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Evaluation of the Release Properties of Microcrystalline Cellulose Derived from *Saccharum officinarum* L. in Paracetamol Tablet Formulation

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Abstract

Microcrystalline cellulose coded MCC-D was obtained from the stem pulp of sugar cane (Saccharum officinarum) by a two-stage sodium hydroxide delignification process followed by sodium hypochlorite bleaching and hydrochloric acid hydrolysis. The product was examined for its physicochemical properties, powder flow characteristics in relation to Avicel(R) PH 101. Wet granulation method was used to formulate various batches of tablets using MCC-D and Avicel® PH 101 as binders at varying concentrations. The tablets were subjected to the following test: weight uniformity, disintegration and dissolution, and all conformed to official monograph. The extraction yield of MCC-D from the alpha cellulose was very good (70%$^{w}/_{w}$). The flow indices showed that both MCC-D has good flow with Hausner index of 1.13. MCC-D compacts showed excellent weight uniformity, disintegration time and dissolution rate in those with not too high concentration and conforming to British Pharmacopoeia and United States pharmacopoeia specifications. The study revealed that microcrystalline cellulose derived from the stem pulp of Saccharum officinarum has good potential for use as an excipient in tablet formulation.

INTRODUCTION

The use of natural substances as medication by man can be said to be as old as the human race itself. It is a common knowledge today that crude plant products were used as medicine by the early man. Purified chemically active principles have been extracted from plants and are also produced synthetically over the years. These principles are known as the "Active Pharmaceutical Ingredients (API) and are mostly not administered alone but usually formulated as dosage. Dosage forms function to deliver the active principles to target site of action and usually contain the active principles together with other pharmacologically inert substances known as excipients.

Excipients of organic origin are of particular interest to formulation scientists because they are reliable, sustainable and will minimize reliance upon fossil fuels derived products [1]. Vegetable products are therefore suitable alternatives to synthetic products because of their minimal toxicity, cost effectiveness and affordability compared to synthetic products. Additives from plant sources are also generally non toxic renewable means for the sustainable supply of less expensive pharmaceuticals [2,3]. Release process of drug from solid dosage form is very important and should be put into consideration in the course of formulating a tablet. The drug release process from immediate release tablets often includes a step at which the tablet disingtegrates into smaller fragments and for this to be determined disintegration test methods have to be performed. Also, another way to study the release of drugs from a solid dosage form is dissolution test; this is an important tool to access factors that affect the bioavailability of a drug from a solid preparation. The cumulative amount of drug that passes into solution is studied as a function of time during dissolution test and the test describes the overall rate of all the processes involved in the release of the drug into a bioavailable form.

S, officinarum. is one of the 6 - 37 species of saccharum (depending on taxonomic system) of tall perennial grasses (family: poaceae, tribe: Andropogeneae), native to warm temperate to tropical regions of Asia. They have stout, jointed, fibrous stalks that are rich in sugar, and measure 2 - 6 meters (6 - 19 feet) tall. *S. officinarum* products include: table sugar, falernum, molasses, rum, cachaca and ethanol etc. The bagasse that remains after sugar cane crushing may be burned to generate heat and electricity. It may also because of its high cellulose content, serve as raw material for pharmaceutical and food producing industries; and because they are by-products, they can be branded as "environmentally friendly" [4]. *S. officinarum* is commonly known as sugar cane and locally (ibibio) as "mbokko" [5].

The objective of this study is to examine the suitability of microcrystalline cellulose isolated from *S. officinarum* L. (MCC-D) as excipient for pharmaceutical tablet formulations.

MATERIALS AND METHODS

Materials:

Paracetamol powder was a gift from SKG Pharma, Lagos, Nigeria. Lactose, talc powder and Corn starch were purchased from BDH, England. Avicel(R) pH 101 and Magnesium stearate were purchased from Sigma Aldrich, USA. Microcrystalline cellulose derived (MCC-D) powder. All other chemicals and reagents used were of laboratory grade.

METHODS

Extraction of Alpha cellulose

The method of Ohwoavworhua et al[6] was used with some slight modifications. The processed sponges from the stem of the plant, *S. officinarum*, were shredded into tiny bits. Forty grams of the shredded sponge was placed in a conical flask along with 400 ml of 2% sodium hydroxide solution and heated in water bath at 80^{o}C 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 muslin cloth. The moist mass was then heated over a water bath at 80^{o}C in 300 ml of an aqueous solution of laboratory prepared sodium hypochlorite for 1 h to effect bleaching of the mass. The bleached mass was subsequently squeezed through the muslin cloth to remove excess liquid and the washed before being subjected to second delignification stage by heating over a water bath at 80^{o}C for 1 hour in 30 ml of 17.5%$^{w}/_{v}$ sodium hydroxide solution. Final bleaching of the cellulose was carried out by heating the material obtained from the previous stage (after thorough washing with distilled water) with 300 ml of a 1:2 aqueous dilution of sodium hypochlorite. The resultant alpha cellulose was repeatedly washed with excess moisture squeezed out with the muslin cloth and the material in the form of small lumps finally dried in a hot air oven at a temperature of 57 - 60^{o}C for 1 hour.

Production of Microcystalline Cellulose

The method of Ohwoavworhua et al [6]. was also used .A 50 g quantity of the alpha 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^{o}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 liters of cooled distilled water which was followed by the vigorous stirring with a spatula and the mixture was allowed to stand overnight. The microcrystalline cellulose crystals were then filtered through a Whatman No. 1 filter paper and washed with distilled water until neutral to litmus paper. After filtration the crystals were dried in a hot air oven at a temperature of 57 - 60^{o}C for 60 minutes and further milling and sieving then carried out to produced crystals that passed through a 500 µm aperture. The resultant microcrystalline cellulose was coded MCC-D.

Physicochemical Properties of MCC-D

Organoleptic properties

The colour, odour, taste and physical appearance of the sample were observed.

Solubility

The solubility of 1 g of MCC-D both in drops and in excess in the following solvents was determined; ethanol, distilled water, acetone and dilute hydrochloric acid.

Test for starch and dextrins

A total of 0.1g of the sample was dispersed in 100 ml of distilled water. One drop of iodine solution was added to 0.1 ml of the resultant mixture, development of a light red brown or light red to purple colour indicated the presence of dextrins

Nine milliliters of the distilled water was added to 1 g of the substance and the mixture boiled for 5 minutes and filtered hot. The production of a blue colour when 0.1 ml of a 0.05 M solution of iodine is added to the filtrate indicates the presence of starch.

pH Determination

The pH of the supernatant liquid obtained after shaking 2 g of the powder with 100 ml of distilled water for 5 minutes was determined using a pH meter.

Powder Flow Properties

Bulk and Tap Densities

A 10 g quantity of the powder sample was placed in a 50 ml clean, dry measuring cylinder and the volume V_i occupied by the sample without tapping was determined. After 5 mechanical taps of the cylinder on a horizontal surface the occupied volume V_f was noted. The means of four determinations was taken.

The bulk and tap densities were calculated as the ratio of sample weight to volume (V_i and V_f respectively).

Hausner's index

This was calculated as the ratio of the tap density to the bulk density of the sample i.e.

$$\frac{\text{Tap density}}{\text{Bulk density}} \quad \text{---------- 3}$$

Carr's Index

This was computed from the following equation

$$\% \text{ Compressibility} = \frac{\text{Tap density - bulk density}}{\text{Tap density}} \times 100\% \quad \text{----4}$$

Angle of Repose

The static angle of repose was measured according to the fixed funnel and free standing cone method. A funnel was clamped to a retort stand with its tip 2 cm above a plain white sheet of paper, placed on a flat horizontal surface.

The powder was carefully poured through the funnel until the apex of the cone thus formed by the powder just reached the tip of the funnel. The mean diameter of the base of the power cone was obtained after four determination and the angle of repose calculated from the following equation:-

$$\text{Ø} = \tan^{-1}(2h/D) \quad \text{----------5}$$

h=height of the powder cone

D= diameter of the cone's base

TABLET PRODUCTION

Paracetamol was used as the active ingredient. The wet granulation method was used to prepare the granules with corn starch and lactose as the disintegrant and bulking agent respectively. Two binders, microcrystalline cellulose derived (MCC-D) and Avicel$^{(R)}$ 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 formular for the tablet is as follows:

Paracetamol 80%$^{w}/_{w}$	500mg
Corn starch 7%$^{w}/_{w}$	43.75mg
Lactose 13%$^{w}/_{w}$	81.25mg
Binder x%$^{w}/_{w}$	
Magnesium stearate	5.0mg
Talc	14mg

This formula was enlarged to produce desired quantity of tablets for the three different pressures in each batch for both MCC-D and Avicel(R). The required amount of paracetamol powder, corn starch and lactose was weighed out accurately using the electronic balance and sieved through a 1.00 mm screen. They were blended together in a mortar and formed into a damp mass using the binder solution. The wet mass was passed through a 4.00 mm screen and dried at 60°C in the hot air oven. 20-30% and 70-80% of the dried granules was passed through a 1.00mm and 2.00mm screen respectively and mixed thoroughly. The accurate amount of magnesium stearate and talc was measured and sieved through a 0.5 mm screen and the granules was lubricated with the mixture. The resulting granules were thoroughly mixed, the die cavity of the tableting machine was set to get the maximum weight of the tablet; the hopper was filled with granules and the tableting was operated. The operating pressure was 10 kg/force.

TABLET CHARACTERISTICS

Tablet Weight

Twenty tablets each of the MCC-D and Avicel(R) PH 101 tablet batches were weighed individually and the average weight for the various batches determined. The percentage deviation of each tablet weight from the mean weight was determined, and the conformity or non-conformity of the tablet batch to official weight uniformity standards consequently established [7,8].

Disintegration Test

A British Pharmacopoeia [9] disintegration apparatus containing distilled water at 37°C was used for this determination. Six tablets each from various batches were placed individually in each of the cylinders of the disintegration apparatus and a guided disc placed on each of the tablets. The apparatus was then started and the time taken for all the fragments of the tablet to pass through the screen noted. The final disintegration time was taken as the mean of two determinations.

Dissolution Test

The method specified in the United States pharmacopoeia [10] was used, using a combination of sodium hydroxide solution and potassium dihydrogen phosphate, a buffer solution of pH 5.8 was prepared this served as the dissolution medium. 50 0mls of the dissolution medium was placed in the vessel of the dissolution apparatus and a tablet form each batch was placed in the dissolution medium at a temperature of 37°C and the dissolution process was carried, out at a speed of 50 rpm. After every 5 minutes interval, 20 ml, from the vessel containing the dissolution medium was filtered using Whatman No.1 filter paper and diluted to 50ml with the dissolution medium. The withdrawn sample was replaced with an equal volume of medium maintained at 37°C. The resultant solution was analyzed for the concentration of dissolved paracetamol using an ultraviolet spectrophotometer and the percentage drug release also determined. This analysis was carried out with reference to a standard paracetamol sample. The determinations were repeated for the each batch of paracetamol tablets.

RESULTS

Percentage yield of microcrystalline cellulose from *S. officinarum*

Percentage yield of alpha cellulose from the stem pulp was 40% while the percentage yield of MCC-D from alpha cellulose was 70%

Table 1. Organoleptic properties

Properties	MCC-D	Avicel
Colour	Off-white	Off-white
Odour	Odourless	Odourless
Taste	Tasteless	Tasteless
Appearance	Granular powder	Granular powder

Table 2. Solubility Test

Solvent	*Solubility*	
	MCC-D	Avicel
Acetone	Insoluble	Insoluble
Dilute hydrochloride acid	Insoluble	Insoluble
Ethanol	Insoluble	Insoluble
Distilled water	Insoluble	Insoluble

Table 3. Test for Starch and Dextrin

	MCC-D	Avicel
Starch	Absent	Absent
Dextrin	Absent	Absent

Table 4. Other Physicochemical Properties of the Celluloses

Parameters	Avicel	MCC-D
Bulk Density (g/ml)	0.544	0.506
Tapped Density (g/ml)	0.630	0.572
Hausner Index	1.16	1.13
Carr's Index	13.57	11.38
Angle of Repose (°)	26.30	25.50
pH	6.00	5.70

Table 5. Tablet Characteristics

Parameters	*AVICEL*						*MCC-D*					
	0%	5%	10%	15%	20%	25%	0%	5%	10%	15%	20%	25%
Weight (mg)	0	648	650	653	660	666	640	646	653	655	664	667
Weight deviation (%)	640	0.1	0.46	0.80	1.30	0.8	0.90	0.65	0.72	0.82	0.70	0.6
Disintegration(min)	1.45	1.90	3.17	1.78	2.70	5.23	1.17	1.32	1.45	3.73	5	4.35
Dissolution (%) at 20 mins	96.5	89.6	85.4	83.5	70.1	59.7	96.5	89.8	85.6	83.7	70.2	60

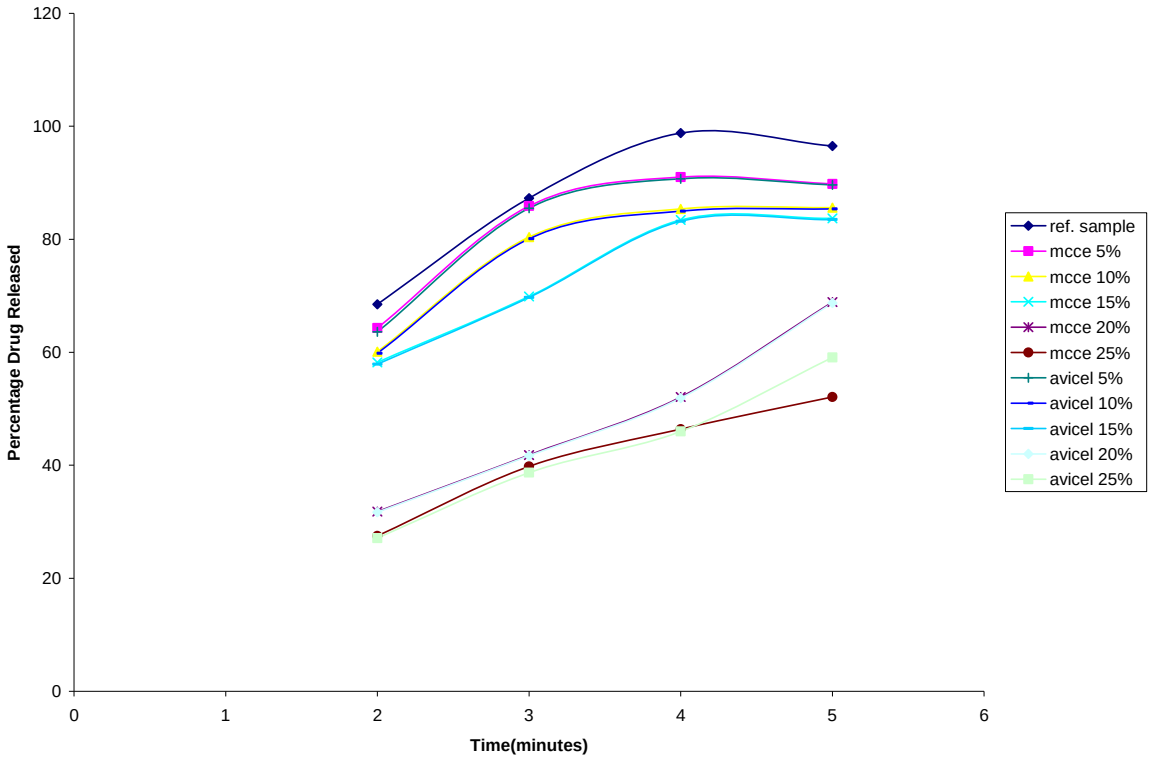

Figure 1. **Release profile of paracetamol tablet formulated**

DISCUSSION

Product yield:

Forty percent yield of alpha cellulose in the form of white, fleecy masses from the starting plant material was quite good, especially when compared with alpha cellulose yield of 32% $^{w}/_{w}$ reported for Cochlosphermum planchonii using a similar extraction method [9] Also, the 70% $^{w}/_{w}$ MCC-D yield from alpha cellulose is quite encouraging.

Physicochemical Properties:

The MCC-D isolated was an almost white, relatively free flowing granular powder and also the Avicel$^{(R)}$ PH 101 and both compiled with British pharmacopoeia , International Pharmacopoeia and National formulary specifications for organoleptic properties, solubility, dextrins and starch. The pH of 5.70 obtained from a 2%$^{w}/_{v}$ dispersion of the product (MCC-D) in distilled water complies with the standard of 5-7.5 outlined in the international pharmacopoeia [11] .

Powder Flow Properties

The flowability of a powder is of critical importance in the production of pharmaceutical dosage form – cohesion and adhesion are phenomena which occur at surfaces, particle size will therefore influence the flowability of a powder. As seen the mean flow rate of MCC-D was greater than that of Avicel$^{(R)}$ PH 101.

A particle will begin to slide when the angle of inclination is large enough to overcome frictional forces. The angles of repose were all between 23.5^{o} - 27.2^{o}, indicating a good flow of both powders with the mean θ of MCC-D lower than that of Avicel$^{(R)}$ PH 101.

The bulk density of a powder is dependent on particle packing and changes as the powder consolidates. MCC-D gives the Carr's index of between 7-15% indicating excellent and good powder flow. Avicel$^{(R)}$ PH 101 however has a Carr's Index of between 11 and 16% which indicates good powder flow.

The two binders at varying concentrations produced Hausner ratios of less than 1.25 indicating that they are good (free flowing) powdered granules.

From the discussion above, it is inferred that MCC-D from *S. officinaum* seems to have good powder flow properties.

Tablet Characteristics

Tablet weight uniformity: The tablets produced from MCC-D and Avicel$^{(R)}$ PH 101compiled with both British pharmacopoeia [8] and the United States pharmacopoeia [12] specifications for tablet weight uniformity, and this is indicative of good flow of the product. Also there is slight increase with increase in pressure.

Tablet disintegration: The disintegration of tablets made from MCC-D at various concentrations compiled with specified standards ($\leq$ 15 minutes for uncoated) [9]. For tablets made from Avicel$^{(R)}$ PH 101, the specified standard for disintegration was also met.

It can be inferred that MCC-D is a potent binder at higher concentration.

Tablet Dissolution

The tolerable limits of the concentration of dissolved paracetamol in dissolution medium for paracetamol states not less than 80% of the labeled amount [12] dissolution profile of batches formulated with 5-15% binder (MCC-D and Avicel$^{(R)}$) were satisfactory with accepted percentage even at high pressures but those with high concentrations (20 and 25%) had low percentage drug release.

CONCLUSION

The yield of MCC-D from the stem pulp of *S. officinarum* was relatively good, the product obtained compiled with official compendia specifications for microcrystalline cellulose with regard to physicochemical properties and pH. Its flow properties were also found to be good in relation to Avicel$^{(R)}$ pH 101.

It has been shown that both MCC-D and Avicel$^{(R)}$ pH 101 at a relatively high concentration formed harder compact with strong interparticulate cohesive bonds, therefore the excipients should be used at moderate concentrations (5-15%) as at this concentration they have greater potency to give higher bioavailability of the drug.

In most pharmaceutical technology operations, altering a process may adversely influence another. For example, increasing compression influence other produce stronger tablets was seen to have great effect by impairing disintegration and prolong dissolution rates.

In conclusion, tablets in which MCC-D was incorporated as binder displayed good release properties and have high potentials for substitution for other more expensive

RECOMMENDATION

It is recommended that further work should be carried out on release characteristics such as swelling factor. The mechanical properties of microcrystalline cellulose derived from plant used in tablet formulation can also be carried out.

From the results obtained in this work, microcrystalline cellulose derived from the stem pulp of *S. officinarum* is recommended for use as a pharmaceutical binder.

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