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Original Article

Characterization of Microcrystalline Cellulose Obtained from Enzymatic Hydrolysis of Alpha-Cellulose and its Application

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ABSTRACT

Objective: This study was aimed to prepare microcrystalline cellulose (MCC) powder from α-cellulose of water hyacinth, find its characteristics and purity compared to Avicel PH 101 as reference and its tablets evaluation. Water hyacinth has great potential as raw materials of MCC fine due to its highest content of cellulose. **Method:** MCC was obtained by enzymatic hydrolysis with cellulase enzymes. The prepared MCC powder was identified by infrared spectroscopy and melting point, then was characterized over several parameters. Then, the MCC was applied to a tablet formulation and evaluated for its weight variation, thickness and diameter, hardness, friability and disintegration time. **Results:** The identity obtained from infrared spectrum was quite similar with reference and the melting point charred between 247-250°C. The powder was moderately fine, odorless, tasteless and yellowish compared to the reference. The characteristics were obtained, including particle size distribution for 741 nm, pH ± 7.49, ash contents ± 0.203%, moisture content ± 3.685%, loss on drying ± 3.8741% also the density, flow rate and angle of repose met the requirements. The results of Scanning Electron Microscope showed similar morphology of crystalline with reference and the diffractogram patterns showed crystalline form Type 2. Tablets were prepared by dry granulation method and the weight variation, thickness and diameters and disintegration time evaluations met the requirements. **Conclusion:** The MCC obtained has quite similar identities and characteristics with commercial available one (Avicel PH 101) and can be used as an excipient.

Key words: Application, Cellulose, Characterization, Enzymatic hydrolysis, Microcrystalline cellulose, Water hyacinth.

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INTRODUCTION

Indonesia has various types of flora, one of them is *Eichhornia crassipes* or commonly known as water hyacinth. It has ability to absorb nutrients, especially nitrogen, phosphate and potassium as well as heavy metals, causing its spread in Indonesian waters. Unfortunately, water hyacinth grows very fast and turns into weeds which is difficult to control.[1] Based from its content, it turns out that water hyacinth also has high cellulose content, which is 60% of cellulose, 8% of hemicellulose and 17% of lignin. High cellulose content in water hyacinth turns it become potentially utilized to produce microcrystalline cellulose.[2] One of the cellulose derivatives namely microcrystalline cellulose, is normally used in the pharmaceutical industry as an excipient in the manufacturing of tablets, especially for direct compression method.[3] Currently, microcrystalline cellulose is still generally produced from woods by controlled hydrolysis of alpha-cellulose, a pulp of fibrous plant, with diluted acid solution.[4] Wood usage is considered less effective because it can reduce the availability of wood and lead to massive deforestation, resulting in ecological imbalances. In addition, chemical hydrolysis is more harmful than enzymatic hydrolysis. Therefore, it is necessary to look for non-wood source as an alternative source and using enzymatic hydrolysis method. The product is expected to have identities and characteristics as a commercial product.

In this study, the microcrystalline cellulose was produced from the water hyacinth powder by enzymatic hydrolysis. Identification was carried out using infrared spectrophotometry and its purity was determined by melting point determination. Characterization of product was performed by determining each physical parameter such as: particle size measurement, X-ray diffractogram analysis, pH, ash content, moisture content, organoleptic, surface morphology by SEM, particle density, flow rate, starch test, angle of repose and loss on drying. Then, the microcrystalline cellulose was applied into a tablet formulation and was evaluated for its appearance, weight variation, thickness and diameters, hardness, friability, and disintegration time. The purpose of this study was to obtain microcrystalline cellulose from water hyacinth powder, to find its quality through infrared spectrometry, melting point test, and other physical and chemical characteristics by comparing with Avicel PH 101 as a reference. In addition, tablet formulation of microcrystalline cellulose from water hyacinth powder was also compared with the results of tablet with the reference and tablet with Microcrystalline Cellulose (MCC) from chemical hydrolysis.

MATERIALS AND METHODS

Sample and Chemical Material

Water hyacinth powder was purchased from Balai Penelitian Tanaman Rempah dan Obat (Balittro), Bogor. Cellulase enzyme was obtained from the previous research work.[5] Avicel PH 101, Crosspovidone, Copovidone, magnesium stearate, paracetamol, sodium hypochloride, sodium nitrite, and sodium sulphite were purchased from Asian Chemical, Semarang. Other reagents and chemicals used in the study are technical grade.

Isolation of Alpha-cellulose

The water hyacinth powder was sifted to a fine powder. About 400 g of water hyacinth powder were mixed with 5.3 liters nitric acid 3.5% w/v in a beaker glass. Then, the mixture was immersed in a water bath for two h at 90°C. The insoluble part was separated by filtration and the residual obtained was washed with distilled water. The residue was immersed into 4 liters of a solution containing sodium hydroxide and sodium sulfite (each 2% w/v) at 50°C for an hour. The filtration and washing were carried out as described above to obtain residue. The residue was bleached by mixing it into 2.67 liters mixture of water and 3.5% w/v sodium hypochlorite solution. The residue obtained from the filtration was heated at 80°C into 2.67 liters of sodium hydroxide 17.5% w/v for 30 min. After being filtrated and washed, the residue obtained was identified as alpha-cellulose. Then, one again the residue was mixed in 2.67 liters mixture of water and 3.5% w/v sodium hypochlorite solution (1:1), and was boiled for 5 min followed by filtration and washing. The residue was cleaned by filtration and washed with distilled water. The residue was dried at 60°C and alpha-cellulose was obtained.[6,7] The result was crushed into a fine powder and then weighed.

Preparation of Microcrystalline Cellulose by Enzymatic Hydrolysis

About 10 g of alpha-cellulose from water hyacinth were dissolved in 100 ml acetate buffer (0.05 M, pH 5) while 5 ml of cellulase enzyme were added and stirred slowly.[5] The mixture was stirred at 160 rpm, at room temperature for 1 h using shaker incubator. Thereafter, the mixture was centrifuged at 10.000 rpm (at 7-10°C for 20 min). The precipitated residue was washed with distilled water to remove the rest of the enzyme in cellulose. Then, the residue was dried and weighed.[8]

Identification and Characterization

Identification to evaluate purity of the products was done with melting point apparatus Analogue Model SMP11 (Stuart Scientific) and functional groups of the products were analyzed by Fourier Transform Infrared Spectroscopy (Shimadzu FTIR-8400S). The identification was repeated using Avicel PH 101 as a reference.

Particle Size

The particle size and particle size distribution of microcrystalline cellulose from water hyacinth was determined using Particle Size Analyzer. The result was compared to Avicel PH 101. Preparation of the powder was performed by dispersing the crystal powder in an appropriate medium which can disperse sample powders and in this study, distilled water was used. The test was repeated using Avicel PH 101 as a reference.

X-ray Diffraction Analysis

About 2g of the pounded sample was placed and measured using XRD Bruker D8 Advance Eco Diffractometer. It was operated in reflection mode (40 kV, 35 mA) and used Cu-Kα radiation lamp ((l_1=1.54060 Å and l_2=1.54439 Å). The result of diffraction pattern was compared with the Powder Diffraction File database to find out the crystal size in the sample. The test was repeated using Avicel PH 101 as reference.

Measurement of pH, Total Ash Determination and Test for The Presence of Starch

All of these were determined following the Farmakope Indonesia, 2014 method.[9]

Moisture Content and Organoleptic

Moisture content of the product was measured with Moisture Content AMB 50 (Adam) at 105°C. 1g of sample was placed in a tarred aluminium plate and measured for its moisture. The test was repeated using Avicel PH 101 as a reference. The appearance, color, taste and smell of the product was observed.

Morphology by Scanning Electron Microscope

The sample was prepared in the form of dried powder and sprinkled as thinly as possible on the Carbon Tabs. Then, the sample was coated with the Quorum Q150R ES Sputter Coater tool. Coating was carried out using gold material with 20 mA current sputter and sputter time 60 sec. The coated sample was then mounted in the stage for analysis. Picture was taken with SEM (Zeiss, EVOMA10). The detector used was secondary electron with a working distance of 9.0 mm and an EHT of 16 kV. The test was repeated using Avicel PH 101 as a reference.

Bulk Density and Tapped Density

Using a 50 ml capacity measuring cylinder and 5 g of obtained MCC the bulk and tapped volume of MCC were determined. Bulk and tapped density of obtained MCC were calculated using equation 1 and 2

$$BD = \frac{5}{BV} \quad (1)$$

$$TD = \frac{5}{TV} \quad (2)$$

(BD = Bulk density; TD = Tapped density; BV = Bulk volume of MCC; TV = Tapped volume of MCC)

Data values obtained from bulk density and tapped density (BD and TD) above were used to calculate the Carr's Index and Hausner Ratio, equation 3 and 4.

Carr's index = Compressibility index

$$= 100 \times \frac{(TD - BD)}{TD} \quad (3)$$

$$\text{Hausner Ratio} = \frac{TD}{BD} \quad (4)$$

The test was repeated using Avicel PH 101 as reference.

Flow Rate of MCC Powder

10 g of MCC was passed through the Erweka flow ability tester. The time taken for 10g of the material to flow was recorded. The same procedure was repeated twice and the average flow rate calculated from the data obtained. The test was repeated using Avicel PH 101 as reference.

Angle of Repose Determination and Loss on Drying

Angle of repose was determined following Lachman, *et al*, 1994 method,[10] while loss on drying was determined following British Pharmacopoiea, 2002 method.[11]

Tablet Formulation

Tablets using MCC obtained from hyacinth powder (F1), Avicel PH 101(F2) and MCC obtained from chemical hydrolysis.[12] (F3) as its excipient were prepared by dry granulation method, based on the formula given in Table 1. The details for each formulation were given in Table 2. All components were mixed then slugged and were passed through a sieve (size 16), and the granules were pressed with medium-compression

Table 1: Formula of MCC Tablet Prepared By Dry Granulation Method (data in mg).[13]

Sr. number	Ingredients	Formula for 1 tablet (400 mg)	Formula for 150 tablets (400 mg)
1	Paracetamol	210	31500
2	Microcrystalline Cellulose	168	25200
3	Copovidone	13	1950
4	Crosspovidone	6	900
5	Magnesium stearate	2	300

Table 2: The Details of Formulation F1, F2 and F3.

Sr. number	Ingredients		
	F1	F2	F3
1	Paracetamol	Paracetamol	Paracetamol
2	Microcrystalline Cellulose From Enzymatic Hydrolysis (EHMCC)	Avicel PH 101	Microcrystalline Cellulose From Chemical Hydrolysis (CHMCC)
3	Copovidone	Copovidone	Copovidone
4	Crosspovidone	Crosspovidone	Crosspovidone
5	Magnesium stearate	Magnesium stearate	Magnesium stearate

Table 3: Particular Size Distribution of EHMCC and Avicel PH 101 as the Reference.

	dv10 (nm)	dv50 (nm)	dv90 (nm)	dv100 (nm)	Z-avg (nm)
Avicel PH 101	33,6	43,3	1380	1720	5831
EHMCC	83,0	522	741	1110	844,3

force. Tablet weight is about 400 mg for a 11-mm biplanar tablet. Each formulation with different types of MCC were evaluated and compared.

Evaluation Parameters

Weight Variation

Ten tablets were selected, weighed on digital weighting balance (Mettler Toledo) and average weight was determined. Then individual tablets were weighed and the individual weight was compared with an average weight and counted for its standard deviation and relative standard deviation.[14]

Thickness and Diameter

Twenty tablets were selected and the thickness and diameter of tablets were determined using Vernier Caliper (Tricle Brand, Shanghai, China).[14]

Hardness

Ten tablets were selected and the crushing strength of the tablets was measured using a ERWEKA Hardness Tester. The hardness is measured in Kp.[15]

Friability

Twenty tablets were weighed and placed in a Friability Tester ERWEKA TAR and the equipment was rotated at 25 rpm for 4 min. The tablets were taken out, de-dusted and reweighed. The percentage friability of the tablets was measured as per the following formula:[16]

$$\text{Percentage friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100 \quad (6)$$

In-vitro Disintegration Test

The test was carried out on 6 tablets using Digital Tablet Disintegration Tester (ED-2 SAPO, Electrolab). Distilled water at 37°C±2°C was used as a disintegration media and the time in second taken for complete disintegration of the tablet with no palable mass remaining in the apparatus was measured in seconds.[17]

RESULTS

The yield obtained was 13.55% w/w alpha-cellulose powder from 400 g water hyacinth powder. The enzyme, in the form of a crude enzyme extract, was obtained from the previous research work[5] and used for preparing the microcrystalline cellulose. The yield of microcrystalline cellulose was 76% w/w from 50g alpha-cellulose. The total amount obtained was 10.29% w/w of microcrystalline cellulose from 369g water hyacinth powder. The MCC obtained can be seen in Figure 1.

Identification for Microcrystalline Cellulose

Melting point determination was used to determine the purity of microcrystalline cellulose obtained from enzymatic hydrolysis (EHMCC). Avicel PH 101 (the reference) was charred at a temperature range 268-270°C while EHMCC first charred when it reached the temperature of 247-250°C. Confirmation of their purity was also observed by making infrared spectrum of both MCC reference (Avicel PH101) and EHMCC (Figure 2).

Characterization of Microcrystalline Cellulose Particle Size Distribution

Poly dispersity Index (pdi) obtained based on the measurement results was in range of 0.688-0.765 so dv value was used because it means the sample is heterogeneous or too polydisperse. The results were shown in Table 3.

Figure 1: Microcrystalline cellulose powder from enzymatic hydrolysis.

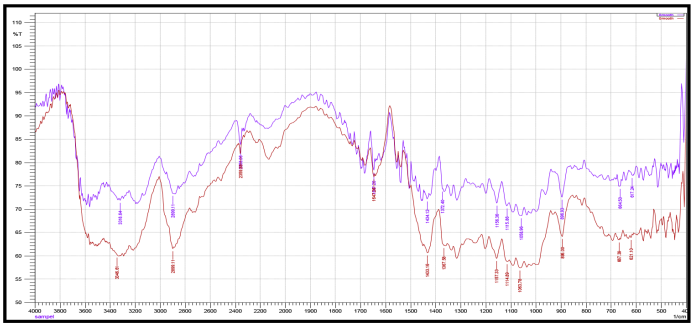
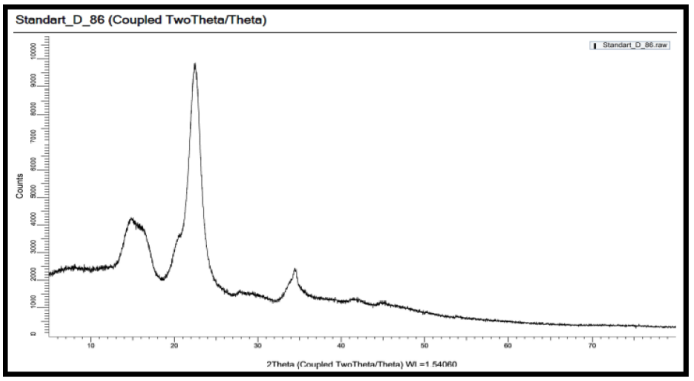
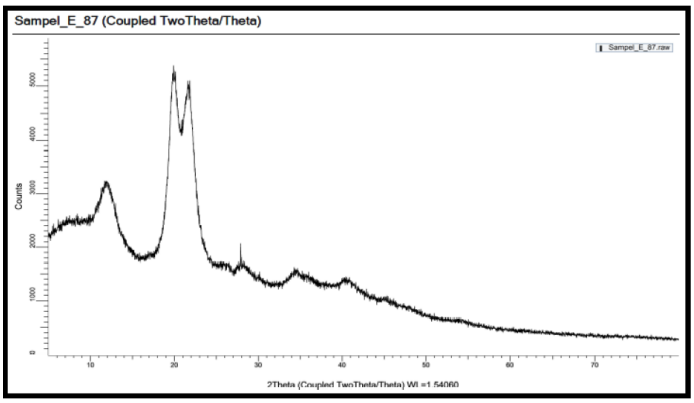


Figure 2: IR-spectrum of microcrystalline cellulose sample (in purple) and reference (in red).



(A)



(B)

Figure 3: Diffractogram of Avicel PH 101 as reference and EHMCC of water hyacinth powder.

X-Ray Diffraction Analysis

Diffractogram pattern of Avicel PH 101 and diffractogram pattern of EHMCC are shown in Figure 3a and 3b, respectively. Both diffractogram pattern have a sharp peak that showing the crystal properties and a wide peak that showing the amorphous properties.

pH and Total Ash Residue

The reference solution (Avicel PH 101) showed a pH value of 7.25 while the sample had a pH value of 7.49. These mean that EHMCC sample showed a little difference to the reference, but both of them still met the requirement of pH of microcrystalline cellulose according to Handbook of Pharmaceutical Excipients, 2009.

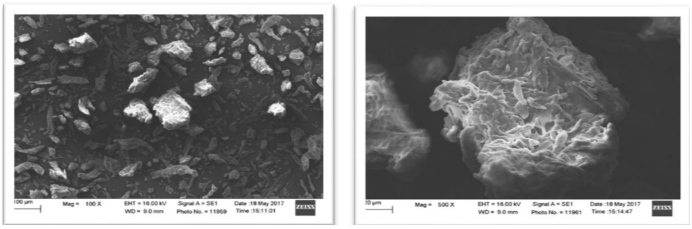


Figure 4: SEM results for Avicel PH 101 (left: 100x and right: 500x magnification).

Table 4: Flow Properties of Avicel PH 101 and EHMCC.

Properties	EHMCC	Avicel PH 101
Bulk density (g/cm^3)	0,2775	0,41
Tapped density (g/cm^3)	0,30835	0,5125
Carr's index	10	20
Flow rate (g/s)	1,0931	0,98875
Angle of repose (°)	25,7457	23,60855
Hausner ratio	1,11	1,25
Moisture content	3,685% w/w	4,115% w/w
Loss on drying	3,8741% w/w	6,7793% w/w

The total ash left after the exposure of Avicel PH 101 to temperature of 600°C was 0.0431% w/w and for the EHMCC was 0.203% w/w. These mean that EHMCC has anorganic content higher than the reference (data not shown).

Organoleptically reference MCC was fine, white-colored, odorless and tasteless. Meanwhile, EHMCC was moderately fine, odorless, tasteless and yellowish compared to the standard reference.

Flow Properties of Avicel PH 101 and EHMCC

The flow properties of pharmaceutical powders are must often adjudged by various parameters such as bulk densities, tapped densities, Carr's index, as well as the flow rate, angle of repose and Hausner ratio. These values were obtained for EHMCC as well as that for Avicel PH 101, as shown in Table 4.

Morphology by Scanning Electron Microscope

SEM analysis results show that microcrystalline was formed in EHMCC (Figure 5). However, there was still some lignin of hyacint fiber in EHMCC. This is possibly due to the manufacturing process that had not reached the optimum purification process. Based on SEM analysis result, EHMCC showed almost similar morphological form with Avicel PH 101 (Figure 4) as reference.

Test for the Presence of the Starch

The result is negative for both EHMCC and Avicel PH 101 since no color change was observed, and not giving blue-violet color in accordance with the requirements.

Tablet Preparation and Evaluations

The present investigation was undertaken to formulate and evaluate the tablets with EHMCC as its excipient (formulation F1). As a comparison, tablets with Avicel PH 101 (formulation F2) and microcrystalline cellulose from chemical hydrolysis.[18] (CHMCC) (formulation F3) were made and evaluated too. For the components, the active compound used was paracetamol, microcrystalline cellulose as its filler, copovidone as its binder, crosspovidone as its super disintegrant and magnesium stearate as

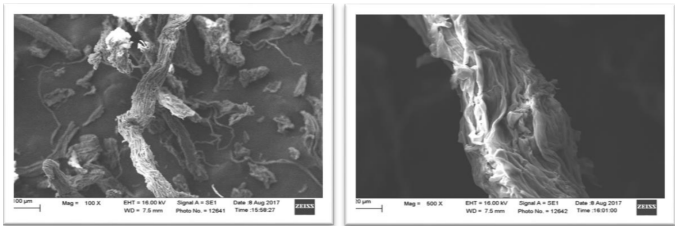


Figure 5: SEM results for EHMCC (left: 100x and right: 500x magnification).

Table 5: Weight Variation results of Formulation F1, F2 and F3.

	F1	F2	F3
Average weight	408,39 mg	414,51 mg	423,63 mg
SD	0,9527	1,192	0,9081
RSD	0,2332%	0,2876%	0,2143%

Table 6: Thickness and Diameter of Formulation F1, F2 and F3.

	F1	F2	F3
Thickness (mm) ± SD	4,335 ± 0,208	3,936 ± 0,066	4,1025 ± 0,02
Diameter (mm) ± SD	11,2165 ± 0,09	11,205 ± 0,022	11,0975 ± 0,011

Table: 7 Hardness and Friability of Formulation F1, F2 and F3.

	F1	F2	F3
Hardness (Kp) ± SD	2,014 ± 0,642	4,418 ± 0,374	1,892 ± 0,335
Friability (%)	16,44%	2,34%	11,48%

its lubricant. Copovidone and crosspovidone are cross-linked excipients, which has better abilities to enhance the quality of tablets. Magnesium stearate was employed as a lubricant because of its excellent lubricant properties. The organoleptic of all tablets were the same, it has white-colored, round shape with a line at the center of the tablet and smooth surface.

Weight Variation

Either formulation F1, F2 and F3 passed for the percentage of weight variation and was well within the acceptable limit for uncoated tablets. The results are shown in Table 5.

Thickness and Diameter

Either formulation F1, F2 and F3 were well within the acceptable limit for uncoated tablets. The results of this test are shown in Table 6.

Hardness, Friability and *in-vitro* Disintegration Test

The results of hardness and friability are shown in Table 7.

DISCUSSION

Avicel PH 101 (the reference) was charred at a temperature range 268-270°C while EHMCC first charred when it reached the temperature of 247-250°C indicating the impurities of EHMCC because the melting point obtained did not meet the requirement. It was assumed that improper process may leave impurities so the melting point temperature obtained was different from the reference.

In the infrared spectrum of both the standard reference and EHMCC (Figure 2) a peak observed at 3600-3300 cm^{-1} indicating the presence of the -OH group and the water absorbed both by the reference and the sample. In the standard reference's spectrum, the peak looks steeper, which indicated that the amount of water absorbed by the standard reference much more than the sample. Then, both in the standard reference and sample, there is a peak in the field 2901 cm^{-1} and 1638 cm^{-1} indicating successively C-H stretching groups and -CH2 and C-OH as described in literature. However, at 1460-1410 cm^{-1}, a wide peak on the reference was observed, whereas in the sample's peak there are two peaks that are suspected to be impurities. In the fingerprint region (about 1400-900 cm^{-1}), there are specific peaks in sample which are relatively similar to the reference, such as in the field 1164-1060 cm^{-1} for cyclic monosaccharides and in the field 1163 cm^{-1} for stretch C-O-C asymmetric. Furthermore, both on the standard reference and samples, there are peaks in the field 899-670 cm^{-1} showing stretch C-O-C pyranose ring and 800-900 cm^{-1} for β-glycoside bonds. Based on the above-described peak figures, the functional groups of sample was similar to the Avicel PH 101 as the reference.

Based on particle size distribution measurements (Table 3), Avicel PH 101 has dv90 for 1380 nm, which means 90% of total particle size were smaller than 1380 nm. Meanwhile, EHMCC has dv90 for 741 nm, which means 90% of total particle size were smaller than 741 nm. From the data obtained, both the standard reference and sample had finer particle size than specified requirements. Comparison of particle size between the reference and sample also shows that the sample has a finer particle size than the reference.

Diffractogram pattern of Avicel PH 101 (Figure 3a) shows a sharp peak at 2θ value for about 22.5324° showing the crystal properties and a wide peak at 2θ value for about 15.6382° showing the amorphous properties. Meanwhile, in the diffractogram pattern of EHMCC (Figure 4), there are two sharp peaks at 2θ value for about 20.1388° and 21.6323° showing the crystal properties and a wide peak at 2θ value for about 12.0172° showing the amorphous properties. The 2θ value of hydrolysis sample indicates that the crystalline type formed is a type 2 crystal where the 2θ values are 20.2° and 21.8° for crystal properties and 12.0° for the amorphous form according to Moharram and Mahmoud, 2007 which has two peaks for the crystalline forms. In addition, the percentage of crystallinity on reference and sample was 69.6% and 71.5%, respectively, showing a little difference.

The compressibility index of EHMCC was 10 are consider excellent and for Avicel PH 101 was 20 are consider fair based on U.S pharmacopoeia 29. The flow rate for the EHMCC was better than Avicel PH 101. The angle of repose for EHMCC was 25,7457° while that Avicel PH 101 was 23,60855°-pharmaceutical powders with angle of repose value between 25-30° are consider excellent based on U.S pharmacopoeia 29. Both the moisture content of EHMCC and Avicel PH 101 were fulfilled the requirement, which is ≤ 5,0%. Then, the loss on drying of both EHMCC and Avicel PH 101 were fulfilled the requirement, which is ≤ 7,0%.

Only formulation F2 (reference) that passed the limit range of hardness (3,5-7,0 Kp). For the friability, neither formulation F1, F2 and F3 passed the requirement (friability percentage ≤ 1,0%). The probable reason is the characteristic of EHMCC and CHMCC itself, in the form of a very fine powder, making them very brittle. These facts demonstrated that the mechanical strength of compact tablet is not only attributed by crystalline properties of EHMCC, but also related to the crystallinity of other starting materials used in formulation.[19] Because the tablet is too squeeze and brittle, it could be considered to making them in the form of coated-tablets. *in vitro* disintegration test was also performed, and either formula F1, F2 and F3 fulfilled the requirement, which showed disintegration time very fast under 30 min. (data not shown).

CONCLUSION

The microcrystalline cellulose obtained from enzymatic hydrolysis of alpha-cellulose from water hyacinth powder has quite similar identities and characteristics with commercial available microcrystalline cellulose and can be used as an excipient.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

FTIR: Fourier Transform Infrared Spectroscopy; **MCC**: Microcrystalline cellulose; **EHMCC**: Enzymatic hydrolysis microcrystalline cellulose; **XRD**: X-ray diffraction; **SEM**: Scanning electron microscope; **CHMCC**: Chemical hydrolysis microcrystalline cellulose.

SUMMARY

- Microcrystalline cellulose (MCC) powder from α-cellulose of water hyacinth was prepared and its characteristics and purity was compared to Avicel PH 101 as reference.
- MCC was obtained by enzymatic hydrolysis, and identified by infrared spectroscopy and melting point, characterized over several parameters, and then was applied to a tablet formulation.
- The characteristics obtained were including particle size distribution about 741 nm, pH ± 7.49, ash contents ± 0.203%, moisture content ± 3.685%, loss on drying ± 3.8741% also the density, flow rate and angle of repose met the requirements. The results of Scanning Electron Microscope showed similar morphology of crystalline with reference.
- Tablets were prepared by dry granulation method and the weight variation, thickness and diameters and disintegration time evaluations met the requirements.

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