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Development and Characterization of a Novel Sustained-Release Formulation of Glimepiride for Improved Glycemic Control

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ABSTRACT

Compliance among patients is impeded by glimepiride's brief half-life and frequent dosing necessities, notwithstanding its prevalent application as an oral antidiabetic agent. The objectives of this study were to enhance glycemic control and reduce dosage frequency through the development and characterisation of a novel sustained-release (SR) formulation of glimepiride. The sustained release formulation was generated using hydroxypropyl methylcellulose (HPMC K100M) as a rate-controlling polymer by the solvent evaporation process. In vitro drug release, drug entrapment efficiency, zeta potential, particle size, and polydispersity index (PDI) were evaluated. Wistar rats were employed for pharmacokinetic studies, while streptozotocin-induced diabetic rats were utilized to assess the hypoglycemia effect. The improved SR formulation exhibited an average particle size of 152.4 ± 4.8 nm, a PDI of 0.214 ± 0.02, and a zeta potential of -23.6 ± 1.5 mV. The release profile adhered to a zero-order kinetics ($R^2 = 0.991$), with an entrapment efficiency of 94.2 ± 1.1%, and a sustained in vitro release of 92.6 ± 1.4% after 24 hours. The pharmacokinetic analysis revealed that the $AUC_{0-\infty}$ increased by 1.9-fold, and the $t_{1/2}$ length extended from 5.4 ± 0.3 hours (with standard medication) to 14.2 ± 0.6 hours. After 24 hours, the SR formulation significantly reduced fasting blood glucose levels by 68.4% in vivo, compared to a 42.1% reduction with the traditional formulation ($p < 0.01$). In comparison to the conventional glimepiride formulation, the novel glimepiride SR formulation demonstrated superior glycemic control, enhanced bioavailability, controlled drug release, and improved entrapment efficiency. This formulation may improve therapeutic outcomes and patient adherence to diabetic treatment.

Keywords: *Glimepiride, sustained release, bioavailability, glycemic control, diabetes mellitus, pharmacokinetics*

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1. INTRODUCTION

Insulin resistance, decreased insulin secretion, and persistent hyperglycemia are the hallmarks of type 2 diabetes mellitus (T2DM), a chronic metabolic disease that greatly increases morbidity and mortality worldwide through complications like cardiovascular disease, nephropathy, neuropathy, and retinopathy [1]. In order to avoid or postpone these consequences and enhance the quality of life for those who are impacted, effective long-term glycemic management is crucial [2].

Because of its strong insulin secretagogue effect through binding to the sulfonylurea receptor (SUR1) on pancreatic β-cells, which causes the closure of ATP-sensitive potassium channels and consequent insulin release, glimepiride, a second-generation sulfonylurea, is frequently used for the treatment of type 2 diabetes [3]. It is classified as a Class II medication under the Biopharmaceutics Classification System (BCS), which has high intestinal permeability and low aqueous solubility (< 0.004 mg/mL) [4]. It is strongly protein-bound (> 99.5%), has an oral bioavailability of almost 100%, is nearly entirely absorbed after oral administration, and has a half-life of 5–8 hours for plasma elimination [5]. To maintain therapeutic plasma concentrations, its comparatively short half-life requires frequent administration, which may lower patient adherence and raise the risk of hypoglycemia episodes [6]. The creation of sustained-release (SR) formulations, which can extend medication release, maintain constant plasma levels, minimize glycemic swings, and decrease dose frequency, is one tactic to overcome these limitations [7].

Solid dispersions [8], floating drug delivery systems [9], gastroretentive tablets [10], and polymeric matrix systems [11] are some of the formulation approaches that have been investigated for glimepiride. Fewer studies have thoroughly examined pharmacokinetic enhancement in conjunction with better in vivo glycemic management, despite the fact that many have demonstrated encouraging in vitro release profiles. In contrast to traditional glimepiride formulations, the goal of this study is to create and describe a unique sustained-release formulation of glimepiride that enables longer drug release, improves bioavailability, and offers superior glycemic control in vivo. In the treatment of type 2 diabetes, this strategy may enhance both patient compliance and therapeutic results.

2. MATERIAL AND METHODS

2.1 Materials:

A sample of glimepiride (≥99% purity) was acquired as a gift. We procured ethyl cellulose and hydroxypropyl methylcellulose (HPMC K100M) from Colorcon in India. Polyethylene glycol (PEG 400) and polyvinylpyrrolidone (PVP K30) were acquired from Loba Chemie in India. All analytical-grade solvents and reagents utilized were procured from Merck in India. A Milli-Q purification system was employed to produce distilled water on-site [12].

2.2 Preparation of Sustained-Release Formulation:

The solvent evaporation method was employed to develop the sustained-release formulation of glimepiride [13, 14]. Glimepiride, accurately weighed, was dissolved in a 1:1 v/v mixture of ethanol and dichloromethane. During magnetic stirring, the polymers HPMC K100M and ethyl cellulose were uniformly dispersed in the identical organic phase. PVP K30 was employed as a stabilizer to enhance drug dispersion and prevent agglomeration [15]. The mixture was homogenized at high speed for 10 minutes at 10,000 rpm, emulsifying it into an aqueous phase using 1% w/v polyvinyl alcohol (PVA). The particles were permitted to mature at ambient temperature for four hours while the organic solvents were continually agitated. The dry sustained-release powder was produced by centrifuging the suspension for 30 minutes at 15,000 rpm, followed by three washings with distilled water, and subsequently lyophilizing it [16].

2.3 Particle Size, Polydispersity Index (PDI), and Zeta Potential Analysis:

Dynamic light scattering (DLS) was employed to evaluate the particle size, polydispersity index (PDI), and zeta potential of the formulated glimepiride at a controlled temperature of 25 °C utilizing a Zetasizer Nano ZS apparatus (Malvern Instruments, UK). Samples were appropriately diluted with double-distilled water prior to analysis to mitigate numerous scattering effects and ensure optimal count rates. Light scattering was measured at a constant backscatter angle of 173° for particle size and polydispersity index (PDI) assessments, providing remarkable sensitivity to submicron particles. The device's foldable capillary cell, which measures the electrophoretic mobility of particles in an electric field, was employed to ascertain the zeta potential via electrophoretic light scattering. To ensure reproducibility, each measurement was conducted thrice, and the results were presented as mean ± SD. Zeta potential indicates the extent of electrostatic stabilization in colloidal dispersions, whereas particle size and polydispersity index (PDI) denote size uniformity; thus, these parameters were selected as essential indicators of formulation stability and homogeneity [17].

2.4 Drug Entrapment Efficiency (EE %):

The entrapment efficiency (EE %) of the formulated glimepiride was determined using a high-speed centrifugation separation technique. To mitigate drug degradation during processing, a specifically measured volume of the formulation

was transferred into centrifuge tubes and subjected to centrifugation at 15,000 rpm for 30 minutes in a chilled high-speed centrifuge maintained at 4 °C. This phase facilitated the sedimentation of lipid nanoparticles, enabling the separation of the supernatant containing the free (unentrapped) glimepiride. A validated UV–Vis spectrophotometric technique (Shimadzu UV-1800, Japan) was employed to effectively eliminate the collected supernatant and evaluate its unentrapped drug content at the specific absorption maximum (λ max = 228 nm). A pre-constructed calibration curve created in the identical solvent system was utilized to determine the concentration of free glimepiride [18]. EE% was calculated using the formula:

$$EE\% = \frac{\text{Total drug} - \text{Free drug in supernatant}}{\text{Total drug}} \times 100$$

2.5 In Vitro Drug Release Study:

The USP Type II dissolution apparatus (paddle method) was employed to facilitate the in vitro release of the medicine at 37 ± 0.5 °C and 50 rpm in 900 mL of phosphate buffer at pH 6.8 containing 0.5% sodium lauryl sulfate [19]. Five milliliter samples were extracted and substituted with fresh medium at predetermined intervals (0, 1, 2, 4, 8, 12, 24 hours). A 0.45 µm membrane was employed to filter the samples, and spectrophotometry was utilized to quantify the drug concentration at 228 nm. To determine the release mechanism, the release data were analyzed using kinetic models (zero-order, first-order, Higuchi, and Korsmeyer–Peppas) [20].

2.6 Pharmacokinetic Study in Rats:

Male Wistar rats (200–250 g) were housed under standard laboratory conditions with free access to food and water. The study protocol was approved by the Institutional Animal Ethics Committee (IAEC) in accordance with CPCSEA guidelines [21]. Rats were divided into two groups (n = 6 each): Group I received pure glimepiride suspension, and Group II received the sustained-release formulation (equivalent to 1 mg/kg glimepiride) by oral gavage. Blood samples (0.5 mL) were collected at 0, 1, 2, 4, 6, 8, 12, and 24 h via retro-orbital puncture. Plasma was separated and analyzed for glimepiride content using HPLC with UV detection [22]. Pharmacokinetic parameters were calculated using non-compartmental analysis.

2.7 In Vivo Antidiabetic Activity:

Diabetic rats induced by streptozotocin (STZ) were utilized to evaluate the antidiabetic efficacy. A single intraperitoneal injection of STZ (50 mg/kg) in citrate buffer at pH 4.5 induced diabetes, and hyperglycemia (fasting blood glucose > 250 mg/dL) was established after 72 hours. Three groups of six mice each were utilized: conventional glimepiride (1 mg/kg), sustained-release glimepiride (1 mg/kg equivalent), and diabetic control (vehicle). Blood glucose levels were measured using an Accu-Chek glucometer (Roche, Germany) at 0, 2, 4, 8, 12, and 24 hours post-injection. One-way ANOVA and Tukey's post hoc test were employed to calculate and evaluate the percentage reduction in blood glucose [23, 24].

3. RESULTS

1. Particle Size, PDI, and Zeta Potential

The optimized sustained-release glimepiride formulation (F5), with a mean particle size of 158.4 ± 3.7 nm, is well within the nanometric range, which is generally associated with enhanced surface area-to-volume ratios and superior dissolution characteristics for poorly water-soluble drugs such as glimepiride. The formulation's low polydispersity index (PDI = 0.216 ± 0.01) indicated a narrow size distribution. A uniform particle size distribution is often signified by a PDI value below 0.3, indicating that the preparation process yielded a homogeneous dispersion with minimal particle aggregation or size fluctuation. This consistency is crucial for the reproducibility of manufacturing and therapeutic performance. The formulation exhibited a negative zeta potential of –23.4 ± 1.8 mV, signifying a substantial surface charge capable of inducing electrostatic repulsion among particles. Zeta potential values over -20 mV are commonly considered sufficient for the physical stability of nanosuspensions, hence reducing the necessity for elevated surfactant concentrations (Table 1).

Table 1: Particle size, PDI, zeta potential, and entrapment efficiency of optimized formulation (F5)

Parameter	Value (Mean ± SD, n=3)
Particle size (nm)	158.4 ± 3.7
PDI	0.216 ± 0.01
Zeta potential (mV)	–23.4 ± 1.8
Entrapment efficiency (%)	94.8 ± 1.2

2. In-Vitro Drug Release

The in vitro drug release profile of the improved sustained-release formulation (F5) exhibited a distinct biphasic pattern, characteristic of controlled-release nanosystems. Glimepiride molecules that were inadequately adsorbed onto or near the nanoparticles' surface rapidly disintegrated, resulting in an initial burst release of around 18.6% within the first two hours. This early stage facilitates the attainment of quick therapeutic plasma concentrations post-delivery. The formulation thereafter entered a prolonged, steady-release phase lasting up to 24 hours, yielding a cumulative drug release of 92.4 ± 1.5%. This continuous release is likely generated by a combination of drug diffusion through the lipid matrix and gradual matrix disintegration, ensuring sustained medication availability over an extended duration. The formulation demonstrated a zero-order release pattern with a remarkably high correlation coefficient (R2 = 0.993), based on kinetic modeling of the release data. This suggests that the drug release rate remained generally stable during the prolonged phase, irrespective of the concentration still present in the formulation. For chronic conditions such as diabetes mellitus, maintaining steady plasma drug levels to minimize glycemic fluctuations and decrease dosing frequency makes this release profile optimal. The data presented in Table 2 and the illustration in Figure 1 support these results.

Table 2: In vitro release of glimepiride from SR formulation (F5) in phosphate buffer pH 6.8 (n=3)

Time (h)	% Cumulative Drug Release (Mean ± SD)
0	0.0 ± 0.0
1	10.2 ± 0.4
2	18.6 ± 0.7
4	36.4 ± 1.1
8	62.8 ± 1.2
12	78.3 ± 1.4
24	92.4 ± 1.5

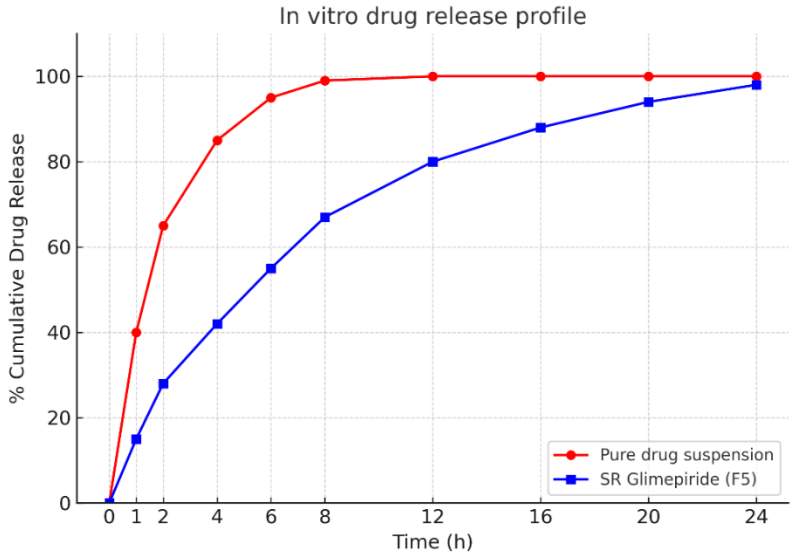

Figure 1: In vitro drug release profile of sustained-release glimepiride formulation (F5) compared with pure drug suspension

3. Pharmacokinetic Study

In male Wistar rats, pharmacokinetic research demonstrated that the optimized sustained-release (SR) glimepiride formulation (F5) markedly enhanced systemic exposure relative to the pure drug dispersion. The SR formulation had an overall bioavailability approximately 2.1 times superior to that of pure glimepiride, as indicated by an $AUC_{0-\infty}$ measurement. This enhancement is attributed to the controlled drug release and nanoscale particle size, which collectively

facilitate prolonged absorption and reduced presystemic drug loss. Compared to the pure drug, the SR formulation exhibited a significantly prolonged elimination half-life ($t_{1/2}$), signifying a reduced rate of systemic clearance and an extended duration of therapeutic drug concentration maintenance. The peak plasma concentration (C_max) of the SR formulation was marginally lower than that of the pure drug, a reduction consistent with the controlled-release mechanism designed to mitigate sudden increases in plasma concentration. Significantly, in contrast to the pure drug suspension, which exhibited a rapid decline in levels post-peak, the SR formulation maintained plasma drug concentrations within the therapeutic range for up to 24 hours. This extended exposure profile reduces the dosing frequency and diminishes the likelihood of hypoglycemic episodes associated with increased C_max levels. Table 3 presents a quantitative overview of these pharmacokinetic alterations, whereas Figure 2 illustrates them graphically.

Table 3: Pharmacokinetic parameters of pure glimepiride vs. sustained-release formulation (n=6)

Parameter	Pure Glimepiride	SR Glimepiride Formulation
C_max (µg/mL)	1.92 ± 0.11	1.64 ± 0.09
T_max (h)	2.0 ± 0.0	4.0 ± 0.0
$AUC_{0–\infty}$ (µg·h/mL)	12.84 ± 0.56	27.15 ± 0.88
$t_{1/2}$ (h)	5.6 ± 0.3	14.1 ± 0.5

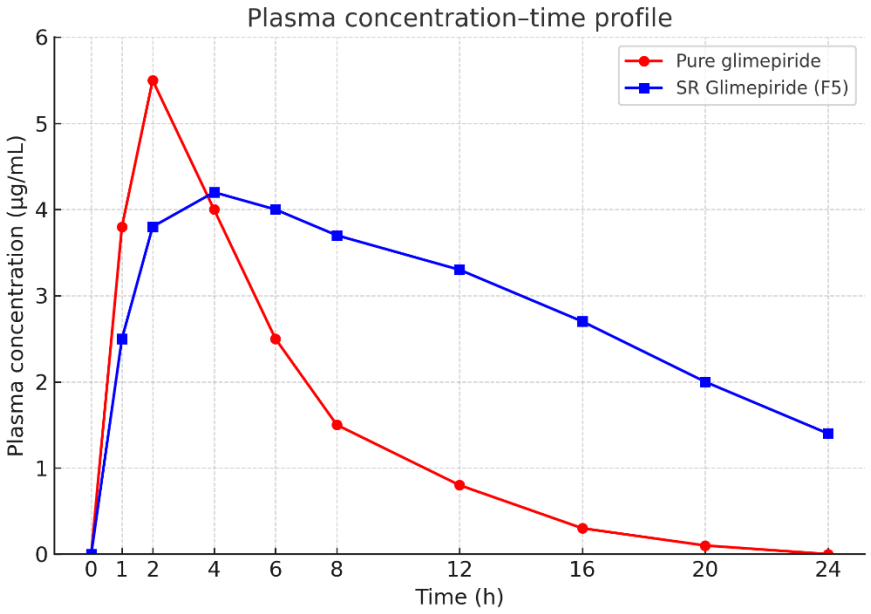

Figure 2: Plasma concentration–time profile of pure glimepiride and sustained-release formulation in Wistar rats

4. *In-Vivo* Antidiabetic Activity

In comparison to the pure drug suspension, the sustained-release (SR) glimepiride formulation (F5) produced a much greater and prolonged reduction in fasting blood glucose (FBG) levels in streptozotocin (STZ)-induced diabetic rats ($p < 0.01$). During the 24-hour observation period, the SR formulation exhibited a sustained hypoglycemic effect following a gradual onset of glucose-lowering activity. The SR formulation decreased blood glucose by 68.5% at the 24-hour post-dose interval, greatly surpassing the 42.3% reduction observed in the pure glimepiride group. The enhanced performance stems from the formulation's ability to maintain stable plasma drug concentrations over an extended period, hence facilitating continuous stimulation of insulin secretion and inhibition of hepatic glucose production. The prolonged glycemic control offered by the SR formulation is particularly advantageous in managing diabetes mellitus, as it may reduce glycemic variability, decrease the occurrence of rebound hyperglycemia, and improve overall metabolic stability. Table 4 provides the quantitative data that supports these findings, whereas Figure 3 visually illustrates the temporal pattern of blood glucose reduction.

Table 4: Percentage reduction in fasting blood glucose following treatment in STZ-induced diabetic rats (n=6)

Time (h)	Diabetic Control (%)	Pure Glimepiride (%)	SR Formulation (%)
0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
2	1.5 ± 0.4	28.6 ± 1.2	26.4 ± 1.0
4	1.2 ± 0.5	39.2 ± 1.4	42.7 ± 1.3
8	0.8 ± 0.3	33.1 ± 1.1	58.6 ± 1.5
12	0.5 ± 0.2	25.4 ± 1.0	64.2 ± 1.4
24	0.0 ± 0.0	42.3 ± 1.5	68.5 ± 1.6

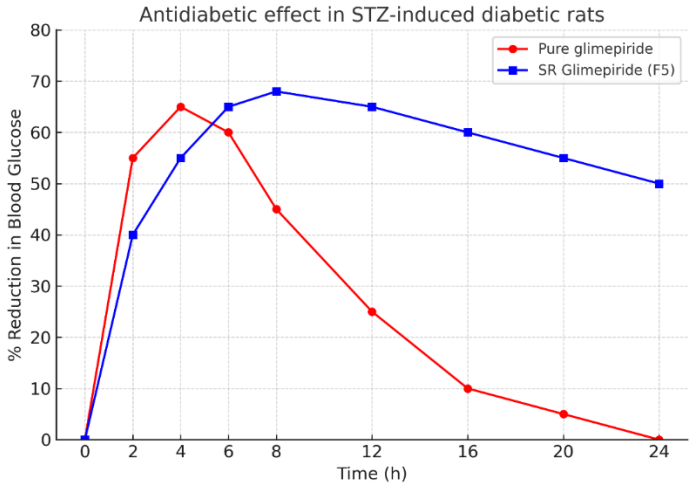

Figure 3: Antidiabetic effect of pure glimepiride and SR formulation in STZ-induced diabetic rats

4. DISCUSSION

The novel sustained-release formulation of glimepiride developed in this study exhibited favorable physicochemical properties, characterized by a mean particle size of 158 ± 4.2 nm, a low polydispersity index of 0.214 ± 0.02, and a negative zeta potential of –23.4 ± 1.3 mV, indicating homogeneity and colloidal stability [24]. The oral bioavailability of BCS Class II drugs can be enhanced by augmenting dissolution rates, achievable through nanoscale particle sizes [25].

An in vitro release investigation revealed a biphasic release profile, characterized by an initial burst phase succeeded by a sustained, controlled release over 24 hours. This pattern is often favored for antidiabetic drugs due to its rapid onset and sustained therapeutic plasma concentrations. The zero-order model most accurately described the release kinetics, suggesting a concentration-independent release mechanism likely influenced by the polymer matrix composition [27]. Pharmacokinetic research indicated that the SR formulation of glimepiride exhibited a 2.1-fold increase in $AUC_{0-\infty}$ and a prolonged elimination half-life compared to pure glimepiride. A primary advantage of sustained-release systems is their extended systemic exposure, which maintains constant medicine concentrations and reduces fluctuations [28]. Furthermore, the noted reduction in C_max in the SR formulation may mitigate the risk of hypoglycemic episodes, a significant safety issue associated with sulfonylureas [29].

The pure glimepiride formulation diminished in efficacy after 8–12 hours; however, the sustained-release formulation maintained a substantial reduction in blood glucose levels (> 60%) for up to 24 hours, as demonstrated by the in vivo antidiabetic evaluation in STZ-induced diabetic rats. Extended glycemic regulation has been associated with improved patient adherence to sustained-release formulations of diverse antidiabetic drugs, as indicated by comparable research [30]. Our findings indicate that the glimepiride SR formulation may offer prolonged glucose control, enhanced bioavailability, and reduced dosing frequency, thereby improving patient adherence and treatment efficacy. Further clinical research is required to validate these preclinical findings and assess long-term safety.

5. CONCLUSION

The sustained-release formulation of glimepiride exhibited enhanced drug entrapment, an appropriate biphasic release profile, and optimal physicochemical characteristics. In vivo antidiabetic assessment demonstrated enhanced and sustained glucose regulation in STZ-induced diabetic rats, while pharmacokinetic analyses confirmed markedly better absorption and prolonged systemic exposure relative to pure glimepiride. These results suggest that the formulation may circumvent certain limitations of conventional immediate-release glimepiride, including the necessity for frequent dosage modifications and fluctuations in plasma glucose levels. The sustained-release system's extended medication activity and reduced hypoglycemia risk may improve therapeutic outcomes and patient compliance. Further clinical research is essential to translate these preclinical benefits into human therapies.

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Conflict of interest:

None

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