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Research Article

Properties of Microcrystalline Cellulose Obtained from Cassava Stem Using Two Extraction Methods in Metronidazole Tablet Formulations

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Abstract

The aim of the study was to investigate the properties of microcrystalline cellulose (MCC) obtained from cassava stems using the nitric acid and sodium hydroxide methods of extraction in comparison with Avicel® PH 101 in metronidazole tablet formulations. Alpha-cellulose from cassava stems was extracted with nitric acid and sodium hydroxide methods and converted to MCC with dilute hydrochloric acid solutions. The MCC powders were subjected to some physicochemical characterization and FTIR analysis and then used with Avicel at different concentrations to formulate batches of metronidazole tablets by wet granulation. The metronidazole granules and tablets properties were evaluated using standard procedures. Results showed a higher yield of 30.22 % for the nitric acid method of extraction with the MCC obtained whiter in colour and fluffy in texture against the creamy colour and granular texture of those from the sodium hydroxide method. FTIR analysis reveals similar absorption spectra for MCC of both methods of extraction. Comparable granules and tablet parameters were gotten for the metronidazole granules and tablets formulated using the MCC of both methods of extraction and Avicel PH 101. This study revealed that the method of extraction can affect the properties of the MCC extracted, though this may not adversely affect its pharmaceutical quality. The comparable tableting parameters of metronidazole tablets formulated with the extracted MCC and Avicel PH 101 may suggest that the extracted MCC can be used as a suitable substitute for Avicel.

Keywords: Microcrystalline cellulose, extraction, disintegrants, metronidazole, tablets

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 [1]. Cellulose is the most abundant natural polymer on earth with an annual biomass production of 50 billion tonnes [2]. MCC, introduced in the early 1960s is regarded as the best excipient for direct compression tableting [3]. Hence, it is one of the most used filler-binders in direct tablet compression. The most common source of pharmaceutical MCC is wood, in which cellulose chains are packed in layers held together by a cross-linking polymer (lignin) and strong hydrogen bonds. Cotton has also been mentioned as a possible cellulose source for MCC [4, 5].

Its popularity in direct compression is due to its excellent binding properties when use as a dry binder [6]. It also works as a disintegrant and lubricant and has a high dilution potential in direct compression formulations. It is also used as a diluent in tablets prepared by wet granulation as well as filler for capsules and spheres. In addition to its dry binding properties and in comparison to brittle excipients, MCC is self-disintegrating [7] with low lubricant requirement due to its extremely low coefficient of friction and its very low residual die wall pressure [8]. However these properties do not replace the need for true disintegrants and lubricants when MCC is used in a formulation. In fact MCC and superdisintegrants may be complementary to promote fast disintegration [9]. It offers other advantages including broad compatibility with APIs, physiological inertness and ease of handling [10]. With the abundant sources of MCC and various methods of extraction being reported [11, 12], the need to evaluate their physicochemical properties in order to ensure that their quality meet the standards of pharmaceutical grade MCC cannot be over-emphasised. The objective of this study was to investigate the properties of microcrystalline cellulose obtained from cassava stem using the nitric acid and sodium hydroxide methods and to compare the physicochemical properties of metronidazole tablets formulated using the extracted MCCs and Avicel® as standard disintegrant.

Materials and Methods

Materials

Avicel® PH 101 (FMC Biopolymers, USA), nitric acid (May and Baker Ltd, UK), sodium hydroxide (Merck, Germany), sodium hypochlorite (Reckitt and Colman Nig. Ltd., Lagos), sodium nitrite and sulphite (BDH Chemicals Ltd. Poole England), phloroglucinol (Hopkin and Williams, UK), metronidazole powder, lactose, maize starch BP, talc and magnesium stearate (William Ransom and Son PLC, Hitchin Hertfordshire, England). Dried cassava stems were collected as harvest wastes from the farms of the Faculty of Agriculture, University of Benin, Benin City, Nigeria.

Methods

Extraction of α-cellulose

Nitric acid method

The extraction was carried out using the method of Ohwoavworhua, *et al*. [13]. The dried cassava stems were cut into small fragments and then micronized in a Fitz mill (Manesty Machines UK) into fine powders. Five hundred grams of the powdered cassava stem was treated with 5 L of 3.5 % nitric acid containing 20 mg of sodium nitrite for 2.5 h in a stainless steel container which was maintained at 100 °C for delignification of the cellulosic material. The sample was washed thoroughly, filtered and then digested with a 5 L solution containing 2 % w/v each of sodium hydroxide and sodium sulphite at a temperature of 50 °C for 1 h. The sample was again thoroughly washed, filtered and further treated with 2 L of 1:1 aqueous dilution of 3.5 %w/v sodium hydroxide at boiling temperature for 30 min. The washed and filtered material (hemi-cellulose) was next treated with 2 L of 17.5 % w/v sodium hydroxide solution at 80 °C for 30 min. The resulting material was again washed thoroughly with distilled water, filtered and then bleached with 2 L of 1:1 aqueous solution of 3.85 %w/v sodium hypochlorite in a stainless steel bucket at 40 °C for 2.5 h. The product (alpha-cellulose) was washed and air dried for 24 h and further oven dried (Kottermanns, Germany) for 1 h at 60 °C. It was

milled in a blender (Kenwood Ltd, UK) and screened through a 212 μm sieve, weighed and the percentage yield calculated before been stored in an air tight container.

Sodium hydroxide method

Using the method of Ohwoanvworhua *et al*. [11], five hundred grams of the powdered cassava stem was treated with 5 L of 2 %w/v solution of sodium hydroxide in a stainless steel container maintained at 100 °C for 3 h for delignification. The sample was then washed with distilled water, filtered and treated with 4 L of 17.5 % w/v sodium hydroxide solution at 80 °C for 1 h in a stainless steel container. The sample was again washed, filtered and bleached with 1 L of 1:1 aqueous solution of 3.85 %w/v sodium hypochlorite solution in a stainless steel container at 40 °C for 1.5 h. The bleached material was then washed, filtered and further treated with 3.5 %w/v sodium hydroxide at boiling temperature for 3 h for further delignification. The resulting material was thoroughly washed with distilled water and filtered and then air dried for 24 h and oven dried for 1 h at 60 °C. The product was milled in a blender and screened through a 212 μm sieve, weighed and the percentage yield calculated before been stored in an air tight container.

Production of microcrystalline cellulose

Five hundred milligrams of the α-cellulose powder obtained from either of the extraction processes was added to a 1.2 L boiling solution of 2.5 M hydrochloric acid in a stainless steel container and allowed to boil for 1 h. The resulting microcrystalline cellulose (MCC) was collected by filtration and the filtrate was thoroughly washed with distilled water until it was neutral to litmus. The microcrystalline cellulose was then dried at room temperature to a constant weight.

Physicochemical characterization of the microcrystalline cellulose

Organoleptic properties

The texture, colour and odour of the microcrystalline cellulose powders from both methods were noted.

Solubility

Using the gravimentric method, the solubility profile of a 100 mg quantity of the microcrystalline cellulose powders from both methods was determined in 2 ml of water at ambient temperature. The MCC powder was dispersed in the water in a test-tube and shaken. The dispersion was filtered and the residue air dried. The dried residue and the filter paper was weighed (KERRO BL3002, England) and the difference in weight was used as a measure of solubility of the powder.

Test for cellulose and lignin

A few drops of iodinated zinc chloride solution was added to 10 mg of the microcrystalline cellulose powders in a test tube and the colour change noted. For lignin content, about 100 mg of the microcrystalline cellulose powders was moistened with a few drops of concentrated hydrochloric acid on a glass slide. Two drops of phloroglucinol was added to the moistened powders and the glass slide heated over a Bunsen burner, until the liquid content was completely evaporated. The slide was examined under a light microscope for any coloration.

FTIR characterization

FTIR analysis of the microcrystalline cellulose powders from both methods was carried out using FTIR-4100 Spectrophotometer (Shimadzu Co. Japan). Using the potassium bromide tablet method, 5 mg of the powder was blended with potassium bromide to give a 200 mg weight powder. The powder was compressed using a Sigma potassium bromide press into a tablet, and then placed in the sample compartment of the spectrophotometer and scanned at a range of 4000 - 750 cm^{-1}.

Preparation of metronidazole granules and tablets

Using the wet granulation method, the formula shown in Table 1 was used in preparing the metronidazole granules and tablets.

Table 1: Formula of prepared metronidazole granules and tablets

Ingredients/Batches	A	B	C	D	E	F	G	H	I	J	K	L	M
	MCC (HNO3)					MCC (NaOH)				MCC (Avicel)			
Metronidazole	200	200	200	200	200	200	200	200	200	200	200	200	200
Lactose	70	62.5	60	55	45	62.5	60	55	45	62.5	60	55	45
Disintegrant	0	7.5	15	22.5	30	7.5	15	22.5	30	7.5	15	22.5	30
Magnesium stearate	5	5	5	5	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5	5	5	5	5

All quantities in mg unit

Each batch was prepared by blending the required quantities of metronidazole and lactose powder in a mixer for 5 min. Half of the amounts of microcrystalline cellulose needed for the batch was added and mixed intimately. The powder mix was granulated with sufficient quantity of 15 %w/v maize starch mucilage (binder) and the wet mass was passed through a 1.40 mm sieve and then dried at 60 ºC for 30 min in a hot air oven. The dry mass was passed through an 850 μm sieve and further dried for 30 min. The granules were subjected at this stage to various pre-compression analyses such as bulk density, tapped density, Carr's (Compressibility) index, Hausner's quotient or ratio, flow rate and angle of repose using standard procedures [14]. Thereafter, the glidant (magnesium stearate), lubricant (talc) and the other half of the disintegrant(s) were intimately mixed with the dry granules in geometric proportion in readiness for compression. Granules sufficient to produce 100 tablets per batch was prepared.

Compression of granules

Batches of the granules were compressed into tablets using a single punch tableting machine (Manesty Machines, UK) at 25 arbitrary units (AU). The die volume was adjusted to compress tablets of uniform weight by using granules weighing between 280 mg in order to achieve tablets equivalent to 200 mg metronidazole. The tablets made were then kept in air tight containers and stored in a desiccator until evaluation.

Tablet evaluations

The following post compression tests were carried out on the compressed tablets using standard procedures: uniformity of tablet weight, crushing strength (hardness), friability, disintegration time and dissolution studies [15].

Uniformity of weight and friability

Twenty tablets from each batch were used for the weight uniformity test. The weight of each tablet was determined and the mean weight and standard deviation was computed. Ten weighed tablets were then placed in a friabilator chamber (Erweka GmbH, Germany) operated at 25 rpm for 4 min. The tablets were brought out, de-dusted and reweighed. Their percentage loss in weight value was calculated. Triplicate determination was carried out and the mean and standard deviation were reported.

Hardness test

Using a motorized tablet hardness tester (Campbell Electronics, Model HT-30/50, India), the crushing strength of each of ten tablets per batch was determined. The mean hardness value and standard deviation was calculated.

Disintegration time

The time taken for six tablets per batch to disintegrate in distilled water at 37 ± 0.5 °C were determined using the BP disintegration tester (MK IV, Manesty Machines, UK). The mean or average time and standard deviation was calculated.

Dissolution test

The *in vitro* dissolution analyses of the various batches of the metronidazole tablets were carried out using the BP paddle method. A dissolution apparatus (Caleva ST7, UK) containing 900 ml of 0.1 M HCl solution maintained at 37 ± 0.5^{0}C with a revolution speed of 50 rpm was used. Samples (5 ml) were withdrawn from the dissolution fluid at specific time intervals over a period of 60 min and replaced with an equivalent volume maintained at same temperature (37± 0.5^{0}C). The withdrawn samples were filtered and diluted appropriately with 0.1 M HCl solution. The resulting solutions were subjected to spectrophotometric analysis at λ max of 275 nm (T70, PG Instruments Ltd). The amount and the percentage of drug released at each time interval was calculated using the equation from the standard calibration plot obtained from pure metronidazole powder.

Statistical analysis

Statistical difference in the tablet parameters of the various batches were subjected to student's t-test at 5 % level of significance using GraphPad InStat 3.10.

Results and Discussion

Organoleptic and chemical properties of the extracted microcrystalline cellulose

The microcrystalline cellulose powder from the nitric acid method was whiter in colour and fluffy in texture against the creamy colour and granular texture of those from the sodium hydroxide method. Powders from both methods were odourless, tasteless, and insoluble in water, turned violet blue on reaction with iodinated zinc chloride solution, indicating the presence of cellulose and negative for the phloroglucinol test, showing absence of lignin. The percentage yields of their extracted α-cellulose were 30.22 and 20.75 % for the nitric acid and sodium hydroxide methods, respectively.

FTIR characterization

The FTIR spectra of the microcrystalline cellulose powders from the nitric acid (Figure 1 (a)) and sodium hydroxide (Figure 1 (b)) methods showed very similar and comparable characteristic pattern.

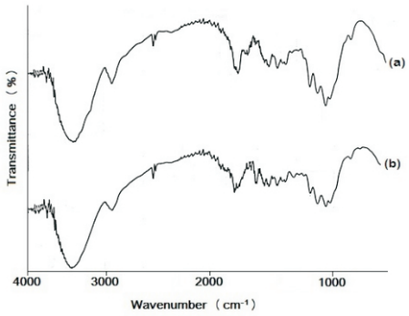

Figure 1: FTIR spectra of the extracted microcrystalline cellulose powders using nitric acid (a) and sodium hydroxide (b) as extracting solvent

The four major peaks of the powders obtained using the nitric acid method (3396.64, 2902.87, 1627.92 and 1060.85 cm^{-1}) coincides with those of the sodium hydroxide method (3444.87, 2904.80, 1647.21, and 1058.92 cm-1) indicating that both powders will have similar physiochemical properties. The absorption band of 3444-3396 cm-1 shows a large number of various types of hydrogen bonds formed by -OH groups and stabilizing certain conformations of macromolecules while the band of 2904-2902 cm^{-1} reveals the symmetric and asymmetric vibrations of CH_2 groups. Deformational vibrations of C-O-H, CH_2 and CH groups are located in the absorption bands of 1647-1627 cm^{-1}. Intensive bands in the field 1060 cm^{-1} are characteristic for cyclic mono saccharides and correspond to valent vibrations of C-O and the C-C ring structures.

Granule properties

The bulk and tapped density values of the metronidazole granules are shown in Table 2.

Table 2: Some physicochemical properties of the metronidazole granules

Micro-crystalline cellulose	Batch	Disintegrant concentration (%w/w)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's index (%)	Hausner's ratio	Angle of repose (°)	Flow rate (g/sec)
Nitric acid extracted	A	0	0.63	0.65	25	1.33	23.5	1.85
	B	2.5	0.40	0.63	20	1.25	23.8	2.94
	C	5	0.50	0.53	20	1.25	21.8	2.78
	D	7.5	0.44	0.55	20	1.25	22.6	2.64
	E	10	0.53	0.63	22	1.34	21.3	2.50
Sodium hydroxide extracted	F	2.5	0.54	0.54	21	1.30	24.8	2.94
	G	5	0.53	0.55	20	1.25	21.8	2.78
	H	7.5	0.52	0.57	20	1.25	25.0	2.94
	I	10	0.50	0.52	22	1.25	24.3	3.33
Avicel	J	2.5	0.31	0.42	23	1.35	23.2	2.60
	K	5	0.40	0.44	20	1.40	22.2	2.40
	L	7.5	0.30	0.34	21	1.40	24.5	2.30
	M	10	0.33	0.40	20	1.20	23.0	2.20

Generally, the granules exhibited no specific pattern in granule consolidation with increase in the concentrations of the microcrystalline cellulose incorporated. The batch A granules with no disintegrant (microcrystalline cellulose) had the highest bulk and tapped densities values of 0.63 and 0.65 g/cm^3, respectively.

The Hausner ratios, Carr's indices, angles of repose and flow rate (Table 2) values indicated that the metronidazole granules irrespective of the disintegrant incorporated, had excellent flow properties. The values obtained for Carr's index ranged from 20 - 25 % while those of Hausner's ratio was from 1.20 - 1.40 and the angles of repose from 21.3 - 23.8°. The batch A granules had the lowest flow rate value of 1.85 g/sec.

Tablet properties

Tablet weight

The results from the evaluations of the formulated metronidazole tablets are presented in Table 3. The weight of the tablets ranged between 279 - 282 mg and they all met the British Pharmacopeia specification that states that not more than two of the individual weights of the 20 tablets should deviate from the average weight by more than ± 5 % and none should deviate by more than ± 10 % [16]. The variations in the tablet weights were not more than ± 4 % of the calculated mean weight.

Micro-crystalline cellulose	Batch	MCC concentration (%w/w)	Tablet weight (g)	Hardness (kp)	Friability (%)	Disintegration time (min)
Nitric acid extracted	A	0	280 ± 0.009	6.0 ± 1.92	1.50 ± 0.35	20.15 ± 1.10
	B	2.5	280 ± 0.008	7.0 ± 1.12	0.73 ± 0.15	16.08 ± 0.25
	C	5	280 ± 0.005	7.0 ± 1.21	0.73 ± 0.09	12.25 ± 0.34
	D	7.5	279 ± 0.010	7.0 ± 1.19	0.75 ± 0.11	5.25 ± 0.61
	E	10	280 ± 0.006	7.5 ± 2.06	0.82 ± 0.08	4.15 ± 0.52
Sodium hydroxide extracted	F	2.5	280 ± 0.005	7.1 ± 1.10	0.99 ± 0.10	13.73 ± 0.19
	G	5	280 ± 0.005	7.2 ± 1.01	0.72 ± 0.12	9.88 ± 0.71
	H	7.5	282 ± 0.008	7.3 ± 0.94	0.73 ± 0.20	3.66 ± 0.62
	I	10	280 ± 0.005	7.4 ± 1.37	0.86 ± 0.15	1.70 ± 0.17
Avicel	J	2.5	282 ± 0.009	7.1 ± 1.50	0.71 ± 0.14	11.97 ± 0.44
	K	5	280 ± 0.005	7.6 ± 1.79	0.86 ± 0.15	9.87 ± 0.14
	L	7.5	280 ± 0.040	8.1 ± 0.99	0.90 ± 0.22	9.05 ± 0.54
	M	10	281 ± 0.006	8.1 ± 1.82	0.97 ± 0.13	6.67 ± 0.55

± Standard deviation

Hardness and friability

Hardness values of the tablets were between 6.0 - 8.1 kp with the highest values observed in batches L and M tablets formulated with 7.5 and 10 % Avicel. The hardness of the tablets was satisfactory, as a crushing strength between 5 - 8 kp is considered optimal for satisfactory tablets [16]. The percentage friability of the tablets was between 0.71 - 1.50 % with the highest values observed in Batch A tablets. The friability of the tablets was observed to increase with increased concentrations of microcrystalline cellulose powder. However, all the tablets did not met the BP specification of a maximum loss of 1 % of the mass of the tablets tested [16].

Disintegration

All the formulated tablets did not disintegrate within 15 min as specified by British Pharmacopeia for uncoated tablets [16], but the results showed a decrease in the disintegration time with increase in the MCC concentrations. Batches I and H tablets gave the lowest disintegration times of 1.70 and 3.66 min, respectively and closely followed by batches E and D tablets with 4.15 and 5.25 min, respectively.

Dissolution

Results from the dissolution studies (Figure 2 (a-c)) show that dissolution increased with increase in concentration of the disintegrants (MCC) regardless of the method of extraction or source of the disintegrant. Batch A tablets had the lowest amount of metronidazole released in 60 min. Only batches E, H, I, L and M passed the BP dissolution test for tablets which specifies that at least 75 % of the drug should be in solution after 45 min [16]. The effect of extraction solvent on the tableting properties of microcrystalline cellulose extracted from cassava stems in metronidazole tablet formulations was investigated. A comparison of the disintegrant activity of the

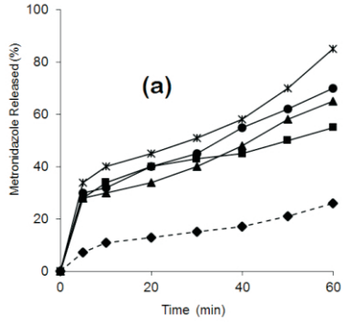

Figure 2(a): Dissolution profiles of metronidazole tablets formulated with different concentrations (%w/w) of MCC extracted with nitric acid. 0 (◆), 2.5 (■), 5 (▲), 7.5 (●), 10 (✳)

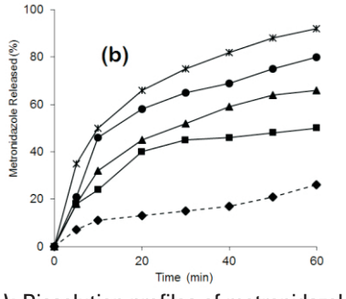

Figure 2(b): Dissolution profiles of metronidazole tablets formulated with different concentrations (%w/w) of MCC extracted with sodium hydroxide.
0 (◆), 2.5 (■), 5 (▲), 7.5 (●), 10 (✳)

extracted MCC with Avicel was also investigated. MCC is used primarily as a tablet disintegrant and sometimes as a filler. Its mechanism of disintegration action is essentially by capillary action including some level of swelling. The two extraction methods used in the study are methods previously used by other researchers. The percentage yields gotten in this study conform to values obtained by other workers in similar studies [17-19]. Percentage yield values ranging from 15-35 % have been considered as appropriate yield of the cellulose material. Some of the physicochemical tests carried out on the extracted microcrystalline powder clearly showed similarities between the products of the two methods of extraction. These similarities are further confirmed by their FTIR spectra which show almost, if not the same spectra pattern. Further confirmation can also be seen in the absorption bands of the FTIR spectra of MCC extracted from cotton in a similar study by Lokshina *et al.* [20].

The extraction method affected the cellulose yield with the nitric acid extraction giving a higher yield of cellulose (30.22 %). This may be as a result of the selective dissolution of other constituents of the powdered cassava stems. It is also likely that a preliminary interaction of nitric acid with the plant cellulose stabilized it against the action of sodium hydroxide which was later used during the extraction process for further delignification. While the lower yield of the sodium hydroxide extraction (20.75 %) could be traced to the repeated use of sodium hydroxide solutions and the several washings carried out during the extraction process leading to a loss of some of the α-cellulose components. Furthermore, textural investigation revealed that a whiter and fluffy α-cellulose was extracted using nitric acid when compared to the off-white coarse particles obtained by sodium hydroxide extraction. There appear to be some preliminary crystallising effect due to nitric acid while sodium hydroxide may cause corrosion of some parts of the cellulose. The extracted α-cellulose as well as MCC did not vary significantly in their physicochemical and tableting properties as all produced granules and tablets with comparable pharmaceutical properties. This therefore means that appropriate selection of solvents and process would be required to obtain MCC of desirable qualities. The effect of varying MCC concentrations across tablet batches also revealed corresponding decrease in disintegration time as MCC concentration is increased irrespective of the method of extraction or the source of MCC (including Avicel PH 101) used. In all cases however, optimal concentrations of MCC had to be attained in order to achieve 100 % metronidazole release. It would appear that while MCC obtained by sodium hydroxide extraction method gave the best disintegration outcome ($p < 0.05$), MCC obtained by nitric acid extraction was more comparable in characteristics with Avicel PH 101, since they demonstrated closely correlated disintegration properties.

Conclusion

This study has revealed that while MCC can be extracted using different methods, the method of extraction can affect the properties of the MCC. However, this effect may not adversely affect its pharmaceutical quality. The comparable tableting parameters of the metronidazole tablets formulated with the extracted MCC and Avicel PH 101 may suggest that the extracted MCC can be used as a suitable substitute for Avicel.

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Conflicts of interest

The authors declare no conflict of interest.

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