Sylvester Okhuelegbe Eraga et al. / Journal of Pharmacy Research 2014,8(8),1132-1139

Research Article
ISSN: 0974-6943

Available online through
http://jprsolutions.info

Formulation and evaluation of bioadhesive tablets of Metronidazole from Gellan gum and gelatin

Sylvester Okhuelegbe Eraga* and Magnus Amara Iwuagwu
Department of Pharmaceutics and Pharmaceutical Technology,Faculty of Pharmacy,
University of Benin, PMB 1154, Benin City, 300001, Nigeria.

Received on:30-06-2014; Revised on: 19-07-2014; Accepted on:09-08-2014

ABSTRACT

Background: The delivery of drugs using a combination of bio-polymers is gaining extensive grounds in the development of newer drug delivery systems. In this work the formulation, evaluation and release profiles of metronidazole bioadhesive tablets formulated with admixtures of gellan gum and gelatin were investigated. **Methods:** Aqueous dispersions of gellan gum and gelatin in ratios of 1:1, 1:2, 2:1, 1:4, 1:0 and 0:1 were prepared in distilled water. Metronidazole tablets were prepared with the dispersions by wet granulation. The bioadhesive strengths of the dispersions and tablets were determined using the coated bead and tensiometric methods, respectively. Tablet parameters evaluated were weight uniformity, friability, hardness, disintegration time, content of active, swelling index and tablet erosion. Release studies were carried out in simulated intestinal and gastric fluid. **Results:** All batches of tablets met compendial specifications with regard to weight uniformity, friability, hardness and content of active except disintegration times. Tablets prepared with gelatin alone had the highest swelling index and bioadhesive strength (40 %, 5 h and 0.253 Nm^{-1}) while those prepared with gellan gum alone had the highest percentage tablet erosion and least bioadhesive strength (15 % and 0.085 Nm^{-1}). Release profiles of API from the tablets showed delayed effect with the highest % release in simulated intestinal fluid from tablets formulated with gum-gelatin ratio 1:1 (80 %, 80 min) followed by the gelatin alone batch (60 %, 80 min). Release kinetics and mechanism were first order and diffusion controlled. **Conclusion:** Gelatin increased the bioadhesive strength of gellan gum. Gellan gum-gelatin ratios of 1:2 and 1:4 were the optimum combinations and were superior in the formulation of metronidazole tablets. The hydrophilic bioadhesive polymers enhanced the steady release of the drug.

KEYWORDS: Bioadhesion, tablets, gellan gum, gelatin, metronidazole

INTRODUCTION

Bioadhesion is the adhesion of macromolecules which could be synthetic or natural to a biological tissue.[1] In drug delivery, it implies the attachment of a drug or a drug carrier system to a specific biological location or tissue, which can be an epithelial tissue or the mucus coat on the tissue surface. When attachment occurs more specifically to a mucosal epithelium, the phenomenon is referred to as mucoadhesion.[2] Bioadhesives has the potential to optimize drug delivery and this has triggered the interest of formulation pharmacists in the past two decades. Such optimization could be at the site of action (e.g., on the cornea or within the oral cavity) or at the absorption site (e.g., in the small intestine or nasal cavity). High water affinity, flexibility for interpenetration into mucus and epithelial tissue, numerous hydrogen bond-forming groups and viscoelastic properties upon hydration are some physicochemical properties of bioadhesives polymers.[3]

***Corresponding author.**
Sylvester Okhuelegbe Eraga
Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, University of Benin, PMB 1154, Benin City, 300001, Nigeria.

Gellan gum is an anionic, high molecular weight, deacetylated exocellular polysaccharide gum produced as a fermentative final product by a pure culture of *Pseudomonas elodea*.[4,5] Drug delivery systems based on gellan gum are becoming more attractive as potential drug delivery devices in the pharmaceutical and biomedical spheres.[6] Gellan gum can be used to produce easy-to-swallow solid dosage forms, such as gels beads and coated tablets, and also to modify the release rates of active ingredients from tablets and capsules. It is also conveniently used for controlled or sustained release of various drugs by the preparation of various types of rate controlling dosage form.[7-11]

Metronidazole (1-(ß-hydroxyethyl)-2-methyl-5-nitroimidazole) is an antibacterial with activity against a variety of anaerobic pathogens that include both gram-negative and gram-positive bacteria.[12] It is clinically effective in trichomoniasis, amebiasis, and giardiasis, as well as in a variety of infections caused by obligate anaerobic bacteria, including *Bacteroides*, *Clostridium*, and microaerophilic bacteria such as *Helicobacter* and *Campylobacter* spp. The drug usually is absorbed completely and promptly after oral administration with a half-life of about 8 hours. Metronidazole is a good candidate for

bioadhesive drug delivery in the treatment of *Helicobacter pylori* because of the advantages of such a system in controlling drug release and helping to maintain an effective concentration of the drug at the site of action by increasing the resident time of the formulation. There is a continuous search for polymers with desirable features such as the localization of the dosage form in specified regions to improve bioavailability of drugs, promote intimate contact of the formulation with the underlying surface for absorption to take place and prolong the residence time of the dosage form to permit once-a-day dosing.[13] The use of two of more polymers to achieve these desirable features in a mucoadhesive dosage form has been the subject of interest of many workers and has been assessed in some dosage forms.[7,11]

The aim of this study was to determine the effect of gelatin on the bioadhesive strength of gellan gum and also to investigate the release properties of metronidazole tablets formulated with admixtures of gellan gum and gelatin.

MATERIALS AND METHODS

Materials

The materials used were procured from local suppliers without further purification. All the reagents used were of certified analytical grade. Metronidazole (Huang Gang Yinhe Aarti Pharmaceutical Co. Ltd, China), sodium hydroxide, sodium chloride, hydrochloric acid, Gelatin, monobasic potassium phosphate, acetone (Merck, Germany), gellan gum (Gelrite®, Kelco, Merck & Co, USA) and agar (Titan Biotech, India). Water was double distilled.

Preparation of gum dispersions

A 5 % aqueous dispersions of the different gellan gum-gelatin ratios (1:1, 1:2, 2:1, 1:4 1:0, 0:1) were prepared using distilled water. The dispersions were stirred and left to hydrate for 5 h. The hydrated dispersions were then used for the beads bioadhesion study.

Preparation of simulated intestinal fluid (SIF) without pancreatin

About 6.8 g of potassium phosphate monobasic and 8 g of sodium hydroxide were dissolved in 250 mL of distilled water. The resulting solution was made up to 1 L in a volumetric flask.[14]

Preparation of simulated gastric fluid (SGF) without pepsin

About 2.0 g of sodium chloride was dissolved in sufficient quantity of distilled water and 7.0 mL of concentrated hydrochloric acid was added. The resulting solution was adjusted to a pH of 1.2 and made up to 1 L with distilled water.[14]

Coating of beads

Glass beads weighing 60 mg each and average diameter of 3 mm were thoroughly cleaned, first with distilled water and then with acetone to maximize the roughness factor. The beads were then immersed in the 5 % aqueous dispersion of the polymers for 5 min with the container gently swirled around to ensure uniform coating. The immersed beads were then air-dried.[15]

Bioadhesive determination using coated beads

The determination was carried out using the method of Attama *et al*.[15] The apparatus designed and used in this determination is shown in Figure 1. It was made of a separating funnel clamped on a retort stand with a rubber tube attached to the end of the separating funnel and a cork support used to position a polythene support at an angle of 30^{o} below the separating funnel. Freshly excised hog ileum of about 10 cm was pinned on the plastic support. A beaker was placed, directly below the set-up to collect the detached beads. Ten coated glass beads were placed on the exposed mucus surface of the tissue. Ten minutes was allowed for mucus-polymer interaction. A 250 mL quantity of SIF without pancreatin was then poured through the funnel and allowed to flow over the beads at a rate of 30 mL/min. The number of detached beads were noted and used as a measure of bioadhesion. This determination was done in triplicate and the average taken as the number of beads detached.

Preparation of bioadhesive tablets

Batches of metronidazole tablets were produced using the different ratios of the gellan gum and gelatin (Table 1). Wet granulation method of tablet production was employed. The metronidazole powder and lactose were carefully weighed into a mixer and dry mixed for five minutes. Aqueous dispersion of the required quantities of gellan gum and gelatin was gradually added to the dry powder mix to form a wet mass. The wet mass was passed through a 710 µm sieve mesh screen and the resulting granules dried at 60 ºC for 3 h in a hot air oven (Gallenkamp, UK). The granules were rescreened through the same sieve and further dried for another 2 h. Talc (5 % of the total weight of

Table 1: Ratios and quantities of the polymers used per tablet.

Batch/Ratio	Gellan	Gelatin	Lactose	Drug
A (1:1)	7.5	7.5	150	100
B (1:2)	5	10	150	100
C (2:1)	10	5	150	100
D (1:4)	3	12	150	100
E (1:0)	15	0	150	100
F (0:1)	0	15	150	100

NB: All weights are in mg units

granules) and magnesium stearate (2 % of the total weight of granules) were added to the granules as glidant and lubricant respectively. The granules were compressed in a tablet press (F3 Manesty Machines, UK) with a force of 48 kgF to give a tablet weight of 280 mg. The tablets were stored in a desiccator containing dry silica gel until evaluation. One hundred tablets were prepared per batch.

Evaluation of bioadhesive tablets

The following tests were carried out on the compressed tablets using standard procedures: tablet weight uniformity, hardness, friability and disintegration time.[16]

Tablet weight uniformity

The weight of each of 20 tablets was determined from each batch using an electronic balance (College B154, Mettler Toledo, Switzerland) and the mean weight and standard deviation were computed.

Tablets hardness

The hardness of each of ten tablets per batch was determined (Campbell Electronics, Model HT-30/50, India). The mean hardness and standard deviation were calculated.

Tablet friability

The weight of ten tablets was determined on the electronic balance. The tablets were then placed in the drum of a Roche friabilator (Erweka, Germany) revolving at 25 rpm which exposed the tablets to rolling and repeated shock resulting from free fall within the apparatus. After four minutes, the tablets were brought out, dedusted and reweighed. The friability, calculated as abrasion resistance B, was computed as percentage loss in weight.

The initial and final weights being W1 and W2 respectively, the abrasion resistance B was calculated using Equation 1;

$$B = [(W1-W2) \div W1] \times 100 \quad \text{- - - - - - - - - - - - 1}$$

Disintegration time

The disintegration times of six tablets per batch of sample were determined in SIF at 37.0±0.5 °C using the B.P. disintegration tester (MK IV, Manesty Machines, UK).

Swelling study

Three tablets were weighed and placed on the gel surface of a 2 % agar gel plates and incubated at 37.0±1 °C. At intervals of 1 h for 5 h, the tablets were removed and their surfaces wiped carefully with blotting paper and reweighed. The initial and final weights being W1 and W2 respectively, the swelling index (SI) was calculated using Equation 2.[17]

$$\text{Swelling Index} = [(W2-W1) \div W1] \times 100 \quad \text{- - - - - - - - 2}$$

Tablet erosion

The tablets from the swelling studies were dried for 24 h at 60 °C in an oven. They were then reweighed (W3) after being kept in a desiccator for 48 h. Tablet erosion was calculated using Equation 3.[18]

$$\% \text{ Tablet Erosion} = [(W1-W3) \div W3] \times 100 \quad \text{- - - - - - - - 3}$$

Preparation of standard calibration curves

Various metronidazole standard concentrations in SIF and SGF ranging from 0.2 to 1.0 µg/mL were prepared from stock solutions and subjected to ultra-violet spectrophotometric analysis at 276 nm (T70, PG Instruments Ltd). All readings were done in triplicate and the mean absorbances plotted against the corresponding concentrations. Linear regression analysis of the data was carried out to obtain the equation for the curve as well as the correlation coefficient, r^2 values in both SIF and SGF.

Content of active drug

Twenty (20) tablets were randomly selected from each batch and crushed to fine powder. A quantity of the powdered tablets equivalent to 100 mg metronidazole was weighed and dissolved in about 50 mL of SIF in a 100 mL volumetric flask. The volume was made up with more SIF and allowed to hydrate for 5 h. Necessary dilutions were carried out to obtain a final concentration of 100 µg/mL, the solution was thereafter filtered through a Whatman No 1 filter paper and the absorbance of the filtrate determined at 276 nm using SIF as blank.

Bioadhesive test

The Leconte du Nouy tensiometer (Model 1 Nr 3014, Akruss Hamburg Germany) was used for the study. The determination was carried out using the method of Attama *et al*.[15] Hog ileum of about 5 cm long and 2 cm wide was longitudinally slit to expose the mucus surface. The ileum was pinned on a cork placed on the metal support of the tensiometer. Above the metal support was a plastic plate hanging on a zeroed lever. One tablet from each batch was glued to the plate using a cyanoacrylate adhesive. The hog ileum on the metal support was raised to establish contact with the glued tablet. A time interval of 5 min was allowed for tablet mucus interaction. Thereafter, the plate was raised by means of a screw until the tablet just detached from the surface of the mucus layer.

The tension required for the tablet to be removed was read off from the tensiometer in degrees and the lever zeroed with some weights. The average of three determinations was recorded. The procedure

was repeated for all the tablet batches. The weights required to zero the lever after each measurement was noted and the tension in Nm/s^2 calculated using Equation 4 below.[19]

$T = [mg \div 2L] \times F$ ---------- 4

Where T = tension, m = weight (kg), g = acceleration due to gravity (m/s^2), L = perimeter of the plastic plate (m), F = 0.94. (a constant dependent on the perimeter)

Dissolution studies

The dissolution profiles were studied using the BP method for the various batches of the tablets in both SIF and SGF. A dissolution medium of 900 mL of SIF or SGF solution maintained at 37.0±0.5 °C with a basket revolution of 50 rpm was used. Three tablets from each batch were used simultaneously for the study. A 5 mL volume of leaching fluid was withdrawn at various intervals and replaced with an equivalent volume maintained at same temperature (37.0±0.5 °C) of the dissolution medium. The sample was filtered and diluted with an equal volume of SIF or SGF. This was continued for 80 minutes. The absorbances of the resulting solutions were analyzed spectrophotometrically at λmax of 276 nm. The concentration and the percentage of drug released at each time interval were determined using the equation from the relevant standard calibration plot.

Kinetic modeling of drug dissolution profiles

The following kinetic drug models (zero order, first order, Higuchi and Korsmeyer-Peppas) were applied to the dissolution data to determine the most appropriate kinetic model of the drug release by applying the curve fitting method on the models.[20,21]

Zero order model; Q = Kt, where, Q is the fraction of drug released at time t and K is the zero order release rate constant.

First order model; In (1-Q) = -Kt, where Q is the fraction of drug released at time t and K is the first order release rate constant.

Higuchi model; $Q = kt^{1/2}$, where Q is the fraction of drug released at time t and k is the release rate constant.

Korsemeyer-Peppas model; Log Q = log K + n log t, where Q is the fraction of drug released at time t, K is the release rate constant and n is the diffusional exponent.

RESULTS AND DISCUSSION

Physical characteristics of the bioadhesive tablets

Table 2 shows some of the physicochemical parameters of the bioadhesive tablets prepared for the various batches of the active drugs. The weights of all the tablets met the British Pharmacopoeia[16] specification, i.e., that not more than two of the individual weights should deviate from the average weight by more than ±5 % and none should deviate by more than ±10 %. The content of active drug in all the samples was within the range required by the BP,[16] that is, not less than 90.0% and not more than 110.0% of the labeled content.

Table 2. Some physicochemical characteristics of the bioadhesive tablets studied.

Batch/ Ratio	Tablet Weight* (mg)	Tablet Hardness* (KgF)	Friability* (%)	Tablet Disintegration Time* (min)	Drug Content (%)
A (1:1)	279.8(5.85)	5.7(0.085)	0.80(0.006)	13.75(3.10)	98
B (1:2)	278.4(6:72)	7.2(0.085)	0.93(0.007)	27.25(1.50)	99
C (2:1)	279.3(4.37)	6.8(1.085)	1.00(0.008)	11.25(1.50)	99.5
D (1:4)	282.7(3.68)	8.7(0.585)	0.90(0.007)	21.25(3.30)	98.8
E (1:0)	283.7(2.73)	5.2(1.085)	1.10(0.008)	7.50(0.58)	101.4
F (0:1)	280.8(4.21)	7.3(0.085)	0.90(0.007)	12.00(0.82)	98.4

Standard deviation in parenthesis

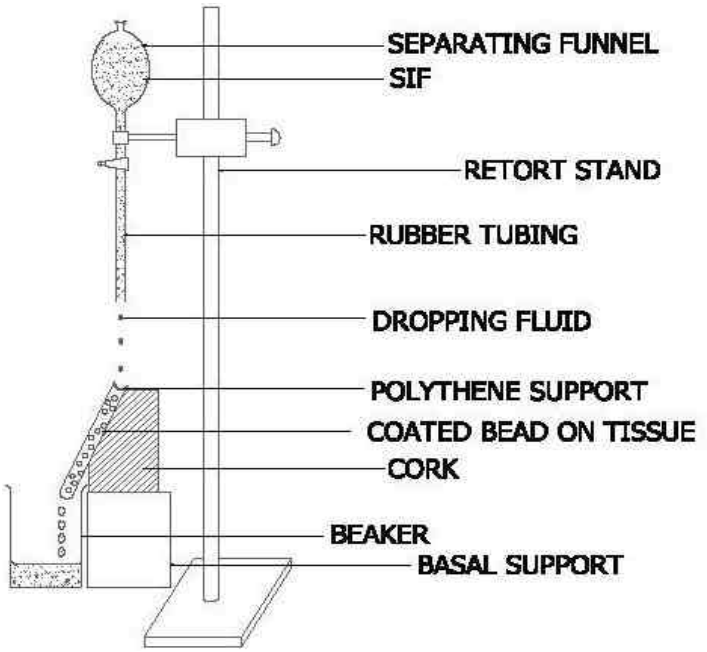

Figure 1: Apparatus for bioadhesion of coated beads

The hardness test is not an official test. However, a minimum hardness of 4 KgF is desirable or satisfactory.[22] From Table 2, all the tablets gave satisfactory hardness values above 5 KgF. The hardness of a tablet is usually affected by the type and quantity of binder and lubricant, and by the compressional force. The hardness value obtained for a tablet could vary from instrument to instrument used to determine it, and experience over the years in formulation has shown that tablets with crushing strength greater than or equal to 5

kgF could be considered acceptable for uncoated tablets.[15] The satisfactory values obtained in this study could be attributed to the additional hardness imparted by the gums (gellan and gelatin) used in the preparation of the tablets.

Friability values of 0.8-1 % are frequently quoted as the upper level of acceptance for pharmaceutical products. Though, in direct compression formulation, values of up to 2 % or above have been reported. The results listed in Table 2 show that all the tablet batches conformed to specifications. The friability test can also be adopted for the measurement of granule strength.[23] It is unlikely that in the normal life of a tablet it will be subjected to a compressive load large enough to fracture it. However, it may well be subjected to tumbling motion, e.g., during coating, packaging or transportation, which whilst not severe enough to break the tablet, may abrade small particles from its surface.[24]

Tablets of batch E (1:0 gellan only) gave the shortest disintegration time of 7.5 min, while those made from batch B (1:2) gave the highest times of 27.25 min. The difference in the disintegration times could be said to be due to absorption of the SIF by the polymers to various extents. The polymers upon swelling, disperse, and the solid state of the tablet is lost. The disintegration time of a tablet is controlled by a number of experimental variables which are often interdependent. These include use of water-repellant lubricants, temperature, medium used, nature of drug, the diluent used and compressional force.[23]

Swelling and tablet erosion studies

The swelling behavior of tablets affected the bioadhesion and drug release profile of the tablets. The weight gained by the tablets was proportional to the rate of hydration and as the weight increased, the swelling index of the tablets increased. The swelling study showed that the amount of gelatin is an important factor in the swelling of the tablets that eventually led to the diffusion of the drug. The highest hydration rate was obtained from Batch D(1:4) and Batch F(0:1) that hydrated above 40 % within 5 h. All the other batches showed appreciable hydration above 30 %, except Batch E(1:0), which was composed of gellan gum alone. It was observed that an increase in gelatin content of the tablets led to a corresponding increase in the swelling rate of the tablets. Gelatin retains large amounts of water because of its hygroscopic nature.

Tablets containing more gellan gum were found to exhibit the highest tablet erosion. This was because of the weak matrix structure of the gum that readily broke down in the presence of water. The plots of swelling index and tablet erosion are shown in Figures 2 and 3.

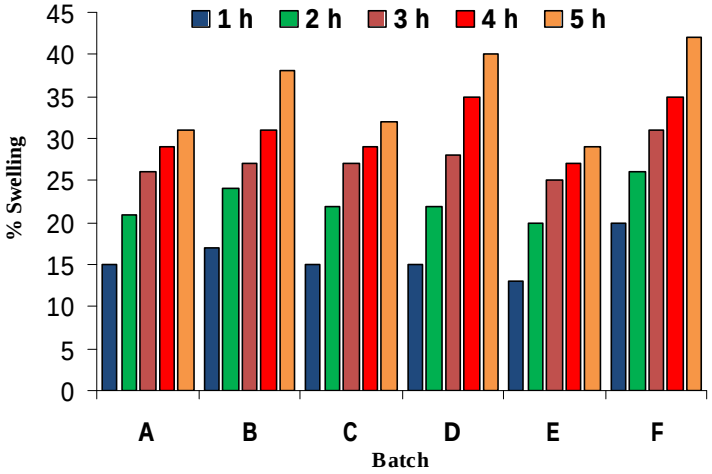

Figure 2: Percentage swelling of bioadhesive tablets

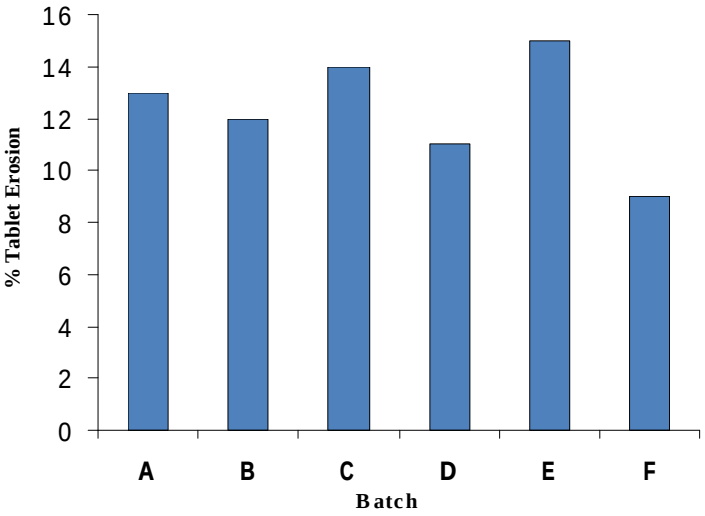

Figure 3: Tablet erosion of bioadhesive tablets

Bioadhesion of coated beads and tablets

Results from the bioadhesion studies using coated beads are shown in Table 3. The 0:1 (gelatin only) dispersion gave the highest bioadhesion index of 80 % bioadhesion. This was followed by the 1:2 and 1:4 disperesions with 60 % bioadhesion. The 1:0 (gellan alone) dispersion gave the least index value of 30 % bioadhesion. Although the coated beads test for bioadhesion is very simple and easy to carry out, it is highly subjective. Despite its subjectiveness, it gave insight into the relative bioadhesiveness of gellan gum and gelatin. Bioadhesion determination using this method is dependent on the mucus content of the hog intestinal surface, speed of washing and angle of inclination of the surface on which the hog ileum is placed. Also, from Table 3, the results of bioadhesion of tablets showed that the gelatin-only batch gave the highest bioadhesion; this was followed by the 1:2 ratio, and the 1:4 ratio batches. The batch containing gellan gum alone gave the least bioadhesive effect. The difference

could be attributed to the level of contact made between the bioadhesive material and the mucus membrane. It could also be attributed to either the good wetting of the tablet surfaces or to the swelling of the tablets or both. This result conforms to that obtained using coated beads, with 0:1 ratio batch yielding the highest value and 1:0 the least.

Table 3: Bioadhesion of the coated beads and tablets.

Ratio	Coated Beads			Tablets	
	Beads Used	Detached Beads	Bioadhesion (%)	Tension* (o)	(Nm^{-1})
1:1	10	5	50	41.35(1.20)	0.112(0.003)
1:2	10	4	60	76.00(3.11)	0.206(0.008)
2:1	10	6	40	55.55(0.78)	0.151(0.002)
1:4	10	4	60	80.85(7.57)	0.219(0.021)
1:0	10	7	30	31.55(0.92)	0.085(0.002)
0:1	10	2	80	93.35(4.74)	0.253(0.013)

Standard deviation in parenthesis

Drug release profile

In-vitro drug release studies revealed differences in the release of metronidazole from the different gellan gum/gelatin tablet formulations in SIF and SGF as shown in Figures 4a and b. In SIF, there were variations in the drug release profile amongst the different batches of the tablets. The fastest release was seen in the tablets prepared with a 1:1 ratio of the gum and gelatin. This was followed by the tablets made with gelatin alone. Tablets made with the other ratios showed delayed release; the slowest release was from ratio 2:1 tablets. In SGF, fast drug release was seen in the tablets made with gelatin alone followed by the tablets containing 1:1 gum and gelatin. The slowest release was from tablets containing gum and gelatin in the ratios of 2:1 and 1:0. The release of the drug increased with decreasing gellan gum and increasing gelatin concentrations. Although gellan gum has poor bioadhesive properties, its hydrophilic and excellent gelling properties delayed drug release.

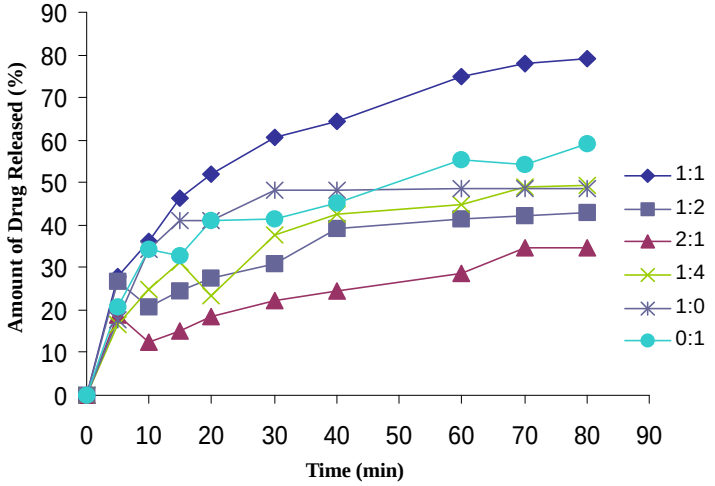

Figure 4a: Dissolution profile of the bioadhesive tablets in SIF

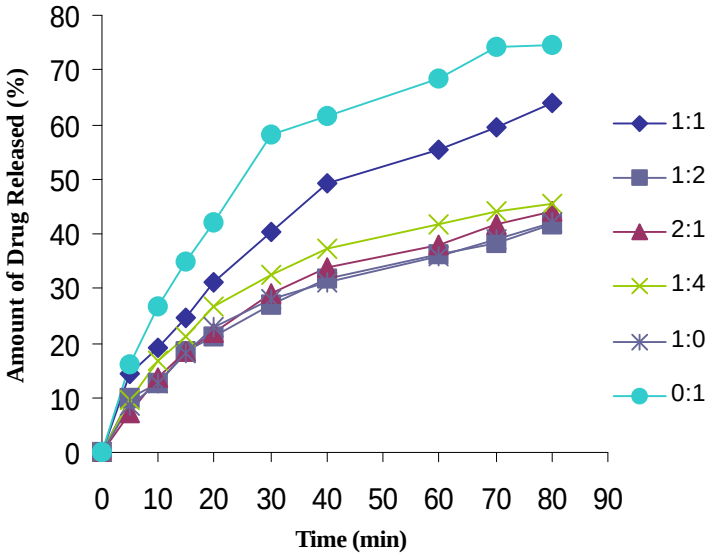

Figure 4b: Dissolution profile of the bioadhesive tablets in SGF

Mechanism and kinetics of drug release

In hydrophilic matrices, the tablets swelled when they came in contact with moisture. Bamba *et al*.,[25] noted that a drug will dissolve and diffuse out of a matrix only after a penetrating solvent has gelled the matrix. Higuchi,[26] in an earlier work enumerated several factors that determine the rate of drug release and affect drug release profile of hydrophilic matrices that are swelling and erosion controlled. These factors include the amount of drug incorporated in the matrix, molecular size of the drug, water solubility of the drug, permeation of water, rate of gelation of the matrix, rate of drug dissolution in the penetrating water, rate of drug diffusion in the gel and the Higuchi porous penetration. For drugs with reasonable aqueous solubility, the release of drug occurs predominantly by dissolution in the infiltrating medium.[26] Similarly, Desai *et al*.,[27] in investigating the release of solid drug dispersed in inert matrices came to the same conclusion as Higuchi.

It has been established that diffusion of water into the tablet and diffusion of dissolved drug out or through the gelled layer are the two limiting processes of drug liberation from matrices.[25] From the R^2 (correlation coefficient) values of the bioadhesive tablets (Table 4), it follows that the relationship between drug release and time is not linear especially in SGF, suggesting a slow release kinetic and a diffusion controlled release mechanism. This is in line with Higuchi,[28] who in analyzing the mechanism of drug release from matrices, postulated two processes that usually prevail; dissolution controlled and diffusion controlled mechanisms. Gellan gum in the bioadhesive tablets studied will control dissolution of the drug in the matrix being more hydrophilic, and secondly, it will also control the gelation rate of the matrix and the diffusion of the drug through the gel.

Table 4: R^2 values for different release models in SIF and SGF

Batch/ Ratio	R^2							
	Zero Order		First Order		Higuchi		Korsmeyer Peppas	
	SIF	SGF	SIF	SGF	SIF	SGF	SIF	SGF
A (1:1)	0.8011	0.9191	0.9563	0.9316	0.9195	0.9867	0.7693	0.8851
B (1:2)	0.7153	0.9064	0.7932	0.9592	0.8056	0.9844	0.7019	0.9025
C (2:1)	0.8292	0.9087	0.7261	0.9702	0.8627	0.9882	0.7547	0.9357
D (1:4)	0.7564	0.8663	0.9902	0.9837	0.8965	0.9692	0.7891	0.8986
E (1:0)	0.5228	0.8664	0.8648	0.9838	0.7102	0.9693	0.7235	0.8984
F (0:1)	0.7646	0.8557	0.9382	0.9595	0.8783	0.9628	0.7611	0.8653

CONCLUSION

The results obtained showed that gelatin possesses greater biaodhesive property than gellan gum and when both are used in combination, gelatin could be said to increase the bioadhesiveness of the gum. In conformation with literature information, deacylated gellan gum, the type used in this work, yields hard, brittle, translucent, non-elastic gels in contrast to the soft, transparent, elastic gels obtainable with the acylated type. Since the bioadhesiveness of gellan gum is relatively low, it could be preferable in eye preparations. Also gelatin being relatively strongly bioadhesive could be employed in preparations intended for gastrointestinal, buccal or rectal use.

From drug-release studies, the batch containing gelatin alone gave a higher release of the drug in SGF than in SIF. This would further suggest its ideal use in preparations meant for the gastric mucosa. All the tablet batches gave appreciable release of the drug. Formulation of highly water soluble drugs (such as metronidazole which served as a model drug employed in this study), using hydrophilic bioadhesive polymers can enhance steady release of the drug.

REFERENCES

1. Peppas NA, Bury PA, Surface interfacial and molecular aspects of polymer bioadhesion on soft tissues, J. Control. Release, 1985, 2, 257-275.
2. Gu JM, Robinson JR, Lung SHS, Binding of acrylic polymers to mucin/epithelial surfaces: structure-property relationships, Crit. Rev. Ther. Drug Carrier Syst., 1988, 5, 21-27.
3. Bromberg LE, Buxton DK, Friden PM, Novel periodontal drug delivery system for treatment of periodontitis. J. Control. Release, 2001, 71, 251-259.
4. Kang KS, Veeder GT, Mirrasoul PJ, Kaneko T, Cottrell IW, Agar-like polysaccharide produced by Pseudomonas species: Production and basic properties, Appl. Environ. Microbiol., 1982, 43, 1086-1091.
5. Jansson PE, Lindberg B, Sandford PA, Structural studies of gellan gum, an extracellular polysaccharide elaborated by Pseudomonas elodea, Carbohydrate Res., 1983, 124, 135-139.
6. Arindam D, Sougata J, Nirmal M, Kalyan KS, Sanat KB, Gellan gum and its versatile approaches in drug delivery system, Int. J. Drug Formul. Res., 2011, 2, 43-59
7. Kubo W, Miyazaki S, Attwood D, Oral sustained delivery of paracetamol from in situ-gelling gellan and sodium alginate formulations, Int. J. Pharm., 2003, 258, 55-64.
8. Paul F, Morin A, Monsan P, Microbial polysaccharides with actual potential industrial applications, Biotechnol. Adv., 1986, 4, 245-259.
9. Coviello T, Dentini M, Rambone G, Desideri P, Carafa M, Murtas E, Riccieri FM, Alhaique F, A novel co-cross-linked polysaccharide: Studies for a controlled delivery matrix, J. Control Release, 1998, 55, 57-66.
10. Santucci E, Alhaique F, Carafa M, Coviello T, Murtas E, Riccieri FM, Gellan for the formulation of sustained delivery beads, J. Control Release, 1996, 42, 157-164.
11. Chilvers GR, Morris VJ, Coacervation of gelatin-gellan gum mixtures and their use in microencapsulation, Carbohydr. Polym., 1987, 7, 111-120.
12. Freeman CD, Klutman NE, Lamp KC, Metronidazole: A therapeutic review and update. Drugs, 1997, 54, 679-708.
13. Lee VHL, Peptide and protein drug delivery Vol. 4. In: Robinson JR (ed.) Advances in parenteral sciences. Marcel Dekker, New York, 1990, 42-43.
14. Osadebe PO, Akabogu IC, Assessment of quality control parameters and interchangeability of multi-sourced Metformin HCl tablets marketed in Nigeria, Boll Chim Farm., 2004, 143, 170-173.
15. Attama AA, Adikwu MU, Okoli ND, Studies on bioadhesive granules I: Granules formulated with Prosopis africana (Prosopis) gum, Chem. Pharm. Bull., 2000, 48, 734-737.
16. British Pharmacopoeia Vol I and Vol II, The Pharmaceutical Press, Her Majesty's Stationer Office, London, 2003, 249-252.
17. Patel VM, Prajapati BG, Patel MM, Formulation, evaluation, and comparison of bilayered and multilayered mucoadhesive buccal devices of propranolol hydrochloride, AAPS Pharm. Sci. Tech., 2007, 8, 147-154.
18. Ramana MV, Nagada C, Himaja M, Design and evaluation of mucoadhesive buccal drug delivery systems containing metoprolol tartrate, Ind. J. Pharm. Sci., 2007, 69, 515-518.
19. Harkins WD, Jordan HF, A method for the determination of surface tension from the maximum pull on a ring, J. Am. Chem. Soc., 1930, 52, 1751-1772.
20. Mumtaz AM, Ch'ng HS, Design of a dissolution apparatus suitable for in situ release study of triamcinolone acetonide from bioadhesive buccal tablets, Int. J. Pharm., 1995, 121, 129-139.
21. Rao YM, Vishnu YV, Chandrasekhar K, Ramesh G, Development of mucoadhesive patches for buccal administration of Carvedilol, Curr. Drug Deliv., 2007, 4, 27-39.
22. Rudnic ED, Schwartz JD, Oral solid dosage forms. In: Alfonso R Gennaro (ed.) Remington: The science and practice of pharmacy. 20th ed., Lippincot Williams and Wilkins Inc., Philadelphia, 2000, 858-893.
23. Ofoefule SI, Tablet dosage forms III. In: Textbook of phar-

maceutical technology and industrial pharmacy. Samakin (Nig) Enterprises, Lagos, 2002, 64.

24. Armstrong NA, Tabletting. In: Aulton ME (ed.) Pharmaceutics: Science of dosage form design. Churchill Livingstone, London, 1997, 662-667.
25. Bamba M, Puiseux JP, Marty JP, Carstensen JT, Physical model for release of drug from gel forming sustained release preparations, Int. J. Pharm., 1979, 3, 87-92.
26. Higuchi T, Rate of release of medicaments from ointment bases containing drugs in suspension, J. Pharm. Sci., 1961, 50, 874-875.
27. Desai SJ, Singh P, Simonelli AP, Higuchi WI, Investigation of factors influencing release of solid drug dispersed in inert matrices I, J. Pharm. Sci., 1966, 55, 1220-1223.
28. Higuchi T, Mechanism of sustained action medication: Theoretical analysis of rate of release of solid drugs dispersed in solid matrices, J. Pharm. Sci., 1963, 52, 1145-1149.

Source of support: Nil, Conflict of interest: None Declared