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Microcrystalline cellulose obtained from *Chasmanthera dependens* plant as a pharmaceutical excipient

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Abstract

This study was aimed at developing pharmaceutical grade microcrystalline cellulose from *Chasmanthera dependens* stem phloem fibres as a tablet excipient. The microcrystalline cellulose coded CD-MCC, was obtained from the phloem fibres by a two-stage sodium hydroxide delignification process followed by sodium hypochlorite bleaching and acid hydrolysis. CD-MCC was examined for its physicochemical and powder properties. The powder properties of CD-MCC were compared to those of best commercial microcrystalline cellulose grade, Avicel PH 101. The extraction yield of CD-MCC was about 17%. The cellulose material was composed of irregularly shaped fibrous cellulose particle with a moisture content of 4.8%. The true density was 1.66. The flow indices showed that CD-MCC flowed poorly. The hydration and swelling capacities were 2.19 and 41.9% respectively. The study revealed that the cellulose material compares favourably with Avicel PH 101 as well as official requirement specified in the British Pharmacopoeia 1993 for microcrystalline cellulose.

Keywords: *Chasmanthera dependens*; Microcrystalline cellulose, Extraction; Characterization

Introduction

Microcrystalline cellulose, (MCC), is described as purified, partially depolymerised cellulose prepared by treating α-cellulose, obtained as a pulp from fibrous plant with mineral acids. MCC is one of the most used filler-binders in direct compression. Its popularity in direct compression is because of its extremely good binding properties as a dry binder. It also works as a disintegrant and a lubricant and has a high dilution potential in direct compression formulations. In addition to its use in direct compression formulations, MCC is used as a diluent in tablets prepared by wet granulation, as filler for capsules and for the production of spheres (Bolhuis and Chowhan, 1996). Commercially available MCC is derived from both gymnosperms (generally conifers) and other softwoods, and from hardwood dicotyledons. These woods differ considerably in chemical composition (proportions of cellulose, hemicelluloses and lignin) and structural organization which affect the composition of the α-cellulose extracted and the composition and crystallinity of MCC finally produced (Landin *et al.*, 1993). Besides the wood pulp as a source of cellulose and its derivatives, the purified cotton linters obtained from *Gossypium* species (Evans, 1989) are also a

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common source. Purified cotton linters and wood pulp are obtained from plantations specially grown in temperate climates, as such its production is expensive and the need for exploring other sources for MCC becomes imperative. Alternative sources for MCC recently investigated include agricultural wastes and other plants parts not traditionally used for MCC production (Alfa *et al.*, 2000; Audu-Peter *et al.*, 2004 and Ohwoavworhua *et al.*, 2004).

Chasmanthera dependens Hochst (Menispermaceae) is a lofty woody climber of forest margins and savannas, especially by rocks. Old stem have distinct bosses and are softly pubescent and the young stems are soft and hairy. It is found throughout tropical Africa, from the semi-deciduous dense forests of West Africa through Chad to Ethiopia. The plant is widely cultivated in home gardens for medicinal purposes (Irvine, 1961). In Nigeria the phloem fibres of stems are used as sponge and the bark is used for venereal discharges or as a general tonic for physical nervous debilities in inflammatory and exhausting diseases (Irvine, 1961). Phytochemical investigation of the stem of this plant has been carried out (Ohiri *et al.*, 1982) and it was discovered that the plant contained starch. Starch from this plant has been evaluated as binder and disintegrant in acetaminophen tablet formulation (Ajayi *et al.*, 1996).

Evans (1986) has reported that strands of phloem fibres of *Corchorus* species (Jute); pericyclic fibres of the stems of *Linum usitatissimum* (Flax) and *Cannabis sativa* are composed of chiefly of cellulose. It is against this background that this study attempted to extract alpha-cellulose and its modified form, microcrystalline cellulose from the phloem fibres of the stem of *C. dependens* as literature survey reveals no report on its use as a possible source of MCC. The MCC obtained was then characterised for its physicochemical and powder properties. The powder properties were however compared with those of commercial grade microcrystalline cellulose.

Experimental

Materials. Sodium hydroxide (BDH, England), sodium hypochlorite as 'Jik' (Reckitt and Colman Ltd, Nigeria), hydrochloric acid (Fisons, UK), Avicel PH 101 (FMC corporation, USA), xylene, phloroglucinol and iodine crystals (Hopkins and Williams, London) were used as obtained. All other chemicals used were of analytical reagent grade and water was double distilled.

Extraction of alpha cellulose. Young stem of *C. dependens* was harvested from the National Institute for Pharmaceutical Research and Development, Abuja, botanical garden. The fibres were separated from the other plant material by retting followed by beating and washing. The phloem fibres obtained were size reduced in a cutter mill and alpha cellulose was then extracted in accordance with literature method (Ohwoavworhua *et al.*, 2004) with minor modification. A 175 g quantity of the material was placed in a stainless steel container to which was added 5 L of 2% w/v sodium hydroxide and digestion was effected for 4 h at 80 ^{0}C in a water bath (FGL 1083 Karl Kolb scientific). Following thorough washing and filtration, it was bleached once with 3.0 L of a 1:1 aqueous dilution of sodium hypochlorite for 10 minutes at 100 ^{0}C. The washed and filtered material was then treated with 2.4 L of 17.5 % w/v sodium hydroxide at 80 ^{0}C for 9 h. The resulting alpha-cellulose was washed thoroughly. The extraction process was completed by whitening with a 1:1 aqueous dilution of sodium hypochlorite for 5 min. at 80 ^{0}C and was washed until it is neutral. The cellulose material was filtered, pressed and manually reduced to small lumps, which were dried in a fluid bed dryer (laboratory model, Copley) at an inlet air temperature of 57 – 60 ^{0}C for 60 min.

Production of microcrystalline cellulose (MCC). The procedure reported earlier (Ohwoavworhua *et al.*, 2004) with slight modification was used. A 50 g quantity of the alpha cellulose obtained was place in a glass container and hydrolyzed with 1.2 L of 2.5 N hydrochloric acid at 100 ^{0}C for 30 min. The hot acid mixture was poured into cold tap water which was followed by vigorous stirring with a glass rod. The product was washed with water until neutral, pressed and dried in a fluid bed dryer at an inlet air temperature of 57 – 60 ^{o}C for 60 min. Following further milling and sieving, the fraction passing through 1.18 mm sieve was obtained and stored at room temperature in a desiccator.

PHYSICOCHEMICAL PROPERTIES OF CD-MCC

The organoleptic characteristic, identification, organic impurities, starch and dextrin, solubility, total ash and water-soluble substances were carried out in accordance with BP (1993) specifications. An optical microscope, Nikon model Larphot 2 (Nikon Inc. Japan) was used for preliminary assessment of the nature of particles in CD-MCC. The combination of low and high power objective lenses of 100 and 400 times magnification was used.

pH determination: This was done by shaking 2 g of the powder material with 100 ml of distilled water for 5 min and the pH of the supernatant liquid was determined using a pH meter (Corning, model 10 England).

Total ash determination: Ash content was estimated using the method in the B.P. (British Pharmacopoeia) 2004, Volume 1.

Powder properties

Particle size analysis. An Endicott's sieves shaker, (Endicott's Ltd UK) was used for this. Test sieves ranging from 1.18 mm to 75 μm were arranged in a descending order. A 40 g quantity of CD-MCC powder was placed on the top sieve and was shaken for 5 min. and the weight of material retained on each sieve determined. The average diameter was calculated as reported by Ansiel *et al*, 2005 using the equation:

$$\text{Average diameter} = [\sum (\% \text{ retained}) \times (\text{mean aperture})]/100 \quad \ldots\ldots\ldots 1$$

True density. The densities of cellulose powders were determined by the liquid displacement method using kerosene as the immerse fluid (Okhamafe *et al.*, 1991).

Flow Properties.

Angle of repose. The static angle of repose, *a,* was measured according to the fixed funnel and free standing cone method (Train, 1958). A funnel was clamped with its tip 2 cm above a graph paper placed on a flat horizontal surface. The powders were carefully poured through the funnel until the apex of the cone thus formed just reached the tip of the funnel. The mean diameters of the base of the powder cones were determined and the tangent of the angle of repose calculated using the equation:

$$\text{Tan } a = 2h/D \quad \ldots\ldots\ldots 2$$

Where h is height of heap of powder and D is the diameter of the base of heap of powder.

Bulk and tap densities. A 30 g quantity of powder samples were each, placed into 250 ml clean, dry measuring cylinder and the volume, V_o, occupied by each of the samples without tapping was determined. After 500 taps using Stampfvolumeter (Model STAV 2003 JEF, Germany), occupied volumes, V_{500} were determined. The bulk and tap densities were determined from these volumes (V_0 and V_{500}) using the equation:

$$\text{Density} = \text{Weight of cellulose/ Volume of cellulose} \quad 3$$

Hausner index. This was calculated as the ratio of tap density to bulk density of the samples.

Compressibility index (C %). This was calculated using bulk and tap densities data when fitted into the equation:

$$\text{Compressibility} = \{(\text{Tapped density} - \text{bulk}$$

density)/Tapped density} x 100 % 4

Powder Porosity. This was derived from the values of true and bulk densities when fitted into the equation:

$$e = 1-B_b/B_p \times 100 \quad \text{.....5}$$

Where B_b is the bulk density, B_p is the true density and e is the porosity

Hydration capacity. The method of Kornblum and Stoopak (1973) was used. A 1.0 g each of the samples was placed in each of four 15 ml plastic centrifuge tubes and 10 ml distilled water was added from a 10 ml measuring cylinder and then stoppered. The contents were mixed on a vortex mixer (Vortex-Gennie Scientific Industry, USA) for 2 min. The mixture was allowed to stand for 10 min. and immediately centrifuged at 1000 rpm for 10 min. on a Gallenkamp bench centrifuge (Gallenkamp, England). The supernatant was carefully decanted and the sediment weighed. The hydration capacity was taken as the ratio of the weight of the sediment to the dry sample weight

Swelling capacity. This was measured at the same time as the hydration capacity determination using the method of Okhamafe *et al.* (1991).

Moisture sorption profile. Two grams of the cellulose materials were accurately weighed and evenly distributed over the surface of a 70 mm tarred *Petri* dish. The samples were then placed in a large desiccator containing distilled water in its reservoir (RH = 100%) at room temperature and over a five-day period, the weight gained by the exposed samples were recorded. The amount of water sorbed was calculated from the weight difference (Ohwoavworhua *et al.*, 2004).

Moisture content. Five grams of powder samples were transferred, each, into a *Petri* dish and then dried in an oven at 60 °C until a constant weight was obtained. The % moisture content was then determined as the ratio of weight of moisture to weight of sample expressed as percentage (Ohwoavworhua *et al.*, 2004).

Results and Discussion

The yield of alpha cellulose was approximately 24 percent w/w of the original material. The yield of the microcrystalline CD-MCC, obtained from alpha-cellulose was approximately 71 percent w/w. Thus the yield of CD-MCC was approximately 17 percent w/w of the starting dry plant material. The results of the physicochemical properties investigated are shown in Table 1. The results indicate a high level of purity of the cellulose material. The organoleptic qualities of the CD-MCC produced were good as the material was odourless, tasteless, off-white and granular in texture. The value obtained for the total ash was very low possibly because cellulosic materials are almost free of inorganic compounds. When vegetable plants are incinerated, they leave an inorganic ash which in the case of many drugs varies within wide limits. The total ash figure is of importance and indicates to some extent the amount of care taken in the preparation of the substance (Evans, 1989).

The powder properties of CD-MCC and Avicel PH 101 are presented in Table 2 while the result of particle size distribution for CD-MCC is as shown in Figure 1. The figure represents a bimodal frequency distribution which is positively skewed. The particle size is in the range of 70-1000 microns, as such CD-MCC powder belongs to the classification conventional powder (Barber, 1993). Over 90 percent of the particle population is less than 375 micron, and the calculated average diameter was 219 micron.

Table 1: Some physicochemical properties of CD-MCC

Test	Observation
Identification	Turns violet-blue with iodinated $ZnCl_2$
Organic impurities	Nil
Starch and dextrins	Nil
pH	7.6
Solubility (in tetrammine copper II solution)	Complete and no residue
Water –soluble substance	< 0.2%
Total ash (%)	0.27 (0.07)*
Microscopy	Irregularly shaped fibrous particles which are mixture of primary particles and spherical aggregates.

*Standard deviation in parenthesis

Table 2: Powder properties of CD-MCC and Avicel PH 101

Parameters	CD-MCC	Avicel PH 101
True density (g/ml)	1.66 (0.05)	1.40 (0.12)
Bulk density (g/ml)	0.37 (0.02)	0.31 (0.04)
Tapped density (g/ml)	0.52 (0.0)	0.42 (0.12)
Porosity (%)	78	78
Flow properties:		
(a) Angle of repose	36.42 (0.56)	41.20 (0.46)
(b) Hausner index	1.41	1.35
(c) Compressibility index (%)	29	26
Hydration capacity	2.19. (0.02)	2.17 (0.01)
Swelling capacity (%)	41.9 (.43)	21.4 (0.24)
Moisture content (%)	4.8(0.22)	7.4 (0.4)
Moisture sorption capacity (%)	15	16.6

Values are mean and standards deviation are in parenthesis; Number of replicates =3

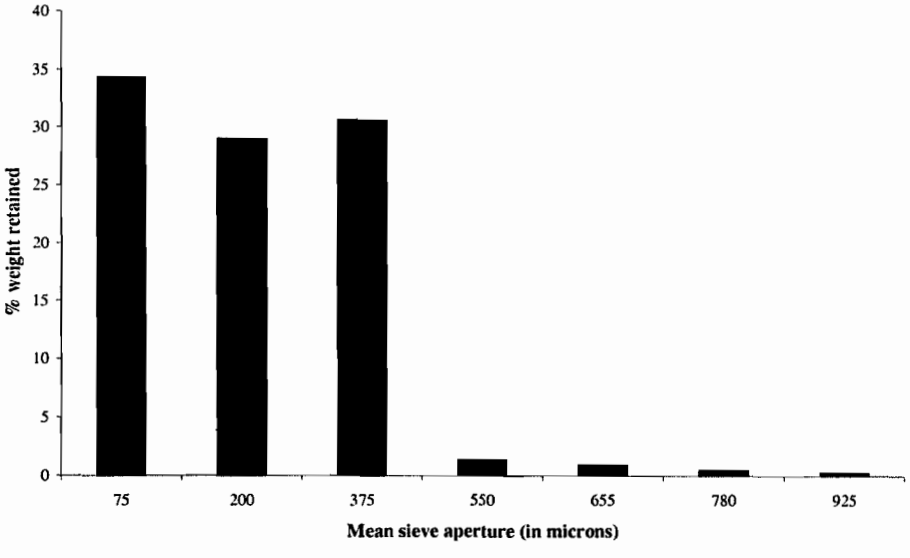

Figure 1: Particle size distribution of CD-MCC powder

The true density for LC- MCC (Table 2), 1.66, is high when compared to 1.40 for Avicel PH 101. This high value for CD-MCC is therefore suggestive that CD-MCC has higher degree of crystallinity than Avicel PH 101. Stamm (1964) has reported that the greater the degree of crystallinity of a cellulose, the greater will be the true density of its substance determined in a non-polar liquid. The moisture content of CD-MCC produced was about 4.8% which is well below the official limit of 8 % (BP, 1993). This low value is indicative of the suitability of CD-MCC as a diluent in the formulation of hydrolysable drugs such as aspirin.

The flow properties of a powder are essential in determining the suitability of it as a direct compression excipient. The angle of repose, Hausner index and Carr's percent compressibility are considered as indirect measurements of powder flowability (Staniforth, 1996). The angle of repose of CD-MCC is high (Table 2), which is indicative of very poor flow (Well and Aulton, 1996). While the Hausner index is indicative of interparticle friction, the Carr's index shows the aptitude of a material to diminish in volume (Staniforth, 1996). As the values of these indices increase, the flow of the powder decreases. In general however, Hausner ratio greater than 1.25 indicates poor flow and Carr's compressibility index below 16 % indicate good flowability while values above 35 % indicate cohesiveness (Staniforth, 1996). Thus, the flow indices (Table 2) showed that both CD-MCC and Avicel PH 101 flowed poorly. As such a glidant will be needed when these materials are to be used in solid dosage formulation.

Swelling which is generally accepted as an indication of tablet disintegration ability (Caramella, 1991); can be assessed by the determination of hydration capacity, swelling capacity and moisture sorption profile.
The hydration capacity value (Table 2) indicates that CD-MCC is capable of absorbing more than twice its own weight of water. The swellability, which reflects the increase in volume of cellulose following water absorption, was 41.9 % (Table 2). It seems therefore, that only a small portion of absorbed water actually penetrated the individual cellulose particles causing them to swell. The bulk of the absorbed water would exist in a 'free' state between the particles. Thus, if the cellulose was incorporated in tablet formulation as a disintegrant it would probably produce tablet disintegration by two mechanisms: capillary or wicking due to interparticulate water and swelling.

The moisture sorption capacity is a measure of moisture sensitivity of materials and the values for CD-MCC and Avicel PH 101 are comparable. Stamm (1964) has reported that the crystallite portion of cellulose does not adsorb water and that the extent of water adsorption by cellulose should thus be proportional to the amount of amorphous cellulose present. Thus, the result is indicative of the high degree of crystallinity expected of these materials. Also, measurement of water sorption is of importance since it reflects the relative physical stability of tablets made from CD-MCC when stored under humid condition. In all, this property showed that the cellulose powders are sensitive to atmospheric moisture and should therefore be stored in air tight container.

Conclusion

The cellulose product, CD-MCC, obtained from *C. dependens* stem phloem fibres conformed to the official specifications in the British Pharmacopoeia (1993). The powder properties indicate that CD-MCC and Avicel PH101 are comparable, hence microcrystalline cellulose obtained from *C. dependens* stem phloem fibres, CD-MCC, is a potential tablet excipient.

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