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Original Article

DEVELOPMENT OF MYCROCRYSTALLINE CELLULOSE ORIGINATE FROM SAGO (*METROXYLON SAGU*) STEM BARK BY HYDROLISIS METHODE USING NITRIC ACID

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ABSTRACT

Objective: Microcrystalline cellulose (MCC) is an essential excipient in tablet formulation. Mostly MCC was obtained from wooden conifer stem fiber, therefore environment issues had been came up. Alternative sources for MCC which offer friendly conifer wood need to be explored. This study aimed to isolate and determine the characteristics of MCC originated from Sago (*Metroxylon sago* Rottb.) stem fibers as an promising alternative of MCC.

Methods: MCC was prepared through pre-hydrolysis using an acetic acid solution, alkali heating using NaOH solution, and acid hydrolysis using nitric acid 0.3 N using three variations of heating temperature, namely 90, 95 and 100 °C. The characterization carried out were pharmaceutical grade, powder properties, FTIR analysis and powder morphology by SEM.

Results: The yields obtained were 66.02; 65.53 and 65.08%, respectively. The characteristics of the MCC sample based on pharmaceutical grade quality were white to yellowish white powder, odorless, tasteless, insoluble in: ether, 96% alcohol, HCl 2N and NaOH 1N. The pH of the MCC suspension were 5.07-5.12, while moisture content were 3.67-4.17%, with loss on drying value as much as 0.37-0.4%, and ash content 1-2.17%. The value of permanganate number were 0.09-0.11, Hausner factor was between 1.05-1.25, and angle of repose were between 11.4-24.8°.

Conclusion: Based on the results, it can be concluded that Sago is potent natural resource for MCC. The resulting MCC revealed physicochemical and characteristic of MCC, which almost similar to Avicel PH 102 as standard.

Keywords: Sago, *Metroxylon sagu*, Hydrolysis, Mycrocrystalline cellulose

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INTRODUCTION

Microcrystalline cellulose (MCC) is a cellulose derivative that is widely used in tablet formulations, both as fillers, binders, and disintegrant [1]. Cellulose was firstly isolated from wooden Conifer *pulp* at 1885 by Charles F. Cross and Edward Bevan [2]. Cellulose is a long-chain polymer of glucose consisting of crystalline and amorphous parts. Amorphous regions are easily subjected to partial depolymerization by hydrolysis using low concentrations of strong acid [3] and enzymatically with cellulase resulting in shorter crystal fragments, namely MCC [4]. Microcrystalline cellulose (MCC) was first discovered in 1955 by Battista and Smith and marketed under the name Avicel®. MCC has various functions in tablet formulations due to its free-flowing property, low moisture content, and commonly used in hygroscopic ingredients. It also has a low density, large particle size distribution and envelops the active pharmaceutical ingredient such as tablet excipients [5]. In addition, the compatibility of MCC is good so that it can be applied to the direct compression and wet granulation methods [6]. However, MCC has a very low coefficient of friction so it is not used as a lubricant [3]. It has a very high porosity of 90–95% of the surface area making it easier for gastrointestinal fluid to enter the tablet mass, resulting in the swelling and disintegration of the tablet. Good swelling capacity results a short disintegration time of tablet.

MCC is a large part of tablet components but nevertheless the price is relatively expensive because it is still imported; therefore it is necessary to do research to find new alternative sources of MCC. Some studies state MCC has been isolated from betung bamboo, but the color is not white like Avicel [7], water hyacinth [8], nata de soya [9], cand hemp plants [10].

In a search of new sources of MCC, another potential plant is sago (*Metroxylon sago*) stem fiber, which is a residue of sago starch production. Sago comes from the trunk of the sago tree and is a staple food for the Tolaki ethnicity in Southeast Sulawesi [11]. Sago plantations are found in Konawe, South Konawe, North Konawe, Kolaka, East Kolaka, and Bombana regencies in Indonesia. Sago starch production in Indonesia reaches 2,795 tons per year [12]. On the other hand, sago stem residues produce 59.51% cellulose [13] so that it can be a potential source of MCC raw materials whose quantities are available for industrial-scale production.

In the optimalization process of MCC isolation from sago stems, the first step was hydrolysis of alpha-cellulose using different type of acid solutions such as hydrochloric acid, nitric acid, and sulfuric acid. The type of acid used will affect the yield and characteristics of the MCC produced [14]. Former study showed that Hydrochloric acid has a better reactivity in the hydrolysis process compared to other acids [15]. Other study revealed that Nitric acid is claimed to dissolve more amorphous cellulose, resulting in more MCC [8]. While study on sulfuric acid claimed that this acid was be able to produce a greater yield compared to using other types of acids [16].

The time of heating and temperature used also showed strong effect on the quality of the MCC production [17]. Hydrolysis at high acid concentrations for a long time caused the degree of crystallinity to decrease due to the opening of the cellulose chain arrangement, thus changing the arrangement of polymer chains and cellulose is easily degraded [18]. As the requirement for pharmaceutical excipient, the product of MCC must fulfill pharmaceutical grade and have good powder physicochemical characteristics. This research was expected to contribute significantly to the discovery of MCC raw materials as excipients in tablet preparations by providing the data on MCC characteristics isolated from Sago stem bark in the exploration of alternative source of MCC.

MATERIALS AND METHODS

Materials

All materials were of at least reagent grade and used as received: aquadest, acetic acid, sodium hydroxide, ether, sodium hypochlorite,

nitric acid, potassium permanganate, sodium thiosulfate, potassium iodide, and sago stem fiber (*Metroxylon sagu*).

Methods

Preparation of sample

Sago stem fiber were obtained from Andaroa Village, Sub-district Sampara, Konawe Regency, Southeast Sulawesi, Indonesia. Samples were washed and dried (50 °C, 3 h). Then mashed to obtain a dry powder sample.

Prehydrolysis of alpha-cellulose

Prehydrolysis of alpha cellulose was carried out by the alkaline heating method. The sample was boiled in 0.1N acetic acid solution (105 °C, 1 h) with a sample with solvent ratio of 1:20, then filtered and rinsed repeatedly until neutral pH. The sample was boiled in a 25% NaOH solution (105 °C, 1 h) with solvent ratio of 1:20, then filtered and rinsed repeatedly until neutral pH. Next, the sample was immersed in 0.35% sodium hypochlorite solution (20 min) with solvent ratio of 1: 8, for bleaching purpose and then was filtered and rinsed repeatedly until neutral pH. The pulp obtained was dried (50 °C, 12-24 h) [10].

Hydrolysis of Microcrystalline Cellulose (MCC)

MCC hydrolysis was carried out by heating with 0.3 N nitric acid. The sample was boiled in nitric acid solution at temperature of 90 °C, 95 °C, and 100 °C (17 min) with a ratio of sample to solvent 1:20. Next, it was filtered and rinsed repeatedly until neutral pH. The pulp obtained was dried (60 °C, 1 h) and crushed. MCC as result powder was stored at room temperature in a desiccator [4, 6, 10, 19]

MCC characterization

Organoleptic

The sample was observed in appearance of shape, color, taste, odor. This test was carried out using the human senses to assess the standard of acceptance of a product by the community [20].

pH measurement

The 25 g MCC was mixed with 100 ml of distilled water, shaken for 5 min and then measured the pH using a pH-meter. The pH requirement is 5.0-7.5 [21].

Loss on drying

Weighing bottles were dried (100-105 °C, 30 min), cooled and weighed to constant weight. The 25 g MCC was thoroughly weighed in the bottle and dried (105 °C, 1 h). The weighing bottle cap was opened during drying and immediately closed upon completion, cooled inside the desiccator until the remaining constant weight was obtained. The drying shrinkage requirement should not more than 6% [23, 24].

$$X = \frac{(A)-(B)}{(A)} 100\%$$

(A)

A = sample before drying (g)

B = sample after drying (g)

Solubility in NaOH 1N

To the sample 0.2 g of MCC, NaOH 1N was added, stirred (5 min), and allowed to stand for 24 h (-20 °C). At the assay, the sample was stirred for 5 min and solubility were observed as the number of saple absorbances [23, 24].

Solubility in HCL 2N

MCC sample as much as 2g was weighed and added by 5 ml of HCl 2N solution, stirred (5 min) and observed for the solubility with the procedure as explained in the assay of sample in NaOH [23, 24].

Solubility in alcohol 96%

To 5 g MCC sample 5 ml of 96% alcohol solution was added, stirred (5 min) and observed for solubility with the former procedure as explained in the assay of sample for solubility tests [10, 24].

Solubility in ether

MCC sample as much as 5g was weighed and added by 5 ml of ether and stirred for 5 min until it is ready for solubility observation with the former procedure as explained in the assay of sample for solubility tests [23, 24].

Permanganat number

The MCC sample as much as 0,6 g was added by 200 ml of distilled water, 25 ml of 0.1 N $KMnO_4$ solution and 25 ml of H_2SO_4 4N, and stirred for 10 min. Next, 5 ml of KI 1N solution was added and stirred well. Amylum 1% as an indicator was added and mixed until the solution became blue. The sample was titrated with $Na_2S_2O_3$ 0.1N (a ml) until colorless solution was obtained. The experiment was conducted in triplo as well as for blanks (b ml) [25, 26]. Permanganat number was calculated using equation as follow:

$$P = \frac{((b-a)N)}{K}$$

b = volume of $Na_2S_2O_3$ of titration without sample (ml)

a = volume of $Na_2S_2O_3$ of titration with sample (ml)

K = sample weight (gram)

N = normality $Na_2S_2O_3$ (N)

Flow properties characterization of MCC

Density

The powder sample was put into measuring cup and measured in volume. The true density was calculated using equation [27]:

$$P = \frac{\text{sample weight (g)}}{\text{sample volume (ml)}}$$

T*apped density* was calculated by tapping the powder sample until the constant volume was obtained and was calculated using equation [27, 28]:

$$A = \frac{\text{sample weight (g)}}{\text{Final volume of sample (ml)}}$$

Compressibility was calculated using equation [29]:

$$\text{Compressibility Index} = \frac{P-A}{A} \text{ x } 100\%$$

Hausner Index was calculated using following equation [29]:

$$\text{Hausner factor} = \frac{A}{P}$$

Once the powder granule was poured from the hopper and has formed a pile on the platform, measure the height of the powder from the platform the highest point on its peak (cm) [30].

Angle of Repose was calculated using following equation:

$$Tg\ \alpha = \frac{ah}{d}$$

h = Height of peak (cm)

d = Diameter of peak cm)

α = angle of repose

Characterization using Fourier Transform Infra-Red (FTIR)

FTIR was used to characterize the functional groups in microcryatalline obtained from Sago stem bark compared with that from AVICEL PH 102 as standard. Spectra of FTIR was conducted using FTIR Alpha with detector RT-DLaTGS ZnSe and scanned at 500-4000 cm^{-1} [31].

RESULTS AND DISCUSSION

Hydrolisis of MCC

The alpha-cellulose isolation process begun with prehydrolysis where sago stem fibers were boiled in a 0.1 N acetic acid solution to soften the material and accelerate the breaking of pentose bonds (hemicellulose) before the delignification process. Furthermore, alkaline heating was carried out by boiling the fibers in a solution of

NaOH 25% until brown cellulose pulp was obtained which means that the pulp was perfectly released of lignin from the sample. NaOH can damage the lignin structure and cause bulging of the cellulose structure, which opens the cellulose pores so that unwanted impurities come out [32, 33]. Furthermore, bleaching was carried out to remove the remaining lignin so that white pulp could formed. To optimize the results, the hydrolysis was performed at three different temperatures. The results of hydrolysis process were evaluated by calculating the Yield value of the process as shown in table 1. The raw material was 50 gram of Sago's stem bark.

Table 1: Yield value of hydrolisis of α-selulosa using temperature variation

Temperature (°C)	Yield (%)*
90	66.20±1.03
95	65.53±1.77
100	65.08±1.30

*Experiment were conducted in triplicate and data reported as mean±SD

Acid concentration is one of the most influenting factors in the hydrolysis process, which provides varied results of the MCC [16]. The use of low concentrations of Nitric acid revealed the optimal results. This was due to the complete degradation process or decomposition of alpha-cellulose and hemicellulose of sago stem fibers. The acid component breaks the alpha and beta bond chains of cellulose into monomers of a single sugar, namely glucose (cellulose is composed of monosaccharides, including glucose with alpha and beta bond) [33].

At the hydrolysis using nitric acid solution of 0.3 N, the H^+group of the acid will convert functional group in the sago fiber into a free radical group and later will bind to the OH^-group of water. The results of hydrolysis showed that there was a difference in yield at temperature variations. The largest yield was obtained at a temperature of 90 °C. H^+ions in HNO_3 are able to penetrate and eliminate amorphous regions of cellulose, thereby increasing the percentage of yield [34].

Hydrolysis is highly affected by duration of heating, temperature and reactivity of the acid catalyst [35]. High temperature of the process resulted in faster processing time. However, the use of strong acids, high temperatures, and over time of heating can result in damage of the cellulose structure so that it fails to be isolated. Low yield of MCC will be obtained as a result [36]. In this experiment, overheated hydrolysis revealed lower yield MCC value (table 1).

Physicochemical characterization

Characterization of mycrocrystalline cellulose from Sago fiber included pharmaceutical grade parameters (USP parameters), physicochemical properties as well as functional group analysis by FTIR and powder morphology by SEM.

Table 2: Pharmaceutical grade parameters of MCC from sago fiber

Parameters	Temperature (°C)			Avicel PH 102 (standard)	Reference
	90	95	100		
Organoleptic	Powder, white, odorless.	Powder, yellowish white, odorless.	Powder, yellowish white, odorless.	Powder, white, odorless.	Powder, white, odorless [6]
Solubility in NaOH 1N	insoluble	insoluble	insoluble	insoluble	insoluble [6]
Solubility in HCl 2N	insoluble	insoluble	insoluble	insoluble	insoluble [6]
Solubility in alcohol 96%	insoluble	insoluble	insoluble	insoluble	insoluble [6]
Solubility in ether	insoluble	insoluble	insoluble	insoluble	insoluble [6]
pH*	5.12±0.20	5.08±0.17	5.07±0.05	6.9±0.13	5-7,5 [24]
Moisture content (%)*	4.17±0.76	3.67±0.76	4.00±0.50	1.05±0.51	<5 [6]
Loss on drying (%)*	0.38±0.16	0.40±0.12	0.37±0.18	0.1±0.06	<6 [24]
Ash content (%)*	0.3±1.43	0.4±1.70	0.5±1.33	0.1±1.78	0,5 [24]
permanganat number*	3.13±1.70	4.65±0.83	2.23±1.58	2.19±0.44	<6 [26]

*Experiment were conducted in triplicate and data reported as mean±SD

Organoleptic test results showed that MCC hydrolyzed at a temperature of 90 °C, meeting the color requirements. While that of 95 °C and 100 °C produced yellowish MCC. This was caused by the high temperature, causing cellulose crystals to be destroyed into carbon, which was characterized by the color of cellulose to be darker.

The pH value was determined by the frequency of washing the residue with distilled water. Higher washing frequency resulted in more neutral pH of the product.

The solubility test results showed that MCC did not dissolve in the solvent tested (NaOH, HCl, ethanol and ether) due to strong hydrogen bonds between hydroxyl groups in adjacent bond chains in the crystalline structure that makes up microcrystalline cellulose. These results were in accordance with the pharmaceutical grade requirements, according to Widia (2018). MCC is a porous, hygroscopic powder particle, insoluble in some solvents, but expands when in contact with water. Glucose molecules are linked via beta-glucoside bonds. Strong intermolecular hydrogen bonds are formed from cellulose polymers and aggregate chains that are close to the crystalline structure that makes up microcrystalline cellulose [33].

Loss on drying or water content measurement aims to provide maximum levels regarding the loss of compounds due to the drying process. Measuring the ash content aims to show the presence of inorganic elements such as minerals which have a melting point higher than the drying temperature [20, 37]. The MCC from sago stem bark showed Loss on drying and ash content value, which fulfilled the requirement (table 2).

The permanganate number test aimed to determine the level of lignin as an impurity still contained in the sample, which will affect its purity [20]. The isolation of MCC from sago fiber using hydrolysis method by acid nitric showed that the method was optimum and provided the MCC with a permanganate number which fulfilled the requirement (table 2).

Flow rate is an important parameter in the selection of filler materials for direct compression of tablets production [37]. The flow properties of the excipient are very important because they are related to the property of powder materials. The flow rate test results show greater results than Avicel pH 102 as standard. The flow rate was determined based on the values of real density, compressible density, compressibility and Hausner factor. The results revealed that MCC produced from sago fiber was not preferable as an excipient for direct compression tablet; thus, it is suggested to be used as an excipient in wet granulation method. The results in line with the particle size of the powder, which showed lower size compared with that of Avicel PH 102 (table 3). Other physical properties of the MCC powder are presented in table 3.

Table 3: Physical properties of MCC powder from sago stem fiber

Parameters	Temperature of hydrolysis (°C)			Avicel PH 102 (Standard)
	90	95	100	
True density (g/ml)*	0.08±0.01	0.07±0.00	0.07±0.00	0.125±0.01
Tap density (g/ml)*	0.11±0.01	0.11±0.00	0.12±0.01	0.142±0.03
Compressibility (%)*	5.46±0.34 very good	7.81±0.61 very good	20.78±0.96 good	5.46±0.67 Very good
Haussner factor*	1.05±0.37 very good	1.07±0.11 very good	1.25±2,43 good	1,05±0.08 very good
Angle of repose*	24.8±0.11	20.21±0.26	11.4±0.12 (failed-not fulfill)	28.9±0.27
Particle size (µm)*	3.9401±0.21	1.9511±0.09	4.815±0.07	75±0.01
Polydispersity Index	0.977±0.08	0.867±0.07	0.992±0.06	maximum 1

*Experiment were conducted in triplicate and data reported as mean±SD

The true density and tap density test aimed to determine the compressibility value, which plays a role in determining tablet hardness. The smaller the compressibility, the tablet hardness will increase. The compressibility test aims to determine the characteristics of the powder when pressurized [38]. A material has good compressibility if it has a compressibility index of less than 25%.

The Hausner factor indicates the flow properties of powder. The smaller the Hausner factor value, the better the flow properties for tablet compression. The flow properties of powder can also be seen from the value of the angle of repose which is the evaluation angle of the free surface of particles forming a cone with respect to a flat plane. Flatter resulting cone resulted in smaller the angle of repose. The acceptable value of the angle of repose is between 20-40°. The fine powder tends to show stronger attractive force between the particles so that a pile of granules will form and it will be difficult to roll [38]. A good powder flow rate will produce tablets with low variations in weight uniformity. Flow properties of MCC granules from sago were assumed as fulfilling the requirement (table 3), except of the one using hydrolysis temperature 100 °C which showed low angle of repose.

Next the FTIR (Fourier Transform Infrared) was performed to MCC using the temperature of hydrolysis of 90 °C as the powder having best properties from former characterization. FTIR testing is based on the intensity and wavelength of infrared radiation absorption, which causes each functional group to vibrate at its characteristic wavenumber. In the spectrum, the wave number 4000-400 cm^{-1} is a reference for seeing molecular vibrations from organic compounds [39].

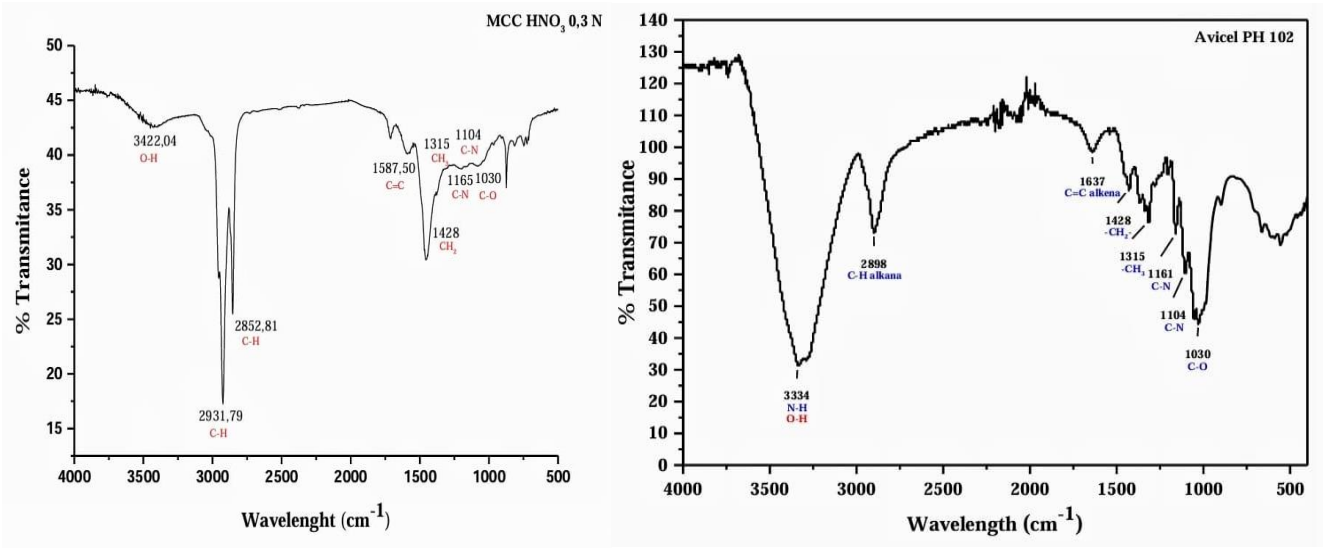
MCC will show the main absorption, indicating the presence of OH groups, hydrogen bonds, C-H alkanes, C-O ether bonds, and alcohols [40]. The absorption peak of Avicel® PH 102 as standard and MCC sample showed the absorption peaks of the OH group at wave numbers 3334 cm^{-1} and 3422.04 cm^{-1}. The absorption peaks of the C-H group are at wave numbers 2898 cm^{-1} and 2931.79 cm^{-1}. The absorption peaks of the C=C group are at wave numbers of 1637 cm^{-1} and 1587.50 cm^{-1}, while CH_2 absorption peaks was at wave numbers 1428 cm^{-1} and 1428 cm^{-1}. CH_3 absorption peaks were at wave numbers 1315 cm^{-1} and 1315 cm^{-1}. C-N absorption peaks were at wave numbers 1161 cm^{-1} and 1165 cm-1, while C-O absorption peaks were at wave numbers 1030 cm^{-1} and 1030 cm^{-1}.

The functional group prediction and compared with Avicel® PH 102 peak as standard revealed that the resulting sample product was MCC. These results are based on the presence of a reduction in the intensity of the functional groups of lignin molecules and an increase in the intensity of cellulose molecules.

There were two sharp peaks at wavelengths 2931.79 cm^{-1} and 2852.81 cm^{-1}, which are thought to be originated from the C-H functional group of cellulose and lignocellulose, whereas when compared with the FTIR spectrum of Avicel® PH 102 they are only found at wave number 2898 cm^{-1}. This was due to the purity level of MCC was not optimal in accordance with the yield value obtained at 66.20%. However, the FTIR spectrum had shown that the resulting compound was MCC (fig. 1).

Morphology study by Scanning Electron Microscope (SEM)

Characterization of powder morphology by using the Scanning Electron Microscope (SEM) instrument had been carried out to determine the morphological and surface characteristics of the powder. The SEM test results for MCC isolated from Sago fiber was compared to that of Avicel® PH 102 as a reference (table 4, fig. 2).



(a) **(b)**

Fig. 1: FTIR study of MCC from sago stem fiber (a) and (b) Avicel PH 102 as standard

Table 4: SEM study of MCC from sago

Study	MCC from sago	Avicel® PH 102	Handbook of pharmaceutical excipient (2009)
Particle shape	The shape of the rod was irregular; the surface texture was uneven and forms more pointed corners	The shape was slightly rounded, the surface texture was uneven and forms fewer pointed corners	The shape is slightly rounded, the surface texture is flat and forms fewer pointed corners

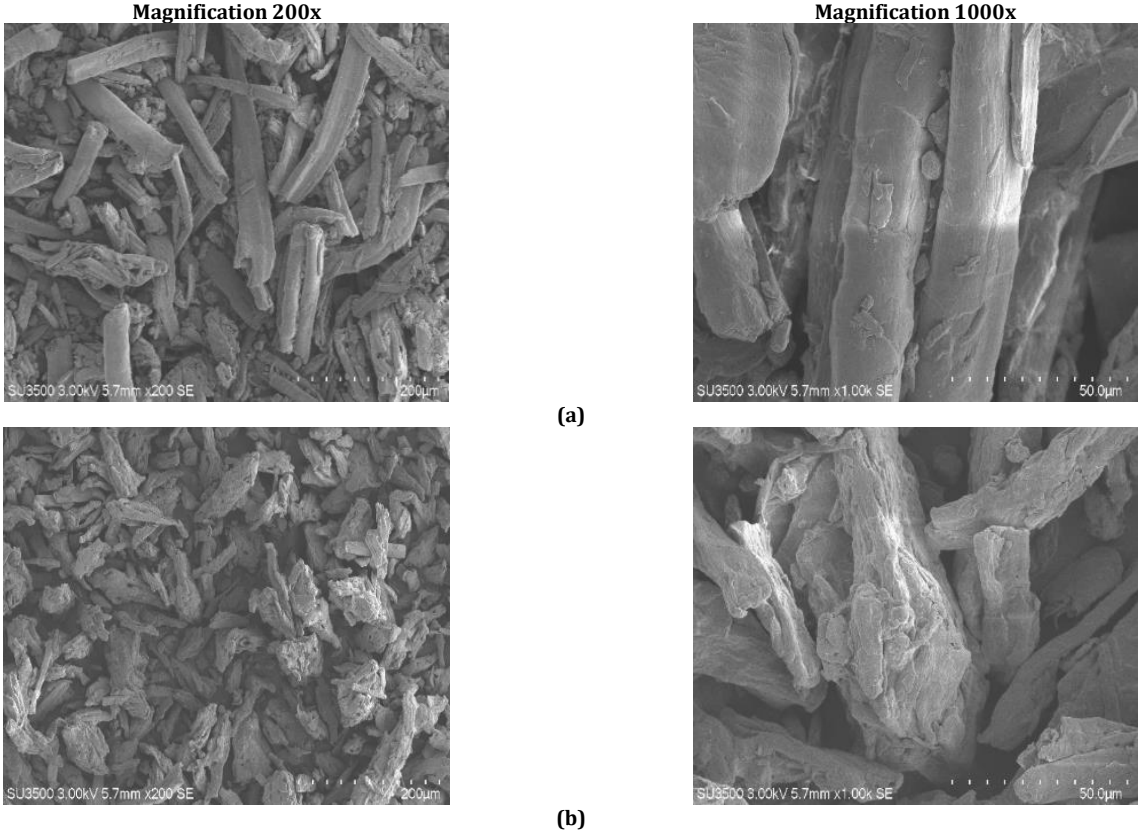


Fig. 2: Morphology of MCC from (a) Sago stem fiber and (b) Avicel PH 102

CONCLUSION

Based on this experiment, it can be concluded that Sago stem fiber (*Metroxylon sago* Rottbol.) is a promising source for Microcrystalline cellulose MCC due to abundant availability as residue from starch isolation as main process. MCC can be obtained from Sago stem fiber by hydrolysis process using various acids. In this experiment, it was found that by using nitric acid (HNO_3) at a concentration of 0.3 N with the best heating temperature 90 °C revealed the optimum product in terms of yield values and physico-chemical properties.

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Nil

AUTHORS CONTRIBUTIONS

All authors are contributed equally

CONFLICT OF INTERESTS

Declared none

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