CHARACTERIZATION OF EXTRACTED MICROCRYSTALLINE CELLULOSE FROM *Theobroma cacao* POD HUSK AS BINDER IN PARACETAMOL TABLET FORMULATION

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ABSTRACT

This study investigated the properties of the extracted microcrystalline cellulose from *Theobroma cacao* pod husk on its action as an alternative binder in the formulation of paracetamol tablets. Specifically, it aimed to determine the organoleptic properties and the physicochemical properties of the extracted MCC and the most effective concentration on its binding property compared with the standard binder, Avicel®. In the formulation of the tablet, the dry and wet granulation method was used. Furthermore, statistical analysis using a non-parametric analysis of variance (Kruskal-Wallis method) showed that the two concentrations of the extracted MCC (5%, and 10%) have a significant effect as an alternative binder in the formulation of paracetamol tablet. Comparing the three doses of the extracted MCC in terms of hardness, 2% concentration, and 5% concentration has not shown any significant differences, meaning they have equal effect. Comparing the concentrations with the positive control, 10 % concentration does not show any significant difference. On the other hand, comparing the concentrations in terms of their friability, results showed that the three concentrations do not have any significant differences, meaning they have equal effect. Comparing them with the positive control, three concentrations have shown a significant difference. In terms of their time to disintegrate, 10% and 5% concentration has no significant difference, same with the 5% and 2% concentration. Comparing with the positive control, 5% concentration has shown no significant difference. Dissolution testing was also performed under standard body temperature using a 6.8 pH phosphate buffer, using the three concentrations; results have shown that there is no significant difference between the three, meaning, they have the same effect in dissolving. Comparing with the positive control, the 5% concentration has shown no significant difference; meaning, it exhibits the same effect as of that of the positive control. Based on the gathered and analyzed data, the researchers, deemed to highlight that *Theobroma cacao* extracted microcrystalline cellulose is applicable as an alternative binder in the formulation of paracetamol tablets.

Keywords: *Theobroma cacao, microcrystalline cellulose, binder, Avicel*

INTRODUCTION

One of the most prevalent methods of drug delivery system is solid oral dosage form. Tablets, as the lightest and most compact of all dosage form, are

known as one of the most popular of these forms which contains medicaments and usually varies in shape from circular, flat or biconvex. The advantages of Tablets include the ease of manufacturing, dispensing and maintaining accuracy of dosage and also considered as more stable than other dosage forms. These are favored by most patients due to its affordability, non-invasiveness and convenience (Taylor, 2010).

According to a need assessment conducted by the World Health Organization (WHO) in 2014, fifteen percent (15%) of the Nigerian citizens, and fifty-nine percent (59%) of the Swiss population prefer solid dosage forms over the other drug preparations. Aside from the Active Pharmaceutical Ingredient (API), excipients or inactive substances are also added to comprise a tablet formulation. Among the excipients which serve a crucial function in the manufacturing process are binders. Binders serve as an adhesive that bind the ingredients together to minimize tablet friability and provide mechanical strength, without affecting dissolution properties (Arceo, et al 2017). As stated in a study of Aistars et al in 2010, binder has three types -natural polymers, sugars, and synthetic polymers- that is to have an optimal binding property based on ease of processing, good compressibility, and non-friable tablets with reasonable dissolution.

Theobroma cacao L. is a small evergreen tree that is a notable source of chocolate and cocoa powder and is considered as an important investment in agro-industrial production (Marsiglia, et al, 2016). Reports have shown that each ton of dry cocoa beans represents ten tons of cocoa pod husk. Presently, cocoa pod husks are causing environmental pollution problem in cocoa producing areas of the world. They serve as potential sources of disease transmission when used as much in cocoa farms (Shodehinde and Adamson, 2017).

A vast majority of pharmaceutical binders are derived from natural sources. An example of which is microcrystalline cellulose (MCC), the most abundant natural polymer on earth with an annual biomass production of 50 billion tons (Carlin, 2008). It is used as a tablet excipient in pharmaceutical industry due to its excellent compressibility, outstanding dry binding properties, low lubricant requirement and very low residual die wall pressure (Arceo et. al., 2017). In a study entitled Extraction, Optimization, Characterization of Microcrystalline cellulose from *Theobroma cacao L.* (Fam. Malvaceae) Pod Husk as binder, microcrystalline cellulose is successfully extracted from the T. cacao's pod husk. MCC is characterized as white or almost white, odorless, free flowing crystalline powder, and also a Purified, partially depolymerized cellulose prepared by treating alpha-cellulose, obtained as a pulp from fibrous plant material with mineral acids.

Research Questions

Generally, this study aimed to evaluate the extracted microcrystalline cellulose from *Theobroma cacao* pod husk as binder in Paracetamol Tablet Formulation.

Specifically, this aimed to answer the following questions:

1. What are the characteristic properties of the extracted MCC from *Theobroma cacao* pod husk in terms of?
    a. Organoleptic properties
        a.1. Color
        a.2. Odor
    b. Physicochemical Properties:
        b.1. Solubility
        b.2. pH
        b.3. Densities
        b.4 Compressibility index
        b.5 Angle of repose
        b.6 Particle size distribution
        b.7 Swelling index
        b.8 Moisture content
2. What is the compatibility test result between the extracted microcrystalline cellulose and the active pharmaceutical ingredient (API) and other excipients?
    a. Paracetamol
    b. Lactose
    c. Corn starch
    d. Talc
    e. Magnesium Stearate
3. Is there significant difference between the positive control and the different extract concentration (2%, 5%, 10%) in terms of:
    a. Hardness
    b. Friability
    c. Disintegration
    d. Dissolution

Hypotheses

Ho1: There is no significant difference in the hardness of different concentration (2%, 5%, 10%) and the positive control.

Ho2: There is no significant difference in the Friability of different concentration (2%, 5%, 10%) and the positive control.

Ho3: There is no significant difference in the disintegration time of different concentration (2%, 5%, 10%) and the positive control.

Ho4: There is no significant difference in the dissolution of different concentration (2%, 5%, 10%) and the positive control.

Significance of the Study

This study helped in the waste management of cacao pod husk which is usually thrown after getting the seeds for chocolate production; hence there was an efficient utilization of these wastes. Through evaluating the effectiveness of the extracted microcrystalline cellulose from T. cacao pod husks used as binder in Paracetamol tablet, this study provided a potential alternative source for commercially produced tablet binders used by drug developers and pharmaceutical industries.

Literature Review

Cacao Pod Husk

The chemical composition of the cocoa pod husks from Malaysia are the following (in % w/w of dried pod husks): Holocellulose, 74.0±0.81; Cellulose, 35.4±0.33; Hemicellulose, 37.0±0.50; Lignin, 14.7±0.35; (Daud, et al, 2013). It is essential to improve the sustainability in economic, environmental and social aspects of the cocoa value chain by converting by products of cocoa production such as cocoa pod husks and cocoa pulp into a valuable new product which could be commercialized such as microcrystalline cellulose (MCC). Nanomaterial such as microcrystalline cellulose (MCC) is highly potential profitable as binding agent that is commonly used in tablet making for pharmaceuticals and naturally derived stabilizer (Zailani I.S.A., et al, 2016).

Pharmaceutical Excipients

Natural polysaccharides are widely used in the pharmaceutical and food industry as excipients and additives due to their low toxicity, biodegradable, availability and low cost. Excipients are essential ingredients of a dosage form which are added to increase volume, aid flow, enable compactness and make a drug convenient to administer. They can also be used to modify the release of drug, thereby, influencing the absorption and subsequent bioavailability of the incorporated drug (N. C. Ngwuluka, et. al, 2010). Excipients are pharmacologically inactive substances that are formulated with the active ingredient in drugs. Most common types of excipients include binders. Microcrystalline cellulose is widely used in the pharmaceutical industry. Apart from being physiologically inert, MCC is

an excellent excipient because of its compressibility in solid dosage forms. Microcrystalline cellulose is mostly used as filler binder in both wet or dry formulation and direct tablet compression. Its popularity in direct compression is due to its excellent binding properties when used as a dry binder. MCC also has disintegrant and lubricant properties. It combines two useful properties of tablet vehicle; it can produce very hard tablets and yet these tablets disintegrate rapidly in water due to swelling of the MCC particles and destruction of the bonding forces holding them together (John Macuja, et. al, 2015).

Microcrystalline Cellulose

MCC is an important ingredient as an excipient in the formulation of tablets. In the study of Ogaji, et al, excipients are defined as substances, other than the active drug of finished dosage form, which have been appropriately evaluated for safety and are included in a drug delivery system to either aid the processing of the drug delivery system during its manufacture, protect, support, or enhance stability, bioavailability, or patient acceptability. Excipients play a very important role in the production of medicine tablets. They help preserve the efficacy, safety, and stability of active pharmaceutical ingredients (APIs) and they ensure that the drug delivers its promised benefits to the patients. Optimal use of excipients can provide pharmaceutical manufacturers with cost savings in drug development, enhanced functionality, and help in drug formulations innovation. The crucial role and application of natural polymeric materials such as microcrystalline cellulose in the pharmaceutical industry is attributed to the fact that it is a biodegradable and toxicologically harmless raw material of low cost and relative abundance. Natural polysaccharides such as MCC are also derived from natural resources that are renewable and can be cultivated or harvested in a sustainable manner. This can provide a constant supply of raw material for the production of commercial MCC (John Macuja, 2010)

Finished Product Quality Control Test

A tablet should pass a set of specifications to be a quality drug. Finished Product Quality Control test (FPQC test) will be used to ensure that the product will meet the standards needed for a product, to be approved before releasing in the market. An FPQC test is a tool significant in determining the product's characteristics both qualitatively and quantitatively, with its procedures and acceptance limit, in which the finished product must comply with. FPQC test involved Disintegration Testing, Dissolution Testing, Friability Testing, and Hardness Testing (Balamuralidhara V., et al. IRJP, 2011).

Disintegration is the first important process, in which the substance will be in smaller particles. As the substance will be in smaller particles, it will be of great importance for the availability of the contents in the body. Disintegration test is an important tool in determining the quality of the product, specifically disintegration

rate. It is developed to measure the products disintegrating property to efficiently liberate the active ingredients for permission to be absorbed.

Friability is important for it will be used to measure the ability of the tablet to withstand mechanical shock. It will be one of the determining factors for the tablets standard to be qualified, which can be measured using Roche Friabilator. This test will be needing twenty tablets to be weighed and placed in the friabilator and then run at 25 rpm for 4 minutes (Sahab Uddin, et al, 2015).

Hardness testing will be used to test the breaking point of the tablet. It will be significant in knowing the integrity of a tablet before storing, handling and using. Hardness test will be measured using Stokes Monsanto Hardness Tester (Sahab Uddin, et al, 2015).

Research Paradigm

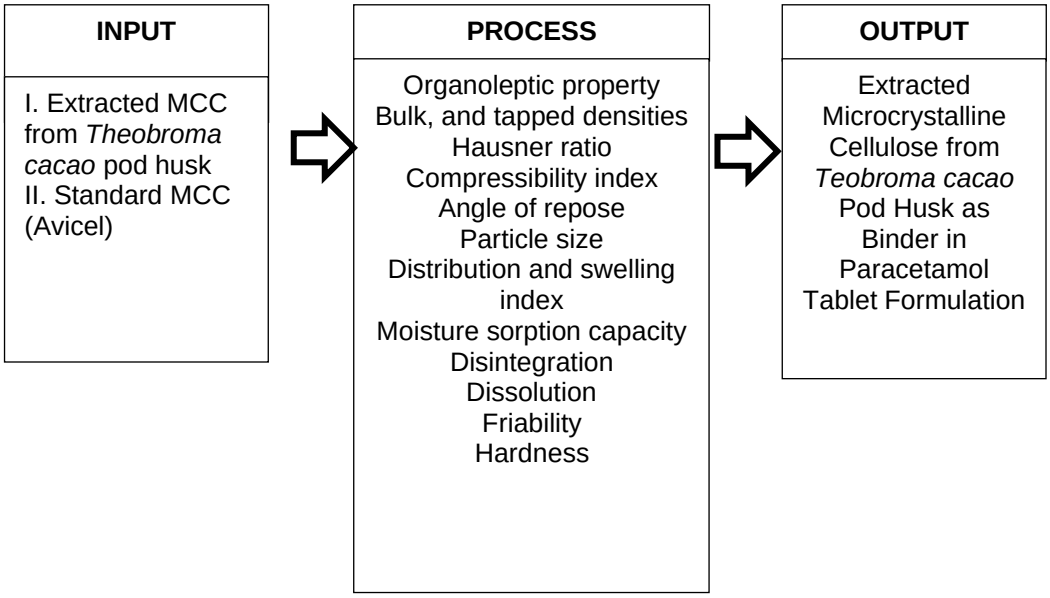

Figure 1. Research Paradigm

The figure above shows how the modifying variable, which is the extracted microcrystalline cellulose from T. cacao pod husks as the experimental control and the positive control which is the commercially produced binders (AVICEL MCC), affect the dependent variables when used as binder excipient in Paracetamol tablet formulation.

METHODS

Research Design

Descriptive Experimental method was used in this research study.

Subject of the Study

The plant sample of *Theobroma cacao* pod husk was collected in Cavite last January 2019. The dried sample collected was cleaned by dusting off the dirt and was crushed and milled into small pieces.

Sample Technique

The botanical verification and authentication of the plant material was done at the Department of Agriculture, Bureau of Plant Industry, Tuguegarao Cagayan.

Procedure of Data Gathering

The following procedures conducted during the laboratory experimentation:

1. **Extraction of Microcrystalline Cellulose** (Arceo et. al, 2017)
   - **1.1.** For 25 grams of dried and milled CPH, 500 mL of 2% w/v sodium hydroxide will be added and digested at hydrolysis temperature (80±10OC) for 5 hours.
   - **1.2.** Then, the resulting mixture will be filtered and washed with distilled water.
   - **1.3.** The extracted material will be then pre-bleached with 500 mL of 1:1 aqueous dilution of sodium hypochlorite at 60±10OC for 15 minutes.
   - **1.4.** It will be washed sufficiently with water and treated with 500 mL of 12% w/v sodium hydroxide at the different base hydrolysis temperatures for 1 hour.
   - **1.5.** The resulting alpha-cellulose will be washed thoroughly with distilled water.
   - **1.6.** The obtained alpha-cellulose will be bleached with 1:1 aqueous dilution of sodium hypochlorite at room temperature for 1 hour and subsequently wash with water until neutral.
   - **1.7.** The cellulose material will be filtered, which will be dried in a hot air oven at 60°C.
   - **1.8.** For 5 grams of the extracted alpha-cellulose, 83 mL of 2.5N hydrochloric acid will used for acid hydrolysis at different temperatures (60±10OC, 80±10OC, and 100±10OC) for 15 minutes.

1.9. The hot acid mixture will be poured into 150 mL of cold tap water which will follow by vigorous stirring and allow to stand overnight.

1.10. The obtained microcrystalline cellulose will be filtered, washed with water until neutral, filtered, pressed and dried in a hot air oven at 60°C.

2. Identification of Microcrystalline Cellulose (USP)

2.1. Prepare Iodinated Zinc Chloride Solution by Dissolve 20g of zinc chloride and 6.5g of potassium iodide in 10.5 mL of water.

2.2. Add 0.5g of iodine, and shake for 15 minutes.

2.3. Place the 10 mg sample on a watch glass, and disperse in 2 mL of Iodinated zinc chloride solution.

2.4. The substance takes on a violet- blue color.

3. Physical Testing

3.1. Organoleptic Evaluation

The color, odor, taste and appearance of the extracted microcrystalline cellulose was examined.

4. Phytochemical screening (Virtual Amrita Laboratories Universalizing Education, 2011)

4.1. Molisch's Test

4.1.1. 2 mL of a sample solution was placed containing the extracted cellulose in a test tube.

4.1.2. Two drops of Molisch's reagent (solution of alpha-naphthol in 95% ethanol) was added.

4.1.3. The resulting solution was added into a test tube containing 2 mL of concentrated sulfuric acid.

4.1.4. A positive test for the presence of cellulose is indicated by the formation of a purple-colored layer at the junction.

4.2. Fehling's Test

4.2.1. 2 mL of the test sample was placed in a test tube.

4.2.2. Equal volumes of Fehling's A and Fehling's B solution were mixed, and added to the test tube.

4.2.3. Placed the mixture in a boiling water bath for a few minutes.

4.3. Benedict's Test

4.3.1. 2 mL of Benedict's reagent was placed in a test tube.

4.3.2. 5-6 drops of the test sample were added and mixed well.

4.3.3. The test tube was placed in a boiling water bath for 5 minutes and observed any change in color or precipitate formation.
4.3.4. The solution was cooled and observed the color change from blue to green, yellow, orange, or red.

4.4. Iodine Test

4.4.1. 2 mL of the test sample was placed in a test tube.
4.4.2. Two drops of iodine solution were added.
4.4.3. A positive test shows formation of a blue-black color.

5. Physicochemical Properties

5.1. **Solubility** (Arceo et al, 2017)

1 part of sample was dissolved per solvent using *Table 1* as reference. Solubility using water, ethanol (95%), and dilute hydrochloric acid as solvents.

Table 1. *Solubility*

Solubility Terms Descriptive Term	Parts of Solvent Required for 1 Part of Solute
Very Soluble	Less than 1
Freely Soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly Soluble	From 30 to 100
Slightly Soluble	From 100 to 1000
Very Slightly Soluble	From 1,000 to 10,000
Insoluble	10,000 and over

5.2. ***pH*** (USP 2009)

5.2.1. 5 g of the extracted cellulose was shaken with 40 mL of carbon dioxide-free water for 20 min and centrifuge.
5.2.2. pH of the supernatant liquid using a pH meter was determined.

5.3. ***Loss on Drying*** (USP 2009)

5.3.1. An appropriate glass-stoppered, shallow weighing bottle was dried for 30 minutes.
5.3.2. Cooled to room temperature.
5.3.3. The weighing bottle was tared.
5.3.4. 1 to 2 g of test specimen was placed in the bottle, replaced the cover and accurately weighed the bottle and the contents.
5.3.5. The loaded bottle was placed in the drying chamber.
5.3.6. The specimen was dried at 105°C for 3 hours.

5.3.7. Upon opening the chamber, close the bottle promptly, and allow it to come to room temperature in a desiccator before weighing.

5.3.8. The sample loses NMT 7 % of its weight.

5.4. Sieve Analysis (USP 2009)

5.4.1. Individual empty sieves and receiving pan were weighed.

5.4.2. Arrange sieves in descending order. 25 g of extracted cellulose was introduced on the top sieve.

5.4.3. The set-up was shaken for 5 minutes.

5.4.4. The weight of material retained on each sieve was determined by subtracting the weight of the empty sieves from the weight of sieves containing the extracted cellulose.

5.5. Bulk Density (USP 2009)

5.5.1. 5 g of extracted cellulose was introduced into a dry 50 mL cylinder without compacting.

5.5.2. The powder was leveled without compacting.

5.5.3. The unsettled apparent volume was read.

5.5.4. The bulk density was calculated, in g per mL by the formula:

$$Tapped\ density = \frac{Weight}{Bulk\ volume}$$

5.6. Tapped Density (USP 2009)

5.6.1. The cylinder was tapped 500 times initially.

5.6.2. The tapped volume was measured.

5.6.3. The tapping was repeated with an additional of 750 times.

5.6.4. The tapped volume was measured.

5.6.5. The difference between the two volumes should be less than 2%.

5.6.6. Repeated tapping in increments of 1,250 taps until the difference between succeeding measurements is less than 2%.

5.6.7. The tapped density was calculated, in g per mL by the formula:

$$Tapped\ density = \frac{Weight\ final}{Tapped\ volume}$$

5.7. Angle of Repose (USP 2009)

5.7.1. Funnel was stoppered with a steel spatula.

5.7.2. The funnel was filled with the extracted cellulose.

5.7.3. The steel spatula was released and allowed the extracted cellulose to flow down.

5.7.4. The funnel height should be maintained approximately 2-4 cm from the top of the powder pile.

5.7.5. The angle of repose was determined by measuring the height and base of the cone of powder and using the formula:

$$\tan(\theta) = \frac{Height}{0.5\ base}$$

The flow property was determined with Table 2

Table 2. *Angle of Repose*

Scales of Flowability Flow Character	Angle of Repose (°)
Excellent	25-30
Good	31-35
Fair	36-40
Passable	41-45
Poor	46-55
Very Poor	56-65
Very Very Poor	>66

5.8. Compressibility Index (USP 2009)

The Compressibility index was calculated using the formula:

$$Compressibility\ index = \frac{Tapped\ Density - Bulk\ Densty}{Tapped\ Density} x100$$

The flow property was determined with Table 3.

Table 3. *Compressibility Index*

Scales of Flowability Flow Character	Carr's Compressibility Index (%)
Excellent	≤10
Good	11-15
Fair	16-20
Passable	21-25
Poor	26-31
Very Poor	32-37

Very Very Poor	>38

5.9. Hausner's Ratio (USP 2009)

The Hausner ratio was determined by the formula:

$$Hausner's\ Ratio = \frac{Tapped\ Density}{Bulk\ Density}$$

The flow property was determined with Table 4

Table 4. *Hausner's Ratio*

Scales of Flowability **Flow Character**	**Hausner Ratio**
Excellent	1.00-1.11
Good	1.12-1.18
Fair	1.19-1.25
Passable	1.26-1.34
Poor	1.35-1.45
Very Poor	1.46-1.59
Very Very Poor	>1.60

5.10.Swelling Capacity (USP 2009)

5.10.1. The tapped volume occupied by 3 g of the powder was noted.

5.10.2. The powder is dispersed in 85 mL of water and diluted to 100 mL with water.

5.10.3. After 24 hours of standing, the volume of the sediment was measured.

5.10.4. The swelling capacity is computed using the formula:

$$\text{Swelling capacity} = \frac{Volume\ of\ sediment}{Volume\ of\ Tapped\ Powder}$$

5.11. Moisture Sorption Capacity (USP 2009)

5.11.1. One gram of the sample was accurately weighed and evenly distributed over the surface of a 70 mm tared Petri dish.

5.11.2. The samples are then placed in a large desiccator containing distilled water in its reservoir at room temperature.

5.11.3. The weight gained by the exposed samples over a five-day period will be recorded and the amount of water absorbed will be calculated from the weight difference.

$$\text{Moisture sorption capacity} = \frac{Weight\ after\ exposure - weight\ before\ exposure}{weight\ before\ exposure} x100$$

6. *Compatibility* Testing (Concepcion et, al 2014)

1. Samples containing the dry mixture of ingredients will be placed in two wide mouth amber bottles.
2. These will be covered, cleaned, and sealed by a lined black plastic cap.
3. For each sample, one bottle will be stored in room temperature while the other will be at 40° Celsius for one month.
4. Samples will be observed weekly for caking, liquefaction, discoloration, odor, and gas formation.

Table 5. *Composition of sample for Compatibility Testing*

Amber Bottle	Sample Mixture
1 and 2	2:1 Paracetamol and Extracted Microcrystalline cellulose
3 and 4	1:1 Magnesium stearate and Extracted Microcrystalline cellulose
5 and 6	1:1 Lactose and Extracted Microcrystalline cellulose
7 and 8	1:1 Corn starch and Extracted Microcrystalline cellulose
9 and 10	1:1 Talc and Extracted Microcrystalline cellulose

7. *Production* of tablets through wet granulation (N. C.Ngwuluka et. al, 2010)

1. Wet granulation method of tablet manufacturing was employed with Microcrystalline Cellulose (MCC) from *Theobroma cacao* pod husk as a binding agent and water as the granulating liquid.
2. Batches of paracetamol tablets were formulated using 2%, 5%, and 10% w/w of the MCC.
3. Paracetamol, lactose, extracted MCC from T. cacao and corn starch were blended to form a damp coherent mass which was screened through a sieve No 10 and dried at 60°C for one hour.
4. Divide the Corn starch into two and incorporate it during wet blending and after drying of granules to act as an intragranular and extra granular disintegrant.
5. For comparative purposes, commercially produced paracetamol tablets were used as standard.

Table 6. *Composition of the paracetamol tablets at different concentrations of the binder*

Ingredients	Batch I (%) 2% binder	Batch II (%) 5% binder	batch III (%) 10% binder

Paracetamol	71.4	71.4	71.4
Lactose	19.6	16.6	11.6
Extracted microcrystalline cellulose (binder)	2	5	10
Corn Starch	5	5	5
Talc	1	1	1
Magnesium Stearate	1	1	1

8. Finished product quality control tests (USP, 2009)

8.1. *Hardness Test*

The hardness of each of the 10 tablets using Stokes Monsanto hardness tester were determined and it was expressed in kg/cm^2.

8.2. *Friability Test* (USP 2009)

1. Sample of tablets with total weight equivalent or as near as possible to 6.5 g was taken and recorded the weight.
2. The tablets were placed in drum and rotated the drum 100 times.
3. Tablets were removed and observed.
4. If there are cracked and/or chipped tablets, the sample automatically fails the test.
5. Weigh tablets and compute for percent loss which should not exceed 1.0%.

8.3. Disintegration test: (Thakur et al, IJPSR, 2016)

1. DT test was carried out according to USP specification.
2. Six tablets were placed in a disintegration filled with distilled water at 37±0.20C.
3. The tablets were considered completely disintegrated when all the particles passed through the wire mesh.
4. Disintegration times recorded are the mean of two determinations.

Dissolution (USP, 2009)

1. Drug release studies was conducted using the USP Dissolution test 1, apparatus 2, and paddle type at a rotational speed of 100 rpm at 37±0.5°C.
2. The dissolution media of use will be 900 mL of pH 6.8 phosphate buffer (adjusted with 0.2 N sodium hydroxide to a pH of 6.8+0.1) for three time points.
3. Sink condition was maintained during the whole experiment.

4. Samples (10 mL) was withdrawn at regular intervals and the same volume of pre-warmed (37±0.5°C) fresh dissolution medium will be replaced to maintain the volume constant.
5. The samples withdrawn was filtered and the drug content in each sample will be analyzed after suitable dilution with a UV spectrophotometer at 233 nm.
6. The dissolution test was performed in triplicate.

Data Analysis

Statistical means was computed based on the three formulations conducted for every test and evaluation through Kruskal-Wallis Rank Sum test.

RESULTS

Table 7. *Organoleptic Characterization of extracted cellulose testing*

Property	**Standard MCC**	**Extracted MCC (*Theobroma cacao*)**
Appearance	Amorphous	Amorphous
Odor	Odorless	Odorless
Color	White	Yellowish

Table 7 shows that the extracted microcrystalline cellulose from *Theobroma cacao* Pod husks has yellowish amorphous appearance with odorless and tasteless properties.

Table 8. *Physicochemical and phytochemical property of microcrystalline cellulose*

TEST	**AVICEL**		**EXTRACTED MCC**	
	Result	Remarks	Result	Remarks
Solubility 1. **Distilled water** 2. **Ethanol** 3. **Diluted HCL**	Insoluble Insoluble Insoluble		Insoluble Insoluble Insoluble	
pH	7.48	neutral	6.06	neutral
Loss on drying	0.4168-	PASS	4.8782	PASS
Bulk Density	0.3998		0.3866	
Tapped Density	0.6573		0.4838	

Angle of Repose	N/A	FAIL	25.8323	Excellent
Compressibility Index	39.0872	Very Very Poor	20.0775	Fair
Hausner's Ratio	1.6475	Very Very Poor	1.2566-	Passable
Swelling Capacity	1.1368		1.3055	
Moisture Sorption	14.50%		20.32%	
Particle size through sieve analysis	23.9 g pass through sieve no. 80	(less than 150 µm)	21.8 g pass through no. sieve 80	(less than 150 µm))

Table 8 showed the physicochemical properties of extracted MCC and the Standard MCC in which it shows that both the extracted and the standard MCC is insoluble in water, ethanol (95 %) and diluted HCl (2.5 N). According to the Excipient Monographs 2 USP 29- NF 24 page 3306, identification test (method A) for the extracted microcrystalline cellulose entailed the evidence of MCC within sample.

Moreover, the extracted MCC is more acidic compared to the standard MCC having a mean pH value of 6.06. Upon drying the sample of extracted MCC at 105 °C, having the percentage loss of 4.87 %, which is within the accepted value of not more than 7.0 % passed the specification.

Furthermore, particle size of the extracted MCC was determined through Sieve analysis. The particle sizes range from more than 850 µm to less than 150 µm and the majority of the particles are within the 150-180 µm size range.

The four phytochemical tests revealed the possible presence of cellulose in the extracted MCC. However, the Molisch's test doesn't show formation of a purple-colored layer at the junction. The Benedict's test showed Blue to Blue-green solution and Fehling's test showed no result of yellow or brownish-red precipitate. Iodine test showed negative result which means it is negative for starch and it entailed that the extracted MCC doesn't contain starch.

The bulk and tapped densities of the extracted MCC were 0.3866 and 0.4838 g/mL, respectively. The powder flowability of the extracted MCC was excellent and the compressibility index showed fair result. Hausner Ratio, swelling, and moisture sorption capacities of the extracted MCC were 1.2566, 1.3055, and 20.32%, respectively.

The compatibility results conducted to test if there are interactions that took place between the extracted binders and the other excipients and the API. Thus, the results showed that there are no compatibility problems that took place.

Table 9. *FPQC Test Result*

	POSITIVE CONTROL	**2%**	**5%**	**10%**
Hardness	17.91	5.07	11.88	18.09
Friability	0.02	0.07	0.02	0.01
Disintegration time	1 min and 29 sec (89 sec)	3 min and 37 sec (217 sec)	5 min and 12 sec (312 sec)	12 min and 10 sec (730 sec)
Dissolution	0.041	0.040	0.036	0.037

Table 9 shows the mean raw data of the finished product quality control of the paracetamol tablet subjected to different quality control procedures under specified parameters and specifications set by the USP.

Table 10. *Kruskal-Wallis Rank Sum test on Hardness Test of Paracetamol Tablet*

Treatment Groups	**df**	**x^2**	**p - value**	**Decision**
2% MCC Binder	3	32.983	0.0000	Reject Ho
5% MMC Binder				
10% MCC Binder				
Positive Control				

Table 10 shows that at p-value of 0.000 at alpha=5%, there is enough evidence to say that there is a statistically significant difference in the hardness between different concentrations of Theobroma cacao.

Since there is a significant difference on the hardness of the different concentration levels, multiple comparison using Dunn's Test can be obtained.

Table 10.1. *Multiple Comparison on Different Concentration Levels in terms of Hardness using Dunn's Test*

Treatment		**z Statistic**	**p - value**	**Decision**
10%	2%	4.8968188	0.0000*	Reject Ho
	5%	2.983999	0.0014*	Reject Ho

2%	5%	-1.9128199	0.0279*	Reject Ho
positive control	10%	0.2295384	0.4092	Accept Ho
	5%	-4.6672805	0.0000*	Reject Ho
	2%	-2.7544606	0.0029*	Reject Ho

Table 10.1 shows that 5% and 2 % concentrations have significant difference when compared to the positive control, which means that they didn't show the same hardness as to the positive control. Treatment 3 (10% conc.) and the positive control at p-value of 0.4092 at alpha of 5% has no significant difference, which means that the positive and the concentration of 10% of the binder has the same binding capacity in terms of their hardness. Hereby, that the 10% concentration of the extracted MCC is the best binder in testing their hardness.

Table 11. *Kruskal-Wallis Rank Sum test on Friability Test of Paracetamol Tablets*

Treatment Groups	df	X^2	p - value	Decision
2% MCC Binder	3	11.335	0.01005	Reject Ho
5% MMC Binder				
10% MCC Binder				
Positive				

Table 11 shows at alpha=5%, there is enough evidence to say that there is a statistically significant difference on friability between the different concentration levels.

Table 11.1. *Multiple Comparison on Different Concentration Levels in terms of Friability using Dunn's Test*

Treatment		z Statistic	p - value	Decision
10%	2%	0.957762	0.1691	Accept Ho
	5%	1.436644	0.0754	Accept Ho
2%	5%	0.478881	0.3160	Accept Ho
positive control	10%	3.273985	0.0005*	Reject Ho
	5%	2.316222	0.0103*	Reject Ho
	2%	1.837341	0.0331*	Reject Ho

Table 11.1 shows that the three concentration of the extracted MCC (2%, 5%, and 10%) compared to the positive control show significance difference, which means that the three concentrations didn't have the same friability capacity as to the positive control.

Table 12. *Kruskal-Wallis Rank Sum test on Disintegration Test of Paracetamol Tablets*

Treatment Groups	df	X^2	p-value	Decision
2% MCC Binder	3	10.385	0.01556	Reject Ho
5% MMC Binder				
10% MCC Binder				
Positive				

Table 12 shows that at alpha=5%, there is enough evidence to say that there is a statistically significant difference on disintegration between the different concentration levels.

Table 12.1. *Multiple Comparison on Different Concentration Levels in terms of Disintegration using Dunn's Test*

Treatment		z Statistic	p - value	Decision
10%	2%	2.038098	0.0208*	Reject Ho
	5%	1.019049	0.1541	Accept Ho
2%	5%	-1.019049	0.1541	Accept Ho
positive control	10%	3.057147	0.0011*	Reject Ho
	5%	1.019049	0.1541	Accept Ho
	2%	2.038098	0.0208*	Reject Ho

Table 12.1. shows that treatment 1 (2% conc.) and treatment 3 (10% conc.) at p-value of 0.0208 and at alpha=5 % have a significant difference, meaning that the two concentrations do not have the same time to disintegrate. The 10 % and 2 % concentrations compared to the positive control has significant difference, which means that the 10 % and 2 % concentrations do not have the same binding capacity in terms of disintegration time. Thus, treatment 2 (5% conc.) and the positive control (Avicel) at p-value of 01541 at alpha of 5% have no significant difference; meaning, the 5 % concentration of the extracted MCC has the same efficacy with that of the positive control in terms of their disintegration time. Furthermore, 5 % concentration has the best binding property in terms of disintegrating.

Table 13. *Kruskal-Wallis Rank Sum test on Dissolution Test of Paracetamol Tablets*

Treatment	df	x^2	p - value	Decision
2% MCC Binder	3	0.6051	0.02224	Reject Ho
5% MMC Binder				
10% MCC Binder				

Positive				

Table 13 shows that at alpha=5%, there is enough evidence to say that there is a statistically significant difference on dissolution between the different concentration levels.

Table 13.1. *Multiple Comparison on Different Concentration Levels according to Dissolution using Dunn's Test*

Treatment		z Statistic	p - value	Decision
10%	**2%**	-0.979715	0.1636	Accept Ho
	5%	0.922085	0.1782	Accept Ho
2%	**5%**	1.901801	0.0286*	Reject Ho
positive control	**10%**	-2.017061	0.0218*	Reject Ho
	5%	-1.037346	0.1498	Accept Ho
	2%	-2.939147	0.0016*	reject Ho

Table 13.1. shows that the treatment 1 (2 % conc.) and treatment 2 (5 % conc) show significant difference, meaning they do not have the same dissolution efficacy. Thus, the treatment 3 (10 % conc) and treatment 1 (2 % conc), compared to the positive control, show significant difference. Moreover, the table also shows that treatment 2 (5% conc.) and the positive control at p-value of 0.1498 at alpha=5% has no significant difference, meaning, that the 5 % concentration has exhibited the same effect in binding as of that of the positive control. Hence, this shows that the 5 % concentration, has the best binding capacity in terms of dissolution testing.

DISCUSSION

This research study was intended to evaluate the extracted microcrystalline cellulose from *Theobroma cacao* as an alternative binder in paracetamol formulation. To attain the objectives of the study, organoleptic assaying, phytochemical analysis and finished product quality control were performed by the researchers.

Physicochemical properties were attested for its compatibility in different excipients together with the active pharmaceutical ingredient. Particle size and moisture content are often considered as the most common critical material attributes with regard to MCC performance in direct compression (Thoorens, 2015). According to Nanostructures for Oral Medicine, humidity and the moisture content of the extracted microcrystalline cellulose has contributed to its high degree of hydrophilicity which aides in the easier dissolution of the cellulose. Particle size determination of the extract has an effect on its surface area, in which it is inversely proportional and it is directly proportional to the dissolution rate (USP,2009). Microcrystalline cellulose tablets will disintegrate and dissolve very slowly in solvents of a relatively low pH(Shangraw, et. al, 2018)

Based on the experiment performed and data gathered, the phytochemical analysis of the microcrystalline cellulose from *Theobroma cacao* has revealed that the sample didn't give a positive result on Molisch's test. In Benedict's tests, the solution has changed from blue to blue-green color which means that it doesn't contain reducing sugar which supported the Fehling's test that has no formation of yellow or brownish-red precipitate. Positive results in Fehling's test will show the said precipitates hence indicating the presence of reducing sugar. Cellulose is a natural polymer (polysaccharide) with a molecular repeat unit comprised of a pair of d- anhydroglucose ring unit joined by beta-1, 4-glycosidic oxygen linkages around which the molecular chain can be bent and twisted (Handbook of textile Fiber structure: Natural, regenerated, Inorganic acid, Specialist Fibres, 2009), which may indicate the possibility of that the extracted MCC to contain cellulose. In Iodine test, only starch will exhibit blue-black color; extracted MCC didn't showed blue-black coloration, proving that the extracted MCC was not a starch extraction. To further test the extracted MCC, Identification test was also performed to identify the presence of MCC and the Extracted MCC gives positive result.

As per USP, the compressibility Index and hausner's ratio are measures of the propensity of a powder to be compressed. The extracted MCC has Fair compressibility index and passable result in hausner's ratio. It showed that the extracted MCC has better property compared to the standard MCC which has a Very Very Poor compressibility index and Very poor Hausner's ratio. Furthermore, they are measures of the powder's ability to settle, and they permit an assessment of the relative importance of interparticulate interactions. In a free-flowing powder, such interactions are less significant, and the bulk and tapped densities will be closer in value (USP <616>). The bulk densities of the Extracted MCC and Standard MCC are 0.3866 and 0.3998, respectively. Tapped density of the Extracted MCC and Standard MCC are 0.4838 and 0.6573, respectively. With the near values of bulk and tapped densities of the extracted MCC, it showed better compressibility index and hausner's ratio compared to the standard.

The tablet formulation was composed of the active pharmaceutical ingredient (API), Paracetamol and other excipients with corresponding uses for the formulation. The extracted MCC was used as a binder excipient in the Paracetamol tablet formulation. An excipient must have an inert property, which is non-reactive to other ingredients of the tablet. Compatibility testing was done to determine that the extracted MCC was nonreactive to the Paracetamol API, Lactose, corn starch, talc, and magnesium stearate. The test was conducted in two (2) room conditions, the room temperature and Forty degrees Celsius. Color change, formation of gas, caking, liquefaction was not manifested.

Paracetamol tablets were formulated using the wet and dry granulation using 3 concentrations (2 %, 5%, 10 %) compared to the marketed microcrystalline cellulose, Avicel® as positive control. The tablets were subjected to quality control

to attest if they have passed the specifications and further analyzed statistically to check if they have a statistical difference with the positive control. Results have shown that the 10 % concentration of the extracted microcrystalline cellulose has shown no significant difference in terms of their hardness with the positive control. According to Jacob et al, tablet hardness has an effect in the dissolution time of the tablet, wherein, it is inversely proportional. In contrast, the higher the tablet hardness is, the lower the friability of the tablet (Gordon, 2008). Data have shown that the three concentrations have shown no significant difference, when compared to the positive control, it is determined that none of the following concentrations have the same efficacy in terms of friability. According to Kituzawa et al, the disintegration time of a plain uncoated tablet has no direct effect with the hardness of the tablet, but has a direct effect in terms of the dissolution. Based on the data gathered and analyzed, the 5 % concentration of the extracted microcrystalline cellulose has exhibited no significant difference in terms of the time to disintegrate. On the same manner, 5% concentration of the extract has also shown no significant difference with respect to the dissolution rate of the tablet in comparison with the marketed microcrystalline cellulose. Moisture content of the extracted microcrystalline cellulose has a strong interaction with respect to the rate of dissolution and the time the tablet has disintegrated (Gordon, 2008)

CONCLUSION

The researchers concluded that the 5% and 10% concentration of the extracted MCC is comparable with the commercially available binder. Thus, extracted microcrystalline cellulose from *Theobroma cacao* pod husks is efficacious as an alternative binder in the formulation of paracetamol tablet.

RECOMMENDATIONS

Based on the aforementioned findings and conclusions drawn, the following recommendations and suggestions are deemed significant:

1. Further use 20 % v/v hydrogen peroxide to treat alpha cellulose in bleaching process to attain white color of MCC.
2. Conduct tablet production using marketed binder (Avicel) with same concentrations with the extracted microcrystalline cellulose from *Theobroma cacao pod husks.*
3. Conduct tablet production using different active pharmaceutical ingredients and determine their compatibility.
4. Test the compatibility of each of the ingredients in one container.

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