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Preparation, Characterization and Release Studies of Naproxen-loaded Microspheres from Natural Gums

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of article.

Abstract

Background: Use of biodegradable natural materials as pharmaceutical excipients is increasing. In this study, Naproxen loaded microbeads were produced, using natural gums obtained from *Cedrela odorata* and *Irvingia gabonensis*

Objective: Aim is to evaluate physicochemical properties of the gums and determining release properties of the formulations.

Materials and Methods: Cedrela gum (CG) and Irvingia gum (IG) were extracted from *Cedrela odorata* and *Irvingia gabonensis* respectively, and characterized by viscosity, density and pH measurements. Naproxen microbeads were formulated (Formulation A2 to A9) with the gums and sodium alginate using ionotropic gelation method. Cross linkers ($CaCl_2$ or $Al_2[SO_4]_3$) were used at different curing times. Scanning electron microscopy (SEM), photomicrographs, entrapment efficiency and release profiles of the formulations were determined.

Results: Physicochemical property tests showed that the gums possess good flow, viscosity and they presented with acidic pH. There was no interaction between FT-IR spectra of the gums and naproxen. SEM revealed microbeads to be almost spherical, having slightly rough surfaces. Microbeads from Formulation A6 had the largest particle size (1500±163.2 µm) while Formulation A9 possessed the smallest particle size A9 (491.6±191.7 µm). All the formulations gave high entrapment efficiency (80 – 96%); microbeads containing IG (Batch A6 – A9) had higher values than those formulated with CG gum (Batch A2 – A5) ($p > 0.05$). Batch A6 (containing IG with $CaCl_2$ at curing time of 15 minutes) gave the highest drug release ($p < 0.05$).

Conclusion: Gums obtained from *Cedrela odorata* and *Irvingia gabonensis* possessed good physicochemical properties and produced microbeads suitable for the controlled release of Naproxen. Formulations containing Irvingia gum showed higher drug release and better entrapment.

***Keywords**:* Microbeads, Native plant gums, Naproxen, Drug release

INTRODUCTION

The oral route been attributed as the most convenient and safest means of drug administration; in spite of the numerous advantages of this method of drug delivery, it also has the disadvantages of possible toxicity, frequent dosing, poor drug targeting and non-biocompatibility with the excipients used (Ummadi *et al*., 2013). Controlled drug delivery has been used to ameliorate many demerits of the oral route. This drug delivery system is a method which is used to deliver drugs over an extended period of time and to maintain drug levels within the intended range (Bhowmik *et al*., 2012). Controlled release delivery system was basically developed in order to have a method of drug release that is expected kinetically

and also reproducible. Therefore, controlled release is a means of predicting and reproducing the drug release kinetics (Tiwari, 2016).

Controlled drug delivery system is one of the frontier areas of science and microencapsulation has been discovered to be a useful technique in the formulation of controlled release drug delivery system (Singh *et al*., 2010). Microencapsulation can be defined as the application of thin coatings to small particles of solid, liquid droplets or dispersion which would hence form microbeads (Garg *et al*., 2018). Microencapsulation can be made to prevent degradation process and also to reduce the dosing frequency or duration of therapy of medications by enclosing either solids, liquid or gases into a small wall made of hard or soft soluble film (Venkatesan *et al*., 2009).

Microbeads can be classified basically into three; namely the mononuclear, polynuclear and matrix (Fig. 1).

Mononuclear microbeads are made up of only the shell and the core. A polynuclear microbead contains numerous cores enclosed with the shell while a matrix contains a homogenous distribution of the core in the shell material.

Microbeads could also exist in different forms:

(a). Bioadhesive microbeads: Bioadhesion is a term used to describe the ability of drug formulations to adhere to the mucosal membrane which include buccal, ocular or nasal cavity. The advantage of bioadhesive microbeads is the ability to initiate and maintain contact for a long time at the site of administration, which brings about the formulation of a controlled-release dosage form, hence reducing the frequency of administration of the preparation for the patients.

(b). Magnetic microbeads: Magnetic microbeads aids in the formulation of a form of targeted-release dosage form because it localizes the drug to the disease site. Magnetic microbeads are introduced into the body system by coating the drug substance with a magnetic substance and then injecting it into the blood. There are various types of magnetic microcapsules and they include;

- Therapeutic magnetic microbeads: It is used in the delivery of therapeutic radioisotopes and chemotherapeutic agents to liver tumors (Jaduputi *et al*., 2012).
- Diagnostic microcapsules: This type of magnetic microbeads acts as contrast agents for magnetic resonance imaging (Ganesan *et al*., 2014).

(c). Floating microbeads: They are referred to as floating microbeads because they remain floatable in the stomach and doesn't affect gastric emptying rate. This ability to remain buoyant in the stomach is due to the fact that their bulk densities are less than that of the gastric fluid (Ganesan *et al*., 2014; Manjanna *et al*., 2015). There are two major types of floating microcapsules and they include;

- Effervescent type: This type of microbeads are prepared using polymers that can swell such as chitosan and other effervescent materials such as sodium bicarbonate, tartaric acid etc (Nasa *et al*., 2010). They have the ability to release carbon dioxide gas which hence allows them to be maintained in the floating condition for a prolonged period of time and it hence leads to the slow release of drugs.
- Non-effervescent type: They are made up of highly swellable cellulose such as hydrocolloids, polysaccharides and matrix forming polymer like polyacrylate. Unlike the effervescent type of floating microbeads which release carbon dioxide and remain suspended, the non-effervescent type of microbeads swells when it comes in contact with gastric fluid (Ganesan *et al*., 2014).

(d). Radioactive microbeads**:** Radioactive microcapsules are used to transferring high radiation dose to a targeted area without damaging the normal surrounding tissues (Amsden and Goosen 1997). It is used to deliver drugs directly to tumours, diabetic ulcers and other disease sites.

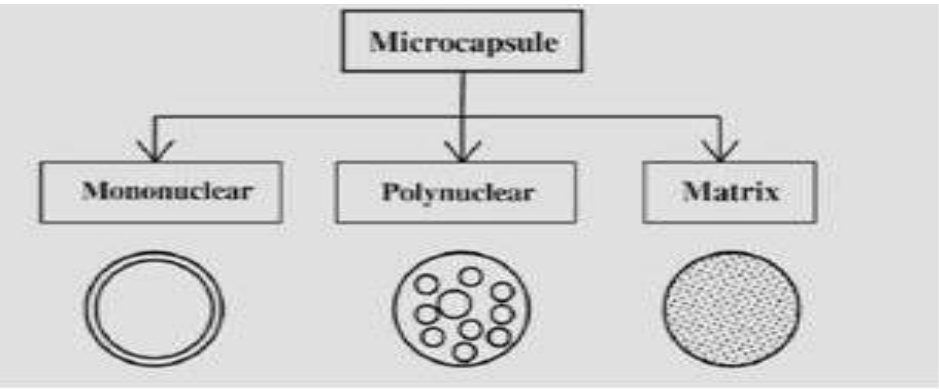

Figure 1: Classification of microbeads (Jaduputi *et al*., 2012; Ganesan *et al*., 2014**).**

Ideal microbeads should possess the following **(**Jaduputi *et al*., 2012; Ganesan *et al*., 2014**).** :

- Ability to allow incorporation of the appropriate drug in the desired concentration.
- The stability of the formulation during and after production must be maintained.
- Ability to deliver active pharmaceutical ingredients at the appropriate time over the intended long period of time.
- Compatibility with active pharmaceutical ingredients to be incorporated and also with the biological system.

One of the techniques of formulating microbeads is Ionotropic gelation; it is basically a physicochemical method with involves the chelation of polymers or polyelectrolytes with polyvalent ions to cause hardening of multidroplets. The chelation of polyelectrolyte results in the cross-linking of the polyelectrolyte molecules to form a shell in the form of polymeric beads (Manjanna *et al*., 2015).

Ionotropic gelation is also based on the ability of polymers to cross-link, in the presence of counter ion, leading to the formation of hydrogels (Patil *et al*., 2010). It should be noted that for cross-linking to occur, the polymer and the counter ions or cross linking agents must be oppositely charged (Ahirrao *et al*., 2013). The counter ions used could be cationic or anionic depending on the properties of the polymer used. The counter ions which could be anionic or cationic in nature are known as the cross-linking agents (Khazaeli *et al*., 2008). Examples of polymers used in ionotropic gelation include sodium alginates, gellan gum and chitosan. Examples of cationic counter ions used include; calcium chloride, barium chloride or potassium chloride (Manjanna *et al*., 2015).

Gums are pathological products, resulting from injury to the plant unfavourable conditions such as drought or breakdown of cell walls (Samia *et al*., 2009). Natural gums possess long chains of sugars (polysaccharides) within native plant materials that are either water-soluble or can absorb water. Natural gums have many advantages over synthetic ones as they are chemically inert, non-toxic, less expensive, biodegradable and widely available (Ravindrakullai and Manjunath, 2013). These natural materials are mostly obtained from plant gums and mucilage of which they are hydrophilic and gel-forming in nature (Avachat *et al*., 2010).

The use of natural products as excipients is increasing because plant resources are renewable and they have the ability to provide regular supply of raw materials if they are cultivated and harvested in a sustainable manner (Perepelkin, 2005). Although, natural gums are useful, they also possess certain disadvantages such as complex structures, expensive and slow purification processes and poor yield. Natural gums have been widely used as binders, disintegrants, emulsifiers, suspending agents, gelling agents (Gupta *et al*., 2013).

The plant, *Cedrela odorata* is a very common specie among *Cedrela* and it is widespread in dry tropical and subtropical forests (Odeniyi *et al*., 2013). Cedrela gum is obtained from The Cedrela odorata tree, which is an important tree species in the family chinaberry, Meliaceae. Its common name is Spanish cedar or Cuban cedar. It is a tree in the new world tropics appearing in the forests of moist and seasonally dry subtropical or tropical life zones. It contains aromatic and insect repelling resins and is often used in honey production. The polysaccharides from the gum contain galactose, arabinose and rhamnose as neutral sugars, and uronic acids as residues. The cationic components of the ash are mainly calcium and magnesium. Cedrela gum has a non-Newtonian flow behaviour characterized by lack of a low-shear limiting Newtonian viscosity plateau even at low shear rates. The average flow index value is low but infinite shear rate viscosity is high. Previous works have shown Cedrela gum to possess mucoadhesive properties (Odeniyi *et al*., 2013; Ayorinde *et al*., 2017) thereby enabling cross-linking

of the polyelectrolyte molecules of the gum to form a shell in the form of polymeric beads.

The *Irvingia gabonensis* plant is commonly known as Bush mango or African mango belonging to the family Irvingiacae and is about 15-40m long (Ogaji *et al*., 2012). *Irvingia gabonensis* is widely distributed in Africa. They have been used as binding agents in tablet formulations (Singh *et al*., 2011) and immunomodulatory agents in vaccine delivery (Ezeasor *et al*., 2019).

Naproxen, a Non-steroidal anti-inflammatory drug is used in the treatment of acute gout, ankylosing spondylitis, idiopathic arthritis, osteoarthritis, inflammation (Brutzkus and Varacallo, 2018). It has both analgesic and antipyretic functions and it can be delivered orally, rectally or topically (Arici *et al*., 2014). Naproxen was selected for this study because of its short half-life of about 1-3 hours, thereby making it suitable for formulation as a sustained release medication (Manjanna *et al*., 2010).

In this study, the aim is to produce Naproxen loaded polymeric microbeads, with natural gums obtained from *Cedrela odorata* and *Irvingia gabonensis*, trees using different formulation conditions. The physicochemical properties and release profiles of the naproxen microbeads produced from the two natural polymers will be evaluated and also be compared

METHODOLOGY

Materials and Methods

Materials

The materials used include Naproxen sodium (Received as gift from Swiss Pharma, Nigeria Ltd.), Plant gums extracted from ground seed of *Irvingia gabonensis* and bark of *Cedrela odorata* tree. Sodium alginate (S.D. Fine Chem Mumbai, India), Aluminium sulphate, Calcium chloride, Sodium chloride (Loba Chemie Pvt. Ltd., Mumbai, India). All reagents used were of Analar grade.

Methods

Gum Extraction

The plants, *Irvingia gabonensis* and *Cedrela odorata* were authenticated at Department of Botany, University of Ibadan. Gums were extracted using the following procedures:

(i). Irvingia gabonensis Gum (IG)

Approximately 35 g of ground seed of *Irvingia gabonensis* was weighed into 1 litre of 1% w/v sodium chloride which was pre-heated to about 70ºC, using a magnetic stirrer (PC-420, Coring, United States of America) the mixture was mixed gently for about 1 hour. After heating, the mixture was then left to stand at room temperature for more than 24 hours. Solidification of lipids component took place at the top and the bottom of the mixture. The lipids were removed by filtration through a stainless sieve. The lipids were air dried and stored in air tight container. The remaining sample which contained the gum was centrifuged for 15minutes in order to remove proteins and impurities. The resultant clear supernatant mucilage was dried in a freeze-drier and stored in another air tight container.

(ii). Cedrela odorata Gum (CG)

Cedrela gum was collected from *Cedrela odorata* tree. The collected gum was purified using established procedure (Ayorinde and Odeniyi, 2017) and then soaked in chloroform/water mixture of 0.5/95.5% (V/V) for 5 days during which stirring was carried out intermittently. Unwanted materials were removed by straining the gum through a muslin cloth. The gum was precipitated from the solution by absolute ethanol; filtered and washed with di-ethyl ether. The gum was dried in the oven (Model DHG-9053A, Ocean Medical, England) at 40 °C for 18 h, milled in a domestic blender. It was sieved and materials of particle size of <200 µm were collected and used for all investigations.

Characterization of the Gums

Density Measurements

The bulk density was determined using 5 g (W_p) of each gum. The 5 g was gently poured into a 50 mL measuring cylinder using a plastic funnel. The cylinder was slightly tilted to obtain a levelled surface of the samples. The volume occupied by each sample of gum was then recorded as V_p. Bulk density was then calculated using the formula:

$$\text{Bulk Density} = \frac{\text{Weight of sample (Wp)}}{\text{Volume of packing (Vp)}} \quad \ldots\ldots (1)$$

The samples in the cylinder were then tapped, using 100 standard taps. The new volume observed was

then recorded as V_pT. Tapped density was then calculated using the formula:

$$\text{Tapped density} = \frac{\text{Weight of the sampe (Wp)}}{\text{Tapped Volume (VpT)}} \quad \ldots\ldots\ldots\ldots (2)$$

Carr's compressibility index and Hausner's ratio were calculated from the results of bulk and tapped density.

$$\text{Carr's Index} = \frac{\text{Tapped Density} - \text{Bulk Density}}{\text{Tapped Density}} \; x\, 100 \quad \ldots\ldots\ldots\ldots (3)$$

$$\text{Hausner's Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}} \quad \ldots\ldots\ldots\ldots\ldots\ldots (4)$$

pH Determination

The pH of a 1%w/v aqueous solution of IG and CG were determined using a digital pH meter (720A, Thermo Electron Corporation, MA, USA) at room temperature.

Viscosity

The viscosity of 2 % w/v aqueous slurry of each of IG and CG was determined using a viscometer, Model RVVDV – II+P (Brookfield Eng. Inc. Middle Boro, MA, USA), at 50 and 100 rpm with spindle 03. Determinations were carried out in duplicates.

Photomicrography

This was carried out to determine the particle shape and size of the materials. Photomicrographs of the Irvingia gum and Cedrela gum were taken at x40, x100 and x 400 magnifications using a digital microscope (VJ-2005 DN Model Bio-Microscope, China). The mean particle diameter was obtained from the photomicrographs.

Fourier Transform Infrared (FT-IR) Spectroscopy

In order to study the compatibility of the polymers and evaluate their effects on functional group of the API, the powdered materials of IG, CG, naproxen and the formulated microbeads were analyzed by FT-IR (FT-IR Spectrum BX II by PerkinElmer, Waltham, MA, USA) in transmission mode. The transmission spectra range was 4000 - 400 cm^{-1} using 64 scans with resolution of 8 cm^{-1}.

Formulation of Naproxen Microbeads

The *Irvingia gabonensis* gum and sodium alginate were mixed to obtain slurry of polymer concentration of 2% w/v at gum to sodium alginate ratios of 1:2. The slurry was mixed for 10 minutes under magnetic agitation. Drug (0.25 g) was added to the slurry to obtain a total polymer to drug ratio of 2:1. The resulting dispersion was extruded using a 10 mL syringe (needle gauge 21, 0.8 mm diameter) into 10% $CaCl_2$ and 10% $Al_2[SO_4]_3$ under magnetic stirrer of 15 minutes and curing time of 30 minutes. The beads were collected by sieving through a mesh size of 0.355 mm, washed repeatedly with potable water, air dried at room temperature for 24 hours and transferred to the oven at 40˚C until completely dried. The above method was repeated using *Cedrela odorata* gum.

Scanning Electron Microscopy (SEM)

The shape and surface morphology of the formulated microbeads were observed using Scanning Electron Microscope JEOL JSM-6060LV (Tokyo, Japan) at 5.0kV. Samples of the microbeads were mounted on aluminum stubs with double sided carbon tape attached to each stub and coated with a gold film under vacuum in a sputter coater and then observed.

Determination of Encapsulation Efficiency

Microbeads containing 50 mg of Naproxen was accurately weighed into a mortar and triturated to obtain fine sized powder. Phosphate buffer of pH 7.4 (20 mL) was then added to the fine powder and allowed to stand for 24 hours. The solution was made up to 100 mL with the phosphate buffer. The absorbance was then taken at 273nm using a UV Spectrumlab 752 s UV-Vis spectrophotometer. From the absorbance value, the amount of naproxen entrapped was determined using the standard curve. The drug entrapment efficiency was then calculated using the formula:

$$Encapsulation\ efficiency = \frac{theoretical\ concentration - experimental\ concentration}{theoretical\ concentration} \times 100 \quad (5)$$

Determination of In-Vitro Release

Drug release study was determined using the Paddle method (USPXXXVI) rotated at 50 rpm. Drug loaded microspheres were accurately weighed and suspended in about 900ml of distilled water maintained at about 37˚C. Samples (10 mL) were then withdrawn at different time intervals and replaced with equal amount of fresh medium. The amount of naproxen released at each time interval was determined with the use of a UV spectrophotometer at wavelength of 273 nm. Determinations were carried out in duplicates.

To study the dissolution rate kinetics, the SolverDD, a Microsoft Excel add-in program was used. In order to determine the mechanism of drug release, the release data was fitted to several models including Zero order, First order, Higuchi and Korsemeyer-Peppas equation (Samia *et al*., 2009):

$$\text{Log } (Mt/Mf) = \text{Log } k + n\text{Log } t \quad \ldots\ldots\ldots\ldots\ldots\ldots (6)$$

This equation describes drug release behaviour from polymeric systems. Mt is the amount of drug release at time t, Mf is the amount of drug release after infinite time; k is a release rate constant incorporating the structural and geometric characteristics of the dosage form and n is the diffusional exponent, which indicates the mechanism of drug release. For a cylinder shaped matrix, the value of n = 0.45 indicates Fickian (case I) release; > 0.45 but < 0.89 for non-Fickian (anomalous) release; and > 0 indicates a super case II type of release. The case II mechanism refers to the erosion of the polymer and anomalous transport (non-Fickian) refers to a combination of both diffusion and erosion controlled drug release.

Statistical Analysis

Results obtained were analysed using ANOVA, followed by a posthoc Tukey's test. More than two sets of data were obtained, to determine the level of significance (p-value) of an effect or the difference between means. Parameters that are significant at 95% confidence were considered significant or different at p = 0.05.

RESULTS AND DISCUSSION

Physicochemical Properties

The physicochemical properties of I. gabonensis gum and Cedrela odorata gums are presented in Table 1.

Results obtained from density measurements were used to calculate Carrs' compressibility index and Hausner's ratio. These two parameters are useful in determining flow and ease of compressibility of materials; low values of the parameters show that the material has good flow properties (Ayorinde et al., 2016). Results in Table 1 show that Cedrela odorata gum has better flow and compressibility properties than Irvingia gabonensis gum .

Table 1: Physicochemical Properties of the Gums

Gum	pH	Bulk density (g/mL)	Tapped density (g/mL)	Carr's index (%)	Hausner's ratio	Viscocity (cPs)
Irvingia gabonensis gum	6.05 ±1.47	0.17±2.09	0.28 ±2.00	39.49 ±1.07	1.65±0.75	15±1.80
Cedrela odorata gum	3.30 ±0.07	0.59±0.50	0.77±2.70	23.53±2.37	1.30 ±2.25	123±2.45

pH is a measure of the degree of acidity or basicity of a material. The pH measurements show that the two gums are acidic, with CG being more acidic. It therefore suggests that CG could be considered for acidic drugs while IG will be suitable for neutral to slightly acidic drugs.

Although Cedrela gum has been reported to be a low viscosity polymer (Odeniyi et al., 2013), it proved to be significantly more viscous than Irvingia gum ($p < 0.05$). The rheology of both gums followed a non-Newtonian pattern.

The FT-IR of naproxen (Figures 2 and 3) revealed an alkyl ketone around the region of 1315 cm-1 and it was noticed that this peak was no longer present upon formulation with I. gabonensis gum. Also at region 1242 cm-1, this is indicative of a C-O stretching band which also disappeared on formulation with I. gabonensis gum. At region, 877 cm-1, this band is typical of CO3 and this band was still retained upon formulation with I. gabonensis gum and it is noticed that this band is also present in I. gabonensis gum on its own. Stretching of band was noticed around the region of 1669 cm-1 to 1388 cm-1. The carbon – hydrogen (alkane, alkene and alkyne) groups observed in both the gums and Naproxen also reduced in intensities with the microbeads; this may

be due to interactions between the alkyl groups and other functional groups in both the API and the gums. Free hydroxyl group was observed to be present in Naproxen at around 3326 cm-1. Naproxen has carboxylic acid and not free hydroxyl group and hence the observed free hydroxyl group could be as a result of the carboxylic acid group dissociating into the free hydroxyl group while in the aqueous dissolution medium. This hydroxyl group was no longer present in the formulations containing the gums.

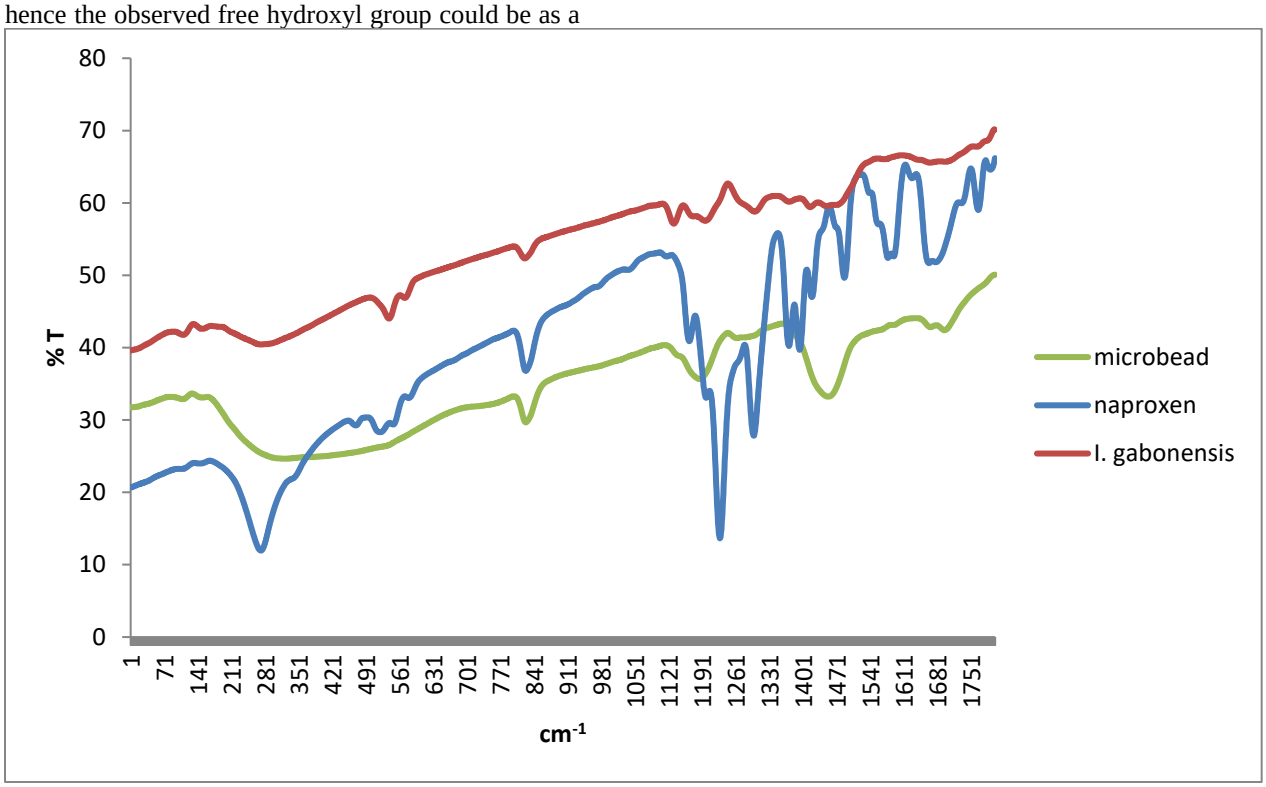

Figure 2: FTIR spectra of (a) Naproxen sodium, (b) *I. gabonensis gum* and (c) microbeads formulated with *I. gabonensis*.

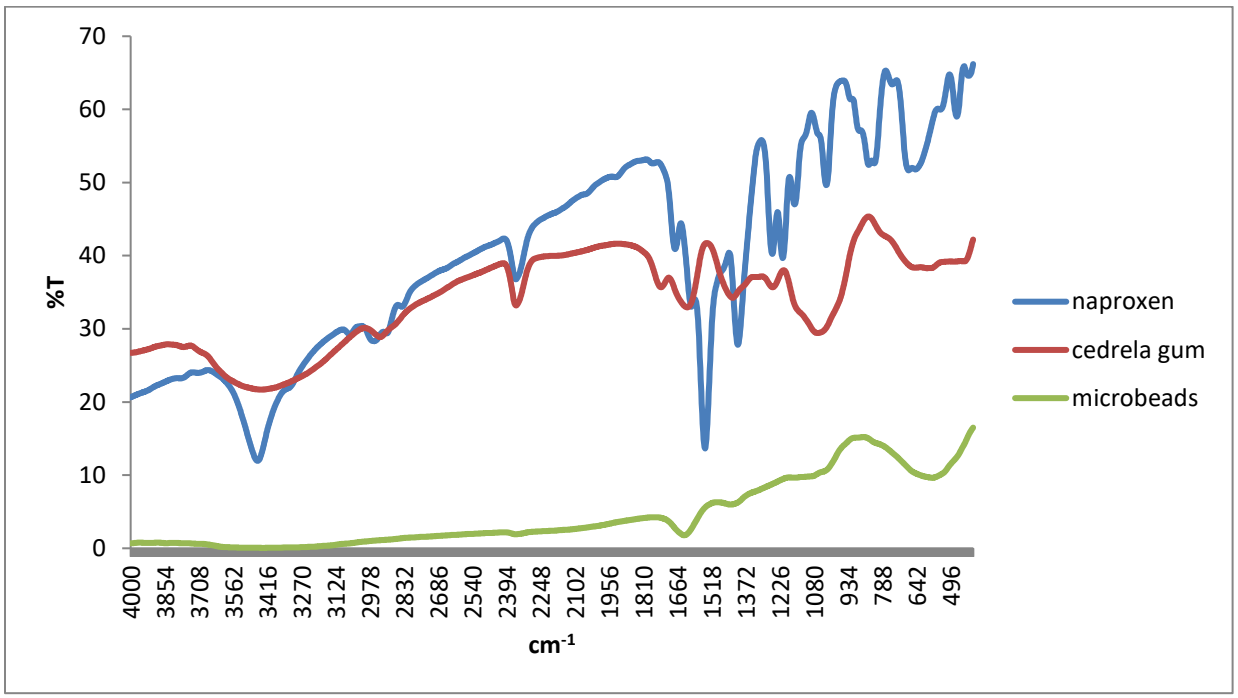

Figure 3: FTIR spectra of (a) Naproxen sodium, (b) *Cedrela odorata* gum and (c) microbeads formulated with *Cedrela odorata* gum.

There were sharp peaks of the aromatic benzene ring at 1472 cm^{-1} - 1630 cm^{-1}, for the gums and Naproxen. These peaks flattened out to show reduced intensities in the microbead formulations.

Comparing the FTIR spectra of the microbeads formulated from I. gabonensis to that formulated from *C. odorata*, a higher level of overlapping of spectrum between microbead formulations and Naproxen was observed in microbeads produced from *I. gabonensis* than from the microbeads produced from *C. odorata*.

Furthermore, carboxylic acid alcohol functional group present in Naproxen and the formulations containing CG was observed to be absent in formulations containing IG. This was found to be a major difference between formulations of the two gums.

Considering microbeads formulated from *C. odorata*, it was also noticed that there was a band at region 877 cm-1 which was found in both naproxen and the gum but this region was absent in the formulated microbeads.

Evaluation of the Naproxen Microbeads

Morphology

It is expected that microbeads formulated with the ionotropic gelation method should be spherical or near spherical in shape (Sudhakar et al., 2015). Results for the scanning electron microscopy (SEM) of the formulations revealed that some of these microbeads are almost spherical while some had other shapes with slightly rough edges. Formulation A1 had a cuboidal shape (Fig. 4a), Formulation A4 was irregularly shaped and has a rough surface (Fig. 4b), Formulation A6 were small and almost spherical in shape (Fig. 4c) while formulation B1 had a mixture of both cuboidal and almost spherical shape (Fig.4d). Formulations A6 and B1 (formulated with I. gabonensis) showed line of cross-linking while this was not visible in microbeads formulated from C. odorata. The imperfect spherical shapes could be attributed to the intrinsic particle shape of the gum polymeric materials, stirring speed used during the microbead formulation, particle size and shape of the API and other materials used in the formula.

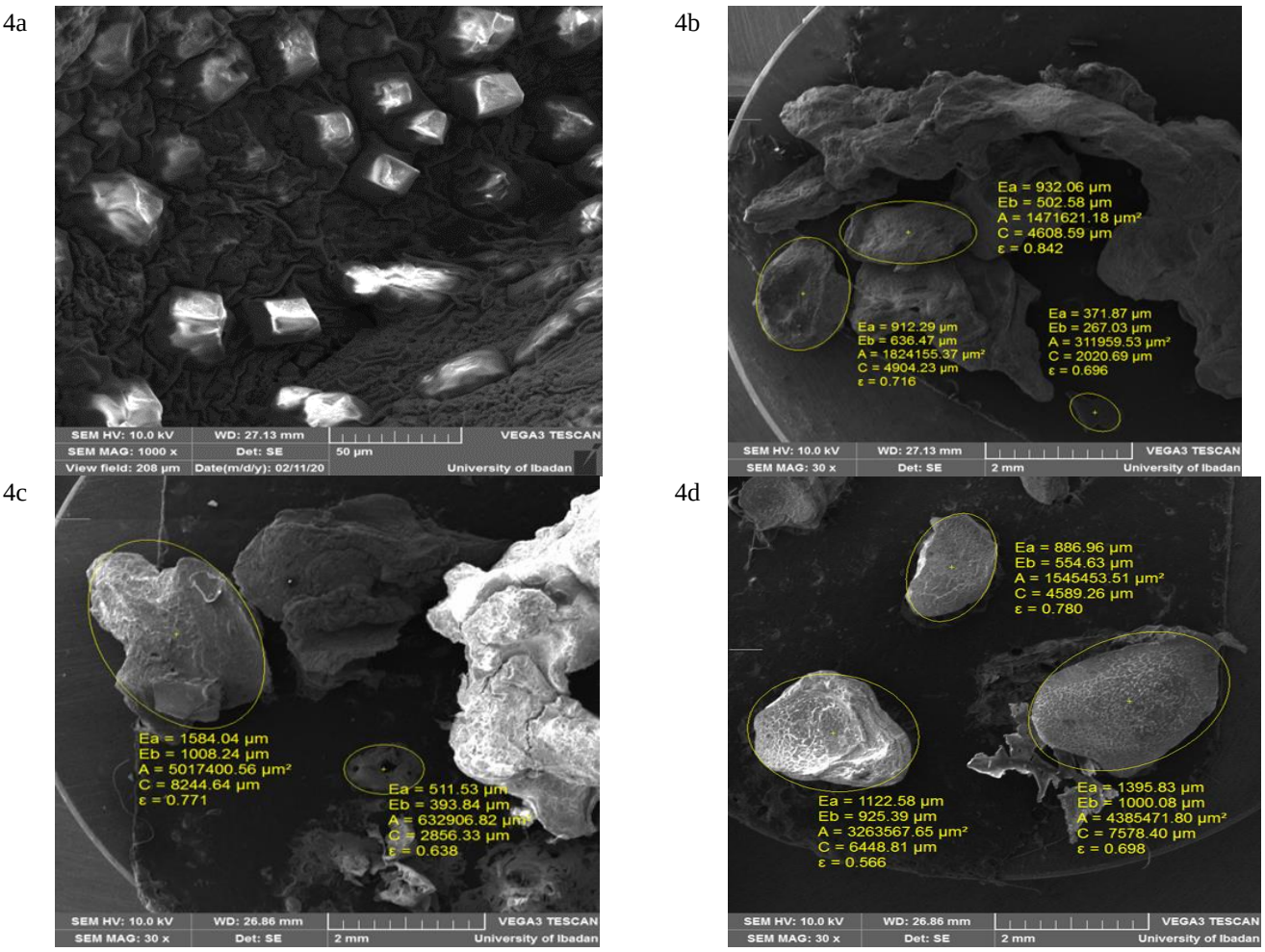

Figure 4: Scanning Electron Microscope Image for Formulation (a) A1, (b) A4, (c) A6 and (d) B1

Photomicrography

The photomicrographs of the formulated microbeads showed the mean particle size of the naproxen microbeads (Fig. 5). From the statistics, the microbeads with the largest particle size is formulation A6 (1500µm ± 163.2) while the microbeads with the smallest particle size is formulation A9 (491.6µm ± 191.7).

The trend of the mean particle size of the microbeads in increasing order is A9<A1<A8<B1<A7<A5<A6.

Reduced particle size is an indication of an increase in area-to-volume ratios of the particles (Banarjee et al., 2012); which shows that the rate of release of the drug from the microbeads of small sizes will be faster. Furthermore, there will be faster absorption of water into smaller particles due to the shorter distance between the surface and centre of the particles; hence there will be an increased rate of swelling (Das and Senapati, 2008).

Entrapment Efficiency

The formulated microbeads had high values of entrapment efficiency, in the range of 80% to 96% (Table 2); this is an indication that the drug is efficiently encapsulated in the microbeads (Banarjee et al., 2012). However, the microbeads formulated with I. gabonensis gum (Batch A6 – A9) had higher entrapment efficiency than microbeads formulated from Cedrela odorata gum (Batch A2 – A5) ($p > 0.05$). Many factors could affect entrapment efficiency in microparticle formulations; these include polymer concentration, drug-polymer ratio, drug-polymer interaction and concentration of the cross linker (Odeniyi et al., 2013). The high

entrapment efficiency obtained indicates optimum combination of these parameters in the formulations.

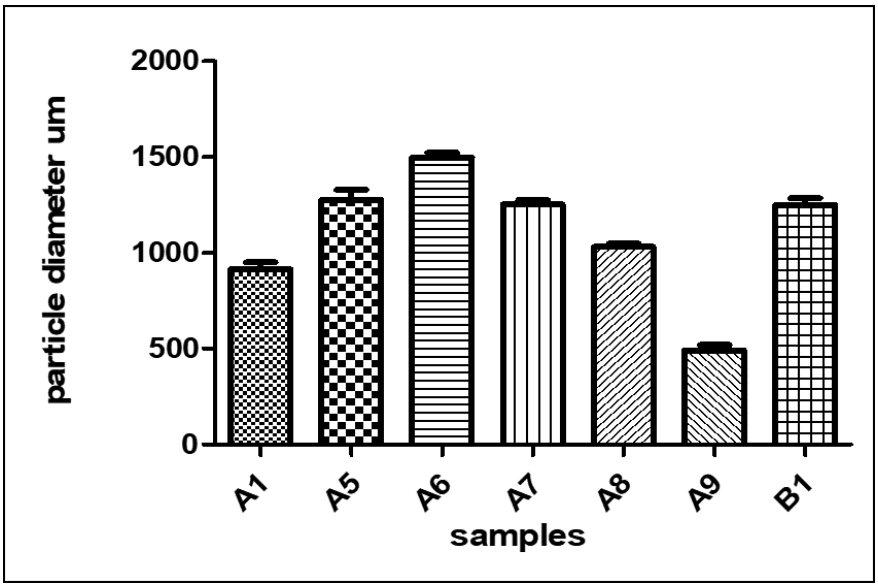

Fig. 5: Particle size distribution of microbead formulations

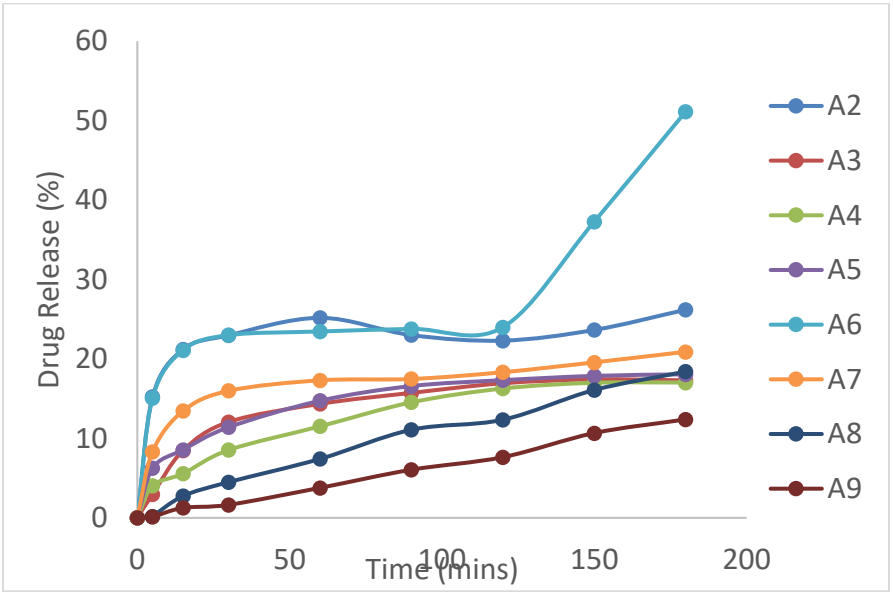

Figure 6: Dissolution release profile of naproxen sodium from Irvingia gabonensis and Cedrela odorata microbeads

Release Profile

Drug bioavailability, dosing frequency and the occurrence of toxic side effects are affected by the drug release kinetics (Sudhakar et al., 2015). Hence, it is important to study the kinetics of drug release from the prepared microbeads. Microbeads of all the batches had more than 15% of their drug released within the first hour (Figure 6). This is referred to as a burst release and results indicate that this type of release can occur in the two gums; this suggests that formulations from the two gums and with the formulation conditions (curing time, cross linkers, polymer: drug ratios) are capable of producing rapid onset of pharmacological action, when desired.

Batch A6 gave the highest drug release ($p < 0.05$), maintaining the release up to 55% (Figure 6). This shows that microbeads prepared with irvingia gum possessed better release profile than preparations containing cederela gum. Results further suggest that formulation conditions for optimum drug release are I. gabonensis gum as the polymer, CaCl2 as cross linker and at a curing time of 15 minutes.

At the curing time of both 15 and 30 minutes, microbeads formulated with CaCl2 had higher t25

and t80 than microbeads formulated with Al2(SO4)3 (Table 2). Therefore, it could be said that CaCl2 produces a higher t25 and t80 than microbeads formulated with Al2(SO4)3.

The delayed release of Al3+- alginate microspheres could be as a result of the ability of Al3+ to form three-dimensional bonding structure with the sodium alginate inside the microbeads and this brings about an extended cross-linking through the microbeads and hence, producing hard microbeads which brings about a slow removal of Al3+ which hence leads to slow disintegration of the microbeads (Dash et al., 2010).

After fitting the percentage drug release of the microbeads into various kinetic mathematical model, it was noticed that the best fit kinetic model was Korsmeyer-Peppas model of drug release. Korsmeyer-Peppas model of kinetic release describes a drug release from a polymeric system equation (Ayorinde et al., 2017; Ferrari et al., 2006).

$Mt / M\infty = Ktn$

Where $Mt / M\infty$ is a fraction of drug released at time t,

K is the release constant,

n is the release exponent.

In the Korsmeyer-Peppas' model, the release exponent is used to characterize the release mechanism of drug (Ferrari et al., 2006) that is, Fickian diffusion. The value of $n \leq 0.43$ indicates a classical Fickian diffusion-controlled release, $n = 0.89$ indicates that the mechanism of release is by swelling while values of n between 0.43 and 0.85 indicates that release is by both swelling and diffusion (Ayorinde et al., 2016; Banarjee et al., 2012).

The Fick's law of diffusion states that "rate of change of concentration of dissolved material with time is directly proportional to concentration difference between two sides of diffusion barrier". The law basically explains that drug diffuses from a region of higher concentration to a region of lower concentration until equilibrium is attained.

The release profiles showed that all batches except A8 and A9 had a release exponent ($n \leq 0.43$ (Table 3). This indicates that batches A2 to A7 had their drug release by diffusion while batches A7 and A8 released drug by swelling and diffusion. Formulations containing Cedrela gum exhibited the same mechanism of release in all the conditions of formulation while formulations containing Irvingia gum had drug release by diffusion only when CaCl2 was used as the cross linker. Previous studies has shown that Cedrela gum produced formulations whose drug release was by Fickian diffusion (Ferrari et al., 2006; Odeniyi et al., 2013; Ayorinde et al., 2017).

Table 2: Formulation and properties of naproxen microbeads

Batch	Gum	Gum: Alginate Ratio	Polymer: Drug Ratio	Cross-linker Concentration (%)	Curing Time (minutes)	Size (µm)	Entrapment efficiency (%)	t_{25} (hr)	t_{80} (hr)
A1 (Blank)	*Cedrela odorata*	2:1	Nil	10% $CaCl_2$	30	961.1±242.1	NA	NA	NA
A2	*Cedrela odorata*	2:1	1:2	10% $CaCl_2$	30	NA	88.12± 0.00	0.718	3607.94
A3	*Cedrela odorata*	2:1	1:2	10% $CaCl_2$	15	NA	89.12± 0.00	7.089	245.71
A4	*Cedrela odorata*	2:1	1:2	10% $Al_2(SO_4)_3$	15	NA	85.16± 0.00	6.354	101.33
A5	*Irvingia gabonensis*	2:1	1:2	10% $Al_2(SO_4)_3$	30	1277±369.3	91.74± 0.00	7.524	404.69
A6	*Irvingia gabonensis*	2:1	1:2	10% $CaCl_2$	15	1500±163.2	80.86± 0.04	0.806	25.56
A7	*Irvingia gabonensis*	2:1	1:2	10% $CaCl_2$	30	1253±161	92.35± 0.00	7.789	2675.38
A8	*Irvingia gabonensis*	2:1	1:2	10% $Al_2(SO_4)_3$	15	1030±128.6	95.28± 0.00	4.393	18.45
A9	*Irvingia gabonensis*	2:1	1:2	10% $Al_2(SO_4)_3$	30	491.6±191.7	94.02± 0.00	5.700	16.74
B1 (Blank)	*Irvingia gabonensis*	2:1	Nil	10% $CaCl_2$	30	1251±249.9	NA	NA	NA

Table 3: Correlation coefficients obtained for the naproxen microbeads using different release models

Batch	Zero order	First order	Higuchi	Hixson-Crowell	Korsmeyer	
	R^2	R^2	R^2	R^2	R^2	N
A2	-0.599	-0.428	0.163	-0.485	**0.551**	0.136
A3	0.360	0.433	0.881	0.409	**0.955**	0.328
A4	0.657	0.707	0.976	0.691	**0.988**	0.420
A5	0.251	0.336	0.868	0.308	**0.988**	0.292
A6	0.467	0.510	0.743	0.497	**0.783**	0.336
A7	-0.274	-0.155	0.634	-0.194	**0.978**	0.199
A8	0.976	0.984	0.913	0.981	**0.993**	0.810
A9	0.995	0.993	0.857	0.994	**0.997**	1.080

CONCLUSION

Naproxen loaded microbeads possessing good physicochemical and release properties were formulated with gums obtained from two native plants: *Cedrela odorata* and *Irvingia gabonensis*. Better release profile and drug entrapment was obtained in formulations containing *Irvingia gabonensis* gum when compared with naproxen loaded microbeads prepared with *Cedrela odorat*a. Drug release from the microbeads was by the mechanism of diffusion in formulations containing Cedrela gum, while Irvingia gum microbeads released the drug by either swelling or diffusion, depending on type of cross linker used in the formulation.

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