Journal of Science and Practice of Pharmacy
December 2023; 10 (1): 505-513
Available at http://www.jsppharm.org; https://doi.org/10.47227/jsppharm.v10i1.3
ISSN: 2449-0458 (print); 2449-0466 (electronic)

Original Research Article

Direct compression of diclofenac sodium tablet using modified *Musa paradisiaca* pseudostem cellulose-corn starch polymer alloy

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Abstract

Background: Biomaterials exhibit different functional properties. The aim of this study is to formulate direct compressible diclofenac sodium tablet using modified pseudostem cellulose and starch complex.

Methods: Cellulose was extracted from *Musa paradisiaca* pseudostem and modified using acid-hydrolysis and fermentation techniques. The modified cellulose was evaluated using FT-IR analysis. Avicel pH-101 was used as control cellulose. Micromeritic properties of the modified cellulose were evaluated using tapped consolidation technique. Co-milling heat technique was used to produce polymer-alloy of 21.7, 43.4 or 87.0% of modified cellulose and 78.3, 56.6, or 13.0% dried corn starch respectively. The dried starch or polymer-alloy was blended with diclofenac sodium, co-povidone and magnesium stearate to produce batches A - G. The blends were analyzed for Kawakita densification properties before being compressed to tablets. The physicochemical and drug-release properties of the tablets were evaluated.

Results: Of the dried pseudostem mass, 52.01% and 48.04% of extracted and modified celluloses respectively were obtained. The FTIR study showed presence of cellulose in the pseudostem extract and no interaction between the cellulose and diclofenac sodium. The celluloses had Hausner's ratios < 1.32 and Carr's indices < 23.54%. The polymer-alloy blends showed Kawakita compressibility < 16.34 and compactibility > 489.30. The control tablets passed physicochemical properties tests. The test tablets had hardness > 12.34 KgF, disintegration time > 144.67 min, and released 7.64 - 77.59% drug in acidic to basic medium over 240 min. The result indicates that the pseudostem-cellulose was flow-able, and produced compactible polymer alloys and extended drug-release tablets.

Conclusion: Direct compression of diclofenac sodium with *Musa paradisiaca* pseudostem cellulose-corn starch polymer-alloy produced compact tablets with extended drug release.

Keywords: Acid-hydrolysis, co-milling, compressibility, drug release

Introduction

Though limited in application by the ease of production and purity of synthetic excipients, biomaterials are more acceptable in drug design because they are relatively non-toxic and biocompatible. The source and method of processing biomaterials affect their physicochemical, functional properties, application and performance in different drug designs [1]. The discoveries of new processing techniques, dosage forms and excipients have continued to evolve and advance the design of novel drug delivery systems [2].

Some natural and modified biomaterials such as celluloses have been approved and included in pharmacopeia as excipients for conventional and novel drug delivery systems [3]. Celluloses have been used as adjuncts in improving wet mass plasticity, powder spheronization, direct compression, modified-release matrix

formulation (such as controlled, extended, delayed and other release formulations) and drug pellet formulation; and have been embedded in solid dosage with drug particles as binder, matrix or dry-coat, or deposited over dosage form as reservoir coating or over drug particles to form pellets/beads [4]. Apart from improving drug dosage formulation properties, cellulose in extra-granular embedded matrix and dry-coating materials function as cushioning excipients in soft-tableting of solid dispersions against crushing and damaging effect of compression forces [5].

Musa paradisiaca pseudostem is a biodegradable plant residue with no agricultural or food value [6-8]. The pseudostem has low density, high affinity for water, high moisture content and high cellulose per dry mass content [6]. The pseudostem cellulose has been reported to have good mechanical strength, bonding and other functional properties [7]. These qualities of pseudostem cellulose have attracted research interest in its application as an alternative or novel excipient in drug delivery systems [8].

The objective of this study is to formulate directly compressible diclofenac sodium tablets from a polymer alloy of easily sourced *Musa paradisiaca* pseudostem cellulose and corn starch. Diclofenac sodium, a non-steroidal anti-inflammatory drug (NSAID) was chosen on the basis of its poor flowability, poor compression properties, and medium dose that uses bulk excipient about twice its drug active weight. Direct compression excipients and procedures have been used to handle these drugs' active drawbacks and produce desired dosage forms such as sustained-release diclofenac formulation with minimal side effects in the stomach [1,4].

Ideal direct compressible excipients are free-flowing to ensure rapid automation and homogenous flow; have high dilution potential and good compressibility; are stable and do not age with time nor deteriorate with moisture and air; and when processed or reworked, do not lose their flow nor compressibility properties [9]. Few excipients have complete ideal direct compression properties. This has necessitated combination of complimentary excipients in direct compression. Advanced co-processing techniques have been used to produce direct compression polymer alloy excipients with superior properties compared to simple physical mixtures of their component [10].

Depending on the source and processing technique, the resultant excipient can be homogenous and hydrophilic or porous and hydrophobic excipient. Hydrophilic excipients may dissolve or degrade to release drug, swell to disperse the drug or swell to form hollow diffusion channels for drug to pass through. While the hydrophobic excipient may form rigid non-swellable porous channel for solvation, diffusion and pressured disintegration and release of drug. Drugs may also be released through dissolution-diffusion, ion exchange and osmotic pressure [11].

Materials

A two-year-old *Musa paradisiaca* plant in Okada Farm, Edo State was identified, and its pseudostem was harvested. Diclofenac sodium (Cato Pharmaceutical, China), Avicel® pH 101 (Sigma-Aldrich), corn starch (Bosida Starch Technology, Royi, Hohhot, China) lactose (DEF Pharma, UK), methylparaben (BOC Sciences Daily Chemical, Portland, London) were gifted by Dizpharm Nigeria Ltd Laboratory, Ibusa, Delta State. Other chemical reagents were of analytic grade and were obtained from the Department of Pharmaceutics Laboratory, Igbinedion University, Okada.

Methods

Collection and identification of *Musa paradisiaca* pseudostem

Mr. Amodu Emmanuel, curator of Pax-Herbal Clinic and Research Laboratories Herbarium, Ewu, Edo State, carried out the taxonomical identification of the plantain plant from Okada Farm, where voucher specimen for the plantain plant, *Musa paradisiaca* (Linn) was prepared, labeled Herbarium number PAX/H/2296 and preserved for future references.

Extraction and modification of *Musa paradisiaca* pseudostem cellulose

The method of Prithivirajan *et al.* [7] for the extraction of cellulose was adopted. The pseudostem of the *Musa paradisiaca* (Linn) plant was harvested, cut into small pieces of about 2 to 3 cm, weighed, and soaked at material/liquor ratio of 1:10 in 250 ml of 5.0%v/v nitric acid at room temperature for 24 h. The resultant fibers were washed thoroughly with distilled water immersed in 250 ml 2.0 M hydrochloric acid and boiled for 15 min. The fiber was washed again with distilled water and

transferred to 10 L capacity bottle and distilled water was added to immersion level. The bottles were stoppered with rubber corks and sealed with paraffin wax. After incubating for 7 days, the fluid was decanted, and the fibers were washed with water, and then boiled with 250 ml 1.0%w/w sodium hydroxide for 15 min. The fibers were again washed with 10 L distilled water and neutralized with 150 ml 0.2%v/v acetic acid.

The fiber was then bleached using 250 ml hydrogen peroxide (0.3%w/v) along with 150 ml of sodium hydroxide (0.1%w/v) and 250 ml of sodium silicate (0.15%w/v) as stabilizer at 90-95 °C for 30 min with material to liquor ratio 1:20. The bleached material was washed with 10 L of distilled water, filtered, dried in a hot air oven (Model DHG-9053A, Ocean Medical, England), pulverized in a mortar, passed through a 0.22 mm stainless sieve, weighed, packed, labeled as modified *Musa paradisiaca* pseudostem cellulose (MMPP cellulose), and stored for use.

Cellulose yield

The dry weight of the chopped *Musa paradisiaca* pseudostem and weight of the MMPP cellulose was used to calculate MMPP cellulose yield. The recorded weight of chopped *Musa paradisiaca* pseudostem was estimated to contain 96% water, as reported by many studies including Gupal *et al.* [6].

Fourier transform infrared (FT-IR) spectroscopy evaluation of cellulose

The MMPP cellulose was placed in a sample holder and scanned at room temperature of 4000 - 675 cm^{-1} wavenumber and 4 and 16 cm^{-1} resolutions in a Shimadzu FTIR-8400S Fourier transmission Infrared Spectrophotometer to generate FT-IR spectrum. The generated FT-IR spectra of the samples were analysed.

For compatibility test, 2.0 mg MMPP cellulose was weighed and made up to 200 mg with KBr. The mixture was blended, pulverized and dried at 110°C for 2 h in a hot air oven. The dried mixture was compressed to 80 mg pellet using 13 mm diameter die and 8 tons of pressure for 3 min. FT-IR spectrum was recorded using the KBr disc on a Shimadzu FTIR-8400S Fourier transmission Infrared Spectrophotometer.

The test was repeated for diclofenac sodium powder. A further test was conducted for 2 mg of 1:1 blend of diclofenac sodium powder and MMPP cellulose. All the readings were taken at scan range of 4000 - 650 cm^{-1} with resolution of 4 cm^{-1} and 16 cm^{-1}. The readings were recorded. The spectra from the FT-IR readings for MMPP cellulose, pure diclofenac, and diclofenac-MMPP cellulose blend were analyzed.

Powder consolidation characterization

Ten (10) grams of MMPP cellulose was poured through a dry funnel into a clean dry 50 ml measuring cylinder. The cylinder was gently tapped three times, and the steady volume of the cellulose was recorded as bulk volume. The bulk density of the cellulose was calculated by dividing the sample weight (10 g) by the recorded bulk volume and recorded. The cylinder was then gently tapped from a height of 3 cm on a table surface 200 times. The volume occupied by the cellulose after the 200 taps was recorded as tapped volume. The ratio of the mass (10 g) of the cellulose to the tapped volume was calculated and recorded as the tapped density of the cellulose. Carr's indices and Hausner's ratios of the cellulose were calculated from the bulk and tapped densities using equations 1 and 2

$$\text{Carr's index} = \frac{\text{tapped density} - \text{bulk density}}{\text{tapped density}} \quad \ldots (1)$$

$$\text{Hausner's ratio} = \frac{\text{tapped density}}{\text{bulk density}} \quad \ldots (2)$$

Preparation of starch-cellulose polymer-alloy

The Kinetsol compounding technique of Thompson *et al.* [10] for preparing polymer alloys was adapted. Using the starch–cellulose proportion in Table 1; dried starch and cellulose were mixed with 5 ml of 20 % ethanol and dried in a hot air oven at 60ºC for 30 min. The hot powder was allowed to cool to get a solid polymer alloy. The polymer alloy was milled for 5 min in a Kenwood Multi-mill tube mill (Kenwood Corporation, Hachiji, Tokyo, Japan) and passed through a 250 µm stainless sieve.

Preparation of diclofenac sodium solid dispersion

Diclofenac sodium, crospovidone and magnesium stearate powders were each passed through a 250 µm stainless sieve. The polymer–alloy was blended with the diclofenac sodium, crospovidone, and magnesium stearate powders to create diclofenac sodium–polymer–alloy solid dispersion. The solid dispersion was labeled as A, B, C, D, E, F, or G, and stored for evaluation and compression.

Table 1: Formula used in the preparation of diclofenac sodium tablets

Material (g)	A	B	C	D	E	F	G
Diclofenac sodium	10.00	10.00	10.00	10.00	10.00	10.00	10.00
Dried starch	25.18	20.15	15.13	5.08	20.15	15.13	5.08
Avicel pH 101	0.00	5.03	10.05	20.10	0.00	0.00	0.00
MMPP cellulose	0.00	0.00	0.00	0.00	5.03	10.05	20.10
Crospovidone	0.72	0.72	0.72	0.72	0.72	0.72	0.72
Magnesium stearate	0.10	0.10	0.10	0.10	0.10	0.10	0.10
Total	36.00	36.00	36.00	36.00	36.00	36.00	36.00

NB: MMPP cellulose = Modified Musa paradisiaca pseudostem cellulose

Pre-compression densification evaluation of diclofenac sodium solid dispersion

Ten gram (10 g) MMPP cellulose was loosely poured through a funnel into 10 ml cylinder that has 11.1 mm diameter. The cylinder was tapped with the finger gently three times to stabilize the bulk volume V_0. The volume of the cellulose was noted, after which the cylinder was tapped on a wooden base from a height of 2.5 cm and at the rate of 20 taps per minute in steps of 10 to 100 taps.

The tapped volumes (V_t) of the sample beds after each step were noted and recorded. The readings were used to calculate volume reduction (C_N) at N tap and consolidation factor using equations 3 and 4 of Ilic *et al*. [12]. Kawakita's densification parameters; comprehension behaviour / Carr's index (1/a) and compactibility/estimate of cohesiveness (1/ab) of the cellulose was determined from the slope and y-intercept respectively of the graph of plot of consolidation factor versus number of taps of Kawakita's equation (equation 5) as stated by Ilic *et al*. [12].

$$C_N = (V_0 - V_t) / V_0 \quad \ldots (3)$$

$$\text{Consolidation factor} = N / C_N \ldots (4)$$

$$N / C_N = 1/a\ N + 1/ab \quad \ldots (5)$$

Compression of the diclofenac sodium solid dispersion

The diclofenac sodium solid dispersion was compressed to tablets using a Type F3 single punch machine (Manesty Machines Limited, England). Flat-faced punches and die set (10.3 mm) were fixed on the turret of the machine, and a set of upper and lower punches were fixed to the cramp, and set to produce 360 mg tablet. The machine was operated at compression pressure of 4.0 metric tonnes, and speed number 2. The tablets produced were stored in a desiccator for 24 h awaiting analysis.

Post-compression evaluation of diclofenac sodium tablets

Weight variation: Twenty tablets from each batch were randomly selected and each of the tablets was weighed using the electronic balance (Mettler, Switzerland), and recorded. The entire 20 tablets in the batch were weighed, and the average weight of each 20 tablets was calculated. The variation of each tablet weight from this average weight and the deviation was calculated.

Crushing strength: Using a Monsanto tablet hardness tester (Monsanto Chemical Company, Liverpool, England), the hardness of ten individual tablets per batch was determined by diametric crushing. The crushing strengths were recorded and used to calculate the mean and standard deviation.

Percentage friability: Tablet friability apparatus (Monita, India Corps Limited, India) was used to determine the friability of twenty selected tablets per batch. The twenty tablets were weighed and placed in the friabilator and operated at 25 rpm for 4 min. The tablets were brought out, de-dusted and weighed. The percentage loss of weight was calculated and recorded as tablet friability.

Disintegration time: Six randomly selected tablets per batch were placed in six baskets of a disintegration tester (DT MK4, Manesty Machine Limited., England) containing 1000 ml of water at 37 ℃ and operated at 30 cycles/ mm. The time taken for all the tablets to completely disintegrate through the basket was recorded. The test was repeated thrice, and the mean and standard derivation were recorded for disintegration time.

Dissolution rate: A randomly selected tablet from a batch was placed inside a dialysis bag (Himedia Dialysis Membrane-60, Mumbai, India). The two ends of the bag were bound tightly with cotton threads. The bound bag was hung to an extended stand that lowered into a

1000 L beaker containing 900 ml of 0.1 N HCl solution (pH 1.2) at 37 ± 0.5°C on a magnetic stirrer. The stirrer was operated at 50 rpm for 2 h, and thereafter the beaker was replaced with another 1 L beaker containing 900 ml phosphate buffer pH 6.8 and operated under the same condition for the remaining 4 h. At various intervals during the 4 h operation, aliquots of 5 ml of the dissolution medium were withdrawn and replaced with 5 ml of corresponding fresh dissolution medium. The aliquots were diluted appropriately with the corresponding dissolution medium and their absorbance reading was taken in a UV/VIS spectrophotometer (T70, PG Instruments Ltd) at 276 nm wavelength. The percentage of drugs released from tablets was calculated. The test was repeated in triplicate and the means and standard deviation of the dissolution rate were recorded.

Statistical analysis

Using a One-way analysis of variance, the physicochemical properties of the tablets were analyzed in a Microsoft Excel spreadsheet.

Results

Cellulose yield

The yield of celluloses from extraction and modification is presented in Table 2.

Table 2: *M. paradisiaca* pseudostem cellulose yield

Part	Measure
Pseudostem	5,180.00 g
Dred pseudostem mass	212.38 g
Extracted cellulose	110.44 g
MMPP cellulose	102.04 g
Extracted dry weight yield	52.01 %
Modified cellulose yield	48.04 %

FT-IR cellulose analysis

The FT-IR spectra for MMPP cellulose, diclofenac sodium, and 1:1 dispersion of diclofenac sodium and MMPP cellulose scanned at 4000 - 650 cm^{-1} are presented in Figures 1, 2 and 3 respectively. The spectrum from the 1:1 dispersion of diclofenac sodium (figure 3) in MMPP cellulose maintained the peaks from the MMPP cellulose (Figure 2) and diclofenac sodium spectra (Figure 1).

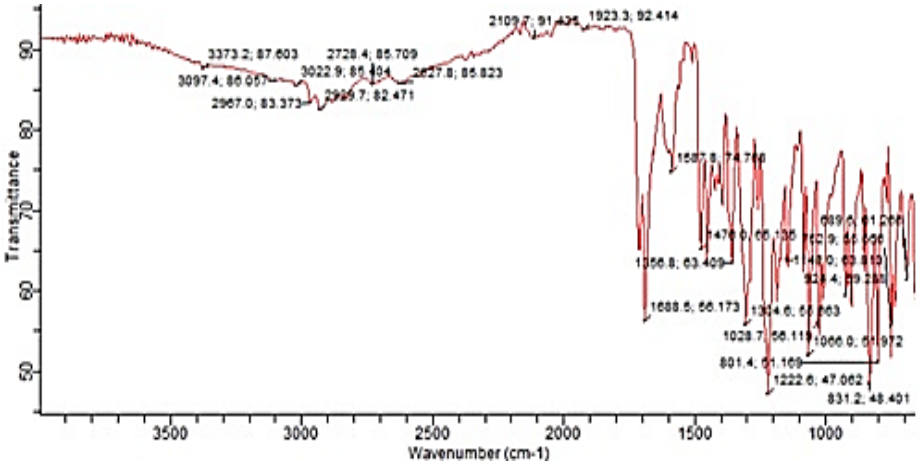

Figure 1: FT-IR spectrum of diclofenac sodium

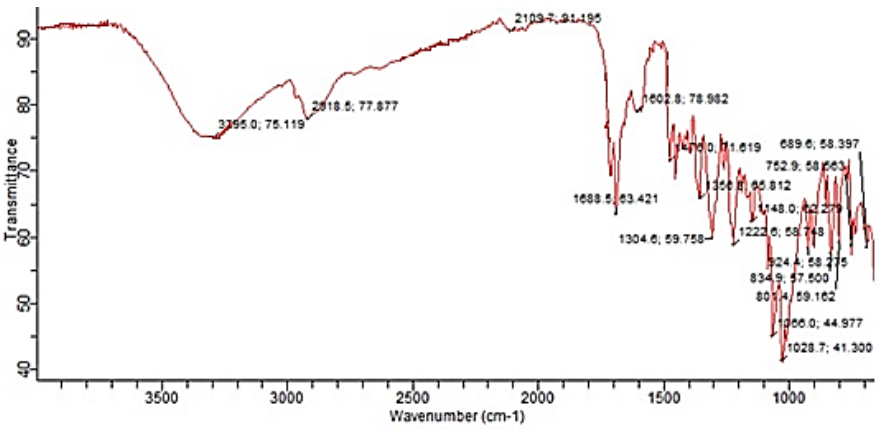

Figure 2: FT-IR spectrum of MMPP cellulose

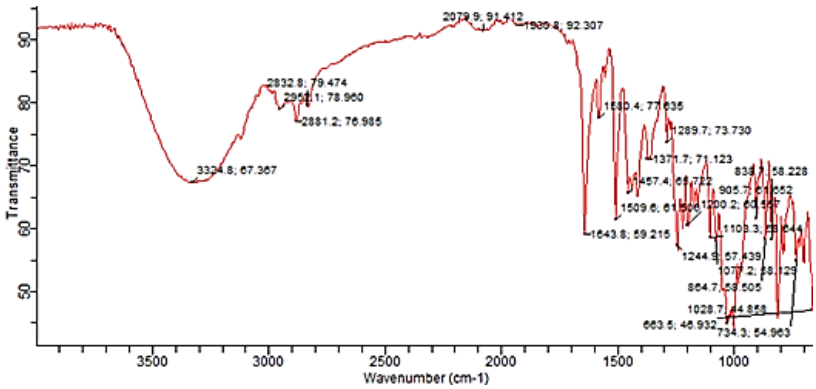

Figure 3: FT-IR spectrum of 1:1 dispersion of diclofenac sodium and MMPP cellulose

Powder consolidation characterization

The tapped powder characterization of MMPP celluloses gave bulk densities (0.51 and 0.37 g/ml), tapped densities (0.60 and 0.49 g/ml), Carr's indices (16.6 and 23.54%) and Hausner's ratios (1.18 and 1.32) for MMPP and Avicel PH 101 celluloses respectively.

Pre-compression densification properties of diclofenac sodium solid dispersion

The densification properties of diclofenac sodium solid dispersion are presented in Figure 4 and used to extract Kawakita's compressibility and compaction properties in Table 3.

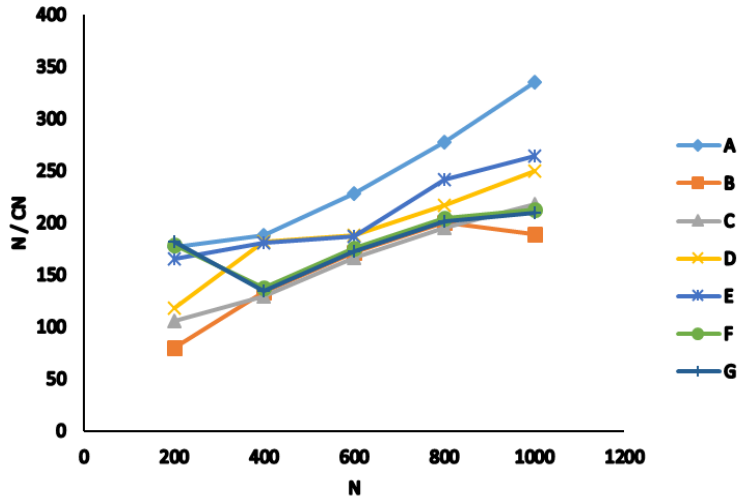

Figure 4: Kawakita's densification plot of diclofenac sodium solid dispersions

Table 3: Kawakita densification properties of solid dispersions

Code	1/a	1/ab	A	1/b
A	0.20	119.00	4.93	586.21
B	0.14	69.48	7.04	489.30
C	0.15	75.59	6.90	521.31
D	0.15	100.91	6.71	677.25
E	0.13	130.40	7.81	1018.75
F	0.07	141.10	14.86	2096.58
G	0.06	143.00	16.34	2336.62

a = maximum degree of compression. 1/b = pressure needed to reach half of the maximum volume reduction

Post-compression properties of diclofenac tablets

The post-compression properties of diclofenac tablet are presented in Table 4 showing moderate tablet hardness (1.07 - 4.13 KgF) and disintegration time (1.17 - 13.33 min.) for starch and Avicel PH 101 tablets, and > 12.4 KgF and 144.67 min. tablet hardness and disintegration time for MMPPC-containing tablets. The drug dissolution rate profile is presented in Figure 5 showing more pronounced extended release for MMPPC-containing tablets.

Table 4: Post-compression properties of diclofenac tablets

Batch	Hardness (KgF)	Friability (%)	DT (min) in pH 2.1	DT(min) in pH 6.8	D_{120} in pH 2.1	D_{240} in pH 6.8
A	1.07 ± 0.61	0.98 ± 0.04	1.17 ± 0.15	-	94.60 ± 0.15	09.12± 0.67
B	2.01 ± 0.43	0.84 ± 0.07	4.33 ± 0.15	-	75.58 ± 0.13	28.29 ± 0.23
C	2.73 ± 0.61	0.91 ± 0.03	8.57 ± 0.15	-	55.85 ± 0.65	42.18 ± 0.65
D	4.13 ± 0.43	0.84 ± 0.07	13.33 ± 0.15	-	21.06 ± 0.92	69.07± 0.21
E	12.34 ± 0.46	0.27 ± 0.12	144.67 ± 0.58	4.50 ± 0.43	20.40 ± 0.39	79.59 ± 0.76
F	12.31 ± 0.42	0.25 ± 0.11	154.91 ± 0.26	7.40 ± 0.14	8.32 ± 0.41	65.77 ± 0.54
G	> 15.00	0.00 ± 0.00	152:42 ± 0.73	8.20 ± 0.32	7.64 ± 0.81	74.93 ± 0.43

± = standard deviation, n = 3.

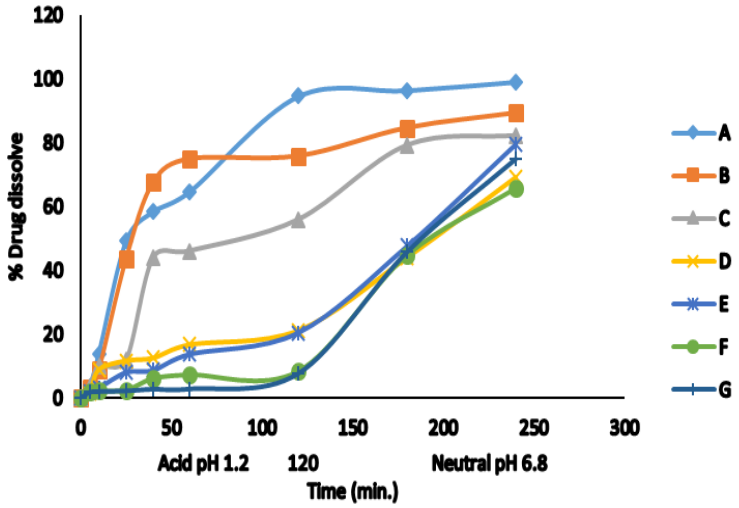

Figure 5: Diclofenac sodium dissolution rate profile in acidic and basic media

Discussion

The 52.01 and 48.04% dried weight yields of extracted and modified *Musa paradisiaca* celluloses respectively are moderate as reported by other researchers such as Gopal *et al*. [6]. Modification of *Musa paradisiaca* pseudostem cellulose to MMPP cellulose by fermentation and acid hydrolysis produced cellulose that is compatible with diclofenac sodium drug active. The MMPP cellulose demonstrated passable flowability for bulk production.

Diclofenac sodium solid dispersions formulated using this MMPP cellulose polymer-alloy and starch produced solid dispersions with good impact-resistant solid dispersions. Upon compression, the solid dispersions produced tablets with excellent mechanical properties, delayed disintegration and dissolution in acid pH, and rapid disintegration and wholesome dissolution in buffer pH.

The presence of broad absorption band between 3500-3200 cm^{-1} in the FT-IR spectrum of MMPP cellulose is indicative of hydroxyl group absorption of water present in cellulose as observed in descriptions by Sain and Panthapulakkal [13]. The presence of 902 – 893,1045, 1105, 1150, 1430-1420, and 2873-2898 cm^{-1} bands are due to cellulosic β-glycosidic linkage, C-O-C pyranose ring, C-O-C glycosidic ether bond, CH_2 scissors vibration motion, and C-H stretching of aryl groups aliphatic bonds respectively of cellulose as observed by researchers. The peak absorption around 2900 cm^{-1} is consistent with observation for cellulose by Shanmugam *et al* [14].

The FT-IR spectrum of the 1:1 dispersion of MMPP cellulose and diclofenac sodium showed no new peak nor trough that cannot be seen in either the pure diclofenac or MMPP cellulose. This indicates that no new chemical compound was formed from the interaction of MMPP cellulose and diclofenac sodium.

The tapped densification results of MMPP celluloses were within 16 – 20 and 1.19 – 1.25 for Carr's index and Hausner ratio respectively indicating fair powder flow. These powder flow properties are critical attributes necessary for

automated and reproducible fill dosages. The increase in compressibility and yield strength from the Kawakita's densification results of the diclofenac sodium polymer-alloy solid dispersions with addition of MMPP cellulose is an indication of non-plastic behaviour of the celluloses as explained in Ilic *et al.* [12].

The higher yield strength with MMPP cellulose-starch polymer-alloy compared with the control Avicel PH 101 cellulose polymer is a result of higher resistance of the denser cellulose materials. Persson *et al*. [15] showed that the higher the yield strength of the material, the harder the expectant compact.

The reduction of compressibility (a) with an increase in the concentration of MMPP cellulose may be a result of their microstructural irregularity and coarsening of cellulose as explained in a study on compressibility [16]. The increase in compressibility (a) with an increase in Avicel PH 101 polymer-alloy can be attributed to its relatively better non-plastic behaviour and metastable state [16]. The polymer alloy of the MMPP celluloses improved tablet hardness and reduced friability. This is in line with the conventional function of cellulose, and true for polymer-alloy as stated in the work of Thompson *et al.* [10] on polymer-alloy.

All the tablets met European Pharmacopoeia [3] specifications for friability and showed excellent mechanical properties. The binding effect of cellulose on the tablet was more pronounced with MMPP cellulose and can be related to the relatively denser solid dispersions created by MMPP polymer alloy in comparison with Avicel PH 101 polymer alloys.

The disintegration times of the tablets increased with an increase in MMPP cellulose concentration and are in line with the binding properties of cellulose as reported in works on cellulose by researchers such as Gohel and Jogani, [9]. Tablets with only starch and those with polymer-alloy of Avicel PH 101 cellulose passed the tablet disintegrated time test (disintegrated within 15 minutes). This is in line with the disintegration properties of disintegrants such as dried starch and Avicel PH 101 as shown in Berardi *et al.* [17].

Tablets with MMPP cellulose polymer-alloy did not disintegrate in pH 1.2 but rapidly disintegrated (< 15 min.) in pH 6.8 buffer medium. This can be related to the tightly compact tablet, dissolution mechanism of MMPP cellulose in neutral to basic medium and release of drug through diffusion and dissolution as reported in experimental studies on dissolution mechanism of cellulose by Dias *et al*. [18] and drug release through polymer coating [11]. The high crushing strength and the slow disintegration of MMPP cellulose polymer-alloy tablets will not be regarded as a problem in extended-release formulation as explained in the in vitro extended-release study by Momoh *et al*. [19] and polymer coating by Kurakula *et al.* [2].

Conclusion

This study shows that extended-release diclofenac sodium tablets can be formulated by direct compression of diclofenac sodium powder and modified *Musa paradisiaca* pseudostem cellulose (MMPP) – corn starch polymer-alloy. The polymer-alloy created a compact that disintegrated and dissolved over a period that stretched from acidic to neutral/basic medium. Using appropriate coating excipient and the modified *Musa paradisiaca* pseudostem cellulose, tablets with extended-release properties that avoid gastric action may be formulated.

Conflict of Interest

No conflict of interest is associated with this work.

Contribution of Authors

We declare that this work was done by the author(s) named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. NDN conceptualized the work, collected data and wrote the manuscript. SE and ICO designed some laboratory processes and read through the manuscript. OAA interpreted identified materials, obtained and interpreted results.

Acknowledgements

We are grateful to Ahmadu Bello University Research Center for allowing us to use their FT-IR. We are grateful to the Department of Pharmaceutics and Pharmaceutical Technology, Dora Akunyili College of Pharmacy, Igbinedion University Laboratory staff that assisted in pseudostem extraction.

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