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The Effect of Native and Pregelatinized Durian Seed Starch (Durio Zibethinus Murr) on The Dissolution Rate of Paracetamol Tablets

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Abstract

Amylum is widely used as an excipient in pharmaceutical formulations, one of which is inert and can be mixed with any drug without causing a chemical reaction. The aim of this research is to know the preparation method of cassava amylum (Durio zibethinus, Murr) native and pregelatinized which is used as binder to dissolution rate of paracetamol tablet with granulation method. The native and pregelatinized amylum produced from cassava is carried out by a preliminary test to determine the nature of physical characteristics and to know the ability as a binder of the tablet. The paracetamol tablets produced from the two methods were tested dissolution using medium buffer phosphate at 37 ± 0,5 ° C (pH 5.8, 50 rpm). The results showed that cassava starch preparation method had an effect on dissolution rate of tablet. Pregelatinized amylum as binder on paracetamol tablet showed Q value (93,17 ± 0,01)% while native amylum showed value of Q (81,76 ± 0,20)%. The use of pregelatinized cassava starch as a binder on paracetamol tablet has better characteristic properties compared with native starch.

INTRODUCTION

Amylum as an excipient in pharmaceutical formulations is very widely used because it can be mixed with almost any drug and is inert without causing chemical reactions. Amylum is often used as an excipient, as a binding agent (Karisma et al., 2012). The binding agent functions to power the cohesion of the powder mass at the time of pressing. The binding agent affects the rate of drug solution. The more strongly an active substance is bound to the excipient, the more it will not be able to dissolve in the body, and will not reach the expected bioavailability (Raini et al., 2010).

Amylum is a reserve polysaccharide that is abundant in plants. In general, amylum consists of 20% water-soluble (amylose) and 80% water-insoluble (amylopectin). Amylose is a straight molecule, consisting of 250–300 units of D-glucose and uniformly connected by a α-1,4-glucoside bond that tends to cause the molecule to be thought of as thread-like (*helix*). Amylopectin is made up of 1,000 or more glucose units, most of which are also linked to α-1,4 bonds. However, there are also a number of α-1.6 bonds found at the branching points. This number of bonds is approximately 4% of the total number of contacts or one for every 25 units of glucose (Femi-Oyewo et al., 2015). Amylopectin in water can form colloidal solutions. When the colloidal solution is heated, a sticky period occurs, this property is used as a binding agent (Kou & Gao, 2019). While amylose has the ability to expand when in contact with liquids, this property is used as a crusher (Beech et al., 2022).

Natural Amylum (*native starch*) is an amylum produced from plants, and has not undergone physical or chemical processing. Amylum *Native* is an amylum obtained from root

bulbs *Durio zibethinus,* Murr, the powder is smooth and white in color. Modification of the physical properties of amylum is carried out in the following ways: *pregelatinized*. The purpose of this modification is to improve its flow properties and compatibility so that it can be used as a binder in direct print tablets and can reduce the use of glidan and non-adhesion. The use of glidan and anti-adhesion can prolong the dissolution rate as it can form a film layer. Modification of amylum *pregelatinized* It is carried out by providing treatment in the form of adding water with the right amount and heating at the appropriate temperature. This method produces amylum with a larger particle size and higher particle density (Adedokun and Itiola, 2011). On amylum *pregelatinized* Due to the right addition of water and heating, a gel formation process occurs, causing the aylum granules to absorb water and expand to form a thick mass.

One of the local amylum-producing plants that can be modified in this way is durian seed amylum. In addition to its relatively low price, durian seed amylum is relatively easy to obtain, so it has the potential to be used as an excipient for solid preparations. The high content of amylopectin of 83% makes durian seed amylum potential to be used as a binding agent in the manufacture of pharmaceutical preparations.

Therefore, it is necessary to conduct research on native durian seed amylum *and* pregelatinized *durian seed amylum*, as a binding agent for the dissolution rate of paracetamol tablets using the granulation method. Several studies have shown that pregelatinized starch generally provides better tablet properties than native starch. Pregelatinization increases particle size and density, improves powder flow, and enhances compactibility, which may result in tablets with greater hardness and lower friability. At the same time, these changes can also alter the disintegration and dissolution profile of the finished product. Thus, a comparison between native and pregelatinized starch is important to determine which form provides the best balance between tablet strength and drug release. This issue becomes more relevant when local natural materials are explored as alternative pharmaceutical excipients.

One potential local source of starch is durian seed (*Durio zibethinus* Murr), an agricultural by-product that is often underutilized despite its high starch content (Awaluddin et al., 2017). Durian seed starch is relatively inexpensive, readily available, and contains a high proportion of amylopectin, which indicates strong potential for use as a binder in tablet formulations (Badejo, 2019; Hong & Liu, 2023; Nama Putra et al., 2022; Sulastri et al., 2024). The use of durian seed starch as a pharmaceutical excipient also offers added value by promoting the utilization of local raw materials and reducing dependence on imported excipients. Nevertheless, the performance of native and pregelatinized durian seed starch in tablet formulations, particularly their influence on tablet dissolution, still requires further investigation.

Although previous research has reported the potential of modified starches as pharmaceutical binders, studies specifically comparing native and pregelatinized durian seed starch in paracetamol tablets remain limited. In particular, there is still insufficient information regarding how the preparation method of durian seed starch affects the physical characteristics of the starch, the resulting tablet properties, and the dissolution rate of paracetamol tablets produced by the granulation method. This gap highlights the importance of evaluating both forms of starch in a systematic manner.

Therefore, this study was conducted to investigate the effect of native and pregelatinized durian seed starch as binders on the dissolution rate of paracetamol tablets prepared by the

granulation method. This research is expected to provide scientific information on the suitability of durian seed starch as a local pharmaceutical excipient and to identify which preparation method produces better tablet characteristics and dissolution performance.

METHOD

Tools

Electromagnetic Sieve Shaker EMS-8, *Electrolab Tap density tester* EDT-1020, Oakton pH 510 *series*, oven, Erweka Tipe TA/TR 120, Erweka *Disintegrator tester* ZT X20, *Electrolab Dissolution tester (USP)* TDL-08L, dan spektrofotometri UV-Vis (Genesys).

Ingredients

Amylum durian seeds were obtained from the village of Banyuning Bali, akuadest (PT. Brataco), paracetamol (PT. Kimia Farma), primojel (PT. Bratachem), talk (PT. Bratachem), Lactose (PT. Bratachem)

Research Stages

1. Manufacture of natural durian seed amylum (*Native starch*)

Durian seed tubers are determined in advance at the Eka Karya Bali Botanical Garden to ensure that the materials used are correct. The tuber material to be used is cleaned and washed, then crushed with a blender with the addition of aqudest, where the durian seed ratio is used: aquadest (2:1 b/v). Next, squeezing and filtering are carried out using flannel fabric. The filtered water is deposited for 24 hours. Furthermore, the resulting supernatant liquid is discarded, then the sediment is washed with aquadest until clean amylum is obtained. The resulting sediment is dried using an oven, using a temperature of 50° C for 24 hours, then mashed and sifted to no.80 mesh.

2. Manufacture of amylum *pregelatinized durian* seeds.

A total of 100 g of durian seed amylum was weighed, then suspended with 100 ml of aquadest (1:1 b/v) and then heated to a temperature of $55^{oC\ for\ 10\ minutes}$ and stirring. The result is dried in the oven at a temperature of $60^{oC\ for}$ 24 hours, and sifting with a mesh size of 20.

3. Amylum characteristic test

Test the characteristics of native durian seed amylum *and* pregelatinized *durian seed amylum*. It is done to find out non-specific parameters. The tests include:

3.1. Uji organoleptik

Amylum durian seeds *Native* and *pregelatinized* weighed 1 gram, then observed the characteristics of the shape, smell, taste, and color of amylum using the five senses (Ministry of Health of the Republic of Indonesia, 2014).

3.2. Microscopic tests

Weighted amylum *Native* and *pregelatinized* 100 mg each, take enough amylum put on a glass object. Next, two drops of aquadest were added, then the shape of the hilus was observed, and the lamella with a microscope using 400x magnification (Ministry of Health of the Republic of Indonesia, 2014).

3.3. Macroscopic test

Measure the fineness of amylum *Native* and *pregelatinized* can be seen through the mesh no of the multi-level sieve. Weigh 100 grams of amylum and then sift mesh no. 20, 40, 60, and 80 on the device.

3.4. Drying shrinkage test

A shallow weighing bottle is covered, then heated to a temperature of 105^{oC} For 30 minutes, add 1 gram of aylum that has been weighed. Weighing along with the contents of a weighing bottle, then in the oven, the lid of the stopper is opened and in the oven. Dried at 105^{oC} until the weight is fixed (Ministry of Health of the Republic of Indonesia, 2014).

3.5. pH test

Amylum mixed *Native* and *pregelatinized* 5 grams with 25 ml of CO-free water$_2$ for 1 minute and then let it sit for 15 minutes. then measured with a pH meter. Amylum *Native* It has a pH of about 5.5-6.5 and 4.5-7 for durian seed amylum *pregelatinized* (Karisma et al., 2012)

4. Amylum Physical Properties Test

It is done on native durian seed amylum *and* pregelatinized *durian seed amylum*. The tests include:

4.1 Humidity test.

Amylum durian seeds *Native* and amylum durian seeds *pregelatinized*. weighed 5 grams then put in the oven for 15 minutes at 105^{0C}. The moisture content according to the parameter is 1-5% (Ansel, 2011)

4.2 Particle size distribution test

Using a multi-level sieve, weighing 100 grams of amylum, sifting is carried out starting from a mesh with sizes of 20, 30, 50, 60, 80, 100 with 10 rpm for 15 minutes. The results obtained from each mesh are weighed and calculated as a percentage of fines. (Ansel, 2011).

4.3 Test flow time and idle angle

Weigh 100 grams of durian seed amylum *Native* and amylum durian seeds *pregelatinized*. Then slowly insert the amylum into the funnel where the lower end is held by a baffle so that the amylum does not flow, then the top is flattened, then the tool is run (Adedokun and Itiola, 2011).

4.4 Compatibility test

Compatibility is the result of calculations obtained from the measurement of bulk type weight and type weight after compression (Mariyani et al., 2012).

5 Tablet Printing

Paracetamol is mixed with lactose, durian seed amylum (*native* / *pregelatinized*), and mg of stearate and mixed until homogeneous. The mixture is then printed with a die size suitable for the weight of 500 mg tablets.

6. Test the physical properties of the tablets

6.1 Uji organoleptis

Tablets produced from durian seed amylum binder *Native* and amylum durian seeds *pregelatinized*., physically observed from the tablets including the smell, color and shape of the tablets (Ansel, 2011).

6.2 Weight uniformity test

Twenty tablets were weighed, then the average weight was calculated. One tablet at a time is weighed, compared to the average weight of the tablet. The uniformity of tablet weight prescribed for tablets weighing >300 mg is no more than 2 tablets whose weight deviates from the average weight of >5% and not a single tablet whose weight deviates from the average weight of >10% (Diós et al., 2015).

6.3 Hardness test

A total of ten tablets will be tested, placed on the platform of the hardness test machine one by one. The number in units of Kg shown on the scale indicates the hardness of the tablet. The hardness requirement of a good tablet is (4-8) Kg.

6.4 Fragility test

The tablets to be tested are beaten free first. Randomly selected and weighed 10 tablets. All tablets are inserted into a fragility test device at 25 rpm for 4 minutes. Next, the tablets are released from the beat again and weighed. The weight of the lost tablet is calculated (%). Lost weight of tablets < 1% (Femi-Oyewo et al., 2015).

6.5 Time test destroyed

6 tablets were randomly selected, then each tablet was put into a time test device. As a medium used water temperature (37 ± 2)° C. The required parameter for the crushing time for tablets is <15 minutes (Al-Gousous and Langguth, 2015).

6.6 Test solution

The solution medium used was 900 mL of phosphate solution pH 5.8, temperature (37±0.5)°C. The stirring speed used is 50 rpm, with a time of 30 minutes (United States Pharmacopeial Convention, 2014).

Data Analysis

The test results were statistically analyzed with a t-test of two free samples, a confidence level of 95%. The t-test was used to see the effect of the method of making amylum on the dissolution rate of paracetamol tablets produced from a significant value (α).

RESULTS AND DISCUSSIONS

1. Amylum characteristic test

1.1 Uji organoleptik

Organoleptically (table 1.) amylum *pregelatinized durian seeds* are brownish-white in color. Meanwhile, the smell and taste produced from the two amylum are in accordance with the provisions of the Indonesian Pharmacopoeia V (2014).

1.2 Microscopic test test

Microscopic observation (table 1.) is *native*, oval-shaped, with a single amylum arrangement, while amylum is *pregelatinized* durian seed amylum, with an amorphous amylum form where the amylum granules break down (figure 1.). This is due to the gelatinization process that causes amylum granules to break,

1.3 Macroscopic test

Amylum native durian seeds are macroscopically classified as a very *fine powder*, because amylum is able to pass through mesh sieve no. 70/200 (table 3.). Amylum *pregelatinized durian seeds* are classified as coarse powder because all of them can pass through the mesh sieve no. 35/50 and 10.04% amylum pass through the mesh sieve no. 70/200.This is in accordance with the Indonesian Pharmacopoeia V (2014).

1.4 Drying shrinkage test

Drying depreciation of durian amylum seeds (Table 1.) *native*, and *pregelatinized* consecutively were (12.91 ± 0.38)%; (11.8 ± 0.59)% and meet the drying shrinkage requirements for amylum contained in the Indonesian Pharmacopoeia V (2014).

1.5 pH Test

Average pH measurement of durian seed amylum (table 1.) *Native* and *pregelatinized* consecutively are (6.30 ± 0.36); (6.53 ± 0.23). From the results of the pH measurement above, meet the required range of 4.0-7.0 (Ansel, 2011).

2. Amylum Physical Properties Test

2.1 Humidity test

Average moisture of amylum durian seeds (table 2.) *Native* and *pregelatinized* respectively were (2.60 ± 0.13)% and (2.54 ± 0.13)%. The amylum has moisture that meets good humidity requirements. (1%-5%) (United States Pharmacopeial Convention, 2014).

2.2 Particle size distribution test

The number of amylum particles of durian seeds (Table 3.) *native* more at a particle size of 0.074 mm (sieve <200 Mesh). This is in stark contrast to *pregelatinized* amylum which has the most particles at a size of 0.398 mm (35/50 Mesh sieve).

2.3 Test flow time and idle angle

Amylum durian seed flow time *pregelatinized* is (10.27 ± 0.56) grams/second, with a silent angle of (26.61 ± 0.66)°, while amylum *Native* is not capable of flow and there is no idle angle (Table 2.). The flow time and idle angle are greatly influenced by the particle shape, particle size distribution and humidity. The flow time is said to be good if 100 grams of amylum requires no more than 25 seconds to flow from the funnel or not less than 4 grams/second. For durian seed amylum *pregelatinized* has a good idle angle because the idle angle that forms enters the range of 25° – 30° (Femi-Oyewo et al., 2015).

2.4 Compatibility test

Average compatibility of amylum durian seeds (Table 4.) *Native* and *pregelatinized* respectively are (2.78)% and (17.013)%. The value of compatibility is the ability of the amylum to compress after being tapped in. It is influenced by the particle size distribution (Wlodarski et al., 2016).

3. Test the physical properties of the tablets

3.1 Uji organoleptis

As seen in table 6, paracetamol tablets with *pregelatinized* durian seed amylum as a binder have a flat circular shape of 11 $\pm$ 0.01 mm in diameter with a brownish-white tablet color and are odorless. and are not *capped*. Meanwhile, paracetamol tablets with native durian seed amylum as a white binder but capping. The compatibility of the amylum and the presence of an excessive number of fines can affect this. To fill the cavity between the particles, the right amount of fines is needed so that the resulting tablets will be more compact, and it is not easy *to capping.* However, large fines can cause *capping*

3.2 Weight uniformity test

The uniformity of tablet weight shown in table 7 shows that both tablet formulas meet the requirements of the Indonesian Pharmacopoeia Edition V (2014). No tablets differed in weight from their average weight >5% and none of their weights deviated from their average weight >10%.

3.3 Hardness test

Average hardness of paracetamol tablets with durian seed amylum *Native* and amylum durian seeds *pregelatinized* as consecutive binders are (3.43 ± 0.20) and (7.04 ± 0.26) kg. From these results (table 7) durian seed amylum *Native* does not meet the requirements of good

hardness which is between 4 kg-8 kg (Ansel, 2011), because the fasteners used have poor binding ability.

3.4 Fragility test

Average fragility of paracetamol tablets with durian seed amylum *Native* and amylum durian seeds *pregelatinized* as binders (table 7) are (1.70 ± 0.05)%, and (0.32 ± 0.01)%. From these results, the durian seed amylum formula *Native* does not meet the requirements of good fragility, i.e. it must not be >1% (Ansel, 2011). Fines affect the fragility of the tablets and the properties of the binding agents in the formulation of the tablet preparation. Formulas with a higher number of fineries will have greater brittleness.

3.5 Time test destroyed

Average time of destruction of paracetamol tablets with durian seed amylum *Native* and amylum durian seeds *pregelatinized* as a binder (Table 7) is (1,49 ± 0.24), and (4,86 ± 0.20) minutes. From these results, the two formulas of durian seed amylum *Native* and *pregelatinized* It meets the destruction time requirement for tablets which is less than 15 minutes (Ministry of Health of the Republic of Indonesia, 2014)

3.6 Test solution

The determination of paracetamol levels can be determined by the UV-Vis spectrophotometry method using calibration curves and linear regression line equations. The value of y = bx + a, obtained is y = 0.439 x + 0.07, with the value of the correlation coefficient (r) being 0.992. The value of the correlation coefficient that has a very strong correlation interpretation is 0.810-0.999. The LOD (Limit of Detection) and LOQ (Limit of Quantitation) values obtained were 0.09 μg and 0.30 μg, respectively. The absorbance value of the solution of paracetamol tablets is shown in table 8. From the results of the absorbance, the dissolved paracetamol concentration is then calculated which can be seen in table 9. The average solution of paracetamol tablets with native durian seed amylum *and* pregelatinized *durian seed amylum* as a binder is shown in table 10.

Based on table 10, it shows that the dissolution rate of paracetamol tablets in formula I and formula II increases every minute. At the 30th minute, the average percentage of dissolved paracetamol levels in formula I and formula II were (93.17±0.01) % and (81.76±0.20) %. The dissolved paracetamol content has met the requirements of paracetamol tablet dissolution test at the USP (*Unites States Pharmacopeia*) which states that not less than 80% (Q) of the active substance must be dissolved for 30 minutes. Based on the criteria for acceptance of the dissolved results, in Pharmacopoeia Indonesia V (2014), at stage S_1, formula I has met the acceptance criteria, where each unit of preparation is not less than Q+5%, where the value of Q is the amount of dissolved active substances, as stated in each monograph. While in formula II, at stage S_1 did not meet the acceptance criteria, then continued at stage S_2, formula II met the acceptance criteria where each unit ≥ Q and there was not a single unit that had a value of < Q – 15%. This shows that the ability of *prgelatinized* durian seed amylum as a binder is stronger than native durian seed amylum so that it is able to resist the release of the active substance paracetamol.

Table 11. shows the results of *the t-test* test in solution of formula I and formula II paracetamol tablets. In this study, the confidence level (α) used was 5% (0.05). The *significance value of* the tablet solution test gives a value that is smaller than the value of α and the value of

t_{is} greater than the t_{table}, so that the decision becomes a minus H_0, that there is a significant difference between formula I and formula II.

The percentage of paracetamol dissolved in formula I paracetamol tablets is greater than that of formula II. In addition, the *flux* formula I is larger than formula II. The greater the value *flux*, then the better the solution produced, because the greater the increase in the concentration of the dissolved active substance. The reason for this is that the destruction time of formula I tablets is faster than that of formula II and the fragility value of formula I is greater than that of formula II.

CONCLUSION

There is an effect of the durian seed amylum preparation method on the rate of dissolution of paracetamol tablets by the granulation method. Based on the physical properties of the tablets, the use *of pregelatinized* durian seed amylum as a tablet binder has better tablet physical properties than tablets that use native durian seed amylum as a binder. The use of native durian seed amyl as a binder in paracetamol tablets resulted in a higher percentage value of dissolved paracetamol content than the use of *pregelatinized durian seed amylum* as a binder in paracetamol tablets. The Q value (corrected level) of paracetamol tablets with native durian seed amylum as a binder was (93.17±0.01)% while the Q value (corrected level) of paracetamol tablets with *pregelatinized* durian seed amylum as a binder was (81.76±0.20)%. Based on these findings, it is suggested that further studies optimize the concentration of native and pregelatinized durian seed starch in tablet formulations in order to obtain an ideal balance between good physical tablet properties and optimal dissolution rate. Future research is also recommended to evaluate other modification methods of durian seed starch, compare its performance with standard commercial binders, and examine its stability and applicability in different types of pharmaceutical formulations. Such studies would strengthen the potential use of durian seed starch as a local and economical pharmaceutical excipient.

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