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Research Article

Design and Evaluation of Melt-extrusion Matrices using Tronated Microfine Celluloses (TMFCs) Hydrogel Derived from *Gmelina arborea* for the Delivery of Acetaminophen

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ABSTRACT

This aim of this study was to produce pharmaceutical grade microfine cellulose from alpha- cellulose derived from sawdust of the tropical tree *Gmelina arborea*, using trona (sodium sesquicarbonate), a known depolymerization agent, evaluate the physicochemical properties of the resulting cellulose and develop melt-extrusion matrices containing acetaminophen using the cellulose. Alpha–cellulose was extracted from sawdust and treated with various concentrations of trona (0.1, 1, 2, 5, 10, 15 and 20 %) to produce tronated microfine cellulose - TMFC. The physicochemical properties of TMFC was determined and compared with Avicel PH 101 (Microcrystalline cellulose, MCC), a standard cellulose. TMFC was then used to prepare melt-extrusion matrices of acetaminophen. Some physicochemical properties of the matrices were determined. Drug dissolution from the melt-extrusion matrices was evaluated in 0.1N HCl (pH 1.2). Results indicate that the physicochemical properties of the α–cellulose were comparable to MCC. R_f values revealed no drug-excipient incompatibility between acetaminophen and TMFC. The physicochemical tests on TMFC showed that these matrices are of sufficiently high mechanical strength and that they had relatively high uniformity in both weight and dimensions. Release studies showed that although TMFC compared favorably with MCC, TCMC slightly increased cumulative drug released from the matrices compared with non-tronated cellulose and achieved sustained release of acetaminophen in the stomach environment (pH 1.2). This study has shown that TMFC prepared from sawdust *Gmelina arborea* could be used along with paraffin wax in the development of melt-extrusion matrices which could be employed to achieve sustained and targeted delivery of acetaminophen in the stomach

INTRODUCTION

The need for development of appropriate carriers for drug delivery has been a concern for bio-medical and pharmaceutical scientists. Researches into strategies to chemically and/or physically modify the structures of natural polysaccharides and, consequently, their physicochemical properties are gaining increasing interest [1-3]. The importance of polymer modification has increased in recent years, particularly because it shows enhancement of the mechanical properties of the final product, among other benefits [4, 5]. The properties of the final material such as biodegradation rate, adhesion to biological substrates, drug solubility inside the polymer matrix, can therefore be modified and tailored to specific applications [6]. A combination of judiciously selected natural or synthetic polymers and other agents (modifiers) has been found to be useful in controlled release and targeted DDS of a large variety of drugs, tissue engineering, biomedical applications and cancer therapy [4, 5, 7]. Characterization techniques used to establish or standardize the potential applications of modified polymers include structural elucidation, physicochemical, rheological, toxicity and compatibility studies [8-10]. These techniques would enable the establishment of the suitability of generated product thereof in the formulation of various dosage forms of drugs [8-10].

Gmelina arborea, a medium-sized deciduous tree up to 40 m tall and 140 cm in diameter [11], is

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relatively abundant in Nigeria and some other tropical countries, where it is grown either in plantations or ornamentally in private and public places. It can withstand dryness for 6 - 7 months, requires an annual rainfall of 750 - 5000 mm [12] and has been screened for bio-oil production [13]. In Nigeria, *Gmelina* is commonly used for furniture making and as building materials for temporary wood structures as it is considered soft wood in building industry while in agronomy, it is considered a hard wood. This could be attributed to the fact that it belonged to deciduous plant family. And because of its present use, it constitutes large percentage of wastes (sawdust) accruing from the wood industry [13]. This study was devoted to the extraction, purification and tronation of cellulose from the agricultural waste product (sawdust) for pharmaceutical application in sustaining the delivery of acetaminophen, an analgesic and antipyretic drug.

Cellulose, a tasteless, odorless, white crystalline material of linear polysaccharide consistency of several D-glucose units linked together by ß, 1-4 glycosidic bond [14], is the most abundant natural polymer which is used as such or its derivatives in a number of applications, including in paper, packaging or lacquer technologies [15]. It is biodegradable due to acid hydrolysis at high temperature and through enzymatic processes [16, 17] and is obtainable from renewable sources, and, thus acceptable from the environmental point of view. Today, cellulose has revolutionalized tableting technology because of its unique compressibility and carrying capacity. It exhibits excellent property as excipient for solid dosage form as it compacts well under minimum compression pressure. It is also safe and physiological inert [18]. However to reach the required application properties, cellulose has to be modified, mostly by a reaction of hydroxyl groups leading to cellulose esters and ethers [19, 20]. It could also be modified by grafting other materials unto cellulose [21] or by tronation (cross-linking with sodium sesquicarbonate).

Many strategies are available for the design and development of modified-release drug delivery formulations. Conventional oral dosage forms often produce fluctuations of drug plasma level that either exceed safe therapeutic level or quickly fall below the minimum effective level; this effect is usually totally dependent on the particular agent's biologic half-life, frequency of administration, and especially the release rate [22]. Melt Extrusion, the process of embedding drug in a polymeric carrier [23] or the process of converting a raw material into a product of uniform shape and density by forcing it through a die under controlled conditions [24], is an efficient technology for producing solid molecular dispersions with considerable advantages over solvent-based processes such as spray drying and co-precipitation. This technology can provide sustained, modified, and targeted drug delivery [25]. In recent years, hot melt extrusion (HME) is being explored in the pharmaceutical field because it offers several advantages over traditional processing methods [26]. HME may be used to disperse drugs in a given matrix at the molecular level, thus forming solid solutions, and this approach is commonly used for delivery of poorly soluble drugs because of its role in increasing the dissolution, absorption, and therapeutic efficacy of drugs. Also, in the case of transdermal drug delivery systems, at least part of the incorporated drug must be in solution since only drug in solution diffuses from the polymeric patch and is available for absorption [27, 28].

Until recent era trona has been used in food and meat industries but, recently, they are being explored for their other pharmaceutical applications. In an attempt to verify the use of tronated microfine cellulose (TMFC) as polymeric matrix in dosage forms, this research work was initiated. This work was conceived with the sole purpose of transforming the huge heaps of sawdust, which constitutes waste product in our environment, into a useful pharmaceutical raw material. The research was based on the hypothesis that trona (sodium sesquicarbonate) could be able to attack the link between the adjacent glucose moieties in the cellulose molecule (C_1-C_4) [14-21]. Cellulose fibres are highly flexible owing to the partial amorphous character of cellulose. The dual nature of cellulose, that is, its crystalline/amorphous nature explains why it was posited that sections of the amorphous part could be attacked by trona which is a widely established depolymerization agent. The scope of present work is to establish microfine cellulose from *Gmelina arborea* as a pharmaceutical grade excipient, against the commercially used one's like MCC (Avicel), modify the cellulose using trona as an artificial chapron for improved utility in drug delivery, adopting melt extrusion technology. For this purpose, paracetamol which is analgesic and antipyretic drug [29] and paraffin wax which is an established matrix-forming material [30] were selected as a model drug.

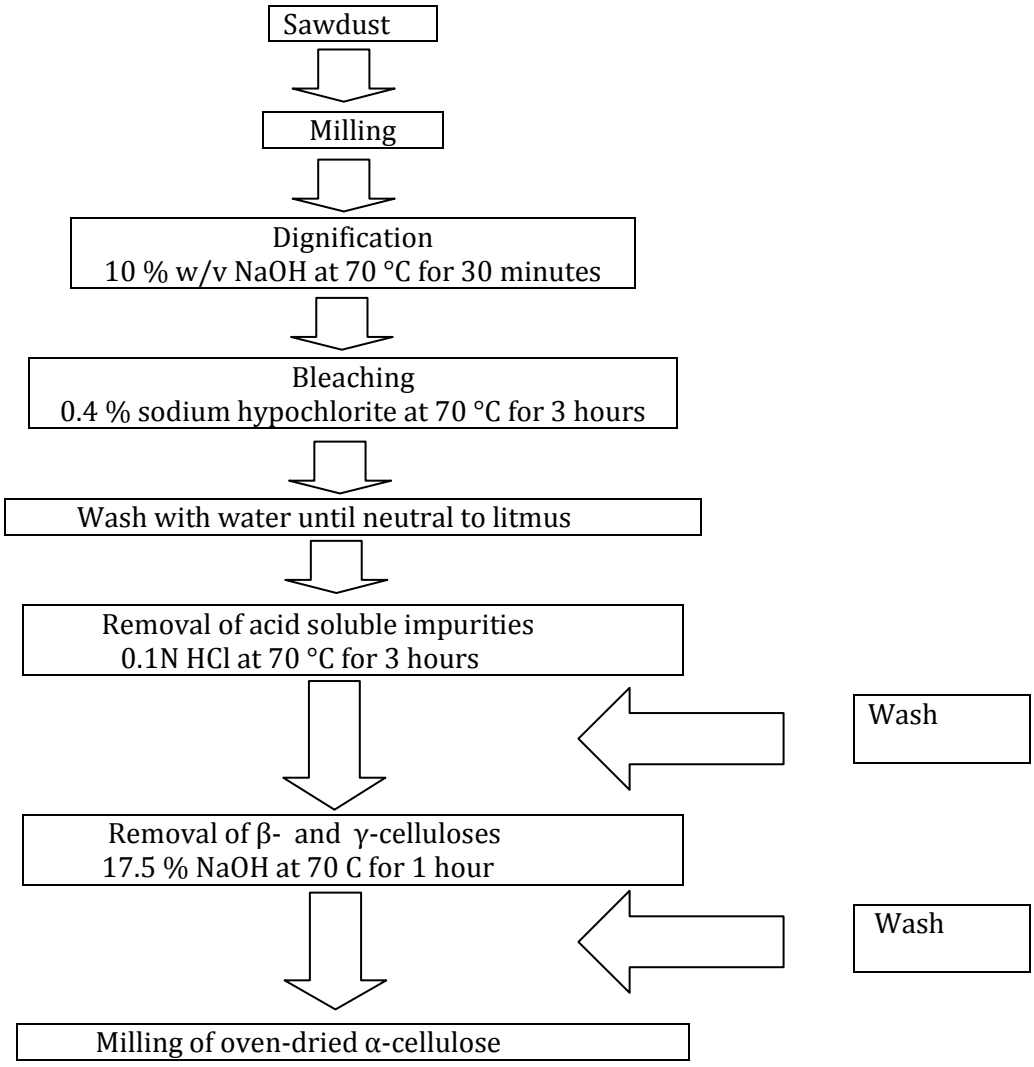


Figure 1: Extraction of cellulose from sawdust.

Thus the objectives of this study were to produce pharmaceutical grade microfine cellulose from the α- cellulose derived from sawdust of the tropical tree *Gmelina arborea* (Family Verbenaceae), using trona as an artificial chapron, evaluate the physicochemical properties of the tronated microfine celluloses (TMFC) compared with Avicel PH101 (Microcrystalline cellulose, MCC), a standard cellulose powder, and to develop melt-extrusion matrices using TMFC and paraffin wax for controlled delivery of acetaminophen.

MATERIALS AND METHODS

Materials

The materials used include microcrystalline cellulose, Avicel PH101 (FMC Corporation, USA), sodium hydroxide, sulphuric acid, hydrochloric acid and acetic acid (BDH, Germany), calcium hypochlorite (Reckitts and Coleman, India). All other chemicals and reagents were analytical grades and were used without further purification. Trona (sodium sesquicarbonate) was processed in the Pharmacy Practice Laboratory, Department of Pharmaceutics, University of Nigeria, Nsukka.

Extraction of α–cellulose from sawdust

Sawdust of *Gmelina arborea* was collected from Timber Shade Market Nsukka, Nigeria, milled using a hammer mill and then subjected to the sequential treatment steps of the classical soda process of wood pulp purification as depicted in Figure 1 to yield high purity α–cellulose.

Tronation of α-cellulose

The α–cellulose obtained above was treated with 1.0 and 5.0 %w/v of trona for 4 and 6 hours at 50 °C and 40 °C respectively. The samples obtained were coded TMFC-1 and TMFC-2 respectively as shown in Table 1. In each case, 20 g of the α–cellulose powder was placed in a 200 ml volumetric flask and 50 ml of trona solution was added. The volumetric flask was then placed on a

thermo-regulated hot plate (Model: EV14, Gerhardt Bonn, Germany). The dispersion in the volumetric flask was then stirred with a Teflon-coated magnetic stirrer at a rate of 50 rpm. Heat was applied and sustained at a pre-determined temperature after which the tronated microcrystalline cellulose (TMFC) was filtered off and washed with deionized water until the washing water was neutral to litmus paper. The final material was then collected and dried at 60 ° C for 4 h in an oven (Gallenkamp OV 880, England).

Percentage yield of α-cellulose

The amount of purified α–cellulose extracted from the sawdust was related to the quantity of the starting material and the percentage yield calculated using equation 1.

$$Yield\ (\%) = \frac{Weight\ of\ pure\ \alpha-cellulose}{Weight\ of\ milled\ sawdust}\ X\ 100 \quad \ldots\ldots (1)$$

Characterization of cellulose powders

Particle size analysis

A small quantity of α-cellulose was placed on a microscope slide and few drops of glycerine added. The resulting smear was then carefully covered with a cover slip, mounted on a photomicroscope (Leica W-6 330-Wetzlar 1, Germany), viewed at a magnification of x100 and the photomicrographs taken using a motican camera mounted on the microscope. The particles viewed were classified into large, medium and small sized particles. The average number of particles in each group was noted. The dimensions of one of the large particles were then determined by counting the number of divisions of the slide occupied by the particles in each case and relating it to the actual dimensions of the particle. The actual particle size in micrometer was ascertained by multiplying the number of divisions obtained by 0.01 mm since each internal division corresponds to 0.01 mm.

Table 1: Cellulose powder samples studied

Sample name	Remarks
Avicel PH101(MCC)	Standard
α-cellulose	Untronated
TMFC-1	Cellulose treated with 1 % trona solution for 4 h at 50 °C
TMFC-2	Cellulose treated with 5 % trona solution for 6 h at 40 °C

It is noteworthy that the particle size of only the α-cellulose powder was studied because it served as the mother material for the production of the tronated microfine cellulose powders.

Solubility determination

Approximately 100 mg quantity of each sample of the cellulose powders was placed in a test tube containing each of the test solvents (cold water, hot water, 0.1M HCl, 0.1M NaOH, tetrahydrofuran and methanol). The powder-solvent mixtures were then agitated and carefully observed for any sign of dissolution. After the preliminary study, a 4 %w/v dispersion of each of the cellulose powders in distilled water was made and subsequently poured into 50 ml volumetric flasks. These dispersions were shaken vigorously and allowed to stand for 24 h. These dispersions were filtered and a 25 ml volume of the filtrate was evaporated to dryness in a pre-weighed dry glass crucible. The weight of the residue reflects the amount of cellulose dissolved in 100 ml of water.

Compressibility

A 1 g quantity of each cellulose powder was compressed on a Manesty F3 tableting machine at a compressional setting of 45 units. The hardness of each of the compacts produced was then determined using a Monsanto hardness tester immediately after compression and after 24 h allowing for elastic recovery.

Densification behavior

A 10 g quantity of each cellulose powder was poured into a 100 ml measuring cylinder and bulk volume was measured. The cylinder was subsequently tapped 50 times from a constant height of 10 cm, the new powder volume was noted and tapping continued for up to 500 taps until there was no further change in the packed (tapped) volume. The ratios of the mass to packed volume, porosity, tapped and bulk densities were calculated.

Swelling volume

Locally fabricated graduated tubes of 20 ml volume (degree of graduation 0.1 ml) were used for this study. A 500 mg quantity of each cellulose powder previously weighed out by means of the Sauter electronic balance was added to 10 ml of distilled water, suspended and fixed in a test tube rack. The powder volume was determined after 60 min and then at hourly intervals until a constant volume was attained.

Moisture content determination

A 5 mg quantity of each powder sample was weighed out and placed in a porcelain dish of known weight. The dish was then placed in an oven (Gallenkamp OV880, England) maintained at 80 °C for 3 h. At the end of the heating period, the dish was removed and cooled in a dessicator containing silica gel. The porcelain dish was weighed, re-heated at 80 °C for a further 1 h, cooled and re-weighed. The heat-cool cycle followed by weighing was continued until there was no further detectable change in weight. The loss in weight corresponding to the moisture content was determined using equation 2.

$$Moisture\ (\%) = \frac{Loss\ in\ weight}{Original\ mass\ of\ powder}\ X\ 100 \quad \ldots\ldots\ldots (2)$$

Equilibrium moisture determination

A 5 g quantity each of the various cellulose powders was placed in a glass beaker and transferred to a relative humidity chamber containing sulphuric acid solutions for maintaining 35, 65, 75, and 100 % RH [31]. After equilibrium, the samples were left in the relative humidity chambers for 24 h after which moisture contents of the samples were measured using the method outlined above (in the preceding subsection). This gave an indication of the equilibrium moisture content of the samples.

Determination of particle true density

The true density (ρ_t) was determined using a 50 ml pycnometer with n-hexane serving as the displacement fluid. The pycnometer was weighed empty using an electronic balance (Sauter, Germany) and its weight was recorded as W_1. It was then filled with n-hexane and re-weighed giving a weight, W_2. The difference in weight was recorded as W_3. A 1g quantity of the cellulose powder was placed in the empty pycnometer, which was then filled with n-hexane. This set-up was then covered and placed in a water bath maintained at 40 °C for 5 min to drive off entrapped air. The pycnometer was then weighed after allowing it to cool for 15 min to give a weight, W_4. The true density of each sample was then calculated by using equation 3.

$$\rho_t(g/ml) = \frac{W_2\ X\ W_3}{50\ (W_1+W_2+W_3-W_4)} \quad \ldots\ldots (3)$$

Where ρ_t is the true density

Determination of browning and charring temperatures

These tests were carried out using standard procedure [32]. A 100 mg quantity of each cellulose powders was put into a capillary tube, which had been previously sealed at one end. The tube was then inserted into the heating chamber of a melting point apparatus (Electrothermal® Fisher Instruments Inc., USA). An enclosed thermometer was used to monitor the temperature changes during the course of the study. The browning temperature was taken to be the temperature at which each of the powders under examination underwent a chromogenic transformation to brown while the charring temperature is the temperature at which the powders charred; that is turned completely black.

Determination of ash value

A 1 g quantity of each powder was placed in a dry weighed porcelain dish which was then put in a heating chamber (Heraeus H. Jurgens and Co. Model M110, Germany) maintained at 500 °C for 2 h. At the end of the heating period, the porcelain dish was cooled and re-weighed. The two-step cycle of heating and cooling was continued intermittently until there was no further detectable change in weight of the residue. The ash value was calculated from the weight of the residue and the original weight of powder. The water soluble ash was also determined.

Determination of pH of slurry

A 2 %w/v aqueous suspension of each of the cellulose powders was prepared in distilled water and the pH determined using a digital pH meter (Electronic Machines Ltd., UK Model 7065, England), after 24 h of storage.

Elemental analysis

A 100 mg quantity of each of the cellulose powders was subjected to elemental analysis to detect trace amounts of some elements following standard methods [33, 34].

Qualitative test for α-cellulose

The test sample was 50 %w/v slurry of α–cellulose prepared and hydrolysed with 72 % H_2SO_4 for 3 h at room temperature. A 5 ml volume of distilled water was then added and the mixture heated on a hot plate (Gerhardt, Model 14, Bonn, Germany) at 100 °C for 2 h. The mixture was then neutralized with 5 ml of 2.0M NaOH and subsequently tested with Fehlings solutions A and B for the presence of reducing sugars.

Test for cellulose

A standard method [35] was employed for this test. The underlying principle of this test is that alpha-cellulose has to be determined in extractive free, lignin-free wood. This test was performed on the holocellulose left after the delignification and bleaching of sawdust pulp. Sawdust powder weighing 2 g was passed through a 250 µm sieve (Gallenkamp, England) and placed in a tarred crucible which was then dried in the oven for 3 h at 80 °C (Gallenkamp Model 880, England). At the end of the heating period, the crucible was cooled in a silica gel filled dessicator. Heating and cooling was continued intermittently until a constant weight was attained. This weight which indicates the percentage moisture content was then recorded and used to calculate the percentage of moisture-free wood.

The specimen of air dry wood (holocellulose) was transferred into a 250 ml beaker provided with a cover plate. A 25 ml volume of 12.5 % NaOH solution was poured into a 50 ml beaker and maintained at 20 °C. A 10 ml volume of this solution was added to the holocellulose in the 250 ml beaker also maintained at 20 °C. The sawdust sample was then manipulated with a glass rod to ensure that the specimen thoroughly soaks up the NaOH solution. The sample was then manipulated with the glass rod after 2 min. Then 5 min after the addition of the first 10 ml portion of 17.5 % NaOH solution, 5 ml was added after 15 min and the sample stirred. The crucible was then allowed to stand for 30 min at 20 °C. After 45 min of caustic treatment, 33 ml of distilled water was added to get 8.3% NaOH. The cellulose was then filtered into a tarred alkali resistant glass crucible and 15 ml of acetic acid (10 % solution) poured into the crucible at room temperature. The set-up was allowed to stand for 5 min to soak up the acid. The crucible was washed with distilled water repeatedly until the cellulose was free of acid as indicated by a neutral pH. The crucible was then dried with a piece of cloth and placed overnight in an oven maintained at 80 °C. The crucible was then removed from the oven and weighed. The percentage of alpha-cellulose was determined using equation 4.

$$Percentage\ \alpha - cellulose = \frac{W_2}{W_1}\ X\ 100 \quad \ldots\ldots (4)$$

Where W_2 is the weight of oven dry cellulose residue and W_1 is the weight of the original oven-dry sawdust samples.

Drug-excipient compatibility studies

Thin layer chromatography (TLC) was used to assess the presence or absence of degradation products of 50:50 mixtures of model drugs and the cellulose powder following their exposure to thermal stress. Mixtures of acetominophen and cellulose powders in the ratio of 50:50 were made and put into neutral glass tubes. The set-up was then stored for 3 days at 75 °C in an oven (Gallenkamp Model 110, England). At the end of the storage period, the chromatographic analysis for degradation products was carried out. The development reagents were chosen based on their demonstrated ability to serve as carriers for acetaminophen [36] as follows: acetaminophen-n-butanol:glacial acetic acid:water (100:22:53). Thin layer chromatographic plates measuring 20 x10 cm were coated with a thin-layer of silica gel (660 BDH), and activated by heating in an oven (Gallenkamp Model 880, England) at 100°C for 1 h. After activation, 100 mg samples of the drug-excipient combinations were suspended in distilled water and used to spot the plates using a micropipette. Suspension of acetaminophen was also used to spot the plates so as to act as reference standard. The plates were subsequently placed in chromatographic tanks containing previously prepared development reagents. The plates were removed from the tanks as soon as the solvent front reached the 15 cm mark. The plates were then dried and carefully scrutinized to identify the locations of the spots of the various samples. The R_f values of the samples were then calculated and used as determinants of drug-excipient incompatibility.

Preparation of waxy matrices

The matrix moulding unit (MMU) (diagram not shown) used for the preparation of the matrices was developed in the Department of Mechanical Engineering, University of Nigeria, Nsukka. It consists of a piece of rectangular Perpex glass sheet having dimensions 12 x 4 cm. The glass sheet has disc-shaped holes drilled into it to a depth of 3 mm and having a diameter of 12 mm. The device is fitted into a polyvinyl chloride (PVC) plastic holder. The plastic material of the matrix moulding device confers many advantages such as high tensile strength and a light weight. Furthermore, the device has the added advantages of being very portable and from the economic perspective, the cost of production is not prohibitive. The MMU is designed to allow for the production of matrices in a single in-line process after a prior mixing stage wherein the components of the desired

matrix are combined in a suitable vessel such as a porcelain dish or a beaker of sufficient volume. This device can be employed in the production of matrices with a wide variety of drug-excipient combinations.

The matrix forming material was put in a 20 ml beaker placed on a hot plate (Gerhardt, Model 14, Bonn, Germany) maintained at 50 °C. After melting the matrix material, the desired quantity of acetaminophen and channeling agent as shown in Table 1 were incorporated into the melt, followed by rapid trituration with a stainless steel spatula. The resulting mixture was carefully poured into the disc moulds in the MMU, which had been hitherto lubricated with glycerine. The MMU was kept in a refrigerator (Thermocool T400, China) for 25 min to allow the melt-drug-channeling agent mixture to solidify. At the end of this cooling period, the MMU was removed from the refrigerator and the matrices carefully extruded from the discs mould and stored in a dessicator filled with silica gel.

Characterization of matrices

Weight uniformity

Twenty matrices were weighed on a Sauter electronic balance and the mean determined.

Friability

This was determined using a Roche friabilitor (Erweka, Type TAR). Three batches of six matrices were put in the friabilator and subjected to a speed of 25 rpm for 4 min. The percentage loss in weight was then calculated.

Drug content of the discs

Three discs of a particular formulation were selected at random and placed in a 250 ml conical flask. The flask was then placed in a hot plate (Gerhardt, Model E14 and Bonn, Germany) maintained at 50 °C. The three discs were melted by gentle heating. Then, 20 ml of acetone was added to the melt-solution to dissolve the fat and 100 ml of 0.1N HCl added followed by rapid agitation. The flask was allowed to stand for 6 h. Next, the contents of the flask were then poured into a separating funnel and allowed to stand for another 2 h. Then 5 ml sample of the aqueous phase was pipette into 100 ml volumetric flask, the volume made to 100 ml with 0.1N HCl and the absorbance of the resulting solution measured at 245 nm for acetaminophen content.

Drug distribution in discs

The test was conducted in order to ascertain the degree of uniformity of drug distribution in the discs. Three discs were cut into four equal parts and the drug content of any three of these pieces which were randomly selected was determined. Each of the pieces selected was weighed separately and placed in a 250 ml-separating funnel. A 20 ml volume of acetone was added and the funnel shaken until all the fat dissolved. The set-up was allowed to stand for 6 h after which 50 ml of 0.1N HCl was added to dissolve the acetaminophen. The funnel was then left standing with intermittent shaking for 12 h. A 10ml volume of the aqueous phase was collected and assayed for drug content at 245 nm wavelength using the Pye-Unicam SP6 450 UV-Vis spectrophotometer.

***In vitro* drug release studies**

Drug dissolution from the melt-extrusion matrices was performed using USP XXII rotating paddle apparatus (Erweka, Germany). Beer's plot for acetominophen at different concentrations was made at a wavelength of 245 nm in 0.1N HCl (pH 1.2). The dissolution medium consisted of 900 ml of freshly prepared 0.1N HCl (pH 1.2) maintained at 37 ± 1ºC. The matrices were securely tied with a thermo-resistant thread and then immersed in the dissolution medium under agitation provided by the paddle at 100 rpm. At predetermined time intervals, 5 ml portions of the dissolution medium were withdrawn, filtered and analyzed spectrophotometrically (Unico 2102 PC UV/Vis Spectrophotometer, USA) at 245 nm. For each sample withdrawn, an equivalent volume (5 ml) of 0.1N HCl maintained at the same temperature was added to the contents of the dissolution medium to maintain sink condition throughout the release period. The amount of drug released at each time interval was determined with reference to the standard Beer's plot for acetominophen in 0.1N HCl. Three replicate release studies were carried out in each case.

Statistical analysis

All experiments were performed in replicates for validity of statistical analysis. Results were expressed as mean ± SD. ANOVA and Student's t-test were performed on the data sets generated using SPSS. Differences were considered significant for $p < 0.05$.

Table 2: Formulation compositions and some physicochemical properties of matrices

Batch Code	Acetominophen (% w/w)	Paraffin wax (%w/w)	Channelling agent (%w/w)	R_f Value of cellulose	Mean weight (mg±SD)	Friability (%)	Drug Content (%)	Higuchi r^2 value
A_1	25	50	25	0.73±0.09	400.10±2.70	0.16	98.46±1.20	0.9464
A_2	25	62	13	0.73±0.09	401.39±6.23	0.22	91.30±0.83	0.9211
A_3	25	69	6	0.73±0.09	399.78±3.56	0.28	95.27±2.24	0.9088
A_4	25	75	0	0.73±0.09	400.90±2.21	0.45	89.52±1.72	0.9950
B_1	25	50	25	0.72±0.12	402.82±4.97	0.18	90.08±0.95	0.8997
B_2	25	62	13	0.72±0.12	401.45±8.06	0.27	92.45±3.56	0.9613
B_3	25	69	6	0.72±0.12	398.70±5.04	0.38	90.89±1.67	0.9123
B_4	25	75	0	0.72±0.12	400.61±9.22	0.44	93.47±2.38	0.9900
C_1	25	50	25	0.71±0.10	402.33±2.55	0.14	91.99±1.99	0.9897
C_2	25	62	13	0.71±0.10	400.77±3.11	0.26	89.43±3.10	0.9993
C_3	25	69	6	0.71±0.10	401.44±1.88	0.29	96.78±3.34	0.9556
C_4	25	75	0	0.71±0.10	400.66±5.49	0.42	94.56±2.11	0.9085
D_1	25	50	25	0.72±0.14	402.90±4.76	0.14	90.22±1.19	0.9458
D_2	25	62	13	0.72±0.14	400.22±8.00	0.25	93.76±2.38	0.9901
D_3	25	69	6	0.72±0.14	401.34±9.22	0.28	96.91±4.00	0.9433
D_4	25	75	0	0.72±0.14	400.56±7.17	0.47	97.55±2.85	0.9466

Where A_1-A_4, B_1-B_4, C_1-C_4, and D_1-D_4 are acetominophen-loaded paraffin wax-based matrices formulated with Avicel PH101, α-cellulose, TMFC-1 and TMFC-2 respectively as channeling agents; r^2= coefficient of determination

RESULTS AND DISCUSSION

The yield (%) of α–cellulose was 11.17 %. The low yield could be attributed to loss of substantial amounts of the starting material in the course of purification to α–cellulose. Some of the α–cellulose was degraded to β– and γ–celluloses which are usually removed by caustic treatment with 17.5 % NaOH. It has been reported that the major loss in the pulping process was that occasioned by the dissolving of lignin, hemi-cellulose and other extractive materials from the wood [37, 38]. Approximately one half of the weight of wood was lost when it was converted into pulp by a chemical process.

Photomicrographs of the cellulose powders revealed the typical highly convoluted morphology of cellulose (not shown). There was insignificant difference in morphology between the standard powder Avicel PH 101 (MCC) and the tronated microfine celluloses (TMFCs). The average particle size range determined for α–cellulose was 50 - 100 nm which corresponds to established standards [39].

Results revealed that the celluloses were insoluble in cold water, hot water, 0.1M HCl, 0.1 NaOH, tetrahydrofuran and methanol. This is in agreement with the fact that cellulose is practically insoluble in water and most organic solvents [40].

These results (Table 3) reveal that the cellulose powders are readily compressible at the compressional force (45 units) studied. The compacts produced are of sufficient mechanical strength. There was a drop in hardness after allowing compacts to stay overnight to allow for elastic recovery. This could be attributed to the uptake of moisture from the environment which led to the weakening of the rigidity of the intermolecular bonds in the compact culminating in the observed decrease in hardness. The comparatively lower values of hardness obtained with the recompressed compacts could be linked to the breakdown of the structure of the cellulose following the application of compressional force. Several studies of the compression properties of microfine cellulose have revealed that it undergoes stress relief deformation by several mechanisms [18-21,41].

Table 3: Hardness values (after compression at a setting of 45 units)

Sample	Immediately	After 24 h	Reworking
MMCC- (Avicel PH101)	16	14	12
α-cellulose	8	6	5
TMFC-1	13	11	9
TMFC-2	12	10	9

Table 4: Some physicochemical properties of the cellulose powders

Powder property	Sample name			
	α-cellulose	MCC	TMFC 1	TMFC2
Bulk volume (ml)	4.24 ± 0.05	3.50 ± 0.011	4.52 ± 0.04	4.57 ± 0.015
Bulk density (g/cm^3)	0.235 ± 0.06	0.285± 0.002	0.272 ± 0.14	0.278 ± 0.009
Trues density(g/cm^3)	1.54 ± 0.012	1.56 ± 0.012	1.53 ± 0.009	1.573 ± 0.024
Water content (%)	4.60 ± 0.022	4.89 ± 0.07	4.85 ± 0.081	4.83 ± 0.052
Ash value (%)				
Total ash	3.25	3.54	3.60	3.58
Water-soluble ash	1.52	1.55	1.54	1.53
pH of slurry	6.25	5.64	8.02	8.59
Browning temperature (^{0})	260	262	222	223
Charring temperature (^{0})	263	263	224	227
Swelling volume (mg/ml)	6.35	4.41	6.10	5.89
Relative increase in weight (%)	27.0	24.0	21.0	27.2

Results of the study of the densification behavior of the cellulose powders and other physicochemical tests are shown in Table 4. The results revealed that insignificant differences existed between the densification behavior of the TMFC samples and standard MCC. Alpha–cellulose showed a higher bulk volume which could be attributed to the fact that it was composed of more amorphous material than the microcrystalline cellulose samples, consistent with previous studies [18-21, 41]. By implication, α–cellulose is less crystalline than the other sample powders. Furthermore, as shown in Table 4, all the cellulose powders swelled appreciably in water, a phenomenon that can be traced to hydrogen bonding between the interacting water and cellulose molecules. Also, MCC showed the lowest equilibrium moisture content while α–cellulose showed the highest. The tronated microfine cellulose powders showed intermediate values.

The hydrolysed cellulose sample gave a brick red precipitate with Fehling's solution A and B thus confirming the presence of a reducing sugar, particularly glucose, in the sample [42].

The samples studied were found to contain 12.68 % alpha-cellulose which is a rather poor proportion. The test however reaffirms the proposition that alpha-cellulose was truly extracted from sawdust.

Results of the elemental analysis are shown in Table 5. These results indicate that the α–cellulose sample employed in this study contains trace amounts of calcium, magnesium, sodium and potassium.

Table 5: Results of elemental analysis of α–cellulose

Element	Percent occurrence
Calcium	0.001
Magnesium	0.016
Sodium	0.050
Potassium	0.007

The results of the TLC studies revealed R_f values shown in Table 1. These values indicate the ratios of the distance moved by the samples of the 50:50 drug-cellulose powder mixture, with respect to the solvent front. It is pertinent to point out that absence of other spots on the chromatographic plate indicates that no degradation products were formed. Furthermore, close inspection of the R_f values revealed that they are within a range of ±0.03 of each other. This observation further validates the ascertion that there was no drug-excipient incompactibility between the test drugs and the sample cellulose powders [36].

Some physicochemical properties of the matrices are shown in Table 1. The results reveal that these matrices are of sufficient high mechanical strength (as shown by the low friability values) and that they have relatively high uniformity in weight. The percentage drug contents of the waxy matrix drug delivery systems were also presented and the result showed high drug content in the matrices. By implication, acetaminophen was properly entrapped by the waxy matrices, consistent with earlier reports on waxy drug delivery systems [43, 44].

The *in vitro* drug release profiles of all batches of the waxy drug delivery systems are shown in Figures 2 - 5. The drug release profiles constitute an invaluable tool for the understanding of the specific features of drug release from the matrix devices [45]. The drug release studies in this work were conducted for 7 h. Drug release from the matrix drug delivery systems occurs principally from the two planar surfaces as well as the annular surface of the discs [46].

The *in vitro* drug release studies revealed that, in general, drug release was retarded by the matrix forming material (paraffin wax). The topographies of the pore network in the discs at the end of the drug release studies are identical. The results indicate that the cellulose powders which are incorporated in the matrices with a view to functioning as channeling agents enhanced the release of the drugs from the matrices. It was obvious from Figures 2-5 that drug release in the presence of channeling agent was higher than in its absence (a situation represented by the blank sample in which no cellulose was included). Also, in all cases, the extent of drug release tended to increase with an increase in the concentration of the channeling agent.

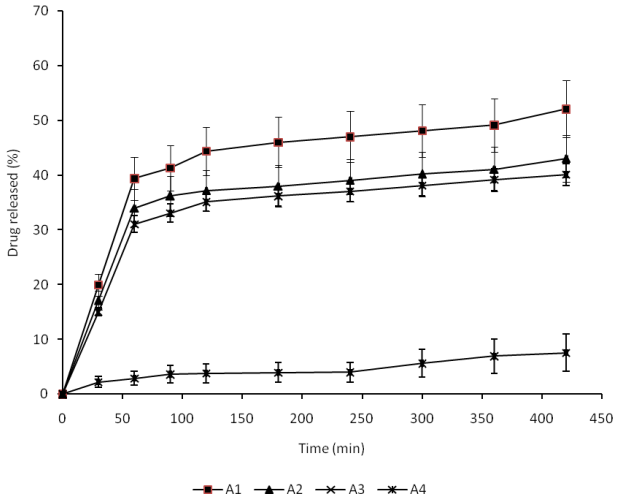
The effect of the matrix materials could be ascribed to differences in the physicochemical properties of the surfaces between the discs. For example, different contact angles between the release medium and the disc surface may occasion dissimilar rates of medium influx into the pore network in the disc culminating in different drug release rates. This has earlier been demonstrated with dika fat and hydroxypropylmethylcellulose matrices [47, 48]. It is noteworthy that the mere presence or creation of pores does not necessarily guarantee release. The chemical nature of the surface (including its hydrophilicity or hydrophobicity) influences drug release [49, 50].

As stated earlier, drug release from matrix devices is greatly influenced by the hydrophobicity of the matrix forming material. Normally, it will take a long time for the release medium to penetrate a highly hydrophobic material to the extent of reaching the core to leach out the incorporated drug. The delay in the release of drug from the matrices would be reduced by the presence of channeling agents in the hydrophobic matrix which facilitates the uptake of the release medium by their channeling action. In the case of cellulose powders, the channeling action is mediated through a swelling process which translates to a wicking action facilitating the uptake of release medium [35].

The relatively higher rate of release of acetaminophen could be traced to its slightly alkaline pH which will engender a high release rate from the matrix into the release medium which is itself acidic [29]. The effect of the channeling agents on drug release from the waxy matrices was investigated in terms of variations in the concentration of the channeling agent on the release rate of the waxy matrices. Increase in the content of cellulose powders at a constant drug concentration in all the waxy matrices led to a marked increase in the release rates of the drug. The cellulose powders brought about an earlier onset of matrix erosion, consistent with previous reports on matrix drug delivery systems [51]. The matrices gave pits on leaching and the higher the concentration of cellulose powder incorporated into the waxy matrices the greater the porosity of the matrices. There was also an increase in the volume fraction accessible (VFA), which determines the rate and extent of drug release from inert matrices [52]. The increase in matrix porosity or volume fraction accessible enhanced the diffusion of the external dissolution medium into the matrix. There was a marked increase in release rate of the incorporated drug with increase in release rate of the incorporated drug with increased percentage of channeling agent. This is in line with similar reported study [53].

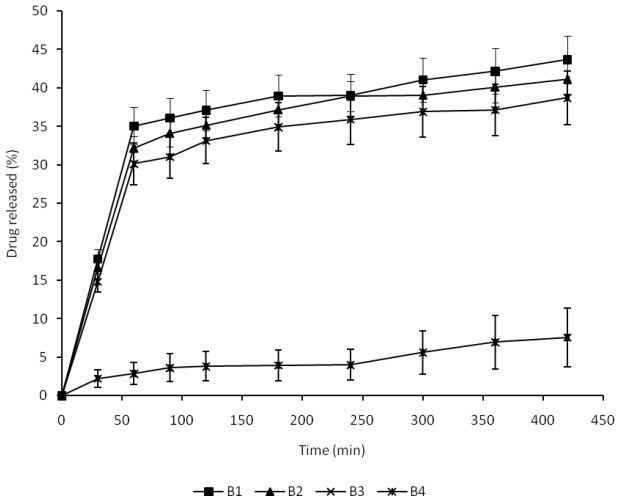
It is discernible from Figures 2 - 5 that the tronated microfine cellulose samples brought about a slight increase in the extent of drug release from the matrices, which could be attributed to the fact that trona caused a slight modification in the surface of cellulose by virtue of its hygroscopic properties [54] and this concomitantly translated to an increase in the swelling volume of cellulose. The cumulative effect of this increase in swelling volume was the slightly higher porosity of tronated microfine cellulose (TMFC) which resulted to a higher cumulative drug released from the waxy matrices.

Acetaminophen is a slightly alkaline drug having a pKa of 9.5 at 25 °C [29]. It is expected to have a high solubility in acidic solutions and neutral solutions and this explains the higher values of cumulative drug released from waxy matrices in 0.1 N HCl (pH 1.2).



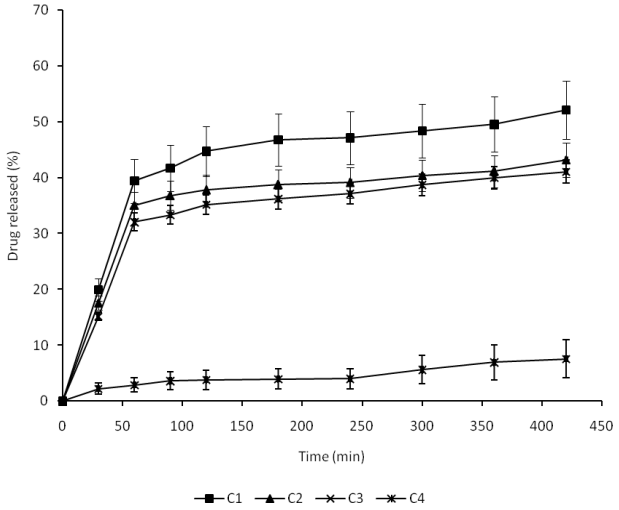
Batches A_1-A_4 are acetaminophen-loaded matrices containing 50 and 25, 62 and 13, 69 and 6, 75 and 0 %w/w of paraffin wax and MCC respectively.

Figure 2: Release profiles of acetaminophen from paraffin wax matrices containing various concentrations of MCC.



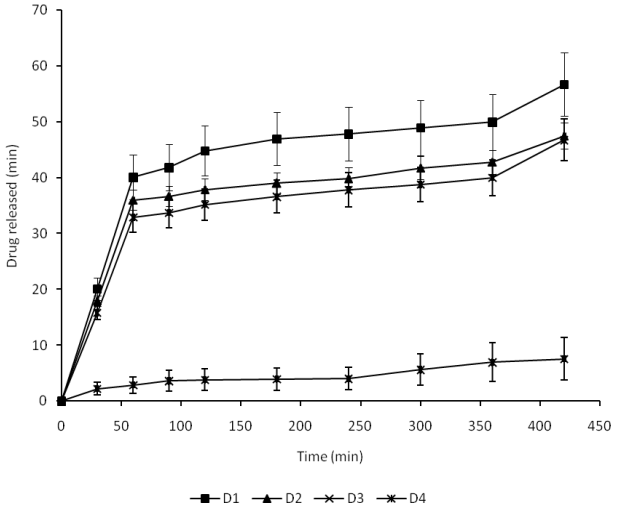
Batches B_1-B_4 are acetaminophen-loaded matrices containing 50 and 25, 62 and 13, 69 and 6, 75 and 0 %w/w of paraffin wax and α-cellulose, respectively.

Figure 3: Release profiles of acetaminophen from paraffin wax matrices containing various concentrations of α-cellulose.



Batches C_1-C_4 are acetaminophen-loaded matrices containing 50 and 25, 62 and 13, 69 and 6, 75 and 0 %w/w of paraffin wax and TMFC-1, respectively.

Figure 4: Release profiles of acetaminophen from paraffin wax matrices containing various concentrations of TMFC-1



Batches D_1-D_4 are acetaminophen-loaded matrices containing 50 and 25, 62 and 13, 69 and 6, 75 and 0 %w/w of paraffin wax and TMFC-2, respectively.

Figure 5: Release profiles of acetaminophen from paraffin wax matrices containing various concentrations of TMFC-2.

The results of the *in vitro* drug release study were fitted into Higuchi kinetic model (cumulative percent released versus square root of time). The kinetic model that best fits the dissolution data was evaluated by comparing the regression coefficient (r^2) values obtained from the plot of the Higuchi square root model, and the result is shown in Table 2. The result indicates that Higuchi kinetic model can be used to explain the release profile of the acetaminophen from the waxy matrices. In other words, a comparative evaluation of the r^2 shows that the release profile followed predominantly Higuchi's model. This implies that the mechanism of drug release involved diffusion, wherein the dissolution fluid penetrates the shell, dissolves the core and leaks out through the interstitial channels or pores [55, 56]. Thus, the

overall release depended on the rate at which dissolution fluid penetrated the wall of the waxy matrices, the rate at which drug dissolved in the dissolution medium and the rate at which the dissolved drug leaked out and dispersed from the surface [57].

CONCLUSIONS

This study has demonstrated that α–cellulose could be extracted from sawdust obtained from a tropical tree with yields of up to 11 % of the total sawdust. The physicochemical properties of the α–cellulose were comparable to Avicel, a standard cellulose. Furthermore, when the α–cellulose that was extracted was treated with various concentrations of trona (sodium sesquicarboante)- a locally available salt, it gave tronated microfine cellulose (TMFC), a novel grade of cellulose, with better physicochemical properties than cellulose. The cellulose produced was employed as a channeling agent in the preparation of waxy matrix drug delivery systems using dika fat (paraffin wax) as matrix forming material for the delivery of acetaminophen. The results obtained from the release studies showed that the tronated microfine cellulose compared well with the standard microfine cellulose in its channeling effect in waxy matrices. These findings indicate that the matrix forming material at three concentration levels (50, 62 and 69 %) ensured controlled release of acetaminophen from the matrices.

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