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Research Article

PHYSICOCHEMICAL AND BINDING PROPERTIES OF CASHEW TREE GUM IN METRONIDAZOLE TABLET FORMULATIONS

KWABENA OFORI-KWAKYE*, YAA ASANTEWAA AND SAMUEL LUGRIE KIPO

Department of Pharmaceutics, Faculty of Pharmacy and Pharmaceutical Sciences, College of Health Sciences, Kwame Nkrumah University of Science and Technology (KNUST), Kumasi, Ghana Email: koforikwakye@yahoo.com; kokwakye.pharm@knust.edu.gh

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ABSTRACT

Cashew gum collected from Ejura cashew plantation in Ghana was evaluated for some physicochemical and binding properties in metronidazole tablet formulations. The moisture content and insoluble matter in crude cashew gum (CCG) and purified cashew gum (PCG) was (11.2 %, 0.35 %) and (10.4 %, 0.28 %), respectively. The gum contains divalent metal ions with the rank order: $Ca^{2+} > Mg^{2+} > Fe^{2+} > Zn^{2+}$, and trace amounts (< 0. 1 mg/kg) of the monovalent ions K^+ and Na^+. The amount of each of the metal ions in CCG was higher than in PCG. The pH of CCG or PCG mucilage was more stable when refrigerated than on storage at 25 °C and 50 °C. The pH of PCG mucilage was less stable than CCG on storage. Addition of a preservative had little influence on the pH of cashew gum mucilage when stored. The viscosity of PCG increased with increase in gum concentration and decreased with increase in temperature. Granules comprising of metronidazole (25.7 % w/w), lactose (63.8 % w/w), maize starch (8.2 % w/w), talc (2.0 % w/w) and magnesium stearate (0.3 % w/w) were prepared by wet granulation using 2 – 8 % w/w PCG mucilage as binder. All the granules possessed good flow properties with Hausner ratio of 1.10 – 1.30 and Carr's index of 9.0 – 23.0 %. Tablets prepared with 4 – 8 % w/w PCG had hardness ≥ 4 kg while tablets prepared with 6 – 8 % w/w PCG had friability of < 1 %, comparable to that prepared with 4 % w/w acacia. The disintegration time of the tablets was < 15 min and increased with increase in PCG concentration. The tablets had fast dissolution in aqueous media with > 94 % drug dissolution in 45 min. This study shows that PCG can be used as a binder in conventional release tablet formulations.

Keywords: Natural gum, Cashew gum, Purification of gum, Metal ion content, Binder.

INTRODUCTION

Gums are high molecular weight polysaccharides which are formed from sugar and uronic units. Gums are hydrophilic in nature and may be classified as natural, semi-synthetic or modified and synthetic. Natural gums including acacia, ghatti, karaya, locust bean, albizia, khaya, guar, tragacanth and xanthan, are obtained as exudates or extractives from the bark of stems, branches and roots of various plants. Plant families notable for the production of gums are Anacardiaceae, Combritaceae, Meliaceae, Rosaceae and Rutaceae [1]. Various reasons have been advanced for the production of gums by plants, including: as products of normal plant metabolism; as a protective mechanism against a pathological condition afflicting the plant; and as a consequence of infection of the plant by microorganisms.

Cashew gum is the exudate from the stem bark of *Anacardium occidentale* Linn (family, Anarcardiaceae). The plant is native to Brazil and grows in many tropical and sub-tropical countries. In Ghana, the plant is found mostly in cashew growing areas such as Sampa, Wenchi, Bole, Jirapa and Ejura where they are commercially cultivated for the utilization of the nuts. Gums from cashew plants from various parts of Ghana are reported to possess the following physicochemical characteristics: moisture content (9.8 – 13.2 %), insoluble matter (1.9 – 4.8 %), total ash (0.5 – 1.2 %), protein content (1.27 – 1.80 %), total sugars (0.96 – 2.10 mg/g), and total phenols (0.21 – 2.26 %) [2]. Cashew gum is chemically composed of 61 % galactose, 14 % arabinose, 7 % rhamnose, 8 % glucose, 5 % glucuronic acid and < 2 % other sugar residues [3, 4] while hydrolysis of the gum yields L-arabinose, L-rhamnose, D-galactose and glucuronic acid [3]. The gum has a highly branched galactan framework comprising of chains of (1→3)-linked β–D-galactopyranosyl units interspersed with β-(1→ 6) linkages [4].

Cashew gum has been studied widely for various pharmaceutical applications as it is inexpensive, non-toxic [5, 6] biodegradable, and possesses appropriate physicochemical characteristics. As cashew gum shares similar characteristics as gum Arabic, it has been suggested for use as an agglutinant for capsule and pills in place of gum Arabic in the pharmaceutical and cosmetic industries [4]. Cashew gum modified by carboxymethylation with monochloroacetic acid as etherifying agent was used to form polyelectrolyte complexes with chitosan [7] for possible use in controlled drug delivery. The gum was employed as a binder in lactose-based tablet formulations containing tartrazine dye where the tablets produced were shown to exhibit good hardness and friability properties [8]. Cashew gum has also recently been utilized as a binder in paracetamol tablet formulations where the gum imparted better mechanical properties to the tablets than povidone or gelatin [9]. The gum has been evaluated as a gelling agent in an aceclofenac topical gel formulation where the gel containing 5 % w/w cashew tree gum was found to be suitable for topical application based on its physicochemical properties [6].

The objective of the current study was to evaluate some physicochemical properties of cashew gum obtained from Ejura cashew plantation in the Ashanti Region of Ghana. The effect of cashew gum mucilage as a binder on the mechanical and drug release properties of metronidazole tablet formulations was also investigated.

MATERIALS AND METHODS

Materials

Cashew gum was obtained from Ejura cashew plantation as natural exudates from the stem barks of the plant *Anarcadium occidentale* Linn (family, Anacardiaceae) at Ejura in the Ashanti Region of Ghana. The plant was authenticated by the curator of the plantation. Metronidazole powder BP was a gift from Kinapharma Ltd (Kumasi, Ghana) and maize starch was obtained from Tradewinds Chemist (Kumasi, Ghana). Acacia, talc, magnesium stearate, lactose, ethanol, sodium benzoate, diethyl ether, hydrochloric acid, nitric acid and perchloric acid were obtained from the chemical store of the Department of Pharmaceutics, KNUST, Kumasi, Ghana. Distilled water was freshly prepared.

Purification of gum

The gum was cleaned by removing the bark and other extraneous materials by hand and dried in a hot air oven at 50 °C for about 8 h until it became sufficiently brittle. The dried gum was manually sorted into light coloured and dark coloured grades. The light coloured grade was selected for further processing by milling in a domestic blender into fine powder and designated as crude cashew gum (CCG). 100 g of CCG was dissolved in 200 ml of distilled water and allowed to stand for 24 h with intermittent stirring. The gum mucilage was strained with calico to remove any insoluble debris or impurities and precipitated with 350 ml of 96 % ethanol. The precipitated gum was re-filtered and washed with diethyl ether and dried in hot air oven at 50 °C for 8 h. The dried purified gum was

milled and screened through 180 µm sieve. The powdered gum was used in subsequent tests and analyses as purified cashew gum (PCG).

Moisture content and insoluble matter of gums

The moisture content and insoluble matter of both CCG and PCG was determined according to British Pharmacopoeia (2007) methods [10].

Metallic ion content of gums

One (1) gram of powdered CCG or PCG was weighed into a 250 ml beaker and 25 ml of concentrated nitric acid added. The sample was digested on a hot plate in a fumed chamber, cooled and 1ml perchloric acid (70 % $HClO_4$) added. About 30 ml distilled water was added to the digest and the mixture boiled for about 10 min and filtered hot into a 100 ml volumetric flask with a Whatman No. 4 filter paper. The solution was then made to the mark with distilled water. One (1) ml of the digest was used to determine the content of calcium, magnesium, zinc and iron in the sample using an Atomic Absorption Spectrophotometer (AAS) (Perkin Elmer Precisely A Analyst 400, PerkinElmer, USA) fitted with an acetylene flame. The AAS was fitted with zinc and iron EDL lamps and magnesium and calcium CHCL lamps set at wavelengths of 213.86 λ, 248.33 λ, 285.21 λ and 422.67 λ, respectively. The determination was done in triplicate. Two (2) ml of the digest was used in the determination of sodium and potassium using the flame photometer method. A single channel flame photometer (Jenway Model PFP7, United Kingdom) operated on methane gas was used. The determination was done in triplicate.

pH of gum mucilage

2 % w/v aqueous mucilage of CCG and PCG were prepared in the presence and absence of 0.2 % w/v sodium benzoate as preservative. The samples were stored at room temperature (~ 25 °C), 50 °C, in a refrigerator (~ 8 °C) and the pH determined at weekly intervals for six weeks, using a standardized pH meter (Trohm pH meter, Switzerland).

Viscosity of gum mucilage

Aqueous mucilage of acacia gum (AG) and PCG (5 – 40 % w/v) were prepared using distilled water. The viscosity of the samples was determined at 25 °C and shear rate of 1 rpm with a Brookfield DV-I+ digital viscometer (spindle number 2) (Brookfield Eng. Labs. Inc., USA). The viscosity of 40 % w/v PCG was also determined at a shear rate of 1 rpm at 25 °C, 30 °C, 45 °C, 60 °C and 80 °C.

Preparation of granules

Different batch of granules comprising of metronidazole (25.7 % w/w), lactose (63.8 % w/w), maize starch (8.2 % w/w), talc (2.0 % w/w) and magnesium stearate (0.3 % w/w) were prepared using the wet granulation technique. The powders, excluding talc and magnesium stearate, were dry-mixed for 5 min in a planetary mixer (Model A120, Hobart Company, UK) and massed with the appropriate amount of binder solution (PCG: 10 % w/v, 20 % w/v, 30 % w/v, 40 % w/v; acacia: 20 % w/v) equivalent to 2 % w/w, 4 % w/w, 6 % w/w and 8 % w/w PCG or 4 % w/w acacia in the granules. The damp mass was screened through 2.36 mm sieve and dried at 60 °C for 1 hour in a hot air oven. The dried granules were screened through 1.00 mm sieve and lubricated with talc and magnesium stearate. The granules were stored in plastic containers for further evaluation and compression into tablets.

Evaluation of granule properties

The bulk density (ρB) was determined by slowly pouring the granules into a 10 ml graduated glass cylinder and the excess granules leveled off with a spatula. The bulk density was obtained by dividing the weight of granules by the volume. The tapped density (ρT) was determined by tapping a graduated glass cylinder containing a known weight of granules 50 times from a height of 2.5 cm on a wooden bench top. The tapped density was obtained by dividing the weight of granules by the minimum volume attained after tapping. The Hausner ratio was calculated as the ratio of the tapped density to the bulk density (ρT/ρB). Hausner ratio values ~ 1.2 portrays low interparticle friction and good granule flowability while values >1.6 signifies cohesive properties and poor granule flowability [11]. The Carr's index (C) is used to predict the compressibility and ease of flow of granules and was calculated as: $C = (\rho T - \rho B) / \rho T * 100$. For Carr's index, values ≤ 16 % indicates good flowability while values > 23 % demonstrates poor flowability [11].

Production of tablets

The different batch of granules produced were compressed into tablets using a lubricated Single punch tabletting machine (DP30 tablet press, Pharmao Industries Co. Ltd., China) fitted with a concave punch and die set. Tablets of weight ~ 400 mg and diameter ~ 11 mm, containing ~100 mg metronidazole was prepared and stored in plastic containers until use.

Determination of tablet properties

The mean tablet weight was determined by weighing twenty (20) randomly sampled tablets individually on a precision balance (Mettler Toledo, USA) and the average determined. The friability of the tablets was determined with a SOTAX F2 Friabilator USP (SOTAX AG, Switzerland). Twenty (20) tablets were randomly selected, de-dusted and weighed on a precision balance. The tablets were placed into the transparent drums of the friabilator and set to rotate at 100 revolutions. The tablets were de-dusted after the test, weighed and the difference in weight expressed as a percentage of the initial weight. Tablet hardness which is the force required to diametrically cause a tablet to fracture was determined using a Dr. Schleuniger Pharmatron tablet hardness tester (Model 5Y, Switzerland). The test was repeated twice and the mean recorded. Disintegration test was carried out in distilled water with the Electrolab Disintegrating Tester (USP) ED-2L (Electrolab, India). Six tablets were placed in the cylindrical glass and the time taken for the tablets to disintegrate was recorded as disintegration time.

***In vitro* dissolution tests**

Dissolution tests were carried out with an Erweka Dissolution Apparatus (Type DT6, Erweka GmbH, Heusenstamm, Germany). The dissolution test conditions used were: 900 ml 0.1 M HCl dissolution medium set at 37 ± 0.5 °C, and a paddle speed of 100 rpm. 5 ml samples were withdrawn at 5, 10, 15, 30, 45 and 60 min intervals and replaced with fresh medium pre-warmed at 37 ± 0.5 °C. Samples were filtered (0.45 µm HA membrane filters), diluted and analysed by UV spectrophotometry (Model Cecil CE 8020, Cecil Instruments, UK) at a wavelength of 278 nm, using a 1cm cell and 0.1M HCl as blank solution. The amount of drug released was determined from regression data ($y = 381.07x + 0.0271$, $R^2 = 0.9994$) obtained from a calibration plot of metronidazole powder in 0.1 M HCl.

RESULTS AND DISCUSSION

The light coloured grade of the crude cashew gum (CCG), rather than the dark coloured grade, was selected for further processing because the light coloured grade is usually preferred in commercial evaluation of gums. The percentage yield of cashew gum obtained after purification in this study was 78.5 %, which is considerably higher than the 55 % reportedly obtained when acetone was used for precipitation of the gum [6]. Table 1 shows the moisture content and insoluble matter in CCG and PCG. In both gums, the moisture content and insoluble matter were < 15 % and < 0.5 %, respectively. The moisture content and insoluble matter in PCG were lower than in CCG even though the differences were not significant ($p > 0.05$). The values obtained are reasonable when compared to limits of 15 % (moisture content) and 0.5 % (insoluble matter) specified for acacia gum [10], a commercial gum commonly used as a pharmaceutical excipient. The moisture content of 10.44 – 11.19 % for cashew gum from Ejura cashew plantation falls within the range of 9.8 – 13.2 % obtained for the gum in a recent study in Ghana [2], and higher than the 7.4 % reported in a study in Brazil [4]. The insoluble matter of 0.28 – 0.35 % is much lower than the 1.9 – 4.8 % reported for the gum in another study in Ghana [2].

Table 1: Moisture content and insoluble matter of cashew tree gum (*mean ± SD, n = 3)*

Sample	Moisture content (%)	Insoluble matter (%)
Crude cashew gum	11.19 ± 0.52	0.35 ± 0.10
Purified cashew gum	10.44 ± 0.16	0.28 ± 0.06

Table 2: Metallic ion content of crude and purified cashew tree gum (*mean ± SD, n = 3)*

Metallic ion	Crude gum	Purified gum
Calcium (mg/kg)	883.5 ± 0.36	662.4 ± 0.37
Iron (mg/kg)	16.7 ± 0.09	2.0 ± 0.01
Magnesium (mg/kg)	54.4 ± 0.06	50.7 ± 0.03
Potassium (mg/kg)	< 0.1	< 0.1
Sodium (mg/kg)	< 0.1	< 0.1
Zinc (mg/kg)	8.3 ± 0.03	4.1 ± 0.01

Table 2 depicts the metallic ion content for both the crude and purified cashew tree gum. The metal ions calcium, magnesium, iron, zinc, potassium and sodium, which are essential minerals needed by the body to satisfy its metabolic needs, were found in cashew gum. Calcium was the predominant metallic ion in both CCG (883.5 mg/kg) and PCG (662.4 mg/kg) while potassium and sodium occurred in trace amounts (< 0.1 mg/kg). This confirms earlier studies [2, 12] which reported that calcium is the predominant cation in cashew gum. The metallic ion content was higher in CCG than in PCG though the differences were not significant ($p > 0.05$). The purification process thus appears to remove some of the metal ions from crude cashew gum. The polyvalent metal ions are known to enhance the viscosity of the gums [13, 14] by inducing the polysaccharide chains in the gums to interact inter- or intra-molecularly [15].

The pH of 2 % w/v CCG and PCG were 4.90 and 5.22, respectively, showing that the crude gum is more acidic than the purified gum. Cashew gums used in this study appeared to be less acidic than gums obtained from other parts of Ghana (pH 3.8 – 4.2) [2]. Figure 1 shows the effect of storage time and temperature on pH of cashew gum mucilage. The pH of unpreserved (Fig. 1a) and preserved (Fig. 1b) cashew gum mucilage increased a week after preparation, then decreased at week 2 and remained relatively constant from week 2 to week 5. The pH of cashew gum mucilage remained relatively stable over time when refrigerated (~ 8 °C), compared to storage at 25 °C and 50 °C. It is therefore advisable to store cashew gum mucilage at low temperatures. Figure 2 shows the influence of gum purification on pH of cashew gum mucilage. For both the unpreserved (Fig. 2a) and preserved (Fig. 2b) mucilage, the pH of the purified gum mucilage was less stable compared to the crude gum on storage. The purification process appears to have removed some stability-inducing chemical constituents from PCG making the mucilage less stable compared to the crude gum. The effect of preservation on the pH of cashew gum mucilage is shown in Figure 3. Addition of a preservative to the gum mucilage appeared to have little influence on the pH upon storage ($p > 0.05$). Thus, the changes in pH observed upon storage of the gum mucilage, may signal chemical instability rather than microbial degradation of the gum.

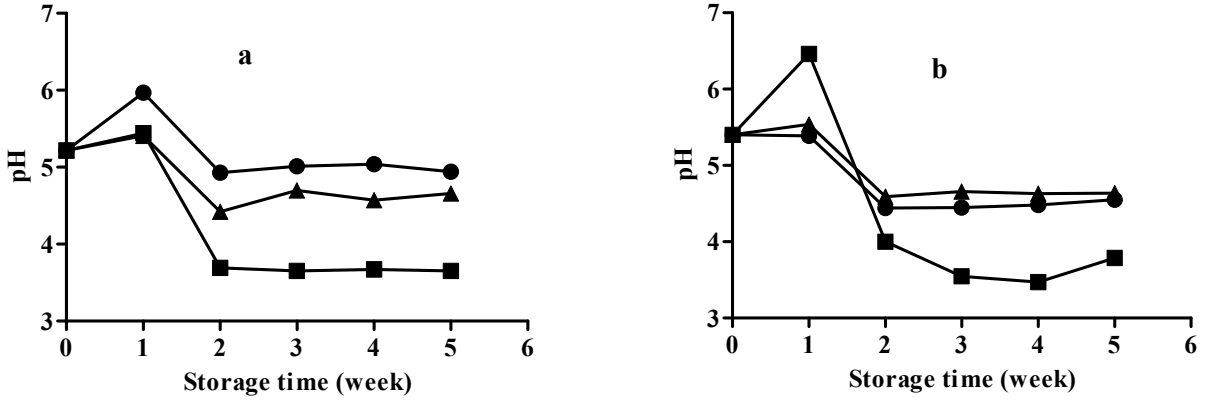

Fig. 1: The influence of storage time and temperature on the pH of a) unpreserved and b) preserved 2 % w/v purified cashew gum. Storage temperature: ● = 8 °C; ■ = 25 °C; ▲= 50 °C

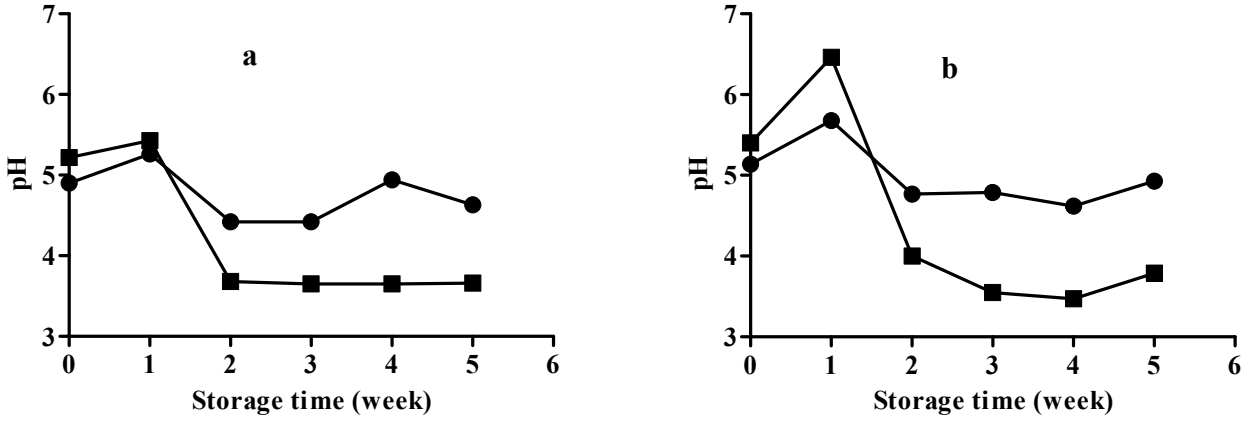

Fig. 2: The influence of gum purification on the pH of a) unpreserved and b) preserved 2 % w/v cashew gum at 25 °C. Nature of gum: ● = crude cashew gum; ■ = purified cashew gum

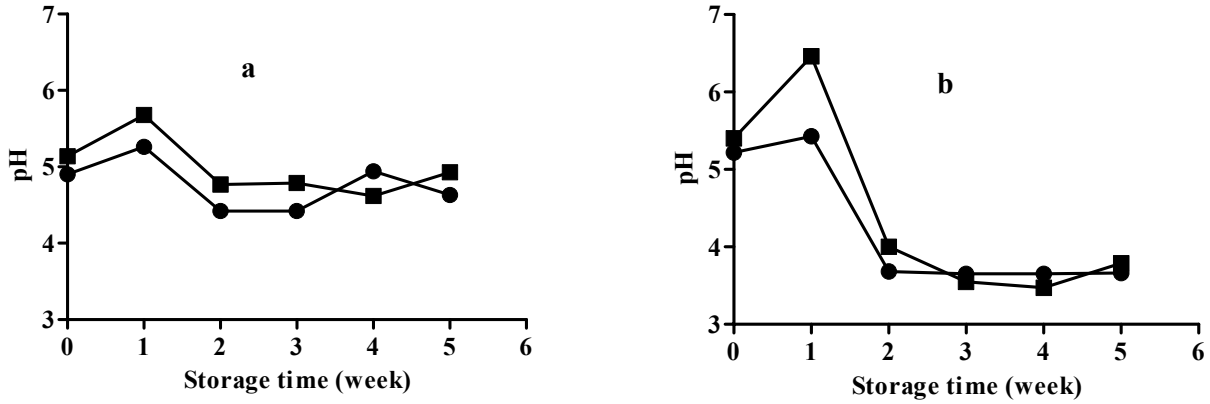

Fig. 3: The effect of preservation on the pH of a) crude and b) purified cashew gum mucilage at 25 °C. State of gum mucilage: ● = unpreserved; ■ = preserved

Figure 4 shows the comparative effect of concentration on the viscosity of PCG and acacia gum. Viscosity increased with increase in gum concentration but cashew gum was less viscous than acacia gum. Gums with high viscosities are said to have better quality [2] than less viscous gums. The effect of temperature on 40 % w/v PCG mucilage is shown in Figure 5. There was a gradual decrease in viscosity as temperature was increased. The viscosity of the gum mucilage decreased from about ~ 300 cP to ~ 100 cP as temperature was increased from 25 °C to 80 °C. There is the need to control the storage temperature of cashew gum mucilage as high temperatures may affect the structural integrity of the gum which may have adverse effects on the physicochemical characteristics of the gum [16].

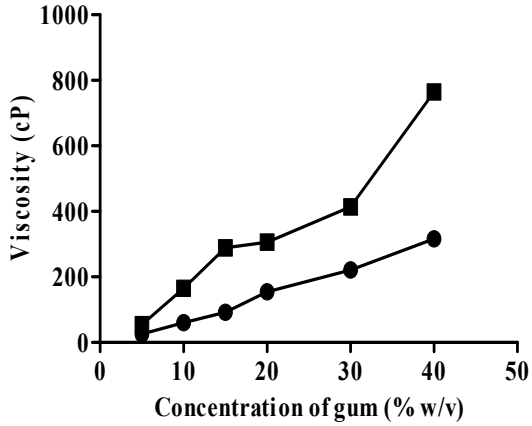

Fig. 4: The effect of concentration on the viscosity of purified cashew gum and acacia at 25 °C. Type of gum: ■ = acacia gum; ● = purified cashew gum

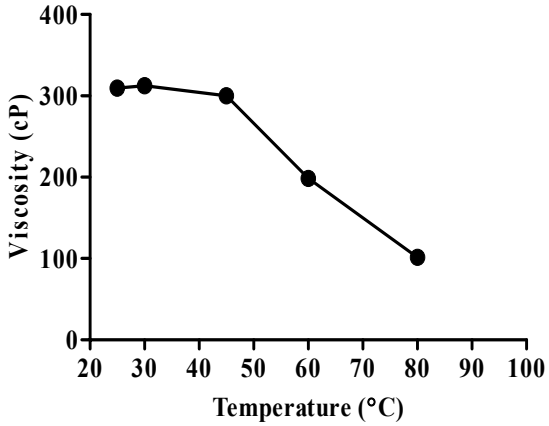

Fig. 5: The effect of temperature on the viscosity of 40 % w/v purified cashew gum

The flow characteristics of granules produced with different concentrations of purified cashew gum mucilage is shown in Table 3. The different batch of granules exhibited good flow properties with Hausner ratio and Carr's index values of 1.10 – 1.30 and 9.0 – 23 %, respectively. There was, however, no direct correlation between the flow properties of granules and the gum concentration used. The flow properties of granules prepared with 4 – 8 % w/w cashew gum were comparable to that of 4 % w/w acacia gum. Table 4 provides details on the physical properties of metronidazole tablets prepared using PCG mucilage as binder compared to acacia. All the tablets prepared had uniform tablet weight. Tablet hardness increased with increase in gum concentration. The hardness of tablets containing 2 % w/w cashew gum was < 4 kg while that containing 4 – 8 % w/w was ≥ 4 kg.

The friability of the tablets decreased with increase in gum concentration. Tablets prepared with 2 – 4 % w/w cashew gum had friability values > 1 % while that of 6 – 8 % w/w had friability < 1 %. Thus, tablets prepared with 4 – 8 % w/w cashew gum passed the BP tablet hardness test [10] while that containing 6 – 8 % w/w cashew gum passed the BP tablet friability test [10]. The disintegration time of the tablets was < 15 min and increased with increase in gum concentration. All the tablets exhibited fast dissolution in aqueous media with > 94 % of the drug released in 45 min. The dissolution rate of the tablets decreased with increase in cashew gum concentration. The fast disintegration and dissolution rate exhibited by the tablets have shown that cashew gum is suitable for use as a binder in conventional tablets intended for fast disintegration and release in the gastrointestinal tract

Table 3: Flow properties of metronidazole granules prepared with purified cashew gum as binding agent

Parameter	Concentration of gum (% w/w)				
	Cashew gum				Acacia gum
	2	4	6	8	4
Bulk density (g/cm^3)	0.581	0.581	0.598	0.590	0.575
Tapped density (g/cm^3)	0.755	0.692	0.657	0.654	0.657
Hausner ratio	1.299	1.191	1.099	1.108	1.143
Carr's index (%)	23.0	16.0	9.0	9.8	12.5

Table 4: Physical properties of metronidazole tablets formulated with purified cashew gum as binder

Parameter	Concentration of gum (% w/w)				
	Cashew gum				Acacia gum
	2	4	6	8	4
Tablet weight (mg)	427 ± 4.2	417 ± 4.9	415 ± 5.6	419 ± 3.1	418 ± 3.2
Hardness (kg)	3.4 ± 0.5	4.0 ± 1.2	4.7 ± 0.5	6.6 ± 0.6	5.0 ± 0.5
Friability (%)	1.56	1.43	0.87	0.53	0.66
Disintegration time (min)	1.0 ± 0.1	1.3 ± 0.1	4.2 ± 0.2	11.2 ± 0.6	9.7 ± 0.3
Dissolution time, $d_{45,}$ (min)	102.8 ± 4.4	97.6 ± 3.3	95.7 ± 1.7	94.7 ± 2.5	93.6 ± 3.2

CONCLUSION

Purification of cashew gum has an effect on the physicochemical properties of the gum such as moisture content, insoluble matter, pH, viscosity and metallic ion content. Purified cashew gum at concentrations of 4 – 8 % w/w was successfully employed as binder in the preparation of metronidazole tablets. The tablets produced demonstrated the requisite physicochemical properties of uniformity of weight, hardness, friability, disintegration and dissolution. Cashew gum can therefore be used as a binder in the production of conventional release tablets.

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