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Preparation and Evaluation of Glibenclamide-loaded Microparticles Using Admixtures of Lipids and Polymer for Improved Oral Delivery

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Abstract: Glibenclamide (GB) is a potent Sulfonylurea used in treating type 2 diabetes mellitus belonging to Biopharmaceutics Classification System (BCS) Class II drugs. This study aimed to design, prepare, and assess glibenclamide-loaded solid microparticles (GSM) for possible improvement of solubility and oral bioavailability. GSM is formulated with a lipid matrix made of Dika wax, goat fat, and polyethylene glycol (PEG 4000) using a hot homogenization method. They were characterized for particle morphology and size, pH stability, encapsulation efficiency, *in vitro* release and evaluated for *in vivo* blood glucose-reducing activities. The morphology and particle sizes showed smooth and spherical particles in the 47.1 ± 0.84 to 66.3 ± 0.58 µm range for the eight batches. The pH of the microparticles was stable. The encapsulation efficiency (%) ranged from 32.1 ± 1.84 to 89.3 ± 0.61. *In vitro* release showed maximum release at 72.30% and 84. 44% for batches A2 and B2 respectively. Maximum blood glucose lowering of 87.65% and 54.24% for batch A_1 and the standard drug after 24 h was observed. This study showed that these microparticles effectively improved the bioavailability of GB as shown by increased hypoglycemic activities.

Keywords: glibenclamide; antidiabetics; blood glucose level; goat fat; Dika fat; microparticles.

1. Introduction

Diabetes mellitus is a metabolic disease that requires both pharmacological and non-pharmacological management to prevent complications such as retinopathy, neuropathy, cardiovascular disease, and nephropathy [1]. The two main types of diabetes mellitus are type 1 diabetes (insulin-dependent diabetes) and type 2 diabetes (non-insulin-dependent diabetes). A serious pathological disorder linked to both categories is hyperglycemia. Over time, it can have several consequences, including cardiovascular and neurological damage. About 95% of diabetic people worldwide have type 2 diabetes, which is the most prevalent kind [2]. GB is a

sulfonylurea-class anti-diabetic medication that has a high level of therapeutic effectiveness in the treatment of type 2 diabetes mellitus [3]. Sulfonylurea derivatives function as insulin secretagogues by inhibiting adenosine triphosphate (ATP)-sensitive potassium channels in the pancreatic islets, prompting insulin secretion [4].

Additionally, these compounds improve the pancreatic ß-cells' ability to respond to insulin [5]. The BCS categorizes GB as a BCS class II drug owing to its high permeability and low solubility [6]. While the drug's high permeability causes several negative effects, its low solubility causes its limited and inconsistent oral bioavailability [7]. The bioavailability of a drug for effective therapeutic response is greatly influenced by its aqueous solubility [8]. Different techniques have been used to enhance the solubility and dissolution characteristics of medications not very soluble in water. Such methods include solid dispersions, cyclo-dextrin complexation, solid self-micro emulsifying drug delivery systems, and micro- or nanoparticles formulations [9-13].

Lately, lipid systems have been used to improve the solubility and bioavailability of GB [14,15]. Much work has gone into employing lipids or polymers to enhance the dissolution of GB, but relatively few have used lipid-polymer hybrids [16]. In this study, we investigated the formulation of GB into lipid-based microparticles containing hydrophilic polymer using different proportions of lipid-matrix and PEG 4000 to enhance oral delivery, increase drug dissolution, and improve aqueous solubility. Given the difficulties in the therapeutic use and effectiveness of GB, such as the low aqueous solubility, poor dissolution rate, low bioavailability, and hypoglycemic adverse effects, [17] the use of a lipid-polymer-based hybrid may be a suitable novel device for the delivery of GB to overcome the solubility and poor dissolution issues related to the drug.

2. Materials and Methods

2.1. Materials.

Polyvinyl alcohol (Sakshi Corp., India), sodium hydroxide, potassium dihydrogen phosphate (KH_2PO_4), and n-hexane (Qualikems, India) were purchased from Jochem Chemicals Nig. Ltd. PEG 4000 (Caryroth, Germany), Glibenclamide (Wako Pure Chemical, Japan), Dika wax and goat fat were extracted from *Irvingia gabonensis* seeds and *Capra aegagrus hircus* respectively. All other reagents and solvents used were of analytical grade.

2.2. Extraction of Dika wax and goat fat.

Irvingia gabonensis seeds were milled in the equipment of the hammer mill type (SFSP-112F, China). Dika wax was extracted using n-hexane by Soxhlet extraction with slight modification [18]. The n-hexane was allowed to evaporate at room temperature. The wax was stored in a refrigerator (4 °C) until used. Goat fat was extracted as described by Nnamani *et al.* [15].

2.3. Preparation of lipid matrix.

A lipid matrix consisting of 1:2 mixture of Dika wax and goat fat extracted from *Capra aegagrus hircus* [15] was prepared by the fusion method. A 30 g quantity of Dika wax and 60 g of goat fat were weighed using an electronic balance (Mettler H8, Switzerland), poured into a crucible, and melted together at 75 °C on a thermo-regulated water bath shaker (WS-100,

England) and stirred thoroughly to obtain an adequate mix. The lipid matrix was allowed to cool and solidify at room temperature.

2.4. Formulation of GSM.

Formulations were optimized by preparing the microparticles with varying amounts of the lipid matrix, surfactant, and polymer (PEG 4000). GB was properly mixed into the melted lipid matrix in each case. The molten lipid matrix containing GB was gently stirred with a magnetic stirrer (SR 1 UM 52188, Remi Equip., India) while the aqueous phase, containing 10 mL of 0.5% $^{w/v}$ PEG 4000 and 5 mL of 1% $^{w/v}$ polyvinyl alcohol (PVA), was added at the same temperature. The mixture was blended with a Probe sonicator (V TECH, Model: VT8723, India) for 5 minutes to obtain the basic emulsion. The resulting GSM was allowed to cool at ambient temperature. After cooling, they were stored in a fridge (4 ºC) until use. The process above was repeated with increasing PEG 4000 concentrations (0.5, 1.0, 1.5, and 2.0%), decreasing lipid matrix amounts (4.5, 4.0, 3.5, and 3.0 g), and decreasing GB concentrations (200 and 100 mg) to produce GSM (A1-A4 and B1-B4). As a control, unloaded GSM (batch C1–C4) without drugs were produced (Table 1).

Table 1. Composition of the solid lipid microparticles.

Formulation (Batch)	PEG 4000 (%)	PVA (1%) (mL)	GB (mg)	Lipid matrix (g)	Distilled water (mL) (q.s.ad).
A1	0.5	5	200	4.5	100
A2	1.0	5	200	4.0	100
A3	1.5	5	200	3.5	100
A4	2.0	5	200	3.0	100
B1	0.5	5	100	4.5	100
B2	1.0	5	100	4.0	100
B3	1.5	5	100	3.5	100
B4	2.0	5	100	3.0	100
C1	0.5	5	-	4.5	100
C2	1.0	5	-	4.0	100
C3	1.5	5	-	3.5	100
C4	2.0	5	-	3.0	100

Key: GB = Glibenclamide, PVA = polyvinyl alcohol, PEG 4000: Polyethylene glycol, q.s.ad. = sufficient quantity to make

2.5. Characterization of the GSM.

2.5.1. Encapsulation efficiency (EE%).

Each formulation's encapsulation efficiency was measured by centrifuging a 5 mL volume of each GSM formulation at 3000 rpm for 60 minutes, resulting in two phases. A syringe was used to measure 1 mL of the aqueous phase, diluted 1000 times with distilled water, and the absorbance of the dilutions was measured with a UV-spectrophotometer (Jenway 6405, UK) at 299 nm, and the EE% was calculated with the following formula: [20]

$$EE\% = \frac{\text{Theoretical drug content} - \text{unencapsulated}}{\text{Theoretical drug content}} x100 \qquad (1)$$

2.5.2. pH-dependent stability studies.

The pH values of the various batches of molten GSM were determined using a pH meter (Hana instrument, Italy). This was done in a time-dependent style (1, 30 and 60 days) [21].

2.5.3. Morphological characterization and particle size analysis.

The GSMs preparations were mounted on the microscope slides and covered with coverslips. The slides were examined under a light microscope at a magnification of 100 to ensure a clear view. The particles were photographed with a digital camera attached to the microscope [22].

2.5.4. *In vitro* drug release.

The release experiments were carried out in freshly made simulated intestinal fluid (SIF) with a pH of 7.4 and a dialysis membrane [23]. A poly-carbonate dialysis membrane was used as the release barrier. The dialysis membrane was pre-treated by soaking in SIF (pH 7.4) for 24 hours. One side of the dialysis membrane was securely tied with a thread resistant to heat, and 5 mL of the molten GSM was put in the dialysis membrane. The dialysis membrane's other end was tied and immersed in the dissolution medium while agitated by the magnetic stirrer at 100 rpm and kept at 37±1 °C. At specified time intervals, 5 mL portions of the dissolution medium were withdrawn and replaced with an equal volume of the blank dissolution medium to keep the dissolution under a sink condition. The drug content of the withdrawn 5 mL portions was then determined using an ultraviolet (UV) spectrophotometer (Jenway model 6405, England) at 299 nm. The preceding steps were repeated for the rest of the samples.

2.5.5. The kinetics of drug release.

The *in vitro* release data were fitted into different models, including Higuchi, first order, zero order, and Korsmeyer-Peppas models, to determine the kinetics and mechanism of the drug release. The model with the highest correlation (R^2) was regarded as the most suitable model that describes the release kinetics. The values of the coefficient (n) of the Korsmeyer-Peppas model were used to describe the mechanism of drug release as Fickan diffusion ($n < 0.45$), non-Fickan or anomalous diffusion ($0.45 < n < 0.89$), or Case II or zero order ($n = 0.89$) for the first 60 - 70% release [24, 25, 26].

2.5.6. Hypoglycemic studies.

Albino male Wistar rats of weight between 152 and 227 g were used in this study. The animals used in this study were sourced from the Faculty of Veterinary Medicine, University of Nigeria. All animal-related procedures in this study were carried out following the ethical guidelines of the Faculty of Veterinary Medicine's Institutional Animal Care and Use Committee, University of Nigeria, Nsukka (Approval Reference Number: FVM-UNN-IACUC-2018-096). Before the induction of diabetes, the rats were provided with a dry chick's mash finisher two times daily and allowed free access to drinking water [27]. They were housed separately in standard housing conditions for two weeks to adapt to the new experimental setting [28]. Diabetes was induced in the animals via a single intra-peritoneal injection of a fresh solution of alloxan monohydrate in 0.9% sodium chloride containing 100 mg/mL at a dose of 150 mg/kg body weight. The rats with blood glucose levels > 200 mg/dL were deemed diabetic when measured with an Accu-Check® glucose meter (Roche, USA) [29]. Six groups of three diabetic rats each were created randomly from the diabetic rats. Before the investigation, all rats were fasted for 24 h with access to only water. Batches A1, A2, B1, and B2 were chosen for the *in vivo* experiments based on the initial assessment of the *in vitro* release

studies and entrapment efficiency. While rats in groups one to four received GSM (A1, A2, B1, and B2) respectively orally in the range of 2 mL per kg body weight, group five rats received pure GB dispersed in purified water at 10 mg/kg body weight. Rats in group six also received distilled water. At pre-set intervals of 0, 1, 3, 6, 9, and 24 hours, blood glucose levels were measured using an Accu-Check® glucose meter.

2.6. Data and statistical analysis.

The data were analyzed with a Student t-test and One-Way Analysis of Variance (ANOVA) using SPSS version 22.0 (IBM Inc., Chicago IL, USA) and Excel Microsoft Office version 2021. All measurements were performed at least three times. Statistical differences between means were considered significant at a 95% level of confidence ($p < 0.05$), and the findings were reported as means ± standard deviation (SD).

3. Results

3.1. Morphology and particle size analysis.

The GSM were smooth and irregular, as presented in Figure 1. A 200 mg weight of glibenclamide was loaded into batches A1-A4 and 100 mg of glibenclamide into batches B1-B4, each containing *an* increasing amount of the lipid matrix 3- 4.5 g.

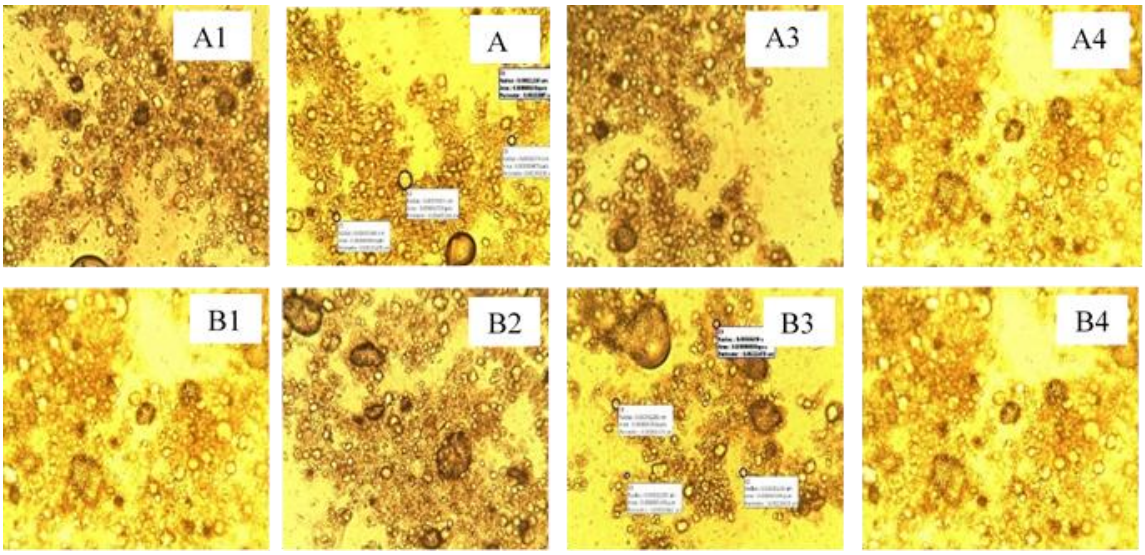

Figure 1. Photomicrographs of glibenclamide-loaded GSM.

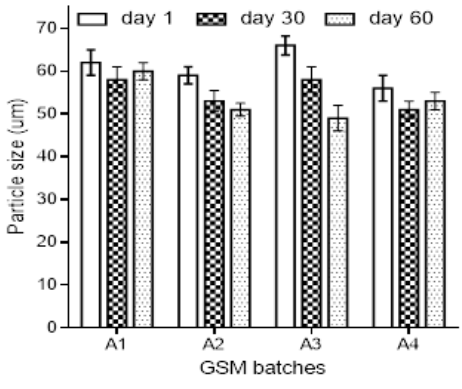

Figure 2. Particle size of GSM batches A1-A4.

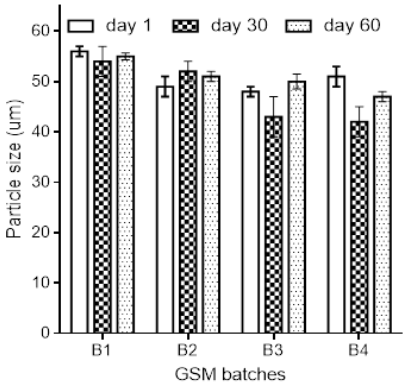

Figure 3. Particle sizes of GSM batches B1-B4.

The particle sizes of batches A1 to A4 decreased over time (1, 30, and 60 days), as shown in Figure 2, except for A3, whose particle sizes rose over time (24 hours and one month). The particle sizes of batches B1 to B4 decreased with time (1, 30, and 60 days) (Fig. 3). Batch B4 had the smallest particle size of 42 µm at 30 days, while batch A3 had the largest particle size of 66 µm 24 hours after the preparation with a significant difference among the batches ($p < 0.05$).

3.2. pH-dependent stability studies.

The results of monitoring the pH after intervals of 1, 7, 30, and 60 days are shown in Figure 4. The pH of batch A1-A4 after 24 h, was within the range of 3.3 ± 0.09 to 3.6 ± 0.09, while that of batch B1-B4 was within the range of 3.0 ± 0.00 to 3.5 ± 0.00. Within 1 week of formulation, there was an increase in pH between the two batches. However, there was no significant difference in pH from 1 week to 2 months ($p < 0.05$). The active components or excipients employed in the formulation did not degrade throughout the study.

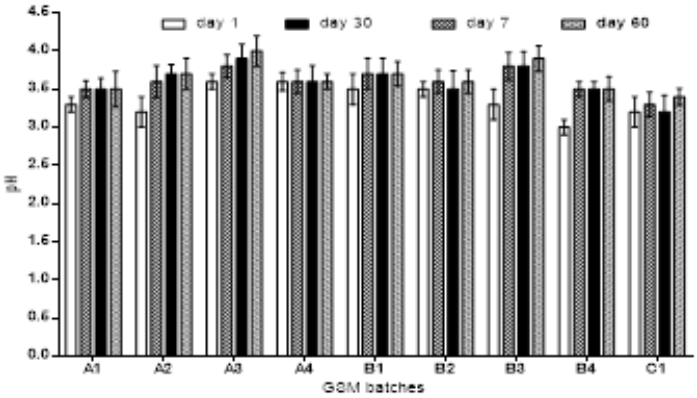

Figure 4. pH stability studies of batch A1-A4 and B1-B4.

3.3. Encapsulation efficiency.

Table 2 represents the results of the encapsulation efficiency of the formulations. It ranged from 32.1 ± 1.84 to 89.3 ± 0.61%. Batches A2 and B2 recorded the highest percentage of EE. Batches A2 and B2 had EE of 86.9 ± 1.94 and 89.3 ± 0.61% for their lipid matrix 4.0, respectively.

Table 2. Encapsulation efficiency (%) of the GSM.

Batch	EE (%) ± SD
A1	82.7±0.69
A2	86.9±1.94
A3	32.1±1.84
A4	43.8±0.74

Batch	EE (%) ± SD
B1	53.0±4.36
B2	89.3±0.61
B3	77.6±0.52
B4	65.2±1.34

3.4. In-vitro drug release.

Figures 5 and 6 show the *in-vitro* release profiles of batches A1-A4 and B1-B4, respectively. Batch A2 had a maximum release of 72.30% out of the four batches A1-A4, while batch B2 had a maximum release of 84.44% among the batches B1-B4. Batch A4 had the least release of 30. 55% among the Batch A group, while batch B4 had the lowest percentage release of 67.77% among the Batch B group. An increase in the lipid matrix gave a corresponding increase in the percentage release. The glibenclamide release kinetics from the different batches of the microparticles are shown in Table 3.

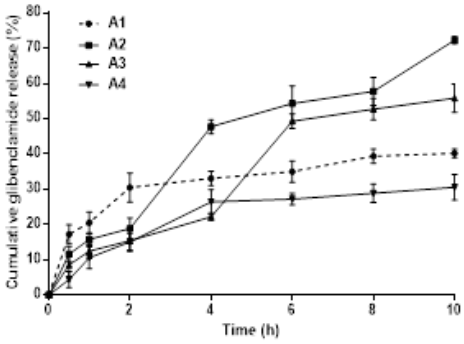

Figure 5. Cumulative % amount of glibenclamide released in SIF 7.4.

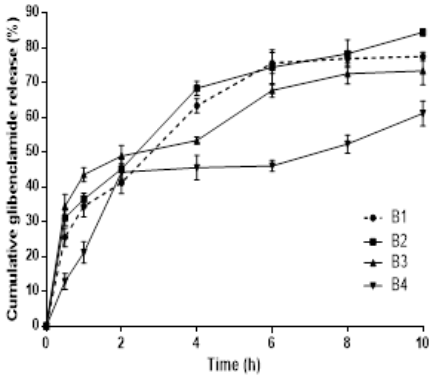

Figure 6. Cumulative % amount of glibenclamide released in SIF pH 7.4.

Table 3. Glibenclamide release kinetics from the microparticles

Batch	Zero order		First order		Higuchi		Korsmeyer	
	R^2	$K(h^{-1})$	R^2	$K(h^{-1})$	R^2	$K(h^{-1/2})$	R^2	n
A1	-1.450	5.1969	0.8542	-0.014	0.2696	14.650	0.9559	0.28
A2	0.8515	7.961	0.959	-0.0508	0.9145	21.396	0.9587	0.64
A3	0.8953	6.3862	0.8309	-0.0326	0.8420	16.952	0.9436	0.66
A4	0.5116	3.8343	0.8469	-0.0136	0.8852	10.638	0.9319	0.62
B1	0.0612	10.060	0.9139	-0.0597	0.9029	28.057	0.9759	0.40
B2	-0.2510	10.7576	0.8955	-0.0581	0.8665	29.655	0.9805	0.27
B3	-1.714	9.4517	0.9346	-0.0423	0.4729	26.863	0.9618	0.35
B4	0.0977	7.2495	0.8209	-0.0393	0.8157	20.240	0.8837	0.27

3.5. In-vivo hypoglycemic studies.

The optimized samples (batches A1, A2, B1, and B2) showed varying degrees of blood glucose reduction over 24 h (Figure 7). From the result obtained, batch A2 showed the highest percentage decrease in blood glucose level at 87.65% after 24 hours. Batch A1 showed a

significant decrease in blood sugar level of 66.80% after 24 h. The GSM with high drug content showed a higher percentage decrease in blood glucose level (batches A1 and A2) than the GSM with lower drug content (batches B1 and B2). The pure glibenclamide sample showed a percentage decrease in blood glucose level of 54.24% after 24 h, while the rats that were administered with distilled water as negative control continued to have an increase in blood sugar levels throughout the 24 h sampling time.

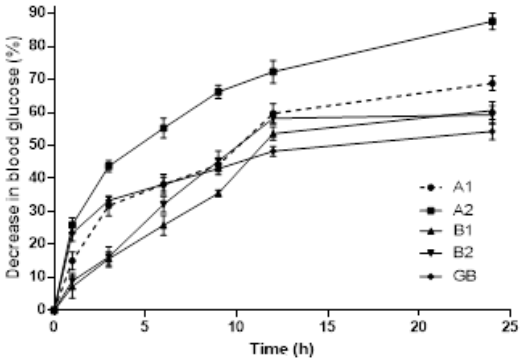

Figure 7. Percentage decrease in blood glucose level.

4. Discussion

GB, like other BCS class II drugs, is characterized by poor aqueous solubility and high permeability. This implies high intracellular penetration *and* extensive body distribution, with tissue levels usually higher than the plasma level. This work was designed to achieve increased solubility and higher bioavailability of GB. To achieve this 12 batches of GSM were prepared, as shown in Fig. 1. Batches C1-C4 were not loaded with GB. The hot homogenization method was used because of its simplicity. The formed GSM appeared smooth and asymmetrical when observed with a microscope connected to a digital camera. The diameters of the particles ranged from 42 to 66 µm. These were in the micro range and have been shown to be related to the quantity of drug solubilized.

The different particle sizes were a result of lipid-polymer content and the nature of the excipients. The prepared GSM was stable, as indicated by consistent pH values over 60 days. pH influences the stability and drug release from the GSM since drug solubility and drug release depend on the pH of the environment. Microparticles have advantages over nanoparticles because the increased surface area of nanoparticles leads to higher clearance in the blood. Particle sizes play a role in microparticles' *in vitro* and *in vivo* activities. Particles bigger than 100 nm remain at the administration site till phagosomal clearance. Lymphatic absorption and node accumulation are negligible between 10 and 80 nm. The particle size of lipid microparticles depends upon lipid-polymer content and the excipients' nature. Smaller particle sizes were observed in lipid-based formulations with higher lipid components (3:1), indicating that the drug solubilized more with reduced particle size in the lipid components [30].

Although there was a negligible change in pH over 60 days, the change was insignificant. This could be attributed to the active ingredient or formulation excipients degrading too little or not at all. The differences between the batches were not statistically significant ($p < 0.05$). pH influences lipid polymer hybrid formulations' stability and drug release [31].

The EE (%) is an important parameter in the lipid-based microparticle formulation. It could be affected by lipid and polymer matrix, presence of surfactants, nature of the lipidic

biomaterials, preparation technique, and lipophilic nature of the drug [32]. The lowest EE was 32.1 ± 1.84 (batch A3), while the highest EE was 89.3 ± 0.61% (batch B2) and A2 (86.9 ± 1.94). Batches A2 and B2 have the same lipid-polymer ratio but different amounts of drug for encapsulation. An optimal amount of drug could be available for encapsulation in each case, thus making the EE dependent upon other variables. However, there was no difference in their mean EE. The encapsulation efficiency of these GB microparticles was found to be influenced by the drug-polymer ratio. In all the formulations, there was an initial high drug release of 20-40% followed by gradual drug release of up to 10 hours. Drugs that are free or only weakly bound may be the cause of the early high drug release. In batch A2, the maximum release was 72.30%, while for batch B_2, the maximum release was 84. 44% after 10 hours. The last release was 30.5% and 67.77% for batches A_4 and B_4, respectively. Batch A1, which had the biggest average particle size of 60 µm, gave a maximum release of 40%. Korsmeyer-Peppas model was chosen to describe the release mechanism since it has a higher correlation $\{R^2\}$ (Table 3). The release exponents n (Table 3) show that drug release in all the batches except batches A2, A3, and A4 was through Fickan diffusion ($n < 0.45$) while the remaining 3 batches were through non-Fickan or anomalous diffusion, implying drug release by more than one mechanisms ($0.45 < n < 0.89$), i.e., coupling of diffusion and erosion mechanisms [33, 34].

The *in vivo* study results revealed that GB release from the GSM enhanced insulin synthesis from islet cells of Langerhans in a regulated manner for 24 h compared to the control. This was shown as a percentage drop in blood sugar levels due to increased level of glibenclamide in the blood as a result of higher drug release (Fig. 7). Hence, glibenclamide-loaded microparticles enhanced the therapeutic activity of the drug, which could be effectively delivered as GSM. The samples used showed varying degrees of blood glucose reduction for 24 h. The highest percentage decrease in blood glucose level at 87.65% after 24 h was recorded in batch A2, while batch A1 showed a blood glucose reduction of 66.80% after 24 h. The lowest percentage of the release, 59.30%, was recorded in batch B2. The batches with 200 mg of glibenclamide showed a higher percentage reduction in blood sugar levels than those with 100 mg of glibenclamide (batches B1 and B2). The pure drug sample showed a percentage decrease in blood glucose of 54.24% after 24h. Blood sugar levels rose steadily throughout 24 hours in the control group that received distilled water as a negative control. GSM was shown to improve *the* bioavailability of some drugs by transforming crystalline drugs into an amorphous form, which has a superior solubilization effect [35].

5. Conclusion

GSM formulation is an innovative technique that is used to improve the delivery of BCS class II drugs such as GB. In some batches, the EE (%) of GSM formulations was greater than 70%. The dissolution rate of GB was improved by preparing GSM using the hot homogenization method. Improved dissolution rate indicated enhanced solubility of glibenclamide. The results of the *in vitro* drug release indicated that GSM could deliver and prolong the release of GB in diabetic rats, suggesting that GSM could replace conventional GB tablets in the treament of type 2 diabetes mellitus.

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Conflicts of Interest

The authors declare no conflict of interest.

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