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Green Synthesis of Biowaste-Derived Pectin from Pomelo (*Citrus Maxima*) Peel and Cacao (*Theobroma Cacao*) Pod Husk as Potential Pharmaceutical Excipient

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ABSTRACT

Recent developments in pharmaceuticals include the emergence of orally disintegrating tablets (ODTs) which offers a novel way of administering oral medication to patients suffering from dysphagia or difficulty in swallowing. This study aimed to obtain biowaste-derived pectin from pomelo (*Citrus maxima*) peels and cacao (*Theobroma cacao*) pod husks and evaluate its potential as disintegrant in ODTs. Furosemide was used as the model drug in this study. Through acid extraction process, pomelo and cacao yielded 3.66% and 2.80% of pectin, respectively. Furosemide, glucose, talc, crospovidone, and pectin were used in four ODT formulations through direct compression method. The process produced 40 tablets for each formulation. These were then evaluated in pre- and post-compression parameters. Results showed that Carr's index (10.46 to 18.75), Hausner's ratio (1.12 to 1.23) and angle of repose (31.64 to 40.62) as pre-compression parameters indicated that the powder blends were of good compressibility and flow ability characteristics, ensuring mixture homogeneity and their suitability for compression. As per post-compression parameters, tablets from different formulations had acceptable and insignificant weight variation (<±7.5%) and tablet thickness (<±5%) which meant that uniform tablets were produced. Moreover, tablets with cacao pectin showed superior performance in terms of wetting time (13s), water absorption ratio (47.95%) and disintegration time (73s) over tablets with pomelo pectin and crospovidone, a synthetic disintegrant. The hydrophilicity and good water uptake of pectin aided in the disintegration of the tablets. It was concluded that biowastes can be sources of pectin and that cacao pectin is a potential tablet disintegrant in ODTs.

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KEYWORDS: *biowaste, cacao, disintegrant, pectin, pomelo, ODT*

1. INTRODUCTION

1.1. Background of the Study

Tablets are considered to be the most common dosage forms that provide systemic administration of therapeutic agents. They are more preferred due to their ease of administration and transportation, stability, low production cost, versatility, pain avoidance and patient compliance. Scientists have innovated a novel drug delivery system known as orally disintegrating tablets or orodispersible tablets (ODTs). Tablets come in different types but ODTs have gained an increasing demand in the market (Abay and Ugurlu 2015).

The emergence of ODTs provided patients with a conventional means of receiving medications. The term, according to European and United States Pharmacopoeias, refers to tablets that dissolves or disintegrates quickly in the oral cavity without the need of water or of chewing (Dey and Maiti 2010).

ODTs provide a wide range of advantages for patients, both hospital-bound and outpatients, who have difficulty in swallowing – a condition called "dysphagia" which affects around 35% of the population (Singh, Bala and Gill 2019). It is very common across all age groups, with the greatest frequency in elderly patients, and clients suffering from various medical conditions including, but not limited to, stroke, cardiac problems, AIDS, Parkinson's disease, psychiatric problems, thyroidectomy, cancer patients receiving head and

neck radiation therapies, many other neurological disorders, as well as when water is not available during travels, motion sickness (kinetosis), sudden episodes of coughing during common colds, allergic conditions, and bronchitis.

These types of tablets must disintegrate fast in the buccal cavity while exhibiting a sufficient mechanical strength to withstand packaging and distribution (Pabari and Ramtoola 2012) Therefore, tablet excipients, especially disintegrants, must have properties to make it possible.

Disintegrants are essential components in a tablet formulation for ODTs as they should oppose the efficiency of the binding properties of other components and the compressional forces during tablet production. The majority of dispersible tablets purchasable in the market nowadays contain synthetic disintegrant formulations. The most common synthetic disintegrant is cross-linked polyvinylpyrrolidone (crospovidone), usually considered as a superdisintegrant. It was shown to have porous structure that facilitates water uptake into the tablet which enhance tablet disintegration – mechanisms referred to as wicking and swelling. However, synthetic polymers could possibly be unsafe and less effective (Alam, Parve and Sharma 2014; Pahwa and Gupta 2011).

Pectin is a naturally-occurring polysaccharide that is usually mainly found in citrus fruits. Its uses span from food production as a gelling agent to medicine as a diarrhea treatment. Lately, researches show that pectin is a promising excipient in drugs like disintegrant.

Biowaste-derived pectins from fruits and vegetables are much more preferred to synthetic materials because pectin is relatively inexpensive, locally- and internationally-available, non-irritating to mucosal linings, non-toxic, environment-friendly, devoid of any side effect, renewable and provide nutritional supplement (Malviya et al. 2010; Alam et al. 2014). This polymer is of newly emerging interest for the pharmaceutical companies across the globe potentially drawing billions of income-generations while adding value to the source wastes from the food industries (Venkatanagaraju et al. 2019).

Pomelo (*Citrus maxima*), the largest of its kind, is a native fruit to South and Southeast Asia. It is also a very common fruit in the Philippines and is available year-round. Being a citrus fruit with a thick skin, it is said to be a good source of pectin. Moreover, cacao (*Theobroma cacao*), is a primary crop in the Philippines as the country produces 15,000 metric tons of the fruit but only its seeds are utilized for chocolate production (DOST-PCCAARD n.d.). These fruits are very common in the Philippines but consuming the fruits leave behind peels that were not used.

On the other hand, furosemide is a potent loop diuretic used in the treatment of congestive heart failure, cirrhosis of the liver, renal disease and chronic hypertension. In the form of oral tablet, it could be administered in 20 mg, 40 mg, and 80 mg dosage depending on the age and medical condition of the patient. It is classified as a class IV drug in biopharmaceutical system due to its low solubility and low permeability and therefore low bioavailability. There is also no known ODT of furosemide available commercially in the market.

In the present project, furosemide ODT was formulated with improvised direct compression method and the potential of pectin derived from pomelo and cacao fruit wastes was compared to crospovidone, a synthetic disintegrant.

1.2. Objectives of the Study

This study chiefly aimed to develop an orally dissolving tablet of furosemide with pectin from pomelo (*Citrus maxima)* and cacao (*Theobroma cacao*) fruit wastes as potential disintegrants.

The specific objectives of this study included the following:

1. obtain pectin from pomelo fruit peel waste and cacao pod husk waste through acid extraction;
2. formulate pectin-based superdisintegrant with the model drug – furosemide; and
3. determine the potential of fruit waste-derived pectin as disintegrant.

1.3. Statement of the Problem

The main objective of this study was to develop an orally dissolving tablet of furosemide with pectin from pomelo (*Citrus maxima)* and cacao (*Theobroma cacao*) fruit wastes as potential disintegrants.

Specifically, it aimed to answer the following:

1. What is the percent yield of pectin extraction obtained from pomelo and cacao fruit powder?
2. What are the pre-compression characteristics of the powder blend of furosemide with crospovidone, pomelo pectin and cacao pectin as disintegrants in terms of:
    a. bulk density;
    b. tapped density;
    c. Carr's index;
    d. Hausner's ratio; and
    e. angle of repose?

3. Is there a significant difference in the pre-compression characteristics of the powder blend of furosemide with different disintegrants?
4. What are the post-compression characteristics of furosemide ODTs with crospovidone, pomelo pectin and cacao pectin as disintegrants in terms of:
    a. weight variation;
    b. tablet thickness;
    c. wetting time;
    d. water absorption ratio; and
    e. disintegration time?
5. Is there a significant difference in the post-compression characteristics of furosemide ODTs with different disintegrants?

1.4. Statement of the Null Hypotheses

Ho1. There is no significant difference in the pre-compression characteristics of furosemide with crospovidone, pomelo pectin and cacao pectin as disintegrants.

Ho2. There is no significant difference in the post-compression characteristics of furosemide with crospovidone, pomelo pectin and cacao pectin as disintegrants.

1.5. Conceptual Framework

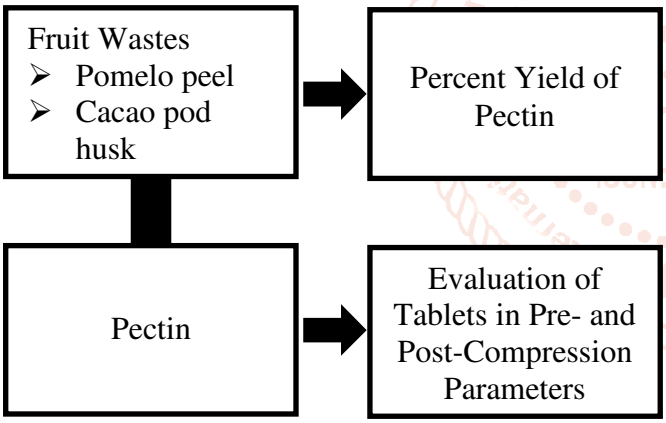


Figure 1 Conceptual framework of the study

Fruit wastes of pomelo peel and cacao pod husk were used as sources of pectin. The biowaste-derived pectin was then used as an excipient in making orally disintegrating tablet (ODT) form of the model drug furosemide. The tablets were then evaluated using the pre-compression parameters in terms of bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose. Post-compression parameters evaluated included weight variation, thickness, wetting time, water absorption ratio and disintegration time.

1.6. Scope and Delimitation

This study was aimed at developing an orally disintegrating furosemide tablet with the use of pectin obtained from pomelo fruit peel and cacao pod husk as disintegrants.

The pomelo fruit peel wastes were obtained from a local public market in Taguig City while cacao pod husk wastes were from San Isidro, San Francisco, Agusan del Sur. The experimentation period was on August 12 – September 26, 2019.

The pomelo pectin extraction was done at the National Institute of Molecular Biology and Biotechnology (BIOTECH) at University of the Philippines, Los Banos, Laguna, Philippines under the supervision of Maria Katrina Alaon and Arsenia B. Sapin, M.Sc. Meanwhile, cacao pectin extraction and tablet compression were done at the Chemical Engineering and Technology Laboratory, Mindanao State University – Iligan Institute of Technology, Iligan City under the supervision of Jocel R. Don, Laboratory Technician.

This study was delimited at certain parameters in evaluating the powder and the tablets. Pre-compression parameters include only bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose. Post-compression parameters include only weight variation, tablet thickness, wetting time, water absorption ratio and disintegration time.

1.7. Significance of the Study

This study formulated a fast disintegrating furosemide tablet using pectin obtained from pomelo and cacao fruit wastes as a natural source of tablet disintegrant. This study will benefit the following:

Patients. This will enable them to take medicines much easier with orally disintegrating tablets, especially furosemide, with the help of excipients from natural sources and at more convenience for them.

Pharmaceutical companies. This will help them consider resorting to natural excipients in formulating their tablets while utilizing wastes at the same time.

Farmers. The utilization of wastes from agricultural products into other usable forms could give them additional income-generating avenue.

Future researchers. This will be used to be their basis in conducting future researches especially on formulating orally disintegrating tablets using natural materials

1.8. Definition of Terms

The following terms were defined operationally as they were used in this study:

Bulk density. This term refers to the ratio of the mass to the volume of an untapped powder sample.

Carr's index. This is also called compressibility index which measures the compressibility of the powder.

Crospovidone. This refers to a synthetic disintegrant that is commonly used in commercially sold tablets.

Disintegrant. This refer to an agent, used in the preparation of tablets, which causes them to disintegrate and release their medicinal substances upon contact with moisture.

Disintegration time. This refers to the time required for the tablet to disintegrate to smaller particles.

Excipient. This refer to an inactive substance that serves as a medium for a drug or active substance.

Furosemide. This refers to the medication given to treat hypertension and edema that is caused by other medical conditions.

Hausner's ratio. It is related to Carr's index and is another indication of powder flowability.

Orally Disintegrating Tablets (ODTs). This refers to a type of pharmaceutical tablet that disintegrates in the mouth even without the aid of water.

Pectin. This refers to a complex polysaccharide present in the cell wall of plants, usually extracted from various fruits.

Post-compression characteristics. These refers to the parameters that describe the characteristics of the formulation after the compression process.

Pre-compression characteristics. These refers to the parameters that describe the characteristics of the formulation before the compression process.

Tapped density. This term refers to the ratio of the mass of the powder to the volume occupied by the powder after it has been tapped for a defined period of time.

Water absorption ratio. This refers to the amount of water the tablet can hold.

Wetting time. This refers to the time required for water to be absorbed by the water and could facilitate disintegration.

1.9. Review of Related Literature

Emergence of orally disintegrating tablets (ODT)

Administration of drugs is most commonly delivered through solid dosage forms. However, taking traditional tablets with water may be disadvantageous to certain groups of people due to a lot of reasons (Garg and Gupta 2013). These groups may include aged people suffering from physiological and neurological conditions like dysphagia, hand tremors, deterioration of common senses, increased choking risk, mental disorders, being bed-ridden and uncooperative patients. In the case of children, ingestion problems may occur due to underdeveloped muscular and nervous control (Garg and Gupta 2013; Velmurugan and Vinushitha 2010).

A fast dissolving tablet (otherwise called a quick dissolving, quick dissolving multiparticulate, quick dissolving, mouth-dissolving, fast melting, or orodispersing tablets) is an oral tablet that doesn't require water for gulping. This British Pharmacopeia defined ODTs as tablets that disperses or disintegrates within 3 minutes in the mouth before swallowing. Furthermore, ODTs should not require water for it be swallowed, should be compatible with other excipients, leave no residue in the mouth after oral administration, among others (Roy 2016).

Advantages of ODTs include accurate dosing, enhanced bioavailability, rapid action, increased patient compliance, ease of administration, cost effective, among others (Garg and Gupta 2013).

There have been a few strategies to set up the orally disintegrating tablet like lyophilization or molding, and compressing wet powders to develop exceptionally porous structure. However, these strategies required the specific machines and are tedious procedures. A method called direct compression is a helpful and modest approach to create tablets with adequate basic trustworthiness. The advantage of direct compression are low assembling costs, high mechanical trustworthiness of the tablets, great dependability, exact dosing, little bundling size, and simple dealing with and simplicity of organization. Accordingly, direct-compression gives off an impression of being a superior alternative for the assembling of orally disintegrating tablets. The quick breaking down tablets arranged by direct pressure technique, when all is said in done, depend on the activity built up by superdisintegrants, for example, crosscarmellose sodium, crosspovidone and sodium starch glycolate (N. Patel, et al. 2011)

Nowadays, synthetic disintegrants are commonly used in the formulation of ODTs. These group includes, sodium starch glycolate, crosscarmellose sodium and crospovidone. Sodium starch glycolate is wide scope of local starches, yet practically practice potato starch is utilized as it gives the item with the best breaking down properties. Croscarmellose sodium is depicted as a cross-connected polymer of carboxymethylcellulose. Aside from the contrasts between the starch and cellulose polymer backbone, there are differences between the manufactured procedures used to change the polymer.

Meanwhile, crospovidone superdisintegrants are widely utilized for its swelling and wicking mechanisms. At the point when analyzed under a checking electron magnifying lens, crospovidone

particles seem granular and highly porous (Mohanachandran, Sindhumol and Kiran 2011).

The effect of disintegration mechanism on wetting, water absorption, and disintegration time of orodispersible tablets were also studied. The mannitol and disintegrants was blended carefully. The tablets were compressed at a high compression force. Data shows that by selecting the appropriate type of disintegrant, it is possible to formulate ODT's with low porosities, to give ODT a high mechanical strength and rapid disintegration properties (Pabari and Ramtoola 2012).

Pectin as Drug Excipient

Pectin is a significant polysaccharide with applications in nourishments, pharmaceuticals, and various different enterprises. In the food industry, it adds body and texture to jellies, jams and puddings. It is used in medicine as a treatment to some conditions like diarrhea, high cholesterol, high triglycerides, diabetes and gastroesophageal reflux disease. Some would also use it to treat heavy metal poisoning (WebMD, n.d.).

These polymers are commonly sourced out from fruits and vegetables but highest amounts of pectin are obtained from citrus fruits and apples. The simplest type of pectin is a linear polymer of galacturonic acid which is soluble in water. Dry powdered pectin, when added to water, tends to hydrate very rapidly.

In recent years, plant derived polymers were of interest in terms of its pharmaceutical applications especially as drug excipients – as it can be used as a diluent, a binder, a thickener, a protective colloid, a gelling agent, a base in suppository, and as a disintegrant (Srivastava and Malviya, Sources of pectin, extracrion and its aplication in pharmaceutical industry - An overview 2011). Pectin is known to be hydrophilic in nature which means that it is easily attracted to water.

A number of researches have already been conducted to evaluate the capability of pectin as a potential drug excipient.Orange peel pectin (Tyagi 2016; Chavan et al. 2017) and banana peel pectin (Bansal et al. 2014) were found to be potential drug excipient. Orange peel pectin was also considered as a good candidate as disintegrant due to its good water uptake capacity leading to a faster disintegration (Srivastava, Singh and Bhargava 2017). Mango peel pectin was also found to have good disintegrating ability due to its good solubility and high swelling index (Shirsand, Shilashri and Gumate 2016; Madhulika and Kuber 2011).

Furosemide as model drug

Furosemide is a loop diuretic (water pill) that keeps patients' body from engrossing an excessive amount of salt. This enables the salt to rather be passed in your urine. Furosemide is utilized to treat liquid maintenance (edema) in individuals with congestive cardiovascular breakdown, liver illness, or a kidney issue, for example, nephrotic disorder. Initial oral dose may range from 20 to 80 mg depending on the medical condition of the patient.

However, this drug is classified as Class IV in the Biopharmaceutical Classification System. This means that it has low solubility, low permeability and low bioavailability. To improve such, ODTs can be a way to increase its bioavailability. Drug candidates that undergo pre-gastric absorption when formulated as ODTs may show increased oral bioavailability (N. Shivappa, et al. 2018). As of now, no ODT form of furosemide is available in the market (Gulsun, Ozturk, et al. 2017)

2. METHODOLOGY

This section presents the discussion of the methods, research design, and layout, the research variables, the subjects, the sampling procedures, the research tools and instruments and the statistical procedures utilized for the analysis and interpretation of data.

2.1. List of Materials

The research apparatus and materials used in the study were as follows: 1 kg pomelo peel, 1 kg cacao pod husk, ziplock bags, funnel, cotton, foil, tray, petri dish, watch glass, mortar and pestle, Erlenmeyer flask (500ml), cylinder (1000-ml,100-ml) beaker, falcon tube, container, stirring rod, tissue paper, scissors, knife, ruler, stopwatch/timer, analytic balance, top loading balance, electric grater, sieve, water bath shaker, centrifuge, pH meter, oven, improvised tablet compressor, Vernier caliper, ethanol solution, distilled water, citric powder, methylene blue dye, Furosemide tablets, glucose, crospovidone, and talc.

2.2. Research Design

A. Formulation of Tablet Samples

Table 2.1.1 Formulation of Tablets

Sample Tablets	Amount of the Active Drug and the Excipients						
	Furosemide (active drug)	Glucose (filler)	Crospovidone (disintegrant)	Pomelo Pectin (disintegrant)	Cacao Pectin (disintegrant)	Talc (lubricant)	Total Weight
F1	x	x	-	-	-	x	x
F2	x	x	x	-	-	x	x
F3	x	x	-	x	-	x	x
F4	x	x	-	-	x	x	x

Direct compression technique was employed to make the tablets. It is a process by which tablets are compressed directly from powder blends of active ingredient and suitable excipients, which will flow uniformly in the cavity and forms a firm compact.

B. Evaluation of Tablet Formulations

B.1. Pre-Compression Parameters

Table 2.2.1 Pre-compresssion Parameters

Sample Tablets	Bulk Density (g/mL)				Tapped Density (g/mL)				Carr's Index (%)				Hausner's Ratio				Angle of Repose (°)			
F1	R1	R2	R3	Ave	R1	R2	R3	Ave	R1	R2	R3	Ave	R1	R2	R3	Ave	R1	R2	R3	Ave
F2	R1	R2	R3	Ave	R1	R2	R3	Ave	R1	R2	R3	Ave	R1	R2	R3	Ave	R1	R2	R3	Ave

B.2 Post-Compression Parameters

Table 2.3.1 Weight Variation of the Tablets in Different Formulations

Sample Tablet	Weight Variation (mg)																			
F1	R1	R2	R3	R4	R5	R6	R7	R8	R9	R10	R11	R12	R13	R14	R15	R16	R17	R18	R19	R20	Ave
F2	R1	R2	R3	R4	R5	R6	R7	R8	R9	R10	R11	R12	R13	R14	R15	R16	R17	R18	R19	R20	Ave
F3	R1	R2	R3	R4	R5	R6	R7	R8	R9	R10	R11	R12	R13	R14	R15	R16	R17	R18	R19	R20	Ave
F4	R1	R2	R3	R4	R5	R6	R7	R8	R9	R10	R11	R12	R13	R14	R15	R16	R17	R18	R19	R20	Ave

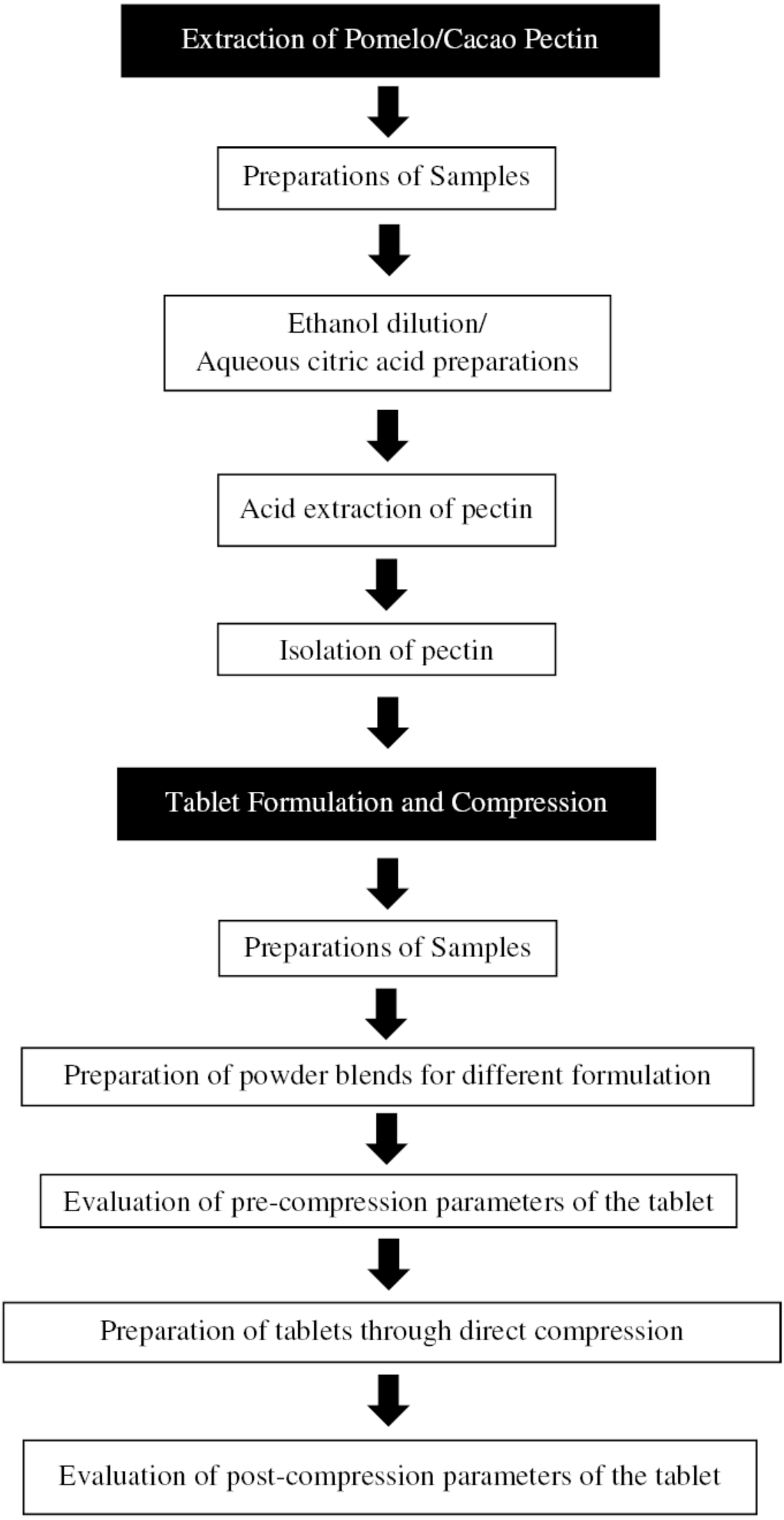
Table 2.3.2 Thickness of the Tablets in Different Formulations

Sample Tablet	Tablet Thickness (mm)										
F1	R1	R2	R3	R4	R5	R6	R7	R8	R9	R10	Ave
F2	R1	R2	R3	R4	R5	R6	R7	R8	R9	R10	Ave
F3	R1	R2	R3	R4	R5	R6	R7	R8	R9	R10	Ave
F4	R1	R2	R3	R4	R5	R6	R7	R8	R9	R10	Ave

Table 2.3.3 Wetting Time, Water Absorption Ratio and Disintegration Time of the Tablets

Sample Tablets	Wetting Time (s)				Water Absorption Ratio				Disintegration Time (s)			
F1	R1	R2	R3	Ave	R1	R2	R3	Ave	R1	R2	R3	Ave
F2	R1	R2	R3	Ave	R1	R2	R3	Ave	R1	R2	R3	Ave
F3	R1	R2	R3	Ave	R1	R2	R3	Ave	R1	R2	R3	Ave
F4	R1	R2	R3	Ave	R1	R2	R3	Ave	R1	R2	R3	Ave

2.3. Flow chart of Procedures



2.4. Methods

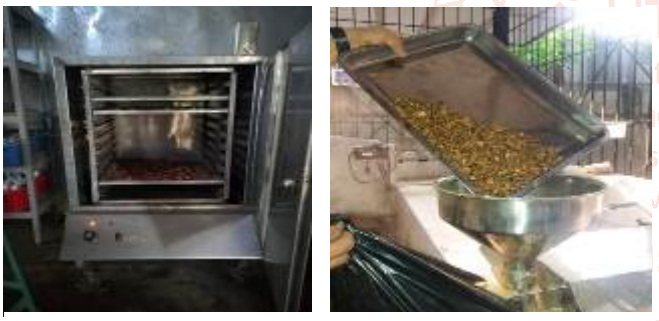
A. Preparation of Samples

Fruits are collected from and fruit peels and pod husks as samples are prepared.

Pomelo peels were obtained as a waste from a local market in Taguig City and cacao peels were collected at Brgy. San Isidro, San Francisco, Agusan del Sur. The samples were washed with distilled water. Pomelo peels were cut into small pieces while cacao pod fruits were cut in halves, the pulp and the seeds were removed and the mucilage that adhered to the husk was scraped the husks were then cut into small pieces

The prepared samples are weighed then dried.

The samples were weighed and then dried under shade for 36 hours and further dried in an oven at 30-40ºC until constant weight was obtained.



The dried samples are further dried in an oven and are powdered through an electric grater.

The samples were then powdered using electric grater. Powdered peels and cocoa pod husk were further passed through sieve #20.

The samples are weighed and stored until use.

Samples were weighed and were stored in air tight container until used.

B. 95% Ethanol and Aqueous Citric acid Preparation

Pure ethanol is diluted into 95% ethanol.

The methods herein were based from the studies of Vriesmann, Teofilo and Petkowicz (2012) and Hamed and Mustafa (2018) for cacao and pomelo, respectively.

Nine hundred fifty milliliters of ethanol was measured from 100% ethanol using graduated cylinder and 50mL of distilled water was then added to dilute 100% to 95%.

Aqueous citric acid is prepared in different

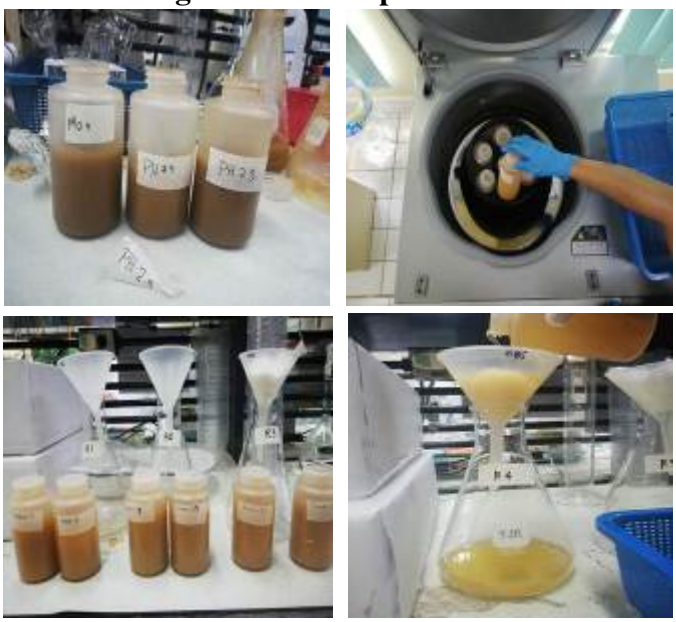
Aqueous citric acid was prepared with different pH levels, 32g and 16g of citric acid powder were weighed separately, each added with 500mL distilled water in separate volume metric flasks. The pH levels of each solutions were then tested using pH meter.

C. Acid extraction of pectin

Powdered samples are treated with acidified water to isolate pectin.

The powdered sample of pomelo fruit peel and cacao pod husk were weighed and transferred to a glass container. Ten grams of cacao pod husk powder and 10 g pomelo fruit peel powder were measured on an analytical balance (B204-S, MK II, Mettler Toledo, Switzerland) and each was blended with 250 mL acidified water with different volumes of 0.1 N citric acid to meet the desired pH of 2.0 and 1.84 (cacao); and 2.5 and 4.5 (pomelo). The mixture was then stirred using a stirrer until all the fruit peel powder was evenly wetted by acidified water in homogenous form. The pectin extraction procedure was continued treating the acidified samples at 70°C for 75 min (cacao pod husk powder) and 85°C for 90 min in a shaking water bath.

D. Obtaining final form of pectin



Centrifugation is done to isolate liquid phase from fruit peels powder.

The samples were transferred to a plastic container and weighed equally and were then centrifuged to separate liquid phase from solid phase of powders. The samples were then filtered using cotton plug and funnel.

Filtered samples are pre-treated with 95% ethanol to precipitate pectin.

Water bath heat-treated samples were then filtered and added to double volume of 95% ethanol (1:2 v/v) to allow pectin precipitation in 2 hours. This allowed pectin flotation which was then separated.

Isolated pectin is dried and powdered.

The resulted pectin substance was dried in a conventional oven (UM500, Memmert GmbH, Schwabach, Germany) at 55 ° until a constant weight was reached. The sample were powdered using a mortar and pestle and was sieved using #60.

E. Powder Blending for the Formulations

Table 2.4.1 Formulation of Tablets

Sample Tablets	Amount of the Active Drug and the Excipients (in mg)						
	Furosemide (active drug)	Glucose (filler)	Crospovidone (disintegrant)	Pomelo Pectin (disintegrant)	Cacao Pectin (disintegrant)	Talc (lubricant)	Total Weight
F1	40	154	-	-	-	6	200
F2	40	138.6	15.4	-	-	6	200
F3	40	138.6	-	15.4	-	6	200
F4	40	138.6	-	-	15.4	6	200

The ratio of the amount of drug and excipients was based on the study of Gulsun et al. (2017). Furosemide and crospovidone were acquired as a gift sample from a medical representative while glucose and talc were laboratory supplies.

The active drug and excipients are mixed and blended thoroughly.

Furosemide tablets were powdered using a mortar and pestle, all the ingredients were then passed through #60 mesh separately to obtain fine powder. The formulation for tablets were followed according to Table 3.5. Furosemide, glucose and the corresponding disintegrants were mixed and blended in mortar and pestle for 15 minutes. Talc was then added to the mixture and blended for 2 minutes. The powder blend of each formulation was then ready for measuring the pre-compression parameters.

F. Evaluation of Tablets on Pre-compression Parameters

The powder blend is weighed and volume is determined.

A. Bulk density

The ingredients in each formulation were sieved and weighed. It was then transferred to 100mL cylinder and dropped in a hard wooden surface 3 times from a height 2.5 cm at an interval of 2 sec. The volume of the powder was read. Bulk density was then computed using the following formula:

$$\text{Bulk density} = \frac{\text{weight of the sample (g)}}{\text{volume of the sample (mL)}}$$

The graduated cylinder with the powder blend is tapped 100 times and tapped density is read.

B. Tapped density

The graduated cylinder with the powder was tapped by letting it fall under its own weight on a wooden surface 100 times or until no changes were observed from a height of 2.5 cm at 2 sec interval. The volume of the powder was read. Tapped density was then computed using the following formula:

$$\text{Tapped density} = \frac{\text{weight of sample (g)}}{\text{tapped volume (mL)}}$$

C. Carr's index

It was computed using the following formula:

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

D. Hausner's Ratio

It was computed using the following formula:

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


The powder blend is passed through the funnel; height and base of the pile are then measured.

E. Angle of Repose

The powder was passed through the funnel. The height of the tip of the funnel just touched the apex of the granules. The height of the tip of the powder and the diameter of the cone was measured. Angle of repose was computed using the following formula:

$$\tan \theta = h/r$$

where: h = height of pile; r = radius of the base of pile; and θ = angle of repose.


Direct compression method is done to produce the tablets in each formulation.

F. Tablet Compression

The different formulations were now ready for compression into tablet. 200 mg from each formulation was prepared to undergo an improvised direct compression method. Weighed dry powder was put inside the cavity of a 7mm diameter metallic ring. The powder was then compressed using a metallic rod that fits the ring perfectly. The researcher ensured consistency in the pressure applied for each tablet to form. For each of the four formulations, 40 tablets were produced.

G. Evaluation of Tablets on Post-compression Parameters

A. Weight Uniformity

Twenty tablets were selected randomly from each formulation. Each tablet was individually weighed. Average weight was then computed.

Tablets are randomly selected and are weighed.

B. Tablet Thickness

Ten tablets were selected randomly from each formulation. Thickness of each tablet was measured using Vernier caliper.

Tablets are randomly selected and are measured in their thickness.

C. Wetting Time

Five pieces of tissue paper were cut to fit a petri dish with 9 cm diameter. 9 mL distilled water + dye (methylene blue) solution was then added to the petri dish with tissue papers. One tablet was carefully placed at the center of the petri dish (t=0). The time required for the solution to reach the upper surface of the tablet was measured. This was done in three replicates for each formulation.

Tablets are individually placed in a petri dish with dye solution and wetting time is measured.

D. Water Absorption Ratio

One tablet was randomly selected and was weighed. A piece of tissue paper was folded twice in a petri dish with 9 cm diameter and 9 mL distilled water was then added. The tablet was carefully placed at the center of the petri dish and was observed until it was completely wet. The tablet was carefully removed and weighed. The absorption ratio was calculated using the formula:

$$R = [(W_a - W_b) / W_b] \times 100$$

where: W_a refers to the weight after wetting and W_b refers to the weight before wetting. The test was done in three replicates for each formulation.

E. Disintegration Time

A tablet was carefully placed in a 9 cm diameter petri dish with 9 mL distilled water at room temperature with no stirring. Time was recorded when the tablet completely disintegrates. The test was done in three replicates for each formulation. (Madan, Sharma and Singh 2009; Prajapati and Patel 2010; Brniak, Jachowicz and Pelka 2015).

Tablets are individually placed in a petri dish with distilled water and disintegration time is measured.

3. RESULTS AND DISCUSSIONS

3.1. Percent Yield of Pectin Extraction

Table 3.1.1 Percent Yield of Biowaste-Derived Pectin

Source	Percent Yield
1 kg pomelo fruit peel	3.66%
1 kg cacao pod husk	2.80%

The table above shows the percent yield of pectin derived from pomelo fruit peel and cacao pod husk. It can be learned that more pectin can be derived from pomelo than in cacao. It was from this derived pectin that this study produced 40 tablets with pomelo pectin and 40 tablets with cacao pectin, along with the other formulations.

3.2. Pre-Compression Parameters of Tablet Formulations

Table 3.2.1 Pre-compression Characteristics of the Different Tablet Formulations

Formulation	Bulk Density (g/mL)	Tapped Density (g/mL)	Carr's Index (%)	Hausner's Ratio	Angle of Repose (°)
F1 (Furosemide)	0.63	0.77	18.18	1.22	40.62
F2 (Furosemide + Crospovidone)	0.60	0.67	10.46	1.12	31.64
F3 (Furosemide + Pomelo Pectin)	0.79	0.90	12.22	1.14	33.69
F4 (Furosemide + Cacao Pectin)	0.65	0.80	18.75	1.23	33.69

The table above shows the evaluation of the pre-compression parameters that describe the powder flow of the tablets made in different formulations.

Bulk density and tapped density were used to calculate Carr's index and Hausner's ratio. It can be seen that F2 has the least Carr's index and Hausner ratio, followed by F3, F4 then F1. According to the United States Pharmacopoeia (USP) standards (Appendix C), F2 and F3 can be described to have good flow character since their Carr's indices and Hausner ratios are found within 11 – 15% and 1.12 – 1.18, respectively, while F1 and F4 have a fair flow character belonging within 16 – 20% and 1.19 – 1.25. Acceptable flow character means that there is a minimum interparticulate interactions within each powder blend.

In terms of angle of repose, F2 has the least angle of repose, followed by F3 and F4 and then F1. According to the USP standards (Appendix C), the values can be interpreted as that F2, F3 and F4 have good flow property whose angles of repose fall within 31° – 35° while F1 has a passable flow property of more than 40°.

This goes to show that the powder formulations were suitable for direct compression and that their good flow characters give better assurance in the content uniformity of the drug formulation.

3.3. Significant Difference in the Pre-Compression Parameters of the Tablets

3.3.1. Bulk Density

Table 3.3.1 One-Way Analysis of Variance in the Bulk Density of the Tablets in Different Formulations

Formulation	Mean	df	p-value	Description
F1 (Furosemide)	0.63[b]	11	.000	Significant
F2 (Furosemide + Crospovidone)	0.60[a]			
F3 (Furosemide + Pomelo Pectin)	0.79[c]			
F4 (Furosemide + Cacao Pectin)	0.65[d]			

The table above shows that there is a significant difference in the bulk density of the powder blends at 0.05 level of significance with a p-value of 0.000. The null hypothesis of this study that there is no significant difference in the pre-compression parameters of the powder blends was rejected. This means that the powder blends exhibit difference in terms of bulk density. This parameter is an important factor to the compressibility of a powder.

Moreover, Post Hoc Analysis was done using Duncan Multiple Range Test and showed that furosemide tablet with crospovidone has the highest bulk density.

3.3.2. Tapped Density

Table 3.3.2 One-Way Analysis of Variance in the Tapped Density of the Tablets in Different Formulations

Formulation	Mean	df	p-value	Description
F1 (Furosemide)	0.77[b]	11	.000	Significant
F2 (Furosemide + Crospovidone)	0.67[a]			
F3 (Furosemide + Pomelo Pectin)	0.90[d]			
F4 (Furosemide + Cacao Pectin)	0.80[c]			

The table above shows that there is a significant difference in the tapped density of the powder blends at 0.05 level of significance with a p-value of 0.000. The null hypothesis of this study that there is no significant difference in the pre-compression parameters of the powder blends was rejected. This means that the powder blends exhibit difference in terms of tapped density. This parameter is also an important factor to the compressibility of a powder.

Moreover, Post Hoc Analysis was done using Duncan Multiple Range Test and showed that furosemide tablet with crospovidone has the highest tapped density.

The significant difference in the bulk and tapped densities would also reflect on the Carr's indices and Hausner's ratios of the powders. This means that each of the formulations are significantly different in terms of their Carr's indices and Hausner's ratio. Nevertheless, all the powder blends were of acceptable compressibility and flowability limits, fit for direct compression.

3.3.3. Angle of Repose

Table 3.3.3 One-Way Analysis of Variance in the Angle of Repose of the Tablets in Different Formulations

Formulation	Mean	df	p-value	Description
F1 (Furosemide)	40.62[c]	11	.000	Significant
F2 (Furosemide + Crospovidone)	31.64[a]			
F3 (Furosemide + Pomelo Pectin)	33.69[b]			
F4 (Furosemide + Cacao Pectin)	33.69[b]			

The table above shows the significant difference of the angles of repose of the powder blends at 0.05 level of significance. The null hypothesis of this study that there is no significant difference in the pre-compression parameters of the powder blends was rejected. This means that the powder blends show significantly different angles of repose which is an indication of the flowability of a powder.

To determine which tablets had significantly better angle of repose, Post Hoc Analysis was done using Duncan Multiple Range Test. It showed that furosemide with crospovidone had the best angle of repose while furosemide with pomelo pectin and with cacao also showed good angle of repose. Nevertheless, all the powders had acceptable flowability characteristic.

3.4. Post-Compression Parameters of Tablet Formulations

Table 3.4.1 Post-compression Characteristics of the Different Tablet Formulations

Formulation	Weight Variation (mg)	Tablet Thickness (mm)	Wetting Time (s)	Water Absorption Ratio	Disintegration Time (s)
F1 (Furosemide)	199.00 ±7.18	3.98 ± 0.06	83 ± 16	12.11 ± 3.20	88 ± 11
F2 (Furosemide + Crospovidone)	198.50 ± 9.88	4.04 ±0.08	109 ± 26	34.57 ± 15.74	134 ± 6
F3 (Furosemide + Pomelo Pectin)	196.00 ± 9.40	3.99 ±0.10	18 ± 12	18.58 ± 11.36	110 ± 37
F4 (Furosemide + Cacao Pectin)	198.50 ± 10.40	4.08 ± 0.10	13 ± 6	47.95 ± 14.92	73 ± 22

The table above summarizes the evaluation of the post-compression parameters of the tablets made in different formulations.

3.4.1. Weight Variation

According to many pharmacopeias, the individual weights of these tablets should be within ±7.5% variation from the average weight of each formulation. Moreover, not more than two individual weights should deviate from the prescribed percent variation and none should deviate by more than twice the prescribed percentage.

The results show that the individual weights of the 20 tablets in each formulation vary from 180 mg to 210 mg. Tablets in F1 had the highest mean weight while tablets in F3 had the lowest mean weight.

Individual weight variation was computed (Appendix A) and showed that the weight variation of the tablets in all formulations were within the prescribed limits. Thus, the direct compression method done by the researcher produced acceptable tablets in terms of uniformity of their weight.

3.4.2. Tablet Thickness

The randomly selected ten tablets from each formulation showed varied thickness ranging from 3.80 to 4.20 mm. The highest average thickness of the tablets was from F4 followed by F2, F3 then F1.

Moreover, the variation of the tablets' thickness from each formulation were within the advised limits of ±5% (Appendix A). This goes to say that the direct compression method done by the researcher produced tablets with uniform thickness. The uniformity in thickness of the tablets of the same formulation also reflects that the powder blend in each formulation are adequately consistent in particle size and size distribution.

3.4.3. Wetting Time

This parameter reflects the inner structure of the tablets and the hydrophilicity of the excipients. In the table shown, tablets of F4 had the quickest wetting time of 13s. This was followed by F3, F1 then F2 with 18s, 83s and 109s, respectively.

Therefore, the tablet with the cacao fruit pectin as its disintegrant is the most hydrophilic among the four. Tablet with pomelo fruit pectin has also a quick wetting time close to that of cacao's. This could be attributed to a more effective water wicking mechanism of pectin (both from cacao and pomelo) compared to crospovidone.

The wetting time of furosemide using crospovidone and mango peel pectin in the study of Shirshand, Shilashri and Gumate (2016) showed shorter wetting time for crospovidone. However, the furosemide tablets with cacao and pomelo pectin in this study were found to have much shorter wetting time than those with mango pectin (average of 56s).

3.4.4. Water Absorption Ratio

This parameter determines the water absorption capacity of the tablets made with different formulations. Accordingly, the tablets from F4 exhibited the highest water absorption ratio of 47.95, followed by F2, F3 then F1 with 34.57, 18.58 and 12.11, respectively.

These results show that the tablets made with cacao pectin as disintegrant have the highest capacity to hold water in them. However, in the study of Shirshand, Shilashri and Gumate (2016), furosemide with mango pectin have more water absorption ratio than cacao and pomelo pectin. Good water uptake capacity aids in faster disintegration of the tablet.

3.4.5. Disintegration Time

This parameter reflects the ability of the tablet to break down into small particles which may offer great chances that the drug will be more available to the body. British Pharmacopeia limits indicate that orodispersible tablets should disintegrate within 3 minutes upon exposure to water.

The table shows that the tablets in F2 have the lowest disintegration time of 73s, followed by F1, F3, then F2 with disintegration times of 88s, 110s and 134s, respectively.

These mean that all the tablets have disintegrated within the prescribed limits. The fast disintegration of tablets with pectin can be attributed to the hydrophilicity and good solubility property of pectin.

3.5. Significant Difference in the Post-Compression Parameters of the Tablets

3.5.1. Weight Variation

Table 3.5.1 One-Way Analysis of Variance in the Weight Variation of the Tablets in Different Formulations

Formulation	Mean	df	p-value	Description
F1 (Furosemide)	199.00	79	.736	Not Significant
F2 (Furosemide + Crospovidone)	198.50			
F3 (Furosemide + Pomelo Pectin)	196.00			
F4 (Furosemide + Cacao Pectin)	198.50			

As shown in the table above, there is no significant difference in the weight variation of the tablets using different formulations at 0.05 significance level as shown in its p-value of 0.736. The null hypothesis of this study that there is no significant difference in the post-compression parameters of the powder blends was accepted. Thus, the direct compression done produced tablets of significantly the same weights.

3.5.2. Tablet Thickness

Table 3.5.2 One-Way Analysis of Variance in the Tablet Thickness of the Tablets in Different Formulations

Formulation	Mean	df	p-value	Description
F1 (Furosemide)	3.98	39	.058	Not Significant
F2 (Furosemide + Crospovidone)	4.04			
F3 (Furosemide + Pomelo Pectin)	3.99			
F4 (Furosemide + Cacao Pectin)	4.08			

The table above shows that there is no significant difference in the thickness of the tablets made in different formulations at 0.05 significance level with its p-value of 0.058. The null hypothesis of this study that there is no significant difference in the post-compression parameters of the powder blends was accepted. Thus, the improvised direct compression done produced tablets of significantly the same thickness.

3.5.3. Wetting Time

Table 3.5.3 One-Way Analysis of Variance in the Wetting Time of the Tablets in Different Formulations

Formulation	Mean	df	p-value	Description
F1 (Furosemide)	83[b]	11	.000	Significant
F2 (Furosemide + Crospovidone)	109[b]			
F3 (Furosemide + Pomelo Pectin)	18[a]			
F4 (Furosemide + Cacao Pectin)	13[a]			

The table above shows that at 0.05 level of significance, there is a significant difference in the wetting time of the different sets of tablets with a p-value of 0.000. The null hypothesis of this study that there is no significant difference in the post-compression parameters of the powder blends was rejected. This suggests that the wetting time varied significantly among the tablets made from four formulations. Furthermore, it also suggests that the type of disintegrant present in a tablet significantly affects the tablet's wetting time.

To determine which tablets had significantly quicker wetting time, Post Hoc Analysis was done using Duncan Multiple Range Test (Appendix B). It then showed that furosemide tablets with cacao and pomelo pectin as disintegrants exhibited superior wetting time over the other formulations. Quicker wetting time determines the hydrophilicity of the tablets when introduced to water. Thus, in this study, cacao and pomelo pectin have better wicking ability than crospovidone as disintegrant.

3.5.4. Water Absorption Ratio

Table 3.5.4 One-Way Analysis of Variance in the Water Absorption Ratio of the Tablets in Different Formulations

Formulation	Mean	df	p-value	Description
F1 (Furosemide)	12.11[b]	11	.029	Significant
F2 (Furosemide + Crospovidone)	34.57[a,b]			
F3 (Furosemide + Pomelo Pectin)	18.58[b]			
F4 (Furosemide + Cacao Pectin)	47.95[a]			

The table above shows that at 0.05 level of significance, there is a significant difference in the water absorption ratio of the different sets of tablets as shown in its p-value of 0.029. The null hypothesis of this study that there is no significant difference in the post-compression parameters of the powder blends was rejected. This means that the tablets exhibited varying water absorption capacities. Furthermore, it further suggests that the excipients present in a tablet significantly affect water absorption ratio.

To determine which tablets had significantly higher water absorption ratio, Post Hoc Analysis was done using Duncan Multiple Range Test (Appendix B). It then showed that furosemide tablets with cacao pectin and with crospovidone were the tablets that have absorbed the highest amount of water.

In this study, it can be learned that cacao pectin exhibited a comparable performance of the synthetic disintegrant crospovidone in terms of its ability to absorb water.

3.5.5. Disintegration Time

Table 3.5.5 One-Way Analysis of Variance in the Disintegration Time of the Tablets in Different Formulations

Formulation	Mean	df	p-value	Description
F1 (Furosemide)	88[a]	11	.044	Significant
F2 (Furosemide + Crospovidone)	134[b]			
F3 (Furosemide + Pomelo Pectin)	110[a,b]			
F4 (Furosemide + Cacao Pectin)	73[a]			

The table above shows that there is a significant difference in the wetting time of the different sets of tablets at 0.05 level of significance as shown in its p-value 0.44. The null hypothesis of this study that there is no significant difference in the post-compression parameters of the powder blends was rejected. This means that the disintegration time of the tablets varied significantly. Furthermore, it further suggests that the disintegrants in each formulation have an effect on the disintegration time of the tablets.

To determine which tablets had significantly quickest disintegration time, Post Hoc Analysis was done using Duncan Multiple Range Test (Appendix B). It then revealed that furosemide tablets with cacao pectin have a significantly short disintegration time.

In this study, it can be learned that cacao pectin and pomelo pectin enabled the tablet to disintegrate quickly. This implies that pectin can fasten the disintegration of a tablet which is very crucial in the formulation of ODTs.

4. CONCLUSIONS AND RECOMMENDATIONS

4.1. Summary

This study was conducted to investigate the potential of pomelo (*Citrus maxima*) and cacao (*Theobroma cacao*) biowaste-derived pectin as tablet excipient, especially as a disintegrant, in orally disintegrating tablets (ODTs). Pectin was obtained through acid extraction and was used in the formulation of furosemide ODT as the model drug. Along with other excipients, direct compression method was done to make 40 tablets for each formulation. Pre- and post-compression parameters of the powder blend and tablet were then evaluated.

4.2. Conclusions

Based on the results of this study, the following were concluded:

1. Biowastes such as fruit peels can be sources of pectin. Pomelo (*Citrus maxima*) and cacao (*Theobroma cacao*) are common local fruits that could be used for pectin extraction.
2. Biowaste-derived pectin can be used as excipients in pharmaceutical drugs due to its good compressibility and flowability characteristics.
3. Cacao pectin is a potential excipient for orodispersible tablets as it has showed superior disintegrating performance compared to other

disintegrants in terms of wetting time, water absorption ratio and disintegration time. Moreover, pomelo pectin also showed promising disintegrant properties.

4.3. Recommendations

The following were recommended by the researcher:

1. Explore more fruits that could provide higher percent yield of pectin.
2. Look into different conditions such as pH level, temperature and time that may affect pectin extraction.
3. Conduct further evaluation of furosemide ODTs with pomelo and cacao pectin as disintegrant like content uniformity, in-vitro dissolution test and in-vivo disintegration test.
4. Determine the post-compression characteristics of other model drugs with natural excipients.