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Research Article

Formulation of floating metronidazole microbeads using *Terminalia mantaly* gum as polymer

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ABSTRACT

The aim of the present study was to evaluate *Terminalia mantaly* gum as a polymer in the formulation of floating metronidazole microbeads. *Terminalia* gum was extracted and characterized by material, proximate and pasting properties. Terminalia gum in combination with sodium alginate at varying concentrations (0-80 $\%^{w}/_{v}$) was used in preparing the microbeads by ionotropic gelation using zinc chloride as the chelating agent. The microbeads were evaluated using shape, size, swelling, buoyancy, entrapment efficiency, drug release profiles and kinetic modelling. The microbeads were spherical to ovoid in shape with size ranging from 1093 to 1209.0 µm. The swelling index was 5 to 184 % and it increased with increase in gum concentration. Total floating time was highest (175.5 h) for formulations having 20% $^{w}/_{w}$ gum and least (5.5 h) for those with 80% $^{w}/_{w}$ gum. The entrapment efficiency generally increased with increase in gum concentration up to 40% $^{w}/_{w}$ and then reduced. The microbeads showed controlled release patterns of metronidazole with highest t_{50} of 2260.3. The drug release kinetics fitted Korsmeyer-Peppas model with non-Fickian anomalous diffusion mechanism. *Terminalia mantaly* gum can be further developed for use as co-polymer in the formulation of floating metronidazole microbeads.

INTRODUCTION

Floating drug delivery systems (FDDS) are dosage forms that remain afloat in the stomach for extended period of time due to their floating properties, thereby increasing the gastric residence time, enhancing drug solubility and bioavailability (Kaza et al., 2009; Nanjwade et al., 2012). Bouyant delivery systems may also provide a beneficial strategy for the treatment of gastric and duodenal cancers (Ajala et al., 2013). Floating microbeads involves the slow delivery of active agents at the required rate and this occurs as the system floats on the gastric content, thereby increasing the gastric contact time leading to a prolonged therapeutic action (Lachman *et al*., 1991). A minimum gastric fluid is needed to achieve proper buoyancy and a minimum level of floating force is also needed to enable the dosage form to be sufficiently buoyant on the surface of the medium (Timmermans and Moes, 1990). Swellable polymers are quite useful in the preparation of floating drug delivery systems. The air entrapped during swelling confers buoyancy and the gel formed acts as a reservoir for sustained drug release. This is because the drug is released slowly by controlled diffusion through the gel layer (Sheth and Tossounian 1984). When the external surface of the dosage form dissolves, the gel layer is assisted by the adjacent hydrocolloid layer becoming hydrated and the drug dissolves within and diffuses out. Polymers used for FDDS are gel-forming or highly swellable polysaccharides and matrix forming systems Examples include carboxymethyl cellulose (Velesco et al., 1999); Hydroxypropylcellulose (Ozeki et al., 1995) and sodium alginate (Odeku et al., 2013; Odeku et al., 2017). Sodium alginate helps in producing

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spherical microbeads when it comes in contact with a crosslinking agent. Its usefulness in gelling and thickening helps in successful encapsulation. It however has low mechanical and barrier properties hence the need to combine it with biopolymers. Alginate is biodegradable, biocompatible and can absorb about 200-300 times more than its own weight (Wang et al., 2016). Despite the usefulness of sodium alginate as described above, in the presence of an ionic cross-linking agent it reduces long-term stability of microbeads in physiological conditions. This is because the gel produced can be dissolved due to the release of divalent ions into the surrounding media due to exchange reactions with monovalent cations. Furthermore, the gel has limited strength, uncontrollable degradation and dissolution properties (Suzuki et al., 1998). For this reason, the blending of a natural polymer without ionic bonds but complex covalent bonds between the molecules helps in reducing the drawbacks of sodium alginate and obtain more stable products.

In our previous study (Odeku et al., 2017), pregelatinized cassava starch blended with sodium alginate was used in producing floating metronidazole microspheres. The results showed that blends of cassava starch and sodium alginate were found useful in the preparation of spherical discrete microspheres that could provide controlled release of metronidazole for up to 18 h. The sizes of the microspheres however were rather large (1.52-2.23 mm). It is desirable to obtain floating metronidazole microbead having lower particle sizes and improved properties hence the need to evaluate other natural polymers like gum. One of the advantages of microbeads is that it has controlled particle size (0.5 -1000 µm); hence variation in sizes should be narrow. Lower sizes are important because it enhances the solubility of poorly soluble drugs while limiting fluctuation within therapeutic range (Da et al., 2019).

Terminalia popularly known as the umbrella tree is a genus of large trees of flowering plants belonging to the family Combretaceae accommodating over 200 species (McGaw *et al.,* 2001). About fifty of these are native to Africa and distributed throughout the sub-saharan region and common examples include *Terminalia randii*, *Terminalia catappa* and *Terminalia mantaly* (McGaw *et al.,* 2001). *Terminalia* trees are planted in several countries in the tropics as a source of high quality solid timber for fine carpentry, joinery, building, flooring and plywood manufacture (Smith *et al.,* 2004). Extracts from the stem and bark of some *Terminalia* species are used traditionally in the treatment of dysentery, diarrhea, hemorrhoids, and wounds.

Recent studies have shown the potentials of *Terminalia* species as suspending agents (Bamiro *et al.,* 2013); directly compressible excipient (Kumar *et al.,* 2008). However, the potentials of one of the widely abundant species in Nigeria, *Terminalia mantaly*, have not been evaluated in the preparation of floating microbeads for controlled drug delivery. Thus, in the present study, *Terminalia mantaly* gum has been evaluated as a polymer in combination with sodium alginate for the formulation of floating metronidazole microbeads. Metronidazole, the active agent used in this study is a drug which has found usefulness in the first line treatment of peptic ulcer caused by *Helicobacter pylori*. When presented as floating gastro-retentive microbeads, the local effect of the drug have been improved as well as the extension of the gastric residence time which is crucial for optimal effect (Choi et al., 2008).

MATERIALS AND METHODS

Metronidazole (gift from Bond Chemicals Industries Limited Awe, Nigeria), zinc chloride (QFC Fine Chem, Mumbai, India), sodium hydrogen carbonate (Qualikems, Mumbai, India), sodium alginate (Carl Roth GmbH and Co.Karlsruhe, Germany). *Terminalia mantaly* gum was obtained from the incised trunk of the *Terminalia mantaly* tree. The plant was authenticated at the Department of Botany, University of Ibadan, Ibadan Herbarium, (voucher number UIH-22701). The gum was collected and purified using established procedure (Bamiro *et al.,* 2010).

Characterization of *Terminalia mantaly* gum

Particle size was determined using optical microscopy in which one hundred particles were measured and the mean obtained.

The solubility of the *Terminalia mantaly* gum was determined using the method of Ajala et al., (2016). An amount (1.0 g) of the gum was weighed (w) into a conical flask, and 10 mL of distilled water was added and shaken slowly for 5 min. It was

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transferred to a pre-weighed centrifuge tube (w_1) and 7.5 mL of distilled water was added and centrifuged at 2200 rpm for 20 min. The supernatant was carefully transferred into a pre-weighed dish (w_2) and dried at 100 ^{o}C to constant weight (w_3), then cooled for 30 min in a dessicator. The solubility was calculated using Eq. (1)

$$\text{Solubility (\%)} = \{(w_2 - w_3)/w\} \text{ X } 100 \quad (1)$$

Water absorption capacity of *Terminalia gum* was determined by weighing 0.5 g of into a 50 mL centrifuge tube, 10 mL of distilled water was added and agitated for 2 min. It was centrifuged at 2200 rpm for 20 min and the supernatant decanted. The residue was weighed (w_1) and the absorbed drops of water were removed by drying at 60 ^{o}C to a constant weight (w_2) in the oven. The water absorption capacity (WAC) was then expressed as the weight of water bound by 100 g of each sample. It was calculated using the Eq (2).

$$\text{Water absorption capacity} = \left(\frac{W2}{W1}\right) * 100 \quad (2)$$

The swelling index was determined by transferring 0.5 g of the gum into 50 mL measuring cylinder and the volume occupied was recorded (v_1). A volume (50 mL) of distilled water was added slowly with agitation for 5 min. The dispersion was left to stand for 24 h. The final volume (v_2) was determined and the swelling capacity was calculated using Eq (3)

$$\text{Swelling index} = \frac{v2-v1}{v1} * 100 \quad (3)$$

The proximate parameters were determined using the methods of Association of Official Analytical Chemists (2000). Pasting properties were also evaluated using a heating and cooling viscometer, series 3 RVA (Rapid Visco Analyser) coupled with Thermocline for Windows software (Newport Scientific Pty. Ltd. Warriewood, NSW Australia). The gum (3.5 g) was weighed and 25 ml of water was added to the canister. The gum slurry was heated at a constant rate of shear using a predetermined time-temperature regime, the viscosity increase was measured as torque on spindle and a curve was obtained.

Preparation of polymer mixtures, viscosity and swelling determinations

Polymer blends (2 g) were thoroughly mixed and 50 ml of distilled water was added gradually, more distilled water was added to obtain total polymer concentration of 2 $\%^{w}/_{v}$. The mixture was placed on a water bath having a temperature of 70 ^{0}C until complete dispersion was obtained. The viscosity of the polymer blends were determined with the aid of a Brookfield Viscometer (model RVVDV –II + P, Brookfield Eng Labs Inc., Middle Boro, MA, USA) at a shear rate of 50 rpm using spindle 04.

In addition, the swelling profiles were determined by weighing 2.5 g of the polymer mixtures and 40 mL of 0.1M hydrochloric acid was added gradually and then made up to 50 mL. The percentage swelling was calculated at various time intervals.

Preparation of microbeads

The method of ionotropic gelation was used in producing the floating metronidazole microbeads (Odeku et al., 2017). Polymer blends (2 g) comprising of Terminalia gum and sodium alginate were thoroughly mixed and 50 ml of distilled water was added gradually, more distilled water was added to obtain total polymer concentration of 2 $\%^{w}/_{v}$. The mixture was placed on a water bath (70 ^{0}C) until complete dispersion. Metronidazole (1 g) was added to the polymer blend such that the ratio of total polymer to drug was 2:1 and sodium bicarbonate (2 $\%^{w}/_{w}$) was added as gas releasing agent. The resulting dispersion was extruded into calcium chloride solution (10 $\%^{w}/_{w}$) using a syringe fitted with 0.90 mm needle at a dropping rate of 2 ml/min and a stirring speed of 300 rpm from Talboys Laboratory stirrer (Model No. 102; Troemner, Thorofare, USA). The metronidazole microbeads produced were allowed 30 min for curing and then left to stand for 1 h to allow further crosslinking of the polymers. The microbeads were harvested by decantation, washed with distilled water, air-dried overnight and later for 24 h in hot air oven (Gallenkamp BS 250 Oven; Riley Industries Ltd, West Midlands UK) at 40 °C.

Particle size and Morphology of microbeads

The particle size of the microbeads was determined using optical light microscope (Nanotech Systems, Peenya, Bengaluru, India). The mean particle size of

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20 microbeads was recorded. The morphology was determined using scanning electron microscope (Tescan Vega 3, Brno, Czech Republic).

Buoyancy determination for microbeads

Buoyancy was determined by placing microbeads (0.01 g) in a 20 mL bottle containing 0.1M HCl. The time taken for the microbeads to rise to the surface and commence floating was taken as the floating lag time (FLT). The duration of time the microbeads remain consistently on the medium is taken as total floating time (TFT).

Swelling index

The floating microbeads (0.1 g) were weighed (w_1) and soaked with the aid of a calico cloth in 20 ml 0.1M HCL in a beaker for 3 h. The weight w_2 of the microbeads was determined after 3 h, after removing the excess fluid with a filter paper. The swelling index of the microbeads was calculated using the formula below:

$$\text{Swelling index} = \{(w_2-w_1)/w_1\} \times 100 \quad (4)$$

Entrapment efficiency

An amount of microbeads equivalent to 50 mg of the drug was weighed and crushed in a mortar with the aid of a pestle. The crushed microbeads were suspended in 50 mL 0.1M HCL, and filtered after 24 h. The filtrate obtained was diluted in the ratio of 1:19 and analyzed with the use of a spectrophotometer (Spectrumab 752s. 752512090 UV-Visible, Spectrophotometer, Shanghai, China) at a wavelength of 277 nm. The drug entrapment efficiency was calculated using the following equation:

$$\text{Entrapment efficiency (\%)} = \left(\frac{\textit{Actual drug content (mg)}}{\textit{Theoretical drug content (mg)}}\right) X100 \quad (5)$$

Drug release study

In-vitro drug release study was done using the paddle method in a Dissolution apparatus (DA-6D Veego Scientific Devices, Mumbai, India) rotated at 50 rpm. An amount of microbeads equivalent to 200 mg of metronidazole was weighed and used for the experiment. The dissolution medium contained 900 mL of 0.1M Hydrochloric acid maintained at a temperature of 37.0 ± 0.5 °C. Sample (5 mL) was withdrawn at certain intervals for a total duration of 6 h and replaced with an equal amount of fresh medium. The sample was diluted and analyzed using auv/vis spectrophotometer (UV-Visible Spectrophotometer, Spectrumab 752s. No. 752512090, Shangai, China) at a wavelength of 277 nm.

The release kinetics was determined using DDsolver, a Microsoft excel add-in. The release data was fitted into different kinetic equations (zero order, first order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas); and values of correlation coefficients were used to identify the model of best fit.

Data presentation and analysis

All experiments were performed in triplicate and the data is presented as mean ± SD. Statistical analysis was performed with one-way Analysis of Variance (ANOVA) using GraphPad Prism® 5 (GraphPad Software Inc., San Diego, USA). Tukey Kramer's Multiple Comparison Test was used to compare the individual differences between the parameters. At 95 % confidence interval, $p<0.05$ was considered significant. The Release data were fitted into different kinetic equations to determine the model of best fit by comparing the correlation coefficients.

RESULTS AND DISCUSSION

Properties of *Terminalia mantaly* gum

The material, proximate and pasting properties of *Terminalia mantaly* gum are presented in Table 1. The average particle size of the gum was found to be 80.40 µm. The solubility of the gum was 22 % and its water absorption capacity was reasonably high. The swelling index was extremely higher than 100 per cent.

Viscosity of polymer mixtures

The viscosity of the polymer mixtures are presented in Table 2. The viscosity of sodium alginate (0 % gum) was significantly higher ($p < 0.05$) than that of *Terminalia mantaly* (100 % gum) gum. Generally, as the concentration of *Terminalia mantaly* gum increased in the polymer blends, the viscosity of the polymer mixtures decreased. This is a reflection of the low viscosity of *Terminalia mantaly* gum. Materials with low viscosity have been shown to demonstrate improved properties in floating drug delivery.

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Table 1. *Material, Proximate and pasting properties of Terminalia mantaly gum*

Parameters	Values
Particle Size (µm)	80.4 ± 31.0
Solubility (%)	22.0 ± 2.8
Water absorption capacity (%)	66.0 ± 2.8
Swelling index (%)	653.0 ± 50.3
Moisture content (%)	11.3 ± 1. 8
Crude fat (%)	9.5 ± 1. 2
Nitrogen (%)	0.4 ± 0.1
Crude protein (%)	2.3 ± 0.9
Pasting temperature (°C)	73.5 ± 0.7
Holding strength (cp)	1761.5 ± 37.5
Peak viscosity (cp)	2927.5± 153.4
Set back viscosity (cp)	838.5 ± 37.5
Final viscosity (cp)	2600.0 ± 0.0

Table 2*: Viscosity of polymer blends containing Terminalia mantaly gum and sodium alginate*

Percent of gum in the polymer blend	Viscosity (cp)
0	225.3 ± 2.3
10	206.0 ± 4.0
20	134.7 ± 6.1
40	92.0 ± 4.0
60	48.0 ± 4.0
80	26.7 ± 2.3
100	29.3 ± 2.3

Table 3. *Properties of floating metronidazole microbeads*

Gum (%)	0	20	40	60	80
Bead size(µm)	1093.0 ± 127.8	1185.0 ± 177.2	1209.0 ± 179.9	1115.0 ± 135.5	1108.0 ± 200.5
Swelling(%)	5.0 ± 1.4	10.0 ± 2.5	37.0 ± 2.8	112.0 ± 2.8	184.0 ± 11.3
Buoyancy FLT (min)	5.19 ± 8.83	1.04 ± 0.65	1.23 ± 1.27	2.02 ± 2.29	0.03 ± 0.00
Buoyancy TFT (h)	100.4 ± 25.5	175.1 ± 30.2	144.1 ± 15.0	48.4 ± 17.4	5.5 ± 3.8
Entrapment efficiency (%)	18.4 ± 2.2	24.3 ± 2.3	20.5 ± 1.7	13.5 ± 2.1	6.9 ± 1.9
t_{15} (min)	300	NA	260	170	60
t_{50} (min)	952.5	1217.7	827.4	603.4	219.1

NA*: Not available because the formulations concerned did not release up to 15 %; FLT-Floating lag time; TFT-Total floating time.*

Properties of floating metronidazole microbeads

The scanning electron micrographs showing the morphology of the microbeads is presented in Figure 2. The microbeads were generally spherical in shape for formulations having gum content between 0 and 60 %, but at 80 %, the shapes seemed flattened. The scanning electron micrographs also showed the surface outlook of the microbeads. The microbeads generally had wrinkles on the surface irrespective of the presence or absence of gum in the polymer used.

Table 4*: Release kinetics of floating metronidazole microbeads*

% of gum		0	20	40	60	80
Zero order	r^2	0.851	0.889	0.917	0.83	0.935
First order		0.883	0.91	0.942	0.884	0.99
Higuchi		0.974	0.964	0.965	0.959	0.923
Hixson-Crowell		0.873	0.903	0.934	0.868	0.987
Korsmeyer-Peppas		0.988	0.989	0.981	0.972	0.98
	n	0.602	0.644	0.67	0.599	0.741

Other properties of the floating metronidazole microbeads are presented in Table 3. Formulation prepared with 100 % *Terminalia mantaly* gum on its own could not form microbeads at the concentration (2 %w/v) used for the polymer. This might have been due to being dilute and possessing low viscosity. The size of the microbead formulations increased with an increase in the concentration of the gum in the formulation up to 40 % and then reduced slightly. It has been reported that an increase in the concentration of gum gives rise to an increase in microbead size (Odeku *et al.*, 2013). From polymer mixtures containing 40 % concentration of the gum, bead sizes slightly reduced. However, statistical analysis showed that the differences in the bead sizes between the batches were not significant ($p > 0.05$); although significant ($p<0.05$) variation in sizes existed within same batches and this is also reflected in the standard variations obtained. The average floating lag time of metronidazole microbeads containing 80 % of the gum was less than 1.00 min in comparison with the formulation containing sodium alginate alone, which was 5.19 min. At greater than 40 % gum content, the metronidazole microbeads had a significantly lower total floating time. According to Merriam Webster dictionary, floating or buoyant force is an upward plunge exerted by a fluid upon a material dispersed or resident within it. When the force is positive, the material moves from within towards the surface and is called floating or buoyancy. Consequently, floating force helps counter the downward pull of gravity upon the same object. For a material to have a high and sustainable floating time, the floating force must continually resist the downward pull of the force of gravity. For these formulations, the total

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floating times were high enough to foster required therapy at the gastrointestinal area.

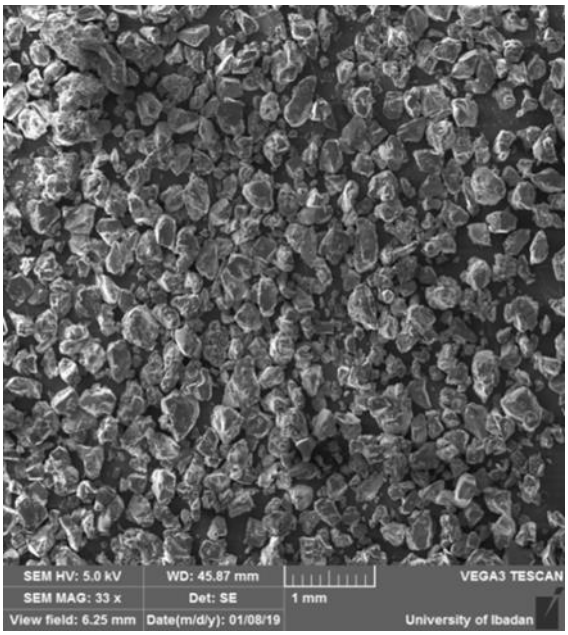

Fig. 1. *Scanning electron micrograph of Terminalia mantaly gum (X500).*

Drug Entrapment efficiency is an important parameter in determining the drug loading of microbeads. The results showed that the drug entrapment efficiencies of the metronidazole microbeads at different concentrations of the polymer blends ranged between 6.92 and 25.57 %. The entrapment generally increased with an increase in the concentration of *Terminalia mantaly* gum up to 40 %. However, above 40 % of the gum, there was a decrease in drug entrapment efficiency. The drug loading seems to be generally moderate for all formulations prepared with polymer blends when compared with the batch prepared sodium alginate alone; although those containing between 10-40 % gum had higher entrapment than the beads from 100 % sodium alginate. Other polymer mixtures containing 60-80 % gum resulted in lower entrapment. Abdalla et al., (2015) did a study on the optimization of entrapment efficiency of sodium alginate without any polymer and obtained 25 % entrapment. Akin-Ajani et al., (2019) also obtained 25 % entrapment for sodium alginate beads in a study of date mucilage as co-polymer in metformin microbead formulation. In both studies, the addition of another polymer like date mucilage, hydroxylpropylmethylcellulose and polyvinyl pyrrollidone boosted drug entrapment. The recorded improvement in the drug loading in the presence of PVP was attributed to the ability of PVP in closing surface pores in the beads with the result that the loss of drug is reduced during the crosslinking step (Abdalla et al., 2015; Narra *et al*., 2012).

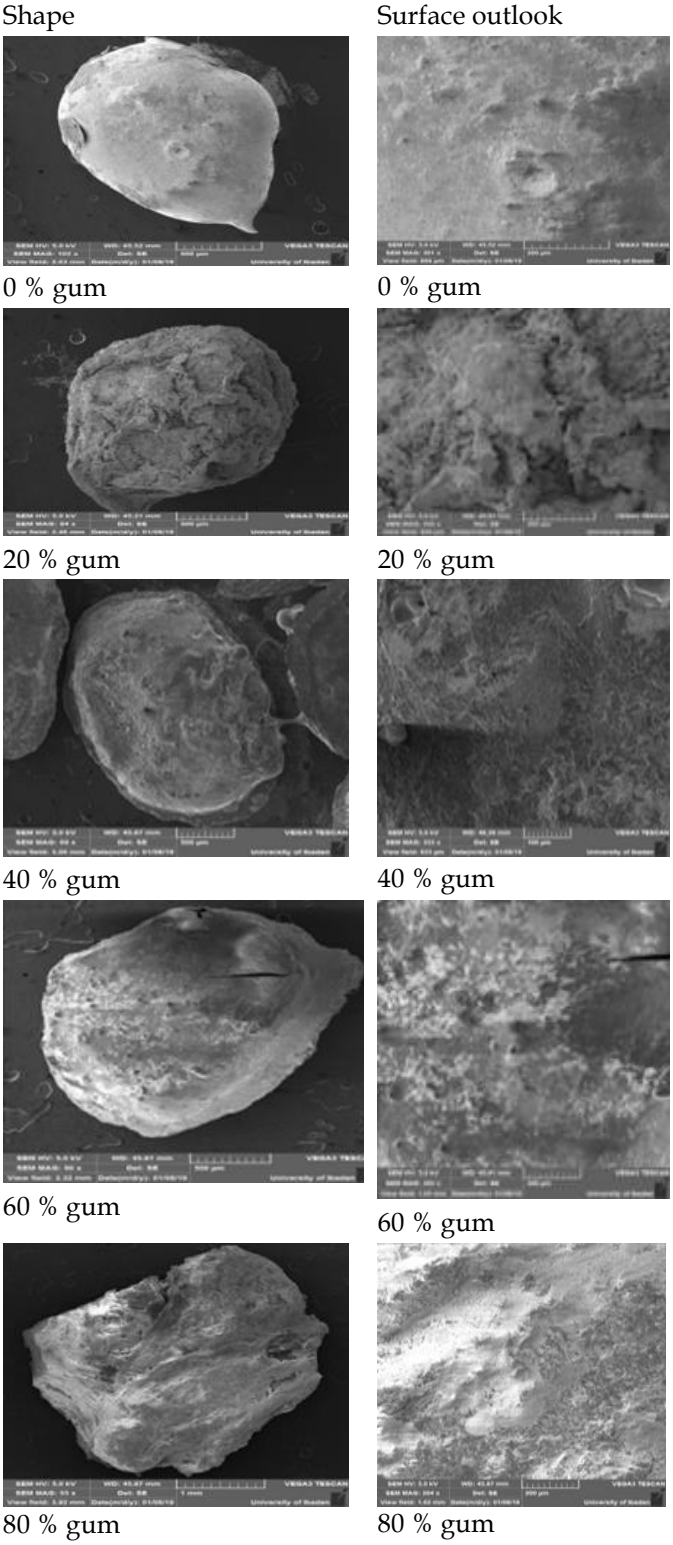

Fig.2. *Scanning electron micrographs of metronidazole floating microbeads prepared with polymer blends containing different concentrations of Terminalia mantaly gum (X500).*

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Similarly, increased entrapment on addition of HPMC was explained as due to the formation of a matrix structure having higher density (Karewicz *et al*., 2010). For the formulations in this study, the presence of gum possibly created the matrix formation at viscosities that are favourable and thus increased loading. At much lower viscosities however, a weakened matrix led to the reduction of loading.

To further understand the properties of the beads, a plot showing the relationship between viscosity, entrapment efficiency and gum concentration was prepared as shown in Figure 3. The plot showed that as the gum concentration increased, the viscosity of polymer blends reduced and the entrapment efficiency increased up till 40 % and then reduced. This showed that low viscosity favoured the entrapment efficiency up to a point indicating that some viscosity is required to enhance drug entrapment. Generally, the features of beads depend on the composition of alginate system and addition of other excipients can affect size, shape, entrapment efficiency and release of drugs from such beads (Rangaraj *et al*., 2010).

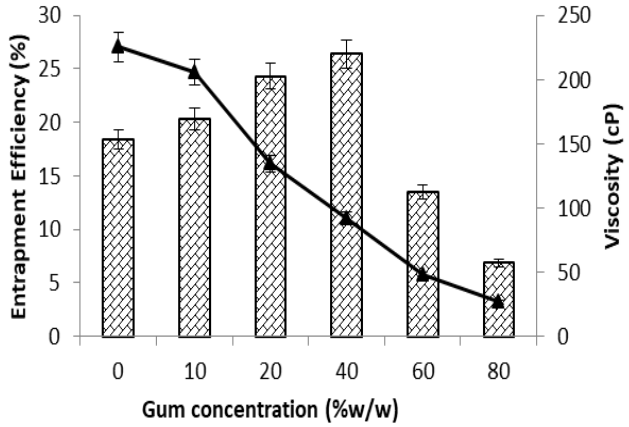

Fig. 3. *Plot showing the relationship between viscosity and entrapment efficiency with increase in gum concentration*

Drug release from floating metronidazole microbeads

The drug release profiles for the microbead formulations are shown in Figure 4 while the dissolution times are presented in Table 3. Generally, the formulations demonstrated controlled release properties and those containing 10, 20, 30, and 50 % of gum did not release up to 15 % in 6 hours. The release profiles of the drug were influenced by the concentration of *Terminalia mantaly* gum. The formulation containing 80 % gum had the fastest drug release and 15 % of the drug in it was released within 1 h showing burst release. For controlled release preparations, an initial high rate of drug release referred to as ''burst release" whereby 15 % of the drug is released within the first hour is not desired due to the adverse pharmacological effect of high blood concentration and can also make the release system to be economically ineffective (Huang and Brazel, 2001).

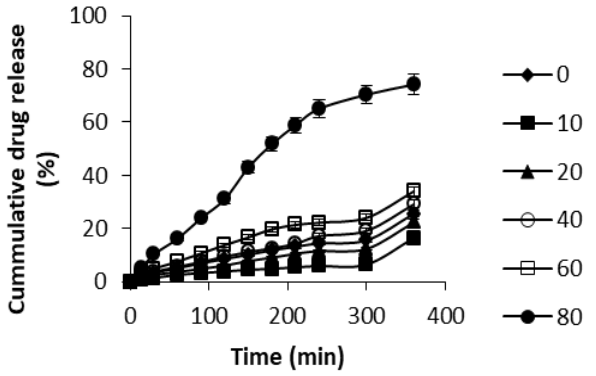

Fig. 4. *Drug release profiles of Metronidazole floating microbeads prepared using polymer mixtures containing different concentrations of Terminalia mantaly gum*

Polymer swelling encourages the in-flow of water into a microbead system as high gum quantity gives room to more water, hence faster drug release. Generally, drug diffusion through the swelling polymeric network is one of the factors that controls drug release from a polymeric matrix in addition to the dissolution process and uptake of the penetrating liquid (Okunlola *et al*., 2010). The dissolution times for the floating metronidazole microbeads at t_{50} ranged from 603.4 min to 1217.7 min respectively showing controlled release properties.

The kinetics of drug release from microbeads is essential because they affect the drug bioavailability, dosing intervals, and the occurrence of toxic side effects (Dubey et al., 2015). The results of kinetic modeling for the release of metronidazole from the microbeads are shown in Table 5. The release kinetics for all the formulations did not fit zero order as none yielded r^2 up to 0.95; with first order, only 80 % fitted the model. Furthermore, with Higuchi, 40 and 80 % did not fit in while the others did; for Hixson-Crowell, only 80 % fitted the model, while 80 %

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agreed with Hopfenberg model. Generally, all the formulations fitted Korsmeyer-Peppas kinetic model of drug release with r^2 ranging from 0.972-0.997. It can therefore be said that the release kinetics for the floating metronidazole microbeads generally fitted Korsmeyer-Peppas model of drug release. The release rate constant in Korsmeyer-Peppas model considers the structural and the geometric characteristics of pharmaceutical formulations. In addition, the Korsmeyer–Peppas model also gives an insight into the type of drug release mechanism occurring from swellable polymeric devices (Dubey *et al.*, 2015). It therefore encompasses the component, *n*, which is the diffusional exponent or release exponent, indicative of the drug release mechanism.
In this study, the release of metronidazole from the microbeads was governed by diffusion and erosion. The value of n = 0.5 indicates Fickian Diffusion (Higuchi matrix), 0.5<n<1.0 indicates anomalous (non-Fickian) diffusion, n=1.0 indicates Case-II Transport (zero-order release) and n > 1.0 indicates Super Case-II transport. The release mechanism using the n value for the beads in this study corresponds to mass transfer following a non-Fickian anomalous diffusion where n was <1. Previous studies using diclofenac and metformin-loaded microbeads have reported super case II transport in which n >1 (Odeku *et al.*, 2013, Akin-Ajani *et al.*, 2019). However, the microbeads in this study have incorporated a floating device, which probably altered its release mechanism. The use of excipients, physicochemical properties of the active drug, polymer type and polymer ratio have all been shown to modify the release kinetics of microbeads (Odeku *et al.*, 2013).

Generally, the low viscosity of *Terminalia mantaly* gum makes it a novel material for preparing floating drug delivery systems. In this regard, the gum becomes comparable to low-viscosity HPMC which is commonly a choice for floating devices (Goud and Pandey, 2016). The low viscosity of Terminalia mantaly gum is comparable to that of Arabic gum. Low viscosity in gums could be due to the presence of wax and proteinous materials which are covalently joined to the polysaccharide moiety (Akiyama et al., 1984). Low viscosity gums have advantages of imparting smooth flow to pharmaceutical rheological products and enhance their pourability. For floating systems, low viscosity gums are useful as they help in maintaining appropriate density of the system to sustain buoyancy. This could account for the high floating times of the formulations.

In addition, the high swellability of Terminalia mantaly makes it a cost-effective material suitable for floating delivery, because there would be no need to add a swelling enhancer like polyvinylpolypyrrolidone for maintainance of buoyancy. The low viscosity and high swellability all add to the novelty of using *Terminalia mantaly* gum as a polymer in the formulation of floating drug delivery system.

CONCLUSIONS

The polymer blends of *Terminalia mantaly* gum and sodium alginate were successfully utilized in the production of floating metronidazole microbeads. Formulations containing 0-60 % of gum were spherical or oval in shape while the 80 % deviated slightly from being spherical. The bead sizes generally increased as gum concentration increased but without significant differences. The swelling index for the beads increased significantly with gum concentration. The total floating time for the microbeads ranged from 5.5 to 175.1 h and the formulation containing 20 % gum showed highest floating time. Drug entrapment efficiency increased as gum concentrations increased from 0 to 40 % after which it reduced steadily. The dissolution times for the floating metronidazole microbeads at t_{50} ranged from 219.1 to 1217.7 min showing controlled release properties.

Generally, all the formulations fitted Korsmeyer-Peppas kinetic model of drug release with r^2 ranging from 0.972-0.997. *Terminalia mantaly* gum can be developed for use as co-polymer in the formulation of floating metronidazole microbeads especially at concentrations not higher than 40 $\%^{w}/_{w}$.

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REFERENCES

Abdalla AM, Usha GK, Rao BP, Chouhan AK (2015). Development and evaluation of nanocarriers of an anticancer drug for the treatment of breast cancer. Int. Res. J. Pharm. 10 (5):106-111.

Ajala TO, Akin-Ajani OD, Odeku OA (2013). Recent advances in oral drug delivery systems. In: Violiani V (ed) Recent advances in drug delivery research. Nova Science Publishers Inc., New York, USA. pp 33-50.

Ajala TO, Akin-Ajani OD, Ihuoma-Chidi C, Odeku OA (2016). Chrysophyllum albidum mucilage as a binding agent in paracetamol tablet formulations. J Pharm Investig 46 (6): 565-573.

Akin-Ajani OD, Itiola OA, Odeku OA (2014) Effect of acid modification on the material and compaction properties of fonio and sweet potato starches. Starch/Starke, 66: 749-759.

Akin-Ajani OD, Ajala TO, Ikehin M (2019). Date mucilage as co-polymer in metformin-loaded microbeads for controlled release. *J. Excipients and Food Chem.* 10 (1): 1-11.

Akiyama, Y., Eda, S. and Kato, K. (1984). *Gum arabic is a kind of arabino-galactan protein. Agri. Biol. Chem*, 48: 235–237.

AOAC (Association of Official Analytical Chemists) International 546 (2000). Official methods of analysis of AOAC international, 17th 547 edition

Bamiro OA, Sinha VR, Kumar R, Odeku OA (2010) Characterization and evaluation of *Terminalia randii*gum as a binder in carvedilol tablet formulation.Acta Pharm Sci. 52:254-62.

Bamiro OA, Ajala TO, Onyinye U, Akinwunmi AG (2013). The suspending properties of Terminalia randii gum in magnesium carbonate suspension. J. Pharm and Pharmacol. 8 (22): 87-92.

Choi BY, Fark HJ, Hwang SJ, Park JB (2008) Floating in situ gelling system of acetohydroxamic acid for clearance of *H. pylori*. Drug Dev Ind Pharm 34:577–587.

Da SP, Diniz MM, De Jong G (2019) Chitosan-alginate beads as encapsulating agents for Yarrowia lipolytica lipase: Morphological, physico-chemical and kinetic characteristics. Int J of Biol Macro; 139: 621-30

Dubey J, Verma A, Verma N (2015) Evaluation of chitosan-based polymeric matrices for sustained stomach specific delivery of propranolol hydrochloride. Indian Journal of Materials Science Article ID 312934: 9 pages.

Gholap SB, Bannerjee SK, Gaikwad DD, Jadhav SL, Thorat RM (2010). Hollow Microsphere: A Review. IJPSRR 1(1):74-79.

Goud M, Pandey V (2016). Gastroretentive drug delivery system. Int. J. Pharma Bio Sci. 6, 158–165. Guo J, Skinner GW, Harcum WW, Barnum PE (1998) Pharmaceutical applications of naturally occurring water soluble polymers. Pharmaceutical Science and Technology 1 (6): 254-261.

Huang X, Brazel CS (2001) Importance and mechanisms of burst release in matrix-controlled drug delivery. J. Control. Rel 73: 121-136.

Kaza R, Usharani E, Nagaraju R, Harlbabu R, Reddy PVS. (2009) Design and evaluation of sustained release floating tablets for the treatment of gastric ulcers. J Pharm Sci Res. 1(4): 81-87.

Karewicza A, Zasadaa K, Szczubiaikaa K, Zapotoeznya S, Lach R, Nawakowskaa M. (2010). 'Smart' alginate-hydroxypropylcellulose microbeads for controlled release of heparin. Int J. Pharm.; 385: 163-169.

Kumar SV, Sasmal D, Pal SC (2008). Rheological characterization and drug release studies of gum exudates of Terminalia catappa Lin. AAPS Pharm. Sci. Tech. 9 (2): 885-890.

Lachman LA, Liberman HA, Kanig JL (1991). The Theory and Practice of Industrial Pharmacy. 3rd edition, Varghese Publishng House, Mumbai, India: pp 414-415.

Lamoudi L, Chaumeil JC, Daoud K (2016). Swelling, erosion and drug release characteristics of Sodium Diclofenac from heterogeneous matrix tablets. JDDST 31: 93-100.

Malviya R, Srivastava P, Kulkarn GT (2011) Application of gum in drug delivery. Biol Res, 5 (1): 1-7.

McGaw LJ, Rabe T, Sparg SG, Jager AK, Eloff JNB, van Staden J. (2001) An investigation on the biological activity of Combretum species, J. Ethmopharmacol; 75: 45-50.

Nanjwade BK, Adichwal SA, Nanjwade VN,Gaikwad KR, Thakare SA, Manvi FV (2012). Development and evaluation of gastroretentive floating tablets of glipizide based on effervescent technology. J Drug Metab Toxicol. 2012; 3:3 DOI:10.4172/21577609.1000121.

Narra K, Dhanalekshimi U, Rangaraj G, Raja D, Kumar CS, Reddy PN, Mandal AB (2012). Effect of Formulation Variables on Rifampicin Loaded Alginate Beads. Iranian J. Pharm Res. 11 (3):715 721.

Odeku OA, Okunlola A, Lamprecht A (2013) Microbead design for sustained drug release using four natural gums. Intern J Biol Macromol 58: 113-120.

Odeku OA, Aderogba AA, Ajala TO, Akin-Ajani OD, Okunlola A (2017) Formulation of floating metronidazole microspheres using cassava starch (Manihot esculenta) as polymer. JPI 47: 445–451.

Okunlola A, Patel RP, Odeku OA (2010) Evaluation of freeze-dried pregelatinized Chinese yam (Dioscorea oppositifolia) starch as a polymer in floating gastroretentive metformin microbeads. J. Drug Del Sci and Tech. 20 (6): 457-465.

Osungbenro T, Jimoh D, Osundeyi E (2010) Functional and pasting properties of composite cassava–sorghum flour meal. Agriculture and Biology of North America. 2151–7517.

Prestogroup.com from http://www.prestogroup.com.

Ozeki T, Yuasa H, Kanaya Y (1995). Control of medicine release from solid dispersion composed of the poly(ethylene oxide) carboxyvinylpolymer interpolymer complex by varying moleculer weight of poly(ethylene oxide). J.Cont. R.; 58(1):87

Rangaraj G, Kishore N, Dhanalekshmi U.M, Raja M.D, Senthil Kumar C, Neelkanta Reddy P (2010). Design and study of formulation variables affecting drug loading and its release from Alginate beads. J. Pharm. Sci. & Res.; 2(2): 77-81.

http://doi.org/10.5920/bjpharm.854

Sheth P, Tossounian J (1984). The hydrodynamically balanced system: rug delivery system for oral use. Drug Dev. Ind. Pharm. 10: 313-339.

Smith M, Bhaskar V, Fernandez J, Courey AJ (2004). Drosophila Ulp 1, a nuclear pore associated SUMO protease, prevents accumulation of cytoplasmic SUMO conjugates J. Biol. Chem. 279 (42): 43805-43814.

Suzuki Y, Nishimura Y, Tanihara M, Suzuki K, Nakaimura T, Shimizu Y, Yamawaki Y, Kakimaru Y (1998). Evaluation of a novel alginate gel dressing. J. Biomed Mater Res. 39: 317-322.

Timmermans J Moes AJ (1990). "How well do floating dosage form floats?" Int.J.Pharm., 62, 207 216.

Velasco MV, Ford JL, Rowe P, Rajabi-iah B (1999). Influence of drug: Hydroxypropylmethyl cellulose ratio, drug and polymer particle size abd compression force on the release of diclofenac sodium from HPMC tablets. J. Control. Release.; 57:75-85.

Wang Q, Ellis PR Ross-Murphy SB (2003). Dissolution kinetics of guar gum powders—II: Effect of concentration and molecular weight. *Carbohyd. Polymers*. 53: 75–83.

Wang, L.; Yang, S.; Cao, J.; Zhao, S.; Wang, W. (2016) Microencapsulation of Ginger Volatile Oil Based on Gelatin/Sodium Alginate Polyelectrolyte Complex. Chem. Pharm. Bull., 64, 21–26.

Yegin BA, Moulari B, Durlu-Kandilci NT, Korkusuz P, Pellequer Y, Lamprecht A (2007) J. Microencap 24: 371–382.