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RESEARCH ARTICLE

COMPARATIVE STUDY OF THE BINDING STRENGTH OF CELLULOSE EXTRACTED FROM CASSAVA PEEL AND COMMERCIAL POLYMERS IN CLOXACILLIN TABLET FORMULATION

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ABSTRACT

Background and aim: This study investigated the comparative binding strength of cellulose extracted from *Manihot esculenta* (cassava) peel (CPC) with commercial acacia gum BP and carnauba wax BP on the mechanical strength in the formulation of Cloxacillin tablets.

Methods: Cellulose extracted from local cassava peel was subjected to phytochemical analysis. Cloxacillin granules were prepared by wet granulation using the three binders at concentrations of 2.5, 5.0, 7.5 and 10 % w/v. Micromeritic parameters of the granules, incorporating flow rate, angle of repose, bulk and tapped densities, Carr's index and Hausner's ratio, were determined. Physicochemical tests (hardness, weight uniformity, friability, disintegration and moisture absorption), and differential scanning calorimetry (DSC) and X-ray diffraction (XRD) were conducted on extracted cellulose.

Results: Phytochemical analysis indicated presence of only flavonoids, alkaloids and tannins. Bulk density values were - CPC 0.725, acacia gum 0.737, carnauba wax 0.741 (g/cc^3); tapped densities - CPC 0.777, acacia gum 0.794, carnauba wax 0.816 (g/cc^3); Hausner's ratio – CPC 1.07, acacia gum 1.08, carnauba wax 1.10; flow rate – CPC 3.33, acacia gum 2.68, carnauba wax 2.45 (g/sec). Angle of repose for all formulations were good ($\leq 20^o$) indicative of good flow properties. Physicochemical tests on Cloxacillin tablets showed mean values for hardness ≥ 4 kg, friability 0.446%, disintegration time 5.63 minutes. The tablets obtained from carnauba wax, however, were not satisfactory. CPC-derived tablets absorbed more moisture than those of acacia. The DSC of CPC had peak melting temperature of about 43.5^{o}C.

Conclusion: Study concludes that the binding strength of CPC compares favourably with that of acacia gum BP in the formulation of Cloxacillin tablets.

Key words: Cloxacillin tablet, binding strength, cassava peel cellulose, micromeritic properties, formulation.

INTRODUCTION

Active pharmaceutical ingredients are rarely produced and administered in isolation; indeed, they are usually combined with other substances to formulate dosage form that serve specific pharmaceutical purposes. These additional substances or excipients include those used to bind primary powders in the formulation to impact strength to the granules [1]. Some of these substances can be biodegradable excipients derived from natural sources that are being used as binders in tablet dosage forms [2]. Binders are categorized based on their incorporation method in tablet formulation as solution binders such as hydroxylpropyl methylcellulose, gelatin, and polyvinyl-pyrrolidone or dry binders like microcrystalline cellulose. Binders are recognized for their ability to influence the compressibility of a tablet formulation, making them a promising material for co-processing to enhance the functionality of excipients [3]. Tablet hardness is a critical parameter in the tableting process, as it directly affects the tablet's mechanical strength and ability to withstand handling and transportation. Inadequate hardness can lead to issues such as breakage, chipping, and friability during manufacturing, packaging, or dispensing. Insufficient tablet hardness can result from insufficient compaction force during compression, improper formulation, or poor powder flow properties. On the other hand, excessive tablet hardness may make the tablet difficult to disintegrate and dissolve, affecting drug release and bioavailability.

Controlling and maintaining optimal tablet hardness is essential for ensuring the quality, efficacy, and patient acceptance of the final tablet product [4]. Cellulose, a primary structural component in trees and plants, finds extensive use in pharmaceutical and industrial products as cellulose derivatives, such as ethers and esters. Depending on their form in solid dosage formulation, cellulose and its derivatives can exhibit distinct drug delivery properties, including immediate, controlled or delayed release preparations [5]. The pharmaceutical industries value natural polymeric materials like microcrystalline cellulose (MCC) due to their biodegradability, non-toxic nature, low cost, and abundant availability. As natural polysaccharides, MCC and others can be sustainably sourced, offering a consistent supply of raw material for commercial production. Their versatility as polymers enables them to achieve unique physicochemical properties by blending with various low- and high-molecular-weight materials [6]. The molecular structure of cellulose features glucose units with specific hydroxyl groups at different ends, providing various properties such as chirality, hydrophilicity, degradability, and chemical reactivity. The presence of hydrogen bonds adds a crystalline fiber structure to cellulose, which can be represented in both crystalline and amorphous states. Cellulose is commonly obtained from plants, with cottonseed hairs offering the purest form, while wood cellulose is separated from lignin and other polysaccharides through chemical pulping and purification processes.

Additionally, cellulose can be derived from algae, specific bacteria, fungi, and other plant sources [7]. In pharmaceutical tablet manufacture, cellulose has been used as a multifunctional excipient, as filler, binder, and disintegrant, respectively. Its excellent compatibility with other excipients, inert nature, and indigestibility make it a preferred choice for solid dosage forms [8, 9].

This study is aimed at sourcing for natural, pharmaceutically-suitable and acceptable

binders for tablet formulation including Cloxacillin tablet in view of the exorbitant cost of imported binders by comparing the binding properties of cellulose extracted from cassava peel with other standard binders.

MATERIALS AND METHOD

***Drugs, chemicals and solvents*:** Cloxacillin trihydrate BP (Venu Health Care Kadi Road India); Lactose anhydrous powder BP (Danone®, Germany); Sulphuric acid JHD® (Gunsgdong Guandgua Chemical Factory Co. Ltd, China), Cornstarch powder BP (Aimidon Demaiz USO, germany), Carnauba wax BP (Burgoynr Reagents Laboratory E903, India), Acacia BP (Kermel UN Number 1690 India), Cassava peel cellulose extracted locally.

***Plant collection, preparation and extraction of cellulose*:** Fresh cassava tubers (*Manihot esculenta*) were purchased from a local farm at Okada, Edo State. Nigeria, in April, 2024. The tubers were authenticated and assigned an Herbarium number IUCP/C023/25 at the Department of Pharmacognosy, College of Pharmacy, Igbinedion University, Okada. Cassava peel was carefully separated from their outer skin, washed thoroughly, and allowed to dry for 5 days under sunlight, milled, and later sieved into fine powder. Cassava peel powder (50 g) was weighed using a top-loading weighing balance followed by addition of 1L 0.5M Sulphuric acid. Mixture was stirred using a glass rod and heated until it reached 90 °C for 2 hours with constant stirring. Thereafter, the residue was filtered and washed with distilled water until a pH 7 was attained. Residue was heated with 2 % Sodium chlorite in a water bath and a few drops of glacial acetic acid for 30 minutes and rinsed with distilled water and air dried at room temperature for 2-3 days. The cellulose obtained was dried in an oven at 50 ^{o}C for 2 hours and stored in an airtight container for further use.

***Preparation of Cloxacillin trihydrate granules with extracted cellulose, acacia gum, and carnauba wax*:** Wet granulation method previously described by Benjabhorn *et al*. [11], was employed to produce 12 batches of granules, each being suitable for preparing 50 tablets of Cloxacillin 500 mg. Different concentrations (2.5, 5.0, 7.5, 10 %w/v) of each binder: acacia gum BP, Carnauba wax BP powder and cassava peels cellulose powder were separately used granulating fluids. For each batch containing 500 mg Cloxacillin trihydrate powder, finely powdered lactose anhydrous and corn starch BP at their appropriate quantities per batch were dry mixed in a bowl mixer. The different binders, at different concentrations, were used as granulating fluids to agglomerate the powder mixture, dried in an oven at 60 °C for 30 minutes. Dried granules were passed through a sieve of aperture size BSS 22 and packed in an airtight glass container for further analysis.

Evaluation of physicochemical properties of Cloxacillin trihydrate granules

***Angle of repose*:** Fifty grams of granules were allowed to flow freely under gravity through a–clamped funnel with its tip 6 cm above a smooth paper placed on a flat horizontal surface. The height of the cone formed, h, and the radius of the base, r, were carefully measured [12]. The tangent of the angle of repose was calculated using the equation:

$$\text{Tan } Ø = \frac{h}{r} \text{ ---------- eq1}$$

***Flow rate*:** The Erweka granules flow tester was used in the determination Fifty grams of the granules was allowed to flow through the orifice of the equipment. The time taken to

pass through was noted, and the rate of flow per second was calculated as [12, 13].

$$\text{Flow rate (g/sec)} = \frac{weight\ of\ granules\ (g)}{time\ of\ flow\ (\text{sec})} \text{ ----------eq 2}$$

***Bulk and tapped densities*:** Fifty-gram granules (w_o) were weighed and carefully poured into a 250 mL measuring cylinder, and the volume (bulk) occupied by each of the samples without tapping was noted. Bulk density was calculated according to equation 3. The cylinder was tapped 100 times on a tabletop and volume was observed. The tapped density was calculated as the ratio of weight to tapped volume as shown in equation 4. [12].

$$\text{Bulk density (g/cm}^3) = \frac{weight\ of\ granules\ (g)}{bulk\ volume\ (cm3)} \text{ ----------eq 3}$$

$$\text{Tapped density (g/cm}^3) = \frac{weight\ of\ granules\ (g)}{tapped\ volume\ (cm3)} \text{ ----------eq 4}$$

With the bulk and tapped densities determined, Carr's index (%) and Hausner's ratio were then calculated as represented in equations 5 and 6, respectively.

$$\text{Carr's index (\%)} = \frac{tapped\ density - bulk\ density}{tapped\ density} \times 100 \text{ ---- eq 5}$$

$$\text{Hausner's ratio} = \frac{tapped\ density}{bulk\ density} \text{ -------- eq 6}$$

Compression of granules into tablets

The granules were carefully mixed with the amount of previously sieved magnesium stearate, talc, and dry corn starch and mixed for 5 minutes. Six hundred milligram of the mixture containing Cloxacillin 500 mg was compressed using the Single Punch tableting machine at a compression pressure of 30 N.

The tablet properties evaluated include weight uniformity, hardness, friability, disintegration time, and moisture absorption test.

***Weight uniformity*:** The British Pharmacopoeia method was used in the determination. Twenty tablets were randomly selected from each batch and weighed collectively and individually, and the mean weight was recorded. The percentage coefficient of the tablet weight variation was calculated from the equation:

$$\text{Percent (\%) variation} = \frac{Standard\ deviation}{Mean\ weight} \times 100 \text{ ----------eq 7}$$

***Friability and hardness tests*:** Ten tablets were randomly selected from each batch and weighed (w_1) and then subjected to movement, free fall shocks on the Friability machine set to rotate at 25 rounds per minute for 4 minutes. The tablets were then dusted and reweighed (w_2), and the differences in the tablet weight determined [14].

$$\text{Friability (\%)} = \frac{w1-w2}{w1} \times 100 \text{ ----------eq 8}$$

The Erweka hardness tester was used to determine the crushing strength of 3 randomly selected tablets from each batch, and the mean was calculated and recorded [15].

***Moisture absorption test*:** This test was carried out to check the effect of relative humidity on the granularity of tablets and to investigate the physical stability. The weight of randomly selected tablets, placed on a petri dish of known weight, was recorded. The sample tablets were then exposed to the atmosphere for 10 days, and the weight changes were recorded every 24 hours.

Disintegration test: The British Pharmacopoeia disintegration test method [16] was used. Six tablets were randomly selected from each batch. The disintegration time for each batch was determined using the Erweka disintegration apparatus. Distilled water was used as the medium, and maintained at 37±1 °C. One tablet each was placed in four test tubes of the machine. The time taken for the individual tablet to disintegrate and its particles to pass through the mesh of the tube was recorded. The mean time for the four tablets was recorded as the disintegration time for each batch.

Differential scanning calorimetry (DSC) and X-ray diffraction (XRD) analysis of extracted cassava peel cellulose were determined, and the results are shown in Figures 6 and 7.

RESULTS AND DISCUSSION

Yield of extracted cellulose from *M. esculenta* was 12.54%. Organoleptic properties presented dark brown, odourless, crystalline peel powder with bland taste (Table 1). Phytochemical analysis showed CPC contained flavonoids, alkaloids, and tannins, while saponins, steroids, cardiac glycosides, terpenoids, and anthraquinone glycosides were absent.

Micromeritic properties of Cloxacillin trihydrate granules

Table 2 shows micromeritic properties of cloxacillin trihydrate granules formulated with CPC, acacia gum and carnauba wax. Angle of repose data were: (CPC: 13.71º - 14.56º), (acacia gum: 11.57º – 22.56º), (carnauba wax: 10.60º – 14.56º). Other data generated included Hausner's ratio (CPC: 1.07), (acacia gum: 1.06 – 1.10), (carnauba wax: 1.08 – 1.14), and Carr's index (CPCa: 6.22 – 7.17), (acacia gum: 5.26 – 9.37), (carnauba wax: 7.65 – 11.97). The micromeritic of the CPC compared favourably with those of standard binders (acacia gum and carnauba wax), indicating good flowability and compressibility of the granules [12].

Figure 1: Dry-milled cellulose powder extracted from cassava peel

Table 1. Phytochemical, organoleptic properties of extracted cassava peel cellulose.

Phytochemical Constituent	**Inference**	**Organoleptic Parameter**	**Result**
Saponin	-	Percentage yield	12.54 %
Flavonoids	+	Color	Dark brown
Steroids	-	Odour	None
Alkaloids	+	Nature	Crystalline
Tannins	+	Taste	Bland

Table 2: Micromeritic properties of Cloxacillin trihydrate granules

Binder type	Binder concentration (%)	Angle of repose (º)	Bulk density (g/cc^3)	Tapped density (g/cc^3)	Carr's index	Hausner's ratio	Flow rate (g/sec)
Cassava peel cellulose	2.5	14.56±0.01	0.724±0.05	0.780±0.01	7.18±0.02	1.07±0.02	3.33±0.10
	5	14.03±0.01	0.724±0.05	0.772±0.02	6.22±0.02	1.07±0.02	3.33±0.10
	7.5	14.38±0.03	0.728±0.03	0.781±0.02	6.79±0.03	1.07±0.02	3.33±0.10
	10	13.71±0.02	0.724±0.03	0.775±0.01	6.58±0.01	1.07±0.02	3.33±0.10
Acacia gum	2.5	14.89±0.02	0.735±0.02	0.785±0.03	6.36±0.02	1.07±0.02	2.86±0.15
	5	19.87±0.03	0.739±0.03	0.780±0.02	5.26±0.01	1.06±0.01	2.86±0.15
	7.5	11.57±0.01	0.740±0.04	0.800±0.04	7.50±0.01	1.08±0.02	2.50±0.12
	10	22.56±0.03	0.735±0.03	0.811±0.03	9.37±0.03	1.10±0.03	2.50±0.12
Carnauba wax	2.5	14.56±0.01	0.712±0.04	0.771±0.03	7.65±0.02	1.08±0.02	2.86±0.15
	5	3.94± 0.04	0.750±0.03	0.821±0.04	8.65±0.02	1.09±0.01	2.50±0.16
	7.5	11.31±0.03	0.750±0.03	0.821±0.04	8.28±0.01	1.09±0.01	2.22±0.16
	10	7.60±0.04	0.753±0.02	0.852±0.02	11.97±0.03	1.14±0.03	2.22±0.15

Table 3: Physicochemical properties of Cloxacillin trihydrate tablets

Binder type/ concentration (%w/v)	Binder concentration (%)	Weight uniformity (mean) (mg)	Friability (%)	Hardness (kg/f)	Disintegration time (min)
Cassava peel cellulose	2.5	0.590±0.02	0.667±0.01	9.17±0.25	4.08±0.15
	5	0.600±0.01	0.554±0.02	10.17±0.20	4.90±0.12
	7.5	0.600±0.02	0.331±0.01	11.33±0.16	6.50±0.13
	10	0.600±0.01	0.166±0.03	14.67±0.21	7.60±0.20
Acacia gum	2.5	0.590±0.02	0.680±0.01	8.17±0.20	4.20±0.10
	5	0.590±0.14	0.575±0.02	9.00±0.22	4.75±0.14
	7.5	0.600±0.01	0.345±0.04	9.33±0.16	5.80±0.15
	10	0.600±0.01	0.250±0.01	11.17±0.16	7.20±0.12s

Table 3 shows the results of the physicochemical analysis of the Cloxacillin trihydrate tablets formulated with different binders. Disintegration time ranged from 4.08 – 7.60 minutes for cassava peel cellulose, 4.20 – 7.20 minutes for acacia gum and consequently conformed to the British Pharmacopoeia requirements, which specified disintegration time less than 15 minutes for uncoated tablets. The compendia specification for uniformity of weight states that for tablets weighing above 324 mg, not more than 2 tablets should deviate from the average weight by more than 7.5% [16]. Cloxacillin trihydrate tablets formulated with various concentrations of cassava peel cellulose and acacia gum passed the weight uniformity test for not having more than 2 tablets deviating from the average by more than 7.5%. Friability testing is used in assessing the physical toughness of compressed and uncoated tablets under mechanical shock and attrition [19]. All the tablets made from the different batches of cassava peel, cellulose and acacia gum passed the friability test, for having values not exceeding 1%. Hardness test is a quantitative estimate of the internal bonding strength of the powder compact, which gives the tablet sufficient strength to maintain its form under applied external forces [14,15]. As shown in Table 3, the hardness of the

tablets increased with increasing binder concentration. This is because increasing the binder concentration increases the intragranular force during compression. All the tablets passed the hardness test for having values not less than 4 kg. The physicochemical properties for all the Cloxacillin trihydrate tablets formulated with carnauba wax could not be evaluated because of the soft and sticky nature of the tablets produced, hence not suitable as a binder in Cloxacillin trihydrate tablet formulation.

Moisture absorption of pharmaceutical products is important since most physicochemical, stability, and functional properties are affected by moisture. It influences the selection of packaging materials and storage of the tablet. Table 6 shows that all the tablets absorbed moisture. The tablets made with cassava peel cellulose absorbed more moisture compared to those made with acacia gum (Mean values of moisture absorbed at Day 5 and Day 10 are: CPC – 0.295g, 0.680g; Acacia gum BP – 0.025 g, 0.030 g respectively). This shows that cassava cellulose could be hygroscopic, and hence, precautionary measures must be taken to select packaging materials and storage conditions [17].

Differential scanning calorimetry (DSC) of the cassava peel cellulose sample

Differential scanning calorimetry is a sensitive technique to study the thermotropic properties of biological macromolecules and extracts. It provides qualitative and quantitative information about endothermic and exothermic processes or changes in heat capacity.

From the graph in Figure 2, the DSC thermograph shows that cellulose extracted from cassava peel has a peak melting temperature of about 43.5 °C. This value corresponds with the crystalline regions of cellulose as they reach their melting point. The layout of the plane and the transition observed suggest that the extracted cellulose is semi-crystalline. X-ray diffraction (XRD) is used for the primary characterization of material structure, crystallite size, and strain in various extracts. It provides information on the crystallinity of materials and polymers for better characterization and optimization. From the results obtained in Figure 3, the cellulose sample shows regions with distinct diffraction peaks (crystallinity) and regions with no distinct diffraction peaks (amorphous). These results obtained from the XRD analysis further confirm that the cellulose analyzed is a semi-crystalline polymer [18].

CONCLUSION

This present study evaluated extracted cellulose from *M. esculenta* peel as a substitute binder in the formulation of Cloxacillin trihydrate tablets. As the concentration of the binder increased, the tablet hardness increased, friability decreased, and the disintegration time increased. The tablets were found to be slightly hygroscopic, hence, caution is needed in the selection of packaging and storage facilities if this binder must be used as an alternative.

Table 4: Moisture absorption results conducted over 10 days

Binder type	Binder conc (%w/v)	Initial weight (g)	Day 1 (g)	Day 2 (g)	Day 3 (g)	Day 4 (g)	Day 5 (g)	Day 6 (g)	Day 7 (g)	Day 8 (g)	Day 9 (g)	Day 10 (g)
Cassava peel cellulose	2.5	5.99	0.52	0.52	0.51	0.52	0.54	0.56	0.59	1.00	1.03	1.07
	5	6.00	0.50	0.51	0.55	0.55	0.56	0.59	1.01	1.01	1.03	1.05
	7.5	6.00	0.06	0.06	0.06	0.07	0.08	0.10	0.18	0.22	0.25	0.4
	10	6.00	0.02	0.03	0.02	0.02	0.06	0.09	0.10	0.24	0.25	0.25
Acacia gum	2.5	5.90	0.02	0.03	0.02	0.02	0.04	0.05	0.05	0.05	0.06	0.04
	5	5.96	0.00	0.02	0.02	0.02	0.03	0.02	0.05	0.04	0.04	0.05
	7.5	6.00	0.00	0.01	0.01	0.03	0.01	0.01	0.02	0.01	0.02	0.02
	10	6.00	0.00	0.00	0.01	0.00	0.02	0.01	0.00	0.01	0.01	0.01

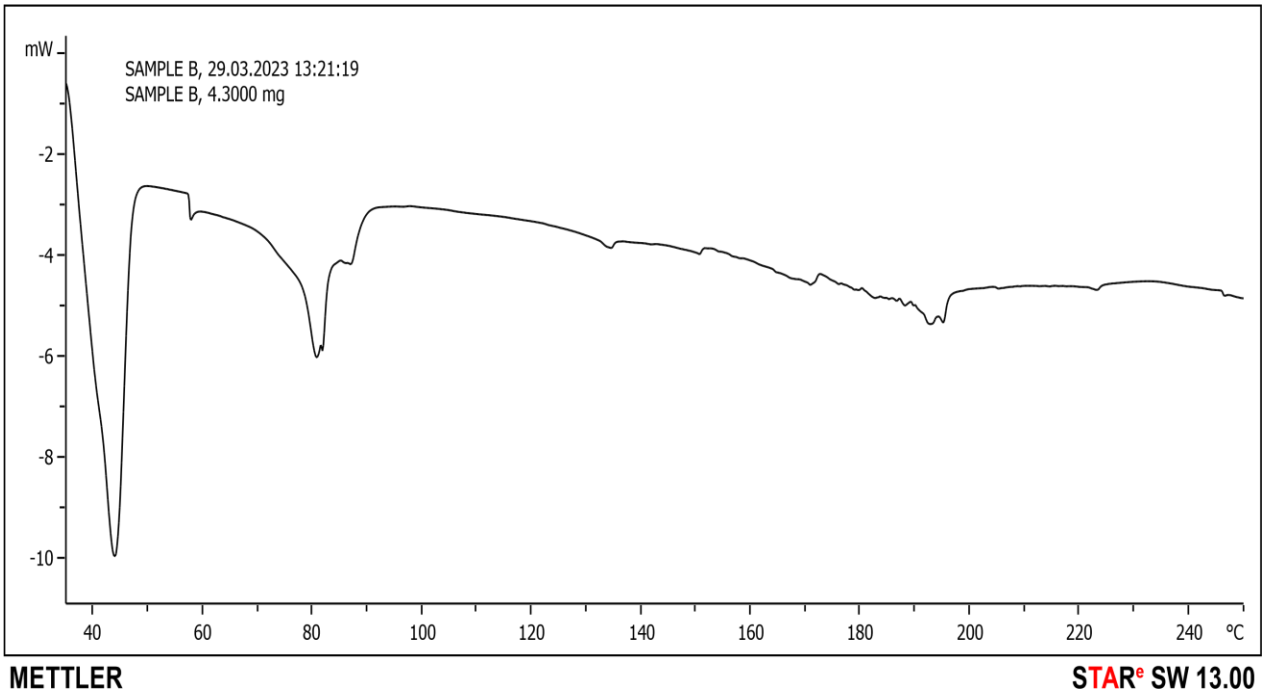
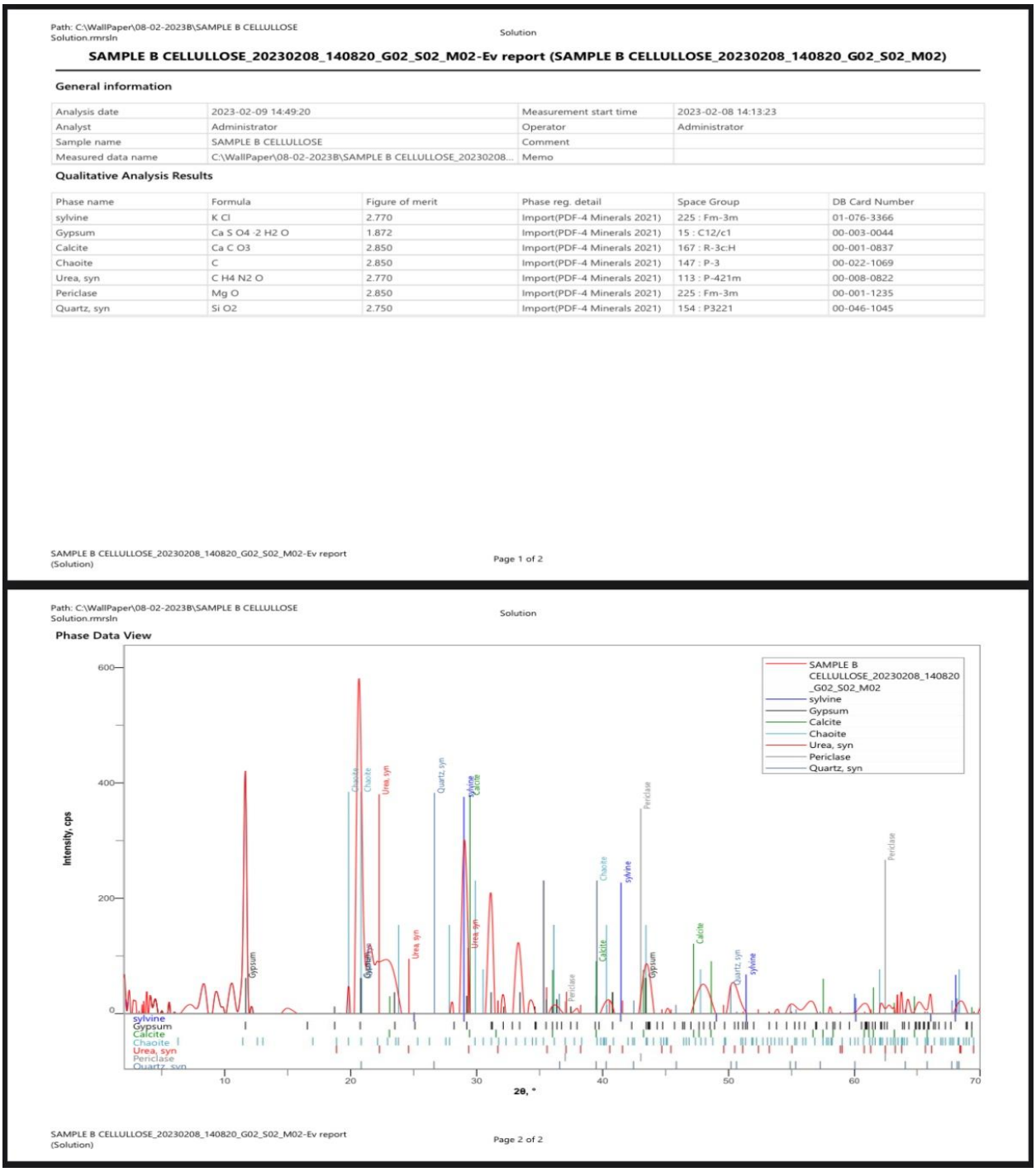


Figure 2. Differential scanning calorimetry of extracted cassava peel cellulose



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Solution

SAMPLE B CELLULLOSE_20230208_140820_G02_S02_M02-Ev report (SAMPLE B CELLULLOSE_20230208_140820_G02_S02_M02)

General information

Analysis date	2023-02-09 14:49:20	Measurement start time	2023-02-08 14:13:23
Analyst	Administrator	Operator	Administrator
Sample name	SAMPLE B CELLULLOSE	Comment	
Measured data name	C:\WallPaper\08-02-2023B\SAMPLE B CELLULLOSE_20230208...	Memo	

Qualitative Analysis Results

Phase name	Formula	Figure of merit	Phase reg. detail	Space Group	DB Card Number
sylvine	K Cl	2.770	Import(PDF-4 Minerals 2021)	225 : Fm-3m	01-076-3366
Gypsum	Ca S O4 -2 H2 O	1.872	Import(PDF-4 Minerals 2021)	15 : C12/c1	00-003-0044
Calcite	Ca C O3	2.850	Import(PDF-4 Minerals 2021)	167 : R-3c:H	00-001-0837
Chaoite	C	2.850	Import(PDF-4 Minerals 2021)	147 : P-3	00-022-1069
Urea, syn	C H4 N2 O	2.770	Import(PDF-4 Minerals 2021)	113 : P-421m	00-008-0822
Periclase	Mg O	2.850	Import(PDF-4 Minerals 2021)	225 : Fm-3m	00-001-1235
Quartz, syn	Si O2	2.750	Import(PDF-4 Minerals 2021)	154 : P3221	00-046-1045

SAMPLE B CELLULLOSE_20230208_140820_G02_S02_M02-Ev report (Solution)

Page 1 of 2

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Solution

Phase Data View

SAMPLE B CELLULLOSE_20230208_140820_G02_S02_M02-Ev report (Solution)

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Figure 3. X-ray diffraction analysis results of extracted cassava peel cellulose

Conflict of interest:

The authors of this research hereby declare that no conflict of interest exists.

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