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Some Pharmacopoeial and Diluent-Binder Properties of α-Cellulose derived from Maize Cob in Selected Tablet Formulations

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ABSTRACT

As part of continuing efforts to develop low-cost pharmaceutical grade cellulose, α-cellulose (MC) was extracted from an agricultural waste (de-grained maize cob) and characterized as a tablet diluent using a commercial brand of microcrystalline cellulose (MCC) and a mixture of lactose and starch (LS) as reference standards. The α-cellulose met the pharmacopoeial specifications (for Powdered Cellulose B.P.), including pH - 6.5 ± 0.5; loss on drying - 6.0%; residue on ignition - 0.03%; and water-soluble substances - 0.9%. Presence of organic impurities and starch was not found. MC compared well with MCC and LS in terms of bulk density (0.36g/cm^3) and true density (1.59g/cm^3). MC, MCC and LS were individually evaluated as tablet diluents for some commonly used drugs, namely, folic acid, chloroquine and vitamin B complex. The tablets were prepared by pre-compression. Based on the tablet parameters examined, (including tensile strength, disintegration time and dissolution data), MC-based tablets compared well with MCC- and LS-based tablets. MC formulations were highly compressible (no binding agent was needed) and yielded folic acid and vitamin B complex tablets that were self-lubricating (no lubricant was needed). However, folic acid-MC and folic acid-MCC tablets, unlike folic-LS tablets, failed to disintegrate within 15 min (BP limit). Chloroquine tablets produced with the three diluents passed all the pharmacopoeial tests (BP) but a lubricant was included in the formulations to eliminate sticking. The findings from this work confirm the tablet diluent-binder potentials of α-cellulose derived from maize cob in tablet produced by the pre-compression method.

Key words: α-cellulose, pharmacopoeial characterization, physicochemical properties, diluent.

INTRODUCTION

The annually renewable agricultural residues represent an abundant, inexpensive, and readily available source of renewable lignocellulosic biomass, and their utilizations are attracting

increased interests around the world, particularly for the production of novel materials for environmentally friendly industrial utilizations after chemical modification [1]. There are millions of tons of agricultural residues produced annually in Nigeria. For example, the quantity of maize cob, groundnut shell, rice husk and sugar cane fibres generated annually in Africa is estimated to total over 12 million metric tons [2]. Perhaps, up to half of these wastes are potential low-cost sources of cellulose but hardly, if any, known attempt has been made at a commercial level to harness these vast but grossly neglected resources to achieve socio-economic benefits for the peoples of the region.

Cellulose is undoubtedly, the world's most plentiful phytochemical compound. Powdered Cellulose B.P. (α-cellulose) is a white or almost white, odourless, and tasteless powder of various particle sizes, ranging from a free-flowing fine or granular dense powder to a coarse, fluffy, non-flowing material [3].

Cellulose and its derivatives have found several applications in the pharmaceutical industry, e.g., as diluents, disintegrants, binders, enteric coatings, drug-release modifiers, suspending agents, mucoadhesive agents, gelling, agents, etc. A number of studies have been carried out in this regard including those involving cellulose derived from various plant residues [4-7]. In a preliminary study on the physicochemical characteristics of celluloses extracted from groundnut shell and rice husk, it was observed that the celluloses exhibited the potentials of a good disintegrant [6]. It is clear from earlier works that the type/nature of the original source of cellulose, extraction procedure and treatment, its physicochemical characteristics, solid dosage formulation process and the type of drug formulated, variously influence the formulation characteristics of cellulose.

The objective of this work was to evaluate the diluent properties of α-cellulose derived from maize cob when used to produce tablets containing a water-soluble pharmaceutical active ingredient (chloroquine phosphate) and low-dose pharmaceutical active ingredients (vitamin B complex and folic acid).

EXPERIMENTAL SECTION

Materials

Riboflavine BP, nicotinamide, stearic acid, thiamine hydrochloride, chloroquine phosphate BP, and Lactose BP were kindly supplied by Emzor Industies Ltd, Lagos, Nigeria. De-grained maize cobs were obtained from a market in Benin City, Edo State, Nigeria. Sodium hydroxide, nitric acid, sodium sulphite and sodium nitrite (all reagent grade) used for the extraction of cellulose from maize cob were manufactured by B.D.H., Poole, UK while sodium hypochlorite was generated from calcium hypochlorite in our laboratory.

Cellulose Isolation

Cellulose was isolated from maize cob using a method described in a previous study [5]. Briefly, the method involved the delignification of the cellulosic material with 3.5% Nitric acid and 0.01% Sodium sulphite at 90^{o}Cfor 2 hours followed by treatment with 2% Sodium hydroxide extraction and 2% Sodium sulphite at 50 ^{o}C for 1 hour and 17.5% Sodium hydroxide at 80 ^{o}C for 0.5hours. Bleaching was carried out with 3.2% Sodium hypochlorite at 40 ^{o}C for 1.5 hours

Pharmacopoeial characterization

Bulk density, true density, angle of repose and porosity of cellulose powder was determined using standard methods, as detailed in an earlier work [5].

The moisture content of the diluents was obtained by spreading approximately 1g of the sample, accurately weighed, on a watch glass, drying for 24h at 110^{o}C and then re-weighed again. The sample was dried for another 24h and weighed again. Percent loss on drying was calculated and presented as the percent moisture content.

The swelling capacity of the cellulose powders were determined by the method of Bowen and Vadino [8]. The volume of the sediment V_y was noted and swelling capacity computed using Eq 1.

$$\text{Swelling capacity (\%)} = \frac{Vy}{V} x\ 100 \qquad \text{.....Eq. 1}$$

where V is the initial volume of the powder.

Formulation of tablets

All the tablets were prepared by precompression. The active ingredient (except for batches containing only the diluents) and the test or standard diluents were mixed manually in a sealed polythene bag for 10 min and then compressed in a Manesty F3 tablet machine at a fixed compression setting. The slugs were broken down into granules in a mortar and passed through a sieve with an aperture size of 710µ. The granules were recompressed into the final tablets in a Manesty F3 tablet machine at a fixed compression setting for all the batches. The compositions were thiamine HCl (5%), riboflavin (3%), nicotamide (20%) and diluent (72%) for vitamin B complex tablets; folic acid (6.25%) and diluent (93.75%) for folic acid tablets; and chloroquine phosphate (83.3%), diluent (15.3%) and magnesium stearate (1.4%) for chloroquine phosphate tablets. All the tablets were stored in well-closed containers pending evaluation.

Evaluation of tablets

The tablets were evaluated using standard methods as described in the previous study [5].

Statistical analysis

Statistical analysis of the results was carried out with the aid of OriginPro 8 SR2, vs.0891 (B891) software (OriginLab Corporation USA). Tukey test for mean comparisons and analysis of variance (AVOVA) were evaluated and the data were considered statistically different at $p<0.05$.

RESULTS AND DISCUSSION

Pharmacopoeial and Physicochemicalcharacteristics

The results of the pharmacopoeial characterization of the celluloses carried out are shown in Table 1 while their physicochemical properties are shown in Table 2.

Table 1:Pharmacopoeial characterization of maize cob cellulose (MC) and a commercial microcrystalline cellulose (MCC).

Diluent	Identification	pH	Loss on drying (%)	Residue on Ignition (%)	Sulfated Ash (%)	Water Soluble Substances (%)	Heavy Metals	Starch
MC	Violet blue	6.5±0.5	6.00±0.02	0.30±0.06	0.90±0.02	10ppm	No red colour	Negative
MCC	Violet blue	6.2±0.7	5.80±0.08	0.04±0.01	0.25±0.05	10ppm	No red colour	Negative

Table 2: Some physicochemical properties of maize cob cellulose (MC), microcrystalline cellulose (MCC), Lactose (L), and Starch (S) powders

Parameter	MC	MCC	L	S
Cellulose yield (%)	30.0 ± 0. 4	N/A	N/A	N/A
Bulk density (gm/cm^3)	0.36 ± 0.01	0.41 ± 0.01	0.67 ± 0.03	0.47± 0.01
True density (gm/cm^3)	1.59 ± 0.01	1.39 ± 0.01	1.53 ± 0.01	1.41± 0.01
Angle of repose (^{o})	46.2 ± 0.6	41.2 ± 0.5	40.1 ± 0.5	42.9 ±0.9
Porosity	0.77	0.71	0.44	0.33
Swelling capacity	1.72 ± 0.01	1.90 ± 0.02	-	-
Moisture content (%)	6.4	5.5	2.0	11.0
Melting point (^{o}C)	230[a]	265[a]	203	[b]

[a] = charring point, [b] = did not melt or char within the temperature range examined N/A = not applicable.

Pharmacopoeial characterization

The yield of the α-cellulose (MC) was approximately 30% w/w of the original waste material. MC was odourless, tasteless and white in colour. The MC and MCC samples became violet-blue in colour when placed on a watch glass and was dispersed in iodinated zinc chloride solution thus indicating the presence of cellulose. The pH of the two celluloses fell within the pharmacopoeial requirement of 5.0 to 7.5. Percent water-soluble substances of both celluloses were within pharmacopoeial limit (BP) (<1%), being less than 1%. There was no red colour when 0.05M iodine was added to the test samples, indicating absence of organic impurities (starch and dextrin) in MC and MCC. Both celluloses complied with the limit test for heavy metals.

The extracted α-cellulose met BP requirements [9], thus further confirming the suitability of the extraction procedure used in this study in the production of high-grade α-cellulose for pharmaceutical applications.

Physicochemical properties of the powders

Bulk Density

MC exhibited the lowest bulk density of 0.36g/cm^3, followed by MCC, 0.41g/cm^3; starch 0.47g/cm^3 and lactose 0.67g/cm^3. The low bulk density of MC makes it a good tablet excipient since the lower the bulk density of an excipient, the lower the amount needed for compression in tablet manufacture. Generally, an excipient with a low bulk density will exhibit a high dilution potential on a weight basis [10].

True Density

As in indicated in Table 2, the true density data are as follows: MC, 1.59g/cm^3; MCC, 1.39g/cm^3; lactose, 1.53g/cm^3 and starch, 1.41g/cm^3. The high true densities of the diluents suggest that all the diluents exhibit good compressibility.

Angle of Repose

The angle of repose (46.2^o) of the MC was higher than that of the other diluents, with MCC, lactose and starch showing angle of repose of 41.2^o, 40.1^o and 42.9^o, respectively. This indicates that the MC exhibited poorer flow properties than the other diluents. This may be partly due to its relatively high moisture content. A glidant, would therefore, be needed when used in solid dosage formulations.

Porosity

The porosity of the MC (0.77) was close to that of MCC (0.71). These values are slightly different from the values reported earlier [5]. This is probably due to differences in particle size

distribution of the cellulose in the two studies since the voids between the larger particles are usually filled by the smaller particles [7,11]. Porosity can vary between wide limits depending on the extent to which void filling occurred. The porosities of the lactose and starch powder were substantially lower at 0.44 and 0.33, respectively. Since powder porosity affects the rate and extent of water uptake into the powder bed, it would be expected that the higher the value of the porosity, the more rapid the rate and extent of water uptake; this might have contributed to the higher moisture content of the two celluloses.

Moisture Content

The moisture content of MC was relatively high: 6.4% compared to 5.5% for MCC. Lactose had moisture content of 2.0% while starch had 11%. Lactose being non-hydroscopic unlike the other diluents exhibited the lowest moisture content. The relative high moisture of MC content may partly be due exposure to the high humidity of the environment just prior to evaluation. Except for lactose, the moisture contents of the diluents were high and hence care needs to be taken if these hygroscopic diluents are to be compressed with hydrolysable and/or moisture-sensitive drugs such as aspirin. Formulation scientists generally consider 3% moisture content as the maximum if the chemical stability of a hydrolysable drug contained in a solid dosage form is to be assured [10]. However, it has been indicated that it is the free (mobile) water fraction rather than the total water content of excipient that is important as far as chemical stability is concerned since the solid-like and bound fractions do not induce hydrolysis. Moisture content somewhat affects the mechanical strength and flowability of cellulose powder when the moisture content is above 5% because water molecules act as a plasticizer, significantly affecting the viscoelastic and mechanical properties of the material, resulting in lower tensile strength tablets. Furthermore, powder flowability has been shown to decrease with increasing moisture content [10].

Diluent properties

The properties of the tablets as well as diluent compacts are summarized in Tables 3 to 6

Table 3: Physico-pharmaceutical properties (± s.d.) of the diluents compacts

Parameter	MC	MCC	L	S	LS
Mean weight (mg)	488 ± 03	488 ± 07	503± 11	501± 06	503± 12
Tablet thickness (mm)	3.7 ± 0.5	3.6 ± 0.5	3.5 ± 0.8	3.6 ± 0.4	3.5 ± 0.8
Porosity	0.653	0.765	0.745	0.780	0.753
Crushing strength (kgf)	3.6 ± 0.5	8.7 ± 0.7	10.1 ± 0.1	1.4 ± 0.5	4.5 ± 0.1
Tensile strength (MPa)	1.05	1.21	1.45	0.20	0.64
Friability test (%)	0.81	0.07	1.26	4.99	4.71
Disintegration time (min)	1.5± 0.2	0.5± 0.1	0.4± 0.3	0.8 ± 0.2	02.5 ± 0.1

Key:MC = maize cob cellulose; MCC = microcrystalline cellulose; L = lactose; S = starch; LS = 1:1 lactose: starch mixture)

Table 4: Physico-pharmaceutical properties (± s.d.) of compressed vitamin B complex tablets containing maize cob cellulose (MC), microcrystalline cellulose (MCC) and 1:1 blend of lactose and starch (LS).

Parameter	MC	MCC	LS
Mean weight (mg)	98.2 ± 6.5	90.2 ± 3.0	98.2 ± 6.5
Tablet thickness (mm)	3.08 ± 1.30	3.03 ± 1.50	3.07 ± 1.20
Porosity	0.351	0.369	0.344
Crushing strength (kgf)	2.4 ± 0.5	2.2 ± 0.5	2.1 ± 0.4
Tensile strength (MPa)	0.75	0.70	0.66
Friability test (%)	0.66	0.37	0.56
Disintegration time (min)	2.9 ± 0.0	2.3 ± 0.1	0.3 ± 0.1

Table 5: Physico-pharmaceutical properties (± s.d.) of compressed chloroquine tablets containing maize cob cellulose (MC), microcrystalline cellulose (MCC) and 1:1 blend of lactose and starch (LS).

Parameter	MC	MCC	LS
Mean weight (mg)	294 ± 17	292 ± 5	289 ± 17
Tablet thickness (mm)	3.96 ± 0.40	3.90 ± 0.30	3.90 ± 1.90
Porosity	0.301	0.284	0.305
Crushing strength (kgf)	4.6 ± 0.4	3.6 ± 0.3	2.3 ± 0.2
Tensile strength (MPa)	0.77	0.60	0.38
Friability test (%)	0.66	0.07	0.93
Disintegration time (min)	2.3 ± 0.0	2.0 ± 0.1	0.8 ± 0.1
Dissolution (t 45min)	91.7	92.3	93.7

Table 6: Physico-pharmaceutical properties of compressed folic acid tablets containing maize cob cellulose (MC), microcrystalline cellulose (MCC) and 1:1 blend of lactose and starch (LS)

Parameter	MC	MCC	LS
Mean weight (mg)	79 ± 6	85 ± 3	80 ± 2
Tablet thickness (mm)	2.69 ± 1.15	2.64 ± 0.62	2.54 ± 0.28
Porosity	0.288	0.291	0.331
Crushing strength (kgf)	6.2 ± 0.8	8.6 ± 1.2	6.1 ± 0.6
Tensile strength (MPa)	2.1	3.2	2.4
Friability test (%)	0.14	0.16	0.11
Disintegration time (min)	>15.00	>15.00	3.0 ± 0.2

Diluent Compacts

The tablet characteristics of the diluents are shown in Table 3. It was observed that while compacts of MC, MCC, and lactose were free of physical defects, the compacts of LS and starch showed 'pitting' on their surfaces which indicates that a lubricant is required. Tablet thickness for all the diluents ranged from 3.5-3.7mm with MC manifesting the highest value. This might be attributed to its low bulk density since an excipient with a low bulk density will exhibit a high dilution potential on a weight basis [10].

Starch compacts had the highest porosity of 0.780 compared to 0.653 of MC compacts which manifested the lowest porosity. Interestingly, MC compacts exhibited the highest disintegration time thus suggesting that the more porous the compact, the more rapid is the fluid penetration into the compact to effect disintegration. MCC and lactose tablets demonstrated the highest compact strength followed by MC and LS compacts, with starch compacts which had a crushing strength of 1.4kgf, the lowest. Since compact strength provides an estimate of interparticulate bonding, this bonding is expected to be weaker in starch compacts due to its higher water content since free water interferes with particle-particle interactions. Thus the high tensile strength of lactose compared to the other diluents might be due to its low moisture content. However, there was no correlation between crushing strength and friability. MC and MCC showed friability of 0.8 and 0.7%, respectively. The high friability values for starch and LS compacts (4.99 and 4.71%, respectively) may probably be due to the pitted surface of the compacts which made them more prone to attrition during the friability test. This implies that friability will be lowered by lubricating the formulation.

The results of the physico-pharmaceutical characteristics of the medicated tablets containing chloroquine phosphate, folic acid and vitamin B complex, respectively are shown in Tables 4-6**.** Since all the batches of tablets were subjected to the same formulation and compression conditions, including the same compression setting, any differences observed in the properties of

the tablets can be attributed to the characteristics of the diluents and active ingredients, as well as interactions.

Vitamin B complex tablets

The diluents at a concentration of 72% produced tablets with comparable physico-pharmaceutical properties as shown in Table 4. Porosity, crushing strength (and hence also tensile strength), friability and disintegration time were similar for each diluent type. Although crushing strength was in the range 2.1-2.4 kgf, which suggests mechanically weak tablets, the friability values (ranging from 0.37-0.66%) indicate that the mechanical integrity of the tablets were satisfactory. All the tablets (disintegration time range: 0.3-2.9 min) easily satisfied the requirement of the British Pharmacopoeia [9], which stipulates an upper limit of 15 min for tablet disintegration. Disintegration test is a measure of the ease with which the bonds formed during compression are broken, with a short disintegration time indicating that the bonds are easily broken. In the Nigeria pharmaceutical industry, the lactose-starch mixture is commonly used for the manufacture of vitamin B complex tablets. Thus, α-cellulose, which is inexpensively derivable from cobs, may be suitable alternative for lactose-starch blend.

Chloroquine Tablets

The physico-pharmaceutical properties of the tablets, which contained 15.33% of the diluent, are shown in Table 5.Since chloroquine tablets do not normally require a diluent, and also in view of the small amount incorporated (15.3%), the additives would be approximately referred to here as dry binders. Tablets formulated withMC showed higher tensile strength than the other compressed tablets.

Since tablet strength is essentially a measure of the number and strength of stable bonds formed in the tablet, it is clear that chloroquine/MC tablets produced more change in interparticulate bonds during compression than others. Furthermore, the low friability values (0.07-0.94%) indicate that the mechanical integrity of all the tablets was adequate. The tablet disintegration data indicate that all the tablets easily satisfied the requirement of the British Pharmacopoeia [9], as they disintegrated within 0.8-2.3 min, which is well below the upper limit of 15 minutes for tablet disintegration. Some factors, including excipient type and tablet porosity, usually play a role in tablet disintegration. It is known that cellulose induces tablet disintegration by a swelling mechanism as well as by capillary or wicking action, and both of these phenomena are dependent on water penetration into the tablet [6]**.** However, while reduction in void space will decrease the rate of water penetration into the tablet matrix thus retarding disintegration, the swollen disintegrant (cellulose) particles will have more immediate crushing effect on the tablet structure thus promoting disintegration. The slow penetration of water into the tablet by capillary action may limit the role of swelling mechanism. Thus, although the porosities of the three tablet formulations were nearly the same, the faster disintegration of the tablets containing L/S may be attributed to reduced interparticulate bonding or tablet cohesiveness.

The British Pharmacopoeia [9] requires that conventional tablets must release 70% of the active principle in no more than 45 minutes. The results demonstrate that all the chloroquine tablets clearly satisfied this requirement as over 90% of the drug was released within 45 minutes in all the cases. The slightly faster dissolution rate of tablets containing LS was probably due to its lower crushing strength which also contributed to faster tablet disintegration. However, it can be inferred from the overall results that chloroquine tablets can be suitably formulated and manufactured with minimal excipients (only MC and MCC and lubricant would be required) by the direct compression method. This would reduce processing time, materials and cost without impacting adversely on the final product weight and quality.

Folic Acid

As in vitamin B complex tablets, the diluents (at a concentration of 93.75%) produced tablets with comparable physico-pharmaceutical properties with one notable exception - tablet disintegration. Tablets containing either of the two celluloses failed to disintegrate within 15 min limit stipulated by BP [9]. The profound hydrophobic character of the active ingredient might have impeded water penetration into the tablets since water is required to initiate the two disintegration mechanisms of capillary and swelling. This is crucial because the celluloses are strong binders and rely on adequate water penetration to achieve swelling. On the other hand, lactose is water soluble while starch is not only hydrophilic but a powerful disintegrant which depends mainly on the capillary mechanism to effect tablet disintegration. It would, therefore, be expected that the high starch content of approximately 47% will easily break up the tablets containing only 6.25% of the hydrophobic drug.

CONCLUSION

The results demonstrate the suitability of cellulose derived from an agricultural waste, maize cob, as a suitable diluent for vitamin B complex tablet formulation and as a dry binder for chloroquine phosphate tablets using the precompression method of tablet production. The tablets generated exhibited satisfactory physico-pharmaceutical characteristics. Thus, maize cob cellulose which can potentially be produced at a commercial level in Nigeria could be a suitable substitute for lactose and starch which are mainly imported into the country. Furthermore, although maize cob cellulose, like microcrystalline cellulose, was found unsuitable for the production of folic acid tablets by the precompression as a result of the hydrophobicity of the drug, which adversely affected tablet disintegration, it seems, likely that incorporation of a suitable disintegrant in the formulation would make the cellulose a suitable diluent. This will be the subject matter of a further investigation.

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