical, chemical and microbiological properties of the excipient and finished product (Gerhardt, 2009). The LOD of starch samples displayed comparable results ($p = 0.149$) and met the USP specifications of official starches. The pH value ($p < 0.001$) and limit of iron of the isolated starches were also within the limits set by the USP.

The quality control tests of the formulations are shown in Table 4. Uniformity of tablet weight and thickness are important parameters that indicate the amount of the active pharmaceutical ingredient present in the dosage form and ensure good packing of tablets (Nguwalka *et al.*, 2010). Both tablets formulated using yellow *M. indica* and *A. heterophyllum* seed starch as binder and disintegrant displayed acceptable uniformity of tablet weight and did not deviate in the allowable 5% difference in weight (USP, 2017), with yellow *M. indica* seed starch tablets showing significantly higher average weight compared to *A. heterophyllum* ($p < 0.001$). Thickness can vary with no change in weight because of the difference in the density of granulation and the pressure applied to the tablets, as well as the speed of tablet compression (Allen, 2013). This resulted in yellow *M. indica* seed starch tablets displaying significantly higher thickness in comparison to *A. heterophyllum* ($p < 0.001$).

Table 4: Quality control tests of paracetamol tablet formulation using starch from yellow *M. indica* and *A. heterophyllum* seeds as binder and disintegrant.

Parameter	Yellow <i>M. indica</i> seed starch	<i>A. heterophyllum</i> seed starch	Acceptance criteria
Average tablet weight, mg	637.90 ± 5.49*	620.80 ± 5.53	544 – 648
Percent difference in weight, %	0.86	0.89	5 ^a
Thickness, mm	5.24 ± 0.041*	5.07 ± 0.036	-
Hardness, kg	4.10 ± 0.21*	8.40 ± 0.30	4–10
Friability, %	0.68 ± 0.025	0.68 ± 0.026	nmt 1.00 ^a
Disintegration time, s	66.67 ± 15.2*	328.00 ± 25.16	1800
Dissolution test (as Q), %	96.00 ± 0.56	95.69 ± 0.33	nlt 80 ^a
Assay, %	101.46 ± 0.12*	97.15 ± 1.64	nlt 90 but nmt 110 ^a

*Significant difference ($p < 0.05$) between starch samples. ^aAcceptance criteria based from the USP 40 Acetaminophen Tablets Monograph. Nmt – not more than, nlt – not less than.

Tablet hardness for both yellow *M. indica* and *A. heterophyllum* seed starch batches met the specification for uncoated tablets, with *A. heterophyllum* exhibiting significantly higher value than yellow *M. indica* ($p < 0.001$). For friability, yellow *M. indica* seed starch tablet batches showed comparable results with *A. heterophyllum* ($p = 0.882$) and conformed to the criteria specified in the USP (2017). These indicate that the produced tablets will be able to resist mechanical stress conditions such as coating, packaging, storage, transportation and further processing (Allen, 2013). These parameters also affect the disintegration time and dissolution rate of the tablets (Ansel *et al.*, 1999).

Disintegration test is a measurement of the time required for the tablet to disintegrate into particles under a given set of conditions (Allen, 2013). While both batches contain the same amount of disintegrant, the yellow *M. indica* seed starch

tablet batch exhibited significantly faster disintegration time as compared to *A. heterophyllus* ($p < 0.001$). High amylose content has been known to resist swelling and disintegration (Reddy *et al.*, 1994). Nonetheless, the produced tablets passed the acceptance criteria for disintegration time.

The rate and extent of absorption, and therapeutic outcome of a drug is determined by the dissolution rate (Nguwalka *et al.*, 2010). Dissolution is affected by the type and concentration of binder, hardness, solubility of the drug, manufacturing process and diluents. Drug release of tablets with yellow *M. indica* and *A. heterophyllus* seed starch conformed with the USP specification and displayed comparable Q values ($p = 0.283$). The assay of acetaminophen (paracetamol) tablet using yellow *M. indica* and *A. heterophyllus* seed starch passed the allowable specifications (USP, 2017). The significant difference in the percentage potency between batches ($p = 0.010$) may be attributed to the differences in tablet weight, thickness, hardness and disintegration times.

CONCLUSION

This study investigated the physicochemical, binder and disintegrant properties of starch collected from yellow *M. indica* and *A. heterophyllus* seeds as potential excipients in paracetamol tablet formulation. The considerable differences in the physicochemical properties of starches were probably due to the distinctiveness of starch isolated from different sources. Although both starches demonstrated passable to poor flow properties, it conformed with the USP specifications for physicochemical properties of official starches, and quality control tests for acetaminophen (paracetamol) tablet. Thus, utilization of seeds from yellow *M. indica* and *A. heterophyllus* provides economically viable sources of starch for pharmaceutical use. Modifications in the extraction method can be conducted to improve flowability. Further study on the use of the yellow *M. indica* seed starch as superdisintegrant is also recommended, due to its fast disintegration at low concentration.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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