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Investigation of Blends of Cashew and Xanthan Gums as a Potential Carrier for Colonic Delivery of Ibuprofen

Mary-Ann Fosu, Kwabena Ofori-Kwakye*, Noble Kuntworbe, Martina Aduenimaa Bonsu

Department of Pharmaceutics, Faculty of Pharmacy and Pharmaceutical Sciences, College of Health Sciences, Kwame Nkrumah University of Science and Technology (KNUST), Kumasi, Ghana.

Abstract : The objective of this study was to investigate blends of cashew and xanthan gum as a potential carrier for colonic delivery of ibuprofen. Crude cashew gum was purified and characterized in terms of some physicochemical properties. Ibuprofen matrix tablet formulations (~200 mg ibuprofen) containing varying blends of cashew and xanthan gum were prepared by direct compression. Drug-excipient compatibility and the physical quality of compressed tablets were determined. *In vitro* swelling behavior and drug release of tablets in simulated stomach (pH 1.2; 2 h), small intestine (pH 7.4; 3 h) and colon (pH 6.8; 7 h), without enzymes, were studied. Cashew gum produced lower moisture content, swelling capacity, total ash, calcium, magnesium, sodium, copper and zinc but showed higher levels of manganese, iron and phosphorus, relative to xanthan gum. FTIR studies showed no interaction between ibuprofen and the excipients and the tablets exhibited higher swelling capacity in phosphate buffers (pH 6.8 and 7.4) than in 0.1 M HCl (pH 1.2). Xanthan-containing tablets showed higher swelling behavior in aqueous media than those containing only cashew gum. *In vitro* release studies showed that formulation F3 (cashew and xanthan 1:1) was most promising for colonic drug delivery with minimal (~13 %) ibuprofen release in simulated upper gastrointestinal conditions, and enhanced release in colonic conditions. All the tablet formulations demonstrated super case II transport mechanism and ibuprofen release involved both diffusion and erosion of the hydrated gum matrices. The studies have demonstrated the potential use of blended cashew and xanthan gums as vehicles for colonic delivery of drugs.
Keywords: Cashew gum, xanthan gum, colonic drug delivery, direct compression, matrix tablets, *in vitro* release.

Introduction

For decades now several researches have been conducted on the delivery of drugs into the colon for the treatment of local and systemic diseases [1-3]. The rate and prevalence of colonic diseases across the different categories of population in the developed and developing countries have been increasing. Colon cancer is ranked the 4th most common cancer globally and rated 171st cause of death in the world. The incidence of inflammatory bowel diseases is highest in Europe, recording 505 ulcerative colitis and 322 Crohn's disease cases per 100,000 persons [4]. In Ghana, occurrence of colon-rectum cancer which was almost negligible in the past is now among the top 50 causes of death with 0.24 % of deaths per 100,000 of the population [5].

Colonic drug delivery has proven to be ideal for the exploitation of new biotechnology drugs such as protein and peptide drugs. This observation is due to the specialized anatomic and physiological features of the

colon including longer resident and transit times, high concentration of microflora, increased pH and decreased enzymatic drug degradation, compared to the upper gastrointestinal tract [6]. Currently, the treatment of colonic diseases involve a combination of drugs for long term use which could possibly result in drug interactions and increased systemic side effects since most of these drugs are given orally or as injectable. Colon-specific drug delivery ensures the reduction in adverse effects in the treatment of colonic diseases, minimization of the extensive first pass metabolism of drugs such as steroids, and prevention of gastric irritation produced by the oral administration of drugs such as non-steroidal anti-inflammatory drugs [7]. Colonic drug delivery through the oral route is more comfortable to patients leading to improved medication compliance compared to the rectal route. Also, though the rectal route offers the shortest route for targeting drugs to the colon, reaching the proximal part of the colon is often very difficult.

Drugs used for colonic delivery should ideally preserve the integrity of the delivery system during passage through the stomach and the small intestines and only release the drugs on reaching the colon. On the other hand, the drug delivery system may exhibit minimal drug release in the upper gastrointestinal tract but achieve accelerated drug release in the colon, a so-called biphasic drug release [3, 8]. To achieve colonic drug delivery, the unique physiological features of the gastrointestinal tract have been exploited to obtain five colon-specific drug delivery technologies, namely: prodrugs/azo polymer systems, time-dependent systems, pH-dependent systems, pressure dependent systems and microbial triggered systems [9-14]. These technologies have been developed and extensively evaluated for their suitability for colonic delivery. In comparison with the other approaches, colonic drug delivery through the microbial triggering system is believed to achieve a higher degree of colonic selectivity [6].

Polysaccharides such as pectin, chitosan, guar gum, xanthan gum, cellulose, cashew gum, amylose and starch can be selectively degraded by the colonic enzymes and are therefore employed as vehicles for the delivery of drugs to the colon [15-19]. Cashew gum is a yellowish brown complex heteropolysaccharide obtained from the incised stem bark of *Anacardium occidentale* L (family: anacardiaceae). Xanthan gum is a polysaccharide secreted by *Xanthomonas campestris*. These gums have been used as pharmaceutical excipients and have advantages of low cost, high safety profiles, biocompatibility and susceptibility to degradation by the colonic microflora [20].

The aim of the current study was to characterize cashew gum in terms of some physicochemical properties and to prepare and evaluate ibuprofen matrix tablets comprising of blends of cashew gum and xanthan gum as a carrier for colonic delivery of the drug.

Materials and methods

Materials

Crude cashew gum was obtained as natural exudates from the stem bark of the plant *Anacardium occidentale* L (family: Anacardiaceae) from the cashew plantation at Bodokrom in the Eastern Region of Ghana, and was purified as described elsewhere [21]. The purified cashew gum with a yield of 75.84 % was passed through 0.18 mm sieve and used for further analysis. Xanthan gum was obtained from Shandong Fufeng Fermentation Co. Ltd. (Shandong Province, China). Ibuprofen powder was purchased from IOL Chemicals and Pharmaceutical Ltd. (India). Microcrystalline cellulose was obtained from Amponsah-Effah Pharmaceuticals Ltd. (Kumasi, Ghana) while magnesium stearate was obtained from the Chemical store, Department of Pharmaceutics, KNUST, Kumasi, Ghana. All other reagents used were of analytical grade.

Physicochemical characterization of cashew and xanthan gums

The moisture content, insoluble matter, swelling index, total ash, water soluble ash and acid insoluble ash were determined using official methods [22]. The pH of 1 % aqueous solution of cashew gum and 0.1 % xanthan gum was determined at 25 °C with an Oaklon pH meter (PC 700). The viscosities of 5-45 % w/v aqueous mucilage of cashew gum and 0.05-0.45 % w/v xanthan gum were determined at room temperature using the rotor 3 of the Haake viscometer 2 plus (Thermo Scientific, Germany). The effects of temperature on the viscosities of 25 %w/v cashew gum and 0.25 %w/v xanthan gum were evaluated at 10, 20, 30, 40 and 50 °C with the rotor 3 of the Haake viscometer 2 plus.

Evaluation of elemental and toxic metal content of gums

The gums were dry digested and the clear supernatant digests after centrifugation were used for elemental analysis. An atomic absorption spectrophotometer (Buck scientific model 210V GP) was used to determine the presence and amounts of iron (Fe), copper (Cu), zinc (Zn), Manganese (Mn), cadmium (Cd), lead (Pb), Mercury (Hg), Arsenic (Ar) and nickel (Ni) in each digest. The file for the type of analysis and hollow lamp was selected with appropriate wavelengths as follows: Fe, 248.3 nm; Cu, 324.8 nm; Zn, 213.9 nm; Mn, 279.5 nm; Cd, 228.9 nm; Pb, 283.3; Hg, 253.7nm; Ar, 193.7nm; and Ni, 341.5nm. The stock standard followed by the prepared sample solutions were analysed for the elements in triplicate determinations [23]. The magnesium (Mg) and calcium (Ca) contents were determined by EDTA titration [24]. Potassium (K) and sodium (Na) were determined in triplicate for each digest by flame photometry (Jenway PFP7 flame photometer) at 766 nm and 589 nm, respectively. The phosphorus (P) content was assessed using spectrophotometry (Jenway 6051 colorimeter) at 430 nm after colour development with the phospho-vanadomolybdate technique [25]. Carbon (C) and nitrogen (N) contents were determined using the modified Walkley-Black wet oxidation [26] and Kjeldahl [23] methods, respectively.

Preparation of powder blends and assessment of flow properties

The composition of five ibuprofen matrix tablet formulations containing cashew and xanthan gums in ratios of 100:0, 0:100, 50:50, 25:75 and 75:25 are presented in Table 1. The specified amounts of ibuprofen, cashew gum, xanthan gum and microcrystalline cellulose were weighed and blended in a mortar for 15 min and were subsequently lubricated with magnesium stearate for 2 min and used for further analysis. The bulk and tapped densities of purified cashew and xanthan gum powders and the powder blends of the ibuprofen matrix formulations were determined using a previously described method [27] from which the hausner's ratio and Carr's indices were subsequently calculated. The angle of repose was determined using the fixed height cone method [27]. The true densities of the gums were determined at 25 °C using the liquid displacement method, with chloroform as the displacement liquid [28].

Table 1. Composition of natural gum-based ibuprofen matrix tablet formulations

Code	Ibuprofen (mg)	Cashew gum (mg)	Xanthan gum (mg)	Microcrystalline cellulose (mg)	Magnesium stearate (mg)
FI	200	300	-	94	6
F2	200	-	300	94	6
F3	200	150	150	94	6
F4	200	75	225	94	6
F5	200	225	75	94	6

Drug-excipient compatibility studies

Twenty milligram portions of cashew gum, xanthan gum, ibuprofen and blended powder of ibuprofen matrix formulation (F3) were individually triturated with 200 mg spectroscopic grade KBr using agate mortar and pestle. The mixtures were spread uniformly in a suitable die and compressed into transparent discs with 8 tons. The FTIR spectra of the discs were obtained with a PerkinElmer Fourier Transform Infrared spectrophotometer (LI600301 spectrum Two Lila, UK) in the mid IR region between 4000 and 400 cm^{-1}. The spectra of the four samples were superimposed and compared to determine whether or not the principal bands present in pure ibuprofen were still present in the blended ibuprofen matrix formulation.

Tablet compression and assessment of tablet properties

The five well-lubricated ibuprofen blended powder formulations were directly compressed into tablets containing ~200 mg ibuprofen with a nominal tablet weight of 600 mg, using a Heysu ZP35D Rotary tablet compression machine (Shanghai, China) fitted with a concave punch and die set. The compressed ibuprofen matrix tablets were assessed for their uniformity of weight, tablet diameter and thickness, friability and hardness. The uniformity of weight test was determined according to the British Pharmacopoeia method [22]. The diameter and thickness of ten randomly selected tablets from each formulation was determined using an electronic Vernier caliper after which their respective mean and standard deviations were calculated. In the friability test, twenty tablets were randomly selected from each formulation, dusted and their initial weights

recorded. The tablets were placed in an Erweka friabilator (Type TA20, Heusenstamm, Germany) and subjected to tumbling from the rotation of the drum for 100 revolutions after which the tablets were removed, excluding any breakdown fragments. The tablets were dusted again and weighed and the percentage loss in weight was calculated [22]. The hardness or crushing strength of five randomly selected tablets from each formulation was determined by diametrical compression using a DKB hardness tester (SR. No 123).

Determination of drug content by HPLC

Twenty randomly selected tablets from each matrix tablet formulation was weighed into a porcelain mortar and powdered with the pestle. A quantity of the powder equivalent to 100 mg ibuprofen was weighed into a 50 ml volumetric flask and dissolved and diluted to volume with a mobile phase consisting of orthophosphoric acid, water and methanol in a ratio of 0.3:24.7:75. The samples were sonicated for 20 min and centrifuged for 15 min after which the supernatant was used for HPLC analysis. To determine the suitability of the HPLC system, three consecutive injections of the reference standard solution (200 mg ibuprofen solution) were made and the percent relative standard deviation (% RSD) was calculated, this should not be more than 2.0 %. Twenty microliters of the test solutions were separately injected through the stationary phase (Agilent (150 x 4.6) mm, C18) at a flow rate of 1.5 ml/min into the chromatograph of the Agilent Technologies 1200 series HPLC Apparatus (Germany) with the detector set at 221 nm. The chromatograms were recorded and the responses for the peaks for ibuprofen were recorded twice for the test samples. The quantity of ibuprofen was determined using the average peak area and the regression data *($y = 0.0624\ x + 0.0132$, $R^2 = 0.998$)* obtained for the calibration plot of ibuprofen powder (0.05 – 0.35 mg/ml) in the mobile phase.

Swelling behavior of tablets

Five tablets of each formulation were weighed individually (Wo) with an analytical balance (Adams Equipment, UK) and separately placed in glass petri dishes containing 50 ml simulated gastric fluid (pH 1.2), 50 ml of simulated small intestinal fluid (pH 7.4) and in 50 ml simulated colonic fluid (pH 6.8), without enzymes. The tablets were carefully removed from the petri dishes and blotted with tissue and reweighed (Wt) at the end of 2, 4, 6, 8 and 24 h. Triplicate determinations were made in each medium. The swelling index was calculated as follows: Swelling index = [Wt-Wo/Wo] x 100.

***In vitro* drug release studies**

In vitro drug release studies were undertaken with an Erweka dissolution apparatus (USP Apparatus 2) in 900 ml of dissolution media at paddle speed of 50 rpm and temperature of 37 ± 0.5^{o}C. Six tablets from each formulation were evaluated for a total of 12 h in simulated gastric fluid for 2 h (0.1M HCl, pH 1.2); followed by simulated small intestinal fluid for 3h (phosphate buffer pH 7.4) and finally in simulated colonic fluid for 7 h (phosphate buffer pH 6.8), without enzymes. At 15 min, 30 min, 1 h, 2 h, 3 h, 4 h, 5 h, 6 h and 7 h, 10 ml samples were withdrawn and replaced with the appropriate fresh dissolution medium maintained at 37 ± 0.5^{o}C. The withdrawn samples were filtered through Whatman filter paper (No. 5) and assayed spectrophotometrically (Labindia analytical UV/VIS spectrophotometer, India) at 221 nm using the appropriate regression data obtained from calibration plots of ibuprofen in 0.1 M HCl (pH 1.2) ($y = 397.6x-0.0001$, $R^2 = 0.9999$); phosphate buffer pH 7.4 ($y = 434.7x-0.0017$, $R^2 = 0.9995$); and phosphate buffer pH 6.8 ($y = 415.3x-0.0773$, $R^2 = 0.9997$). The drug release data was fitted into the zero order [29], first order [30], Higuchi model [31], Hixson-Crowell model [32] and the Korsmeyer-Peppas model [33] to determine the kinetics and mechanism of drug release from the ibuprofen matrix tablets.

Statistical analysis

Differences between the swelling and *in vitro* drug release profiles of the five tablet formulations were analysed statistically with one-way ANOVA followed by Newman-Keul's multiple comparison test using GraphPad Prism Version 5.00 (GraphPad Software Inc., USA). P values of paired samples < 0.05 were considered to be significantly different.

Results and discussion

Physicochemical properties of the gums

Table 2 presents the comparative physicochemical properties of cashew and xanthan gums. The two gums had low moisture contents (<15 %) and could be used as excipients for the formulation of moisture

sensitive drugs like aspirin. The level of moisture influences the microbial stability, storability, flow properties, viscosity, and density of gum powders [34]. Cashew gum showed low insoluble matter which falls within the official permissible limit of ≤ 0.5 % w/w [22, 35]. The insoluble matter is a measure of the quantity of contaminants such as stones, sand, debris, and scrapes from the bark of the tree present in the powdered gums. The low level of insoluble matter is testament to the efficiency of the gum purification and will enhances the aqueous solubility of the gum powder. The two gums exhibited low acidity in the aqueous medium and the acidity could be attributed to the presence of uronic acid, and or acidic substituents such as sulphuric acid present. The suitability of a pharmaceutical excipient in a formulation depends partly on its pH in aqueous media since the physiological activity and stability of most preparations are pH-dependent. The gums exhibited high swelling behaviors in aqueous medium with xanthan gum demonstrating a considerably higher swelling capacity than cashew gum. The swelling indices of the gum powders indicate their ability to swell in aqueous media to release embedded drugs and thus show their hydrophilic character and potential as binding and matrixing agents. Generally, polymers which demonstrate high swelling capacities produce long disintegration and dissolution times when used as matrixing agents or as film or compression coatings for multiparticulates and tablets. These polymers swell in aqueous media to form a gel which decreases the capillary flow of liquid into the tablets and increase the diffusional path length of the drug molecules.

Cashew gum showed lower total ash and water soluble ash but higher acid insoluble ash values than xanthan gum. Thus, xanthan gum contained higher amount of water soluble contaminants while cashew gum had higher levels of sand as acid insoluble contaminants. The ash content of a gum is a measure of the total quantity of minerals present in the gum while the mineral content is the total quantity of specific inorganic components such as calcium, zinc, sodium etc. present in the gum. The measure of both the mineral and ash content is important in determining the quality, nutritional benefits and microbial stability of the gum. The low values of total ash, acid insoluble ash and water soluble ash indicate that the gums have much organic content than inorganic content and show a low level of contamination during collection, extraction, purification and handling of the gums. The gum powders demonstrated fair flow properties with Carr's index, hausner ratio and angle of repose values of 17.11-26.04 %, 1.21-1.35, 30.2-31.4°, respectively.

Table 2. Comparative physicochemical properties of cashew and xanthan gums

Parameter	Cashew gum	Xanthan gum
Physical properties		
Moisture content (%)	7.00 ± 1.00	10.67 ± 0.06
Insoluble matter (%)	0.03 ± 0.01	ND
pH (1 % w/v mucilage)	5.09 ± 0.01	*5.86 ± 0.03
Swelling index (%)	94.0 ± 0.2	140.0 ± 0.0
Total ash (% w/w)	1.30 ± 0.4	5.23 ± 0.20
Water soluble ash (% w/w)	0.88 ± 0.01	2.21 ± 0.16
Acid insoluble ash (% w/w)	0.36 ± 0.01	0.10 ± 0.01
Viscosity (25 % w/v) (dPas)	0.58	**1.19
Flow properties		
Bulk density (g/ml)	0.732 ± 0.015	0.476 ± 0.000
Tapped density (g/ml)	0.884 ± 0.044	0.644 ± 0.021
True density (g/ml)	1.619 ± 0.099	1.575 ± 0.049
Carr's index (%)	17.11 ± 2.45	26.04 ± 2.41
Hausner ratio	1.21 ± 0.03	1.35 ± 0.04
Angle of repose (°)	30.2 ± 0.4	31.4 ± 0.8

*pH of 0.1 % solution @25 °C
**Viscosity of 0.25 % aqueous mucilage

Table 3 presents the results of the elemental content of the two gums. Cashew gum contained lower amounts of calcium, magnesium, sodium, copper, and zinc but higher levels of phosphorus, potassium, iron and manganese, compared to xanthan gum. Iron and manganese were the predominant minerals in cashew gum whiles iron, copper and zinc were predominant in xanthan gum. The results of the mineral content obtained in the current study were lower than that obtained previously [21], due possibly to the difference in the source of the gums and different times of gum collection. The gums being polysaccharides showed high levels of carbon

content (43-44 %). The gums are organic compounds and are therefore susceptible to microbial contamination if not properly stored. Cashew and xanthan gum showed very low levels of the toxic metals mercury, lead, nickel, cadmium and arsenic, rendering them safe for use as pharmaceutical excipients. Gums obtained from plants contain many metal ions as neutralized cations. Mineral ions such as calcium and potassium are medically beneficial when present in gums and used at recommended concentrations, while others like mercury and cadmium are toxic even at low concentrations and can render the gum unfit for use as a pharmaceutical excipient. The presence of some mineral ions can affect the physicochemical properties of the gum such as the aqueous solubility and viscosity.

Table 3. Mineral and toxic metal ion contents of gums

Element	Cashew gum	Xanthan gum
Minerals		
Phosphorus (g/100g)	0.12 ± 0.00	0.05 ± 0.02
Calcium (g/100g)	0.02 ± 0.04	0.96 ± 0.03
Magnesium (g/100g)	0.01 ± 0.00	0.59 ± 0.05
Potassium (g/100g)	0.43 ± 0.01	0.37 ± 0.01
Sodium (g/100g)	0.03 ± 0.00	0.33 ± 0.02
Copper (g/100g)	1.40 ± 0.10	4.50 ± 0.14
Iron (g/100g)	10.60 ± 0.40	5.50 ± 0.14
Manganese (g/100g)	8.23 ± 0.06	0.55 ± 0.07
Zinc (g/100g)	2.20 ± 0.20	4.95 ± 0.21
Toxic metals		
Mercury (µg/g)	0.039 ± 0.001	0.675 ± 0.001
Lead (µg/g)	0.544 ± 0.001	0.534 ± 0.001
Nickel (µg/g)	<0.001	<0.001
Cadmium (µg/g)	0.020 ± 0.000	0.048 ± 0.000
Arsenic (µg/g)	0.039 ± 0.000	0.280 ± 0.014
Other elements		
Carbon (g/100g)	44.29 ± 0.10	43.09 ± 1.69
Nitrogen (g/100g)	0.07 ± 0.01	0.57 ± 0.02

The viscosities of the gum mucilage were determined to predict the performance of the gums in dipping, coating or gel forming operations. Though the concentration of xanthan gum used in this determination was one hundredth that of cashew gum, xanthan gum gave higher viscosities than cashew gum. This implies that xanthan gum is a more viscous gum and would form a thicker colloidal hydrophilic gel in a matrix tablet formulation, making xanthan gum a better drug release retardant than cashew gum. The gums showed increased viscosities with increase in concentration [19]. This is due to the increase in internal resistance of the gum mucilage to flow resulting from exertion of intermolecular friction when layers of the mucilage slides over each other. There was a decrease in viscosity of the gums for every 10 °C rise in temperature (Figure 1), due possibly to the disentanglement of the polymer chain as temperature increases [36].

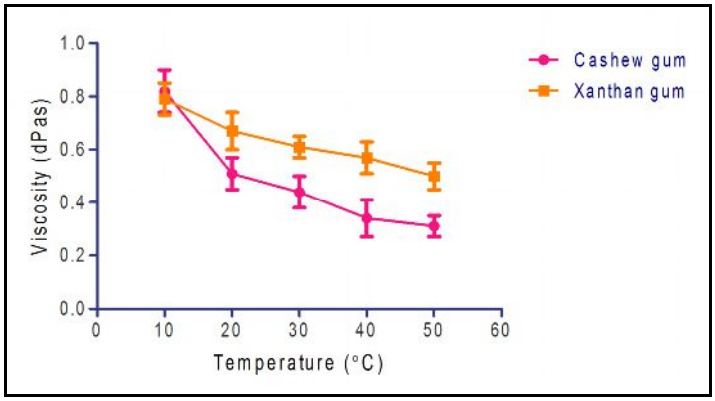

Figure 1. Effect of temperature on the viscosities of cashew (25 %w/v) and xanthan (0.25 %w/v) gum mucilages

Figure 2 shows the FTIR spectra of cashew gum, xanthan gum, ibuprofen and the blended powder of the two gums and ibuprofen. The FTIR spectra of xanthan gum showed an alcoholic –OH stretch around 3300 cm^{-1}, -CH stretch in methyl and methylene groups between 2500 and 2900 cm^{-1}, -C=O stretch of acetate at 1650 cm^{-1}, -COO group at 600 cm^{-1} and 1400 cm^{-1}. Carbonyl acetate deformation stretch between 1050 and 1200 cm^{-1} (broad band) and a β-glycoside linkages at 700-900 cm^{-1}. That of cashew gum showed an alcoholic –OH stretch (broad band between 3200 and 3600 cm^{-1}) and at 1327 cm^{-1} in the fingerprint region. There is also an aldehyde –C=O stretch at 1643.42 cm^{-1}, a methyl and methylene –CH at 2808.48 cm^{-1} and 2924.1 cm^{-1} respectively and a –COO stretch at 618.01 and 1504.51 cm^{-1}. This is a clear indication that xanthan and cashew are polysaccharides. Finally, the FTIR spectrum of pure ibuprofen showed a carbonyl C=O stretch at 1700 cm^{-1}, a broad band representing the O-H of a carboxylic acid dimer around 3200 cm^{-1}, a needle like and very sharp peaks of C=C of the benzene ring at 1520 and 1480 cm^{-1} in the functional group region and three major bands at 720, 760 and 850 cm^{-1} in the fingerprint region which is a confirmation of its aromaticity. This shows that, ibuprofen obtained was indeed pure. The FTIR spectrum for the combined mixture showed no interaction occurred between ibuprofen, cashew gum and xanthan gum as all the principal bands in the individual compounds were present in the combined mixture.

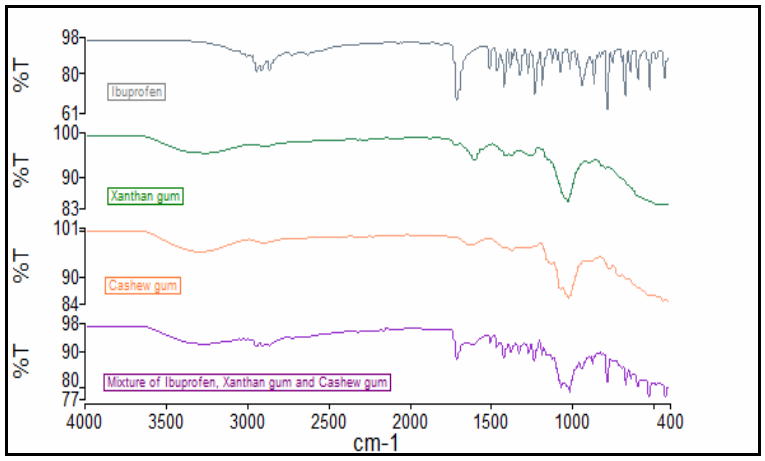

Figure 2. FTIR spectra of cashew gum, xanthan gum, ibuprofen and the mixture of the two

Flow properties of powder blends and quality assessment of matrix tablets

Table 4 presents the flow properties of the ibuprofen matrix formulations. The various powder blends with Carr's index of 32.79-39.42 %, hausner's ratio of 1.49-1.65 and angle of repose of 40.4-42.2° showed poor flow properties [27]. As a result, manual filling of the dies, addition of more glidant or agitation of the hopper would be required to enable the powder blends to flow appropriately to fill the die for direct compression. The individual gum powders exhibited better flow properties than the blended powder formulations due to the poor flow properties of ibuprofen powder [37]. Poor flow properties can result in powder segregation, flow obstruction and irregular flow during the direct compression of the powdered blends. Table 5 shows the quality parameters of the ibuprofen matrix tablet formulations. The uniformity of weight test measures the level of weight uniformity in a batch of tablets and influences the amount of active ingredient contained in the tablets. The average weight of the tablet formulations was >324 mg and hence to pass this test, not more than two of the tablets should deviate from the mean weight by more than ±5% and none should deviate by ±10% [35]. All the tablet formulations passed the uniformity of weight test. The weight of a compressed tablet is dependent on the density of the powder blend and the diameter and thickness of the resulting tablet. The average diameter of the tablets ranged from 13.01-13.03 mm. The slight changes in the diameter could be due to uneven surface of the punch and dies during tablet compression. Uniformity of tablet thickness is also an important quality control tool since it ensures uniformity in tablet appearance and uniformity of tablet packaging containers. By monitoring the thickness of the tablet at regular time intervals, problems associated with uniformity of tablet weight and content can be detected at the early stage of production. The results obtained showed fairly uniform tablet thickness ($p>0.05$).

Table 4. Flow properties of powder blends of natural gum-based ibuprofen formulations

Code	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Hausner ratio	Angle of repose (°)
F1	0.454 ± 0.000	0.683 ± 0.027	33.34 ± 2.62	1.50 ± 0.06	41.2 ± 1.0
F2	0.395 ± 0.019	0.653 ± 0.024	39.42 ± 2.55	1.65 ± 0.07	41.2 ± 0.4
F3	0.395 ± 0.009	0.625 ± 0.000	36.82 ± 1.42	1.58 ± 0.04	41.6 ± 0.5
F4	0.429 ± 0.010	0.639 ± 0.024	32.79 ± 0.09	1.49 ± 0.09	40.4 ± 0.8
F5	0.429 ± 0.022	0.639 ± 0.024	32.83 ± 0.87	1.49 ± 0.02	42.2 ± 0.4

Table 5. Quality parameters of natural gum-based ibuprofen matrix tablet formulations

Code	*Average weight (mg), *n = 20*	Diameter (mm), *n = 10*	Thickness (mm), *n = 5*	Friability (%), *n = 20*	Hardness (Kgf), *n = 10*	Drug content (%), *n = 3*
F1	603.0 ± 12.6	13.03 ± 0.05	3.13 ± 0.16	2.36	4.08 ± 0.08	97.78 ± 0.28
F2	601.1 ± 13.5	13.03 ± 0.07	3.12 ± 0.10	2.15	5.18 ± 0.47	96.79 ± 2.50
F3	599.1 ± 12.8	13.02 ± 0.04	3.16 ± 0.08	1.88	4.20 ± 0.19	102.10 ± 0.95
F4	610.7 ± 2.9	13.01 ± 0.03	3.09 ± 0.10	3.00	4.64 ± 0.61	108.40 ± 1.21
F5	607.9 ± 9.2	13.02 ± 0.06	3.08 ± 0.10	2.08	4.40 ± 0.38	103.60 ± 0.78

*No tablet deviated by ± 5 % and none by ± 10 %

The essence of a friability test is to ensure that the tablets can withstand abrasion, friction and shock during transportation, packaging and handling. A weight loss of ≤1% of the weight of tablet being tested is generally considered acceptable for pharmaceutical products. All the batches failed the friability test with formulation F4 recording the highest weight loss of 3%. Tablets which are formulated via direct compression are generally known to be more friable than those produced via granulation due to the absence of a binder. Tablet hardness as one of the most important quality control measures is undertaken during the compression process. Tablets which are too soft will not be able to withstand handling and further processing such as coating and packaging. Also, tablets which are too hard may not undergo disintegration at the required period to meet disintegration and dissolution specifications. A tablet hardness of 4 kgf is the minimum satisfactory force for a tablet and all the ibuprofen matrix tablets passed the test due to the application of an appropriate tablet compression force. The drug content of the formulations ranged from 97.8-108.4 %. Assay is a very important quality control tool which aids in the identification and subsequent elimination of substandard and counterfeit drugs. From the results, all the formulations of ibuprofen matrix tablets contained the required amount of ibuprofen as specified [35]. This implies that the different formulations of ibuprofen matrix tablets contains the stipulated amount of the drug to achieve the desired therapeutic effect.

***In vitro* swelling and drug release studies**

The swelling behavior of the matrix tablets in simulated gastrointestinal fluid are shown in Figure 3. Matrix tablets which contained increased amounts of xanthan gum showed increased swelling capacities in the different pH media with time but the increases were not significant ($p>0.05$). Formulation F1 which contained only cashew gum as a carrier exhibited significantly lower ($p<0.05$) swelling capacities in the three aqueous media. All the formulations, except FI, showed a high swelling behavior in phosphate buffer (pH 7.4 and 6.8) compared to 0.1M HCl (pH 1.2). The enhanced swelling capacity of ibuprofen matrix tablets in phosphate buffer could be due to the ions present in the buffer [38]. The ions present in the buffer may cross-link with the gums to cause an increase in their hydrophilicity resulting in increase in their swelling capacities. Xanthan gum is expected to form a more viscous hydrated gel layer in aqueous medium compared to cashew gum and can form a better protective barrier to restrict the entry of water into the matrix tablet. The movement of dissolved ibuprofen out of the matrix tablets is expected to be reduced because of the increase in diffusion pathway of the dissolved drug in xanthan gum compared to cashew gum.

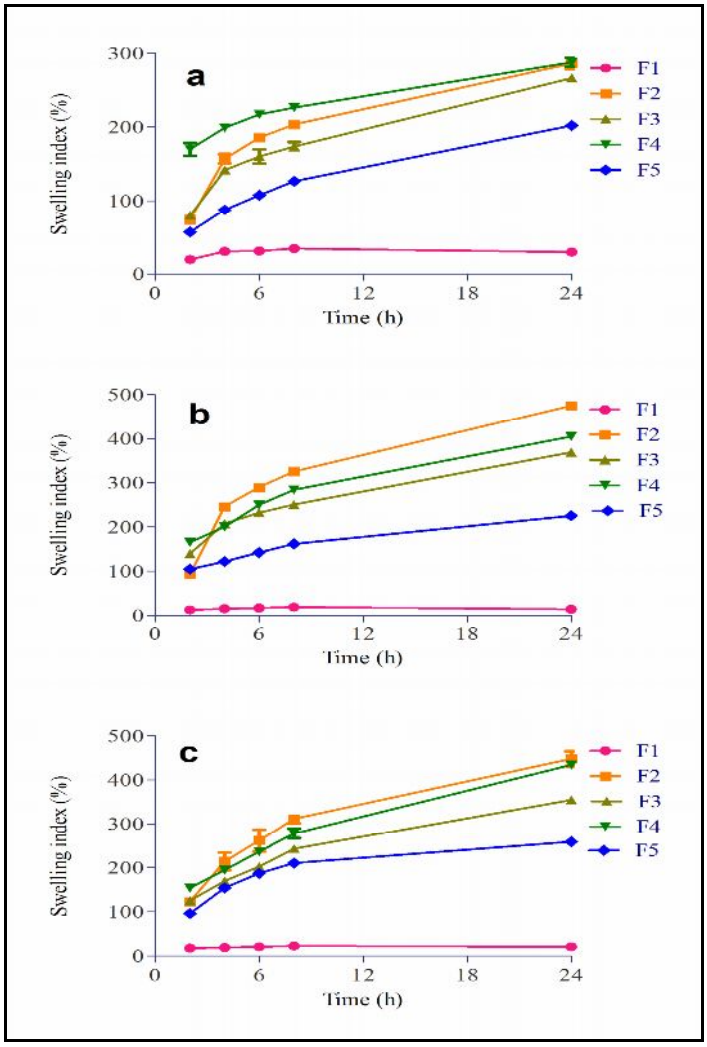

Figure 3. Swelling profiles of the gum-based ibuprofen matrix tablet formulations in a) 0.1 M HCl (pH 1.2), b) phosphate buffer pH 7.4, and c) phosphate buffer pH 6.8. (Mean ± S.D., *n = 3*)

Figure 4 shows the drug release profiles of the ibuprofen matrix tablet formulations in simulated gastrointestinal conditions. Tablets intended for colonic delivery should demonstrate minimal or no drug release in the upper gastrointestinal tract but exhibit marked drug release in the colon through the action of the colonic microflora. Natural gums such as those of cashew and xanthan are susceptible to degradation by the colonic microflora [20]. All the ibuprofen matrix tablets remained intact with considerable swelling over the 12 h dissolution studies. However, xanthan gum-containing matrix tablets (F2-F5) showed greater swelling capacity than cashew gum only matrix tablets (F1). All the tablet formulations showed very minimal drug release (< 2 %) in the simulated gastric conditions in 2 h. In simulated upper gastrointestinal conditions (gastric and small intestinal conditions) formulation F3 showed 13.2 % drug release while formulations F1, F2, F4 and F5 showed between 25.8-33.6 % drug releases. This result demonstrates that formulation F3 which contains 50 % xanthan and 50 % cashew gums is the best formulation for retarding drug release in the upper gastrointestinal tract and is most suitable for the colonic delivery of ibuprofen. The other formulations that showed greater drug release in the simulated upper gastrointestinal conditions could be coated with a suitable polymer to improve the retardation of drug release there. After the 12 h dissolution studies, formulation F3 recorded 36.65 % release while F5 showed the highest ibuprofen release of 55.22 %. There were however, no significant differences ($p>0.05$) in the release of ibuprofen from the tablet formulations, except between F3 and F5 ($p<0.05$). It is expected that ibuprofen release from the natural gum-based matrix tablets would be accelerated in the presence of colonic microflora [20].

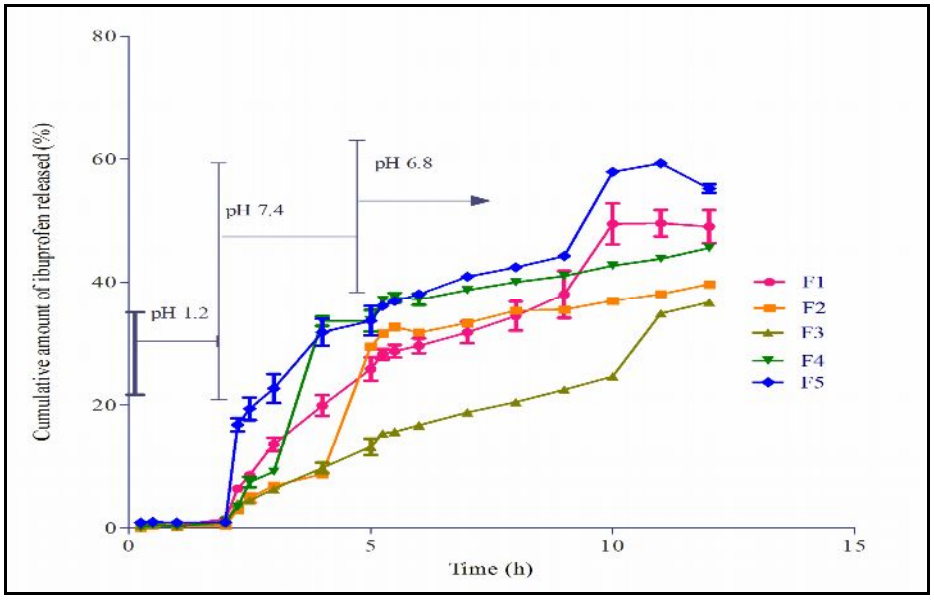

Figure 4: Drug release profiles of gum-based ibuprofen matrix tablet formulations in simulated gastrointestinal fluids (pH 1.2, 2 h; phosphate buffer pH 7.4, 3 h; phosphate buffer pH 6.8, 7 h) (Mean ± S.D., *n* = *3*)

The *in vitro* dissolution data was analysed using five mathematical models to determine the release kinetics of the ibuprofen matrix tablets. The R^2 values signifies how well a drug release profile best fits any of the kinetic models. Results presented in Table 6 indicate that formulations F1 and F3 followed the zero order release kinetics (constant release) with R^2 values of 0.9619 and 0.9715 respectively. This demonstrates that the release of ibuprofen from the matrix tablet is independent of the concentration of drug embedded in the matrix tablet. Formulation F5 fitted the Higuchi model (R^2 = 0.9439), thus ibuprofen in F5 was embedded in an insoluble matrix and its release from the matrix is dependent on the square root of time based on Fickian diffusion. Formulations F2 (R^2 = 0.8791) and F4 (R^2 = 0.8991) also best fitted the Korsemayer-Peppas model, indicating that the diffusional release of ibuprofen from F2 and F4 was similar to that from a polymeric film [39]. The value of '*n*' in the Korsmeyer-Peppas equation is used to characterize the release mechanism of the drug. For cylindrical tablets, $0.45 \leq n$ shows a Fickian diffusion mechanism, $0.45 < n < 0.89$ demonstrates non-Fickian transport, $n = 0.89$ denotes Case II (relaxational) transport, and $n > 0.89$ also shows super case II transport [40, 41]. From the results, all the '*n*' values were above 0.89. This shows that, all the matrix tablet formulations exhibited super case II transport mechanism of drug release. Thus, ibuprofen release from the matrix tablets was by diffusion and relaxation of the polymer chains.

Table 6. Kinetics and mechanism of ibuprofen release from the matrix tablet formulations

Code	Zero order		First order		Higuchi		Hixson-Crowell		Korsmeyer-Peppas	
	K_0	R^2	K_1	R^2	K_H	R^2	K_{HC}	R^2	n	R^2
F1	4.6961	0.9619	0.1629	0.7090	19.1980	0.9458	0.2562	0.8325	1.4101	0.8763
F2	4.0999	0.83703	0.2034	0.6839	17.1420	0.8608	0.2721	0.7771	1.7961	0.8791
F3	3.0747	0.9715	0.1604	0.7668	12.2390	0.9056	0.2220	0.8916	1.3357	0.8761
F4	4.5490	0.8088	0.1927	0.6426	19.3930	0.8649	0.2722	0.7315	1.7753	0.8991
F5	5.1761	0.9119	0.1498	0.6118	21.7100	0.9439	0.2501	0.7269	1.3432	0.8110

K_0, K_1, K_H and K_{HC} are kinetic constants for zero order, first order, Higuchi model and Hixson-Crowell model, respectively; R^2 = correlation coefficient; *n* = diffusion constant

Conclusions

Cashew gum was purified and characterized in terms of its physicochemical properties relative to that of xanthan gum. Cashew gum was less viscous and possessed lower swelling capacity than xanthan gum but exhibited the necessary physicochemical characteristics to be used as an excipient. Ibuprofen matrix tablets were produced using various ratios of cashew and xanthan gums as carriers. *In vitro* swelling and drug release

studies showed that the gums could swell extensively in aqueous media and could retard drug release to varying levels in simulated upper gastrointestinal tract conditions. Tablet formulation F3 containing cashew and xanthan gums in a 1: 1 ratio was the best formulation for colonic delivery of ibuprofen. It was concluded from the study that blends of cashew and xanthan gums have enormous potential as a carrier for the successful delivery of drugs to the colon.

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