The design of ibuprofen-loaded microbeads using polymers obtained from *Xanthosoma sagittifolium* and *Dillenia indica*

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Abstract

Background. Ibuprofen is used both for acute and chronic disorders, such as ankylosing spondylitis, osteoarthritis and rheumatoid arthritis; however, ibuprofen causes gastrointestinal disturbances. Therefore, it would be desirable to design it as a sustained-release preparation.

Objectives. To design ibuprofen microbeads using polymers obtained from *Xanthosoma sagittifolium* starch and *Dillenia indica* mucilage to provide sustained-release delivery of ibuprofen.

Material and methods. The polymers were extracted using standard methods and characterized by their material, physicochemical, elemental, and rheological profiles. Microbeads loaded with ibuprofen were prepared using the ionotropic gelation method utilizing blends of the polymers and sodium alginate. The microbeads were evaluated using particle shape, particle size, swelling index, entrapment efficiency, and release assays.

Results. The results showed that the polymers have distinct material and physicochemical properties unique to their botanical sources. The microbeads were spherical and free-flowing, and they rolled without friction. The swelling properties ranged from $47.62 \pm 2.74\%$ to $79.49 \pm 3.66\%$. The particle size of the microbeads ranged from $88.14 \pm 68.57 \mu\text{m}$ to $214.90 \pm 66.95 \mu\text{m}$, while the encapsulation efficiencies ranged from $20.67 \pm 4.66\%$ to $83.61 \pm 6.35\%$. The dissolution times suggested that the concentration of the natural polymers in the bead formulation could be used to modulate the dissolution properties. Generally, formulations containing the mucilage yielded higher dissolution times than those containing the starch. The kinetics of drug release from the microbeads containing the polymer blends generally fitted the Korsmeyer–Peppas model. The highest similarity was found between formulations C6 and D4 with f_2 of 81.07.

Conclusions. The microbeads prepared with polymers obtained from *Xanthosoma* and *Dillenia* showed acceptable physicochemical properties, dependent upon polymer type, blend and concentration.

Key words: polymers, sodium alginate, ibuprofen microbeads, *Xanthoxylum sagittifolium* starch, *Dillenia indica* mucilage

Introduction

The oral route of drug administration constitutes the most convenient and preferred means of drug delivery into the systemic circulation. This is due to the ease of administration, the higher patient acceptance, adherence and compliance to medication, and the cost-effective manufacturing process.¹ Tablets and capsules are the most common oral dosage forms and are mostly prepared for immediate release, which enables rapid absorption.² Nonetheless, drugs with a low therapeutic index are prone to eliciting adverse effects because of fluctuating drug levels. In addition, drugs with a short half-life need to be frequently administered, which affects patient adherence and overall compliance to the treatment regimen.

The production of polymeric gel beads is a novel approach for achieving the controlled release of many therapeutic agents.³ Microbeads are free-flowing and roll without friction, thus ensuring a dust-free environment during processing, in addition to a constant release rate for active agents embedded in the core.⁵ Beads are discrete, spherical microcapsules that serve as a solid substrate; the drug is coated on this substrate or encapsulated within the core. Microbeads provide sustained-release properties and more uniform distribution of drugs within the gastrointestinal tract and enhance drug bioavailability. They are also called microspheres and described as carrier-linked drug delivery systems, in which particle size ranges from 1 μm to 1000 μm and the active drug is embedded in the core and coated at the outer layers with polymers. Microspheres can be described as structures made up of a continuous phase of 1 or more miscible polymers in which drug particles are dispersed at the molecular or macroscopic level. Microspheres constitute an important part of particulate drug delivery systems by virtue of their small size and efficient carrier capacity. Thus, drugs embedded in the microsphere matrix are released at a slow, constant and controlled rate; therefore, they are capable of being used for targeted delivery. The size, surface charge and surface hydrophilicity of microspheres have all been found to be important in determining the fate of the particles *in vivo*.⁴ The use of small and round microbeads of the same size nullifies the disadvantages that are encountered with powders and granules.

Ibuprofen is widely known as a first-line non-steroidal anti-inflammatory drug (NSAID) for rheumatoid arthritis and chronic arthropathies. It also has an analgesic property and a mild antipyretic action. It acts mainly by inhibiting prostaglandin synthesis, reducing the production of pro-inflammatory cytokines such as interleukin 1 β (IL-1 β) and tumor necrosis factor α (TNF- α). It inhibits the lipoxygenase pathway, leading to a decrease in the production of leukotrienes by the leukocytes and the synovial cells. Furthermore, it masks the T cells, thereby suppressing the production of rheumatoid factors.

It is more active than indomethacin, naproxen and other NSAIDs. This drug is indicated for the relief of mild to moderate pain and inflammation in conditions such as dysmenorrhea, migraine, and postoperative and dental pain. In these disorders, an immediately available dose is required. Ibuprofen is also used in chronic disorders – such as ankylosing spondylitis, osteoarthritis and rheumatoid arthritis – for which a sustained release is desirable. The most frequent adverse effect occurring with ibuprofen is gastrointestinal disturbance; peptic ulceration, gastrointestinal bleeding, nausea, dyspepsia, dizziness, and unexplained rash have also been reported.⁶ Low single-dose administration of ibuprofen and its short half-life in plasma (about 1.8–2.0 h) make it a very good candidate for the formulation of controlled-release, multiple-unit dosage forms.

Dillenia indica L. is a large evergreen shrub native to southeastern Asia, India, Bangladesh, and Sri Lanka.⁷ The common English name is elephant apple or Indian catmon. Its characteristic fruits are large, round and greenish yellow, have many seeds and are edible.⁷ The fruit pulp is bitter-sour and is used in curries, jams and jellies in India. It is often mixed with coconut and spices to make chutneys. The leaf, bark and fruit of this plant are traditionally used as medicine in different forms for their therapeutic value, such as their antidiabetic, antioxidant and antimicrobial properties.^{8,9} The mucilage of the fruit is used to wash hair and has a conditioning effect.¹⁰ There is potential to exploit the usefulness of *Dillenia* mucilage in microbead formulation, thus harnessing its potential as a pharmaceutical drug carrier. Cocoyam (*Xanthosoma sagittifolium* L. Schott) contains between 22% and 40% of starch, which is an essential component of food, providing about 60–70% of the daily caloric intake of humans.¹¹ Cocoyam starches are used as fillers in biodegradable plastics, as well as in aerosols because of their small size.¹² Despite the usefulness of cocoyam starch, it has remained largely underutilized, especially in different industrial applications.

The focus of the study, therefore, was to develop ibuprofen as microbeads using polymers obtained from *Dillenia indica* and *Xanthoxylum sagittifolium*. It is hoped that the ibuprofen microbeads will enable the administration of the drug as a controlled-release oral preparation which will protect the gastric mucous membrane from drug irritation, mask its unpleasant taste, avoid premature release in the gastrointestinal tract, reduce the frequency of administration, enhance patient compliance, minimize total drug quantity, improve bioavailability, prevent fluctuation in drug levels, and reduce the incidence of gastrointestinal disturbances. The use of natural polymers obtained from renewable resources will also aid in the development of local industries if those materials are eventually found to be acceptable. In the present study, therefore, an ibuprofen microbead was designed using polymers obtained from *Dillenia indica* and *Xanthoxylum sagittifolium*.

Material and methods

Material

The materials used were: sodium alginate (Carl Roth GmbH & Co, Karlsruhe, Germany), calcium acetate (Alfa Aesar GmbH & Co, Karlsruhe, Germany); potassium dihydrogen phosphate (Lab Tech Chemicals, Windsor, Australia), disodium hydrogen dodecahydrate (Hopkin and Williams, Essex, UK), sodium hydroxide pellets (Lab Tech Chemicals), xylene (BDH Chemicals Ltd., Poole, UK), and ibuprofen (Fidson Healthcare Plc, Ota, Nigeria). All other reagents were of analytical grade. The tubers of *Xanthosoma sagittifolium* (cocoyam) were procured from a local market in Ibadan, in the southwestern part of Nigeria, while the *Dillenia indica* fruits were obtained from the botanical garden of the University of Ibadan, Nigeria.

Extraction and purification of polymers

Preparation of *Xanthosoma* starch

The *Xanthosoma* starch was extracted from mature tubers according to an established procedure. The cocoyam tubers were peeled, cut into pieces, washed, weighed (10.0 kg), and soaked in distilled water containing sodium metabisulfite for 24 h to encourage softening. The mass was then reduced to a fine pulp through wet milling using a milling machine (GEC Machines Ltd., Blackheath, UK). The fine pulp was passed through a muslin cloth to remove all debris and fibers, resulting in a milky liquid. This liquid was washed several times with distilled water and sieved through a 250-micrometer mesh sieve. The washing was continued until the supernatant no longer tested positive in an acidity test. The starch was dried at 50°C for 18 h. The dried starch was powdered in a laboratory mill, passed through a 125-micrometer mesh sieve, and weighed before being packaged in an airtight container and stored at room temperature.

Preparation of *Dillenia* mucilage¹³

Fruits of *Dillenia indica* were cut open and the inner part containing the mucilaginous material was scooped out and soaked for 24 h in chloroform water. It was strained through a muslin cloth to remove extraneous materials and then precipitated using ethanol (96% v/v). The precipitated mucilage was filtered and washed with diethyl ether before being dried at 50°C for 48 h. It was pulverized and kept in airtight containers.

Determination of particle size for polymers

The particle sizes were measured using an optical microscope fitted with a camera and Motic MC 1000 computer software (Motic China Group Co. Ltd., Xiamen, China). One hundred particles were measured and the mean size was calculated.

Determination of particle density

The particle densities were determined using a pycnometer with xylene as the displacement fluid. An empty 50-milliliter pycnometer was weighed (W), then filled with xylene; the excess fluid was wiped off and the full bottle was weighed (W_1). The difference between W_1 and W was recorded as W_2 . A two-gram sample was weighed (W_3) and transferred into the full pycnometer. The excess solvent was wiped off and the bottle was weighed again (W_4). The particle density (pt) in g/cm³ was then calculated using Equation 1:

$$\text{particle density} = \frac{W_2 * W_3}{50 \{ (W_3 - W_4) + (W_2 - W_1) \}} \quad (1)$$

Determination of ash content

A porcelain crucible was washed and dried in an oven. It was then allowed to cool in a desiccator before being weighed. The dried polymer material was weighed into the empty crucible. The material was ignited over a low flame in the fume cupboard to char the organic matter. The crucible was then placed in a muffle furnace maintained at 600°C for 6 h. On removal from the furnace, the crucible was transferred into a desiccator, cooled and weighed immediately. The percentage of ash content was calculated using Equation 2:

$$\text{ash content (\%)} = \frac{(\text{weight of crucible + ash}) - (\text{weight of empty crucible}) \times 100}{\text{sample weight}} \quad (2)$$

Crude fat analysis

Each thimble was loaded with about 3 g of the starch sample and plugged with cotton wool.¹⁴ The thimbles were dried and then inserted into a SoxtecTM HT device (Foss, Hilleroed, Denmark) and extracted for 15 min in the “boiling” position, then for 45 min in the “rising” position. The solvent was then evaporated and the cups were released and dried at 100°C for 30 min. After this, the cups were cooled in a desiccator and weighed. The same procedure was repeated for the mucilage and the fat content was calculated using Equation 3,

$$\text{fat content (\%)} = \frac{(W_3 - W_2)}{W_1} \times 100 \quad (3)$$

where W_3 = the weight of the cup with the extracted fat
 W_2 = the weight of the empty cup
 W_1 = the weight of the sample.

Determination of crude protein content

The dried starch sample (1 g) was weighed into a digestion tube and 15 mL of concentrated sulfuric acid was added to it. Seven Kjeldahl catalyst tablets were added into the tube which was pre-set at 410°C. It was then digested for 45 min until there was a clear solution.

The tube was placed in the distillation unit and 50 mL of 40% sodium hydroxide solution was dispersed into it. The digest was distilled into 25 mL of 4% boric acid for 5 min. The distillate was titrated against 0.47 M hydrochloric acid until a grey color was obtained.

$$\% \text{ crude protein} = \% \text{ total nitrogen} \times \text{conversion factor} \quad (4)$$

Determination of swelling index

The starch or mucilage was transferred to a 100-milliliter cylinder (V_1), 90 mL of distilled water was added, and the slurry was shaken for 5 min and then topped up to 100 mL. The suspension was allowed to stand for 24 h and the sedimentation volume (V_2) was measured. The swelling index was calculated using Equation 5:

$$\text{Swelling index} = \frac{V_2 - V_1}{V_1} \times 100 \quad (5)$$

Solubility

Starch/mucilage (1 g) was weighed (W) into a 150-milliliter conical flask. Distilled water (15 mL) was added and the mixture shaken for 5 min, then placed into a heated water bath and kept at 80°C for 40 min with constant stirring. The starch slurry was then transferred into a pre-weighed centrifuge tube (W_1); 7.5 mL of distilled water was added and the slurry centrifuged at 2200 rpm for 20 min. The supernatant was carefully decanted into a tarred dish (W_2) and dried at 100°C to a constant weight (W_3), then it was cooled in a desiccator. The solubility was calculated using Equation 6:

$$\text{Solubility (\%)} = \frac{(W_2 - W_3)}{W_1} \times 100 \quad (6)$$

Water absorption capacity

To each 1-gram sample, 15 mL of distilled water was added in a weighed 25-milliliter centrifuge tube. The tube was agitated in a vortex mixer for 2 min and centrifuged at 4000 rpm for 20 min. It was then decanted and the clear supernatant discarded. The residue was weighed (W_1). The adhering droplets of water were removed by drying the residue at 60°C to a constant weight (W_2). The water absorption capacity (WAC) was then calculated as the weight of water bound by 100 g of dry powder.

Fourier-transform infrared spectroscopy

The Fourier-transform infrared (FTIR) spectra were recorded on the polymer samples prepared in potassium bromide (KBr) discs using an FTIR system (Spectrum BX 273; PerkinElmer, Waltham, USA). The scanning range was 350–4400 cm^{-1} .

Preformulation studies

Preformulation studies were carried out in order to optimize the formulation and physicochemical properties of the microbeads. Several formulation trials were carried out using varying concentrations (5%, 7.5% and 10% w/v) of the extracted polymers alone. The polymers alone did not form discrete beads, and the few which did form could not retain their integrity outside the chelating agents. Thus, various polymer blends consisting of different ratios of natural polymers and sodium alginate were used, as shown in Table 4.

Preparation of microbeads

Ibuprofen microbeads were prepared from the hot gel blend (90°C) of natural polymer and sodium alginate using the ionotropic gelation method.¹⁵ The natural polymer and sodium alginate were blended in order to obtain a total polymer concentration of 2% w/v at ratios of 1:1, 1:2, 1:3, 1:4, 2:1, 3:1, and 4:1. An appropriate quantity of the drug (1 g) was added, such that the ratio of total polymer to drug was 2:1. The resulting dispersion was extruded using a syringe with a 0.90-millimeter needle at a dropping rate of 2 mL/min into a calcium acetate solution (10% w/v) maintained under agitation at 300 rpm using a magnetic stirrer (Talboys Laboratory Stirrer Model No. 102; Troemner, Thorofare, USA). The formed beads were allowed to cure for 30 min and were then left standing for another 30 min. The beads were collected by decanting, washed repeatedly with distilled water, and then dried for 24 h in a hot-air oven (Gallenkamp BS 250 Oven; Riley Industries Ltd, West Midlands UK) at 40°C.

Size and morphology of beads

The particle sizes of the microbeads were determined using the optical microscopy method. The particle sizes of 100 prepared microbeads were determined with optical microscopy using a light microscope (Leitz Laborlux II; Leica Microsystems, Wetzlar, Germany). The shape of the beads was also determined using light microscopy.

Swellability of beads

In order to determine the swellability, 100 mg of microbeads was soaked in 20 mL of phosphate buffer (pH 6.8) for 3 h. The microbeads were then removed and excess buffer was wiped away using a dry filter paper; the final weight of microbeads was determined. The swollen microbeads were handled carefully in order to avoid any loss of mass due to erosion. The experiment was repeated after 6 h and 24 h. Swellability – otherwise known as the swelling index – was computed using Equation 7,

$$\text{swelling index (\%)} = \frac{C}{I} \times 100 \quad (7)$$

where C is the weight gain and I is the initial weight of the microbeads.

Entrapment efficiency

The ibuprofen microbeads (50 mg) were accurately weighed and crushed in a glass mortar and suspended in 10 mL of phosphate buffer (pH 6.8) with intermittent stirring. After 24 h, the solution was filtered. The filtrate was appropriately diluted using phosphate buffer (pH 6.8) and analyzed spectrophotometrically at 225 nm with a UV/VIS spectrophotometer (LAMBDA 12; Perkin Elmer GmbH, Rodgau, Germany). The drug entrapment efficiency (E) was calculated as in Equation 8,

$$E (\%) = \frac{A}{T} \times 100 \quad (8)$$

where A and T are the actual and theoretical contents of ibuprofen, respectively.

Drug release study

The drug release behavior of the microbeads was evaluated in 900 mL of phosphate buffer (pH 6.8) maintained at $37 \pm 0.5^\circ\text{C}$ using the paddle method (USP XXI), rotated at 100 rpm. Samples (10 mL) were withdrawn at different time intervals and replaced with an equal amount of fresh medium. The amount of ibuprofen released was determined at a wavelength of 225 nm using a UV/visible spectrophotometer (LAMBDA 12). Measurements were done in triplicate.

Modeling of release profile

Data obtained from in vitro release studies were used in various kinetic equations to determine the kinetics and mechanism of drug release from the microbeads. The results of the drug release for the formulation was fitted to zero order, first order, Higuchi, Hixson–Crowell, Korsmeyer–Peppas, and Hopfenberg equations.^{16–19} The model of best fit was identified by comparing the values of correlation coefficients.

Data presentation and analysis

The experiments were conducted in triplicate and the mean determined. Statistical analysis was carried out using analysis of variance in GraphPad Prism v. 4.0 (GraphPad Software Inc., San Diego, USA) to compare the differences between formulations. The similarity factor (f_2) was used to determine whether formulations prepared using the extracted polymers were similar to those prepared using the standard polymer sodium alginate. A p-value ≤ 0.05 was considered statistically significant.

Results and discussion

Material and physicochemical properties of the polymers

The material and physicochemical properties of *Xanthosoma sagittifolium* starch and *Dillenia indica* mucilage are presented in Table 1. It includes values for pH, moisture content, solubility, water absorption capacity, swelling index, crude protein, fat, ash and carbohydrate contents, density values, and flow parameters. There were distinct differences between the starch and mucilage, though both polymers had low values of water absorption capacity. Generally, low values of this parameter indicate a compact structure of polymers.²⁰ In this study, the starch was found to be more compact than the mucilage. The starch also had low levels ($<1\%$) of protein fat and ash content, which implies high purity as a high ash content would imply the presence of sand. The content of these proximate parameters usually vary with the botanical source of the starch: for the mucilage, which is gummy, the protein and fat content were $>1\%$ and the ash content was also very low. Generally, gums and mucilage have nitrogenous compounds, hence the protein. The starch had a higher carbohydrate content than the mucilage. The carbohydrate content is higher than any other proximate parameter, illustrating that they are true polysaccharides.

The pH of the starch was higher than that of the mucilage, but within the acceptable range for excipients used in oral formulations. It is not expected that the pH should be acidic, hence in terms of PH, the polymers were acceptable. The moisture content of the mucilage was higher than that of the starch, but both were within the acceptable range to keep an excipient free of microbial growth and deterioration. The maximum water content prescribed for safe storage of starch is 13%w/w, while pharmacopoeial limit for natural gums and mucilage is $\leq 15.0\%$; the moisture in a material should be moderate to prevent enzymatic activation of the degradation processes.²¹

Table 1. Material and physicochemical properties of *Xanthosoma sagittifolium* starch and *Dillenia indica* mucilage

Parameters	<i>Xanthosoma sagittifolium</i> starch	<i>Dillenia indica</i> mucilage
pH	6.471 $\pm$ 0.281	4.120 $\pm$ 0.181
Moisture content [%]	6.011 $\pm$ 0.005	7.271 $\pm$ 0.010
Solubility [%]	1.851 $\pm$ 0.07	2.462 $\pm$ 0.101
Water absorption capacity [%]	8.23 $\pm$ 0.25	5.67 $\pm$ 2.12
Swelling index [%]	1.172 $\pm$ 0.112	272.741 $\pm$ 0.211
Crude protein [%]	0.470 $\pm$ 0.001	4.841 $\pm$ 0.002
Fat [%]	0.401 $\pm$ 0.004	3.402 $\pm$ 0.021
Ash [%]	0.498 $\pm$ 0.022	0.461 $\pm$ 0.003
Carbohydrate [%]	91.23 $\pm$ 1.03	89.56 $\pm$ 0.17
Particle density [g/mL]	1.257 $\pm$ 0.004	1.358 $\pm$ 0.023
Particle size [μm]	16.870 $\pm$ 8.08	47.372 $\pm$ 5.26

The moisture content of the natural polymers used in this study was within the pharmacopoeial limits, testifying to their quality. The mucilage was more soluble than the starch, but the starch was better at binding water. The mucilage was bulkier and had denser particles than the starch, while the tapped density for the starch was higher, indicating an improved packing property over the mucilage. The mucilage has significantly larger particles ($p < 0.05$).

The functional group bands of the natural polymers obtained from FTIR spectra are presented in Table 2. The characteristic functional groups are reflected from the peaks of absorbance. The different classes of functional groups present in the polymers imply that they are complex polysaccharides.

Viscosity of polymer blends

The viscosity of polymer blends is presented in Table 3. *Dillenia* had higher viscosity (52.00 ± 0.01 cP) than *Xanthosoma* (14.00 ± 0.06 cP) at the same concentration, but the viscosity of alginate (532.00 ± 14.00 cP) was significantly higher ($p < 0.05$) than of each of the polymers. Generally, *Dillenia*/alginate blends yielded significantly higher viscosities ($p < 0.05$).

Physicochemical properties of the microbeads

The freshly prepared microbeads were spherical in shape, as shown in Fig. 1. Those prepared using *Xanthosoma* alginate blends (C1 and C4) were whitish in color, while those prepared using *Dillenia*/alginate blends were light brown in color. The photomicrographs of the dried microbeads

Table 2. Antibacterial activity and MIC of SaZnONPs against some pathogenic bacteria

Wavenumber [cm ⁻¹]	Class	Assignment
<i>Xanthosoma</i>		
604	alkynes	R CH
880	aromatics, amines	C–H out of plane
894	alkenes	R ² C=CH ₂
1172	alkyl halides	R–F
1306	carboxylic acid esters	C–O stretch
2950	alkanes	CH ₂ CH ₃
3040	aromatics	Ar–H
<i>Dillenia</i>		
772	aromatics	C–H out of plane
1095	alcohols	C–O stretch
1451	alkanes	CH ₂ CH ₃
1541	miscellaneous	N–H out of plane
2705	aldehydes	RCHO C–H
3353	carboxylic acids	dimer OH
3447	amines	N–H stretch

Table 3. The composition and viscosity of polymer blends used for the formulation of ibuprofen-loaded microbeads (mean $\pm$ SD; $n = 3$)

S/N	Polymers	Polymer ratio	Microbead formulation code	Viscosity [cP]
1	Alginate	1:0	A1	532.00 $\pm$ 4.00
2	<i>Xanthosoma</i> /alginate	1:1	C1	666.67 $\pm$ 15.28
3	<i>Xanthosoma</i> /alginate	1:2	C2	763.33 $\pm$ 15.28
4	<i>Xanthosoma</i> /alginate	1:3	C3	826.67 $\pm$ 24.17
5	<i>Xanthosoma</i> /alginate	1:4	C4	896.00 $\pm$ 4.57
6	<i>Xanthosoma</i> /alginate	2:1	C5	520.00 $\pm$ 4.00
7	<i>Xanthosoma</i> /alginate	3:1	C6	470.00 $\pm$ 17.32
8	<i>Xanthosoma</i> /alginate	4:1	C7	372.00 $\pm$ 4.00
9	<i>Xanthosoma</i> /alginate	1:0	C8	14.00 $\pm$ 0.06
10	<i>Dillenia</i> /alginate	1:1	D1	3883.33 $\pm$ 76.38
11	<i>Dillenia</i> /alginate	1:2	D2	4029.33 $\pm$ 8.33
12	<i>Dillenia</i> /alginate	1:3	D3	4516.67 $\pm$ 37.86
13	<i>Dillenia</i> /alginate	1:4	D4	4856.67 $\pm$ 40.42
14	<i>Dillenia</i> /alginate	2:1	D5	2256.00 $\pm$ 4.00
15	<i>Dillenia</i> /alginate	3:1	D6	2532.00 $\pm$ 4.00
16	<i>Dillenia</i> /alginate	4:1	D7	2800.00 $\pm$ 62.45
17	<i>Dillenia</i> /alginate	1:0	D8	52.00 $\pm$ 0.01

SD – standard deviation; S/N – sample number.

are presented in Fig. 2. Generally, they were spherical and had a rough surface, possibly due to the drying procedures. The bead shape and rough surface are consistent with the findings of Akin-Ajani et al.²² who used date mucilage blended with sodium alginate to prepare beads.

The physicochemical properties and dissolution times of the microbeads are presented in Table 4. The microbeads prepared with blends of the polymers and alginate yielded a higher swelling index than the one from alginate alone. Microbeads from *Xanthosoma*/alginate blends resulted in a swelling index ranging between $47.62 \pm 2.74\%$ and $60.52 \pm 5.02\%$, while *Dillenia*/alginate blends yielded a $51.92 \pm 3.45\%$ to $79.49 \pm 3.66\%$ swelling index. This shows that *Dillenia* imparted higher swelling properties than *Xanthosoma*. Equal blends of *Xanthosoma* and alginate resulted in $50.17 \pm 4.91\%$, while blends of *Dillenia* and alginate ($70.32 \pm 2.43\%$) had significantly higher swelling ($p < 0.05$). Generally, swelling increased over time, but the differences were not significant; within 3 h, the beads would have swollen to about 90% of their capacity.

Bead size is an important parameter in the evaluation of microbeads, since the size determines where it fits within the classification.²³ All the formulations were within the acceptable size range for microbeads (1–1000 μ m). The size of the beads prepared using *Xanthosoma*/alginate blends was from 88.14 ± 68.57 μ m to 189.00 ± 54.20 μ m. The sizes increased as the concentration of alginate increased in the blends (C1 to C4), which was also true for beads which contained more *Xanthosoma* than alginate (C5 to C7). The particle size for the beads prepared using *Dillenia*/alginate

Polymer blends of *Xanthosoma sagittifolium* starch and sodium alginate in ratio 1:1 (C1)

Polymer blends of *Xanthosoma sagittifolium* starch and sodium alginate in ratio 1:4 (C4)

Polymer blends of *Dillenia indica* and sodium alginate in ratio 1:1 (D1)

Polymer blends of *Dillenia indica* and sodium alginate ratio 1:3 (D3)

Fig. 1. Representative figures of freshly prepared ibuprofen-loaded microbeads using different polymer blends

Table 4. Physicochemical properties and dissolution times of ibuprofen-loaded microbeads prepared with polymer blends

Formulation code	Swelling index		Mean particle size [μm]	Encapsulation efficiency [%]	Dissolution times [min]	
	3 h	24 h			t ₂₅	t ₈₀
A1	44.41 ±2.67	53.49 ±3.78	178.80 ±2.46	57.72 ±3.31	94.68	302.96
C1	50.17 ±4.91	59.18 ±4.44	88.14 ±68.57	52.90 ±2.77	84.95	271.84
C2	47.62 ±2.74	50.02 ±5.23	88.37 ±59.74	56.60 ±4.24	77.74	248.77
C3	56.54 ±4.32	64.22 ±3.45	147.20 ±46.46	64.86 ±5.43	83.82	268.24
C4	50.02 ±1.89	60.98 ±3.08	189.00 ±54.20	71.83 ±5.63	111.27	356.06
C5	52.70 ±3.28	56.96 ±7.09	158.23 ±62.81	40.00 ±3.94	107.18	342.99
C6	49.95 ±3.57	57.84 ±6.78	162.70 ±57.46	51.96 ±5.22	85.44	273.41
C7	60.52 ±5.02	69.22 ±3.45	183.10 ±46.55	83.61 ±6.35	79.38	254.01
D1	70.32 ±2.43	75.09 ±5.62	170.70 ±50.54	69.51 ±5.11	121.36	388.34
D2	57.98 ±5.12	63.28 ±5.32	175.10 ±50.06	20.67 ±4.66	76.97	246.29
D3	51.92 ±3.45	57.23 ±4.14	175.50 ±53.88	28.13 ±5.39	113.36	362.76
D4	57.36 ±3.62	60.24 ±5.68	190.00 ±66.36	60.82 ±7.18	86.70	277.44
D5	68.25 ±4.55	76.77 ±4.65	214.90 ±66.13	52.39 ±3.79	97.94	313.39
D6	79.49 ±3.66	82.83 ±5.56	174.11 ±54.92	64.09 ±4.66	128.14	410.05
D7	76.77 ±7.09	78.21 ±5.64	195.32 ±53.06	66.07 ±5.35	125.78	402.50

Fig. 2. Photomicrographs of ibuprofen-loaded microbeads containing polymer blends. A1 – sodium alginate only as polymer. C1–C7 – polymer blends of *Xanthosoma* and alginate. D1–D7 – polymer blends of *Dillenia indica* and alginate

blends was from $170.70 \pm 50.54 \mu\text{m}$ to $214.90 \pm 66.95 \mu\text{m}$. The beads were therefore larger than those prepared using *Xanthosoma*. The sizes also increased as the concentration of alginate increased in the blends (D1 to D4), but there was no particular trend for beads which contained more *Dillenia* than alginate (D5 to D7).

The range of encapsulation efficiency (EE) for beads containing *Xanthosoma*/alginate blends in increasing concentrations of alginate (C1 to C4) was from $52.90 \pm 2.77\%$ to $71.83 \pm 5.63\%$. *Xanthosoma*/alginate blends containing increasing amounts of *Xanthosoma* (C5 to C7) yielded beads with an EE range from $40.00 \pm 3.94\%$ to $83.61 \pm 6.35\%$. *Dillenia*/alginate blends with increasing concentrations of alginate (D1 to D4) resulted in EE values ranging from $20.67 \pm 4.66\%$ to $69.1 \pm 5.11\%$. D1, which consisted of an equal blend of *Dillenia* and alginate, offered the highest EE.

The microbeads from polymer blends with increasing concentrations of *Dillenia* (D5 to D7) yielded increasing levels of EE, ranging between $52.39 \pm 3.79\%$ and $66.07 \pm 5.35\%$. This implies that for microbeads prepared using starch, the more the alginate, the higher the EE for *Xanthosoma*/alginate polymer blends C1–C4. For C5–C7, the EE increased as the concentration of starch increased. This implies that the starch and sodium alginate particles interacted in such a way that the EE of the system improved. In both directions of blending starch and sodium alginate, there was a positive outcome on the EE. For microbeads prepared using *Dillenia* and sodium alginate blends, formulation D1 – with an equal concentration of the polymers – offered the highest EE. As the concentration of alginate increased (D1–D4), there seemed to be no particular pattern in the EE. However, as the concentration of *Dillenia* increased in the polymer blend

(D5–D7), there was a consistent increase in EE. This indicates that an increase in the amount of *Dillenia* in the polymer blend favored the encapsulation of ibuprofen.

Drug release properties of the microbeads

In vitro dissolution has been recognized as an important element in drug development. It can also be used as a substitute for the assessment of bio-equivalence. The mechanism of drug release is affected by the properties of the core materials, including solubility, diffusibility and partition coefficient.²⁴ In addition, diffusion-controlled drug release occurs where the drug molecules are uniformly dispersed within the polymer.²⁵ The release profiles of ibuprofen from the microbead formulations in Fig. 3 demonstrate a moderate release over time. Formulation C4 from a *Xanthosoma*/alginate blend ratio of 1–4 (i.e., 20% starch), formula D1 from a *Dillenia*/alginate blend ratio of 1:1 (50% mucilage) and formulation A1 (100% sodium alginate) all exhibited a gradual release over time and were considered to deliver optimum properties in this regard. In controlled release formulations, it is not desirable that an initial high rate of drug release – usually referred to as “burst release” (a situation in which 15% of a drug is released within the 1st hour) – should occur. This allows for avoiding adverse drug effects and the possibility of rendering the delivery system ineffective.²⁶ In formulations C4, D1 and A1, the release profiles show that the embedded drugs were not loosely bound to the surface of the beads, hence the gradual release.

The dissolution times shown in Table 4 for microbeads prepared with starch in alginate polymer blends demonstrate that the concentration of the natural polymers could be used to modulate the dissolution properties from the microbead formulations. Generally, as alginate increased in the starch/alginate blends (1:2 to 1:4), the dissolution times for ibuprofen release increased, show-

ing that delayed release properties were conferred onto the formulation. However, equal quantities of starch and alginate (1:1) did not follow this pattern in the blends, as its dissolution times resembled a 1:3 ratio. Thus, the ranking of dissolution times among the microbead formulations of starch/alginate blends containing increasing alginate quantity was C4 > C1 > C3 > C > C2.

Formulations C5–C7 contained increasing quantities of the starch, and the dissolution times from these blends reduced as the starch concentration increased. This suggests that larger concentrations of the starch may not confer delayed release properties as much as the other concentrations. For delayed release properties, formula C4 produced the longest dissolution times – 25% of the drug was released in nearly 2 h and 80% was released in approx. 6 h; these dissolution times were much longer than those of formulations prepared using alginate alone. The presence of starch modified the dissolution times which the alginate provided to the microbeads.

Generally, formulations containing the mucilage and alginate blends yielded longer dissolution times compared to those containing the starch. The dissolution times of microbeads prepared with blends of mucilage and alginate in increasing alginate concentrations (1:1 to 1:4) were ranked as follows: D1 > D3 > D4 > D2. As with the starch/alginate blends, a 1:2 ratio produced the shortest dissolution times. A 1:1 mucilage/alginate blend yielded the longest dissolution times, whereas with the starch 1:4 was the longest. Formula D1 yielded dissolution times of over 2 h for a release of 25% and almost 6.5 h for 80% drug release. The ranking of dissolution times for formulations obtained from mucilage/alginate blends with increasing concentrations of mucilage (2:1 to 4:1 ratios) was D6 > D7 > D5. This shows that a 3:1 ratio produced microbeads with the slowest release, thus conferring better delayed-release properties on the formulations.

In terms of dissolution times, formula D6 containing a 3:1 mucilage/alginate blend provided optimal values: 25% drug release was achieved in over 2 h, while 80%

Fig. 3. Dissolution profiles of ibuprofen-loaded microbeads prepared with polymer blends. A1 – sodium alginate only as polymer. C1–C7 – polymer blends of *Xanthosoma* and alginate. D1–D7 – polymer blends of *Dillenia indica* and alginate

was released after nearly 7 h. These results are comparable to the studies of Odeku et al. on the design of microbeads using 4 natural gums.²⁶ Their report showed that the dissolution times of beads containing natural gums (irvingia, khaya and cissus) were longer at a ratio of 3:1 for natural gum/alginate blends. In the current study, *Dillenia* mucilage seemed to follow the pattern of 3 of the natural gums.

The kinetics of drug release is important due to its influence on drug bioavailability, dosage intervals, and the occurrence of toxicity or unwelcome side effects.²⁴ The correlation coefficients obtained from fitting the release data to different kinetic models are presented in Table 5. The kinetics of drug release from the microbeads containing the polymer blends fitted the Korsmeyer–Peppas (A1, C1, C2, C3, C5, C6, and D1–D7) and Hopfenberg (C4 and C7) models using correlation coefficients ($r^2 = 0.9902$ – 0.9970).

The Korsmeyer–Peppas model of drug release is useful in describing the release from polymeric systems. The rate of release for the model is related to the structural and geometric properties of the drug delivery systems, in this case with the polymers serving as carriers. The model also provides a release exponent “n”, which corresponds to the mechanism of the release. Generally, in this study, the drug release from the microbeads was controlled by a combination of diffusion and erosion mechanisms. The release mechanism using the n-value for most of the beads corresponds to mass transfer following a non-Fickian anomalous $0.5 < n < 1.0$ diffusion. However, formula C4 yielded an n-value of 1.045 and A1 (made from alginate) of 1.105, which indicates that the drug release from these microbeads was controlled

by super case II transport, in which a pronounced acceleration of drug release from the microbeads occurred toward the latter stages of release, resulting in a more rapid relaxation-controlled transport. In addition, the drug release from formulations C4 and C7, prepared from *Xanthosoma*/alginate blends, fit the Hopfenberg model ($r^2 = 0.9955$ and 0.9966 , respectively).

The Hopfenberg model describes the release of a drug from spherical formulations, and the mathematical model is used for correlating the drug release from a surface-eroding polymer for as long as the surface remains constant during the degradation process. The physicochemical properties of the drug and the polymer, as well as the drug-to-polymer ratio, have been shown to govern the release of a drug from formulations, which could mean that the amount of the polymer could be used to modify the release properties of the microbeads.

Conclusions

The polymers obtained from *Xanthosoma sagittifolium* and *Dillenia indica* had different physicochemical properties, such as particle size, shape and viscosity. The ibuprofen microbeads were discrete, generally spherical and with a particle size $< 250 \mu\text{m}$. The bead swelling depended on the type and concentration of the natural polymer present in the polymer blend. The entrapment efficiencies for the beads ranged from 20% to 30% and the microbeads demonstrated controlled release properties. Ibuprofen microbeads were successfully formulated with properties varying according to polymer type and concentration.

Table 5. Correlation coefficients obtained for ibuprofen microbeads using different mathematical models ($n = 3$)

Formulation code	Zero order	First order	Higuchi	Korsmeyer–Peppas		Hixson–Crowell	Hopfenberg
				r^2	n		
A1	0.9936	0.9257	0.8344	0.9966*	1.105	0.9529	0.9951
C1	0.9189	0.9724	0.9662	0.9918*	0.649	0.9736	0.9743
C2	0.8526	0.9788	0.9809	0.9892*	0.575	0.9720	0.9788
C3	0.9734	0.9712	0.9351	0.9974*	0.772	0.9872	0.9934
C4	0.9940	0.9494	0.8566	0.9945	1.045	0.9679	0.9955*
C5	0.9164	0.9801	0.9678	0.9926*	0.646	0.9700	0.9801
C6	0.9837	0.9584	0.9171	0.9956	0.828	0.9783	0.9924
C7	0.9467	0.9784	0.9427	0.9896	0.718	0.9936	0.9966
D1	0.9947	0.9810	0.8912	0.9970*	0.918	0.9909	0.9965
D2	0.8454	0.9803	0.9798	0.9873*	0.571	0.9759	0.9806
D3	0.9182	0.9687	0.9618	0.9878*	0.652	0.9603	0.9687
D4	0.9782	0.9635	0.9281	0.9960*	0.795	0.9799	0.9887
D5	0.9550	0.9697	0.9403	0.9885*	0.732	0.9742	0.9744
D6	0.9094	0.9704	0.9693	0.9916*	0.636	0.9569	0.9704
D7	0.9621	0.9785	0.9372	0.9902*	0.749	0.9783	0.9789

* Highest correlation coefficient of drug release kinetics.

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