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Adedokun, M.O
Department of Pharmaceutics and Pharmaceutical Technology
Faculty of Pharmacy, University of Uyo, Uyo, Akwa-Ibom State, Nigeria.
Email: mo_adedokun@yahoo.com

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Preliminary investigation of Mechanical Properties of Paracetamol Tablets Formulated with Microcrystalline Cellulose Binder Derived from *Saccharum officinarum*, L.

Adedokun, M.O.* and Nkori, R.E.
Department of Pharmaceutics and Pharmaceutical Technology
Faculty of Pharmacy, University of Uyo, Uyo, Akwa-Ibom State, Nigeria.

Abstract

Microcrystalline cellulose (MCC) is a multifunctional excipient in drug formulation. However, the dependent of most developing countries on importation of this excipient invariably increases the cost of drug production. Thus, this work preliminarily assessed the suitability of the MCC derived from partially processed stem of *Saccharum officinarum*, L. (DMCC) comparatively with commercial MCC (Avicel® PH 101) incorporated as binders in a paracetamol tablet formulation. The excipients were assessed based on their physicochemical and flow properties. The formulated tablets, compressed at three different loads – 10, 15 and 20 KgF – were evaluated for weight uniformity, crushing strength and friability. The flow indices showed that both DMCC and Avicel® PH 101 have comparably good flowability. Tablets containing DMCC showed excellent weight uniformity, crushing strength and friability and all conformed to official monograph. There were no significant difference between the parameters determined for the two binders ($p<0.05$). The higher the compression load, the higher was the crushing strength and vice versa for friability. The difference between the values of these parameters was statistically significant ($p>0.05$). The results obtained are suggestive of the fact that the use of DMCC as binder compared well with the commercial MCC and may thus be developed as a potential substitute in some tablet formulations.

Keywords: Microcrystalline cellulose; *Saccharum officinarum*; crushing strength; friability

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INTRODUCTION

In recent times, developing countries are highly reliant on importation of raw materials and finished products [1]. This constitutes one of the most challenging considerations in the scheme of pharmaceutical and medical sciences. Hence the pursuit for newer and more potent drugs and excipients that are safe and economical. Plant kingdom is a reservoir of novel formulation enhanced excipients and has over time generated more concerns in tableting in pharmaceutical firms [2]. As a result of this, pharmaceutical industries in developing countries have recognized the importance of utilizing local and naturally occurring materials. One category of such products that has enjoyed elaborate and considerable use in the pharmaceutical industry is cellulose. This is occasioned by the fact that the latter and its numerous derivatives such as microcrystalline cellulose act as multifunctional excipient in drug formulation and food industries [3].

Microcrystalline cellulose (MCC) is purified, partially depolymerised cellulose prepared by treating alpha - cellulose obtained as a pulp from fibrous plants with mineral acids. MCC has been used as an excipient for direct compression because of its good flowability, compatibility and compressibility. It can be used as a binding agent in tableting of drugs at higher concentration[4]. Binding agents impacts cohesive qualities to powdered material. They precipitate cohesiveness to the tablet formulation ensuring that the tablet remains intact after compression as well as improving the free flowing qualities by the formation of granules of desired hardness and size. About 5200 metric tones of MCC is used annually in Nigeria but, despite the abundance of local flora, Nigeria still obtains a great proportion of MCC from imports this invariably increase the cost of drug production [1].

Sugarcane which has high cellulose content belongs to the genus Saccharum of the tribe Andropogoneae (family Poaceae). It is a tall growing monocotyledonous crop plant that is cultivated in the tropical and subtropical regions of the world primarily for its ability to store high concentrations of sucrose in the internodes of the stem. Modern varieties that cultivated for sugar production are complex inter-specific hybrids (Saccharum spp.) that have arisen through intensive selective breeding of species within Saccharum genus [5].

Friability is a measure of the resistance of tablets to surface abrasion and is assessed by determining the weight loss on subjecting the tablets to a standardized agitation procedure for a specified period of time. More specifically, a certain weight of de-dusted tablets (w_0) is subjected to a well defined level of agitation in a fixed geometry, closed container for a specific time. They are then re-weighed (w). The measure of abrasion resistance or friability, ƒ, is usually expressed as [6,7,8]:

$$ƒ = 100 (1-w / w_0) \quad [1]$$

Values of ƒ from 0.8 to 1.0% are usually quoted as upper limit of acceptability for pharmaceutical tablets [6,8]. Crushing strength, an index of the bond potential of compressed tablet, is usually computed from the determined load required to cause fracture [9]. A small and portable hardness tester was manufactured and introduced in the mid-1930s by Monsanto[10]. The instrument measures the force required to break the tablet when the force generated by a coil spring is applied diametrically to the tablet. A crushing strength value of 4KgF is considered to be minimum for a satisfactorily compressed tablet [11].

This study is aimed at isolating microcrystalline cellulose from the partially processed stem of *Saccharum officinarum*, L., evaluating its binding capacity by assessing the mechanical properties of paracetamol tablets formulated with microcrystalline cellulose binder in comparison with the commercial grade – Avicel®PH 101.

MATERIALS AND METHODS

Materials:

The materials used were Paracetamol B.P. (SKG Pharma, Lagos, Nigeria) Lactose, talc powder, Corn starch (BDH, England), Avicel® PH 101, Magnesium stearate (Sigma Aldrich, USA). Microcrystalline cellulose powder derived from *Saccharum officinarum*, L. was prepared in the laboratory of the Department of Pharmaceutics and Pharmaceutical Technology, University of Uyo, Nigeria. Other chemicals and reagents used were of analytical grade.

Extraction of alpha cellulose and preparation of microcrystalline cellulose:

The procedure described by Ohwoavworhua et al. [12] was employed with some modifications to extract α-cellulose from *S. officinarum*. The α-cellulose was then used to prepare microcrystalline cellulose. The processed sponges from the stem of the plant were shredded into tiny bits and 40 g of the shredded sponge was soaked in 400 ml 2% sodium hydroxide solution in a conical flask and heated in water bath at 80^0C for 4 h to delignify the sponge after which the excess liquid was drained off. The resultant moist mass was then washed several times with distilled water and excess moisture again squeezed through a piece of calico cloth. The moist mass was then heated over a water bath at 80^0C in 300 ml of an aqueous solution of laboratory prepared sodium hypochlorite for 1 h to bleach the mass. The bleached mass was again squeezed through the calico cloth to remove excess liquid and then washed it was delignified the second time by heating over a water bath at 80^0C for 1 hour in 30 ml of 17.5%w/v sodium hydroxide solution. After thorough

washing of the resultant mass with distilled water, final bleaching was done by heating the material with 300 ml of a 1:2 aqueous dilution of sodium hypochlorite. The resultant α - cellulose was repeatedly washed with excess moisture squeezed out through the calico cloth and the small lumps obtained was finally dried in a hot air oven at a temperature of 57 - 60^{0}C for 1 hour.

A 50 g quantity of the α - cellulose obtained was placed in a conical flask and hydrolyzed with 0.8 L of 2.5 N hydrochloric acid at a boiling temperature of 105^{0}C for 15 minutes the heating being effected by suspending the conical flask in a hot bath of paraffin oil. After heating, the hot acid mixture was poured into 2.5 L of cooled distilled water and vigorously stirred with a spatula and then allowed to stand overnight. The microcrystalline cellulose crystals formed were then filtered through a Whatman No. 1 filter paper and washed with distilled water until neutral to litmus paper test. The crystals were then dried in a hot air oven at a temperature of 57 - 600C for 60 minutes. The crystals were then milled and screened through a sieve of 500 µm aperture size. The prepared microcrystalline cellulose (coded DMCC) was weighed and stored in airtight amber-coloured bottle for subsequent experiments.

Assessment of physicochemical properties:

Organoleptic properties:

The colour, odour, taste and physical appearance of the experimental microcrystalline cellulose (DMCC) and the standard (Avicel® PH 101) were observed.

Solubility:

The solubility of 1g each of DMCC and Avicel® PH 101 both in drops and in excess of distilled water, ethanol, acetone and dilute hydrochloric acid, was determined.

Test for starch and dextrins:

A 9.0 ml of distilled water was added to 1g of DMCC and the mixture boiled for 5 minutes and filtered hot. The production of a blue colour when 1.0 ml of a 0.05 M of iodine solution was added to the filtrate indicated the presence of starch.

A quantity of 0.1g of the sample was dispersed in 100ml of distilled water and a drop of iodine solution was added. The development of a light red brown or light red to purple colour indicated the presence of dextrins. The procedures were repeated for Avicel® PH 101.

Determination moisture content and pH:

A 5g of each sample was dried in a ceramic crucible at 1050C for 3 hours. The percentage moisture content was then determined as the ratio of the weight of moisture lost to the weight of the initial sample weight expressed as a percentage. The mean of three determinations was taken. The pH of the supernatant liquid obtained after shaking 2g of the powder with 100ml of distilled water for 5 minutes was determined on a pH meter (Kent Industrial Measurements, England).

Particle size analysis:

A stack of sieves ranging from 50µm to 250µm were mounted on an electric sieve shaker (Endocotts EFL 2000/1) in descending order of aperture size. A 20g quantity each of DMCC and Avicel® PH 101 was placed on the top sieve and the set-up was shaken for 5 minutes. The weight of materials retained on each sieve was determined and the average diameter was computed using the following equation:

Average diameter ($\overline{d}$) = [Σ (% retained) x (mean sieve aperture)]/100 [2]

Particle density:

The particle density (ρ_p) of the samples was determined by the liquid displacement method. A 50ml density bottle with its stopper was thoroughly dried and weighed and then filled to the brim with xylene. The stopper was then replaced and the weight of the bottle and the xylene taken after excess solvent had been wiped off (a).

Some xylene was then poured off and 1g of the sample (W) carefully introduced into the bottle and more xylene then added to fill the bottle. The stopper was replaced and the excess xylene wiped off after which the weight of the bottle including that of the sample and xylene (b) was determined. The particle density of the sample was computed according to the following equation [13]:

$\rho_p = S_g [W /(a + w)-b]$ [3]

POWDER FLOW PROPERTIES

Bulk and tapped densities:

30g of each starch sample was carefully poured at an angle of 45^{0}C through a glass funnel, into a 100ml glass measuring cylinder of an internal diameter of 28mm [14,15]. The height, h (cm) of the powder bed and the internal radius, r (cm) of the measuring cylinder were used to compute the loose bulk volume V_0, Thus:

$V_0=\pi r^2 h$ [4]

The value so obtained was in turn used to calculate the bulk density, ρ_b (g/cm^3)

$\rho_{b=} M/V_0$ [5]

The bulk sample was subjected to about 100 taps at a standardized rate of 38 taps per minute to obtain tapped volume Vt which was similarly used to calculate tapped density (ρ_t, g/cm^3) [8].

Hausner's and Carr's indices:

The Hausner's quotient was determined as the ratio of the tapped density to the bulk density of the sample while Carr's compressibility Index (I) was computed using the following equation:

$I(\%) = 100(\rho_t - \rho_b) /\rho_t$ [6]

All determinations were done in quadruplicate and mean values were recorded

Determination of angle of repose:

The static angle of repose was determined using the fixed base cone method [16,17]. A 30 g quantity of the sample was transferred into an open-ended cylinder placed on a static base cone on a horizontal surface. The cylinder was gradually withdrawn vertically and the sample formed a cone-shaped heap. The height of the sample (h) was determined using a cathetometer; the radius (r) was gotten by dividing the fixed diameter by two. Angle of repose (θ) for each sample was gotten using the equation;

$\theta = \tan^{-1} h/r$ [7]

Preparation of paracetamol tablets

Basic formulation of paracetamol was made as follows:

Paracetamol	80%w/w
Corn starch	7%w/w
Lactose	13%w/w
Binder	x%w/w

Wet granulation method was used to prepare Paracetamol granules with corn starch and lactose as disintegrant and diluent, respectively. Two binders, the derived microcrystalline cellulose (DMCC) and Avicel® PH 101 were employed at varying concentrations for the different batches of each group. The weight of each tablet was targeted between 644 mg – 670 mg. The formula was enlarged to produce required quantity of tablets for the three different pressures in each batch for both DMCC and Avicel® PH 101 (10kgF, 15kgF and 20kgF). The required quantities of paracetamol, corn starch and lactose powders were weighed out accurately and sieved through a 1.00 mm screen. They were blended together in a mortar and formed into a damp mass using the binder suspension. The wet mass was passed through a 4.00 mm screen and dried at 60^0C for 1 hour. 20% and 80% of the dried granules was passed through a 1.00 mm and 2.00 mm screen respectively, and mixed thoroughly. The required quantities of magnesium stearate and talc were weighed, sieved through a 0.5 mm screen, then mixed and used to lubricate the granules. The resulting granules were thoroughly mixed and compression was made at three different pressures of 10kgF, 15kgF and 20kgF.

Tablet weight uniformity:

The method stated in the Pharmaceutical Codex was employed. 20 tablets each from batches of paracetamol tablets formulated DMCC and Avicel® PH 101 binders were individually weighed and the average weight for each of the various batches was determined. The percentage deviation of each tablet weight from the mean weight was determined and the degree of conformity of each tablet batch to official standard was subsequently established [18,19].

Tablet hardness test:

One tablet each from each of the batches was held diametrically in the jaws of a hardness tester and the force in KgF required to crush it noted. The mean of ten determinations was taken.

Tablet friability:

20 tablets from each of the batches at various pressures were dedusted, weighed and put in separate drums of a Roche friabilitors. The tablets were then tumbled for 4 minutes at a speed of 25 revolutions per minute. They were then removed, dedusted and weighed again. The friability of the tablet expressed as a percentage was obtained using equation [1].

The procedure was carried out for all the batches.

Statistical analysis:

Statistical analysis was carried out on all the parameters obtained in evaluating the mechanical properties of formulated tablets using two-way Analysis of Variance (ANOVA) on a computer software GraphPad Prism® 4 (GraphPad Software Inc., San Diego, USA). Post-hoc (Turkey-Kramer multiple comparison) test was employed to compare the individual differences between the samples. Probability, p values greater than 0.05 (that is, 5%) were considered insignificant at 95% confidence interval.

RESULTS AND DISCUSSION

From the partially processed stem of *Saccharum officinarum*, L. 40.4%w/w of α - cellulose was obtained and this in turn yielded 70%w/w of microcrystalline cellulose (DMCC). The yields from other plants was reported by some workers: *Costus afer* yielded 7.82% and 81.5%w/w [20] while *Cochlospermum planchonii* yielded 23% and 67% [14] of α - cellulose and microcrystalline cellulose, respectively. Thus, sourcing MCC from *Saccharum officinarum* L. appeared very economical.

The physicochemical properties of DMCC and the commercial grade (Avicel® PH 101) are presented in Table 1. Both materials were odourless, off-white and granular in texture. They were also free from starch and dextrins, thus complying with the specifications in the pharmacopoeia. The pH value of 4.17 obtained from 2%w/w dispersion of DMCC in distilled water was lower than that of Avicel® PH 101 (5.88) and did not comply with the standard 5-7.5 outlined in the International Pharmacopeia [19]. Thus, care has to be taken when using this excipient in tablet formulation so as to ensure the stability of the drug component. The calculated average particle diameter of DMCC was 84.16µm compared to 93µm for Avicel® PH 101, both in the range of 70-1000µm thus belong to the "conventional powder"[21]. The particle density of 1.995g/ml determined for DMCC was high compared to 1.583g/ml for Avicel® PH 101 and is suggestive of the fact that the latter would exhibit better compressibility than the former [22]. The moisture content of DMCC was about 7.1% and is above the official limit of 6% stated in the British pharmacopoeia. Therefore, DMCC would

need to be further dried if it is to be used as an excipient in the formulation of hydrolysable drugs such as aspirin.

Physicochemical Properties			Binder	
			DMCC	**Avicel® PH 101**
Organoleptic		Colour	Off-white	Off-white
		Odour	Odourless	Odourless
		Taste	Tasteless	Tasteless
		Appearance	Granular powder	Granular powder
Solubility:	Distilled water	Drops	Insoluble	Insoluble
		Excess	Insoluble	Insoluble
	Acetone	Drops	Insoluble	Insoluble
		Excess	Insoluble	Insoluble
	Ethanol	Drops	Insoluble	Insoluble
		Excess	Insoluble	Insoluble
	Dil. hydrochloride acid	Drops	Insoluble	Insoluble
		Excess	Insoluble	Insoluble
Starch and Dextrins		Starch	Absent	Absent
		Dextrin	Absent	Absent
pH			4.17	5.88
Mean particle diameter ($\overline{d}$)			84.2 µm	93.0 µm
Particle density (g/cm^3)			1.995	1.583g/ml

Table 1: Physiochemical properties of DMCC and Avicel® PH 101

Flow and density parameters	Binder	
	DMCC	**Avicel® PH 101**
Bulk density (g/ml)	0.534	0.549
Tapped density (g/ml)	0.593	0.631
Hausner's ratio	1.11	1.15
Carr's index	9.95	13.00
Angle of repose (^{0})	27.10	26.63

Table 2: Some flow and density properties of DMCC and Avicel® PH 101

Parameters	Concentration of binder (%w/w)										
	DMCC						Avicel$^{(R)}$ PH 101				
	0	5	10	15	20	25	5	10	15	20	25
Weight (mg)	640	646	653	655	664	667	648	650	653	660	666
Wt. variation (mg)	0.90	0.65	0.72	0.82	0.70	0.60	0.10	0.46	0.80	1.30	0.80
C_s (KgF) (at 10 KgF)	1.5	2.5	3.9	4.2	4.9	5.3	2.3	3.8	4.2	4.8	5.3
F (%)(at 10 KgF)	11.01	9.02	0.65	0.56	0.62	0.56	8.23	0.82	0.80	0.72	0.63

Table 3: Values of weight variation (mg), crushing strength (KgF) and friability (%) for paracetamol tablets formulated with DMCC and Avicel® PH 101 binders

The flow property is important in determining the suitability of powder as tablet excipient. From Table 2, the angle of repose of DMCC (27.100) compared favourably with that of Avicel® PH 101 (26.630) and was indicative of good flowability. Carr's and Hausner's indices of 9.95% and 1.11 respectively for DMCC also compared reasonably well with those of Avicel® PH 101 (13.00 and 1.15) and further established the good flow properties of DMCC. Some quality parameters for compressed tablets formulated with DMCC and Avicel® PH 101 binders, including weight variation, crushing strength (C_s) and friability (F), are as shown in Table 3. The tablets were found to comply with official compendial specifications for tablet weight uniformity [23,24] and this is indicative of good flow of the product. For conventional tablets, a minimum C_s of 4kgF and maximum of F of 0.8 - 1% [5,7] are considered acceptable, the mean$_{Cs}$ and F of batches of tablets produced with high concentrations of binders were found to comply with these standards. Tablet C_s increased with increase in concentration of the binders in the formulation and vice versa for F. Thus the formulated tablets at high binder concentrations could be considered to generally possess acceptable resistance to abrasion, chipping and breakage. Figures 1 and 2 show the plots of concentration of binder against C_s, and F respectively, for tablets prepared at three compression loads of 10, 15 and 20 KgF. From the plots, the maximum and minimum values of C_s and F, respectively were generally obtained at above concentration of 20 %w/w of binder, in line with officially recommended proportions of MCC as tablet binder [3]. The plots also indicated that the optimum values of these parameters were obtained at the compression load of 20 KgF.

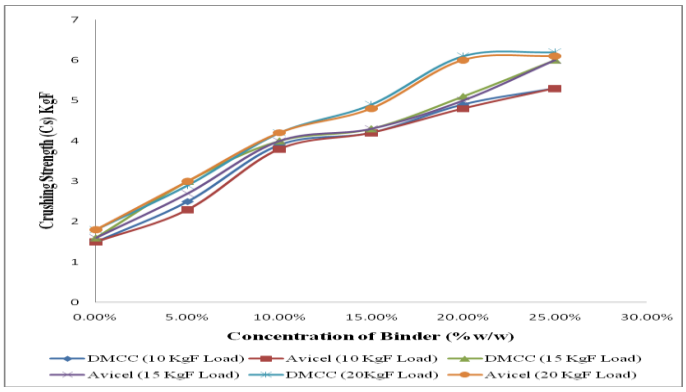

Figure 1: Plots of Concentration of Binder against Crushing Strength of tablets prepared at various compression loads

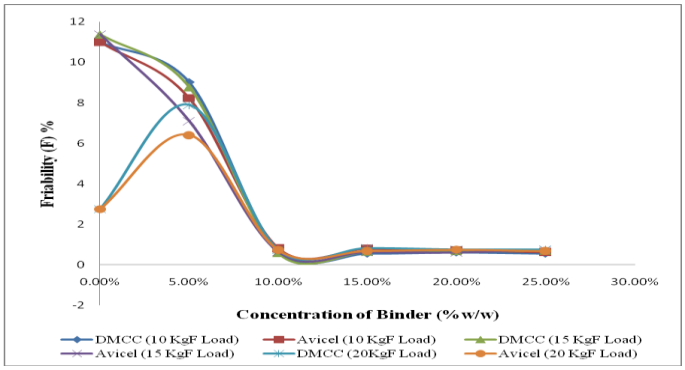

Figure 2: Plots of Concentration of Binder against Friability (%) of tablets prepared at various compression loads

CONCLUSION

Microcrystalline cellulose obtained from the partially processed stem of *Saccharum officinarum* gave a reasonable yield. It also complied with the official compendial specifications as regards organoleptic and physiochemical properties. The flow properties indicate that the fluidity of DMCC is adequate for it to be used as binder in tablets. The results of this investigation gave some insights into the flow characteristics of the experimental microcrystalline cellulose and its influence on the mechanical properties of the compressed tablets. The similarity in these properties exhibited by both the prepared and the commercial MCC suggests that the former may serve as suitable alternatives to the latter in tablet formulation.

Due to the observed increase in the hardness and friability of the tablets with increased concentration of microcrystalline, further studies on the possible use of the material in sustained release formulation is recommended.

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