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Microbead design for sustained drug release using four natural gums

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ABSTRACT

Four natural gums, namely albizia, cissus, irvingia and khaya gums have been characterized and evaluated as polymers for the formulation of microbeads for controlled delivery of diclofenac sodium. The natural gums were characterized for their material properties using standard methods. Diclofenac microbeads were prepared by ionotropic gelation using gel blends of the natural gums and sodium alginate at different ratios and zinc chloride solution (10%w/v) as the crosslinking agent. The microbeads were assessed using SEM, swelling characteristics, drug entrapment efficiencies and release properties. Data obtained from *in vitro* dissolution studies were fitted to various kinetic equations to determine the kinetics and mechanisms of drug release, and the similarity factor, f_2, was used to compare the different formulations. The results showed that the natural gum polymers varied considerably in their material properties. Spherical and discrete microbeads with particle size of 1.48–2.41 μm were obtained with entrapment efficiencies of 44.0–71.3%w/w. Drug release was found to depend on the type and concentration of polymer gum used with formulations containing gum:alginate ratio of 3:1 showing the highest dissolution times. Controlled release of diclofenac was obtained over for 5 h. Drug release from the beads containing the polymer blends of the four gums and sodium alginate fitted the Korsmeyer–Peppas model which appeared to be dependent on the nature of natural gum in the polymer blend while the beads containing alginate alone fitted the Hopfenberg model. Beads containing albizia and cissus had comparable release profiles to those containing khaya ($f_2 > 50$). The results suggest that the natural gums could be potentially useful for the formulation controlled release microbeads.

1. Introduction

One approach for controlled release formulation of therapeutic agents is the production of polymeric gel beads. Beads are discrete, spherical microcapsules that serve as solid substrate on which the drug is coated or encapsulated in the core [1,2]. Microbeads provide sustained release properties and more uniform distribution of drugs within the gastrointestinal tract and enhance drug bioavailability [2]. Microbeads have been prepared from a variety of polymeric materials including polysaccharides [3], polyalphahydroxy-acids including polylactide and copolymers [4], polyacrylates, polyalkylcyanoacrylates [5] and proteins [6]. Several natural and synthetic polymers have been used for the preparation of microsbeads for controlled release [7–10]. Among them are alginic acid [7], sodium alginates [10], chitosan [11] and pectin [12]. Sodium alginate, a water soluble salt of alginic acid, is a linear polysaccharides composed of variable amounts of (1–4)-β-D-mannuronic acid and its epimer, α-L-glucouronic acid, extracted from marine brown algae [13]. Alginates are known to form stable, bioadhesive gel with divalent cations such as Ca^{2+}, Sr^{2+}, Zn^{2+} and Ba^{2+} under mild conditions that are suitable for biomacromolecules and living cells [14].

The discovery and design of novel polymers are important in order to expand the scope of new drug delivery systems and meet the special needs of drug formulators [15]. There are several natural gums which are widely available in the tropics that are underutilized which could find application in the pharmaceutical industry. Natural gums have been found to fulfil pharmaceutical requirements of being non-toxic, stable, biodegradable, relatively inexpensive and having flexible regulatory issues when compared to the synthetic polymers. In addition, they can be subjected to physical and chemical modifications to alter their physicochemical properties resulting in a wide range of functional properties that may permit their application as polymers in drug delivery [16,17].

Among the natural gums that have been evaluated for drug delivery are albizia, irvingia, khaya and cissus gums. Albizia gum, obtained from the incised trunk of the tree, *Albizia zygia* (DC) J.F. Macbr, family Leguminosae, and khaya gum obtained from the

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incised trunk of the tree, *Khaya grandifoliola* CDC, family Meliaceae, have been shown to be useful as binding agents in tablet formulations [18,19], directly compressible matrix system for controlled drug delivery [20,21] and as compression coating materials for drug targeting to the colon [21]. On the other hand, cissus gum obtained from the stem and roots of *Cissus pulpunea* Guill and Perr, family Ampelidacae, and irvingia gum obtained from the nuts of *Irvingia gabonensis* (O'Rourke) Bail, family Irvingiacae, have been shown to possess binding properties in tablet formulations [22,23]. These natural gums have been shown to comprise of mannose, galactose, glucuronic acid and 4-*o*-methylglucuronic acid although the proportion vary depending on the botanical source [24,25]. They are hydrophilic and have the ability to hydrate rapidly in cold water and attain high viscosity at relatively low concentrations [20]. Thus in the present study, four natural gums, namely albizia, cissus, irvingia and khaya gums, have been characterized and evaluated as polymers for controlled delivery of diclofenac sodium. The effects of different concentrations of these polymers and sodium alginate on the drug release properties from the microbeads were also evaluated.

Diclofenac sodium is a potent non-steroidal anti-inflammatory drug with short biological half-life (1–2 h) that requires multiple dosing. Long-term administration of diclofenac often lead to adverse effects such as gastrointestinal disturbances, peptic ulceration and gastrointestinal bleeding which may result in poor patient compliance and inefficient therapy [26]. The formulation of diclofenac as controlled release microbeads will offer a means of delivering the drug in a sustained manner with reduced side effects.

2. Materials and methods

2.1. Materials

The materials used were diclofenac sodium (Fagron GmbH & Co., Barsbttel, Germany), sodium alginate (Carl Roth GmbH & Co., Karlsruhe, Germany), zinc chloride (Alfa Aesar GmbH & Co., Karlsruhe, Germany). Albizia and khaya gums were obtained from the incised trunks of *Albizia zygia* and *Khaya grandifoliola* respectively (Botanical Gardens, University of Ibadan, Ibadan, Nigeria), while cissus gum was obtained from the stems of *Cissus pulpunea* (Tose village, Oyo state, Nigeria) and irvingia gum was obtained from the dried kernels of *Irvingia gabonensis* (Agudama-Ekpetiama local market, Yenagoa, Nigeria). All other reagents were of analytical grade.

2.2. Extraction of gums

Crude khaya and albizia gums were dried in an oven at 50 °C for 48 h and then milled using a laboratory mill. The gums were hydrated in double strength chloroform water for 5 days with intermittent stirring to ensure dissolution of the gums. On the other hand, cissus gum was obtained by soaking the stems of *Cissus pulpunea* in chloroform water for 48 h. The gums were strained through a calico cloth to remove extraneous materials and then precipitated using absolute ethanol. The precipitated gum was filtered and the washed with diethyl ether. The purified gums were dried in hot air oven at 40 °C for 48 h and then pulverized and kept in air-tight containers [27].

Dried kernels of *Irvingia gabonensis* (without the seed coats) were powdered using a laboratory mill and then macerated in petroleum ether for 24 h. The extract was separated from the residue and the residue was repeatedly soaked in petroleum ether until there was no more fat obtained in the petroleum ether. The fat-free residue was hydrated in chloroform water double strength for 5 days and irvingia gum was precipitated with ethanol as previously described for the other gums [23].

2.3. Characterization of gums

2.3.1. Particle size analysis

Particle size distribution of the natural gums was carried out using laser light diffractometer with a dry feeder (Sympatec Rodos SR 544, Sympatec, Germany). The mean particle size and surface volume were calculated.

2.3.2. Brunauer–Emmett–Teller (BET) surface area analysis

High speed gas absorption analyser (Nova 3200, version 6.11, Quantochrome Corporation, USA) was used to determine specific surface area of the gum powders.

2.3.3. Porosity measurement

The percent porosity of the gum powders was determined using the Pascal 440 mercury porosimeter (Thermo Fischer Scientific, Massachusetts, USA) with a maximum pressure of 400 MPa.

2.3.4. X-ray diffraction analysis

The X-ray diffraction pattern was recorded with a copper anode x-ray tube (Cu-K$\acute{\alpha}_1$ radiation) using an X-ray diffractometer (Phillips PW 1830, Almelo, Holland). The gum powders were packed tightly in sample holders and each sample was exposed to the X-ray beam at 45 kV and 40 mA at the rate of 5 kV/20 min. The scanning region of the diffraction angle (2θ) was from 3° to 50°.

2.3.5. Particle density measurements

The particle densities of the gums were determined by the ultrapycnometer method using helium gas (Ultrapycnometer 1000 version 2.12. Quantachrome Corporation, Florida, USA).

2.3.6. Thermogravimetric analysis

The moisture content (%) of the natural gums was determined using TGA (Pyris 1 Thermogravimetric Analyzer, TGA 7, Perkin Elmer Instruments, USA). The samples were placed in ceramic pans and heated at a heating rate of 10 °C/min, from 60 to 300 °C. It was held for 1 min at 60 °C.

2.3.7. Viscosity analysis

The viscosity values of 2%w/v aqueous dispersion of sodium alginate, the natural gums and the various blends of gum:alginate were measured at 25 °C using Roto Visco 1 viscometer (Haake, Germany).

2.3.8. Preliminary formulation studies

Preformulation studies were carried out in order to optimize the formulation and physicochemical properties of the microbeads. Several formulation trials were done with varying ratios of the natural gum: sodium alginate, type and concentration of cross-linking agent, stirring speed and curing time. The detailed compositions of the optimized microbeads are presented in Table 1.

2.3.9. Preparation of microbeads

Diclofenac microbeads were prepared from a gel blend of natural gum and sodium alginate to obtain a total polymer concentration of 2%w/v. Diclofenac sodium (1 g) was added such that the ratio of total polymer to drug was 2:1. The resulting dispersion was extruded into zinc chloride solution (10%w/v) using a syringe with 0.90 mm needle at a dropping rate of 2 ml/min and stirring speed of 300 rpm. The formed beads were allowed 30 min for curing and then left standing for 1 h to allow further cross-linking. The beads were collected by decantation, washed with distilled water and then dried for 24 h in hot air oven at 40 °C temperature.

Table 1
The composition and viscosity of polymer blends used for the formulation of microbeads and the formulation code (mean ± SD, $n = 3$).

Polymer (s)	Polymer ratio	Formulation code	Viscosity (Pas)
Alginate	1:0	S1	290.00 ± 0.07
Albizia:Alginate	1:0	–	26.00 ± 0.04
	1:1	A1	112.00 ± 3.54
	2:1	A2	52.00 ± 1.06
	3:1	A3	40.00 ± 1.41
Cissus:Alginate	1:0	–	11.60 ± 0.10
	1:1	C1	122.00 ± 2.83
	2:1	C2	106.00 ± 2.83
	3:1	C3	50.00 ± 3.54
Irvingia:Alginate	1:0	–	6.50 ± 0.08
	1:1	V1	120.00 ± 2.82
	2:1	V2	49.00 ± 1.41
	3:1	V3	44.00 ± 1.41
Khaya-Alginate	1:0	–	19.50 ± 0.02
	1:1	K1	61.00 ± 0.71
	2:1	K2	64.00 ± 0.00
	3:1	K3	81.00 ± 2.12

2.4. Characterization of microbeads

2.4.1. Size and morphology

The microbeads were sputtered with gold and their morphology and surface characteristics were analyzed using scanning electron microscopy (Hitachi Model S- 2460 N, Japan) at an accelerating voltage of 25 kV. The particle sizes of 100 microbeads were determined by optical microscopy using a computerized microscope fitted with a coloured video (Leitz Laborlux II, Wetzlar, Germany).

2.4.2. Swelling index

For estimating the swelling index, 100 mg of microbeads was soaked in 20 ml of phosphate buffer pH 6.8 and the weight of the beads was determined after 3 h. Swelling index was calculated by using the equation:

$$\text{Swelling index}\,(\%) = \frac{\text{Change in weight (mg)}}{\text{Original weight (mg)}} \times 100 \quad (1)$$

2.4.3. Entrapment efficiency

Drug-loaded microbeads (50 mg) were accurately weighed and crushed in a glass mortar with a pestle and then suspended in 10 mL of phosphate buffer, pH 6.8. After 24 h, the solution was filtered and the filtrate was appropriately diluted using phosphate buffer, pH 6.8 and analyzed using UV/vis spectrophotometer (LAMBDA 12, Perkin Elmer GmbH, Germany) at 274 nm. The drug entrapment efficiency (E) was calculated using the formula:

$$E\,(\%) = \frac{\text{Practical drug content}}{\text{Theoretical drug content}} \times 100 \quad (2)$$

2.4.4. Differential scanning calorimetry (DSC) analysis

DSC analyses of the natural gums; sodium alginate; pristine diclofenac sodium and drug-loaded microbeads were performed on a DSC (Perkin Elmer Differential Scanning Colorimeter Pyris 1 CCA7, USA) in sealed stainless steel pans. The sample pan and the reference pan were heated from −10 to 300 °C at a rate of 20 °C/min, held for 2 min at 300 °C and cooled to −10 °C at 20 °C/min. The gelatinization enthalpy (ΔH), the onset, peak and conclusion temperatures (T_o, T_p and T_c respectively) were then determined.

2.4.5. Drug release study

The *in vitro* dissolution studies were carried out using the paddle method (USP XXI), rotated at 50 rpm in 900 ml of phosphate buffer, pH 6.8, maintained at 37 ± 0.5 °C. The microbeads (100 mg) were placed in the dissolution medium. Samples (10 ml) were withdrawn at different intervals and replaced with equal amounts of fresh medium. The sample was diluted and the amount of diclofenac sodium released was determined at wavelength of 274 nm, using a UV/visible spectrophotometer (LAMBDA 12, Perkin Elmer GmbH, Germany). Determinations were done in triplicates.

2.4.6. Modelling and comparison of release profiles

Data obtained from *in vitro* release studies were fitted to various kinetic equations to determine the kinetics and mechanism (s) of drug release from the microbeads. The results of the drug release for the formulations was fitted to zero order, first order, Higuchi, Hixson–Crowell, Korsemeyer–Peppas and Hopfenberg equations [28–33]. The model of best fit was identified by comparing the values of correlation coefficients.

2.4.7. Comparison of dissolution profiles

The dissolution profiles of the microbead formulations prepared with the natural gum:alginate blends that gave the slowest release were compared to that containing sodium alginate alone using the similarity factor, f_2 [34]. The similarity factor (Eq. (3)) is a logarithmic reciprocal square root transformation of one plus the average mean squared (the average sum of squares) differences of drug percent dissolved between the test and reference products over all time points.

$$f_2 = 50 \times \log\left\{\left[1 + (1/n)\sum_{j=1}^{n}\left|R_j - T_j\right|^2\right]^{-0.5} \times 100\right\} \quad (3)$$

where n is the number of dissolution time points, and R_j and T_j are the reference and test dissolution values at time t. Two dissolution profiles are considered similar when the f_2 value is 50–100.

2.4.8. Data analysis

Statistical analysis was carried out using the analysis of variance (ANOVA) on the computer software GraphPad Prism® 4 (Graphpad Software Inc. San Diego, CA, USA) to compare the differences between the different formulations. At 95% confidence interval, probability, p values less than or equal to 0.05 were considered significant.

3. Results and discussions

3.1. Properties of natural gums

The results of the material properties of natural gums are presented in Table 2. The material properties of the four natural gums were found to vary depending on the botanical source of the gum. Particle size and specific surface area have been shown to influence polymer dispersion and hydration [35]. The ranking of the mean particle size was irvingia > albizia > khaya > cissus. Irvingia gum had a significantly ($p < 0.05$) higher particle size and wider particle size distribution than the other natural gums. It has been shown that as the particle size of polymer gums increases, the gums becomes more easily dispersible but hydrates more slowly [35].

One of the major determinants of hydration kinetics is particle size which reflects the change in surface area exposed to water and is a result of the internal surface of pores and the external surface of the powder particles. The result of the specific surface area of the gums measured using BET (Table 2), shows that the ranking of the specific surface area was khaya > >irvingia > albizia > cissus.

Table 2
Material properties of the natural gums (mean ± SD, $n = 3$).

Polymer	X_{50} (μm)	S_v (m^2/cm^3)	Specific surface area (sq m/g)	Porosity (%)	Particle density ($g\,cm^3$)	Moisture content (%)	T_g (°C)	ΔH_{gel} (J/g)
Albizia	73.5 ± 2.6	0.12 ± 0.01	1.03 ± 0.15	43.5 ± 14.7	1.76 ± 0.01	8.1 ± 2.2	242.9	7.77
Cissus	60.5 ± 1.3	0.20 ± 0.01	1.03 ± 0.15	52.4 ± 1.9	1.59 ± 0.00	7.5 ± 1.5	264.2	9.26
Irvingia	138.5 ± 5.6	0.08 ± 0.00	3.17 ± 0.19	63.6 ± 12.8	1.20 ± 0.00	13.0 ± 3.4	48.8	4.44
Khaya	68.4 ± 2.8	0.13 ± 0.01	10.91 ± 1.19	51.2 ± 13.7	1.80 ± 0.00	15.4 ± 2.0	136.8	1.99

Thus, materials like khaya gum with significantly ($p < 0.001$) higher surface areas is more likely to react and dissolve faster than the other gum with a lower surface area, like cissus.

The pore structure of powder materials is important in characterizing the material and can be used to predict their behaviour under different conditions. Porosity determines important physical properties of powder materials such as mechanical strength, permeability and adsorption properties and is expressed as a percentage of the total volume of voids to the total volume of the gum [36]. The ranking of the porosity presented in Table 2 was irvingia > cissus > khaya > albizia. All the natural gums except albizia showed porosity values greater than 48% with irvingia gum which had the highest mean particle size exhibiting the highest porosity of 63.6%. It has been reported that a porosity value greater than 48% shows that the particles in the powder are in the form of aggregates and are not of greatly different sizes [37]. The ranking of the particle density was khaya > albizia > cissus > irvingia. This indicates that irvingia and cissus gums with higher porosity had lower density values. The difference observed in the density of the gums could also be due to the difference in shape and particle size distribution.

Gums are known to be hygroscopic and they absorb moisture from the air depending on their physicochemical properties and the relative humidity of the environment. Pharmacopeial limits for moisture content of natural gums like acacia and tragacanth has been set at ≤15.0% [38]. Higher levels of water can lead to microbial spoilage and subsequent deterioration in polymer quality. The moisture contents of the natural gums (Table 2) determined by thermogravimetric analysis (TGA) were within the pharmacopoeial limits except for khaya gum which showed a slightly higher value (15.4%). The mechanistic reason for this is still unclear. However, khaya gum should be carefully stored to prevent absorption of moisture which could lead to deterioration. It can also be observed that irvingia and khaya gums showed significantly ($p < 0.05$) higher moisture content than cissus and albizia gums.

The X-ray diffraction patterns of the four natural gums are presented in Fig. 1. It has been shown that the relative amount of each type of scattering of the X-ray diffraction pattern is an indication of the degree of crystallinity of each polymer [39]. The results indicate that the natural gums were largely amorphous in nature although irvingia gum exhibited some degree of crystallinity as indicated by the increase in the intensity of the peaks. The mechanical strength, swelling behaviour and capacity to undergo hydrolysis and subsequently biodegradation have been shown to be directly influenced by the crystallinity of the polymers.

The results of the DSC which have been used extensively to measure the phase transitions of natural gums are presented in Fig. 2 and the transition temperatures are presented in Table 2. The heat flow curves of the gums showed an endothermic peak at different temperatures except for irvingia gum which showed an exothermic peak at 48.1 °C. This indicates that the natural gums vary considerable in their phase transition and degree of crystallinity [7]. The ranking of the glass transition temperature was cissus > albizia > khaya > irvingia. However, irvingia gum exhibited significantly ($p < 0.001$) lower glass transition temperatures than the other natural gums while sodium alginate exhibited higher transition temperature (253.2 °C).

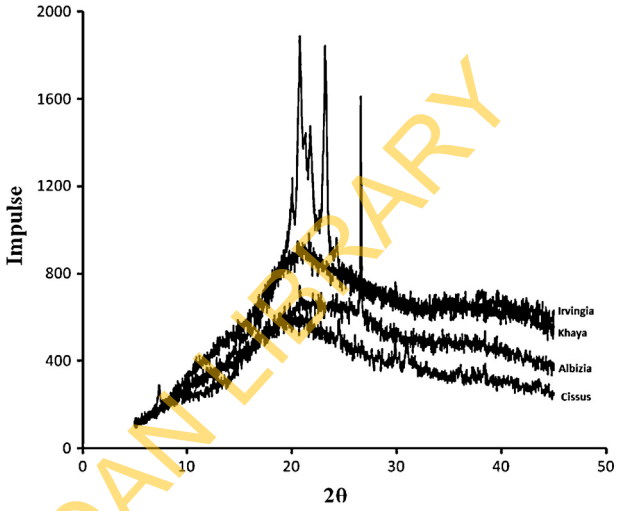

Fig. 1. X-ray diffraction analysis of the natural gums.

The viscosity of the four natural gums, sodium alginate and the polymer blends used in the formulation of the microbeads are presented in Table 1. The ranking of the viscosity of 2%w/v dispersion of the natural gums was albizia > khaya > cissus > irvingia. Sodium alginate exhibited significantly ($p < 0.001$) higher viscosity than all the natural gums. However, when the polymer blends of sodium alginate and the natural gums are considered, the viscosity of the polymer blends decreased with increase in the concentration of the natural gum in the blends except for khaya gum which showed increase in viscosity. Thus, the natural gum polymers appeared to modify the viscosity of sodium alginate to varying degrees.

3.2. Preliminary formulation studies

The preformulation studies done using polymer blends consisting of the natural gums and sodium alginate at ratios of natural gum:alginate of 4:1, 3:1, 2:1 and 1:1 to produce total polymer concentrations of 1%w/v, 2%w/v and 4%w/v (data not shown), showed that at the concentration of 1%w/v, the polymer blend appeared to be too dilute to form rigid, spherical beads while at

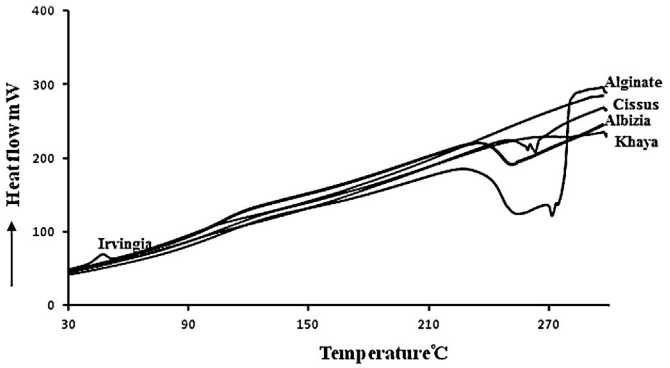

Fig. 2. DSC thermograms of the natural gums.

the concentration of 4%w/v, the polymer blends were too viscous for easy extrusion through the 0.90 mm needle. Furthermore, polymer blends at ratio of 4:1 of gum to sodium alginate did not form well-defined microbeads. However, total polymer concentration of 2%w/v at ratios of 3:1, 2:1 and 1:1 gave rigid spherical microbeads. Thus, the total polymer concentration of 2%w/w was used for further formulation studies.

When the stirring speed of 200 rpm was used, the microbeads were generally irregular in shape but became more spherical when the stirring speed was increased to 300 rpm. However, when the stirring speed was increased to 400 rpm, the microbeads became irregular in shape (data not shown). The crosslinking agents – calcium chloride, zinc chloride and zinc acetate, used at the concentration of 5.0, 7.5 and 10.0%w/v gave varying degrees of crosslinking. Increasing the concentration of the crosslinking agents from 5% to 10%w/v produced microbeads that were well defined and more spherical in shape. Zinc chloride at a concentration of 10%w/v generally produced the most spherical and stable microbeads while beads produced using calcium chloride and zinc acetate were less stable (data not shown).

The curing time was also found to affect the quality of the microbeads produced. Increasing the curing time from 15 to 30 min produced more spherical and free-flowing beads. However, when the curing time was increased to 1 h, the microbeads which were initially formed began to disintegrate. It was observed that when the microbeads were left standing for 1 h after curing for 30 min, the microbeads were more stable and did not disintegrate during the recovery. This indicates that keeping the microbeads in the crosslinking agent for a period of time allowed for further crosslinking to occur in the gel [40].

3.3. Physicochemical properties of the microbeads

The SEMs of the diclofenac-loaded microbeads are shown in Fig. 3. The beads were spherical in shape but exhibited a rough surface morphology with visible wrinkles. This is consistent with previous reports on alginate beads where solid drug crystals which were sparingly soluble in water such as diclofenac sodium and sulindac were encapsulated [10]. The wrinkles observed on the particle surface could be due to the drying procedure and properties of the drug [10]. The DSC thermogram of diclofenac loaded beads (data not shown) showed that there was no change observed in the thermal behaviour of diclofenac in the drug loaded beads. The result also suggests that diclofenac was completely entrapped in the polymeric network of the microbeads and there was no chemical interaction between the drug and the polymer blends.

The properties of the optimized diclofenac microbeads are shown in Table 3. The results showed that the size of the microbeads increased with increase in the concentration of the natural gums. The ranking of the particle size of the microbeads for the various formulation containing the polymer blends was generally albizia > cissus > khaya > irvingia > alginate. Thus, microbeads containing albizia:alginate blends had the largest particle size while the beads containing sodium alginate alone showed the smallest particle size. Statistical analysis showed that there were significant differences ($p < 0.05$) between the particle size of the sodium alginate beads and those of the natural polymer-alginate blends.

The swelling index of the microbeads after 3 h is presented in Table 3. It was observed that the microbeads absorbed phosphate buffer rapidly and there was an increase in the size of the microbeads within the first 3 h (data not shown). However, erosion and breakdown of the beads was observed after 3 h in phosphate buffer. This may be as a result of the degradation of the polymer backbone into smaller fragments resulting in the disintegration of the microbeads [41]. The ranking of the swelling index for the microbead formulations was generally alginate > khaya > cissus > irvingia > albizia. There were significant ($p < 0.05$) differences in the swelling properties of the beads and the degree of swelling appears to depend on the type and concentration of the natural gum in the polymer blends. However, microbeads containing sodium alginate alone exhibited similar swelling to those containing khaya and cissus at a ratio of 1:1.

The entrapment efficiencies of the microbeads (Table 3) ranged from 44.0% to 71.3%. The relatively low encapsulation efficiency could be as a result of the poor water solubility of the drug [42,43]. In addition, it has been reported that migration of drug during drying and storage can result in a heterogeneous distribution of the drug in the polymer matrix [44]. During the air drying process, water flows to the matrix surfaces before evaporation and the drug diffuses towards the surface by convection resulting in heterogeneous distribution in the matrix. This convection-induced migration has been reduced by freeze-drying the microparticles [44]. The entrapment efficiency generally increased with increase in the concentration of the natural gums in the polymer blends. Thus, the presence of the natural gums in the polymer blends appeared to delay or hinder the drug diffusion within the polymer droplet [45]. The ranking for the entrapment efficiency for the formulations was khaya > irvingia > alginate > cissus > albizia. Formulations containing khaya and irvingia gums exhibited significantly ($p < 0.05$) higher entrapment efficiencies than those containing alginate alone and the other gums. Factors that have been shown to affect the entrapment efficiency of drug in microbeads include the nature of drug, concentration of polymer, drug–polymer ratio and stirring speed [11].

3.4. Drug release study

The release profiles of diclofenac from the microbead formulations are shown in Fig. 4 and the values of t_{15} and t_{80} (time required for 15% and 80% of diclofenac to be released respectively) are presented in Table 3. The dissolution profiles showed that there was a gradual increase in the amount of drug release over time. Microbead formulations containing irvingia gum and alginate showed an initial lag time of about 1 h where the drug release was less than 1% while the lag time was about 30 min for formulations containing albizia, cissus and khaya gums. For controlled release preparations, an initial high rate of drug release usually referred to as “burst release” where 15% of drug is released within the first hour, is undesirable because it can have adverse pharmacological effects and can also make the delivery system to be economically ineffective [44]. The release profiles indicated that generally, the beads did not exhibit burst release, indicating that the drugs were embedded in the beads and were not loosely bound to the surface of the beads [9]. However, there was an increase in the amount of drug release with time. According to Alderman [46] when the hydrophilic matrix system is placed in an *in vitro* dissolution medium, drug particles initially pass into solution from the surface (immediate release). The solid matrix begins to swell (polymer relaxation) as soon as hydration with solvent molecules commences and diffusion of the dissolved drug and erosion of gelatinous viscous polymer layer into aggregates occurs. This in turn leads to desaggregation into fine particles that leads to release of the drug content by dissolution. The results also showed that the dissolution times, t_{15} and t_{80}, generally increased with increase in the concentration of the natural gums in the polymer blends with microbeads formulations containing natural gum:alginate at the ratio of 3 to 1 showing higher dissolution times except for formulations containing albizia gum. The ranking for the dissolution times, t_{15} and t_{80}, for the formulations was generally irvingia > alginate > albizia > khaya > cissus. The dissolution times depended on the type and concentration of natural gum present in the polymer blends used in the formulation of

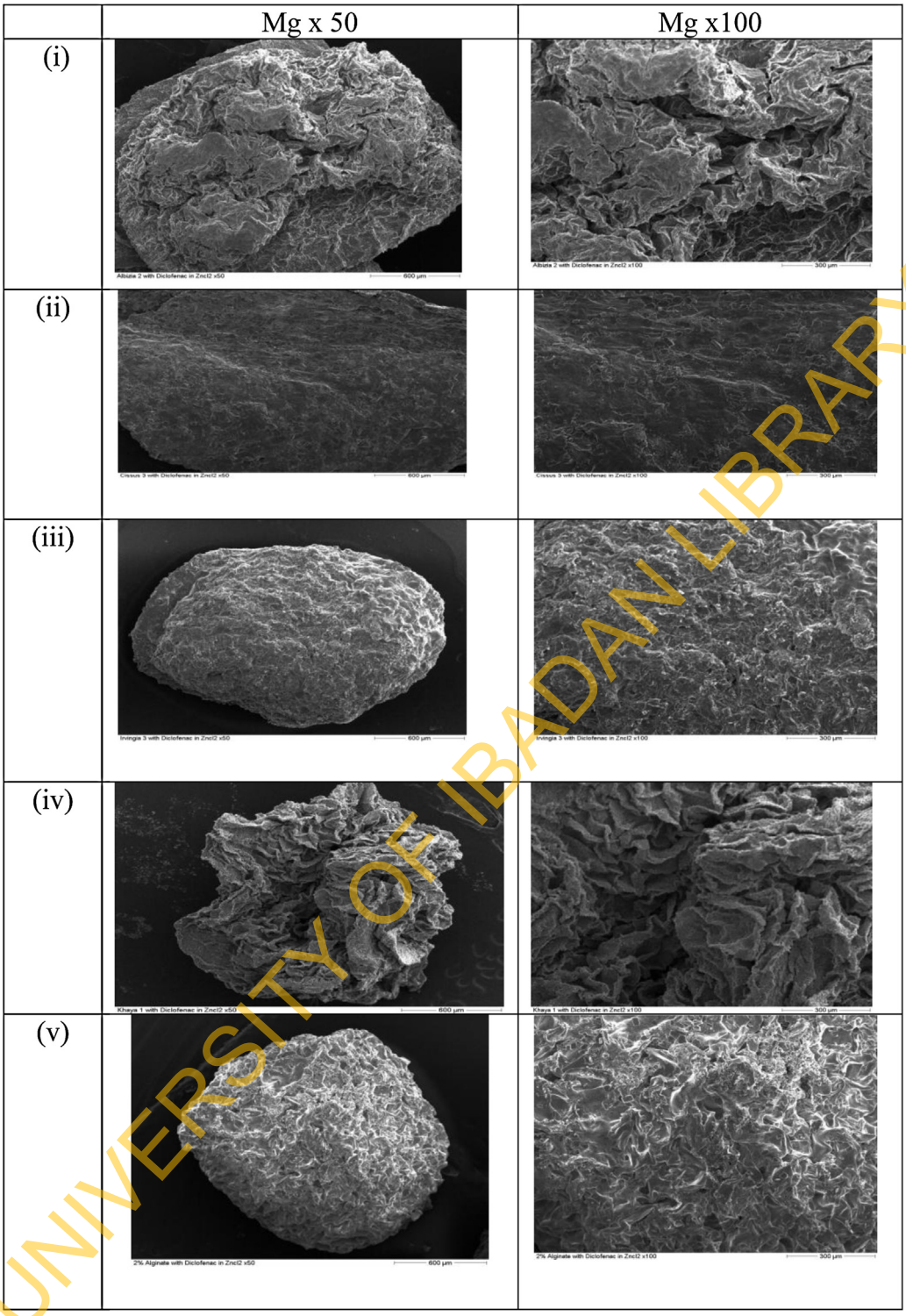

Fig. 3. Scanning electron micrographs of diclofenac microbead formulations containing the natural gum:alginate blends at the ratio of 3:1: (i) albizia-alginate; (ii) cissus-alginate; (iv) irvingia-alginate; (iv) khaya-alginate; (v) 2% sodium alginate.

the microbeads. Thus, the concentration of natural gums could be used to modulate drug release from the microbeads. At natural gum:alginate ratio of 3 to 1, formulation containing irvingia gum (V3) and sodium alginate alone (S1) showed significantly ($p < 0.05$) higher dissolution times than those containing the other polymer blends. On the other hand, there were no significant differences ($p > 0.05$) between the dissolution times of microbeads containing khaya, albizia and cissus gums. Furthermore, while formulations containing khaya, albizia and cissus gums released 100% of the drug within 5 h, those containing irvingia gum provided a slower release and complete drug release was achieved only after 7 h. Thus the natural gum could be useful for the preparation of microbeads with different release profiles depending on the concentration used and the intended use of the tablets. Generally, 5 h of controlled release can be considered adequate in view of the relatively low percent of total polymer used (2%w/v) in the formulation as well as the short

Table 3
Properties of diclofenac microbead formulations containing the polymer blends (mean ± SD, $n = 3$).

Formulation code	Particle size (mm)	Swelling index (%)	Entrapment efficiency (%)	t_{15} (h)	t_{80} (h)
S1	1.49 ± 0.13	16.9 ± 3.1	55.0 ± 5.6	1.9 ± 0.9	4.5 ± 2.1
A1	2.14 ± 0.15	9.2 ± 2.5	44.0 ± 4.1	1.5 ± 0.9	3.5 ± 1.1
A2	2.29 ± 0.18	7.6 ± 2.1	60.8 ± 6.3	1.6 ± 0.1	3.9 ± 0.9
A3	2.41 ± 0.20	6.9 ± 1.1	51.3 ± 5.2	0.9 ± 0.6	3.0 ± 0.9
C1	1.98 ± 0.18	16.6 ± 4.6	48.8 ± 5.1	0.8 ± 0.3	2.9 ± 0.8
C2	2.18 ± 0.12	11.6 ± 1.8	52.5 ± 5.1	1.0 ± 0.7	3.2 ± 0.9
C3	2.41 ± 0.17	9.4 ± 2.0	54.3 ± 3.8	1.1 ± 0.4	3.3 ± 1.1
V1	1.48 ± 0.06	6.5 ± 1.7	60.8 ± 6.4	2.0 ± 0.1	4.0 ± 1.2
V2	1.57 ± 0.09	4.9 ± 0.9	61.3 ± 4.5	2.6 ± 0.8	5.3 ± 1.9
V3	1.62 ± 0.17	4.4 ± 1.2	68.8 ± 5.1	2.8 ± 0.5	5.4 ± 1.4
K1	1.73 ± 0.12	16.8 ± 3.3	71.3 ± 7.1	0.9 ± 0.5	3.0 ± 0.4
K2	1.93 ± 0.15	11.8 ± 2.4	63.3 ± 5.6	1.0 ± 0.9	3.0 ± 0.9
K3	1.98 ± 0.18	10.2 ± 2.1	66.5 ± 4.5	1.0 ± 0.7	3.2 ± 0.5

Table 4
Correlation coefficients obtained for the diclofenac microbeads using different mathematical models ($n = 3$).

Formulation code	Zero order	First order	Higuchi	Hixson–Crowell	Korsmeyer		Hopfenberg
					r^2	n	
S1	0.965	0.880	0.762	0.869	0.963	2.310	0.993[a]
A3	0.905	0.798	0.880	0.765	0.997[a]	1.410	0.981
C3	0.953	0.903	0.861	0.830	0.997[a]	1.554	0.985
V3	0.876	0.818	0.659	0.797	0.997[a]	2.626	0.955
K3	0.929	0.871	0.880	0.819	0.997[a]	1.436	0.981

[a] Highest correlation coefficient of drug release kinetics.

half life of diclofenac sodium (1–2 h). In addition, sustained release formulations are used not only to extend the bioavailability of a drug but to simultaneously reduce the maximum plasma concentration of the drug (C_{max}). Thus, the reduction in the fluctuation of the drug concentration in the blood becomes more important than reducing the number of daily drug intakes.

The kinetics of drug release from the microbeads is important because they influence the drug bioavailability, dosage intervals and the occurrence of toxic or untoward side effects [47]. The correlation coefficients which were used as an indicator for best fit are presented in Table 4. Drug release from the microbead formulations containing all the polymer blends fitted the Korsmeyer–Peppas model with correlation coefficients, $r^2 = 0.997$. This indicates that drug release from the microbeads was controlled by a combination of diffusion and erosion mechanisms. The drug release mechanism from the formulations containing the natural gums is considered to be super case II transport, in which a pronounced acceleration in drug release by the polymer blend occurs towards the latter stages of release, resulting in a more rapid relaxation-controlled transport [48]. This is consistent with previous reports on release kinetics of microbead formulations of diclofenac sodium [42,49]. However, the drug release for the beads containing alginate alone fitted the Hopfenberg model which describes the release of drug from spherical formulations. Hopfenberg developed the mathematical model to correlate the drug release from surface eroding polymer as long as the surface remains constant during degradation process.

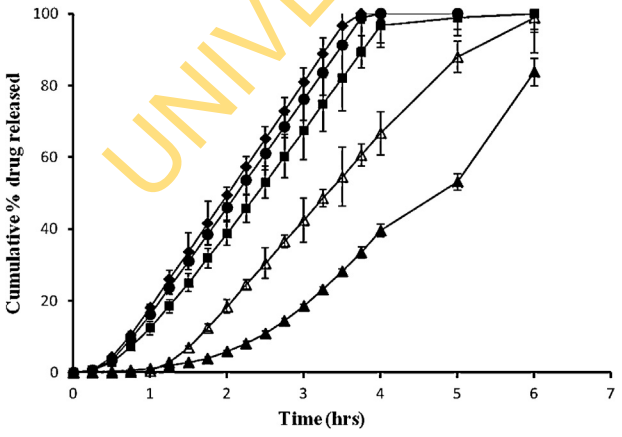

Fig. 4. Dissolution profiles of diclofenac microbead formulations containing the natural gum:alginate blends at the ratio of 3:1: ♦, albizia:alginate; ■, cissus:alginate; ▲, irvingia:alginate and ●, khaya:alginate; △, 2% sodium alginate.

The similarity factor, f_2 has been used by the FDA for the comparison of dissolution profiles of various brands of drugs containing the same drug, for the microbeads. The FDA has set a public standard of f_2 value between 50 and 100 to indicate similarity between two dissolution profiles and f_2 of 100 for two identical profiles [34,47]. From the results, similarity was observed between the dissolution profiles of formulations A3 and C3 ($f = 50.9$), formulations A3 and K3 ($f_2 = 72.9$) and formulations C3 and K3 ($f_2 = 58.9$). This indicates that microbeads containing albizia and cissus had comparable release profiles to those containing khaya gum ($f_2 > 50$). However, there was dissimilarity between the dissolution profiles of the formulations containing the blends of the four polymer gums and those of the microbeads containing alginate alone ($f_2 < 50$). The dissolution profiles from the formulation containing irvingia gum were also dissimilar to the microbead formulations containing the other natural gums. Thus, drug release from the microbeads was completely altered by the addition of the polymer gums into the formulation.

4. Conclusion

Microbeads designed using the four natural gums namely albizia, cissus, irvingia and khaya gums were useful in combination with sodium alginate for the formulation of sustained release microbeads for over 5 h. Formulations containing khaya and irvingia gums had significantly ($p < 0.05$) higher entrapment efficiency than those of all the other formulations. Drug release from the microbeads was dependent on the type and amount of natural

gum present in the formulation. Microbead formulations containing irvingia gum showed the highest sustained release with good entrapment efficiency. The natural gums could provide a more cost effective alternative to synthetic polymers in the formulation of controlled drug delivery systems.

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