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CO-PROCESSED EXCIPIENTS EFFECT OF PARTIALLY PREGELATINIZED CASSAVA STARCH (MANIHOT UTILISSIMA) AND HPMC K-100 ON THE MECHANICAL PROPERTIES OF LOSARTAN POTASSIUM TABLETS

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Abstract

Background: Based on previous research, partially pregelatinized cassava starch produces brittle tablets with a friability value of >1%. Partial pregelatinization and co-processing are the methods used to improve these physical properties. In this research, HPMC K-100 was used in the cassava starch co-processing to provide mechanical strength to the tablets. Objective: Co-processed excipient production of partially pregelatinized cassava starch and HPMC K-100 was aimed to improve the mechanical properties of tablets. Method: Four formulas were made, including F1 (only partially pregelatinized cassava starch) and F2, F3, and F4, resulting from co-processing with HPMC K-100 with concentrations of 2%, 3%, and 4%. Pregelatinized cassava starch was suspended in water at a temperature of 55oC, heated and stirred for 70 minutes, mixed with HPMC K-100 solution, and dried in an oven. F1 as a comparison (T1) and the best formula (T2) were then molded into tablets with losartan potassium as the model active substance. Result: F4 is the best formula with a flow rate of 16.08 g/second, angle of repose of 26.91o, % compressibility of 13.33%, and tensile strength of 1.0063 mPa at a pressure of 50 kg/cm2. Tablet evaluation shows that T1 does not meet the hardness test requirements, and broken tablets are also found in the friability test, while T2 meets the requirements with a hardness value of 4.53 kg/cm2 and an F value of <1%. Conclusion: Co-processed excipients of partially pregelatinized cassava starch and HPMC K-100 with a concentration of 4% can increase tablet hardness and reduce tablet friability.

Keywords: Cassava Starch; HPMC K-100; Partially Pregelatinized; Co-Processed Tablets.

INTRODUCTION

Pregelatinization is one of the methods for modifying starch, i.e., by changing the structure of natural starch by heating suspensions of starch in water at a specific temperature. There are two types of starch pregelatinization: fully pregelatinized and partially pregelatinized. Partial starch makes starch flowable and has good compressibility. In contrast, total starch produces cold-water-soluble starch that can be used as a bonding agent in wet granulation methods (1) (Sheskey dkk., 2017). Partially pregelatinized cassava starch has many functions in tablet formulation, including as a filler, a binder, and a disintegrant, in addition to having better flowability 2. (Zhang et al., 2013). (3)

Based on research conducted by Yusuf et al., partially pregelatinized cassava starch produces brittle tablets with a friability value of >1%, as in the dry state, its binding capacity is low(4) (Yusuf et al., 2008). Thus, it is necessary to develop excipients from cassava starch, one of which is the co-process method. Co-processing is done by combining two or more existing excipients to produce excipients with complementary and superior properties to the original material (4). (Sulaiman & Sulaiman, 2020). Co-processing of cassava starch can be done using synthetic or natural polymers (6). This polymer is a binder to increase the starch's binding capacity and produce tablets that

meet the requirements(7).(Trisna Dewi et al., 2019). Hydroxypropyl methylcellulose (HPMC) is a polymer that is generally used as a binder in tablet excipients due to its cohesive properties and ability to provide mechanical strength to tablets (8) (Okunlola, 2018).

Based on this background, in order to improve the mechanical properties of tablets as described above, excipients were manufactured using a co-process method between partially pregelatinized cassava starch (manihot utilissima) and HPMC K-100 using the active substance losartan potassium as a model due to its small dosage of 50 mg per tablet, so that its flow and compressibility are affected by the tablet excipients. (5)(Sulaiman & Sulaiman, 2020).

METHOD

Materials

Losartan potassium (Zhejiang Huahai Pharmaceutical Co.,LTD.), cassava starch (CV. Glory Persada Manunggal), HPMC K-100 (Ashland), moisture balance (Amstech), polarizing microscope (Olympus), tap density tester (TDTF ZS-2E), flowability tester, friability tester (CS-2), disintegration tester (TDTF ZBS-6E), hardness tester (Erweka), tablet punch machine (Athena)

Methods

Manufacturing of Partially Pregelatinized Cassava Starch

Cassava starch was divided into 4 parts: F1, F2, F3, and F4. Each of them was suspended in water that had been heated to a temperature of 55oC until a cassava starch suspension rate of 40% b/b was obtained. The cassava starch suspension was then heated to 55oC while being stirred for 70 minutes. For F1, it was dried at 45oC for 24 hours and then sieved using an 18-mesh sieve. Then it was redried in the oven at 45oC to a water content of ±3% and sieved using a 60-mesh sieve (9).

Co-process Excipient Manufacturing of Partially Pregelatinized Cassava Starch & HPMC

Table 1: Co-process Excipient Formula

Materials	Formula			
	F1	F2	F3	F4
Partially pregelatinized cassava starch suspension	700 g	700 g	700 g	700 g
HPMC K-100	-	2%	3%	4%

HPMC K-100 solution was made with a ratio of 2%, 3%, and 4% of the weight of cassava starch using cold water. Each HPMC K-100 solution was mixed into a partially pregelatinized cassava starch suspension with the formula shown in Table 1. The mixing process was carried out for 10 minutes while stirring. The mixture was then dried in an oven at 45 oC for 24 hours, and a wet mass was formed, which was then sieved using an 18-mesh sieve. After sieving, the mixture was re-dried in an oven at 45 oC until the water content in the granules was ±3%. Then sieving was carried out again using a 60-mesh sieve.

Flowability

100 g of granule was weighed, and then put into the funnel on the flowability tester. The time it took for the granules to flow through the funnel was calculated using a stopwatch. The granule flow rate was obtained by dividing the granule weight in grams by the time in seconds. If the obtained flow rate was >10 grams per second, the granules were considered to be flowing well (10) (Elisabeth et al., 2018).

Repose Angle Test

The height (h) of the granule falling from the flow rate tester was measured using a caliper, and its diameter (D) was measured using a ruler. The angle of repose was obtained from the anti-tangent ratio of height (h) and diameter (D).

Compressibility Index

100 g of granule was weighed and put into a measuring glass on a tap density tester. The initial granule volume (Vo) was recorded. The instrument at beats 10, 500, and 1250 was set, and the granule volume at each beat of V10, V500, and V1250 was also recorded.

Compactability Test

Granules were weighed at 500 mg. The sample was inserted into a 13-mm-diameter die and compressed under a range of pressures of 10, 20, 30, 40, and 50 kg/cm2. The diameter and thickness of each tablet were measured using a thickness meter, and the tablets were tested using a hardness tester. The tensile strength is determined as follows (Rowe et al., 1974):

$$\sigma = "2F" / \pi Dt$$

Where σ is tensile strength (Mpa), F is tablet hardness (N), D is tablet diameter (mm), and t is tablet thickness (mm). The compactability profile was obtained by plotting compression pressure and tensile strength.

Losartan Potassium Tablet Manufacturing with Direct Compression Method

Losartan potassium tablets were made in two formulas, namely T1 and T2, with a weight of 150 mg per tablet. T1 contains 50 mg losartan potassium powder and 100 mg partially pregelatinized cassava starch, while T2 contains 50 mg losartan potassium powder and co-processed excipients of partially pregelatinized cassava starch and 4% HPMC K-100 as much as 100 mg. The two ingredients were mixed and stirred until homogeneous, then pressed using a tablet punch machine. The losartan potassium tablet formula can be seen in Table 2.

Table 2: Losartan Potassium Tablet Formula

Materials	Quantity	
	T1	T2
Losartan potassium	50 mg	50 mg
Partially pregelatinized cassava starch	100 mg	-
Co-processed excipient	-	100 mg

Description:

T1 = Losartan potassium: Partially pregelatinized cassava starch (1:2)

T2 = Losartan potassium: Co-processed excipient (1:2)

Tablet Evaluation

Tablet Hardness Test

The tablet was placed in a hardness tester. Tablet hardness meets the requirements if the value obtained is from 4 to 8 or 10 kg (11) (Bano et al., 2011).

Tablet Friability Test

The tablets were taken using tweezers and cleaned one by one from the dust attached using a brush. The tablets were weighed, and the initial weight (Wo) was recorded. The friability tester drum was cleaned with a brush. The tablet was inserted, and the device was operated at a speed of 25 rotations per minute (rpm) of 100x rotations for 4 minutes.

Disintegration Time Test

Each of the six tubes consisted of one basket, and one tablet was put in each basket, and then a disc was put in each tube. The medium used is water at a temperature of 37oC. If there are one or two tablets that do not completely disintegrate in less than 15 minutes for uncoated tablets, then the test is carried out using 12 additional tablets. The disintegration time test for further testing meets the requirements when no less than 16 of the 18 tablets tested must completely disintegrate (Ministry of Health of the Republic of Indonesia, 2020).

RESULTS AND DISCUSSION

Based on the granule evaluation results (table 3), it is found that all formulas have very good flow rates and angles of repose. Powder that has good flow properties does not create voids in die and fills the die constantly, resulting in tablets with a uniform weight (12) (Prasetya, 2019). Non-uniform weights when making tablets can affect the dosage per tablet, resulting in the therapeutic effect not being achieved (13) (Rahmat et al., 2019). The pregelatinization process causes the particle size of the granules to increase due to the weakening of the hydrogen bonds between amylose and amylopectin, which causes the granules to absorb water and expand rapidly so that a larger particle size is obtained (14)(Lestari et al., 2019). The larger the particle size, the smaller the cohesive force between the granule particles, as the large cohesive force makes it difficult for the granules to flow freely (10)(Elisabeth et al., 2018).

Table 3: Granule Evaluation Result

Sample	Flow Rate (g/second)	Repose angle (º)	Compressibility Index (%)
F1	15,89±0,53	26,16±1,75	14,00±1,41
F2	15,08±0,14	27,25±0,38	14,33±2,51
F3	16,07±0,09	27,01±0,30	15,33±1,15
F4	16,08±0,31	26,91±0,94	13,33±2,08

Description:

F1 = Partially pregelatinized cassava starch

F2 = Partially pregelatinized cassava starch and 2% HPMC K-100 co-process

F3 = Partially pregelatinized cassava starch and 3% HPMC K-100 co-process

F4 = Partially pregelatinized cassava starch and 4% HPMC K-100 co-process

The compressibility index is affected by particle shape and particle size(8). Based on the granule evaluation results, all formulas fall into the good compressibility index category in the range of 11–15% due to the pregelatinization process that causes an increase in the particle size of the starch granules; the larger the particle size, the better the flow properties and the smaller the density(10) (Elisabeth et al., 2018). Apart from that, the compressibility index is affected by porosity, which is the gap between powder particles or granules; the smaller the porosity, the better the compressibility (12) (Prasetya, 2019).

The compactibility test aims to determine whether the powder or granules to be compressed can produce a compact mass after being given a certain pressure. This test is used as a parameter to determine the hardness and brittleness of tablets. The hardness or compactibility of a material is determined by the characteristics of a change of shape (deformation). The compactibility test meets the requirements if the tensile strength ratio is in the range of 1-4 mPa (15). The tensile strength can be seen in Figure 1.

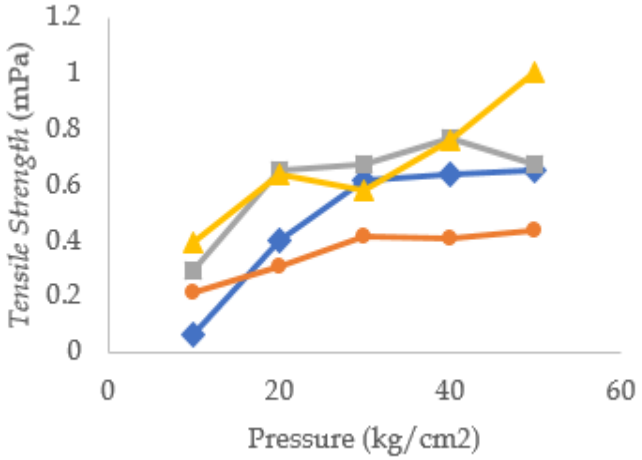

Figure 1: Tensile strength Curve

Description:

- F1 = Partially pregelatinized cassava strength
- F2 = Partially pregelatinized cassava strength and 2% HPMC K-100 co-process
- F3 = Partially pregelatinized cassava strength and 3% HPMC K-100 co-process
- F4 = Partially pregelatinized cassava strength and 4% HPMC K-100 co-process

Figure 1 shows that F4 has a tensile strength value that meets the requirements at a pressure of 50 kg/cm2.

This is because, compared to other formulas, the formula has co-processed excipients with the highest bonding concentration, namely 4% HPMC K-100. The higher the concentration of the binder, the higher the hardness of the tablet and the lower the brittleness (16)(Fadhilah & Saryanti, 2019)(17). The presence of a binder causes an

increase in interparticle bonding. With pressure, the binder is forced into the interparticle space, which produces a stronger bond between the granular particles (18). (Chasanah et al., 2017).(19) F1, F2, and F3 have lower tensile strength values as F1 does not contain any bonding material, whereas F2 or F3 contain less bonding than F4. Based on the granule evaluation results of the three co-processed excipient formulas, F4 is the best formula to be molded into T2 tablets. At the same time, as a comparison, F1 is used to be molded into T1 tablets. Before molding into tablets, each formula is mixed with losartan potassium, which acts as the active substance. In this study, losartan potassium is chosen as the model active substance as it has poor flow properties with a Hausner ratio of 1.45 (20). By using co-processed excipients that can function as fillers and binders with good flow properties and compressibility and by adding as much as 2–3 times the weight of the active substance, the properties of the tablet are fully affected by the excipient so that the effects of the excipient can be seen (5)(Sulaiman & Sulaiman, 2020).

Table 4: Losartan Potassium Tablet Evaluation

Formula	Hardness (kg/cm^2)	Friability (%)	Disintegration time (second)
T1	2,57± 0,64	-	298,5±20,54
T2	4,53± 0,79	0,99	395,8±31,58

Description:

T1= losartan potassium: partially pregelatinized cassava starch (1:2)

T2 = losartan potassium: co-processed expicient of partially pregelatinized cassava starch and 4 % HPMC K-100 (1:2)

Tablets must have sufficient mechanical strength to withstand manufacturing, packaging, and transportation handling. A tablet is declared to meet the requirements if its hardness is 4 to 8 or 10 kg (11) (Bano et al., 2011). Based on the results, T1 does not meet the requirements as the formula only contains partially pregelatinized cassava starch without any co-processed excipients. Starch contains amylose, which acts as a disintegrator, and amylopectin, which acts as a binder. However, due to the heating process in modified cassava starch, the composition of amylopectin in cassava starch is reduced, thereby reducing its binding capacity (21). Apart from that, other literature states that partially pregelatinized cassava starch has low binding capacity when in dry conditions (4)(Yusuf et al., 2008). The T2 tablet meets the hardness test requirements due to the co-process method carried out in T2 between partially pregelatinized cassava starch and 4% HPMC K-100, which acts as a filler and a binder, so that the presence of HPMC K-100, which acts as a binder, can result in a gradual decrease in tablet porosity due to more interparticle cavities filled by the binders (18). (Chasanah et al., 2017). (19)

The friability test result shows that T1 does not meet the requirements as there is capping on the tablet when molded, which is caused by T1, which only contains partially pregelatinized cassava starch without co-processed excipients. In the pregelatinization process, heating causes the amylopectin levels in cassava starch to decrease, reducing its binding capacity (Lachman, 1994). The friability test results on T2 obtained a friability value of 0.99%, which meets the requirements of F<1%. This proves that tablets with high hardness will have lower brittleness (Chasanah et al., 2017).

The disintegration time test result shows that both formulas meet the requirements, with the disintegration time being <15 minutes. T1 has a faster disintegration time than T2 due to the absence of binders in T1, which can reduce the porosity of the tablet so that water can quickly enter the tablet, whereas T2 contains HPMC K-100 binder, which causes a decrease in the tablet porosities, making it difficult for water to get into the tablet and causing a longer disintegration time for the tablet. (22) (Audu-Peter & Ibrahim, 2016).

CONCLUSIONS AND SUGGESTIONS

Cassava starch modified by a partial pregelatinization process can be used to make excipients by a co-process method with HPMC K-100. This co-processed excipient can improve the mechanical properties of tablets, such as tensile strength and tablet hardness. It can also reduce tablet friability. The active substance used as a model is losartan potassium.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

We declare that the work presented in this article is original and all responsibility for claims relating to the contents of this article will be borne by us.

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