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Research Article
Formulation and Evaluation of Effervescent Floating Matrix Tablets of a Biguanide Using *Grewia mollis* Gum.

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Abstract

Background and Objective: The objective of this study was to formulate an effervescent floating drug delivery system of metformin using *Grewia mollis* gum in order to achieve extended release and improve its absorption at the site of action. **Materials and Method:** Effervescent floating matrix granules of metformin were formulated by wet granulation method using the extracted natural gum at different concentrations (2, 4, 6 and 8% w/w). Sodium bicarbonate (30%) and tartaric acid (5%) were added as the gas generating agents. All granules were analyzed for micromeritic properties. Granules were compressed at an optimized compression pressure of 35 arbitrary unit on the tableting machine load scale. Tablets were evaluated for hardness and *in vitro* buoyancy test. Drug-excipient compatibility study was done using Fourier Transform Infra-red spectroscopy (FTIR). **Results:** All the formulated Gastroretentive Floating Matrix (GRFM) granules were free flowing with angle of repose and Carr's index $\leq 31^{\circ}$ and $\leq 14\%$, respectively. The floating lag time for GRFM tablets formulated with *Grewia mollis* was ≤ 610 sec. All GRFM granules were compressible with tablet hardness between 2.0-7.3 KPa. There was a significant difference in tablet hardness with increase in binder concentration ($p<0.05$). Generally, GRFM tablet percentage friability decreased with increase in binder concentration ($\leq 0.98\%$). The FTIR studies shows that the excipients and the Active Pharmaceutical Ingredient (API) i.e., metformin were compatible. **Conclusion:** *Grewia mollis* gum has been exploited in the formulation of gastro-floating matrix tablets of metformin which may find useful application for drugs that have narrow absorption window in the upper part of the gastrointestinal tract (GIT).

Key words: Effervescent, *Grewia mollis* Gum, metformin hydrochloride, buoyancy

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Gastroretentive drug delivery systems (GRDDS) are retained in the stomach after oral administration and release their active ingredients there in a controlled and sustained manner, such that the drug is released continuously to its site of absorption in the upper part of the Gastrointestinal Tract (GIT)[1].

Floating dosage forms can remain in the stomach for a long time and hence markedly increase the gastric residence time of drugs. Increased gastric retention increases bioavailability, reduces side-effect and increases the sustained delivery of drug thereby reducing the frequency of dosing which in turn improves patient adherence to therapy[2]. It is also suitable for targeted delivery of drug to the stomach and the proximal part of the small intestine making it appropriate for the local treatment of diseases in the region e.g., anti-ulcer drugs, antibacterial for *Helicobacter pylori* infection[3].

Over the years, extensive research has been done and still ongoing both in the academia and industry on drug delivery systems designed to be retained in the stomach and proximal small intestine because these systems help to provide new products with sustainable therapeutic activity and substantial benefits to the patient[4]. Examples of these systems include mucoadhesive and bioadhesive systems, swelling and expanding systems, floating systems, modified systems and high density systems[5].

Metformin is an oral anti-hyperglycemic agent used in the management of type II diabetes mellitus or non-insulin dependent diabetes mellitus (NIDDM). Diabetes mellitus is a syndrome typified by chronic increase in blood sugar level and disturbances of carbohydrate, fat and protein metabolism associated with deficiencies in insulin secretion or insulin resistance[6]. Effervescent floating drug delivery system of metformin can be retained in the stomach due to its lower bulk density than the gastric fluid and stay afloat in the upper part of the GIT for a long period of time without affecting the gastric emptying rate of other contents. Metformin hydrochloride belongs to the class of biguanide and it is one of the first line of treatment in combination with a sulphonylurea in the management of chronic non-insulin diabetes mellitus in adults[7].

Grewia polysaccharide gum is obtained by extraction from the inner stem bark of the edible plant *Grewia mollis* Juss. (Fam. Tiliaceae). Grewia polysaccharide gum grows abundantly in the middle belt region of Nigeria where it is found growing wild or cultivated and is used as a food delicacy by the local people. The gum has been isolated and some of its physicochemical properties have been evaluated[8]. The polysaccharide gum consists of glucose and rhamnose as the main monosaccharide components and galacturonic acid as the main sugar acid[8]. Grewia polysaccharide gum may provide an alternative to other natural polysaccharide or their synthetic counterparts and save foreign exchange in the regions of the world where it is in abundant supply.

The binding[9], bioadhesive[10] and mechanical[11] properties of the gum have been reported. However, its use as a matrix former in the formulation of floating drug delivery system has not been investigated. The aim of this study was to formulate a floating drug delivery system of metformin using the effervescent method which can prolong the release of the active ingredient in the upper part of the GIT for up to 10 h.

MATERIALS AND METHODS

This study was carried out at the laboratory of the Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, University of Benin, Benin, Nigeria and the total time duration of the research work was 6 months (from June-December, 2018). The active pharmaceutical ingredient (API) used in the study as drug model was metformin (Cipla Ltd, Goa, India), Eudragit RL_{100} was received from Rhoma Pharma, Darmstadt, Germany, *Grewia mollis* Gum. (GMG) mucilage was used as a matrix former and was extracted by method described previously[10]. Sodium bicarbonate and tartaric acid were used as gas generating agents. All other chemicals were of analytical grades.

Evaluation of the granules: The packing properties were obtained by measuring the bulk density (BD) and tapped density (TD) using standard procedures[11] and values were obtained using Eq. 1 and 2, respectively. From the resulting data, Carr's Index (CI)[12] was determined using the Eq. 3:

$$\text{Bulk density } \left(\text{g cm}^{-3}\right) = \frac{\text{Mass of granules}}{\text{Initial volume of granules}} \quad (1)$$

$$\text{Tap density } \left(\text{g cm}^{-3}\right) = \frac{\text{Mass of granules}}{\text{Tapped volume of granules}} \quad (2)$$

$$\text{CI} = \frac{\text{TD} - \text{BD}}{\text{TD}} \times 100 \quad (3)$$

The flow properties of the granules were determined by measuring the angle of repose formed when a sample of the granules (15 g) was allowed to fall freely through the stem of a funnel onto a plain bench surface[13]. The angle of repose was determined using Eq. 4. Talc was then incorporated extra granularly and the granules compressed into tablets using a single punch tableting machine:

$$\theta = \text{Tan}^{-1}\, h/r \quad (4)$$

where, θ is the angle of repose, h is the height of powder heap in cm, r is the radius of base of the heap in cm.

Preparation of gastroretentive floating matrix tablets of metformin: A Manesty Single Punch Tableting Machine (Type F3 Manesty Machines, UK) was used to produce the tablets. Talc (1%) was added as a glidant. The gastroretentive floating matrix granules equivalent to 500 mg of metformin were placed in the die and compressed at a pressure of 35 arbitrary units on the load scale to formulate. A constant pressure was maintained for all the batches of metformin tablets produced. The batch size was 50 tablets and the tablet target weight was 750 mg. The resulting tablets were collected, dusted and stored in an air tight jar containing activated silica gel as a desiccant (Table 1).

Table 1: Formula for the GRFMTs

Ingredients	Quantity
Metformin powder	500 mg
Grewia mollis Gum	2, 4, 6, 8% w/w
Eudragit RL_{100}	1%
Sodium bicarbonate	30%
Tartaric acid	5%
Talc	1%
Lactose	Qs

Evaluation of gastroretentive floating matrix tablets (GRFMTs)

Tablet hardness and friability: The tablet hardness was gotten from diametrical compression using the Campbell Electronics Hardness tester machine (HT-30/50, India). The pressure needed to break a tablet placed in the anvil of the hardness tester was determined. Ten tablets were used for the determination. The mean value and standard error of mean were recorded. Ten tablets were randomly selected for the friability test using the Roche Friabilator (Erweka Germany). The initial weight of the tablets was determined before they were placed in the friabilator. The friabilator was allowed to operate at 25 rpm after which the final weight of the tablets was determined. These values were used to calculate the percentage friability using Eq. 6:

$$\text{Friability (\%)} = \frac{w_1 - w_2}{w_1} \times 100 \quad (6)$$

where, w_1 and w_2 are initial weight and final weight of the tablets, respectively.

Floating lag time (FLT) and *in vitro* buoyancy test: The method described by Jimenez-Castellanos *et al.*[14] was adopted. A 1000 mL beaker was filled with 900 mL simulated gastric fluid (0.1 N HCl). A tablet was placed inside the beaker and the media kept stagnant at 37±2°C. The picture was taken and the time required for the tablet to rise and float on the surface was determined as the floating lag time. The time duration for which the tablet floated and remained afloat without breaking was determined as the *in vitro* buoyancy time.

***In vitro* dissolution studies and drug release kinetics:** The paddle method was used. Dissolution studies were performed using 900 mL of 0.1 N HCl as the dissolution medium maintained at 37±1.5°C. One tablet was immersed in the dissolution medium. The dissolution fluid was stirred at 100 rpm with the dissolution paddle. At pre-determined time intervals (5, 10, 15 and 30 min; 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 h), 5 mL samples of the leaching fluid were withdrawn using a pipette fitted with a cotton wool plug. Equal amount of fresh dissolution medium kept at the same temperature was used to replace the withdrawn sample. The withdrawn samples were filtered, adequately diluted and their absorbances determined with a UV/Visible spectrophotometer at a maximum wavelength (λ_{max}) of 218 nm. The determination was carried out in triplicate and the mean results reported. The corresponding amount of metformin released at any time t, was then computed from the standard calibration curve.

The data gotten from the dissolution studies of the floating matrix tablet of metformin were subjected to various drug release kinetics to determine the pattern of release kinetics. The models include: Zero order, first order and Higuchi square root of time relationship[15]. The mechanism of drug release from the formulation was obtained using Korsmeyer and Peppas model[16,17]. The linear regression coefficient (r^2) for each rate order was computed. The dissolution profile was considered to have followed a specific release[18] order if the r^2 value was >0.95.

Drug-excipients compatibility study

Fourier transform infra-red (FTIR) studies: In order to check for incompatibility, the optimised formulations were subjected to FTIR studies using the Fourier Transform Infrared Spectrophotometer (Spectrum BX, Perkin Elmer, Beaconsfield Bucks, England). The potassium bromide (KBr) pellet method was used. About 5 mg of the sample was blended with KBr to 200 mg. The powder was compressed using a sigma KBr press into a tablet shape. The tablet was placed in the sample compartment and the IR can was read. The pure samples, physical mixtures and the optimized tablet (8% w/w grewia gum) formulations were scanned at a range of 4000-500 cm^{-1}.

Statistical analysis: The data obtained were recorded as mean±standard error of mean (SEM). All the data were subjected to Student t-test statistical analysis to test for significance of difference. The $p<0.05$ was considered to be significant.

RESULTS

Pre-compression parameters

Micromeritic studies of the floating granules: The results of the flow properties of the granules formulated by different concentrations of GM gum mucilage are shown in Table 2. All the granules produced with GM gum had angle of repose ranging from 25.0-31.0° while Carr's index values ranged from 11-14%. The Hausner's ratio was between 1.12-1.16.

Post-compression parameters

Evaluation of binder concentration on the physicochemical properties of gastroretentive floating matrix tablets (GRFMTs) of metformin: The result of the effect of different binder concentration on the physicochemical properties of GRFMTs of metformin formulated with GM gum is shown in Table 3. The floating matrix tablets formulated using GM gum had tablet hardness value between 2.0-7.3 Kpa. The friability test values for the GRFMTs formulated with GM gum mucilage were ≤0.97% (Table 3).

Effect of the gum concentration on floating lag time (FLT) and *in vitro* buoyancy studies: The results of FLT and *in vitro* buoyancy studies on GRFMTs of metformin formulated with GM gum mucilage are presented in Table 4. The GRFMTs formulated using GM gum displayed a FLT between 180-610 sec.

The pictorial view of the *in vitro* buoyancy characteristic of FMT formulated with GM gum is presented in Fig. 1 which shows when the tablet was immersed in the simulated gastric fluid. Figure 1a shows when the tablet was immediately immersed in the fluid, Fig. 1b and c shows when the carbon (iv) oxide was generated thereby imparting buoyancy on the tablets causing the tablet to overcome the force of gravity and floats while Fig. 1d shows when the tablet remain afloat on top of the simulated gastric fluid over a long period of time releasing the active ingredient form the matrix system.

Table 2: Micromeritic properties of the gastroretentive floating matrix granules of metformin prepared with *Grewia mollis* Gum and Eudragit® RL_{100}

G. mollis: Eudragit® $RL_{100\ (\%w/w)}$	Bulk density (g cm^{-3})	Tap density (g cm^{-3})	Angle of repose (°)	Carr's index (%)	Hausner's ratio
GM1	0.49±0.02	0.56±0.01	31.0±1.0	13±1.7	1.14±0.02
GM2	0.49±0.01	0.57±0.02	25.8±1.2	14±1.0	1.16±0.01
GM3	0.49±0.01	0.55±0.02	25.0±1.1	11±1.0	1.12±0.01
GM4	0.47±0.02	0.53±0.01	29.1±1.0	11±1.7	1.14±0.03
GM5	0.43±0.01	0.48±0.02	26.6±1.3	11±1.0	1.12±0.02

GM1 (GMG alone), GM2 (2:1), GM3 (4:1), GM4 (6:1), GM5 (8:1)

Table 3: Some physicotechnical properties of metformin tablets (Hardness and Friability, n = 3)

G.mollis: Eudragit®RL_{100}(% w/w) formulation	Hardness (KPa)	Friability (%)
GM1	2.0±0.12	0.97±0.01
GM2	2.8±0.10	0.91±0.01
GM3	4.9±0.17	0.86±0.02
GM4	6.2±0.10	0.82±0.01
GM5	7.3±0.15	0.78±0.02

Table 4: Floating lag time and *In vitro* buoyancy values of GFMTs using GMG

Formulation concentration of GMG: Eudragit® RL_{100}	GM1	GM2	GM3	GM4	GM5
Floating lag time (sec)	180	365	495	520	610
Buoyancy time without rupture of tablet (h)	<12	>12	>12	>12	>12

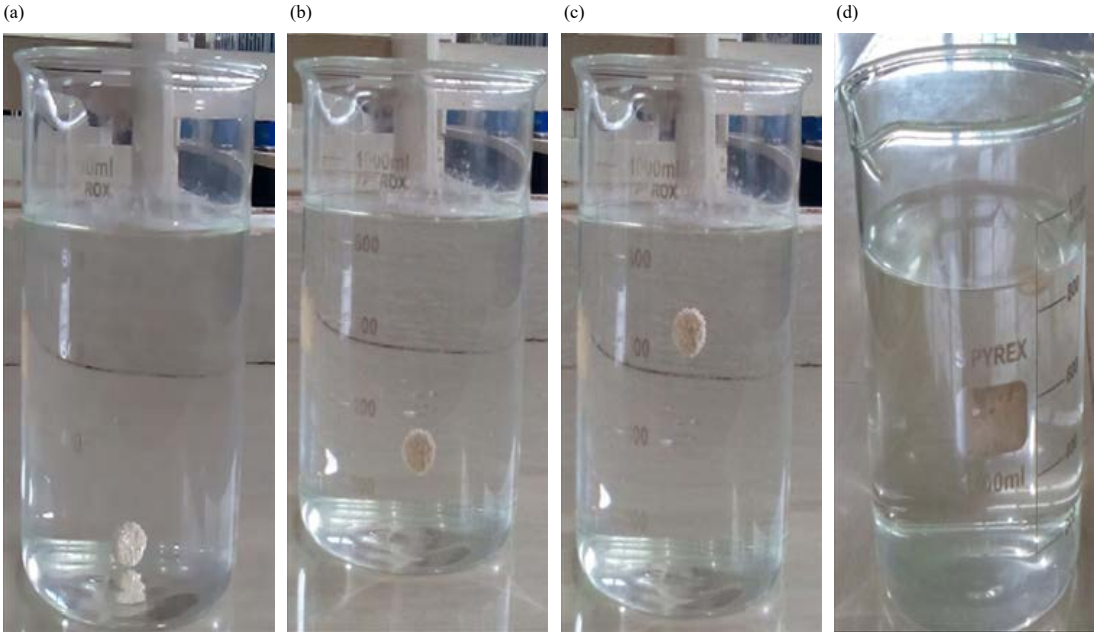

Fig. 1(a-d): Photographs showing the *in vitro* buoyancy characteristics of GMG (a) Photograph taken immediately after placing the tablet into the beaker, (b and c) Photographs taken during the intermediate stages of tablet floating and (d) Photograph taken immediately after the tablet floated onto the surface indicating a floating lag time of 495 sec

Table 5: Dissolution parameters of gastro-floating metformin tablets formulated with *Grewia mollis* Gum (m_∞%), (t_∞hr), (m_∞/t_∞)

GMG: Eudragit® RL_{100} (%w/w)	m_∞ (%)	t_∞ (h)	m_∞/t_∞ (% h^{-1})
GM1	98	4	24.5
GM2	93	6	15.5
GM3	91	9	10.1
GM4	84	10	8.4
GM5	87	10	8.7

m_∞ (%): Maximum release, t_∞ (h): Time to attain maximum release, m_∞/t_∞ (%h^{-1}): Dissolution rate

Table 6: Correlation coefficient and release kinetics of GRFMT of metformin (n = 3) prepared with varying concentrations of GMG

	Zero		First		Higuchi		Korsmeyer and Peppas	
Models								
Formulations	r^2	K_0	r^2	K_1	r^2	K_H	r^2	n
GM1	0.80	25.43	0.94	-0.48	0.95	47.64	0.95	0.51
GM2	0.84	23.05	0.94	-0.25	0.98	38.95	0.98	0.48
GM3	0.83	24.25	0.96	-0.13	0.98	31.41	0.97	0.46
IG4	0.86	21.92	0.95	-0.11	0.99	28.71	0.96	0.46
IG5	0.90	19.46	0.97	-0.09	0.99	28.14	0.98	0.47

Release profile of GRFMTs of metformin: The results of the dissolution parameters are presented in Table 5. For instance, maximum drug released (m_∞), time to achieve maximum release (t_∞) and dissolution rate (m_∞/t_∞) for batch GM1 was 98%, 4 h and 24.5% h^{-1}, respectively while the corresponding values for batch GM5 was 87%, 10 h and 8.7% h^{-1}.

Release kinetics of the GRFMTs of metformin: The data gotten from the *in vitro* release studies were subjected to zero order (cumulative percent drug released against time), first order (log of percent drug unreleased against time), Higuchi's (Percent drug released against square root of time) and Korsmeyer and Peppas (log of percent drug released against log of time) equations. The results of the release kinetics obtained from GRFMTs are shown in Table 6.

Results of compatibility studies: The results of the drug-excipient compatibility studies are presented in Fig. 2. It was observed that there were no obvious changes in peaks due to the presence of other excipients and also due to compression to final tablets. This indicates that the active ingredient (metformin) and the other excipients were compatible.

DISCUSSION

The results of the flow properties show that all the granules displayed good flow which is very vital in ensuring content and weight uniformities during tableting. Hence, the evaluation of all these pre-compression parameters provides a means of monitoring batch to batch variation.

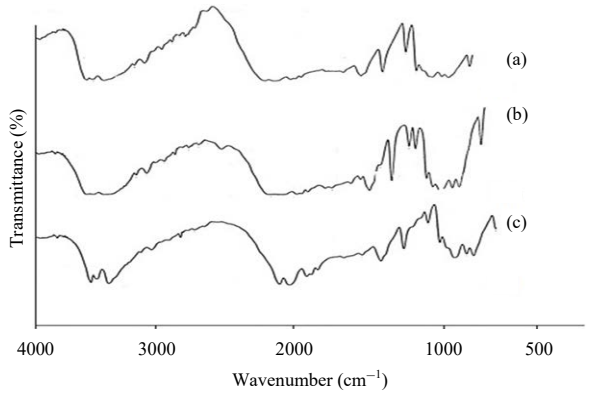

Fig. 2: FTIR Spectra of (a) Pure metformin sample, (b) 8% w/w tablet formulation and (c) Admixture of metformin, grewia gum, sodium bicarbonate and tartaric acid

Tablet hardness is an indication of the ability of the tablet to withstand pressure. It was noticed that with an increase in the binder concentration of the GM gum there was a significant increase in the hardness of the tablet ($p<0.05$). This could be due to the fact that binders, when incorporated provide cohesive binding of particles and hence making sure that granules and tablets with the desired mechanical strength are formulated[19].

The friability values decreased with an increase in the GM gum concentration and they were within the official standard limit (<1%) which is a sign of good mechanical strength of the tablets. This friability result also shows the ability of the tablet to withstand mechanical stress during packaging, transportation and storage[20].

It was observed that an increase in the concentration of the GM gum caused a significant increase in the FLT. This may be due to an increase in the inter-particulate cohesive forces acting within the floating tablet matrix attributed to enhanced binding properties of the GM gum. The floating matrix tablets in batch GM1 were found to have a very short FLT (180 sec) compared to the other batches. The reason for this significant time difference could be because the batch GM1 contains only 2% w/w of GM gum mucilage without the incorporation of 1% w/w Eudragit® RL_{100} which serves to sustain the integrity of the tablets. The polymer Eudragit® RL_{100} increased the adhesion and compaction of the particles within the tablet matrix as shown by the increasing FLT of batches GM2-GM5. The indication is that the binding ability of the GM gum increased the FLT[20].

Sodium bicarbonate and tartaric acid were used to achieve effervescent. Sodium bicarbonate generated carbon (iv) oxide in the presence of the dissolution medium (0.1 N HCl). The carbon (iv) oxide gas released is trapped inside the gel formed by hydration of the polymers within the tablet, hence lowering the density of the tablet[21]. The *in vitro* buoyancy of GRFMTs was induced by the gas generating agents without compromising the matrix integrity. Batch GM1 showed buoyancy duration without rupture of <12 h while the other batches showed buoyancy duration of >12h. This may have been due to the reduced binder effect of GM gum alone in comparison to the additive binder effect observed with the addition of Eudragit RL_{100} (batches GM2-GM5). The indication is that the addition of Eudragit RL_{100} helped to increase the integrity of the tablet formulation therefore showing buoyancy duration[20] of >12 h.

The *in vitro* drug release from batch GM1 tablet formulated using 2% w/w of the GM gum mucilage alone exhibited a faster release of drug content compared to the other batches containing Eudragit® RL_{100}. For example, batch GM1 released about 98% of its drug content within 4 h while batches GM2-GM5 released about 70-85% of the drug contents for up to 10 h. Thus, there was a more sustained release of drugs from batches GM2-GM5. This indicated that drug release from batch GM1 of the GRFMTs produced using 2% w/w of the GM gum alone displayed a faster release of drug content compared to the other batches containing GM gum and 1% w/w Eudragit RL_{100}. It was equally observed that there was a significant retardation in the release profile of the GRFMTs as concentration of the gums increased. The higher the concentration of the gums, the slower the drug release from the matrix system studied. This revealed that the release profile from the GRFMT depended on the concentration of the gum[7].

It was observed that all the formulations did not follow a zero order release behavior since the plot exhibited poor linearity with regression values (r^2) ranging from 0.80-0.90. When data were plotted as per first order equation, the formulations showed a fair linearity with regression values r^2 ranging between 0.94-0.97. This means that the amount of drug released was influenced by the extent of drug left in the system. The *in vitro* release profiles of all the floating matrix tablets were also subjected to Higuchi's equation. The plot presented higher linearity with regression values, r^2 ranging between 0.95-0.99 for batches GM1-GM5. This showed that release kinetics for batches GM1-GM5 was in line with this model since it gave higher correlation values when compared to the other models analyzed. This established the fact that the drug release from the GRFMT was predominantly by Higuchi model which states that the quantity of drug released is dependent on the square root of time. Previous researchers have reported similar findings with matrix tablets using different polymers[22].

The mechanism of drug release was determined by fitting the data into Korsmeyer *et al.*[16] and Peppas[17] equation. Their r^2 values ranged between 0.95-0.98 while their release exponent (n) was between 0.46-0.51. This means that diffusion was the main mechanism of drug release from these dosage forms. Formulations GM1 to GM5 have their release exponent (n) >0.45, hence, their release mechanism was by Non-Fickian diffusion. It was previously reported by Darunkiasorn and Phaechamud[23], that the release of drug from polymeric matrix systems was by diffusion mechanism[20].

CONCLUSION

The GRFMTs of metformin has been formulated using GM gum mucilage. The formulated gastroretentive floating matrix tablets can extend the medication for up to 10 h. This could be used in the design of sustained drug release formulation for drugs with short biological half-life and narrow absorption window in the stomach.

SIGNIFICANCE STATEMENT

This study discovered that *Grewia mollis* Gum can be used in the formulation of gastro floating drug delivery system of metformin and this can be beneficial in the formulation of controlled release dosage form of metformin which will increase the adherence of diabetic patients to the medication. This study will help the researchers to explore this natural gum in the formulation of floating drug delivery system of metformin that many researchers were not able to explore. Thus a new natural polymer and binder in the formulation of sustained drug release may be arrived at.

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