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DEVELOPMENT OF MULTIPARTICULATE METRONIDAZOLE USING POLYMER COMPOSITE OF SESAME LEAF AND OKRA POD GUMS FOR SUSTAINED RELEASE

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Abstract: Background: **Gastric retention and sustained drug delivery are targeted drug delivery systems aimed at achieving clinical outcomes that are farfetched with conventional drug delivery systems. This study aimed to design a sustained release hybrid multiparticulate metronidazole particulate delivery that is swell-able, floatable and bio-adhesive using natural polymer composites.**

Methods: **Sesame leaf and okra pod mucilages were precipitated with absolute ethanol (99%) and characterized for flow properties, swelling index, pH, proximate composition and compatibility using Fourier's Transformed Infrared spectroscopy (FTIR). F1-F8 metronidazole multiparticulates were prepared by extruding the drug-polymer blend into a cross-linking agent. The polymer composites were made of sodium alginate and sesame leaf gum or okra pod gum in 10:3, 5:2, 2:1 and a combination of all the polymers in 5:1:1 and 4:1:1 in which the polymer composites were pre-gelatinized at 50°C. The formed particles were evaluated for swelling index, floating properties, *ex vivo* bio-adhesion, effect of particle size and polymer concentration on drug release, morphology using scanned electron microscopy (SEM), X-ray diffraction (XRD) for compatibility and stability, drug content, entrapment efficiency and *in-vitro* dissolution studies.**

Results: **The pH of sesame leaf and okra pod gums was 6.41±0.00 and 7.16±0.00 respectively, an acceptable biological range. Sesame leaf gum had a poorer flow property with Carr's Index 50°±0.06 and Hausner's ratio 1.67°±0.06, when compared with okra pod gum of Carr's Index 19.4°±0.06 and Hausner's ratio of 1.24°±0.06. Also, the swelling index of sesame leaf gum (1390±0.02%) was close to three times that of okra pod gum (480±0.03%). The FTIR showed no significant change between the spectra of dry powder mix and F7 (polymer composite 5:1:1) as the functional groups were consistent in all the spectra. The XRD showed no significant changes in the diffractograms as B type crystallinity occurred at 22° for pure metronidazole and F7. The percentage yield ranges from 19.6 to 30.3% and swelling index range 40.9 to 107.2% of the particles. Floating buoyancy was 74.5% for F4 and 10.2% for F8 while the floating lag time for F4 (polymer composite 10:3 of sodium alginate and okra pod gum) and F8 (polymer composite 4:1:1) were 336±29s and 933±45s respectively. The *ex vivo* bio-adhesion showed F3 (polymer composite 5:2 of sodium alginate and sesame leaf gum) and F7 with 129.3±8.1s and 941.7±40.1s detachment time respectively. Entrapment efficiencies also range from 34.2% to 51.7% with F2 having the highest drug entrapment. From the**

dissolution studies, 4.1-7.9µg/ml of metronidazole was constantly released over 24 h, and at 95% confidence interval using anova test, the particle size and the polymer concentration 4.8-6% w/v has statistically significant effect on the amount of drug release per time. Sustained release model was Higuchi's and the mechanism of drug release was quasi-Fickian diffusion.

Conclusion: **The metronidazole multiparticulates (sodium alginate and sesame leaf gum or okra pod gum in 10:3, 5:2, 2:1 and a combination of all polymers in 5:1:1 and 4:1:1) were all swellable and sustained release over 24 h maintaining a narrow range of release 4.1-7.9 mcg/ml per time. The best bio-adhesive formulation was F7 while best floating behavior was exhibited by F4 with floating buoyancy of 74.5% and the best swellable hollow spheres was F6.**

Keywords: **Sesame leaf gum, okra pod gum, sodium alginate, sustained release and Gastro retention.**

1. INTRODUCTION

Novel drug delivery technologies are now essential tools for many pharmaceutical and biotech companies because the aim is to achieve clinical outcomes that are not met with conventional therapies. By incorporating drugs into controlled delivery systems, superior performance and acceptability of drugs is attained, either by increasing efficacy, improving safety, or improving patient compliance (Misra & Shahiwala, 2020).

Multiparticulate (MP) technologies are heavily utilized for today's increasingly specialized or personalized medicines. Multiparticulates are highly flexible for meeting required drug delivery profiles, incorporating taste and odour masking, multiple-dose ranges and ease of administration. It is based on subunits such as granules, beads, microspheres, pellets, spheroids and minitab. In multiparticulate drug delivery systems (MPDDS), drug substances are divided into a number of subunits, typically consisting of thousands of spherical particles having diameter of about 0.05-2.00 mm (Dey *et al.*, 2008). Multi-particulates can be prepared by several methods. Some of these methods may be broadly classified as pelletization, granulation, spray drying, and spray congealing (Streubel *et al*., 2006).

Precision Spheres (1-13mm) are highly spherical particles. Large and colourful particles are a good tool as reference particles in simulation experiments and are effectively utilized in vision systems and fluidized bed applications (Cospheric 2020). Hollows spheres are floating spheroids with microporous surfaces that provide buoyancy to materials and aid in improving the density of materials. Evaporated solvents or air that are generated or entrapped are released instantly or over time and this leaves cavities or pore within the spheres (Dong *et al*., 2010). Water soluble polymers are also used to design hydrodynamic systems (HDS) that result in floatable systems.

Metronidazole is a 5-nitroimidazole derivative with activity against protozoa. The drug also has well established bactericidal activity against obligate anaerobic bacteria (USP, 2009). The mode of action involves reduction of metronidazole by bacterial nitroreductases to an unstable intermediate, which interacts with DNA, effectively preventing further replication. After oral administration, metronidazole is well absorbed from the gastrointestinal tract to the extent of about 100%. Peak plasma concentrations of 5 and 10 mcg/ml are achieved usually within 1 to 2 hours, after single doses of 250 and 500 mg, respectively. Metronidazole is given in doses of 400 to 800 mg three times daily by mouth for 5 to 10 days or an alternative adult dose of 1.5 to 2.5 g as a single dose daily for 2 to 3 days in amaebiasis and dosing is based on disease to be treated. Frequency of intake impedes patient compliance and high dose exposures are triggers to adverse drug events, hence the need for a sustained delivery system.

Sesame leaf gum is obtained from the mucilage of *Sesame radiatum* (Pedaliaceae). Apart from the characterization (Nep *et al*., 2016) of the mucilage from the leaves and wide application of sesame seed oil (Auwalu and Babatunde, 2007), the use of sesame leaf gum as a drug delivery polymer or copolymer has not been reported. Whereas okra pod gum, *Abelmoschus esculentus* L. (Malvaceae) has been extensively researched and reported as polymer in drug delivery (Amiri *et al*., 2021).

Synthetic polymers used in the production of sustained release products have a major impact on the cost of the drug product especially in low and middle-income economies. By using readily available natural polymers, affordable medicines will be accessible (Ozoude *et al* 2020). Different studies have been carried out on several pharmaceutical applications of okra pod gum and none has been reported for sesame leaf gum as polymer or copolymer in drug delivery systems to the best of the authors' knowledge in the formulation of multiparticulate delivery systems.

A controlled drug delivery system with prolonged residence time in the stomach is the goal of gastro-retentive drug delivery systems (GRDDS). The GRDDSs are primarily categorized into following types: floating drug delivery system, bio-adhesive drug delivery system (BDDSS), swelling and expanding delivery system, combinational/amalgamative delivery system, and micro-particulate delivery system (Patil *et al*., 2021)

This research aims to develop sustained release combinational gastro-retentive delivery system that utilizes the mechanism of floating, swelling and bio-adhesion while overcoming the disadvantages of each other (Singh *et al.*, 2021).

2. MATERIALS

Sesame leaf (LUH8824) was gotten from local market (Farin gada) in Jos, Plateau State while Okra pod (LUH8825) was gotten from Oyingbo market, Lagos and were respectively identified and authenticated by the Department of Botany, University of Lagos with voucher specimen numbers assigned and samples were deposited in the herbarium. Metronidazole (Yixing Jiangshan Biotech, CAS No. 443-48-1), absolute ethanol (Puritan Products, USA), sodium alginate, N-hexane, and calcium chloride all of analytical grades were obtained from Adels Crystal Lake ltd.

3. METHODS

Extraction of Sesame Leaf and Okra Pod Gum:

Sesamum radiatum fresh leaves were (5 kg) macerated in 6 L of distilled water for 30 min at room temperature (27°C). The mucilage was filtered from the leaves using a muslin cloth and then precipitated with 3 volumes of 99% v/v ethanol. The precipitate was then filtered using a 200 µm sieve and oven dried at 50°C for 24 h. The extracted gum was then characterized with no further purification as reported by Nep *et al*., (2016). Also, the extraction of fresh okra pod gum (*Abelmoshus esculentus*) was based on Zaharuddin *et al*., (2014) method with little modification. 1 kg of unripe and tender Okra fruits was obtained from the local market. The seeds were removed as they do not contain any mucilage. The fruits were washed and sliced into two or three with a knife. The sliced mass was soaked in distilled water for 4 h to extract out the mucilage. After soaking, a white muslin cloth was used to filter out the viscous gum extract (mucilage). Absolute alcohol was added to precipitate the gum at a ratio of 3 parts of alcohol to 1 part of the gum extract. Then, the precipitated gum was dried in the oven at 60^{o} C for 12 h. Size reduction and screening of the dried gum were conducted using a stainless-steel grinder and no. 30 stainless steel mesh sieve. Airtight powder bottles were used to store the undersized fractions. Subsequently, physicochemical characterization of the Okra gum powder was conducted.

Swelling Index

It was calculated by weighing a butter paper of size 2x2 cm. Then butter paper was dipped in a Petri dish containing water and reweighed. After this 10 mg of the powdered sample was kept in a butter paper placing this on a Petri dish containing 15 ml of water and the swelling index was calculated after 24 h and the result was calculated using the formula equation 1, (Tyagi *et al.*, 2021).

$$Swelling\ Index = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100 \quad \text{---------- (1)}$$

The pH of Mucilage

1% w/v solution in water was determined using a digital pH meter as in Tyagi *et al*., (2021).

Solubility of Mucilage

Solubility was determined by shaking the powdered gum 1 g on 10 ml in different solvent such as acetone, ethyl alcohol, benzene, chloroform, and glycerine as by Tyagi *et al.*, (2021)

Micrometrics Properties: Bulk Density and Bulkiness

Fixed quantities of the isolated mucilage were transferred into a graduated measuring cylinder. The cylinder was placed on the bulk density apparatus and the volume covered by the mucilage was noted down. Then, the powder was tapped in a bulk density apparatus until a constant volume was obtained. The final bulk volume was noted following Ozoude *et al.*, (2020).

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Bulk density tapped density and bulkiness were calculated using the equations 2 and 3.

$$\text{Bulk density} = \frac{\text{Weight of powder}}{\text{Weight of apparent volume}} \quad \text{---------- (2)}$$

$$\text{Tapped Density} = \frac{\text{Weight of powder}}{\text{Tapped volume}} \quad \text{---------- (3)}$$

Angle of Repose

Angle of repose was determined by fixed height funnel method. The height (h) of the heap formed was measured and the radius (r) of the cone base was also observed and calculated according to Tyagi *et al.*, (2021). And the angle of repose was calculated using equation 4.

$$\text{Tan } Ø = \frac{h}{R} \quad \text{---------- (4)}$$

Where;

Ø = Angle of repose

h = Height of pile

r = Radius of pile

Carr's Consolidation Index (Compressibility) And Hausner's Ratio

Finely powdered mucilage (5 g) was transferred into a measuring cylinder and compressibility, Hausner's ratio were calculated using bulk density apparatus as described by Tyagi *et al*., (2021). Equations 5 and 6 were used to determine the Carr's index and Hausner's ratio.

$$\text{Carr's Index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100 \quad \text{---------- (5)}$$

$$\text{Hausner's Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}} \quad \text{----------(6)}$$

Determination of Moisture Content

The sample (2 g) was put into a pre-weighed, pre-dried and cooled crucible and then dried in the oven at 80°C for 2 h and at 105°C to obtain a constant weight. The crucible and its content were cooled in a desiccator for some time, after which it was reweighed. The moisture content was calculated and expressed as % moisture accordingly as in Maciel *et al*., (2016).

Determination of Ash Content

The crucible was washed, cleaned, and placed in a hot-air circulation oven for 2 h and then transferred into a muffle furnace to burn off all organic matter and stabilize the weight of the crucible at a temperature of 550°C, after which it was cooled to room temperature in a desiccator. The sample (2 g) was weighed into the crucible placed in the muffle furnace, ashed at 600°C for 3 h, cooled in a desiccator at room temperature and re-weighed. The ash content was calculated and expressed as % ash content as shown by Tanvir *et al*., (2017).

Determination of Crude Lipids

The sample (2 g) was extracted for lipids with 300 ml of petroleum ether (40-60°C) for 3 h in a Soxhlet extractor. The content of the thimble (extracted lipids) was dried in an oven at 80°C for a 2 min, cooled in a desiccator and then reweighed. The drying and cooling was continued to obtain a constant weight and the percentage lipid was calculated and expressed as % crude lipid according to Tanvir *et al*., (2017).

Determination of Fibre Content

The sample (2 g) was dissolved in 100 ml of 0.25 N H_2SO_4 and heated for 1 h in a water bath, filtered and the residue obtained. The residue was dissolved in 100 ml of 0.3 N NaOH solution, heated under reflux for additional 1. The mixture was filtered through a fibre sieve cloth and 10 ml of acetone was added to dissolve any organic constituent. The residue was washed with 50 ml of hot water twice on the sieve cloth before it was finally transferred into the crucible. The residue in the crucible was oven dried overnight at 105°C to remove moisture, then cooled in a desiccator and weighed to obtain the weight (w1). The crucible with content was transferred to the muffle furnace for ashing at 550°C for 4 h. The crucible and its ashed content were cooled in the desiccator and reweighed to obtain the weight (w2). The difference w1 – w2 gave the weight of fibre (AOAC, 1999).

Determination of Crude Protein Content Using Kejhdal Method

The sample (2 g) was mixed with 3 g of copper sulphate catalyst and 25 ml of concentrated sulphuric acid. The mixture was heated over a Bunsen flame in a fume cupboard to expel any poison gas. It was then heated with shaking at intervals for 1 h until the mixture became clear. Distilled water (400 ml), 2% boric acid (50 ml) and methyl red indicator (1 ml) were added. The solution was made alkaline by the addition of 75 ml of 50% NaOH solution. The ammonia was distilled into the boric acid solution and 250 ml of the distillate was collected and titrated with 0.1 M hydrochloric acid. The percentage crude protein was calculated from the % nitrogen of the sample as described by Maciel *et al*., (2016).

Fourier's Transform Infra-Red (FTIR) Spectroscopy

FTIR study was conducted to check compatibility of drug with polymer and polymer blends comprising metronidazole and sesame leaf gum, metronidazole and okra pod gum, metronidazole, sesame leaf gum and okra pod gum, sesame and okra pod gum and metronidazole powder alone. The FTIR spectrum of F7 (Drug-polymer composite of all the polymers) was also evaluated. Fourier's transform Infrared Spectrophotometer was determined by using KBr dispersion method. The baseline correction was done using dried potassium bromide. Then the spectrum of dried mixture of metronidazole and potassium bromide was run followed by metronidazole with various polymers by using FTIR spectrophotometer. The absorption maximums in the spectrum obtained with the substance being examined correspond in position and relative intensity to those in the reference spectrum (Hemmalakshmi *et al*., 2017).

X-Ray Diffraction (XRD)

Scan speed of 4° per minute in the 2θ range of 5°–60° was set for X-ray diffraction. Metronidazole and F7 transition study were carried out to evaluate the rate of transition of the powder and F7 hollow spheres. The samples were heated in a temperature-controlled water bath. The experiment was started at 30°C and the temperature was increased up to 80°C with an increment of 5°C every 5 min. The samples were incubated at the specified temperature for 5 min and were observed by inverted test tube method. The temperature at which the sample started to flow was regarded as crystallinity transition (Ilomuanya *et al*., 2021)

DESIGN OF EXPERIMENT

Due to the dynamics of variabilities in formulations, dependent and independent factors were chosen to ensure evaluations meet the stated objectives. The height of release of polymer dispersion was chosen to be 1 m for F1-F4 and 0.5 m for F5-F8. The percentage of sodium alginate was kept at 4% w/v. Concentrations of calcium chloride from 1%, 5%, 10%, 20% 30% and 50% w/v were evaluated for stable and visible spheres. Finally, the percentage of sesame leaf and okra pod gums were varied from 0.8-2% w/v and mixed at 0.8% w/v and 1% w/v as shown in Table 1.

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Table 1: Formulation of metronidazole hollow spheres

S/N.	BATCH. NO.	DRUG (%w/v)	SODIUM ALGINATE (%w/v)	SESAME LEAF GUM (%w/v)	OKRA POD GUM (%w/v)	FINAL WEIGHT (g)	YIELD OF HOLLOW SPHERES (g)	VOLUME OF WATER (ml)
1	F1	4	4	1.2	-	27.3	5.34	25
2	F2	4	4	1.6	-	27.4	6.37	25
3	F3	4	4	2.0	-	27.5	7.42	25
4	F4	4	4	-	1.2	27.3	8.28	25
5	F5	4	4	-	1.6	27.4	8.01	25
6	F6	4	4	-	2.0	27.5	8.18	25
7	F7	4	4	0.8	0.8	27.4	8.04	25
8	F8	4	4	1	1	27.5	8.00	25

KEYS: F1 – F8 Formulations with different polymer concentrations and combinations

FORMULATION BY IONIC GELATION METHOD (SYRINGES METHOD)

The hollow spheres were prepared by extruding the drug-polymer blend into the cross-linking agent in which sodium alginate and each of sesame leaf gum and okra pod gum are in 2:1, 5:2, 10:3 and a combination of all polymers in 5:1:1 and 4:1:1 as shown in Table 1. Sodium alginate was first dispersed in of 25 ml of water with continuous stirring to form homogeneous dispersion, then sesame leaf or okra pod gums or combination of both were added according to the batch formula at 50°C until homogenous dispersion is achieved. The heat was turned off while stirring continued at 500 rpm for 2 h. The polymer ratios were decided based on preliminary research. Metronidazole was then added to the above dispersion and thoroughly mixed for homogeneity. The drug-polymer mixture was released into 50% w/v calcium chloride solution using a 21G gauge needle by stirring at 50 rpm. The spheroids thus formed were allowed for 30 min, then the calcium chloride solution was decanted, washed with distilled water and N-hexane was used to harden the hollow spheres. The formed spheroids were dried for 12 h at 60°C (Chaturvedi *et al.*, 2012 and Odeku *et al.*, 2017).

EVALUATION AND CHARACTERIZATION OF HOLLOW SPHERES

Particle Size Determination

The particle sizes were estimated by determining the particle diameter according to Ozoude *et al*., 2020.

Percentage Yield

The total amount of hollow spheres obtained were weighed and evaluated for percentage yield according to the equation (7).

$$\text{Percentage yield} = \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100 \quad \text{---------- (7)}$$

Swelling Index of metronidazole spheres

The same method was followed as highlighted in equation (1)

Floating Properties

The floating lag time and buoyancy of the spheres were carried out using the tablet disintegration apparatus. The spheres were spread over the surface of the dispersing medium (200 ml), which was agitated by a paddle rotated at 100 rpm. The medium was 0.1N HCl and at 37°C and agitation continued for 17 min. During agitation the floating lag times were recorded as the time particles started floating on agitation and after agitation, the hollow spheres that floated over the surface of medium and those that settled to the bottom of the flask were recovered separately. After drying, each fraction of the hollow microspheres was weighed. The buoyancy (eq. 8) (Kawashima *et al.*, 1991) was estimated as thus,

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$$\text{Buoyancy (\%)} = \frac{\text{Weight of floating particles}}{\text{Weight of floating particles + Weight of settled particles}} \quad \text{---------- (8)}$$

***Ex vivo* Muco-adhesion Time**

Several techniques for *in vitro* determination of bio-adhesion have been reported, which include tensile testing, shear stress testing, adhesion weight method, fluorescent probe method, flow channel techniques and colloidal gold staining method (Harikrishnan *et al*., 2016). A modified USP apparatus II with 8 chambers was used for determination of the *ex vivo* residence time. The medium was constituted of 600 ml (pH 1.2) of 0.1 N HCl maintained at 37±0.5 °C. The sheep gastric mucosa was tangled to the surface of a glass slab and connected vertically to the paddle of the apparatus. The glass slide allowed moving at 50 rpm. The times taken for complete displacement of the hollow spheres from the mucosal surface were noted.

Drug Content Estimation and Entrapment Efficiency

Metronidazole spheres (100 mg) from each batch were initially stirred in 3 ml sodium citrate solution (1% w/v) until complete dissolution. A quantity of 7 ml of methanol was added to the above solution to solubilize the metronidazole. The filtrate was assayed for drug content by measuring the absorbance at 277 nm after suitable dilution by UV-Visible spectrophotometer and encapsulation efficiency was calculated using the equation 9 (Vaidya *et al*., 2009).

$$\text{Entrapment efficiency} = \frac{\text{Estimated \% drug content in hollow spheres}}{\text{Theoretical \% drug content in hollow spheres}} \times 100 \quad \text{------ (9)}$$

***In- Vitro* Drug Release Studies**

In-vitro drug release study was carried out in USP dissolution test apparatus. A quantity of microspheres equivalent to 100 mg of Metronidazole microspheres was kept in basket type apparatus and immersed in 900 ml of acid buffer (pH 1.2) in 1000 ml dissolution flask and temperature was maintained at 37 ± 0.5ºC throughout the study. At predetermined time intervals 2 ml of samples was withdrawn by means of a syringe fitted with pre-filter and the same was replaced into the dissolution flask containing pH 1.2. The absorbance of the sample was measured at 277 nm after required dilution with the fresh medium (pH 1.2) as described by Chaturvedi *et al*., (2012),

Kinetics of *In-Vitro* Drug Release

In-vitro drug released data was subjected to *in- vitro* kinetic models such as zero *order*, first order, second order, Higuchi's model, Korsmeyer-Peppas and Hixson-Crowell erosion kinetics and the mechanism of drug released was determined by the slope of Korsmeyer-Peppas equation 10 (Vaidya *et al*., 2009).

$$\boldsymbol{Mt/M\infty = Kt^n} \quad \text{---------- (10)}$$

Where

M_t - represents amount of the released drug at time t,

M_∞- is the overall amount of the drug (whole dose) released after 24 h

K- is the diffusional characteristic of drug/ polymer system constant

n- is a diffusional exponent that characterizes the mechanism of release of drug.

Statistical Analysis:

Statistical analysis was done using Microsoft Excel 365 with enhanced online analytical data analysis. Two-way Anova with repetition was used to test the effect of polymer concentration on the particle size of metronidazole loaded hollow

spheres (F1-F8) and the effect of height of release into the cross-linking agent, high (1 m) F1 to F4 and low (0.5 m) F5 to F8 on particle size of the hollow spheres at 0.05 α-value. Also, a one factor Anova was used to test the effect of the polymer concentration (4.8 % w/v to 6 % w/v) on the mean amount of drug released over 24 h at 0.05 α-value.

4. RESULTS

Ethanolic extraction of sesame leaf and okra pod gum yielded 0.8% and 0.2% respectively. The comparison of flow properties, proximate analysis and pH of sesame leaf and okra pod gums is shown in Table 2. Both sesame leaf gum and okra pod gums were insoluble in water, ethanol, methanol, acetone, and isopropyl alcohol. Percentage Purity of metronidazole was determined to be 83.52%.

Table 2: Comparison of flow properties and proximate analysis of sesame leaf and okra pod gums

Flow Properties	SESAME LEAF GUM	OKRA POD GUM	REMARKS
Bulk Density	0.24°±0.060	0.50±0.006	Fluffy sesame leaf power, denser okra pod gum
Tapped Density	0.40±0.000	0.62±0.006	
Carr's Index	50.00°±0.060	19.40°±0.060	Extremely Poor Flow for Sesame Leaf Gum and Fair Flow for Okra Pod Gum
Hausner's Ratio	1.67°±0.060	1.24°±0.060	Moderate Flow for Okra Pod Gum While Cohesive for Sesame Leaf Gum
Compressibility Index	36.40°±0.060	21.30°±0.060	Fair Flow for Okra Pod Gum and Extremely Poor Flow for Sesame Leaf Gum
Angle Of Repose	49.80°±0.250	41.90°±0.060	Fair To Passable Flow for Okra Pod Gum and Cohesive behaviour for Sesame Pod Gum
Proximate analysis			
Oil/lipid	1.00%	0.75%	
Moisture	8.50%	8.00%	
Ash	76.00%	90.00%	
Fibre	1.77%	1.83%	
Protein	0.19%	0.05%	
pH	6.41±0.00	7.16±0.00	
Swelling index	1390.00±0.02%	480.00±0.03%	

Compatibility studies

Fourier's Transform Infrared spectroscopy (FTIR)

FTIR was used to check the appearance of functional groups in the samples and Figures 1-2 shows the various comparisons of API, gums and F7 for possible interactions

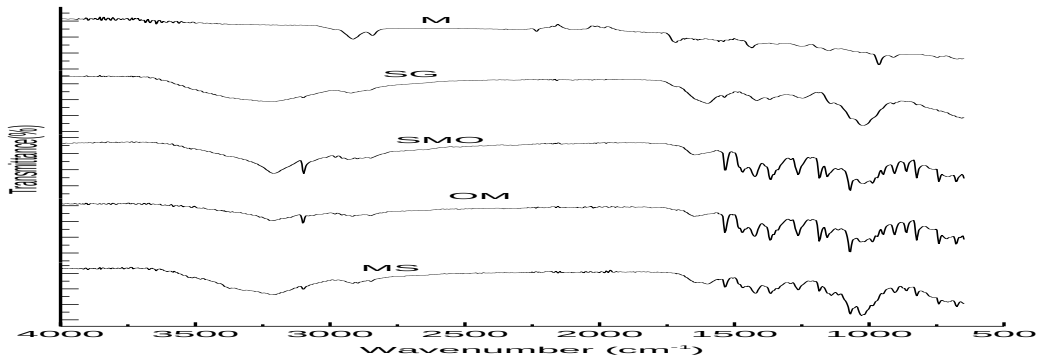

Figure 1: Multi-Y plots of MS, OM, SMO, SG and M

Keys: M= metronidazole powder, MS= metronidazole plus sesame leaf gum powder mix, MSO= metronidazole plus sesame leaf gum plus okra pod gum powder mix, OM= okra pod gum plus metronidazole powder mix, MS= metronidazole plus sesame leaf gum powder mix,

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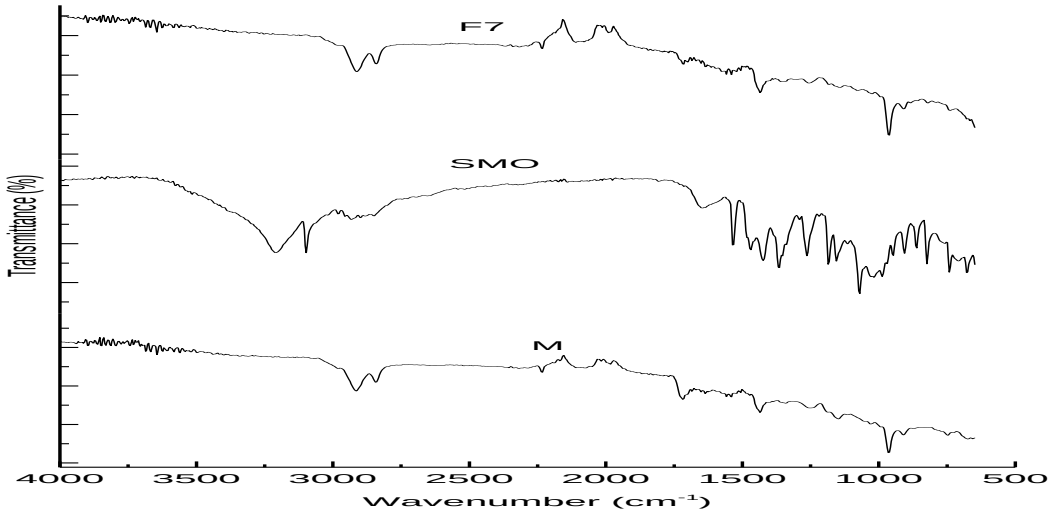

Figure 2: Stacked Plot of M. SMO and F7

Keys: F7= hollow spheres containing metronidazole 4% w/v plus sodium alginate 4% w/v plus sesame leaf gum 0.8% w/v plus okra pod gum 0.8% w/v, MSO= metronidazole plus sesame leaf gum plus okra pod gum powder mix and M= metronidazole powder

X-Ray Diffraction (XRD)

The diffractograms of metronidazole and F7 are shown in Figures 3.

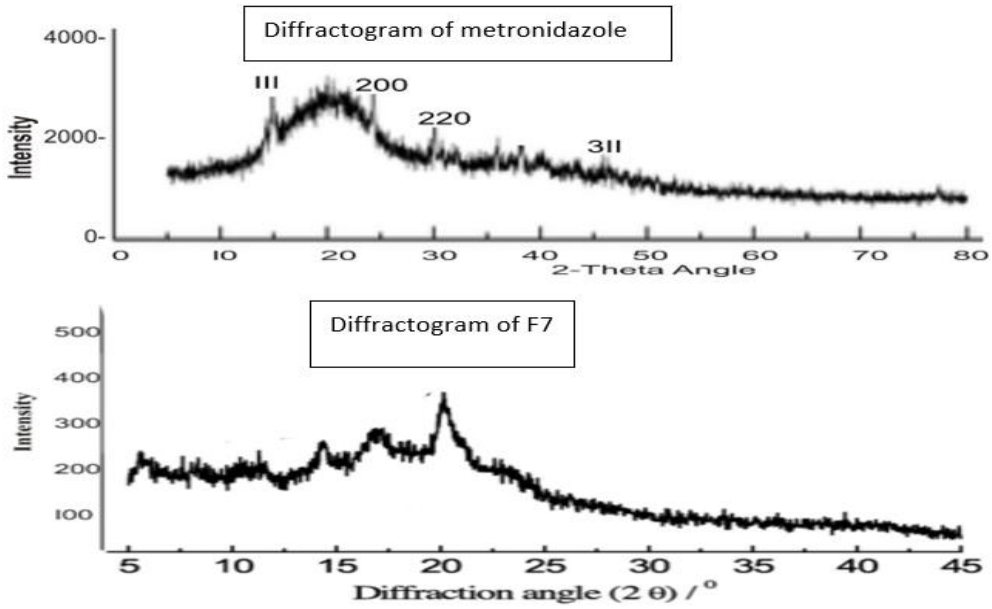

Figure 3: X-Ray Diffraction of metronidazole and F7

Keys: F7= hollow spheres containing metronidazole 4% w/v plus sodium alginate 4% w/v plus sesame leaf gum 0.8% w/v plus okra pod gum 0.8% w/v

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Scanning Electron Microscopy (SEM)

The scanned electron microscopy is shown in Figures 4 and 5.

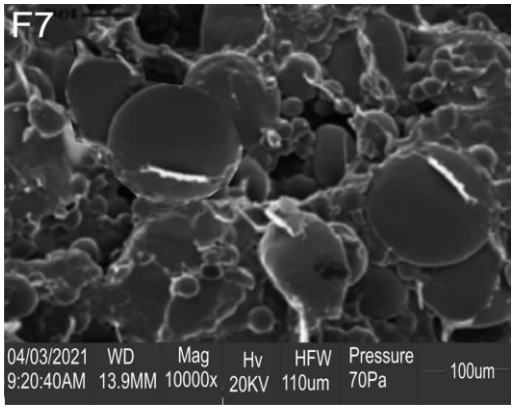

Figure 4: F7 at 10000 magnifications

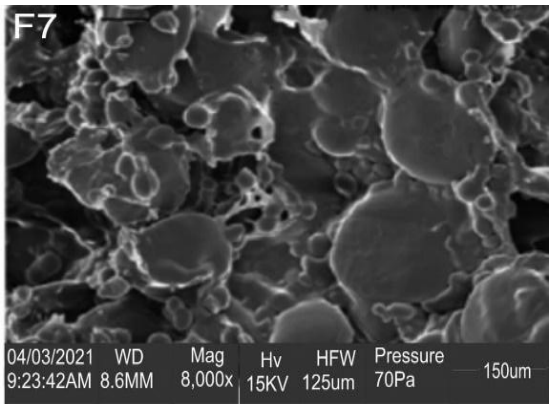

Figure 5: F7 at 8000 magnifications.

Keys: F7= hollow spheres containing metronidazole 4% w/v plus sodium alginate 4% w/v plus sesame leaf gum 0.8% w/v plus okra pod gum 0.8% w/v

Particle Size Evaluation of Metronidazole Spheres

The particle sizes are shown in Table 3 based on the diameter of five randomly selected particles in each batch and how the height of release of drug-polymer dispersion into the cross-linking agent affects the particle sizes.

Table 3: Particle sizes of metronidazole hollow spheres

CODE	HEIGHT	PARTICLE SIZE DISTRIBUTION (cm)					MEDIAN	MEAN	SD	MEAN±SD
F1	HIGH (1 m)	0.40	0.40	0.30	0.30	0.20	0.30	0.32	0.08	0.32±0.08
F2		0.35	0.35	0.30	0.40	0.40	0.35	0.36	0.04	0.36±0.04
F3		0.40	0.50	0.30	0.45	0.40	0.40	0.41	0.07	0.41±0.07
F4		0.35	0.40	0.30	0.40	0.40	0.40	0.37	0.04	0.37±0.04
F5	LOW (0.5 m)	0.50	0.45	0.35	0.40	0.40	0.40	0.42	0.06	0.42±0.06
F6		0.60	0.45	0.30	0.60	0.35	0.45	0.46	0.14	0.46±0.14
F7		0.45	0.50	0.40	0.40	0.40	0.40	0.43	0.04	0.43±0.04
F8		0.50	0.45	0.40	0.40	0.45	0.45	0.44	0.04	0.44±0.04

KEYS: F1 – F8 Formulations with different polymer concentrations and combinations

Drug Content, Entrapment Efficiency and % Yield

The swelling index which shows the water permeation ability of each formulation, % yield, drug content and entrapment efficiency is shown in Table 4.

Table 4: The Swelling Index, % Yield, Drug content, and Entrapment Efficiency of multiparticulate metronidazole.

Code	Swelling Index	% Yield	Drug content (mcg/ml)	Entrapment Efficiency %
F1	87.8	19.6	130.56	37.0
F2	84.8	23.3	179.94	51.7
F3	89.6	27.0	114.13	34.2
F4	82.7	30.3	151.56	42.9
F5	82.5	29.2	137.19	39.4
F6	107.2	29.7	126.44	37.8
F7	89.9	29.3	125.69	36.1
F8	40.9	29.1	167.56	50.2

KEYS: F1 – F8 Formulations with different polymer concentrations and combinations

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Floating Behaviour and Bio-adhesive

The Floating behavior and bio-adhesive properties of metronidazole hollow spheres is shown in Table 5.

Table 5: Floating and bio-adhesive properties of metronidazole hollow spheres.

Floating Lag time						
Code	**Floating Lag Time**			**Mean**	**SD**	**Mean±SD**
F2	698	702	640	680	35	680±35
F4	328	368	312	336	29	336±29
F6	525	498	567	530	35	530±35
F8	917	984	899	933	45	933±45

Floating Buoyancy									
Code	**weight of floating particles (mg)**			**Mean weight of floating particles (mg)**		**Weight of settled Particles (mg)**		**Mean Weight of settled Particles (mg)**	**Buoyancy (%)**
F2	12.3	10.4	11.3	11.3	18.2	18.9	19.1	18.7	37.7
F4	23.2	25.1	24.2	24.2	7.7	8.4	8.9	8.3	74.5
F6	8.6	9.6	8.3	8.8	14.8	15.2	13.7	14.6	37.6
F8	3.5	5.4	3.9	4.3	27.4	27.9	28.3	27.9	10.2

Ex vivo Bioadhesion Time						
Codes	**Time of complete detachment**			**Mean**	**SD**	**Mean±SD**
F1	180	170	185	178.3	7.6	178.3±7.6
F3	120	134	134	129.3	8.1	129.3±8.1
F5	300	310	320	310.0	10.0	310.0±10.0
F7	900	945	980	941.7	40.1	941.7±40.1

KEYS: F1 – F8 Formulations with different polymer concentrations and combinations

***In Vitro* Drug Release Studies**

The amount of metronidazole released per time across the formulation batches is shown in Figure 6. This indicates that the aggressive absorption and subsequent distribution of metronidazole following oral administration has been simulated to be effectively retarded.

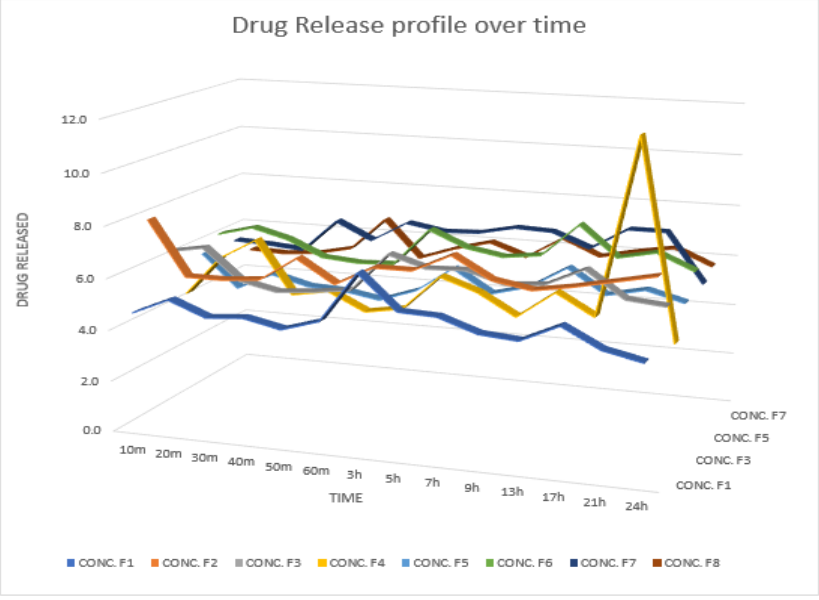

Figure 6: Comparative drug release of metronidazole hollow spheres over 24 h.

KEYS: F1 – F8 Formulations with different polymer concentrations and combinations

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Kinetics of Drug Release

The drug release profile was simulated using the following mathematical models shown in Figures 7-15.

Zero Order Kinetics

The comparative zero order release kinetics of the metronidazole spheres are shown in Figure 7. F1/F5, F3/F4 and F5and F7 are highly correlated in the zero-order kinetics for optimization with reference to concentration variations in Figures 4.15-4.21

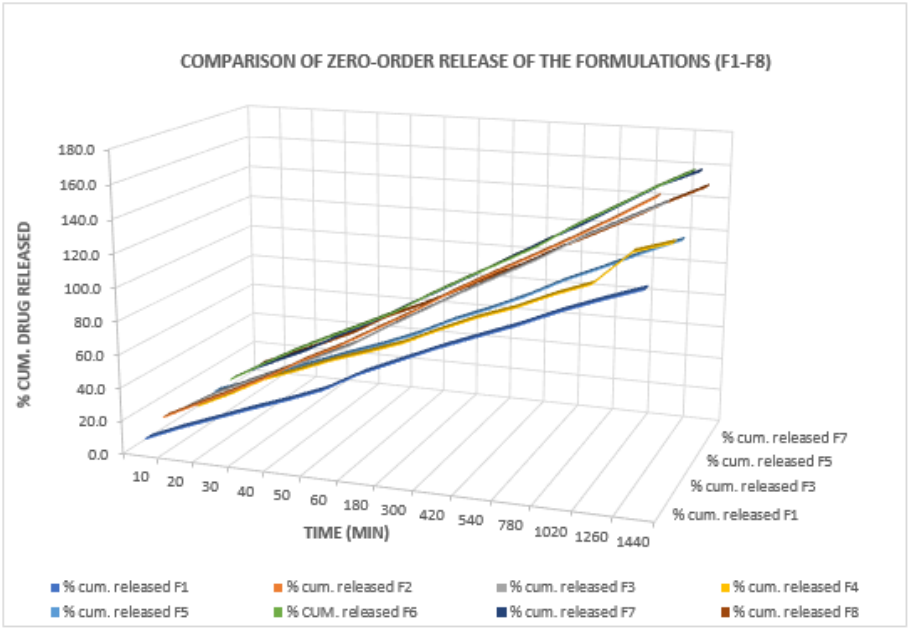

Figure 7: Zero Order Comparison of metronidazole spheres (F1-F8).

KEYS: F1 – F8= Formulations with different polymer concentrations and combinations

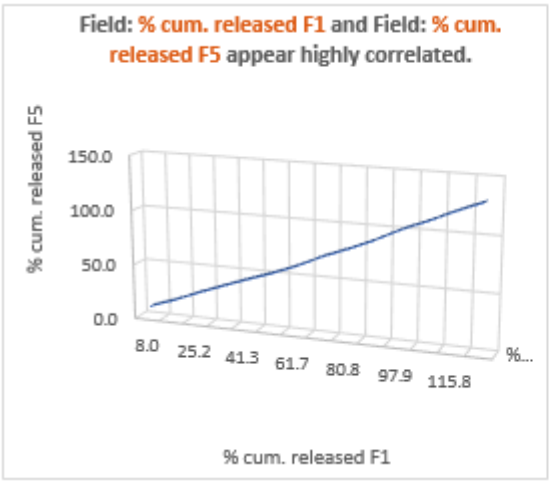

Figure 8: Correlation of F1 and F5

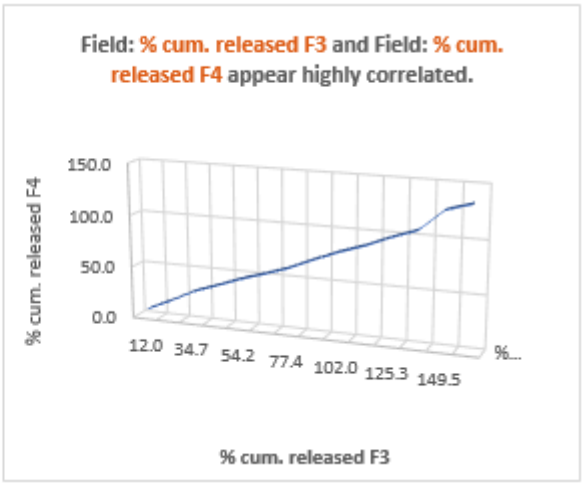

Figure 9: Correlation of F3 and F4

Keys: **F1**= hollow spheres containing metronidazole 4% w/v plus sodium alginate 4% w/v plus sesame leaf gum 1.2% w/v and **F5**= hollow spheres containing metronidazole 4% w/v plus sodium alginate 4% w/v plus okra pod gum 1.6% w/v

Keys: **F3**= hollow spheres containing metronidazole 4% w/v plus sodium alginate 4% w/v plus sesame leaf gum 2% w/v and **F4**= hollow spheres containing metronidazole 4% w/v plus sodium alginate 4% w/v plus okra pod gum 1.2% w/v

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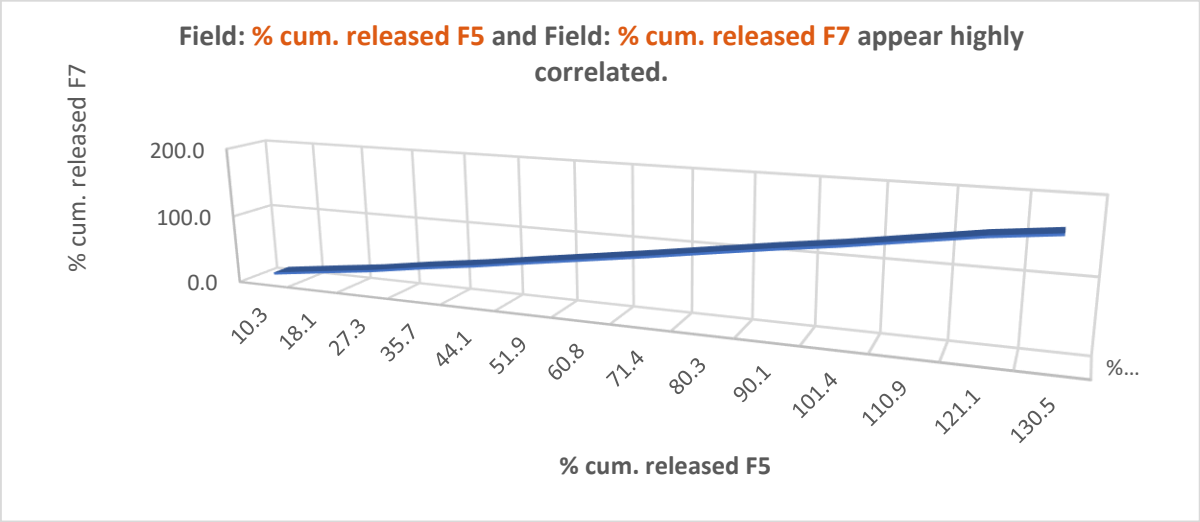
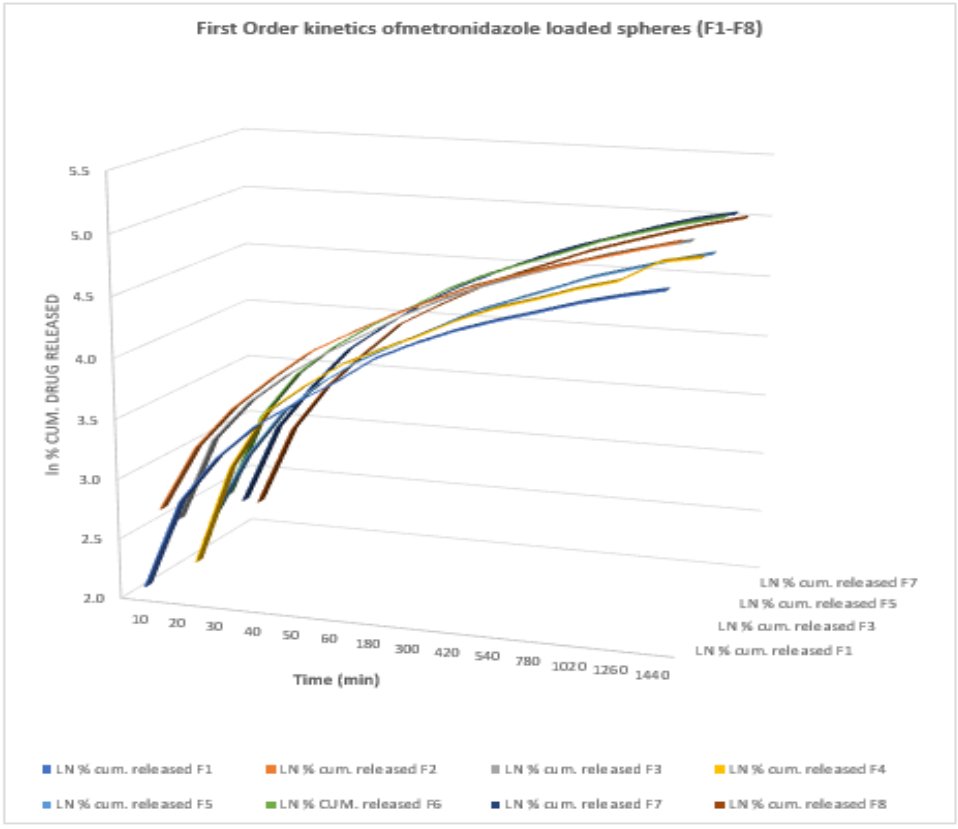


Figure 10: Correlation of F5 and F7

Keys: **F5**= hollow spheres containing metronidazole 4% w/v plus sodium alginate 4% w/v plus okra pod gum 2% w/v and **F7**= hollow spheres containing metronidazole 4% w/v plus sodium alginate 4% w/v plus okra pod gum 0.8% w/v plus sesame leaf gum 0.8% w/v.

First Order Kinetics

The first order release kinetics of metronidazole spheres is represented in Figure 11.



KEYS: F1 – F8= Formulations with different polymer concentrations and combinations

Figure 12: Comparison of First order kinetics of metronidazole spheres.

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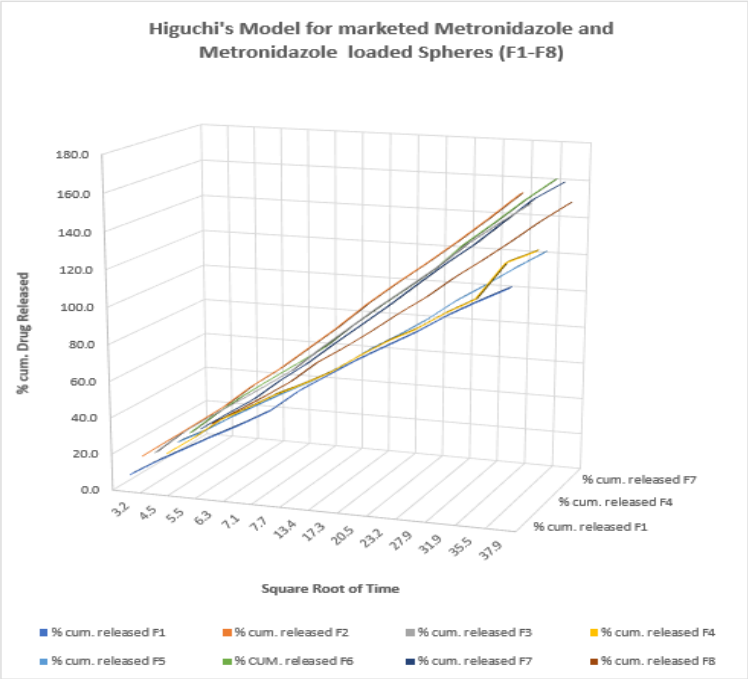
Higuchi's Release Model

The Figure 13 shows the Higuchi's release model.

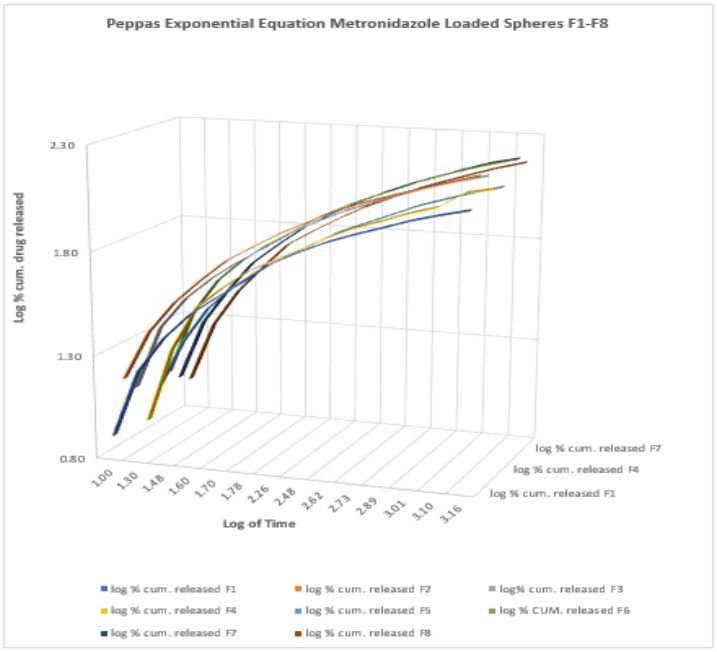


KEYS: F1 – F8= Formulations with different polymer concentrations and combinations

Figure 13: Comparison of Higuchi's model of metronidazole spheres F1-F8

Korsmeyer-Peppas Erosion Model

The Korsmeyer-Peppas Erosion Model is shown in Figure 14.



KEYS: F1 – F8= Formulations with different polymer concentrations and combinations

Figure 14: Comparison of Korsmeyer-Peppas exponential equation of metronidazole spheres.

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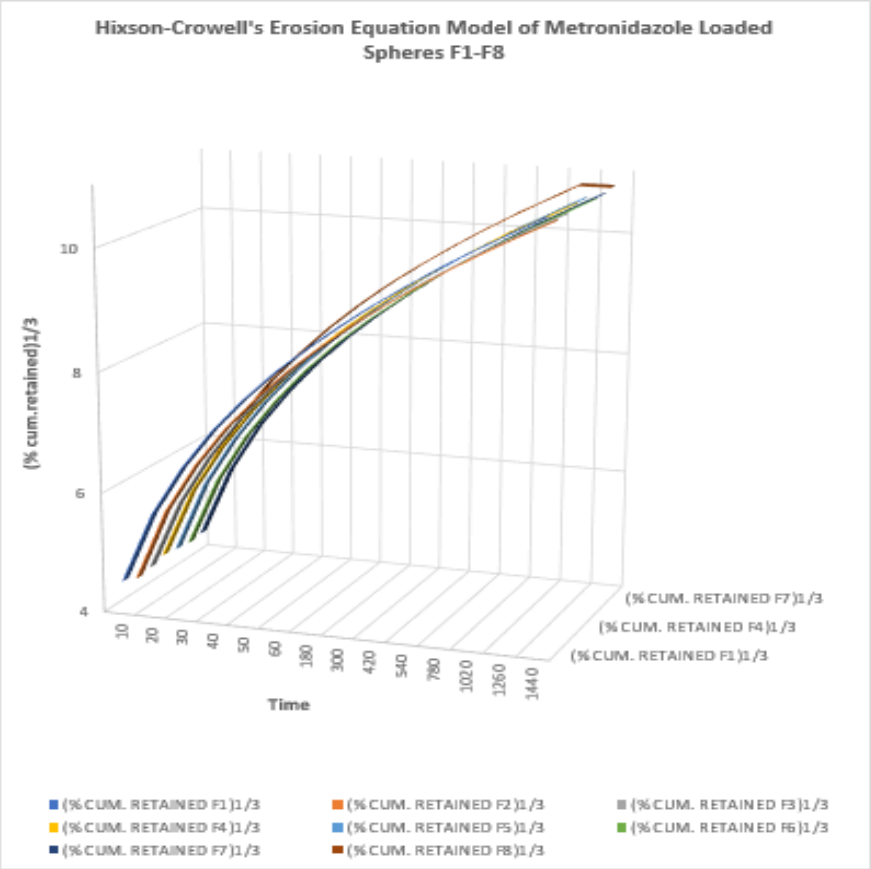

Hixson-Crowell's Erosion Equation

The Hixson-Crowell's Erosion release model is depicted by Figure 15.

KEYS: F1 – F8= Formulations with different polymer concentrations and combinations

Figure 15: Comparison of Hixson-Crowell's erosion equation release of metronidazole spheres

BEST FIT MODEL OF KINETIC RELEASE MECHANISM

The best release model in Table 6 is the Higuchi's model which shows that the fraction of drug released is directly proportional to the square root of time and the mechanism of release is the quasi non-fictian diffusion shown by Korsmeyer-.Peppas model.

Table 6: Best fit model of kinetic release and mechanism of release

CODE	ZERO ORDER	FIRST ORDER	HIGUCHI	KORMEYER-PEPPAS		HIXSON-CROWELL	BEST FIT
	R^2	R^2	R^2	R^2	n	R^2	
F1	0.8572	0.5810	0.9595	0.9103	0.4567	0.6810	HIGUCHI
F2	0.8700	0.6184	0.9622	0.9285	0.4235	0.6810	HIGUCHI
F3	0.8743	0.6070	0.9662	0.9220	0.4327	0.6820	HIGUCHI
F4	0.8850	0.5721	0.9587	0.8813	0.4498	0.6840	HIGUCHI
F5	0.8831	0.6213	0.9680	0.9263	0.4334	0.6810	HIGUCHI
F6	0.8761	0.5990	0.9650	0.9129	0.4392	0.6830	HIGUCHI
F7	0.8689	0.5887	0.9622	0.9112	0.4678	0,684	HIGUCHI
F8	0.8701	0.5865	0.9610	0.9076	0.4658	0.6850	HIGUCHI

KEYS: F1 – F8= Formulations with different polymer concentrations and combinations

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5. DISCUSSION

Extraction Sesame Leaf and Okra Pod Gums

The ethanolic extract of sesame leaf gum and okra pod gums yielded 0.8% and 0.2% respectively. Also, the low yield is heavily compensated by the high swelling index 1390±0.02% and 480±0.03% of sesame leaf and okra pod gums respectively as shown in Table 1 for scalable pilots and commercialization

Flow Properties

Bulk density gives an estimate of the ability of a material to flow from a hopper into the die cavity of a rotary compression machine while tapped density is a measure of how well a powder can be packed in a confined space on repeated tapping. In general, the higher the bulk and tapped densities the better for a material to flow and rearrange under compression (Azubuike & Okhamafe 2012). Table 1 also shows the comparative flow properties of sesame leaf gum and okra pod gums with an overall extremely poor flow rate for sesame leaf gum and fair flow rate for okra pod gum. Sesame leaf gum is fluffy hence less dense than okra pod gum with true densities of 0.24 g/ml and 0.5 g/ml respectively. Carr's Index 50 and 19.4 indicate extremely poor flow for sesame leaf gum and fair flow for okra pod gum while Hausner's ratio 1.67 and 1.24 indicates moderate flow for okra pod gum while cohesive for sesame leaf gum. Compressibility Index 36.4 and 21.3 fair flow for okra pod gum and extremely poor flow for sesame leaf gum as seen in. Olorunsola *et al*., (2021).

Comparison of Proximate Analysis

Table 1 also clearly shows the comparative proximate analysis of both sesame leaf gum and okra pod gums. Sesame leaf gum has higher oil/lipid, moisture content and protein content of 1% against 0.75%, 8.5% against 8% and 0.193% against 0.047% of okra pod gum respectively. While okra pod gum has higher ash and fibre content of 90% against 76% and 1.83% against 1.77% of sesame pod gum respectively. The pH of sesame leaf gum was 6.41 while that of okra pod gum was 7.16. This shows that little or no buffering may be required for external applications with reference to the pH but additional purification of the gums is needed for the polymers to exact their full functionalities due high fibre content and low ash values.

Solubility of Gums.

Both sesame leaf gum and okra pod gums were insoluble in water, ethanol, methanol, acetone, and isopropyl alcohol over 24 h but effectively formed gel when homogenized. Natural gums are good sources of colloidal system formulations.

Solubility of Metronidazole, Melting Point and Percentage Purity

Slightly soluble in water, pH of a saturated aqueous solution at 30°C is about 6.65. The melting point of the test metronidazole was 175°C with selected detected compound of 1-(2 hydroxy-ethyl)-2-hydroxy methyl-5-nitroimidazole was also active. The drug purity was determined to be 83.52%.

Fourier's transform infrared spectroscopy (FTIR)

FTIR spectra of individual metronidazole and the combination of drug with polymers are shown in Figure 1 and 2. The characteristic peaks of Metronidazole were not changed as the characteristic functional group in the pre-formulation FTIR spectra and in the FTIR spectra of F7 (drug-polymer composite of 5:5:1:1) were unchanged.

X-Ray Diffraction

The X-ray diffractogram of F7 (drug-polymer composite of 5:5:1:1), Figure 3 shows no significant difference when compared with diffractogram of metronidazole benzoate as B type crystallinity occurred at 22° for pure metronidazole and F7. Although some peaks show up in the diffractogram of F7, this may be due to the polymer composite of the formulation.

Scanned Electron Microscopy

The hollow spheres F7 (5:5:1:1) were observed under a Scanning Electron Microscopy. The surfaces were smooth.

Particle Size analysis

The particle sizes range consists of 0.32±0.08 cm to 0.46±0.14 cm shown in Table 4. This falls within the subunit ranges of pellets and minitab of a multiparticulate delivery system that can be tailored for individualized or precision medicine.

Floating Behaviour

As shown in Table 5 the floating lag time was best with F4 and F8 having the worst floating lag time of 129.3±8.1 and 941.7±40.1 seconds respectively. The buoyancy was also best for F4 at 74.5% and worst for F8 which was 10.2%. This implies that despite the bulk density of okra pod gum being denser than sesame leaf gum, it is more rapid in forming a hydrodynamic system (HDS). Incorporation of fluffy sesame leaf gum enhanced permeation of the polymer composite to thus making the hollow spheres less buoyant.

Bio-adhesion

Though F8 (drug: polymers composite 4:4:1:1 of all polymers) exhibited poor floating property and this is likely due to the water permeation property of sesame leaf gum that allows for quick weight increase, the bio-adhesion of F7 (drug: polymers composite 5:5:1:1) was good as the time of detachment was the highest and may likely be through the combined effects of sesame leaf and okra pod gums. F1 (drug: polymers composite 10:10:3) of sesame leaf blend was the first to be detached from the mucosa; this may be attributed to weak hydrogen bonding between the polymers and the wall of the mucosa.

Drug Content, Entrapment Efficiency and % Yield

Table 4 shows the actual drug content of F1-F8 with F2 (polymer composite of 5:2 sodium alginate and sesame leaf gum) and F8 (polymer composite ratio of 5:1:1 of sodium alginate, sesame leaf gum and okra pod gum) having entrapment efficiency above 50%. The percentage yield of the hollow spheres ranges from 19.6% to 30.3%. F6 (polymer composite ratio of 5:2 of sodium alginate and okra pod gum) was reported with the highest swelling index of 107.2 this implies that allowable water incorporation for wet granulation is large and permeation for drug release through diffusion is an advantage.

Dissolution studies

As shown in Figure 6, the amount of drug released over 24 h maintained a narrow range of 4.1-7.9 mcg/ml for F1-F8 with F4 (hollow spheres containing metronidazole 4% w/v plus sodium alginate 4% w/v plus okra pod gum 1.2% w/v) skewed only at 21 h with a release of 11.7 mcg/ml.

Best Fit Model of Kinetic Release Mechanism

The comparative zero order release kinetics of formulations are shown in Figure 7-9, F1 vs F5, F3 vs F4 and F5 vs F7 are highly correlated in the zero-order kinetics. Higuchi's model is the best fit kinetics (Fig. 13). The release series is thus, F5<F3<F6<F7=F2<F8<F1 based on the regression coefficient. The mechanism of drug release based on Korsmeyer-Peppas exponential equation Table 3.2 is quasi-fickian diffusion with n<0.5.

6. CONCLUSION

The metronidazole loaded hollow spheres produced with polymer composite ratios of sodium alginate and sesame leaf gum or okra pod gum 2:1, 5:2, 10:3 and a combination of all polymers in 5:1:1 and 4:1:1 were swellable and sustained release over 24 h maintaining a narrow range of 4.1-7.9 mcg/ml per time. It follows Higuchi's release model in which the amount of drug released is proportional to the square root of time and the mechanism of drug release was quasi-fictian diffusion. The best bio-adhesive formulation was F7 (polymer composite of 5:1:1 of sodium alginate, sesame leaf gum and okra pod gum) while best floating behavior was exhibited by F4 (polymer composite ratio of 10:3 sodium alginate and okra pod gum) with floating buoyancy of 74.5%

Abbreviations

DSC – Differential Scanning Calorimetry, DDS – DRUG Delivery System, ER – Extended Release, F1 to F8 – Formulations of metronidazole, FTIR – Fourier's Transformed Infrared spectroscopy, GIT – Gastro-Intestinal Tract, HDS – Hydrodynamic System, IR – Immediate Release, MP – Multiparticulate, MDDS – Multiparticulate Drug Delivery System, MPDDS - Multiparticulate Drug Delivery System, PID – Pelvic Inflammatory Disorder, SEM – Scanning Electron Microscopy, SR – Sustain Release, STD – Sexually transmitted Disease, UTI – Urinary Tract Infection, WHO – World Health Organization, XRD – X-ray Diffraction

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Authors' contributions

All authors have read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Competing interests

The authors declare that they have

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