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DESIGN AND *IN VITRO* EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF METFORMIN PRODUCED USING DETARIUM MICROCARPUM GUM

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ABSTRACT

Objective: The objective of this study was to evaluate sustained release matrix tablets of metformin formulated using *Detarium microcarpum* gum (DMG) as the matrix polymer.

Methods: DMG was produced by acetone desolvation of the filtrate obtained by maceration of powdered seeds of *Detarium microcarpum* in distilled water. Metformin matrix tablets were prepared by direct compression technique using DMG or sodium carboxymethylcellulose (NaCMC) alone, or their combinations as the polymer matrix. The tablets were evaluated for hardness, friability, weight uniformity, drug content, swelling behaviour *and in vitro* dissolution. They were compared to a marketed product.

INTRODUCTION

Extended or sustained-release products are formulated to make the drug available over an extended period after ingestion. This allows a reduction in dosing frequency compared to a drug presented as a conventional dosage form [1-3]. Properly designed sustained release dosage form provides benefits such as low-cost, simple processing, improved efficacy, reduced adverse events, flexibility in terms of the range of release profiles attainable, increased convenience and patient compliance [4-6]. Extended-release can be achieved through several methods such as matrix formation [7], floating drug delivery system [8], mucoadhesive drug delivery system [9], and microencapsulation [10], but the hydrophilic matrix is one of the least complicated methods for formulating an extended-release preparation. Hydrophilic matrix polymers include hydroxypropyl methylcellulose (HPMC), hydroxyethylcellulose (HEC), hydroxypropyl cellulose (HPC) and sodium

carboxymethylcellulose (NaCMC). The transport phenomena involved in the drug release from hydrophilic matrices are complex because their microstructure and macrostructure, when exposed to water, are strongly time-dependent. When they come in contact with the gastrointestinal fluid, they swell, gel, and ultimately dissolve slowly (matrix erosion) [2, 6, 7, 11]. The gel forms a viscous layer, which acts as a protective barrier that regulates the influx of water and the efflux of the drug in solution. The dissolution can be diffusion controlled depending on the molecular weight and thickness of the diffusion boundary layer [2, 3].

Detarium microcarpum, Guill. and Perr. (Fabaceae) is a wild plant found in some parts of the semi-arid sub-Saharan and tropical zones of Africa. The seeds are edible and are used for the thickening of soups in some parts of Nigeria. It possesses unique characteristic behaviour in hot water, displaying different degrees of the viscoelastic properties. It has been reported to contain a high concentration of water-soluble non-starch polysaccharide, which is mainly xyloglucan [12].

Metformin is an oral anti-hyperglycemic drug used in the management of non-insulin-dependent diabetes mellitus (NIDDM). It is the only available biguanide. It improves glucose tolerance in NIDDM subjects, lowering both basal and postprandial plasma glucose. It reduces hepatic glucose production, lowers intestinal absorption of glucose, and increases insulin sensitivity. Metformin in contrast to sulfonylureas, does not cause hypoglycemia in either diabetic or nondiabetic subjects and does not produce hyperinsulinemia [13]. Metformin is a highly hydrophilic drug and its oral bioavailability is 50 to 60% [14, 15]. It has a plasma elimination half-life of 6.2 h with a peak plasma concentration of 4.8 h [14].

The aim of this study was to evaluate sustained release matrix tablets of metformin formulated using *Detarium microcarpum* gum as the polymer matrix former. *Detarium microcarpum* is found abundantly in the Southeast region of Nigeria and the use of the gum in matrix tablet production will result in great economic benefit to the region.

MATERIALS AND METHODS

Materials

All the chemicals used were of analytical grade. They include metformin (Kores Chemical Ltd, India), microcrystalline cellulose (Avicel-PH 101) (FMC Biopolymer, Philadelphia, USA), sodium carboxymethylcellulose (BDH Chemicals Ltd Poole England), acetone (Guangxing Guanghua Chemical, China) and magnesium stearate (Kem Light Chemicals Ltd, Mumbai, India), potassium dihydrogen orthophosphate, dipotassium hydrogen phosphate (BDH Chemicals Ltd Poole England), hydrochloric acid (JHD, Guangdong Guanghua Chemical Factory Co. Ltd., Shanfua, Guangdong, China).

Methods

The study was carried out by isolation of DMG, drug–excipients compatibility studies, drug/excipients-mix micromeritics studies, preparation of sustained-release metformin matrix tablets, evaluation of sustained-release metformin matrix tablets, kinetics and mechanism of drug release, and analysis of data.

Isolation of *Detarium microcarpum* gum

Seeds of *Detarium microcarpum* were bought from Ogbete market in Enugu, Nigeria. They were identified by Mr. Felix Nwafor a taxonomist in the Department of Pharmacognosy and Environmental Medicine, Faculty of Pharmaceutical Sciences, University of Nigeria, Nsukka, Nigeria. The sample was deposited in the herbarium with voucher number PCG/UNN/0067. The gum was extracted using the method of [16] with slight modification. The seeds were dried and ground to powder. A 200 g quantity of the powder was macerated in 1.5 litres of distilled water for 24 h. The filtrate was precipitated with equal volumes of acetone. The precipitated gum was washed twice with acetone, air-dried and kept in an airtight container. The percentage yield of the gum was calculated using equation 1.

$$\text{Percentage yield (\%)} = \frac{\text{weight of the dry gum (g)}}{\text{weight of the ground seed powder (g)}} \times 100\% \quad \ldots. (1)$$

Drug–excipients compatibility studies

This was evaluated using Fourier transformed infrared (FTIR) spectroscopy operating between 4000 and 600 cm^{-1}. Sampling was done using the potassium bromide pellets technique.

Micromeritics of the drug/excipients mix

The bulk density and tapped density of the drug/excipient mix for the different formulations were determined and were used to calculate the Carr's index and Hausner's ratio.

Bulk density

A 10 g quantity of the metformin–excipient mix was weighed and put in a 25 ml measuring cylinder. The volume was measured and recorded as the bulk volume. The bulk density was calculated using equation 2.

$$\text{Bulk density} = \frac{\text{weight of powder mix (g)}}{\text{Bulk volume of the powder mix (ml)}} \quad \ldots. (2)$$

Tapped density

The metformin powder mix contained in the 25 ml measuring cylinder was tapped 100 times and the new volume was recorded as the tapped volume. The Tapped density was calculated using equation 3.

$$\text{Tapped density} = \frac{\text{Weight of the powder mix (g)}}{\text{Tapped volume of the powder mix (ml)}} \quad \ldots. (3)$$

Carr's index

This was calculated using equation 4.

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{bulk density}}{\text{Tapped density}} \times 100\% \quad (4)$$

Hausner's ratio

This was calculated using equation 5.

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \quad \ldots\ldots (5)$$

Angle of repose

The funnel method was used. The drug-excipient powder-mix was poured through a funnel clamped to a retort stand to form a heap (cone) at the base. The angle the powder-mix made with the base, angle of repose (ɵ) was calculated using equation 6.

$$\text{Tak } \theta = \frac{h}{r} \quad \ldots. (6)$$

Where h = height of the heap (cone) and r = radius of the cone.

Preparation of sustained-release metformin matrix tablets

The metformin matrix tablets were formulated by the direct compression method using the formula on table 1. Metformin was mixed properly with DMG or NaCMC or a combination of the two and MCC. Talc and magnesium stearate were added and mixed lightly for a short period. The metformin/excipient mix was compressed at a

Bulk volume of the powder mix (ml) ... (2)

predetermined pressure using a single punch tablet machine with 13 mm punches (Manesty Machine Ltd, B3B Liverpool, England).

Table 1: Composition of sustained-release metformin matrix tablets

Ingredients	MTF1	MTF2	MTF3	MTF4	MTF5	MTF6
Metformin (mg)	500	500	500	500	500	500
DMG (mg)	160	240	80	120	160	-
NaCMC (mg)	-	-	160	120	80	240
MCC (mg)	116	36	36	36	36	36
Talc (mg)	16	16	16	16	16	16
Magnesium stearate (mg)	8	8	8	8	8	8
Total (mg)	800	800	800	800	800	800

Evaluation of sustained-release metformin matrix tablets

The formulated tablets were evaluated based on their physical characteristics and compared with a marketed product, Glucodix ER® (produced by Stallion laboratories, India, and marketed in Nigeria by Codix Pharma.) used as the control.

Uniformity of weight

Twenty tablets were randomly picked from the formulations and weighed individually. The difference between their weights and their average weight was recorded and used in calculating the percentage weight deviation.

Hardness

Five tablets were randomly selected from the formulations and tested for hardness using a digital tablet hardness test apparatus (Veego tablet test apparatus, India). The readings displayed were recorded.

Friability

Ten tablets selected randomly from the formulation were weighed together and placed in the drum of a friabilator (Veego friability test apparatus, India). They were tumbled for 4 min at 25 rpm, de- dusted, and reweighed. Friability was calculated using equation 7

$$\text{Friability} = \frac{(\text{initial weight} - \text{final weight})}{\text{initial weight}} \times 100\% \quad \ldots (7)$$

Thickness and diameter

Five tablets were selected randomly and their thickness and diameter measured using the thickness and diameter functions respectively of a digital tablet hardness test apparatus (Veego Instruments, India).

Drug content

Ten tablets were randomly selected from each of the formulations, weighed, and crushed in a mortar with pestle, respectively. A quantity of powder that contained the equivalent of 100 mg of metformin was weighed and dissolved in 100 ml of 0.1N HCl. This was filtered through a 0.45-µm filter paper and the filtrate was diluted with 0.1 N HCl to obtain a 10 µg/ml solution. The drug content was analyzed spectrophotometrically at 233 nm using a Carry 60 UV-VIS spectrophotometer (Agilent Technologies, Malaysia). The drug content was determined by matching absorbance value obtained to the calibration curve of metformin.

***In vitro* dissolution studies**

This was done using USP apparatus I (rotating basket). The metformin tablet was placed in the basket immersed in 900 ml of 0.1

N HCl as a dissolution medium in the dissolution chamber. The basket was rotated at 100 rpm and maintained at a temperature of 37±1 °C. Samples (5 ml) were withdrawn after 0.5, 1, and 2 h and replaced with a pre-heated fresh dissolution medium. The samples were filtered, appropriately diluted, and analyzed using a Carry 60 UV–VIS spectrophotometer (Agilent Technologies, Malaysia) at 233 nm. After 2 h, the dissolution medium was changed to phosphate buffer pH 6.8, and samples were taken hourly for 10 h.

Swelling studies

The method used was a slight modification of the method used by [17]. Tablets were weighed individually (W1) and placed in respective Petri dishes. A 25 ml quantity of 0.1N HCl was added to each Petri dish. After 1 h, the 0.1 N HCl was drained and the Petri dish dried using tissue paper. The swollen tablets were reweighed (W2). This process was repeated after 3, 6, 9, and 12 h, respectively. The swelling index (S. I) was calculated using equation 8.

$$\text{Swelling index} = \frac{(W2-W1)}{W1} \times 100\% \quad (8)$$

Where W2 = final weight of tablet and W1 = initial weight of tablet.

Stability studies

Tablets from the optimized formulation (MTF2) were stored in an airtight container and kept in a stability chamber for 3 mo at a temperature and relative humidity of 40 °C±2 °C/75% RH±5% RH. They were evaluated for hardness, friability and *in vitro* drug release.

Kinetics and mechanism of drug release

The kinetics and mechanism of the drug release from the tablets were assessed by fitting the drug release data to the following release kinetic models: Zero-order release model, First order release model, Higuchi square root model, Hixson-Crowell cube root model, and Korsmeyer–Peppas model [18-20] and the most appropriate model was chosen based on goodness of fit test [19].

Analysis of data

Statistical analysis was done using Microsoft Excel and SPSS version 22.0. Data were analyzed by one–way ANOVA. Differences between means were assessed by a two-tailed Student's t–test. $P<0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

The percentage yield for DMG was 76.39±1.17%w/w. The yield was very high and this will make the cost of the gum to be low and affordable.

Micromeritics

The angle of repose, Hausner's ratio and Carr's index for the drug/excipient powder-mix were as shown on table 2. Angle of repose value of less than 25 indicates excellent flow [21] and the value obtained for all the formulations were below 25. Hausner ratio values of less than 1.25 indicate good flow, while greater than 1.25 indicates poor flow. The flow for those between 1.25 and 1.5 can be improved by the addition of glidant [21]. Only formulation MTF6 had Hausner's ratio value of less than 1.25, others were above 1.25 but below 1.5. The Carr's index value of 18 to 21 indicates fair to passable flow, while 23 to 35 shows poor flow [21]. Apart from formulation MTF6 that had Carr's index of 18.77±4.54, others had Carr's index values of between 23.48±1.31 and 26.92±1.20. The flow properties of all the formulations could be improved by the addition of glidant such as 0.2% Aerosil.

Table 2: Powder flow characteristics for the metformin/excipients mix

Formulation code	Angle of Repose (°)	Hausner's ratio	Carr's index
MTF1	24.76±0.94	1.31±0.00	23.81±0.00
MTF2	23.85±0.84	1.37±0.02	26.92±1.20
MTF3	21.43±0.00	1.31±0.02	23.48±1.31
MTF4	21.79±2.27	1.31±0.00	23.81±0.00
MTF5	24.58±1.13	1.31±0.04	23.61±2.08
MTF6	18.75±0.34	1.23±0.07	18.77±4.54

Notes: All data values are expressed as mean±SD, n = 3

Evaluation of tablets

The result shown in table 3 indicated that the friability values of tablets from all the formulations were below 1% and were within specification. Friability is a measure of the tablets' ability to withstand the abrasion that may occur during handling or transportation.

Tablets from all the formulations had hardness values above 4 Kgf. Hardness shows the ability of the tablets to withstand mechanical shocks during further handling and transportation. Tablets having adequate hardness do not usually crack or break when subjected to moderate pressure. Hardness is dependent on the nature and concentration of binder (gum), nature, and concentration of disintegrant and on compression force applied [22].

Metformin tablets should contain between 95% and 105% of metformin active [23]. The drug contents for the different formulations were between 95.11% and 104.17%, and they were all within the specified limits. There was no significant difference ($p<0.5$) between the ideal drug content (100%) and that of the different formulations. When powders are properly mixed according to the tablet composition, the resultant tablets are usually of uniform weight and drug content.

The mean tablet weights for the different formulations were shown in table 3. All the formulations had a percentage mean weight deviation of less than 5% and were within the specified limit. Tablets that weigh more than 250 mg should have a percentage mean weight deviation of not more than 5% [23].

Table 3: The physical characteristics of metformin matrix tablets

Formulation code	Friability (%) n=10	Hardness (kgf) n=5	Thickness (mm) n=5	Diameter (mm) n=5	Weight uniformity (g) n=20	Drug content (%) n=5
MTF1	0.50	8.50±0.75	4.96±0.04	13.01±0.04	0.794±0.008	104.17
MTF2	0.80	9.27±0.69	5.19±0.12	13.04±0.06	0.797±0.005	98.82
MTF3	0.40	14.57±0.52	5.18±0.11	13.05±0.02	0.795±0.006	95.55
MTF4	0.56	13.40±1.76	5.17±0.06	13.01±0.05	0.796±0.009	102.42
MTF5	0.56	10.87±2.48	5.17±0.12	13.06±0.04	0.797±0.007	95.83
MTF6	0.72	11.72±0.19	5.30±0.08	13.10±0.02	0.799±0.007	95.11
Control	0.18	16.13±2.07	5.68±0.08	9.22±0.04	0.661±0.009	96.02

Notes: all data (except friability and drug content), given as mean±SD

Swelling studies

The swelling index for the different formulations is shown on fig. 1. The swelling index for formulation MTF1 was 80% after 1 h, but it started to decline from 3 h. Matrix erosion sets in after 6 h and after 12 h, about 70% of the matrix tablet structure has broken down. The swelling index for formulations MTF2 to MTF6 increased progressively until the 12th hour when there was a decline except for formulations MTF3 and MTF4. The control showed a progressive increase in swelling index even at 12 h. Polymer matrix tablets containing gum that have long swelling time will have their medicaments released relatively slow [24]. Matrix tablets upon contact with water, hydrates, swells, and gels. The more the swelling time, the thicker the gel formed and this results in a longer time taken for the drug to diffuse across the gel. From the swelling studies result shown in fig. 1, it is expected that matrix tablets from formulations MTF2 to MTF6 will have strong release retardant property.

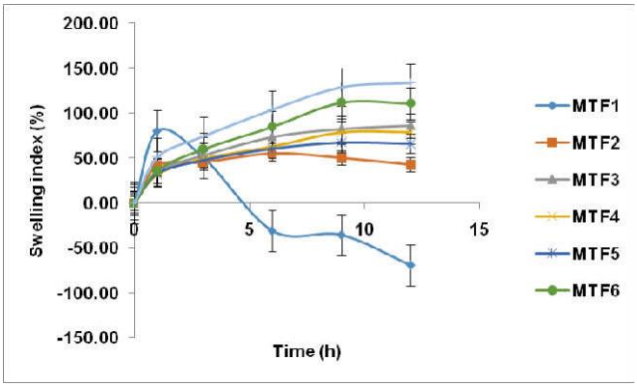

Fig. 1: Swelling behavior of sustained release metformin matrix tablets (mean±SD, n=3), Key: DMG–*Detariummicrocarpum* gum, NaCMC– sodium carboxymethyl cellulose, MTF1 (20% DMG), MTF2 (30% DMG), MTF3 (10% DMG/20% NaCMC), MTF4 (15% DMG/15% NaCMC), MTF5 (20% DMG/10% NaCMC), MTF6 (30% NaCMC)

***In vitro* dissolution studies**

The %drug release of metformin from the sustained release matrix tablets is shown in fig. 2. For formulation MTF1, 51.98% of the drug was released within 0.5 h. Seventy-five percent of the drug was released within 2 h and 100% within 8 h. This shows that formulation MTF1 could not be used for sustained release delivery of metformin. For formulations MTF2 to MTF6, the time for the release of 75% of the drug ranged from 3 to 11 h. The time for 100% release was between 12 h and above. Formulations MTF2 and MTF6 showed good sustained release behaviour, as they released 75% of the drug within 7 to 9 h and 100% release in more than 12 h.

Formulations MTF1 and MTF2 contained 20% and 30% concentration of DMG respectively and as shown in the swelling studies, MTF3 forms a thicker gel and swelling time was longer which resulted in greater drug release retarding effect. Formulations MTF3 to MTF6 that had long swelling time also showed high drug release retarding effects.

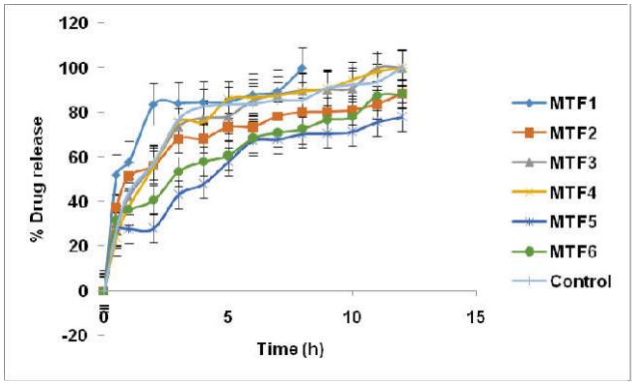

Fig. 2: %Drug release from the sustained release metformin matrix tablets (mean±SD, n=3), Key: DMG–*Detarium microcarpum* gum, NaCMC–sodium carboxymethyl cellulose, MTF1 (20% DMG), MTF2 (30% DMG), MTF3 (10% DMG/20% NaCMC), MTF4 (15% DMG/15% NaCMC), MTF5 (20% DMG/10% NaCMC), MTF6 (30% NaCMC)

Drug–excipient compatibility studies

No significant shifts or reduction in the intensity of the FTIR bands of metformin hydrochloride were observed as shown in fig. 3 and 4. This showed that there was no incompatibility between metformin and DMG. Metformin shows characteristic bands at specific regions of the FTIR spectrum [25]. As shown in fig. 3 and 4, the FTIR spectrum for metformin and that of metformin plus DMG showed typical bands at 3124.4 and 3118.5 cm–1 respectively due to N-H stretching vibration of C = N–H groups (3400–3100 cm-1). A band at 1596.3 and 1597.6 cm-1 was shown by metformin and metformin plus DMG, respectively, for C = N stretching vibrations (1685–1580 cm-1). A band at 2831.6 and 2831.9 cm-1 for metformin and metformin plus DMG respectively representing symmetric CH3 stretching vibration (2885–2865 cm-1) was observed. A weak band (1220–1020 cm-1) representing C–N vibrations for aliphatic compounds was noted at 1038.8 and 1042.7 cm-1 for metformin and metformin plus DMG, respectively.

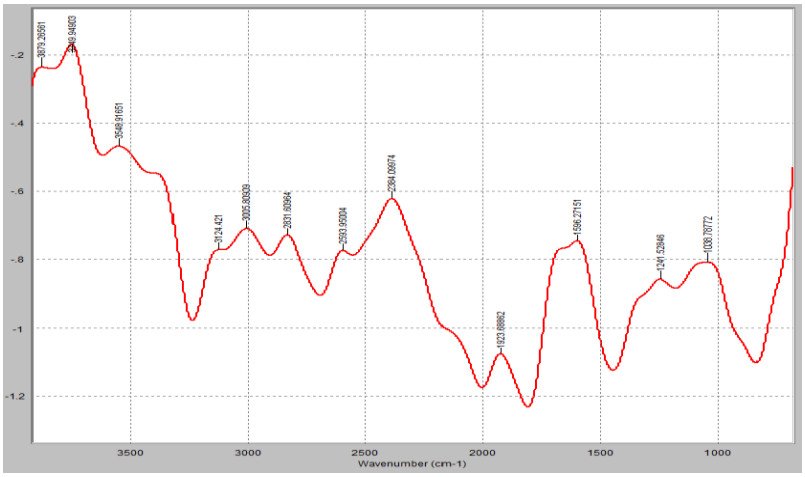

Fig. 3: FTIR spectrum of metformin

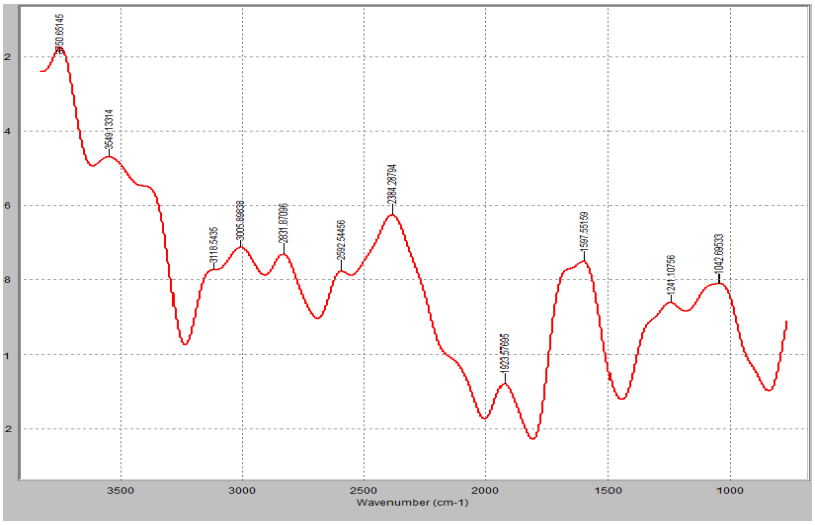

Fig. 4: FTIR spectrum of metformin plus *Detarium microcarpum* gum

Table 4: Kinetic models for the release of metformin from matrix tablets

Kinetic model		**MTF1**	**MTF2**	**MTF3**	**MTF4**	**MTF5**	**MTF6**	**Control**
Zero-order	K0	15.780	9.499	10.700	10.790	8.102	8.942	10.630
	R2	-0.21	-0.26	0.264	0.313	0.581	0.438	0.121
First	K1	0.269	0.136	0.235	0.295	0.115	0.152	0.223
Order	R2	0.768	0.898	0.944	0.930	0.948	0.959	0.919
Higuchi	KH	39.82	28.95	32.24	32.49	24.06	26.70	32.22
Model	R2	0.689	0.724	0.896	0.899	0.955	0.944	0.842
Hixson-	KHC	0.106	0.071	0.076	0.073	0.069	0.066	0.069
Crowell	R2	0.645	0.728	0.858	0.875	0.922	0.870	0.766
Korsmeyer	K	0.692	0.621	0.500	0.473	0.460	0.502	0.515
-								
Peppas	R2	0.240	0.317	0.414	0.444	0.450	0.394	0.399
	N	0.718	0.640	0.761	0.795	0.744	0.704	0.746

Kinetics and mechanism of release The predominant kinetics of release of

metformin from the sustained release matrix tablets, as shown in table 4 was by first- order for all the formulations except for formulation MTF6 where the Higuchi model was also prominent. Higuchi model was the predominant model for formulation MTF5 though the contribution of the first-order model was also prominent.

The mechanism of release was by non-Fickian or anomalous diffusion ($0.45<n<0.89$) [20]. The drug was released by diffusion through the gel formed as a result of hydration of gum and later through erosion of the matrix.

Stability studies

There was no significant difference ($p \leq 0.05$) in friability and hardness values for optimized formulation (MTF2) after 3 mo of storage at 40±2 °C/75±5% RH as shown on table 5. The result as shown in fig. 5 indicated that there was no change in drug release ($p \leq 0.05$) after 3 mo of storage at 40±2 °C/75±5% RH.

Table 5: Stability results for formulation MTF2 after 3 mo at 40±2 °C/75± % RH

Formulation code	0 mo		3 mo	
	Friability (%)	Hardness (kgf)	Friability (%)	Hardness (Kgf)
MTF2	0.80	9.27±0.69	0.77	9.22±1.88

Notes: Hardness data values are expressed as mean±SD, n = 3)

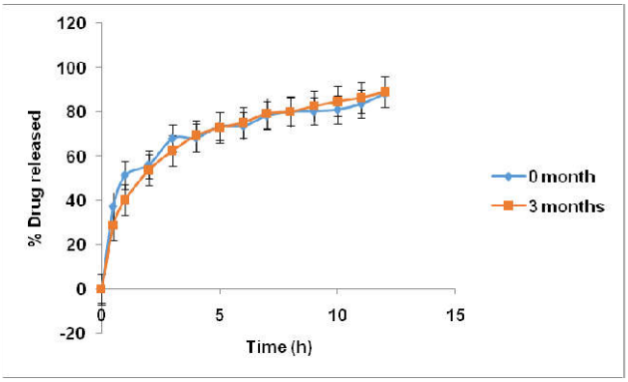

Fig. 5: % drug release from formulation MTF2 at 0 and after 3 mo at 40±2 °C/75±5% RH (mean±SD, n=3), MTF2 (30% *Detarium microcarpum* gum)

CONCLUSION

The yield of gum from *Detarium microcarpum* seeds was very high (76.39±1.17%w/w). DMG did not show any incompatibility with metformin. Matrix tablets of metformin were successfully formulated using different concentrations of *Detarium microcarpum* gum alone or in combination with sodium carboxymethylcellulose as polymer matrix former. Formulations MTF2 (30% DMG), MTF5 (20% DMG and 10% NaCMC) and MTF6 (30% NaCMC) were able to sustain the release of metformin from the matrix tablets for up to 12 h. Accelerated stability studies showed that the formulated tablets were stable.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

No conflict of interest declared.

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