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Physical Modification and Characterization of Starch Using Pregelatinization and Co-process of Various Tubers from Yogyakarta as an Excipient

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Abstract. Starch is an economical excipient that is used in oral dosage form. It has poor compressibility and flowability. Pregelatinization and co-process as a physical modification technique have been conducted widely; nevertheless, the single modification shows a limitation. This study aims to assess and characterize the starch result of the modification of various tubers by a combination of modification methods. The starches from various tubers were extracted by sedimentation. Starch pregelatinization was conducted by manufacturing a starch suspension and was heated at 55^{o}C for 70 minutes, and then it was mixed using concentrations HPMC k15 of 2, 3, and 4% (w/w) of the starch weight. The evaluations that were conducted are general identification, amylose concentration, physical properties, and physicochemical identification. The obtained starch of the extraction was 10-18% of the fresh tubers, with the concentration of amylose around 21-37%. The shape and particle size of the starch affected the amylose concentration. The starch modification showed an improvement of the granules physical properties by addition of HPMC. The amylose concentration of yam starch was 37.60% and showed the optimum modification result in the addition of HPMC 4%. There were no changes in the physicochemical properties of the result of IR and X-ray diffraction analysis. The melting point of yam starch-HPMC 4% was 151.24^{o}C with reduction of the maximum weight at 328.52^{o}C. This study indicated that the yam starch has the highest amylose concentration with optimum granules result of the modification in addition of HPMC 4% that could be used as an alternative excipient..

INTRODUCTION

Tuber plants grow in tropical and subtropical regions, such as Indonesia. There are abundant types of tubers in Indonesia, and even the local tubers in Yogyakarta Special Province reach 65 different types including *ubi jalar* (sweet potato), *ubi kayu* (cassava), *garut* (arrowroot), *talas* (taro), *uwi* (yam), *gembili* (lesser yam), and others. Starch or starch is one of the non-active ingredients/excipients used as an economical filler for tablets, and most medications therefore use oral preparations and 70% of them are in tablet dosage form [1-2]. Starch is vastly applied as a filler, binder, glidant, and disintegrant in oral dosage forms, such as corn starch (*Zea mays*), potato starch (*Solanum tuberosum*), rice starch (*Oryza sativa*), cassava starch (*Manihot utilissima*), and wheat starch (*Triticum aestivum*) [3].

Taro (*Colocassia esculenta*), lesser yam (*Dioscorea esculenta*), sweet potato (*Ipomoea batatas*), and cassava (*Manihot utilissima*). However, are less commonly used as additional ingredient in drug preparation since their starch generally has poor flowability and compressibility. Until recently, most of the tablet formulations are conducted with direct compression method using filler-binder to increase the production effectivity. The excipients that possess bad flowability and compactibility can not be formulated using direct compression method for the reason that the tablet resulted will possess bad friability and experience splitting or capping [4-5].

One of the efforts to improve the physicochemical properties of starch is conducted by refining the size and shape of starch particles. Partial pregelatinization and co-process are frequently used as physical modification

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techniques, but the result of this single modification has a limitation for excipient use. Partial pregelatinization is a thermal modification technique commonly used to improve the physical properties of starch affected by temperature and water so as to obtain irreversible particle shape. Such cellulose-derived polymer as HPMC (Hydroxypropyl Methylcellulose) is a plastic material excipient used to improve particle shape by joining or binding to other particles. Furthermore, a previous study revealed that HPMC as a binder polymer in the making of co-processed excipient for lactose granule demonstrated better flowability than other binders [6-8].

MATERIALS AND METHODS

Materials

Taro (*Colocasia esculenta*), cassava (*Manihot utilissima*), sweet potato (*Ipomoea batatas*), and lesser yam (*Dioscorea esculenta*) were obtained from the vendors in Yogyakarta Special Province (especially in traditional market of Sleman, Gunung Kidul, and Bantul). The ready-to-harvest tubers were used in this study and the tubers were identified in Laboratorium Botani-Farmasi, Universitas Islam Indonesia. HPMC (Hydroxypropyl Methylcellulose) Metochel^{TM} k15 was provided by the Laboratory of Pharmaceutical Technology of Islamic University of Indonesia. The standard amylose was obtained from ChemMix, Yogyakarta. Other chemicals were of analytical grades.

Extraction of Starch

The extraction used a sedimentation technique by first peeling and washing the tubers before a grater machine was utilized to grate them. Water was added to the grated tubers, which was then squeezed to obtain starch in the form of white sediment. The starch extraction was optimized by resting the sediment for 12-24 hours, then separating and drying it in an oven to a temperature of 45^{o}C. The dry starch was then filtered using 80 mesh and stored in a room-temperature chamber [9].

Identification of Starch

Starch identification was performed to examine the typical characteristics of taro starch that include percentage content, organoleptic, microscopic identification, identification of SEM (Phenom), moisture content, and amylose-amylopectin content [4, 10-12].

Identification of Amylose and Amylopectin Content

As much as 10 mg starch was put into a 25mL flask, then 1 mL of 95% ethanol and 1mL of NaOH 1 N were added. Aquadest was poured up to the ring mark to obtain 200 ppm aliquot. Based on the series of amylose content, the aliquot was measured for 10, 20, 30, 40, and 50 ppm to be placed in 10 mL flask. Then, 1mL buffer of ammonium chloride (NH_4Cl) 0.9N and 1 mL of iodine solution (1.5% KI and 0.15% I_2) were added. Aquadest was poured to obtain 10 mL solution. The color change and stability were then observed and read using a UV/Vis spectrophotometer at 614 nm wavelength [13-14].

Identification of Flowability

Flow Rate

As much as 100 gram starch and modified starch granule were tested using a flowability tester and recorded for the flow rate of powder or granule. The test was replicated 3 times with gram/second (g/sec) measurement parameter [12].

Angle of Repose

As much as 100 gram starch and modified starch granule were evaluated for the angle of repose by placing it in a funnel (equipment). When the funnel lid was opened, the resulted angle was noted. The powder's peak height was measured as H (cm), and the diameter of distribution area was measured as R (cm) [12].

$$Tan\ \alpha = \frac{h}{r}$$

Identification of Compressibility

Carr's Index

Taro starch and modified taro starch granule were put into a 100 mL flask, and then the volume was weighed and recorded as bulk volume (V_0). The cylinder was tapped for 500 times, and the volume was recorded as tapped volume (V_{500}). The test was replicated 3 times [4].

$$CI = 100x\ \frac{Tapped\ Density - Bulk\ density}{Tapped\ Density}$$

Hausner Ratio

The value of Hausner ratio was obtained by comparing Tapped Density with Bulk Density[4].

Identification of Particle-Size Distribution

As much as 50 grams of modified starch was tested for the particle-size distribution using a sieve shaker sized 12, 14, 16, 18, 20, 30, 40, and 60 mesh for 10 minutes [15].

$$d_{av} = \frac{\sum(\%\ Granule\ Weight\ x\ Mean\ Diameter\ of\ Mesh)}{100}$$

Granule Compactibility

The granule mass was compressed at the same volume and pressure on a low punch scale of 13 mm with a tablet volume capacity of 650 mg. The obtained 6 tablets were measured for the hardness using a hardness tester and compared to Starch® 1500 [16]

Identification of Physicochemical Properties

The starch and modified starch were identified using Fourier Transform Infrared (Nicolet Avatar IR 360) to analyze the functional groups in starch both before and after the modification. The Differential Scanning Calorimetry (Shimadzu, DSC-60 Plus) identified the transition phases in a particle, the Thermo-Gravimetric Analysis (Shimadzu, Simultaneous DTA-TG) studied the weight decrease due to temperature, and the X-Ray Diffraction (Shimadzu, XRD-6000) examined the crystal form of starch and modified starch. The amylose content in each obtained starch was then measured.

RESULTS AND DISCUSSION

Identification of Starch

The starch obtained from tuber extraction is approximately 10-18% the weight of fresh tubers. Each starch has distinct characteristics, such as the shape and granule size, that can affect the amylose content [7]. The high mucilage content in taro and lesser yam can inhibit starch sedimentation during extraction; a pre-treatment is therefore required to improve the extraction result.

The general characteristics of starch include fine powder, polygonal shape, and <30um in size. The microscopic observation shows that there are different starch particle shapes; taro starch has irregular polygonal shape lesser yam starch is polygonal, cassava starch has polygonal and partly round shape, and sweet potato starch has polygonal and partly oval shape. This distinctive characteristic may be due to the difference in amylose content leading to physicochemical property differences.

Based on the observation result, the starch obtained from various tubers has different characteristics due to a variety of factors including the mineral factor as well as the amylose-amylopectin content.

The modified starch has a larger size than the unmodified one not only because of the partial pregelatinization that changes the particle shape but also due to the addition of HPMC as a polymer and binder at once. When HPMC binds starch particles to each other, they become granule that has a larger size than the initial one. The excipient in tablet formulation should have at least good flowability, which is affected by the round particle shape and the large particle size with a filler-binder characteristic.

The identification using SEM for modified sweet potato starch illustrated in **FIGURE 1,** indicates that granules are formed with a size of 70µm, larger than the unmodified starch of sweet potato (a). In addition, it is observable that the HPMC sticks to and binds the starch to each other leading to the formation of modified starch granule (b).

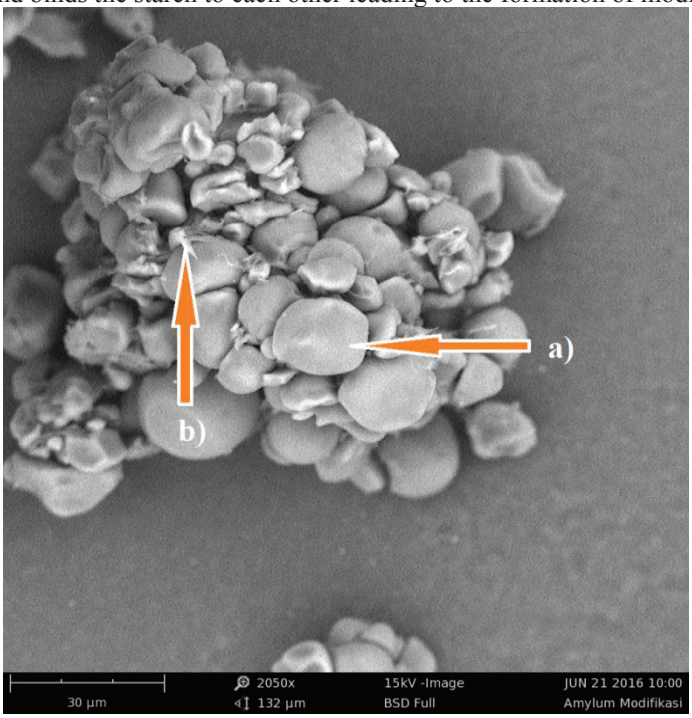

FIGURE 1. Identification of 4% Sweet Potato Starch using Scanning Electron Microscopy (SEM); a) Starch of Sweet Potato (Polygonal), b) HPMC (Amorphous) Attached to Sweet Potato Starch

Identification of Amylose and Amylopectin Content

Amylose is a monomer with spiral or helical shape that will form an inclusion complex with iodine through hydrogen binding. Therefore, the number of amylose units can be analyzed quantitatively based on the color intensity [17]. Sweet potato starch contains 40.40% amylose, the highest amylose content of all. The shape and size of starch is related to the amylose-amylopectin content as explained in the previous study by Wani, et al. [7]. The high amylose content can be used as an excipient by forming plastic deformation. The starch of sweet potato contains higher amylose compared to the others as much as 37.6 % (b/b). The difference in amylose content can affect the starch gelatinization and termination of glycosidic bond.

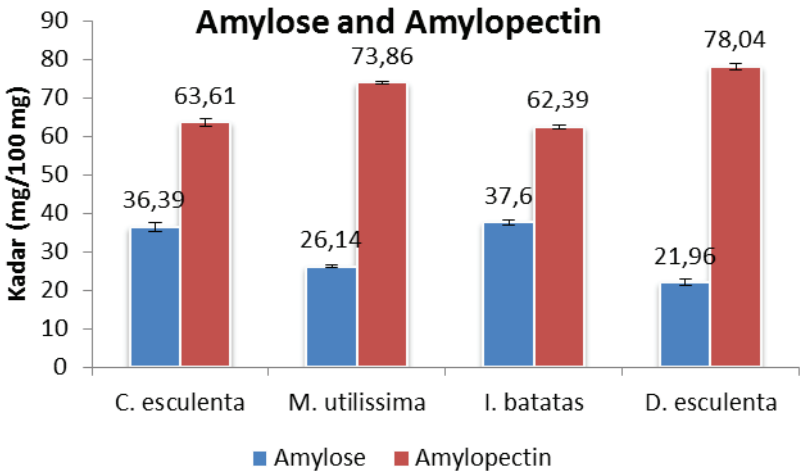

FIGURE 2. Identification of Amylose and Amylopectin Content in Taro Starch

Identification of Flowability

The result showed that the four types of starch have poor flowability. The flowability parameter is affected by the particle shape and size, in which the larger the particle surface area, the higher the cohesion between particles. Unmodified starch has a small size and non-spherical/round shape. In contrast, the formation of granule in modified starch can narrow the surface area, resulting in higher flowability value represented by increased flow rate and reduced angle of repose.

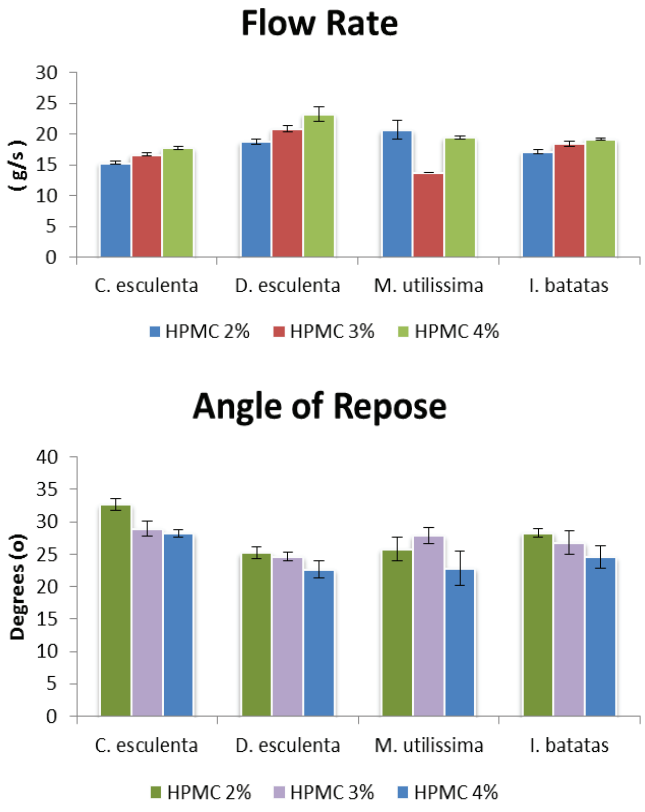

FIGURE 3. Identification of Flowability of Modified Starch; Flow Rate and Angle of Repose

Identification of Compressibility

Compressibility depends on the uniformity of particle size and is related to the porosity and cohesivity between particles. A high porosity value indicates non-uniformity of particle size that will affect the uniformity of tablet weight. The identification indicated that all of the unmodified starch types have high porosity, while the modified starch has lower porosity. In addition, the sweet potato starch-HPMC 4% and taro starch-HPMC 4% have lower porosity compared to the modified starch and Starch® 1500.

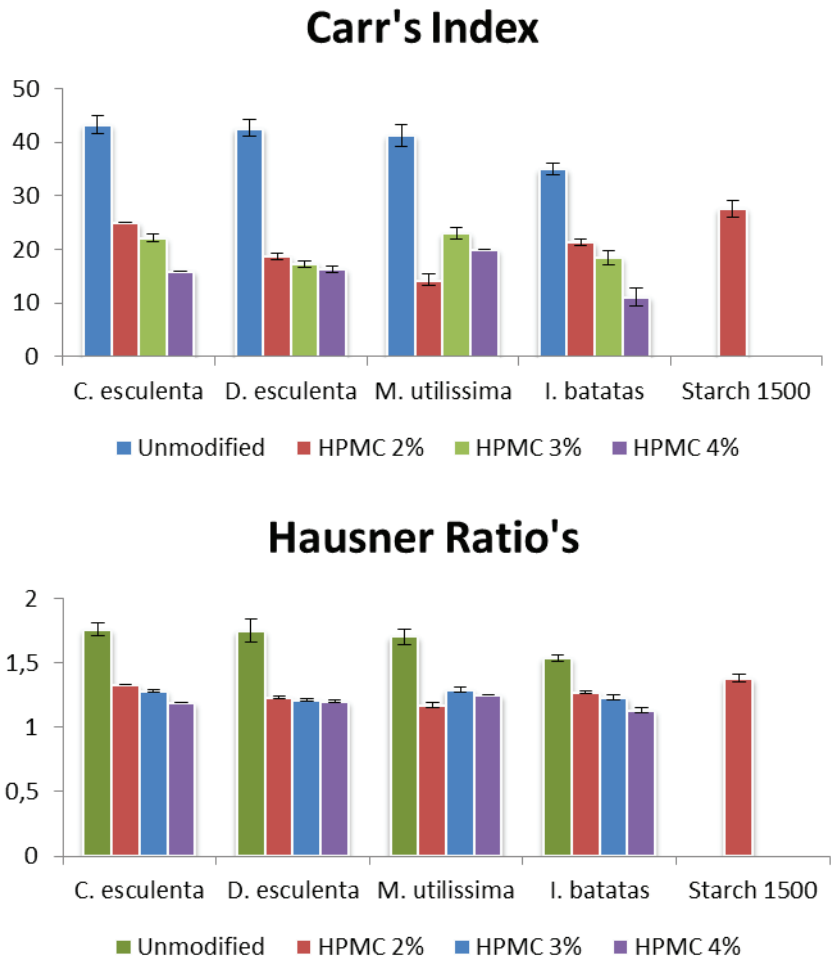

FIGURE 4. Identification of Compressibility, Carr's Index, and Hausner Ratio

Identification of Particle-Size Distribution

Sieve shaker analysis is used to study the mean diameter of modified granule. There is an increase in the granule size when compared with the unmodified starch. The HPMC that binds the particles has increased the particle size by forming granule from starch as well as increased the flowability and compressibility.

TABLE 1. Identification of Particle-Size Distribution

Sample	Starch + HPMC 2%	Starch + HPMC 3%	Starch + HPMC 4%
Starch of Taro	270.69 µm	377.20 µm	398.92 µm
Starch of Sweet Potato	394.26 µm	543.74 µm	497.29 µm
Starch of Cassava	510.65 µm	506.99 µm	418.34 µm
Starch of Lesser Yam	347.62 µm	367.99 µm	361.62 µm

Identification of Compactibility

Apart from flowability and compressibility evaluation, identification of compactibility is also necessary to analyze the formation of granule into plastic deformation as one of the requirements of tablet excipient. The result showed that the modified starch has better compactibility than unmodified starch, while the starch of sweet potato shows that increased compactibility is correlated with increased HPMC level; the compactibility value in sweet potato starch – HPMC 4% is 4.33 Kg.

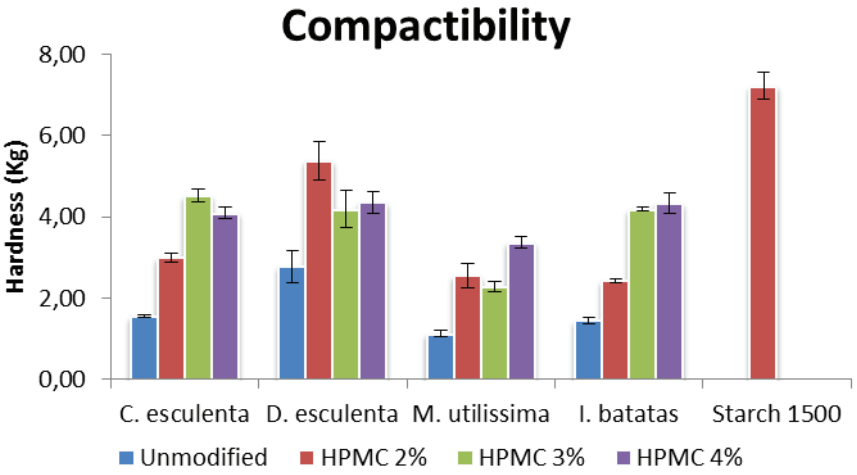

FIGURE 5. Identification of Compactibility of Unmodified Starch and Modified Starch

Identification of Physicochemical Properties

Identification using FTIR

The identification is intended to study the functional groups based on the chemical structure influenced by modification. The structural transformation occurs as a result of modification process or addition of other substances. According to the result, the unmodified starch and modified starch generally undergo no structural transformation. Therefore, the combination of partial pregelatinization and co-process methods does not change the chemical structure although further identification is required to examine the transformation of chemical structure.

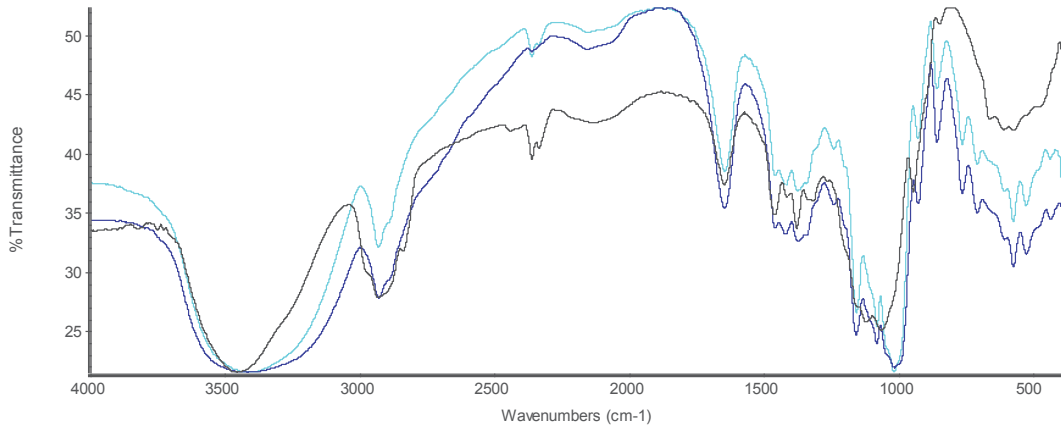

FIGURE 6. Overlay Infrared spectra of sweet potato starch (green), HPMC (black), and sweet potato starch + HPMC 4% (blue)

Identification using DSC

This identification analyzes the influence of modification on heat energy, which includes the melting point as well as fusing point of sweet potato starch – HPMC 4%. The result showed that the fusing point of sweet potato starch – HPMC 4% is 151.24°C, and the absorbed energy is -7.77 kJ/g (endotherm). Addition of a substance (mixture) can raise the melting point as well as the fusing point compared to those of the original substance.

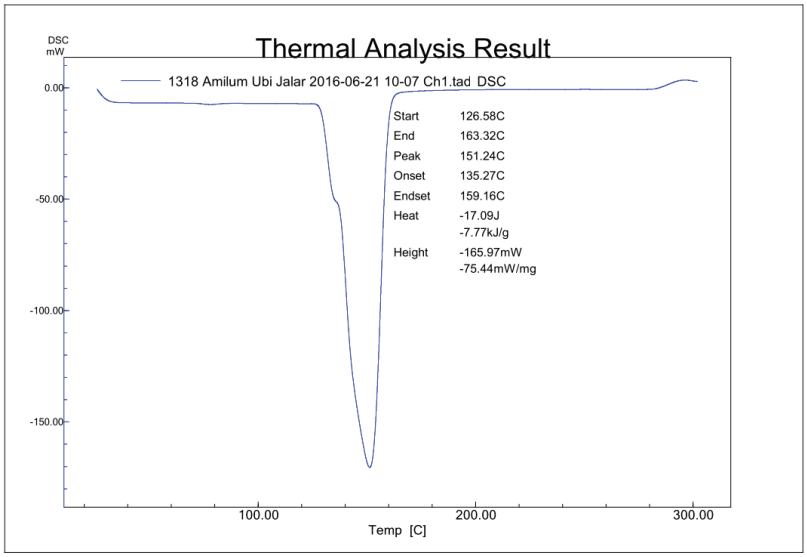

FIGURE 7. Peak Analysis using Differential Scanning Calorimetry (DSC)

Identification using TGA

This identification is required to examine the weight change due to temperature change up to 600°C that can be used to study the stability of excipient during a heat-related process.

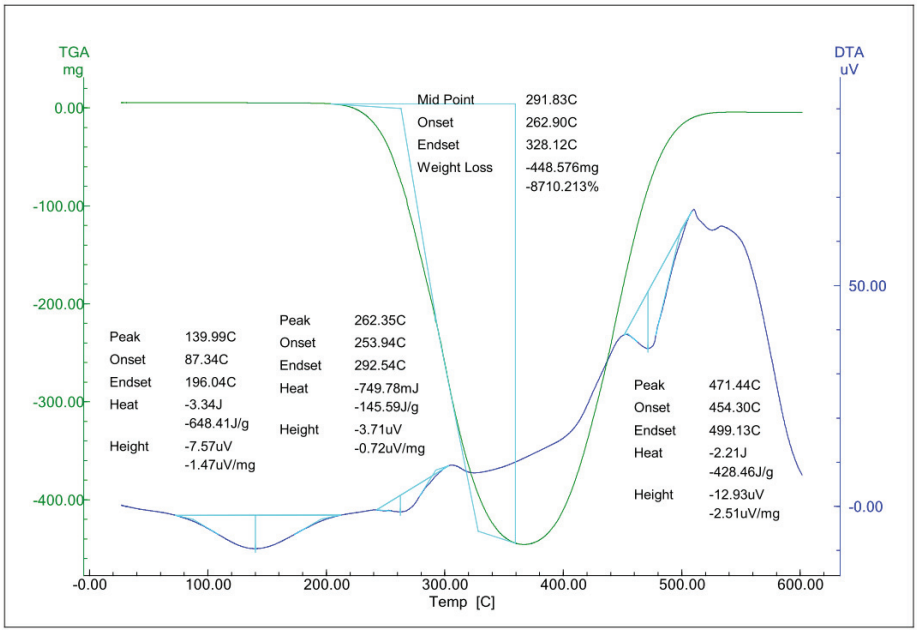

FIGURE 8. Peak Analysis using Thermo-Gravimetric Analysis (TGA)

Based on the identification result, the sweet potato starch – HPMC 4% starts to experience weight decrease at a temperature of 262 and reaches a maximum decrease at 328.52°C. Therefore, a process that reaches this temperature range can affect both the stability and quality of excipient.

Identification using XRD

Crystal form can affect the mixing of a substance with other excipient. In addition, it can identify the polymorphism of the modified excipient. There is peak formed in the sweet potato starch – HPMC 4% as a combination of 2 excipients, which are starch and HPMC.

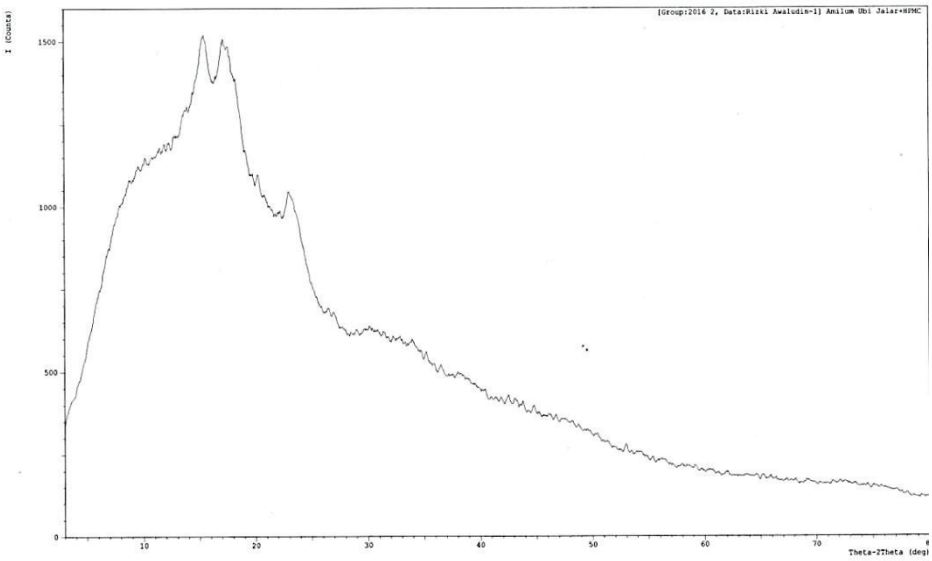

FIGURE 9. Spectrum using XRD Analysis

CONCLUSION

Manufacturing excipient through modification using a combination of partial pregelatinization and co-process methods increases the flowability, compressibility, and compactibility compared to the unmodified starch. The sweet potato starch – HPMC 4% shows that the HPMC addition and physical properties are correlated with the typical physicochemical properties though it does not show a change in chemical structure.

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