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Evaluation of the Direct Compression Properties of Microcrystalline Cellulose Obtained from Cassava Fermentation Waste in Paracetamol Tablet Formulations

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of article.

Abstract

Background: Natural materials have gained a lot of significance in the field of drug delivery because of their cost effectiveness and ready availability.
Purpose: The study aimed at evaluating the direct compression property of microcrystalline cellulose from cassava fermentation waste in directly compressed paracetamol tablet formulations.
Methods: Alkali delignification of the dried cassava fermentation fibres, followed by bleaching and acid depolymerisation was employed in the extraction of α-cellulose and conversion to microcrystalline cellulose (MCC). The MCC obtained and Avicel® were used at different concentrations (5.0-15 %w/w) to formulate batches of paracetamol tablets by directed compression. A comparative evaluation of the formulated paracetamol granules and tablets properties were undertaken.
Results: The paracetamol granules formulated showed good flowability with Hausner's ratios of 1.15-1.25, Carr's indices of 13.10-20.00 % and angles of repose ≤ 34.41°. The formulated tablets showed good hardness (> 5.0 kgf) and disintegration time within 10 min. Only tablets containing 5.0 and 7.5 %w/w of the test MCC failed the BP dissolution test specification for tablets which stipulates that at least 70 % of the drug should be in solution after 30 min.
Conclusion: This study has shown that the extracted MCC has direct compression ability evidenced in the mechanical strength of the formulated paracetamol tablets. The tablet properties of the formulated paracetamol tablets revealed pharmaceutically acceptable tablets though they were not comparable with Avicel® at all concentrations and the MCC may serve as an alternative local source for direct compression excipient.

Keywords: Cassava, microcrystalline cellulose, direct compression, paracetamol, tablets

INTRODUCTION

Direct compression excipients forms part of a tablet formulation and they can be natural or synthetic in origin. Natural materials have gained a lot of significance in the field of drug delivery because of their cost effectiveness and ready availability. They can also be non-toxic, eco-friendly, capable of undergoing chemical modifications, degradable and biocompatible due to their natural origin (Uwaezuoke *et al.*, 2014).

The growing movement from the use of synthetic materials to renewable resources, waste management and green technology has led to the emphasis on sourcing pharmaceutical excipients from natural sources such as plants, animals and agricultural waste (Eraga *et al*., 2015). Materials resulting from the production of primary products and have no further use are generally considered as waste and disposed. These waste products can be efficiently utilized and transformed into pharmaceutical excipients to obtain higher profit and at the same time, minimizing the environmental impact from their disposal (Uwaezuoke *et al*., 2014).

Significant amounts of wastes are produced in agricultural processes, which contain high quantities of cellulose, a linear polysaccharide constituting the major component of the rigid cell wall of plants (Kalia *et al.*, 2011, Di Donato *et al.*, 2015). Cellulose is the most abundant natural polymer on earth with an annual biomass production of 50 billion tonnes (Carlin, 2008).

Microcrystalline cellulose (MCC) is a purified, partially depolymerized cellulose prepared by treating α-cellulose obtained as a pulp from fibrous plant with mineral acids (Ohwoavworhua and Adelakun, 2005). MCC is used in a variety of oral pharmaceutical formulations such as tablets, capsules, sachets and pellets because of its self-disintegrating, dry binding and filler properties. Its popularity in direct compression is due to its excellent binding properties when use as a dry binder (Bolhuis and Armstrong, 2006). It also works as a disintegrant and lubricant and has a high dilution potential in direct compression formulations (Saigal *et al*., 2009). In fact MCC and super-disintegrants may be complementary to promote fast disintegration (Mostafa *et al*., 2013). With direct compression or dry granulation method of tablet production increasingly gaining importance over the wet granulation technique because of the advantages of reduced cost and time of production leading to improved productivity, the need for local sourcing of direct compression excipients cannot be overlooked. Hence this study seeks to assess the direct compression properties of MCC extracted from the waste product generated from the processing of fermented cassava tubers in paracetamol tablet formulations and to compare the tablet parameters of these formulations with those prepared with Avicel®.

METHODOLOGY

Materials

Avicel® PH 101 and croscarmellose sodium (FMC Biopolymers, USA), sodium hydroxide (Merck, Germany), sodium hypochlorite (Reckitt and Colman Nig. Ltd., Lagos), paracetamol powder, lactose, talc and magnesium stearate (William Ransom and Son PLC, Hitchin Hertfordshire, England). Cassava fermentation waste was collected from a cassava processor in a local market in Benin City, Nigeria.

Methods

Extraction of α-cellulose and production of MCC

The processes employed in the extraction of the α-cellulose from the fermented cassava waste and subsequent production of MCC have been previously reported (Eraga *et al*., 2015). Briefly, the collected waste was washed, dried and milled into fine fibre material. Using the method of Ohwoanvworhua, *et al*., (2004), five hundred grams of the powdered cassava fermentation waste 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. Thereafter, the sample was bleached with 1 L of 20 %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 before being dried and milled. Fifty grams of the α-cellulose powder 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 MCC was then dried at room temperature to a constant weight.

Physicochemical characterization of the microcrystalline cellulose

The physicochemical evaluations of the MCC have been reported earlier (Eraga *et al*., 2015).

Preparation of paracetamol powder blends and tablets

Seven (7) batches of paracetamol powder blends were prepared using the formula shown in Table 1. Each batch was prepared by mixing the required quantities of paracetamol and lactose powder in a mixer for 5 min. The amounts of the test MCC or Avicel® and croscarmellose sodium for the batch were added to the powder mix and mixed intimately. The powder blend was slugged into a large tablet using a single punch heavy duty tableting machine (Koln Niehi, Germany). The slugs were broken down into granules using a mortar and pestle and passed through a 710 μm mesh screen (BSS, Endecotts, England). Thereafter, the lubricant (magnesium stearate), glidant (talc) were added and mixed in geometric proportion to the granules in readiness for compression. The granules was subjected at this stage to various pre-compression analyses such as bulk density, tapped density, Carr's (Compressibility) index, Hausner's ratio, flow rate and angle of repose using standard procedures.

Table 1: Formula of prepared paracetamol powder blends and tablets

Ingredients (mg)	Batches						
	A	**B**	**C**	**D**	**E**	**F**	**G**
Paracetamol	500	500	500	500	500	500	500
Lactose	100	75	50	25	-	100	50
Croscarmellose sodium	5	5	5	5	5	5	5
MCC	50	75	100	125	150	-	-
Avicel®	-	-	-	-	-	50	100
Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5

Direct compression of tablets

Batches of the prepared granules were directly compressed into tablets using a single punch tableting machine (Manesty Machines, UK) at 30 KN. The die volume was adjusted to compress tablets of uniform weight by using granules weighing 660 mg in order to achieve tablets equivalent to 500 mg paracetamol. The tablets made were then kept in air tight containers and stored in a desiccator until evaluation.

Tablet evaluations

The following post-compression evaluations were carried out on the compressed tablets using standard procedures: uniformity of tablet weight, tablet dimensions, crushing strength (hardness), friability, disintegration time and dissolution studies (BP, 2003).

Tablet weight and dimensions

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. A micrometre screw gauge (Gallenkamp) was used to measure the thickness and diameter of each of ten tablets per batch and their mean values and standard deviation was recorded.

Crushing strength and friability

The force required to break each of ten (10) tablets per batch by diametrical compression using a motorized tablet hardness tester (Campbell Electronics, Model HT-30/50, India) was determined and the mean value and standard deviation were recorded as the crushing strength of the tablets. Friability was determined by placing ten (10) previously weighed tablets in the drum of a friabilator (Erweka GmbH, Germany) revolving at 25 rpm which exposed the tablets to rolling and repeated shock resulting from free fall within the apparatus. After 4 min, the tablets were brought out, de-dusted and reweighed. The weight was then recorded and friability calculated as percentage loss in weight.

Disintegration time

The disintegration time for the batches of tablets was determined using the BP tablet disintegration test apparatus (Manesty Machines Ltd, UK). A tablet was placed in each of the six tubes of the apparatus. Distilled water, used as the disintegration medium was maintained at 37 ± 0.5 ºC and the time taken for the entire tablet to disintegrate completely was determined and the mean value and standard deviation were recorded.

Dissolution profiles

The dissolution tests were carried out using the BP paddle method. A dissolution test apparatus (Caleva ST7, UK) containing 900 ml of 0.1 N HCl solution maintained at 37 ± 0.5 °C with a revolution speed of 50 rpm was used. Six (6) tablets selected at random from each batch were used simultaneously for the study. A 5 ml aliquot was withdrawn from the dissolution medium at 5 min intervals for 60 min. The withdrawn fluid was replaced with an equivalent volume maintained at same temperature (37 ± 0.5 ºC). The aliquot was filtered and diluted with an equal volume of 0.1 N HCl solution. The absorbances of the resulting solutions were measured at λmax 245 nm, using the UV/Visible spectrophotometer (T70, PG Instruments Ltd, USA). The percentage of drug released was then calculated using the equation from the standard calibration plot obtained from the pure drug.

STATISTICAL ANALYSIS

Descriptive statistics was done for all data using Microsoft Excel (2007). Differences between mean was determined using one-way ANOVA while $p < 0.05$ was considered significant.

RESULTS AND DISCUSSION

Granule properties

Results from the pre-compression evaluations of the formulated batches of paracetamol granules are outlined in Table 2. The bulk and tapped densities of the granules showed a range of values indicative of granule particle packing ranging from loose to fairly close packing. The range of values from their Hausner's ratios and Carr's indices indicated granules with 'excellent' to 'fair' flow properties (Carr, 1965). Their angles of repose and flow rates values also showed granules with good to fair flowability. The granules improved in their flowability with increase in the amounts of the test MCC as evident in their decreasing Hausner's ratios, Carr's indices, angles of repose and increasing flow rates with increasing concentrations of the MCC. This observation suggests an increase in the porosity of the granule particles resulting from a decrease in cohesiveness and densification of the particles with increase in the concentration of the test MCC (Abdulsamad *et al*., 2008, Chitedze *et al*., 2012).

Table 2: The micromeritic properties of prepared granules

Source of MCC	Batch	MCC concentration (% w/w)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Hausner's ratio	Carr's index (%)	Angle of repose (°)	Flow rate (g/s)
Extracted MCC	A	5	0.80	0.64	1.25	20.00	34.41	12.77
	B	7.5	0.82	0.67	1.22	18.29	32.25	13.14
	C	10	0.83	0.70	1.19	15.66	32.18	15.74
	D	12.5	0.83	0.71	1.17	14.46	31.10	18.94
	E	15	0.84	0.73	1.15	13.10	30.23	20.10
Avicel®	F	5	0.83	0.70	1.19	16.05	31.95	15.38
	G	10	0.84	0.72	1.17	14.29	30.64	18.40

Tablet properties

Weight and dimensions

The tablets' weights and dimensions are presented in Table 4. The mean weight of the tablets was between 650 - 660 mg, while the mean diameter and thickness ranged between 12.55 - 12.72 mm and 4.14 - 4.26 mm, respectively. The variations in these values within and between the batches were not significant ($p > 0.05$). The tablets' weight variations also met the BP specification of not more than two of the individual weights should deviate from the average weight by more than ± 5 % and none should deviate by more than ± 10 % (BP, 2009).

Crushing strength and friability

The mean crushing strength values of the formulated paracetamol tablets were between 5.01 - 8.80 kgf while their friability values were 0.52 - 1.20 % (Table 3). The crushing strength values increased while the friability values decreased with increase in the test MCC and Avicel®. These values would suggest tablets with good mechanical strength as they met the BP specification of an optimum crushing strength values of 5.0 - 8.0 kgf and friability values of 0.8 - 1.0 % maximum loss in weight of tested tablets (BP, 2009). The increasing hardness and decreasing friability of the tablets with increasing concentrations of the test MCC and Avicel® may be attributable to the increased inter-particulate bonding promoted by the inherent binding ability of the test MCC and Avicel® upon compression (Oyi *et al*., 2009).

Table 3: Some physicochemical characteristics of the paracetamol tablets

Batch	Weight (g)	Dimensions (mm)		Crushing strength (kgf)	Friability (%)	Disintegration time (min)
		Diameter	Thickness			
A	0.65 (0.02)	12.61 (0.03)	4.17 (0.14)	5.01 (0.11)	1.20 (0.15)	10.50 (2.16)
B	0.65 (0.04)	12.71 (0.02)	4.14 (0.11)	6.70 (0.14)	1.00 (0.12)	6.51 (2.60)
C	0.66 (0.02)	12.72 (0.09)	4.43 (0.02)	7.10 (0.15)	0.98 (0.02)	4.32 (2.10)
D	0.65 (0.03)	12.55 (0.01)	4.19 (0.06)	7.90 (0.16)	0.89 (0.06)	3.59 (1.60)
E	0.66 (0.01)	12.57 (0.02)	4.26 (0.07)	8.80 (0.14)	0.79 (0.10)	2.12 (0.59)
F	0.65 (0.02)	12.60 (0.09)	4.19 (0.03)	7.00 (0.14)	0.69 (0.10)	3.00 (1.60)
G	0.65 (0.01)	12.56 (0.03)	4.14 (0.02)	8.40 (0.12)	0.52 (0.04)	2.01 (0.25)

Standard deviation in parenthesis

Disintegration time

The disintegration times of the formulated tablets are shown in Table 3. All the formulated tablets disintegrated within 15 min as specified by the British Pharmacopoeia (BP, 2009) for uncoated tablets. The formulated tablets containing 5.0 %w/w of the test MCC exhibited the longest disintegration time of 10.50 min while those containing 10 %w/w of Avicel® showed the shortest disintegration time of 2.01 min. The disintegration times of the tablets decreased with increase in the test MCC and Avicel® amounts probably due to the increase in their swelling ability facilitated by the increased water uptake into the tablets and the subsequent generation of a higher swelling force which would initiate the active mechanism of disintegration at a faster rate (Alebiowu and Itiola, 2003; Abdallah *et al*., 2016). Also, the fast tablet disintegration exhibited by most batches of tablets may be due to the disintegrant (croscarmellose sodium) being complemented by the test MCC or Avicel® that are known for their self-disintegrating properties (Mostafa *et al*., 2013).

Dissolution profiles

The plot from the *in-vitro* dissolution studies of the different batches of the paracetamol tablets is presented in Figure 1. All the formulated tablets except batches A and B tablets prepared with 5.0 and 7.5 %w/w of the test MCC, passed the BP dissolution test for tablets which specifies that at least 70 % of the drug should be in solution after 30 min (BP, 2009). There was an increase in drug dissolution with both increase in the amounts of the test MCC and Avicel® contained in the tablets and a decrease in disintegration time. This implies that the dissolution of drugs from the tablets correlated with the disintegration times of the tablets in this study. The faster the disintegration of the tablet, the earlier the onset of drug dissolution. This observation shows that the disintegration times played a vital role in the dissolution of drug from the tablets since disintegration determines largely the extent and area of contact between the tablets primary particles and dissolution fluid (Iwuagwu *et al*., 2001, Odeku and Itiola, 2003).

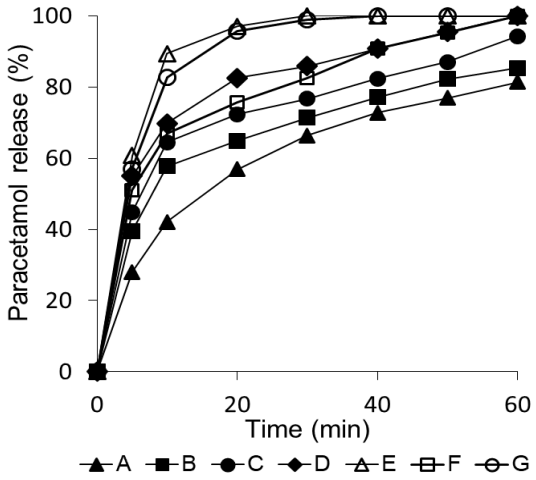

Figure 1: *Dissolution profiles of the different batches of the paracetamol tablets prepared with the test MCC (A-E) and Avicel® (F,G)*

CONCLUSION

This study has shown that the test MCC extracted from cassava fermentation waste has direct compression ability shown in the mechanical strength of the formulated paracetamol tablets. The tablet properties of the formulated paracetamol tablets also revealed pharmaceutically acceptable tablets as they met compendial standards in their crushing strengths, friability, disintegration times and dissolution profiles (except two batches of tablets in their friability), though they were not comparable with Avicel® at same concentrations. This shows that the extracted test MCC can be used as an alternative to Avicel® since it is sourced locally and cost effective. Also, the different stages of the extraction process can be significantly improved to obtain MCC with improved performance.

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