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ORIGINAL ARTICLE

Formulation of floating metronidazole microspheres using cassava starch *(Manihot esculenta)* as polymer

Oluwatoyin A. Odeku[1] · Aderemi A. Aderogba[1] · Tolulope O. Ajala[1] · Olufunke D. Akin-Ajani[1] · Adenike Okunlola[1]

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Abstract Floating gastroretentive microspheres have been used to prolong the gastric residence time after oral administration and improve the local effect of metronidazole in the stomach in the treatment of peptic ulcer caused by *Helicobacter pylori*. In the present study, cassava starch, obtained from the tubers of *Manihot esculenta* has been pregelatinized and used as polymer in combination with sodium alginate for the formulation of floating gastroretentive metronidazole microspheres. Metronidazole microspheres were prepared by ionic gelation method using pregelatinized cassava starch and sodium alginate at different concentrations as polymers and calcium chloride (2% w/v) as chelating agent. Sodium bicarbonate (2% w/w) was used as gas releasing agent. Microspheres were characterized using the particle size, swelling index, floating lag time (FLT), total floating time and drug release properties. Spherical discrete microspheres with size ranging from 1.52 to 2.23 mm were obtained with FLT of less than 5 min and drug entrapment efficiency of 42–60% w/w. The microsphere maintained buoyancy for over 19 h and the microspheres provided controlled release of metronidazole for up to 18 h. Drug release from the microspheres, swelling index and buoyancy depended on the concentration of cassava starch in the polymer blend. Formulations containing high concentration of cassava starch showing shorter floating lag time and faster drug release. Thus, buoyancy and rate of drug release appeared to be modulated by the concentration of cassava starch in the polymer blend. The results showed that pregelatinized cassava could be useful in the formulation of floating gastroretentive metronidazole microspheres.

Keywords Starch · Microspheres · Cassava · Metronidazole · Floating gastroretentive

Introduction

Oral sustained drug delivery systems are complicated by limited gastric residence time, which can prevent complete drug release, and lead to reduced efficacy of administered dose (Pawar and Dhavale 2014). Prolonged residence time in the stomach is of particular importance for drugs that are locally active in the stomach or primarily absorbed from stomach and upper part of GIT (Choi et al. 2008). They are also useful for drugs with narrow absorption window in GIT, unstable in the intestinal or colonic environment and those that disturb normal colonic bacteria, and exhibit low solubility at high pH values (Choi et al. 2008; Nayak et al. 2010; Mahant and Nasa 2011).

Floating drug delivery systems are dosage forms that remain afloat in the stomach for extended period of time by virtue of their floating properties, thereby increasing the gastric residence time, enhancing drug solubility and bioavailability (Kaza et al. 2009; Nanjwade et al. 2012). The residual system, which is biodegradable, is emptied from the stomach after drug release. Factors that have been shown to affect gastro retention include specific gravity of food, which depend on the nature of food, frequency of food intake and caloric content (Nayak et al. 2010). Floating systems require high level of fluids in the stomach to remain buoyant without affecting the rate of gastric emptying. Some floating dosage forms have been coated with bioadhesive polymers, which enables them to adhere to

✉ Oluwatoyin A. Odeku
pejuodeku@yahoo.com; o.odeku@ui.edu.ng

[1] Department of Pharmaceutics & Industrial Pharmacy, Faculty of Pharmacy, University of Ibadan, Ibadan, Nigeria

the mucous lining of the stomach wall to facilitate more efficient drug delivery (Nayak et al. 2010; Nanjwade et al. 2012).

Various dosage forms like tablets, capsules, beads, microparticles, pellets and granules have been evaluated for floating systems. Single unit system such as tablet or capsule shows higher inter and intra-subject variability and are generally unreliable and non-reproducible in prolonging the gastric retention time. However, multiparticulate systems like microspheres, microbeads and microparticles may be more suitable because they are often better dispersed in the gastrointestinal fluid with reduced localized mucosal damage (Singh and Kim 2000; Garg and Gupta 2008).

Helicobacter pylori is one of the major causative agents of peptic ulcer and about 10% of the general population have been said to be at risk of developing ulcer (Pandit et al. 2008; Snowden 2008). The first-line treatment for *H. pylori* infection is a triple therapy, using the combination of two antibiotics (clarithromycin plus either amoxicillin or metronidazole) and a proton pump inhibitor for at least 7 days. When the triple therapy fails, quadruple therapy containing bismuth or quadruple therapies containing clarithromycin are used. The clear shortcoming is the complicated schedule, requiring a large number of daily doses, making treatment more expensive. Although many antibacterial agents have low in vitro minimum inhibitory concentration (MIC) against *H. pylori*, no single agent is effective in the in vivo treatment of the infection when administered alone (Ateshkadi et al. 1993; Murray 1993). This has been attributed to the fact that the organism resides in the mucus gel of the mucosa and the acidity of the gastric fluid will rapidly degrade many antibacterial agents, like penicillin and erythromycin (Emara et al. 2013). Moreover, the drug must diffuse into the mucus layer to give concentration sufficient for antibacterial activity but the contact time of antibacterial agent with the organism is usually not sufficiently long for successful eradication of *H. pylori* from the gastric mucosa (Shah et al. 1999). Floating multiparticulate systems like microspheres could offer greater safety for clinical use and more effective treatment of *H. pylori* (Patel et al. 2006).

Cassava starch is obtained from the tubers of *Manihot esculenta* Crantz (family Euphorbiaceae) also known as yucca (Central America), mandioca or manioca (Brazil), tapioca (India and Malaysia), and cassada or cassava (Africa and Southeast Asia) (Defloor et al. 1998). It is a woody shrub native to South America extensively cultivated as an annual crop in tropical and subtropical regions for its edible starchy tuberous root (Moorthy 1994; Tonukari 2004). It is a major source of carbohydrates and third-largest source of food carbohydrates in the tropics, after rice and maize. Nigeria is the world's largest producer of cassava with a production of about 37.5 million tons in 2010 (FAO 2013). Cassava starch consists of small spherical granules with an average granule size of 14.7 μm, gelatinization temperature of 59.6–87.2 °C and amylose content of 13.6–23.8% (Perez et al. 1998; Odeku 2013). Thus in the present study, cassava starch, which has been found to be useful as excipients in tablet and capsule formulations (Itiola and Amoo 1998; Itiola and Odeku 2005), has been evaluated as a polymer in combination with sodium alginate for the formulation floating gastroretentive metronidazole microspheres.

Materials and methods

Materials

Metronidazole, calcium carbonate and sodium bicarbonate (Finar Chemicals Ltd. Ahmedabad, India) and sodium alginate (Carl Roth GmbH & Co. Karlsruhe, Germany). Tubers of *Manihot esculenta* Crantz were obtained from local farmers in Ibadan, Nigeria and authenticated. The starch was extracted using established procedure (Itiola and Odeku 2005). All other reagents used were of analytical grade.

Preliminary formulation studies

Pregelatinized cassava starch was prepared using the method of Odeku et al. (2008). Briefly, aqueous starch slurry (20% w/v) was heated over a water bath with continuous stirring for 15 min until a clear paste was formed. Preformulation studies were carried out to determine the ability of pregelatinized cassava starch alone or in combination with sodium alginate to form stable spherical microspheres. Several formulations were prepared using varying concentration of freshly pregelatinized cassava starch alone and in combination with sodium alginate, varying chelating agents (calcium chloride and zinc chloride) at different concentrations (2, 5 and 10% w/v), stirring speed (200, 300 and 400 rpm) and curing time (15, 30 and 60 min). However, stable microspheres were formed with gel blends of pregelatinized cassava starch (10–50% w/w) and sodium alginate using 2% w/v calcium chloride as chelating agent at stirring speed of 300 rpm and curing time of 30 min.

Preparation of metronidazole microspheres

Metronidazole microspheres were prepared from a blend of freshly pregelatinized cassava starch and sodium alginate at a total polymer concentration of 2% w/v. 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 to impart buoyancy.

The resulting dispersion was extruded into calcium chloride solution (2% w/v) using a syringe with 0.90 mm needle at a dropping rate of 2 ml/min and a stirring speed of 300 rpm. The formed microspheres were allowed 30 min for curing and then left to stand for 1 h to allow further crosslinking of the polymers. The microspheres were collected by decantation, washed with distilled water and then dried for 24 h in hot air oven at 40 °C.

Characterization of microspheres

Size and morphology

The particle size of the microspheres was determined using optical microscopy. The surface morphology of the microsphere was analyzed by scanning electron microscopy. The microspheres were sputtered with gold, and their morphology and surface characteristics were analyzed using scanning electron microscopy (Hitachi Model S- 2460 N, Japan) at an accelerating voltage of 25 KV (Odeku et al. 2013).

Buoyancy studies

The floating capability of the microspheres was determined by placing the microspheres in a dissolution apparatus containing 900 ml of 0.1 N HCl, pH 1.2. The floating lag time (FLT) was taken as the time for the microspheres to rise to the surface and float, while the total floating time (TFT) was taken as the duration of time the microspheres constantly remained on the surface of the medium.

Swelling index

Microspheres (100 mg) were soaked in 20 ml of phosphate buffer, pH 6.8, and the final weight after 3 h was determined. The swelling index was calculated using the equation:

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

Entrapment efficiency

The entrapment efficiency was determined by accurately weighing 50 mg of microspheres into a glass mortar and crushing with a pestle. The crushed microspheres were suspended in 10 mL of phosphate buffer, pH 6.8. After 24 h, the solution was filtered and the filtrate was appropriately diluted using phosphate buffer, pH 6.8 and analyzed spectrophotometrically at 277 nm using UV/VIS spectrophotometer (LAMBDA 12 Perkin-Elmer GmbH, Germany). The drug entrapment efficiency (E) was calculated using the formula:

$$\text{Entrapment efficiency}(E) = \frac{\text{Practical drug content (mg)}}{\text{Theoretical drug content (mg)}} \times 100 \quad (2)$$

Drug release study

The in vitro dissolution studies were carried out using the paddle method (USP XXI), rotated at 50 rpm in 900 ml of phosphate buffer, pH 6.8, maintained at 37 ± 0.5 °C. The microspheres (100 mg) were placed in the dissolution medium and samples (5 ml) were withdrawn at different intervals and replaced with equal amounts of fresh medium. The sample was diluted and the amount of metronidazole released was determined at wavelength of 277 nm, using a UV/Visible spectrophotometer (LAMBDA 12, Perkin-Elmer GmbH, Urberlingen, Germany). Determinations were done in triplicates.

Modeling and comparison of release profiles

The data obtained from the release studies were fitted to different kinetic equations to find out the kinetics and mechanism of drug release from the matrix tablets. The drug released data was fitted to zero order, Higuchi, first order, Hixson–Crowell and Korsemeyer–Peppas models.

Zero-order equation (Wagner 1969):

$$Q = Q_0 + k_0 t \quad (3)$$

where Q is the amount of drug release at time t, k_0 is the apparent dissolution rate constant or zero order release constant and Q is the initial concentration of the drug in the solution resulting from a burst effect.

First-order equation (Gibaldi and Feldman 1967; Wagner 1969):

$$\ln Q = \ln Q_0 + k_1 t \quad (4)$$

where k_1 is the first order released constant, in this case, the drug released at each time is proportional to the residual drug inside the dosage form.

Higuchi equation (Higuchi 1961):

$$Q = k_H t^{1/2} \quad (5)$$

where Q is the amount of drug released at time t, and k_H is the Higuchi release constant. This is the most widely used model to describe the drug release from pharmaceutical matrices.

Hixson-Crowell equation (Hixson and Crowell 1931; Costa and Lobo 2001):

$$Q_o^{1/3} - Q_t^{1/3} = k_s t \quad (6)$$

where Q_o is the initial amount of drug in the matrix tablet, Q_t is the amount of drug remaining in the pharmaceutical

dosage form at time t, and k_s is a constant incorporating the surface/volume ratio.

Korsmeyer–Peppas equation (Korsemeyer et al. 1983):

$$Qt/Qa = k_k t^n \quad (7)$$

where, k_k is the release rate constant which considers the structural and geometric characteristics of the formulations, and n is the diffusional exponent or release exponent, indicative of the drug release mechanism. 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 (Korsemeyer et al. 1983; Costa and Lobo 2001).

Data analysis

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

Results and discussions

Preliminary formulation studies showed that pregelatinized cassava starch alone was not suitable for the formulation of microspheres. However, blends of pregelatinized cassava starch and sodium alginate were suitable for the formulation of stable spherical floating microspheres. The SEM of the floating metronidazole microspheres prepared using different concentration of cassava starch are shown in Fig. 1, while the properties of the microspheres are presented in Table 1. The shape of the microspheres was spherical to ovoid. The shape of the microspheres appeared to be less spherical as the amount of starch increases in the polymer blend. Microspheres containing sodium alginate alone demonstrated smoother surface in agreement with other work done using sodium alginate (Odeku et al. 2013), but appeared to be more porous as the concentration of starch increased in the polymer blend.

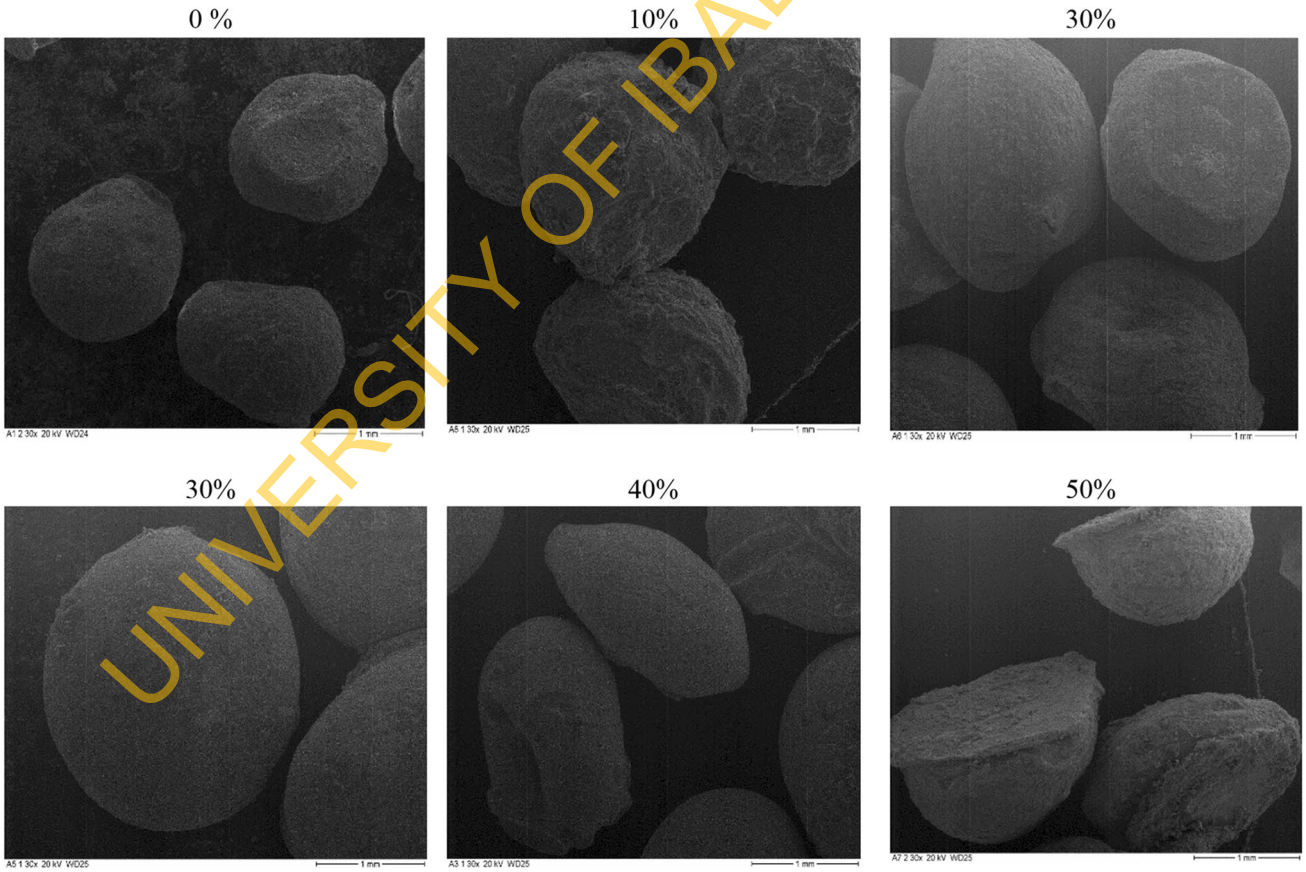

Fig. 1 SEM images showing shape and the surface characteristics of floating metronidazole microspheres containing different concentration of cassava starch

Table 1 Properties of floating metronidazole microspheres (mean ± SD, n = 3)

Starch conc. (%)	Mean size (mm)	Buoyancy		Swelling Index (%)	Entrapment efficiency (%)
		FLT (min)	TFT (h)		
0	1.52 ± 0.12	6.05 ± 0.11	16.20 ± 0.90	9.60 ± 1.21	30.22 ± 2.01
10	1.73 ± 0.05	3.50 ± 0.04	18.20 ± 1.10	51.62 ± 1.04	42.40 ± 1.24
20	1.84 ± 0.23	3.25 ± 0.09	18.45 ± 0.08	53.93 ± 0.98	44.76 ± 0.92
30	2.08 ± 0.09	3.00 ± 0.23	19.00 ± 0.23	63.45 ± 1.24	60.37 ± 1.02
50	2.23 ± 0.14	2.88 ± 0.06	19.30 ± 0.14	76.17 ± 1.11	54.17 ± 0.64

FLT floating lag time, *TFT* total floating time

The mean particle size of the microspheres ranged from 1.52 to 2.23 mm with microspheres containing sodium alginate alone showing the lowest values and those containing 50% pregelatinized cassava starch showing the highest values. Thus, the size of the microspheres increased with increase in the starch content in the polymer blend used in the formulation.

Floating gastro-retentive dosage forms are expected to remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. The result indicates that microspheres showed a floating lag time which was dependent on the amount of starch in the polymer blend. The formulations containing the blend of pregelatinized cassava starch and alginate showed significantly ($p < 0.05$) shorter floating lag time than the formulation containing sodium alginate alone. Metronidazole microspheres containing a blend of 50% cassava starch and sodium alginate floated in dissolution medium with a lag time of less than 3 min and remained buoyant for over 19 h. This may be due to the higher porosity of the microspheres containing cassava starch, which will enhance fast release of carbon dioxide and thus accelerate the hydration of the floating metronidazole microspheres. Thus, the concentration of pregelatinized cassava starch in the formulation could be used to modulate the buoyancy of the microspheres.

The swelling index of the microspheres also increased with increase in the concentration of starch in the polymer blend. Metronidazole microspheres showed significantly ($p < 0.01$) higher swelling index than those containing sodium alginate alone as the polymer. Thus, the pregelatinized cassava starch enhanced the swelling index of the microspheres in a concentration-dependent manner.

The drug entrapment efficiency is an essential parameter for assessing the drug loading of microspheres. The result showed that the entrapment efficiencies of the metronidazole microspheres range from 30 to 60% w/w. The drug entrapment efficiency generally increased with increase in the concentration of starch up to 40% but showed a decrease at 50%. This could be attributed to the porous nature of the starch-gel matrix which allowed considerable drug loading up to a certain concentration beyond which saturation occurred (Okunlola et al. 2010). The increased porosity of the microsphere could also facilitate the diffusion of the drug from the microspheres. In addition, the entrapment efficiency generally increase as the mean particle size of the microspheres increased. Statistical analysis showed that there were significant differences ($p < 0.05$) in the entrapment efficiencies of the microspheres.

Drug release properties

The drug release profiles of the floating microspheres are shown in Fig. 2 while the dissolution times, t_{15} and t_{50} (time required for 15 and 50% drug release, respectively) are presented in Fig. 3. The drug release patterns obtained for the floating microspheres were almost linear. For most controlled release preparations, an initial high rate of drug release is usually observed at the beginning of the controlled release process, which can be due to a number of mechanisms including surface desorption, pore diffusion or lack of a diffusion barrier to regulate the diffusion process. The initial non-steady period is usually referred to as "burst release" (Huang and Brazel 2001). While burst release of drugs may be utilized in the administration of certain drugs, in controlled release systems, it can have adverse pharmacological effects and can be economically ineffective (Huang and Brazel 2001). The drug release profile and the time taken for 15% of metronidazole release were higher than 1 h. This indicated that the microspheres did not exhibit burst release signifying that the drugs were embedded in the microspheres and were not loosely bound to the surface of the microspheres (Jha and Bhattacharya 2008). The values of t_{15} also decreased with increase in concentration of cassava starch in the polymer blend probably due to the increased porosity of the microspheres until 20% w/w of starch after which there was a slight increase in the values. This could be due to increase interaction between pregelatinized starch and sodium alginate.

The t_{50} values (time for 50% drug release) for the formulations ranged from 4 to 6.5 h. The drug release from the floating microspheres appeared to be controlled by

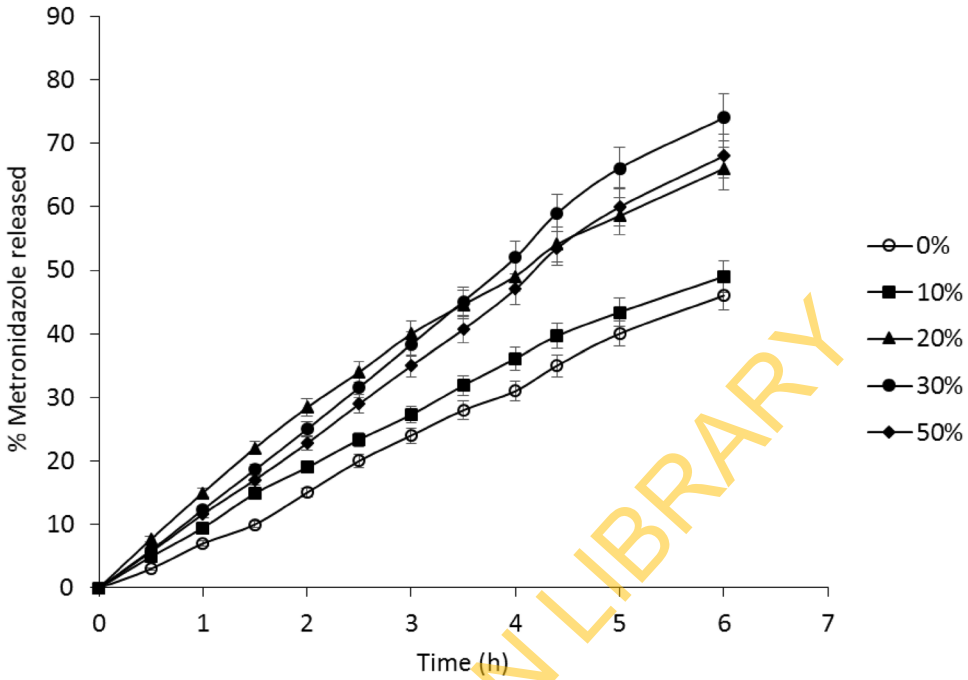

Fig. 2 Plot of percent metronidazole released from floating microspheres containing different starch concentration at different time

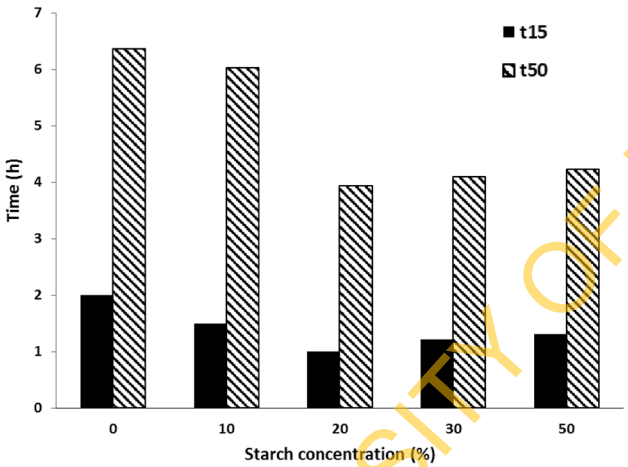

Fig. 3 Values of t_{15} and t_{50} for floating metronidazole microspheres containing different concentration of cassava starch

the concentration of starch in the formulation and the t_{50} decrease with increase in the concentration of cassava starch. This is could be due to the fact that the presence of the starch rendered the gel-matrix more porous, thereby facilitating faster of the drug.

The correlation coefficients of the different drug kinetic models have been used as an indicator of best fit for each of the models considered and the values of the correlation coefficients are presented in Table 2. The release of metronidazole from the floating microspheres followed the zero order kinetics and Korsemeyer-Peppas models with the correlation coefficients ≥ 0.990 on all cases. The release parameters indicated that the mechanism for the release of metronidazole microspheres was Case-II Transport (zero-order release) as indicated by the release exponent, n (Korsemeyer et al. 1983; Costa and Lobo 2001). This indicates drug release from these formulations is controlled by more than one process, usually a combination of diffusion and erosion mechanisms (Okunlola et al. 2010; Odeku et al. 2013) and is independent of the time and drug concentration. This indicates that manipulating the concentration of pregelatinized cassava starch can be used to modulate the release metronidazole from the floating microspheres.

Table 2 Correlation coefficients obtained for metronidazole microspheres using different mathematical models (n = 3)

Starch conc.(%)	Zero order	First order	Higuchi	Hixson-Crowell	Korsmeyer	
					r^2	n
0	0.997	0.993	0.912	0.949	0.997	1.043
10	0.991	0.999	0.943	0.976	0.998	0.938
20	0.990	0.998	0.961	0.987	0.997	0.878
30	0.998	0.972	0.916	0.957	0.999	1.014
50	0.998	0.978	0.917	0.961	0.999	1.020

Conclusion

The result showed that blends of cassava starch and sodium alginate could be useful in the preparation of spherical discrete microspheres that could provide controlled release of metronidazole for up to 18 h. The drug release from the microspheres, swelling and buoyancy, depended on the concentration of cassava starch in the polymer blend with formulations containing high concentration of cassava starch showing shorter floating lag time and faster drug release. This indicates that cassava starch could be useful for the formulation of floating gastroretentive dosage form for the delivery of metronidazole and could find application in the treatment of *H. pylori* infections.

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