CELLULOSE NANOCRYSTAL-INCORPORATED CO-PROCESSED EXCIPIENT IN TABLET FORMULATION

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The objective of the current work is to develop a new co-processed excipient based on cellulose nanocrystals and investigate its pharmaceutical excipient properties. Cellulose nanocrystals were isolated from the pseudostem of *Musa balbisiana*, following TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy)-mediated oxidation, and then co-processed with potato starch by the wet granulation method. Physicochemical properties, including the flow property, consolidation characteristics and rate of consolidation, were investigated, and a Kawakita plot was also generated. The compressibility, compactibility and tabletability of the novel excipient were determined. The equivalent circle diameter of the excipient particle was calculated as 4.09±0.90 µm, exhibiting a fair to passable flow property. The mean yield pressure from the Heckel plot was found to be 82.64 MPa, indicating its ability to undergo plastic deformation at relatively lower compression pressures. When compared to sodium starch glycolate, a standard tablet disintegrant, the cellulose nanocrystal-based co-processed excipient produced better dissolution of the model drug paracetamol.

Keywords: *Musa balbisiana* pseudostem, nanocellulose, tabletability, Heckel plot, sustainable excipient

INTRODUCTION

Cellulose and its derivatives have been the most important green and sustainable materials used as functional excipients in drug delivery systems. Traditionally, excipients are considered inert ingredients added to facilitate the manufacturing, administration, and storage of a drug product. Over the years, however, the importance of excipients in lending functionalities to the dosage form, beyond their conventional roles, has become more apparent. Several studies have shown that excipients can be used to control and modulate the release of the active drug, stabilize the product, and increase its dissolution rate, permeability, and bioavailability.[1-4] In addition, the emergence of new drugs, with challenging physicochemical properties, and the evolution of high-speed manufacturing equipment in pharmaceutical industries[5] also established the need for excipients adaptable to the requirements of contemporary industry.

Despite several advancements made in the way drugs are delivered, conventional tablets remain the most commonly used dosage form for drug delivery today, constituting approximately 70% of the drug market.[6-7] The development of novel functional excipients for the present-day state-of-the-art industry is of paramount importance. The three approaches followed in the development of novel excipients include the evaluation of new chemical entities as excipients, the introduction of new grades of existing excipients and the combination of existing excipients, called co-processing.[8] The need for rigorous safety and toxicity evaluation for new chemical entities and exhaustion of candidates for new grades of existing excipients make the relatively simple and cost-effective co-processing approach a promising route for the development of novel excipients.

Co-processing is a process of blending excipients to generate a novel excipient with improved functionality, including flowability, compressibility and disintegration time.[9] During co-processing, two or more established excipients are combined through any one of the suitable manufacturing operations, such as spray drying, wet granulation, co-fusion, co-dispersion, and co-crystallization, to facilitate their interactions at the sub-particle level.[10] Considerable progress has

been made in the development of polysaccharide-based co-processed excipients (CPEs), where cellulose, starch and gum exudates are among the central components. The interaction during co-processing must not bring significant chemical changes, but it should be beyond simple physical mixing to result in a composite material that blends the advantages of the constituent materials to make it more suitable for direct compression tabletting.[7] Therefore, methods, such as spray-drying, co-milling, wet granulation, and co-crystallization, are used in the co-processing of excipients.[5] Several starch- and cellulose-based CPEs, such as Cellactose®, Prosolv®, Starlac®, Microcelac® *etc*., have been developed, combining brittle and plastic materials in various proportions and are available commercially.[6,11] On the other hand, there are also certain commercial CPEs, such as Avicel CE 15®, which combines microcrystalline cellulose and guar gum, and Compressol S®, consisting of mannitol and sorbitol.[6]

While cellulose, both in macro- and microcrystalline forms, is commonly used in the development of CPEs, the potential of cellulose nanocrystals (CNCs) in CPEs has yet to be explored. CNCs, due to their safety, reactive surfaces, varying sources, and sustainability,[12-14] are attractive candidates in the development of functional CPEs for tablet manufacturing. Moreover, CNCs exhibit high surface area, hydrophilicity and swelling properties,[15-16] which are the necessary functional qualities to surpass the cohesive forces of a tablet in effecting tablet disintegration into multiple fragments for dissolution.

Therefore, the formulation of a co-processed excipient based on natural polymers, namely, cellulose nanocrystals and potato starch, is the main objective of this work. Previous studies have shown that chemical similarities between cellulose and starch chains favor their interaction, resulting in good interfacial adhesion between the two molecules.[17-19] Thus, nanocellulose has been used as a filler in the development of several starch-based composite materials.[17,20] In this study, we hypothesize that CNCs would favourably interact with starch, and their inclusion in the CPE would facilitate rapid wetting and swelling of the composite material to intensify and amplify the inherent tablet disintegrant property of starch. In addition, both CNCs and starch are isolated from renewable resources and are biodegradable, and their development into pharmaceutical excipients would contribute to achieving the objectives of the United Nations Sustainable Development Goals in pharmaceutical fields.[21-22]

To the best of our knowledge, a CPE for the direct compression of tablets containing CNCs has yet to be developed and reported. In our previous study, we reported the isolation and characterization of CNCs from the pseudostem of *Musa balbisiana* following mixed-acid hydrolysis[23] and TEMPO- mediated oxidation methods.[24] In the present study, CNCs isolated through TEMPO-mediated oxidation were used in the development of the CPE. *M. balbisiana* was chosen due to its widespread availability and sustainability. We attempt to prove our hypothesis by performing various physicochemical characterization methods. We also investigate the compression, compactibility and tabletability characteristics of the new CPE. Furthermore, the consolidation and rearrangement characteristics, along with the flow properties, were investigated, and Kawakita plots were also generated. Different functional properties of the new CPE in tablet formulation, such as disintegration efficiency ratio, were also investigated.

EXPERIMENTAL

Collection of materials

The pseudostem of *Musa balbisiana* was collected from Aizawl, Mizoram, in India, and air dried after cutting into small pieces, and cellulose was isolated,[23] as shown in Figure 1. CNCs were isolated from the extracted cellulose following TEMPO-mediated oxidation, as reported by Saito *et al*., which was then ultrasonicated.[24-25] The presence of heavy metals in the cellulose sample was analyzed using atomic absorption spectroscopy (AAS, iCE 3000, ThermoFisher Scientific). Antimony (Sb), cadmium (Cd), copper (Cu), iron (Fe), lead (Pb) and zinc (Zn) were determined. All other reagents and chemicals used in the experiments were of analytical grade and were used as supplied, without any further purification. Avicel PH101 (Fluka Analytical, Sigma-Aldrich, Germany) was obtained as a gift from the Department of Pharmacy, RIPANS, Mizoram. CNCs were obtained and stored as a suspension/gel in aqueous solvent with a solid content of 5.56% w/w until further use. All the chemicals used, other than Avicel PH101, were obtained from CDH, New Delhi.

Preparation of co-processed excipient

CNC-based CPE was prepared by the wet granulation method, and the different formulations are given in Table 1.

Figure 1: *Musa balbisiana* in the wild, the pseudostem and suspension of the isolated cellulose nanocrystal

Table 1
Formulation and characterization of granules and prepared tablets

Formulation	Characterization parameters									
	Amount (% w/w)		Carr's index	Hausner ratio	Angle of repose (θ)	Density (g/cc)	Tablet properties			
	CNC	Starch					Hardness (N)	Friability (%)	D.T. (s)	T.S. (MPa)
O	0	100	25.6±0.6	1.34±0.01	30.96±2.9	0.612±0.02	49.67±1.49	0.24±0.15	30±1.2	0.461±0.02
A	2	98	16.6±2.1	1.20±0.22	23.98±1.2	0.620±0.02	47.67±4.16	0.25±0.11	30±5.2	0.384±0.07
B	4	96	24.0±1.4	1.31±0.31	24.89±1.1	0.609±0.01	78.33±2.08	0.34±0.02	40±4.5	0.627±0.06
C	6	94	25.4±2.3	1.34±0.26	26.49±0.9	0.595±0.04	82.67±4.73	0.46±0.06	40±2.1	0.752±0.04
D	8	92	19.5±2.7	1.24±0.18	25.33±1.3	0.619±0.01	84.33±2.52	0.36±0.18	40±4.2	0.756±0.04
E	10	90	22.2±1.2	1.28±0.22	24.69±1.2	0.591±0.03	115.7±5.68	0.22±0.05	36±5.7	0.797±0.04

*D.T. = Disintegration time; T.S. = Tensile strength in MPa

The required amount of potato starch was taken in a mortar, and then the right amount of CNC suspension/gel was added to it. Granulation was performed by kneading using a mortar and pestle, with the addition of a small amount of water. The endpoint of the granulation process was achieved when the wet components formed an agglomerate, but just crumbled upon touching. The wet mass was then passed through sieve number 22 and then dried in a hot air oven at 50 °C for 24 h.

Characterization of the co-processed excipient

Particle size and morphological study

To study the morphology of the prepared co-processed excipient, the size and shape of Formulation E were analyzed using an optical microscope (Primostar, Zeiss) at 10X magnification. The area and perimeter of the particles were collected from the software, from which the equivalent circle diameter (ECD) was calculated.[26]

$$ECD = 2\sqrt{\frac{A}{\pi}} \quad (1)$$

Micromeritic properties

After taking 5 g of the CPE sample and pouring it into a measuring cylinder, the bulk density was determined from the ratio of the mass to the volume it occupied. The cylinder was tapped until the volume of the sample was constant, and then the tapped density was calculated. The liquid displacement method using xylene as a displacement liquid was followed in the determination of the true density. The porosity of the samples was calculated from the following equation:[26]

$$Porosity = \left(1 - \frac{V_{true}}{V_{bulk}}\right) x\,100 \quad (2)$$

where V_{true} and V_{bulk} represent the true volume and bulk volume, respectively.

To determine the flow property of the CPE samples, Carr's index (CI), Hausner's ratio (HR) and angle of repose (AR) were experimentally determined from the following equations:[26]

$$CI = \frac{Tapped\ density - Bulk\ density}{Tapped\ density} x\,100 \quad (3)$$

$$HR = \frac{Tapped\ density}{Bulk\ density} \quad (4)$$

$$AR = tan^{-1}\frac{h}{r} \quad (5)$$

where h is the height of the powder pile and r is the radius of the pile during AR determination.

FTIR study

To characterize and assess the interaction between the granulation components, FTIR spectroscopy was performed (Spectrum Two FTIR Spectrophotometer, Perkin Elmer). Formulation E (10% CNC) was taken, and the transmittance was recorded between 500 and 4000 cm^{-1}. FTIR spectra were recorded for the CPE, potato starch and cellulose samples.

TGA study

Thermogravimetric analysis was also performed on the CPE, potato starch and cellulose samples to investigate their thermal stability and detect any possible signs of degradation due to co-processing. Analysis was performed using a TGA 4000 (Perkin Elmer, Germany) between 35 °C and 800 °C, while maintaining nitrogen purging at 20 mL/min. Approximately 5 mg of the samples were taken for each analysis, and the thermograms were recorded for CPE, starch and nanocellulose samples.

Kawakita plot

To evaluate the packing and rearrangement characteristics of the new CPE, a Kawakita plot was developed following the method previously reported by other authors.[27] Briefly, 10 g of the excipient (CPE) was taken in a 100 mL measuring cylinder, which was tapped 100 times. At 20, 40, 60, 80 and 100 tappings, the volume of the excipient for each ratio was recorded. From the volume against the number of tappings, a Kawakita plot was generated, and the packing and densification were characterized further:[27]

$$\frac{N}{C_N} = \frac{1}{a}N + \frac{1}{ab} \quad (6)$$

where $C_N = \frac{V_0 - V_N}{V_0}$.

In the above equation, V_0 and V_N signify the initial volume of the excipient and after N number of tappings, respectively. Plotting N/C_N vs N produces a straight line from which constants a and b were determined. From the slope $1/a$, the constant a was calculated, which also indicates Carr's index value, and the intercept on the y-axis can be used to calculate $1/b$, which represents the cohesiveness of the excipient powder/granules.

Consolidation index and rate of consolidation

The consolidation index and the rate of consolidation can be used to correlate the applied force and the relative decrease in powder volume and density. A previously reported method,[28] was followed in their calculation:

$$log\,(\rho_{td} - \rho_{bd}) = K log N + C \quad (7)$$

where K is the rate of consolidation and C represents the consolidation index of the granules. N implies the number of taps, and ρ_{td} and ρ_{bd} are the tapped density and bulk density of the granules, respectively. A plot of $\rho_{td} - \rho_{bd}$ against N was generated to determine the values of K and C.

Preparation of tablets

The compression and compaction properties of the newly prepared co-processed excipient and their properties as tablet disintegrants were evaluated by preparing a tablet containing 800 mg of the co-processed excipient. The required amount of the dried co-processed excipient was taken in a mortar and

blended for 5 minutes, using a spatula, with the required amount of magnesium stearate and talc as lubricant and anti-adherent, so that there is 1% each for magnesium stearate and talc for every 800 mg of the tablet. Tablet compression was performed at 4 tons compression force using a single rotary tablet press (Lab Press LP-1, Shakti Pharmatech, India) equipped with a 16-mm flat face punch. The basic quality control tests for tablets, including weight variation, friability, disintegration time and compact hardness, were determined for each tablet prepared with different formulations of the nanocellulose-based co-processed excipient.

To investigate the influence of the CPE on the dissolution of the active ingredient, 800 mg paracetamol tablets containing the CNC-based CPE as a test disintegrant and sodium starch glycolate as a standard disintegrant were prepared. The tablets were prepared to contain 800 mg paracetamol and 10% disintegrant with 1% each of talc and magnesium stearate. Granules were prepared by the wet granulation method as described previously, and after drying, tablets were prepared by compression at 4 tons.

Tensile strength

To determine the tensile strength (T) of the prepared tablet, the following equation was followed in its calculation:[29]

$$T = \frac{2F}{\pi dt} \quad (8)$$

where T is the tensile strength of the tablets, F is the tablet's breaking strength expressed in Newtons, and d and t are the diameter and thickness of the tablets in cm, respectively.

Heckel plot (compressibility profile)

The Heckel plot provides insight into the compressibility of the co-processed excipient, and it was generated for Formulation E (10% CNCs). After talc and magnesium stearate were added at 1% each to the formulation, 800 mg tablets were prepared at different compression forces (2, 3, 4 and 6 tons) using a 16 mm flat face punch. The prepared tablets were then evaluated for their solid fractions at different pressures, and a Heckel plot was then generated through the following equation:[29,30]

$$ln \frac{1}{1-D} = KP + A \quad (9)$$

where D indicates the relative density of the tablet at the applied pressure, P is determined from the ratio of the tablet's density to the true density of the powder, K is the slope determined from the straight-line portion of the Heckel plot and the mean yield pressure, and Py is calculated by taking the reciprocal of the slope.

Compactibility profile

To assess the compactibility of the CPE, a compactibility profile was investigated. Compactibility relates the tensile strength of the tablet with its porosity or solid fraction. The Rhyskewitch-Duckworth equation, as given below, was used to develop a plot of tablet tensile strength T against its solid fraction or porosity:[31,32]

$$logT = k \times (S.F) + A \quad (10)$$

where A and k are empirical constants, and $S.F$ is the solid fraction or the compact porosity.

Tabletability profile

Tabletability is the term used to denote the relationship between the tensile strength of a tablet and its compression pressure.[32,33] To investigate this profile, tablets (Formulation E, containing 10% CNCs) prepared as per the procedures described in the Heckel plot section were taken, and their tensile strength was determined. A plot of tablet tensile strength, T, against compression pressure, P, was developed as per the following equation:

$$log\, T = K log P + B \quad (11)$$

where K and B are empirical constants.

Lubricant sensitivity

To determine the lubricant sensitivity (LS) of the co-processed excipient prepared, Formulation E was lubricated with 1% (w/w) magnesium stearate, passed through 22 mesh sieves, and compressed into 800 mg tablets at 4 tons compression force. The co-processed excipient without magnesium stearate lubricant was also compressed in a similar fashion, and LS was calculated by the following equation:[26]

$$LS = \frac{H_0 - H_{lub}}{H_0} \quad (12)$$

where H_{lub} and H_0 are the hardness of the tablets prepared with and without lubricants, respectively.

Disintegration efficiency ratio (DER)

The DER relates the mechanical properties of the tablets to their disintegration properties and can be calculated from the following formula:[34]

$$DER = \frac{C_a/F_r}{D_T} \quad (13)$$

where C_a indicates the crushing strength of the tablets and percent friability is denoted as F_r, while D_T signifies the disintegration time for the tablets. The DER for tablets prepared from Formulation E compressed at different compression pressures was determined and compared.

***In vitro* dissolution performance**

The dissolution study was performed in a single-stage dissolution apparatus (IP Type I, Paddle type at 50 rpm) using 900 mL of phosphate buffer (pH 6.8) maintained at a temperature of 37±0.5 °C. Samples were withdrawn after 30 minutes and filtered, and the absorbance was determined at 242 nm using a UV-Vis spectrophotometer (UV-1280, Shimadzu, Japan). The percent dissolution of the active drug paracetamol after 30 minutes was then compared between tablets

prepared with CNC-based CPE as a disintegrant and those prepared with standard sodium starch glycolate (SSG).

Statistical analysis

All statistical analyses were performed using Microsoft Excel software (Microsoft 365). Data are expressed as the means ± SD, and the results were taken from independent experiments performed at least in triplicate. *p* values of 0.05 or less were considered statistically significant.

RESULTS AND DISCUSSION

Physicochemical characteristics

AAS analysis of the cellulose sample shows the presence of Cu, Pb, Fe, and Zn, however, Cd and Sb were not detected. The concentration found for Cu was 0.0489 ppm, for Fe – 1.158 ppm, Pb –0.7865 ppm and Zn – 0.7615 ppm. For drugs and excipients, Pharmacopoeias set permissible limits for metals and metalloids. The general limit for these metals is about 10 ppm.[29] The concentrations of these heavy metals, especially Pb and Cu, were found to be within the limit and Cd was not detected. Therefore, the cellulose source was deemed to be safe for pharmaceutical applications.

The CNC-potato starch-derived co-processed excipient was prepared successfully following the wet granulation method. Different formulations were prepared as given in Table 1. Interspecies and intratissular variability in starch granule shape and size has been reported, with sizes ranging from 1 µm to over 100 µm.[35] In the investigation of the particle size of Formulation E, the average area and perimeter of the particles were 13.74±6.73 μm^2 and 12.7±2.83 µm, respectively. The equivalent circle diameter of the particle was calculated as 4.09±0.90 µm. The average area and perimeter of the starch particles were found to be 3.80±1.86 μm^2 and 6.71±1.50 µm, respectively. The equivalent spherical diameter for starch particles was 2.14±0.51 µm. On investigating the morphology of the prepared excipient, the particles were found to be mostly spherical in shape (Fig. 2). The granulation process resulted in an increase in the particle size of the powder.

Powder flow is affected by various factors, including porosity, density and surface texture, including the shape and size of powder or granules.[36] To investigate the flow properties of the newly co-processed excipient, different micromeritics attributes were evaluated. The Carr's index and Hausner ratio values, along with the angle of repose, are provided in Table 1. The Carr's index of the co-processed excipient was found to be between 16 and 25, and the Hausner ratio – between 1.20 and 1.34. Depending on the formulation, the angle of repose lies between 23 and 31. Powder flow and packing properties are important in pharmaceutical tablet preparations, because they influence the consistency of powder/granule die-filling, which will in turn affect the uniformity of tablet weight during manufacturing.[37] Bulk and tapped densities are simple indices of powder or granule flowability. Higher bulk density indicates powder cohesiveness, while lower bulk density is an indicator of higher porosity, which facilitates compressibility but may weaken the flow property of the powder.[30,38] The Hausner ratio and Carr's index, the main indicators of powder flowability, are also calculated from bulk and tapped densities. The Carr's index and Hausner ratio observed for the co-processed excipient fall between fair and passable scale of flowability, as per the USP 1174 Powder flow indicator. However, the angle of repose found between 23 and 26 falls within excellent flow, and 30.96 – obtained with the starch granules, falls in the region between excellent and good flow. Co-processing of starch with CNCs resulted in a significant change in Carr's index ($p = 0.00042$), along with the angle of repose ($p = 0.0019$), while there was no significant change in the Hausner ratio (P = 0.9858), friability ($p = 0.1515$) or disintegration time ($p = 0.0653$) with co-processing.

FTIR spectroscopy was performed, and the spectra of all three samples are depicted in Figure 3. All the samples exhibit typical polysaccharide FTIR spectra. Generally, the region between 1200 cm^{-1} and 800 cm^{-1} is considered the fingerprint region for polysaccharides.[39] Tracing the peaks of all the samples, including the formulated granules, exhibited similar bands of absorbance, but to a slightly different intensity.

The lack of appearance of new peaks suggests the formation of no new covalent bonds or new functional groups during the process of granulation.[40] A strong and broad band with peaks at approximately 3263 cm^{-1} is observed in all three polysaccharide samples, and this band is assigned to the stretching vibration of abundant -OH in polysaccharides. This may result from the presence of moisture in the samples, and the broadest band was observed in the formulated granules. The vibration band observed at

approximately 2928 cm^{-1} in all the samples is attributed to the stretching vibrations of skeletal -CH and -CH_2 in polysaccharides.[39] The C-O bending vibration associated with the -OH groups is observed at approximately 1633 cm^{-1} in all the samples, but with slightly different intensities. A band assigned to the C-O stretching vibration is observed at 1149 cm^{-1}, and the bands at 1052 cm^{-1} and 991 cm^{-1} may be attributed to the C-O-C pyranose ring skeletal vibration.[41] As the formation of no new peaks was observed and the characteristic diagnostic peaks of polysaccharides were observed in the formulated granules, the molecular interaction between starch and cellulose could be mostly hydrogen bonding. This was also supported by the findings reported previously.[40]

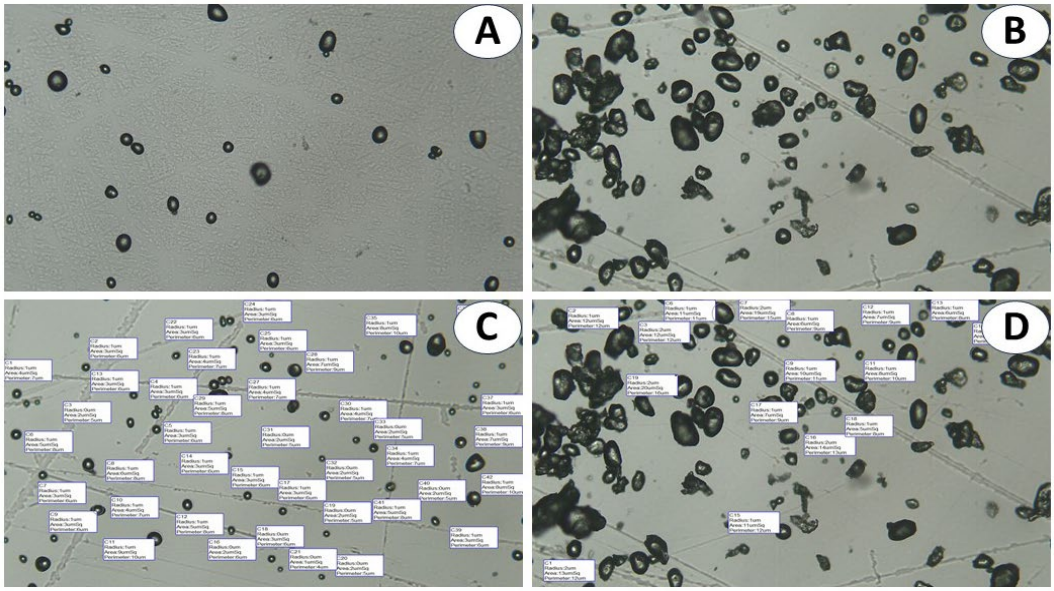

Figure 2: Photomicrographs of potato starch (A and C), and CNC-based co-processed excipient (B and D)

The thermal properties and stability of nanocellulose, starch and Formulation E, as investigated by TGA-DSC, are depicted in Figure 3. Compared to both starch and CPE, nanocellulose exhibited higher thermal stability. All the samples show a multistep event of degradation, which is characteristic of polysaccharide thermograms.

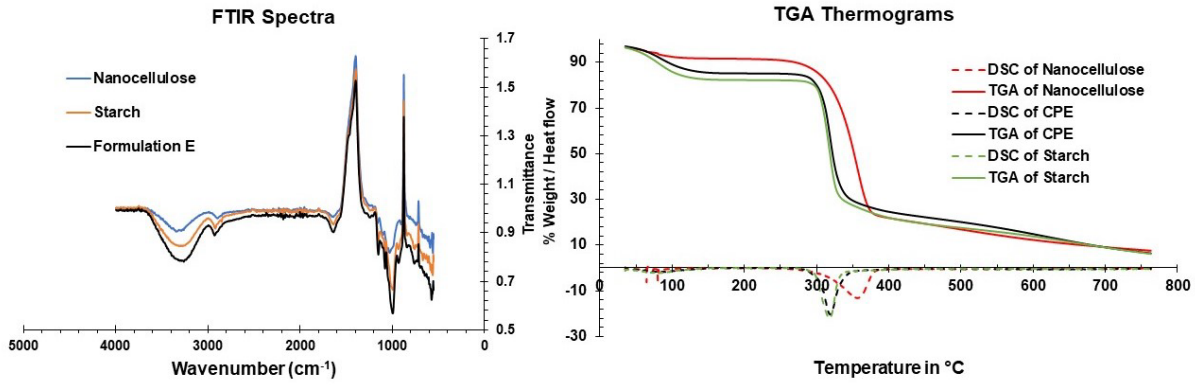

Figure 3: FTIR spectra and TGA thermograms of the samples

On tracing the thermogram, the first thermal event takes place at approximately 50 °C in all the samples characterized by the material's weight loss, which continues until approximately 120 °C. This weight loss can be attributed to the moisture content or the loss of loosely bound water, and at

approximately 120 °C, such bound or chemisorbed water is mostly evaporated.[23] The extent of weight loss differs among the different materials. At 120 °C, a weight loss of approximately 8% was observed in nanocellulose, while approximately 13% and 16% weight losses were observed for the CPE and the native potato starch, respectively. This weight loss corresponds well with the moisture content determined for the CPE and the moisture content of potato starch stated in the literature. After a gradual weight loss, a significant second thermal event occurred at approximately 300 °C, and a sharp weight loss was observed in all the samples. The weight loss was much more rapid in both the native starch and the CPE, while it took a relatively longer time in the nanocellulose sample. This sharp weight loss is attributed to the pyrolysis of crystals involving various decomposition–gasification processes.[23] As evident from the corresponding DSC curves, the maximum degradation temperature (T_{max}) occurred at 317 °C, 319 °C, and 358 °C for the native starch, the CPE and nanocellulose. This shows the enhanced thermal stability of the CPE compared to the native starch. The temperature of 50% weight loss was found to be 318 °C, 322 °C, and 351 °C. By the end of the analysis, at approximately 762 °C, approximately 6% weight remained in all the samples. Results from the TG-DSC analysis showed that co-processing resulted in slightly increased thermal stability of the native starch and corroborated the moisture content determined for the samples.

Figure 4 shows the Kawakita plots for the different formulations of the co-processed excipient and the potato starch alone. The ‘a’ and ‘1/b’ values obtained from the Kawakita plots of the various formulations are given in Table 2. The ‘a’ value that ranges between 0.164 and 0.360 closely agrees with the Carr’s index values obtained. The Carr’s index value of 21% or the ‘a’ value of 0.21 has been considered as the limit value between good and bad flow powders, where no problems in tablet manufacturing were observed for powder with ‘a’ value below 0.21.[27] The rearrangement and consolidation of the particles under the applied tappings are characterized by Kawakita plots. The values of ‘a’ and ‘1/b’ determined from the plots are indicative of Carr’s index and cohesiveness of the powder granules, respectively.[27] Lower values of ‘a’ represent closer packing of the powder granules; however, they are not considered to be conclusive evidence of the packing and rearrangement characteristics.[28] The ‘1/b’ value indicates the cohesive energy of interaction, and a higher value of 1/b is considered to disrupt the particle rearrangement during compression. A good correlation was generally observed between the ‘a’ and ‘1/b’ values.[27] However, the correlation was not remarkable in the current study, which indicates the complexity of factors that may contribute to the particle-particle interactions among the samples.

The consolidation characteristic of the powder granules was determined from the consolidation index (C) and the rate of consolidation (K), which are calculated from the plot of log of density changes against log number of taps. K is an indication of the rate of packing of powder, while C stipulates the effect of packing on flow; the higher this index is, the higher the flow properties of the powder.[42] The analysis of these indexes showed that there was a difference in the rate of consolidation and the consolidation index, but the difference was not statistically significant (p>0.05).

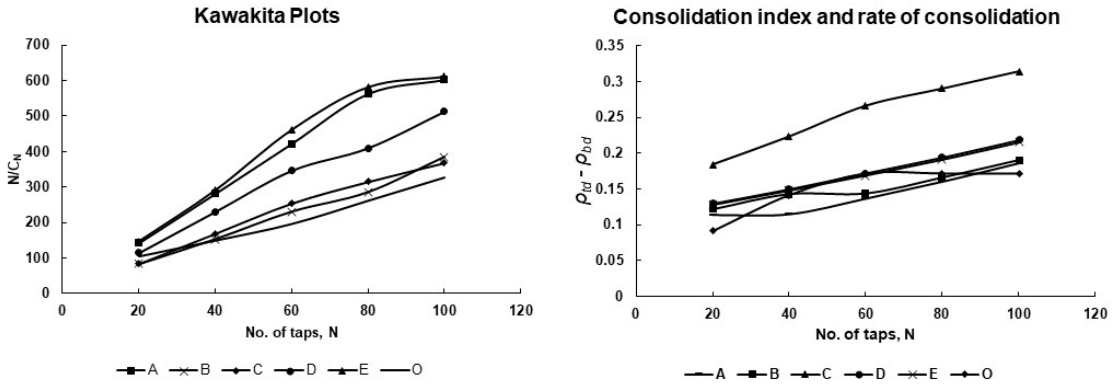

Figure 4: Kawakita and consolidation plots of different formulations

Table 2
Calculation of 'a' and '1/b' values from Kawakita plots and rate of consolidation and consolidation index values

Formulation	'a' value	'1/b' value	'K'	'C'
O	0.360	14.6	0.0009	0.092
A	0.167	8.62	0.001	0.0837
B	0.272	1.99	0.0008	0.1051
C	0.281	6.97	0.0016	0.1573
D	0.205	6.43	0.0011	0.1068
E	0.164	8.62	0.0011	0.1051

Both values increase with increasing CNC content in the co-processed excipient and then slightly decrease as the CNC concentration approaches 10%.

Tablets were prepared by compressing the different formulations at 4 tons of compression force. Different quality control tests were performed, and the results showed the influence of CNC concentrations on various parameters investigated. Up to 2% CNCs, there was no increase in the hardness and tensile strength of the tablet; in fact, the values observed were slightly less than those of pure starch, but the difference was not statistically significant ($p = 0.1639$). This shows that up to 2%, CNCs have no positive effect on the hardness and tensile strength of the starch tablets prepared through wet granulation. However, from 4% CNCs, the hardness tends to increase with an increase in the amount of CNCs in the formulation, and the tensile strength also shows an increase. Compared to 0% CNCs (Formulation O), the increase in hardness of the tablets prepared with 10% CNCs (Formulation E) was found to be statistically significant ($p = 0.0003$). There was a rapid disintegration of the tablet (<1 minute) in all the formulations, including that of the pure starch granules. There were no significant differences ($p = 0.0653$) in the disintegration time observed between all the formulations. Similarly, all the tablets of the different formulations were within the permissible percent friability of 1%, and there were no significant differences ($p = 0.1516$) in percent friability among the different formulations.

Starch is among the earliest known disintegrants used in the formulation of pharmaceutical tablets. While starches produce rapid disintegration of tablets through a mechanism involving a combination of swelling or wicking or deformation, their tensile strength is reduced at higher concentrations,[43] which is their main weakness as a tablet disintegrant. Several modified starches have been developed to improve the overall tableting property of native starches. The results from the analysis showed that co-processing of CNCs with native starch was able to improve certain micromeritic properties, while also improving the hardness and tensile strength of the tablets prepared. The co-processed excipient was still able to show disintegration properties comparable to those of native starch. As reported previously, the reinforcement characteristics of CNCs resulted in improved mechanical properties of starch and other polysaccharide films when CNCs were used as fillers.[17,44] Due to the small nanocellulose whiskers and the resultant high contact surface area, the formation of hydrogen bonds between the polysaccharides was promoted, leading to improved tensile strength of the tablets prepared with the co-processed excipient compared to those with pristine starch.[44] However, due to the hydrophilic nature of the cellulose nanocrystals, the rapid wetting and swelling nature of the native starch was not compromised, leading to similar or comparable disintegration times for the tablets prepared with the native starch and the co-processed excipient.

Compressibility profile (Heckel plot)

To investigate the compressibility of the excipient, the relationship between the density of the tablet and the applied pressure to achieve it, is plotted for Formulation E, as shown in Figure 5. The plot represents the material's ability to deform plastically under pressure.[30] The mean yield pressure (P_y) was calculated from the plot by taking the reciprocal of the slope. The yield pressure (P_y) calculated from the Heckel plot in the current study was 82.64 MPa. A critical process in tablet manufacturing is powder compression. Both the physico-mechanical properties of the powder and the facets of the compression process, including the pressure or stress applied and the degree and rate of deformation, influence the powder compression

behaviour. Powder compressibility implies the degree of densification achieved at a given pressure.[45] The relationship between the density of the prepared tablets and the applied pressure was plotted to determine the compressibility. This plot is an indication of the material's plastic deformation under pressure.[30] The reciprocal of the slope from this plot provides the mean yield pressure (P_y). A high P_y demonstrates a higher yield strength that requires higher forces of compaction in commencing deformation.[28] A high value of P_y may not be adaptable to modern high-speed tableting machines, as the dwell time available for the compression of powders to form a compact is minimal in such machines. This mean yield pressure of 82.64 MPa obtained from the Heckel plot is lower than the 153.84 MPa and 99.01 MPa we reported for microcrystalline cellulose in our previous study,[26] as well as 140.85 MPa to 181.82 MPa for other previously reported co-processed excipients,[28] but very close to the 81 MPa and 78 MPa reported for *Assam bora* rice starch and Starch 1500®, respectively.[46]

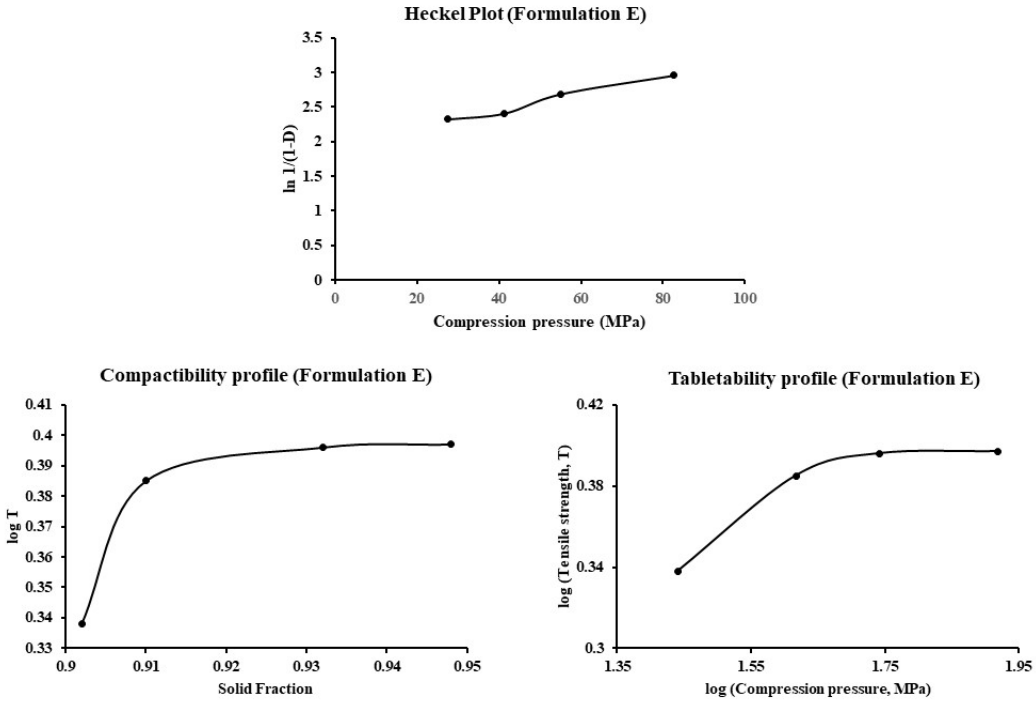

Figure 5: Heckel, compactibility and tabletability profile plots

Compactibility profile

Compactibility demonstrates the relationship between the tensile strength of a tablet and its solid fraction, which is the ratio of the tablet density to the material density. The compactibility profile of the CNC-based co-processed excipient is provided in Figure 4. As shown in the graph, the tensile strength of the tablet initially increased exponentially, but levelled off at a higher solid fraction. In a typical relationship, the tensile strength of the tablet increases exponentially with an increase in its solid fraction. A low solid fraction may weaken the tablet; however, over-compaction to a very high solid fraction also introduces flaws into the tablet by reducing its strength.[32] A lower plastic deforming material can reduce the tablet porosity. A desirable condition is making a tablet with a tensile strength sufficient to withstand the handling and pass the quality control test, but with suitable solid fractions or porosity to allow wetting of the tablet by the medium and its subsequent dissolution.

Tabletability profile

Tabletability is the relationship between the tablet tensile strength and compression pressure. In our sample, the tensile strength increases with increasing compression pressure, levelling off at higher compression pressures (Fig. 5). From the plot, it was observed that a compression force of

3-4 tons was sufficient to obtain the highest tensile strength for the compact, increasing the compression force beyond this did not result in higher tensile strength for the tablet. The tablet strength usually increases with increasing compression pressure, gradually levelling off. Under certain conditions, a decrease in tablet strength with increasing pressure is observed, which indicates over-compaction and is a source of defects in tablets.[32] On tracing the tabletability graph, it was observed that the tensile strength of the tablet increases with increasing compression pressure but levelling off at higher compression pressures. The highest tensile strength of the tablet was achieved with a compression force of 3-4 tons and increasing the compression force beyond this did not lead to higher tablet tensile strength.

Lubricant sensitivity

In the current study, the lubricant sensitivity of the co-processed excipient and standard microcrystalline cellulose was determined using magnesium stearate at 1% as the hydrophobic lubricant. The lubricant sensitivity of the standard was found to be 0.0019, while that of the new CNC-based co-processed excipient was 0.0044. Pharmaceutically important excipients, such as microcrystalline cellulose[41] and Starch 1500®,[46] are known to be sensitive to lubricants. The results for lubricant sensitivity of the co-processed excipient and standard microcrystalline cellulose indicate that the newly co-processed excipient was more sensitive to the lubricant than microcrystalline cellulose. Previous studies have also shown that materials with low yield pressure and *Py* values are more sensitive to magnesium stearate than those with higher yield pressure values.[46]

Disintegration efficiency and dissolution study

The disintegration efficiency ratio was calculated, and the values ranged between 0.027 in tablets compressed at 4 tons and 0.141 in those at 2 tons. The disintegration efficiency ratio, which is a product of the tablet's crushing strength and friability divided by the disintegration time, indicates the ability of the excipient to act as a tablet disintegrant. The disintegration efficiency decreases as the compression force increases. This may be due to the reduction in tablet porosity resulting in the limitation of wetting of the tablets by the medium.

The *in vitro* dissolution of paracetamol tablets prepared with 10% CPE as a disintegrant was compared with those prepared with 10% sodium starch glycolate as a standard disintegrant. After a 30-minute dissolution test, the dissolution medium was analysed for paracetamol dissolved using a UV-Vis spectrophotometer. The results from the analysis showed a percentage dissolution of 95.17±0.76% for the tablets prepared with the novel cellulose nanocrystal-based co-processed excipient and 82.52±2.54% for the standard sodium starch glycolate. The *in vitro* dissolution study shows that the new co-processed excipient exhibits better dissolution of the sample drug than that of sodium starch glycolate based tablets. Since nanocelluloses are amphiphilic in nature, their surface-active property and ability to stabilize an emulsion is well documented.[47] Since tablet disintegration is not the sole criterion for enhanced dissolution and bioavailability of active drugs, the disintegrant property of the CNC-based CPE coupled with the surface-active property of the CNCs may contribute to the enhanced dissolution of the active drug, paracetamol, observed in the study.

CONCLUSION

The CNC-based co-processed excipient was successfully prepared following the wet granulation method. Cellulose, the most abundant biopolymer on earth, is considered an almost inexhaustible raw material source for preparing eco-friendly and biocompatible functional materials. Thus, isolation of CNCs from the sustainable pseudostem of *Musa balbisiana* and their development into functional pharmaceutical excipients have the potential to substitute nondegradable materials obtained from rapidly depleting and environmentally harmful petroleum-based products. The evaluation of the flow characteristics of different formulations showed that the excipient exhibited fair to passable flow. Formulation E (10% CNC) was used to study the compressibility, compactibility and tabletability of the excipient. The results showed that the co-processed excipient exhibited good plastic deformation, compactibility and tabletability within the studied compression pressure. The lubricant sensitivity was compared with that of microcrystalline cellulose as a standard, and it was found that the newly co-processed excipient was more lubricant sensitive than microcrystalline cellulose. Compared to a standard fast disintegrant sodium starch glycolate, paracetamol tablets prepared with the novel co-

processed excipient demonstrate better dissolution of the model active constituent paracetamol. A test for the heavy metal content of the cellulose also indicates that the material is safe for pharmaceutical excipient. The result thus obtained signifies the satisfactory attributes of the newly developed nanocellulose-based co-processed excipient as a rapid disintegrant for tablet formulation, serving as a sustainable functional excipient.

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