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Processing Pharmaceutical Grade Microcrystalline Cellulose from Sengon Wood Sawdust (Falcatariamoluccana (Miq.) Barneby & J.W.Grimes)

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ABSTRACT: Microcrystalline Cellulose (MCC) serves a diverse range of functions in various food, cosmetic, and pharmaceutical. It plays a crucial role as an excipient in the pharmaceutical industry, especially in tablet manufacturing, including as a filler, binder, and disintegrant. Sengon Wood Sawdust (SWS) contains 50.85% cellulose so it has the potential to be a promising source of MCC both in terms of its function in the pharmaceutical industry and in efforts to increase the benefits and economic value of wood industry waste. MCC extraction was carried out in three stages, namely alkaline delignification to obtain α-cellulose, continued with acid hydrolysis, and bleaching to obtain MCC. This process has been known to increase cellulose content up to 85.01%. This study aims to determine the pharmacopoeial properties of Microcrystalline Cellulose from Sengon Wood Sawdust (SWS-MCC). Several pharmacopoeial properties were assessed, including compressibility tests, considering its intended use as a drug delivery biomaterial. The research results show that SWS-MCC is similar to Avicel® PH 102 as a commercial comparison and meets all pharmacopoeial parameters, that have been carried out including microbial excipient quality. Several results also reveal that SWS-MCC is better than Avicel® PH 102, including moisture content (4.38%), flow rate (88.384 g/s), angle of repose (36.17°), Carr's index (12.67%), and Hausner ratio (1.15). It was concluded that SWS, despite being waste, holds promise as a cost-effective, functional, and sustainable as a pharmaceutical excipient, especially for direct compression tableting.

KEYWORDS: Direct Compression Tablet, Microcrystalline Cellulose, Pharmacopoeial Properties, Pharmaceutical Excipients, Sengon Wood Sawdust.

I. INTRODUCTION

Microcrystalline cellulose (MCC) is pure cellulose isolated from alpha cellulose as pulp with mineral acids derived from fibrous plant material [1]. Cellulose is the main component of plant cell walls, providing the largest support amount compared to other components. Cellulose is found in woody and non-woody plant fibers [2]. In the literature, it is found that several sources of natural materials can be processed to produce MCC, including brown algae [3], olive fiber[4], water hyacinth [5], fodder grass [6], parawood sawdust [7], jackfruit rind [8], and black tea [9]. MCC isolation methods have been widely developed, including alkaline, acidic, and enzymatic hydrolysis. Alkaline hydrolysis is performed to delignify lignocellulosic materials to break down the structure of lignin and cellulose [10] done by others [11][12][13]. Acid hydrolysis is widely utilized in MCC isolation, among others [14] [15]. Enzymatic methods have also been reported in previous studies [16][17].

MCC is known as a biomaterial with good compressibility, stability, and chemical non-reactivity[18]. Due to these properties, MCC has become one of the most important functional materials in the pharmaceutical industry, especially in the manufacture of direct-printed tablets, so causing the needs for MCC increase. Commercially available MCC comes from hardwood and is expensive. In Indonesia, the Sengon wood industry is currently developing rapidly. Apart from the affordable price, the attractive fiber and color of Sengon wood are also a reason for consumers. Since

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the market demand for Sengon wood products increases, making production also increases. The increase in Sengon wood production results in industrial waste that needs to be concerned.

Sengon wood sawdust waste is widely used to produce a Wood Plastic Composite (WPC) board [19] and media for mushroom cultivation [20]. The cellulose content of Sengon wood sawdust waste is 52.47% [21]so it has the potential to be used as raw material for making MCC. This encouraged the researchers to develop MCC processing from Sengon wood sawdust waste although research on several MCC isolation methods has been developed and has succeeded in increasing the crystallinity index and cellulose content [22][23]. The aim of this research is to provide an explanation of the pharmacopoeial, physicochemical, and microbiological properties of MCC Sengon wood sawdust waste. Currently, there is limited information available regarding its implementation the pharmaceutical industry, hence the need for this study. This will provide added value from Sengon wood sawdust waste, and can produce a source of cheap raw materials for industry.

The rapid development in of the pharmaceutical industry underscores the significance of developing new biomaterials that integrate quality principles. Material properties, including excipients can significantly impact the quality of the end product. Therefore, extensive needs to be carried out for the development of these materials. It has been suggested that pharmacopoeial specifications are not always an absolute indicator of excipient quality [24]. The functional aspect of the excipient is a key element beyond the compendia specifications. Excipient identification and critical parameters are able to ensure the consistency of the resulting product [18]. In this study, the researchers report on the pharmacopoeial, physicochemical, and microbiological properties of MCC from Sengon wood sawdust waste with Avicel PH 102 as a commercial comparison.

II. MATERIALS AND METHODS

Materials

Sengon wood sawdust is obtained from Sengon wood pith waste from CV. Cahaya Abadi Chipp (Kaliwungu-Kendal), sodium hydroxide (NaOH), hydrochloric acid (HCl), sodium hypochlorite (NaOCl), and Avicel PH 102 (American International Chemical /AIC) as commercial standard.

Methods

Alkaline Delignification

Sengon wood pith was sanded using a grid machine number 250 dried for 24 hours and sieved through 40 mesh until Sengon Wood Sawdust (SWS) was obtained. Delignification of SWS used 2% NaOH solution with a ratio of (1:19.20) at 50°C for 30 minutes. Then, it was heated in a closed container on a hot plate at a controlled temperature. The processing results were washed with aquadest and bleached with 5% NaOCl at 70°C for one hour. The bleached product was then filtered, rinsed with aqua distillate until neutral, and then dried for 24 h to obtain Sengon wood sawdust cellulose (SWS-C) [21].

Acid Hydrolysis

Hydrolysis of SWS-C was carried out using 4 N HCl with a ratio of (1:40) at 80□ C with constant stirring for four hours. The results obtained were filtered and washed repeatedly with distilled water and bleached using 10% NaOCl 75□ C for one hour. The dregs were rinsed again using distilled water until neutral, dried for twenty-four hours and sieved through 60 mesh. The final product obtained was called Sengon wood sawdust microcrystalline cellulose (SWS-MCC).

Physicochemical Characterization of SWS-MCC

Organoleptic characteristics, identification of cellulose, organic impurities, starch, solubility, total ash, and loss on drying were carried out by specifications [1] [25].

pH Determination

The pH was determined by mixing 2 g of SWS-MCC and 100 mL of distilled water, shaking for five minutes [26]. The supernatant obtained was measured with pH meter (Transinstruments HP9010).

Heavy Metals

Lead (Pb) and Cadmium (Cd) levels were analyzed using atomic absorption spectrometry (AAS) (ContrAA 300) while Mercury (Hg) levels used a mercury analyzer (Lab Analyzer 254) [27][28].

Flow Rate and Angle of Repose

The flow properties of SWS-MCC were determined by measuring the flow rate and angle of repose using the funnel method [29] using a flowability tester (Erweka GT) with a funnel diameter of 15 mm. The bottom of the funnel would

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open automatically, then the powder would flow and its flow rate and repose could be determined [30].

Moisture Content

Determined using a moisture content tool set at a temperature of 105□ C forautomatic time to constant weight. The standard requirement for MCC moisture content was not more than 5%[1].

Density, Carr's index, and Hausner ratio

Bulk and tapped density were determined by adding a certain amount of SWS-MCC into a 100 mL measuring cup that has been cleaned and dried. The initial volume was recorded as (Vo) and then mounted on a tap density tool, the compressed volume was measured on several taps as V10, V500, and V1250. Stop the test if the difference between V500 and V1250 was not more than 2 mL and recorded it as Vt. Then, the density was determined by dividing the sample weight by Vo (bulk density), Vt (tapped density) Carr's index, and Hausner ratio[25].

Compactability

SWS-MCC was printed using a single punch tablet printing machine with pressures of 4,5,6 and 7mm. Compactability was determined based on the hardness level of the tablet produced [31].

Microbial limits

Microbial limits were analyzed including the total aerobic microbial count, the total combined molds and yeasts and the absence of E. coli and Salmonella sp. [32][25][33].

Particle size and particle size distribution

Particle Size Analyzer (PSA) and Malvern ® Mastersizer 3000 (Malvern Instruments, UK) were used to measure the particle size of SWS-MCC. Tests were carried out under dry dispersion conditions with dispersant refractive index 1.0, analysis model (general purpose), weighted residual (0.53%), and laser obscuration (0.88%).

III. RESULT AND DISCUSSION

Delignification of SWS using NaOH aims to break lignocellulose bonds to obtain SWS-C. NaOH in solution will form a strong alkali that releases heat, so it can function as a reducing agent, which will degrade lignin in lignocellulose bonds. In the delignification process, α-cellulose levels were obtained, which were still relatively low compared to native[21]. This is due to the nature of lignocellulose in wood materials, where the bond is stronger than non-wood, making hydrolysis using HCl is needed to separate the crystalline and amorphous forms of cellulose so that the α-cellulose content increases significantly [21]. As a result of hydrolysis, a dark-colored powder was obtained (Figure 1.) and then bleaching was carried out. In this stage, besides bleaching, there was also a hydrolysis reaction of α-cellulose by hydrochloric acid, which was formed during bleaching for a long time. The formation of hydrochloric acid in the bleaching process was based on the mechanism of abstraction of hydrogen atoms from organic substrates by chlorine [26] so bleaching also plays a role in increasing the levels of α-cellulose and SWS-MCC obtained.

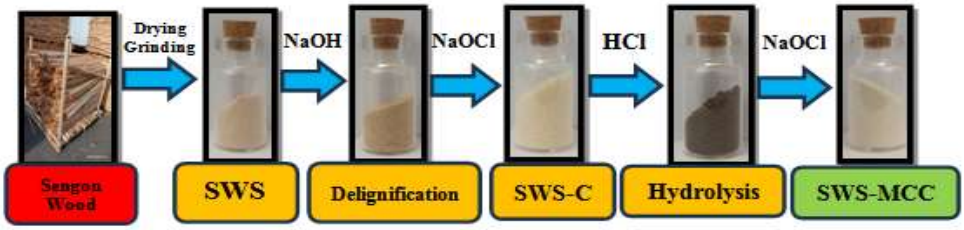

Figure 1. The Process for Isolation of SWS-MCC

The SWS-MCC produced has organoleptic qualities, odorless, tasteless, and beige white with a granular texture. The physicochemical properties of SWS-MCC are presented in Table 1. and have good quality as evidenced by the identification results showing positive results for cellulose (violet-blue) and reinforced by the absence of starch being identified as indicated by the absence of color change after the water solution was heated and the solution was added the iodine [11]. This indicates that there is no amylose content (straight chain compound)[34]in SWS-MCC. Loss on drying was carried out to determine the maximum concentration range of compounds lost during the drying process. Ash content provides an overview of the mineral content originating from both raw materials and during the manufacturing process. The total ash value was very low because the cellulose material is

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relatively free from organic compounds and ~~is~~ also caused by non-cellulosic components, which degraded slowly during the delignification and hydrolysis processes [35]. Ash content SWS-MCC obtained lower results than other results [3], which indicates that the chosen treatment is appropriate. The solubility of SWS-MCC showed good condition in water, while NaOH and H_2SO_4 is low. Solubility in NaOH was carried out to determine the level of purity of cellulose because α-cellulose (pure cellulose) has long chains, so it did not dissolve in strong bases. The pH value, organic impurities, ash content, loss on drying, and solubility of SWS-MCC were based on the criteria specifications required for pharmaceutical grade MCC[1] and similar to Avicel PH 102 as standard commercial.

Table 1. Physical and Chemical Characteristics of SWS-MCC

Type of Assay	Results		Limit Requirements
	SWS-MCC	Avicel PH 102	
Identification	Violet-blue	Violet-blue	Violet-blue
pH	Neutral	Neutral	Neutral
Starch	Nil	Nil	Nil
Organic impurities	Nil	Nil	Nil
Ash content (%)	0.09% ± 0.02	0.01% ± 0.01	≤ 0.1%
Loss on drying (%)	6.29% ± 0.004	6.87% ± 0.004	≤ 7%
Solubility	Undissolved	Undissolved	Undissolved

Besides physical and chemical characteristics, the heavy metal requirements of the Republic of Indonesia Food and Drug Supervisory Agency were met by SWS-MCC. Quantification of heavy metals (Pb and Cd) was carried out using atomic absorption spectrophotometry (AAS) while Hg qualification used a mercury analyzer. This test was carried out to ensure the safety (non-toxic) of SWS-MCC so that it is safe to use as a pharmaceutical excipient. Microbial limits were carried out to ensure free SWS-MCC from pathogenic and non-pathogenic microbes. Media that could grow bacteria and fungi was used, meaning that all the nutrients the microbes need to grow were met. The results show that the Total Yeast/mold Count and Total Aerobic Microbial Count SWS-MCC meet the specified requirement limits [1]. Negative results for E. coli and Salmonella sp. show high excipient quality. Although the Pharmacopoeia ~~does~~ did not specify microbial standards that must be met by MCC, it is required for pharmaceutical grade starch. In the future, if non-sterile excipients including MCC are needed to meet microbial limit requirements, these results can provide information that SWS-MCC meets these standards. Microbiological and heavy metal determination results for SWS-MCC are presented in Table 2.

Table 2. Microbiological and Heavy Metal Determination Result for SWS-MCC

Type of Assay	Results		Limit Requirements
	SWS-MCC	Avicel PH 102	
Total Yeast/mould Count	$1.1x10^2$ cfu/g	$5.5x10^1$ cfu/g	$\leq 10^2$ cfu/g
Total Aerobic Microbial Count	$1.2x10^2$ cfu/g	$1.4x10^3$ cfu/g	$\leq 10^3$ cfu/g
E. coli	Negative	Negative	Negative
Salmonella sp.	Negative	Negative	Negative
Pb (Lead)	Negative	Negative	≤ 10 mg/Kg
Cd (Cadmium)	Negative	Negative	≤ 0.3 mg/Kg
Hg (Mercury)	0.26 mg/Kg	0.21 mg/Kg	≤ 0.5 mg/Kg

The flow ability characteristics of SWS-MCC can be seen in Table 3. It shows that flow rate is faster than the commercial standard, but both flow rates appear to be significantly better than the limit requirements. Flow rate is influenced by particle size and moisture content. Fines produced cause electrostatic forces to arise between particles which result in slowed particle movement. Fines have a larger outer surface, so their binding capacity increases and as a result the flow rate of fines or small particles is lower [34]. The SWS-MCC flow rate is not only faster than commercial standards but

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also than several previously reported studies [11]. The MCC angle of repose limit requirement is 34.4°- 49°[1] and fulfilled. In Table 3, the angle of repose of SWS-MCC is lower, meaning that it has better flowability than previously reported [14], similar to [5]. SWS-MCC has a moisture content of 4.38%, this value is lower than commercial standards and meets the required limits [1]. Moisture content is a key parameter that influences the mechanical properties and flow of MCC in various stages of the manufacturing process [36]. The higher the moisture content can increase the binding force between particles, thereby forming larger aggregates with non-uniform shapes and sizes, making it difficult to flow. The results are slightly greater than in previous studies [37].

Table 3. Characterization of SWS-MCC

Type of Assay	Results		Limit Requirements
	SWS-MCC	Avicel PH 102	
Flowability:			
Flow rate	88.384 g/s ± 4.38	29.104 g/s ± 3.32	1.41 g/s
Angel of repose	36.17°± 0.58	45.27°± 1.22	34.4° - 49°
Moisture content	4.38% ± 0.15	4.93% ± 0.07	< 5%
Bulk density	0.641 g/mL ± 0.017	0.371 g/mL ± 0.009	0.13 – 0.8 g/mL
Tapped density	0.733 g/mL ± 0.010	0.457 g/mL ± 0.002	0.35 – 0.478 g/mL
True density	1.624 g/mL ± 0.007	1.466 g/mL ± 0.040	1.42 – 1.668 g/mL
Hausner ratio	1.15 ± 0.02	1.23 ± 0.02	1.12 – 1.18
Carr's index	12.67% ± 1.15	18.67% ± 1.53	11% - 15%
Compactibility	21.04 ± 0.59	6.41 ± 0.23	-

In this research, density values (bulk, true and tapped) were also determined, as well as the Hausner ratio and Carr's index as the indicators of powder flowability. As seen in Table 3, it shows that SWS-MCC has free flow (good) according to the criteria [1]. Powder flow properties are a complex interaction of particle shape, particle size distribution, and intra/inter particulate forces [38]. Based on the Hausner ratio and Carr's index values, it can describe the highly compressible powders from SWS-MCC. This is greatly influenced by the morphology of the particles, which are spherical and are easy to compress. These properties are expected from direct compress pharmaceutical grade excipient tablets. This research shows better results than other raw materials [11][39][18] and is comparable to[14].

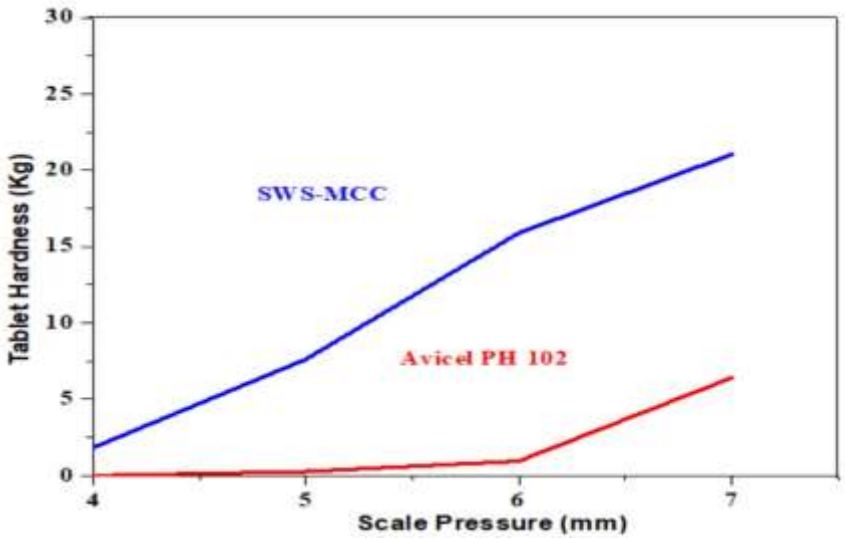

Figure 2. Compactability of SWS-MCC and Avicel PH 102 tablet

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The compatability of SWS-MCC in the research was measured using the hardness level approach of tablets printed with a punch pressure scale of 4, 5, 6, 7 mm. Figure 2 shows that as the punch pressure increases, the resulting tablet becomes harder. SWS-MCC has greater compact ability compared to the commercial standard (Avicel PH 102). It can be seen that SWS-MCC from low pressure shows that the tablet hardness results are low, while Avicel tablets are so fragile that the measured hardness is 0 kg. Upon further addition of pressure, SWS-MCC shows a significant increase in tablet hardness, while Avicel PH 102 does not show similar results. Meanwhile, Avicel PH 102 shows a significant increase in hardness at a pressure of 7 mm (6.4 kg) and at the same pressure SWS-MCC shows a maximum pressure with a compact ability of 21.04 kg. Compact ability is directly proportional to particle size [40], this relationship was not only seen in MCC but also other excipients as previously reported [34][41].

Table 4. Particle size of analyzed SWS, SWS-MCC and Avicel PH 102

	Dx (10) (μm)	Dx (50) (μm)	Dx(90) (μm)	Dx (100) (μm)	Span
SWS	11,654	41,038	124,030	395,607	2,738
SWS-MCC	38,169	134,257	287,840	575,054	1,860
Avicel PH 102	26,570	110,489	234,472	452,794	1,882

The results of PSA measurements on SWS-MCC and Avicel as a commercial comparison are presented in Table 4. and Figure 3. It can be seen that the particle size distribution pattern of SWS-MCC is very similar to the commercial comparison (Figure 3) with the median mass diameter or particle volume distribution respectively being 134,257μm and 110,489μm. When compared with SWS, it can be seen that SWS-MCC has a wider peak with a larger volume density and the curve points to the right, this is possibly caused by stronger particle aggregation during the hydrolysis process [39]. The measurement results obtained showed that the average particle volume from SWS, SWS-MCC, and Avicel is 56,828 respectively.μm, 150,471μm, and 122,542μm. The surface area of SWS-MCC particles (72,585μm) is indicated to be almost three times wider than SWS (21,944μm), the greater the surface area of the particles indicates that the particle size of SWS-MCC is smaller than SWS. Therefore, it is clear that the acid hydrolysis process has a significant effect on the unbinding of cellulose chains and their agglomeration [42][39]. Acid hydrolysis also causes the disintegration of the amorphous regions of long cellulose fibrils, thereby reducing the size of the resulting MCC particles [43][44].

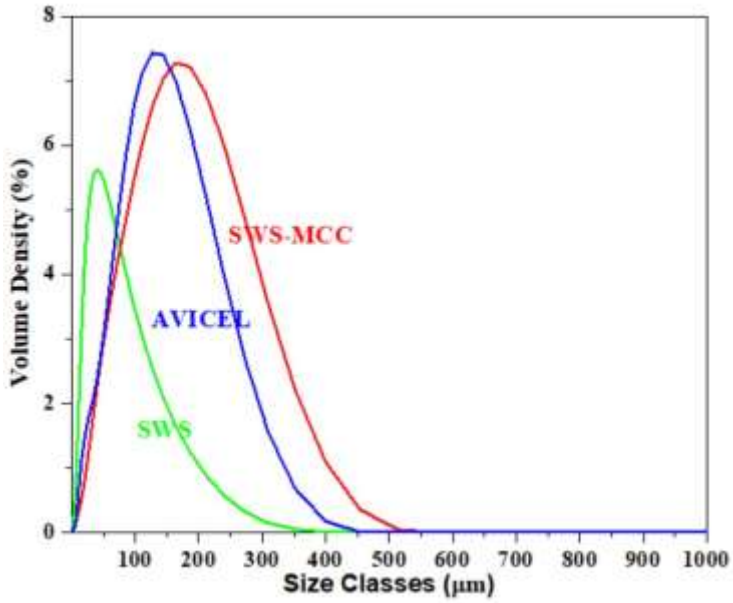

Figure 3. Particle Size Distribution Profiles of SWS, SWS-MCC and Avicel.

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IV. CONCLUSION

MCC obtained from the hydrolysis of α-cellulose of Sengon wood sawdust has pharmacopoeial, physicochemical, and microbiological properties suitable for pharmaceutical applications. The properties of SWS-MCC show similar or even better results than the commercial standard (Avicel® PH 102), including moisture content (4.38%), flow rate (88.384 g/s), angle of repose (36.17°), Carr's index (12.67%), Hausner ratio (1.15), and compactability of 21.04 kg. Therefore, it is concluded that SWS is a potential waste as due to its cost-effectiveness, functionality, and sustainability as a pharmaceutical excipient, especially for direct compression tableting.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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