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Original Article

An in vivo Evaluation Study of Remogliflozin Etabonate Solid Dispersions: Influence of Hydrophilic and Hydrophobic Carriers on Drug Release

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ABSTRACT

Background: Remogliflozin Etabonate (RE), a novel antidiabetic drug, suffers from poor aqueous solubility, which limits its oral bioavailability. This study aimed to develop and compare Solid Dispersion (SD) formulations of RE using various hydrophilic and hydrophobic carriers to enhance its dissolution rate. **Materials and Methods:** Six solid dispersion Formulations (F1-F6) were prepared using different carriers. All formulations were evaluated for in vitro drug release. Then in vivo evaluation study was performed to assess drug-release study by HPLC Method by four different groups, that is Normal Control, Diabetic Control, Standard control and Test. The Several parameters are performed. Healthy adult Wistar rats of either sex, aged 3-4 months and weighing 250-300 g, were obtained from the institutional animal house. Antidiabetic Study was performed in STZ Induced Diabetic Rats. Histopathological Evaluation, Bioavailability and Pharmacokinetic Study, Acute Toxicity Study were performed as per OECD Guideline. ANOVA model for one-way model was performed to analyse the variance of the results. **Results:** Formulation F1 demonstrated the most rapid and complete drug release (98.57% at 18 hr), while F6 showed the slowest (92.08% at 24 hr). The order of cumulative drug release at 18 hr was: F1 (98.57%) > F2 (93.01%) > F3 (92.99%) > F4 (92.02%) > F5 (91.24%) > F6 (90.10%). So, as per the results F6 was shown the potent batch. *In vivo* data suggested the drug release study by HPLC Method for selected potent and effective formulation, correlating with improved dissolution. At α=0.05, the critical F-value for (d_f 1=1), (d_f 2=4) is approximately 7.71. Since: [52.35 > 7.71]. The difference between the two-group means is statistically significant (p<0.05). **Conclusion:** The solid dispersion approach, particularly using the carrier system in F6, significantly enhanced the dissolution rate of Remogliflozin etabonate. F6 represents a promising strategy for developing an orally bioavailable formulation of RE.

Keywords: Acute Toxicity Study, Adult Wistar rats, Bioavailability, Histopathological Evaluation, HPLC method, *In vivo* study, Pharmacokinetic Study, Remogliflozin etabonate, Solid dispersion, STZ-induced Diabetic Rats.

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INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disorder characterized by hyperglycemia resulting from insulin resistance and progressive pancreatic β cell dysfunction. Globally, the prevalence of T2DM has reached epidemic proportions, with the International Diabetes Federation estimating that over 500 million adults are currently living with diabetes, a number projected to exceed 700 million by 2045.[1-5] The management of T2DM requires a multifaceted approach involving lifestyle modifications and pharmacological interventions. Among the various classes of oral antidiabetic agents, Sodium Glucose Co Transporter 2 (SGLT2) inhibitors have emerged as a significant therapeutic advancement due to their unique insulin independent mechanism of action.

Remogliflozin Etabonate (RE) is a novel, orally active prodrug belonging to the gliflozin class of SGLT2 inhibitors. Chemically designated as ethyl [(2R,3S,4S,5R,6S)-3,4,5-trihydroxy-6-[5-methyl-1-propan-2-yl-4-[(4-propan-2-yloxyphenyl)methyl] pyrazol-3-yl]oxyoxan-2-yl]methyl carbonate with a molecular formula of $C_{26}H_{38}N_2O_9$ and molecular weight of 522.60 g/mol, RE acts by selectively inhibiting SGLT2 receptors in the proximal renal tubules, thereby reducing glucose reabsorption and promoting urinary glucose excretion. This mechanism effectively lowers blood glucose levels independent of insulin secretion, offering advantages in terms of reduced risk of hypoglycemia and potential weight loss benefits.[6-10]

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Following oral administration, RE is rapidly converted to its active metabolite remogliflozin, which is further metabolized to additional active metabolites GSK279782 and GSK333081.[11] Clinical pharmacokinetic studies have demonstrated that RE exhibits favorable linear pharmacokinetics with rapid absorption and conversion, showing no clinically relevant food effects. However, like many SGLT2 inhibitors, RE faces significant formulation challenges due to its poor aqueous solubility.[12] Although RE is reported to be soluble in organic solvents such as methanol and DMSO, its solubility in aqueous media is limited, classifying it as a BCS Class II or IV compound depending on the specific salt form and conditions. This poor solubility directly impacts dissolution rate, which is often the rate limiting step for oral absorption of such compounds.

The challenge of poor aqueous solubility affects approximately 40-45% of newly discovered drug candidates, significantly hindering their clinical translation and market entry. Various formulation strategies have been explored to address this issue, including salt formation, co solvent solubilization, particle size reduction, and complexation with cyclodextrins.[13] However, these conventional approaches often have inherent limitations such as incomplete solubilization, stability concerns, or impractical manufacturing requirements. Among the emerging technologies, solid dispersion has garnered significant attention as a robust and versatile platform for enhancing the dissolution and bioavailability of poorly water soluble drugs.[14-17]

Solid dispersion technology was first introduced by Sekiguchi and Obi in 1961 and has since evolved into a widely adopted formulation strategy. In a solid dispersion, one or more Active Pharmaceutical Ingredients (APIs) are molecularly dispersed within an inert hydrophilic or hydrophobic carrier matrix, resulting in a solid state system that can significantly improve drug wettability, reduce particle size to the molecular level, and, in many cases, convert the crystalline drug to an amorphous form with higher free energy and apparent solubility. The enhanced performance of solid dispersions is attributed to multiple mechanisms: improved particle wetting due to hydrophilic carriers, reduction of drug particle size, conversion of the drug to a metastable amorphous state, and the potential formation of molecular level drug carrier interactions that inhibit recrystallization.[14-17] Sustained Release (SR) formulations reduce dosing frequency, maintain therapeutic drug levels, minimize peak related side effects, and improve adherence. Hydrophilic matrix systems using Hydroxypropyl Methylcellulose (HPMC) and enteric polymers like Eudragit L 100 are widely used for SR.[18-25] HPMC hydrates to form a gel layer that controls drug diffusion, while Eudragit L 100 provides pH dependent release modulation.

The objectives of this study were: to prepare sustained release matrix tablets of Remogliflozin etabonate by wet granulation (formulations F1-F6) with increasing proportions of HPMC K100LV and Eudragit L 100; to evaluate *in vivo* study of the potent batch, to assess acute toxicity according to OECD 423 guidelines,[26,27] antidiabetic efficacy in a 28 day streptozotocin induced diabetic rat model,28,29 and histopathological changes; to determine pharmacokinetic parameters (0.6 mg/kg, oral and intraperitoneal routes) in Wistar rats using a validated HPLC method,[30-33] and to conduct accelerated stability studies as per ICH Q1A(R2) guidelines on the optimized formulation F6.

MATERIALS AND METHODS

Acute Toxicity Study (OECD 423)

Animals

Healthy adult Wistar rats of either sex, aged 3-4 months and weighing 250-300 g, were obtained from the institutional animal house. Animals were housed in polypropylene cages with stainless steel mesh tops under standard conditions (12 hr light/dark cycle, 22±2°C, 50-60% relative humidity) and had free access to standard pellet diet and water *ad libitum*. The study was approved by the Institutional Animal Ethics Committee (IAEC) and followed CPCSEA guidelines.

Study Design (OECD 423)

The acute toxicity study was conducted in accordance with OECD Guideline 423 (Acute Oral Toxicity - Acute Toxic Class Method).27,28 Twenty four rats were randomly divided into four groups (n=4 per group):

- **Group 1 (Normal Control):** Healthy rats receiving no treatment.
- **Group 2 (Diabetic Control):** Diabetic rats (streptozotocin induced) receiving no drug.
- **Group 3 (Standard Control):** Diabetic rats receiving standard antidiabetic drug (Remogliflozin etabonate solution).
- **Group 4 (Test):** Diabetic rats treated with the sustained-release formulation F6.

Induction of Diabetes for Groups 2-4

Diabetes was induced by a single intraperitoneal injection of streptozotocin (STZ) at 55 mg/kg body weight, freshly dissolved in ice cold 0.1 M citrate buffer (pH 4.5). After 72 hr, fasting blood glucose was measured; animals with glucose ≥250 mg/dL were considered diabetic.

Dosing

All treatments were administered orally once daily for 15 consecutive days. The dose volume was 0.5 mL (as per protocol). Group 1 received no treatment; Group 2 received no drug; Group 3 received Remogliflozin etabonate solution (equivalent to

0.6 mg/kg); Group 4 received Formulation 6 suspension in 0.5% sodium Carboxymethyl Cellulose (CMC) at the same dose.

Observations

Animals were observed daily for clinical signs of toxicity (changes in skin, fur, eyes, mucous membranes, respiration, posture, behavior) and mortality. Body weights were recorded on day 0 and day 15. At the end of the study, all animals were euthanized, and a necropsy was performed to examine gross pathological changes in liver, kidney, heart, lungs, and spleen.

Antidiabetic Study in STZ Induced Diabetic Rats

Animals

Male Wistar rats weighing 250-300 g were used. Animals were housed under standard conditions (12 hr light/dark cycle, 22±2°C, 50-60% RH) with free access to food and water. The study was approved by the IAEC.

Induction of Diabetes

After overnight fasting (12-16 hr), diabetes was induced by a single intraperitoneal injection of Streptozotocin (STZ) at 55 mg/kg body weight, freshly dissolved in ice cold 0.1 M citrate buffer (pH 4.5). To prevent hypoglycemic mortality due to acute insulin release, animals were provided with 5-10% glucose solution in drinking water for 24 hr post injection. After 72 hr, fasting blood glucose was measured using a glucometer; rats with glucose levels ≥250 mg/dL were considered diabetic and included in the study.

Experimental Groups

Sixteen diabetic rats were randomly divided into four groups (n=4 per group):

- **Normal control:** Healthy rats received vehicle only (0.5% CMC).
- **Diabetic control:** Diabetic rats received no treatment.
- **Standard control:** Diabetic rats received Remogliflozin etabonate solution (0.6 mg/kg, oral).
- **Test group (F6):** Diabetic rats received Formulation 6 suspension (equivalent to 0.6 mg/kg RE, oral).

Treatment Protocol

All treatments were administered orally once daily for 28 consecutive days. Body weight and fasting blood glucose levels were monitored on day 0 (before treatment) and at the end of the study (day 28). Blood samples were collected from the retro orbital plexus after an overnight fast.

Histopathological Evaluation Bioavailability

At the end of the 28 day antidiabetic study, animals were euthanized by CO_2 asphyxiation. Vital organs - liver, stomach, and pancreas - were immediately excised, washed with ice cold saline, and fixed in 10% neutral buffered formalin for 24 hr. Tissues were then dehydrated through graded alcohols, cleared in xylene, and embedded in paraffin wax. Sections of 5 µm thickness were cut using a rotary microtome, mounted on glass slides, and stained with Hematoxylin and Eosin (H&E) according to standard protocols. Stained sections were examined under a light microscope (Olympus BX51) at 10× magnification. Photomicrographs were captured using a digital camera. Histopathological changes were evaluated by a blinded pathologist.[29,30]

Bioavailability and Pharmacokinetics Study

HPLC Method Development and Validation

Chemicals and Reagents

Remogliflozin etabonate reference standard (purity 98.46%) was obtained. Methanol, acetonitrile, and sodium perchlorate were of HPLC grade. Perchloric acid (1%) was used for pH adjustment. Water was purified using a Milli Q system.

Chromatographic Conditions

The analysis was performed on a Jasco PU 2080 HPLC system equipped with a Jasco MD 2015 UV/vis detector and Chromatostage software. Separation was achieved on a HIQ SIL C18 HS column (5 µm, 4.6 mm × 250 mm, 100 Å) maintained at 27°C. The mobile phase consisted of methanol, acetonitrile, and 0.1 M sodium perchlorate in the ratio 40:30:30 (v/v), adjusted to pH 6.1 with 1% perchloric acid. Isocratic elution was performed at a flow rate of 0.8 mL/min. The injection volume was 20 µL, and UV detection was set at 230 nm (λmax of RE). The total run time was 12 min.[31-33]

Preparation of Standard Solutions

A stock solution of RE (100 µg/mL) was prepared in methanol. Working standards of 2, 4, 8, 10, 15, and 20 µg/mL were obtained by serial dilution. Each solution was injected in triplicate, and peak areas were recorded to construct a calibration curve.

Method Validation

The method was validated for linearity, accuracy, precision, and specificity as per ICH Q2(R1) guidelines. The retention time of RE was 6.85±0.06 min.[31-33]

Table 1: Experimental Design.

Group(s)	Details of the group	Testing Parameters
Group 1	Normal Control (NC)	Body Weight,
Group 2	Diabetic Control	Blood-Glucose Level
Group 3	Standard Control	Bioavailability
Group 4	Diabetic rats + Formulation 6	Acute Toxicity

Table 2: Group Details.

Parameters	Group1 (Normal Control)	Group 2 (Diabetic Control)	Group 3 (Standard Control)	Group 4 (Diabetic Rats +Formulation 6)
No. of rats	04	04	04	04
Bodyweight (ABW, g)	Day0:264.8±6.1 Day15:274.9±6.8	Day0:262.1±6.7 Day15:255.4±7.2	Day0:263.9±6.3 Day15:271.6±6.5	Day0:263.2±6.6 Day15:268.7±6.9
Necropsy findings	No gross pathological abnormalities in liver, kidney, heart, lungs, or spleen	Mild hepatomegaly and renal congestion consistent with diabetic pathology	No abnormal macroscopic findings	No treatment-related gross pathological changes observed
Mortality	0/4	0/4	0/4	0/4
Clinical signs of toxicity (as per OECD rubrics)	0(Normal skin, fur, eyes, respiration, posture, and behavior)	0 (Polyphagia and polydipsiarelated to diabetes)	0	0
Gross observation Day 0	Normal posture, alert, glossy fur	Mild hypoactivity, diabetic phenotype	Normal posture and activity	Normal posture, no visible abnormalities
Gross observation Day 15)	Healthy appearance, increased body mass	Reduced grooming, slight weight loss	Improved activity and coat condition	Normal behavior, healthy appearance

Pharmacokinetic Study in Rats

Animals

Male Wistar rats (250-300 g, n=4 per group) were used. Animals were fasted overnight before the experiment but had free access to water.

Study Design

Four groups (*n*=4 each) received:

- **Group I:** Remogliflozin etabonate solution (0.6 mg/kg) intraperitoneally.
- **Group II:** Remogliflozin etabonate solution (0.6 mg/kg) orally.
- **Group III:** Formulation 6 solution (equivalent to 0.6 mg/kg RE) intraperitoneally.
- **Group IV:** Formulation 6 solution (0.6 mg/kg RE) orally.

Blood Sampling

Blood samples (≈0.5 mL) were collected from the retro orbital plexus into heparinized tubes at pre dose (0) and at 0.5, 1, 2, 4, 8, and 12 hr post dose. Plasma was separated by centrifugation at 4000 rpm for 10 min and stored at -20°C until analysis.

Sample Preparation

To 100 µL of plasma, 400 µL of distilled water was added. RE and RE from F6 were extracted with 500 µL of dichloromethane by vortex mixing for 15 min, followed by centrifugation at 3000 rpm for 10 min. The lower organic layer was collected, and the extraction was repeated. Pooled organic layers were dried under a stream of nitrogen. The residue was reconstituted in 1.0 mL of methanol (HPLC grade) and injected into the HPLC system.

Pharmacokinetic Analysis

Non compartmental analysis (Phoenix WinNonlin) was used to calculate the Cmax (peak plasma concentration), Tmax (time to reach Cmax), AUC0-t (area under curve from 0 to last measured time), AUC0-∞ (extrapolated to infinity), t1/2(elimination half life), Relative oral bioavailability (Frel)=(AUCTest / AUCControl) × 100.

Statistical Analysis

Data expressed as mean±SEM. Comparisons between groups were performed using one way ANOVA followed by Tukey's *post hoc* test. A p value <0.05 was considered statistically significant.

RESULTS AND DISCUSSION

Pharmacodynamic studies

The pharmacodynamics studies are achieved by using four adult male albino Wister rats with 250-300 g, weight with its initial weight 250-300 g. The rats were accommodating in suitable environmental conditions and photoperiod of 12 hr light and 12 hr dark cycle. Animals were given standard rodent feed and tap water.

Experimental Design

The optimized batch of Remogliflozin Etabonate (API) was administered as tablets, orally with small amount of water. The experimental rats were subdivided in four groups of four animals each.

At pre-determined time periods, 0.5 mL blood was collected from tail vein of rats and put into heparinized plastic tubes. Collected blood sample were centrifuged for 10 min at 2000 rpm and stored at -20°C till further use. The concentration of drug is estimated by HPLC method (Table 1).

Acute Toxicity Study

No mortality was observed in any group during the 15 day observation period. Clinical signs of toxicity (as per OECD rubrics) were absent in Groups 1, 3, and 4. Group 2 (diabetic control) showed polyphagia and polydipsia, which are characteristic of diabetes, but no drug related toxicity was shown in Table 2.

Body weight changes

- Group 1 (Normal control): Increased from 264.8±6.1 g to 274.9±6.8 g.
- Group 2 (Diabetic control): Decreased from 262.1±6.7 g to 255.4±7.2 g.
- Group 3 (Standard control): Increased from 263.9±6.3 g to 271.6±6.5 g.
- Group 4 (F6 treated): Increased from 263.2±6.6 g to 268.7±6.9 g.

Necropsy findings

- Group 1: No gross pathological abnormalities.

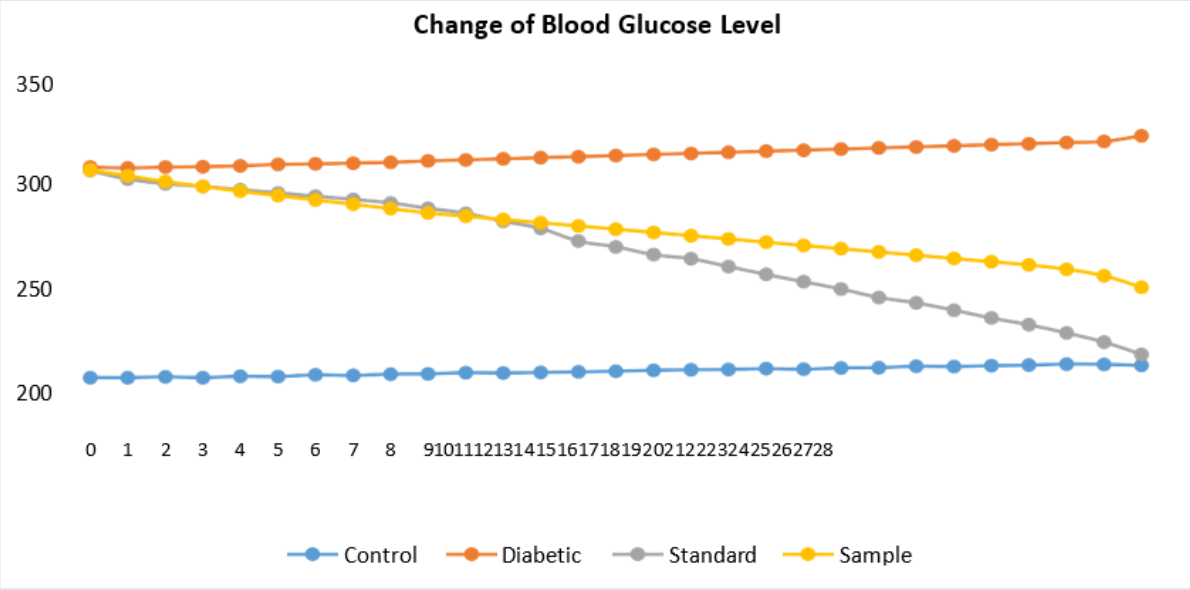


Figure 1: Comparative blood glucose level (Average of Glucose Level vs Day).

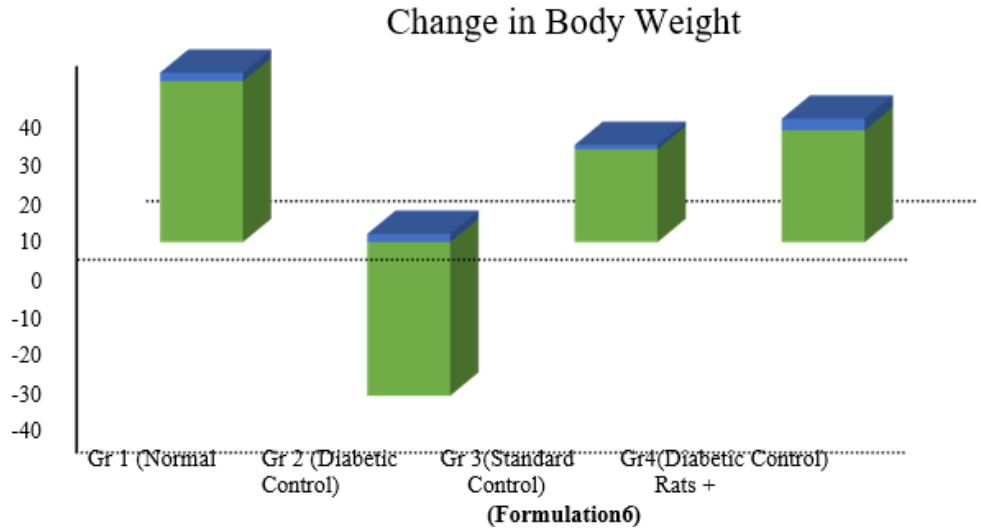


Figure 2: Effect of Treatment on Body Weight Changes in Experimental Rats. All values are Mean±SEM, n=4,* p<0.05 vs. control.

Table 3: Effect of Formulation6 on blood glucose levels and body weight changes in normal and streptozotocin-induced diabetic rats.

Treatment	Blood Glucose (mg/dL)		Change in body weight
	Initial	Final	
Gr1 (Normal Control)	77.5±1.55	88.75±1.49	33.4±1.74
Gr2 (Diabetic Control)	269.75±4.97	300.75±5.17	-31.85±1.71
Gr3 (Standard Control)	268.5±3.12	99±3.65	19.27±0.90
Gr4 (Diabetic Rats+Formulation 6)	269.25±2.93	160.95±3.3	23.22±2.39

- Group 2: Mild hepatomegaly and renal congestion consistent with diabetic pathology.
- Group 3: No abnormal macroscopic findings.
- Group 4: No treatment related gross pathological changes.

Thus, Formulation F6 was well tolerated with no signs of acute toxicity.

The OECD 423 guideline is a standard for acute oral toxicity testing that uses a stepwise procedure with a limited number of animals. In this study, F6 did not cause any mortality or clinical signs of toxicity at the administered dose (0.5 mL, equivalent to ~0.6 mg/kg RE). The absence of treatment related gross pathological changes in liver, kidney, heart, lungs, or spleen further supports the safety profile of the sustained release formulation.

Diabetic control animals (Group 2) exhibited weight loss and diabetic associated organ changes (hepatomegaly, renal congestion), which are expected due to uncontrolled hyperglycemia. In contrast, F6 treated diabetic rats not only maintained but slightly increased body weight, suggesting that the sustained release formulation effectively improved metabolic control without additional toxicity. These results indicate that F6 has a wide safety margin and is suitable for further efficacy studies (Table 3).

Antidiabetic Study

Blood glucose levels

1. **Normal control:** Initial 77.5±1.55 mg/dL, final 88.75±1.49 mg/dL (normal range).

2. **Diabetic control:** Initial 269.75±4.97 mg/dL, final 300.75±5.17 mg/dL (progressive hyperglycemia).

3. **Standard control:** Initial 268.5±3.1 mg/dL, final 99±3.65 mg/dL (63% reduction, $p<0.05$ vs diabetic control).

4. **F6 treated:** Initial 269.25±2.93 mg/dL, final 160.95±3.32 mg/dL (40% reduction, $p<0.05$ vs diabetic control).

Body weight changes

- **Normal control:** +33.4±1.74 g (healthy weight gain).
- **Diabetic control:** -31.85±1.71 g (significant weight loss).
- **Standard control:** +19.27±0.90 g (improved weight gain).
- **F6 Treated:** +3.22±2.39 g (prevention of weight loss, $p<0.05$ vs diabetic control). (Days)

Thus, F6 significantly reduced fasting blood glucose and prevented diabetic weight loss, although the effect was less pronounced than the standard control presented in Figure 1.

The STZ induced diabetic rat model is well established for evaluating antidiabetic agents. STZ selectively destroys pancreatic β cells, leading to insulin deficiency and hyperglycemia. In this study, untreated diabetic controls showed severe hyperglycemia (300.75 mg/dL) and marked weight loss, confirming successful diabetes induction (Figures 2-4).

Treatment with the standard RE solution reduced blood glucose to near normal levels (99 mg/dL), demonstrating the potent antihyperglycemic activity of Remogliflozin etabonate. The sustained release formulation F6 lowered blood glucose to 160.95 mg/dL, which, although higher than the standard, represents a clinically meaningful reduction of 40%. Moreover, F6 completely reversed the weight loss seen in diabetic controls, with a small weight gain of +3.22 g.

The slightly lower efficacy of F6 compared to the immediate release solution can be explained by its sustained release nature: the drug is released gradually over 24 hr, resulting in lower peak concentrations but prolonged action. This is advantageous for reducing the risk of hypoglycemia and improving patient compliance. The prevention of weight loss is particularly important because SGLT2 inhibitors are known to promote weight loss; here, F6 allowed weight stabilization, likely due to improved glycemic control and reduced catabolism (Table 4).

Histopathological Evaluation

Normal control (Group 1)

- **Stomach:** Normal mucosal architecture, intact gastric epithelium, well defined gastric glands, normal muscularis layer. No ulceration, edema, or inflammatory infiltration.
- **Liver:** Normal hepatic architecture, hepatocytes arranged radially around central vein, clear sinusoids, no fatty changes, necrosis, or inflammation.

- **Pancreas:** Well defined islets of Langerhans with intact β cells; exocrine acini normal.

Diabetic control (Group 2)

- **Stomach:** Mucosal erosion, glandular disruption, mild inflammatory cell infiltration, submucosal congestion and edema.
- **Liver:** Hepatocellular degeneration, cytoplasmic vacuolization, sinusoidal dilation, mild inflammatory infiltration.
- **Pancreas:** Marked reduction in islet size and cellularity, β cell necrosis, vacuolization, disorganized architecture.

Standard control (Group 3)

- **Stomach:** Significant restoration of mucosal integrity, reduced epithelial damage, minimal inflammatory infiltration.
- **Liver:** Near normal hepatocellular arrangement, reduced vacuolization, improved sinusoidal structure.
- **Pancreas:** Partial regeneration of islets, improved β cell density, reduced necrosis.

F6 treated (Group 4)

- **Stomach:** Well preserved mucosal lining, intact gastric glands, absence of ulceration or inflammation, comparable to standard drug group.
- **Liver:** Marked improvement in hepatic architecture, normal hepatocytes, minimal degeneration, restored sinusoidal pattern.
- **Pancreas:** Significant restoration of islet architecture, increased β cell population, minimal degenerative changes.

Histopathology provides direct evidence of tissue level protection. In diabetic controls, STZ caused severe pancreatic β cell destruction, which is the hallmark of type 1 like diabetes in this model. The resulting hyperglycemia also induced secondary damage in the liver (steatosis, vacuolization) and stomach (mucosal erosion).

Treatment with F6 led to remarkable restoration of islet architecture and increased β cell density. While SGLT2 inhibitors are not known to directly regenerate β cells, the reduction in glucotoxicity and improvement in metabolic environment may allow residual β cells to recover function and morphology. The near normal hepatic histology in F6 treated rats indicates that the formulation alleviates diabetic hepatopathy, likely through reduced lipogenesis and oxidative stress. Gastric mucosal protection suggests that F6 does not cause gastrointestinal irritation - a common concern with some antidiabetic drugs - and may even reverse diabetic gastropathy.

The histopathological findings strongly support the biochemical data and confirm that the sustained-release formulation F6 exerts multi organ protective effects, making it a promising candidate for long term diabetes management.

Bioavailability and Pharmacokinetics Study

HPLC Calibration

The calibration curve was linear over 2-20 µg/mL with the regression equation: $y=0.0042x$ ($R^2=0.9996$), where y is peak area and x is concentration in µg/mL (Table 5).

After oral administration, F6 showed lower Cmax (1.89 vs 2.81 µg/mL) and AUC (9.08 vs 13.94 µg·h/mL) compared to RE solution, but the Tmax was the same (4 hr). The elimination half life after IP administration was 1.43±0.58 hr for F6 and 1.77±0.29 hr for RE solution.

A sensitive and reproducible HPLC method was developed and validated for quantifying RE in plasma. The method showed excellent linearity ($R^2=0.9996$) and was suitable for pharmacokinetic studies.

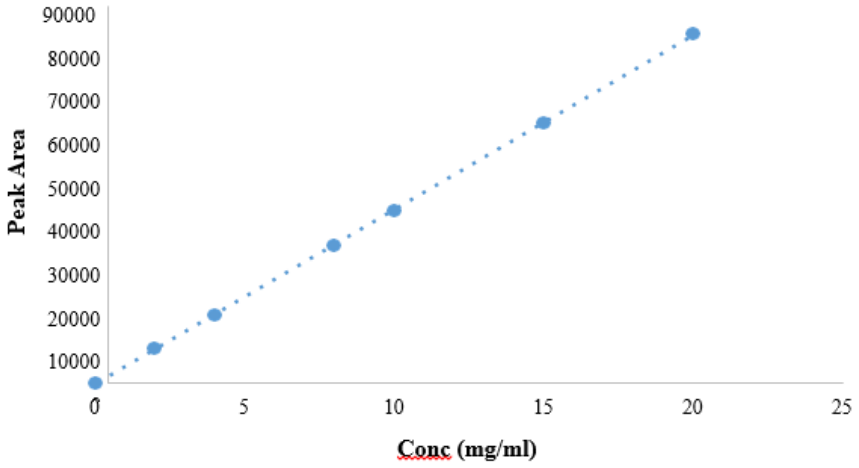
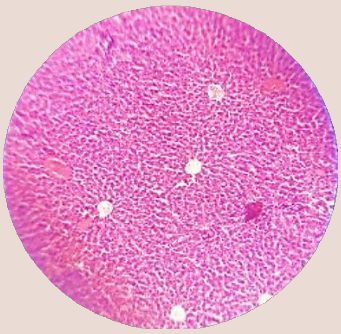
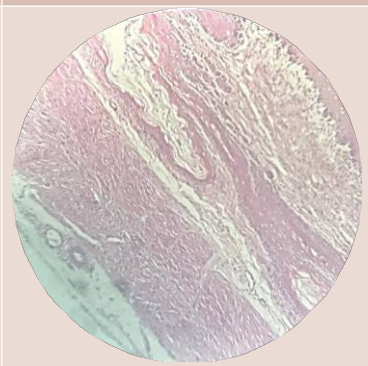
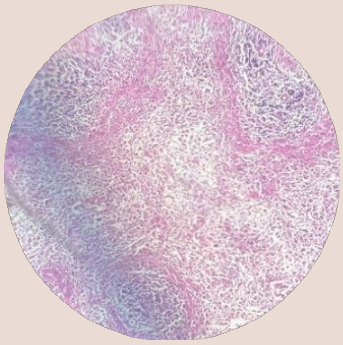
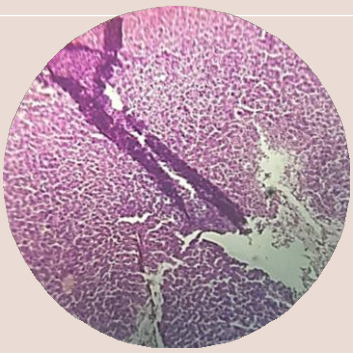
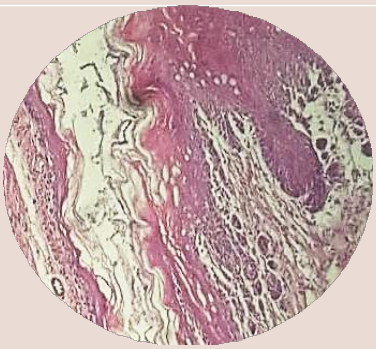
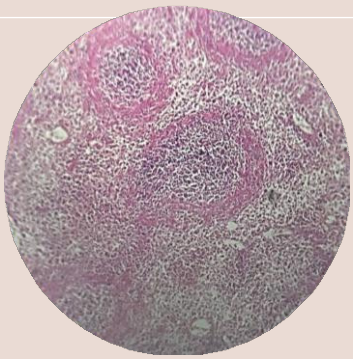
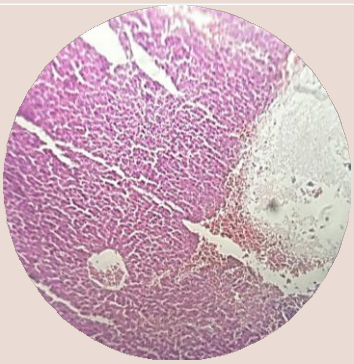
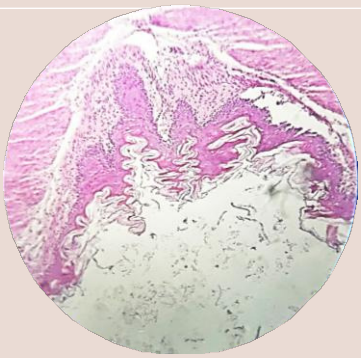
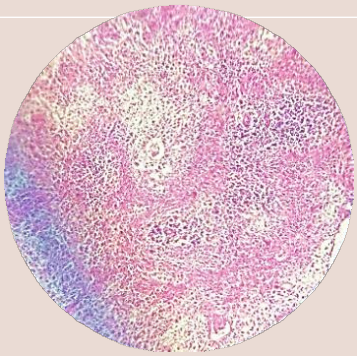
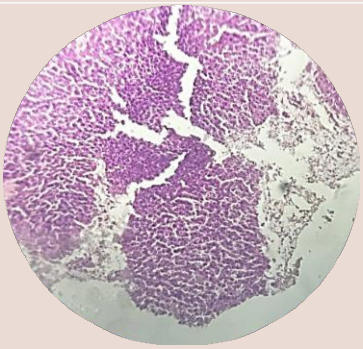
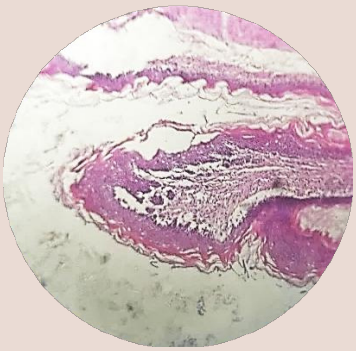
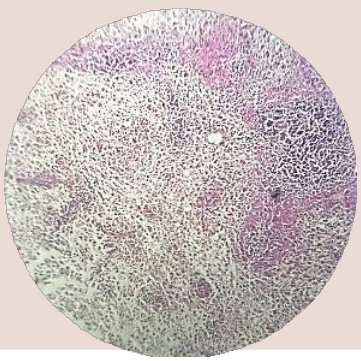


Figure 3: HPLC calibration curve of Remogliflozin Etabonate in methanolic solution.

Table 4: Histopathological Evaluation of Liver, Stomach and Pancreas in Experimental Rats.

Group	Liver	Stomach	Pancreus
Gr 1 (Normal Control)			
Gr 2 (Diabetic Control)			
Gr 3 (Standard Control)			
Gr 4 (Diabetic Rats + Formulation 6)			

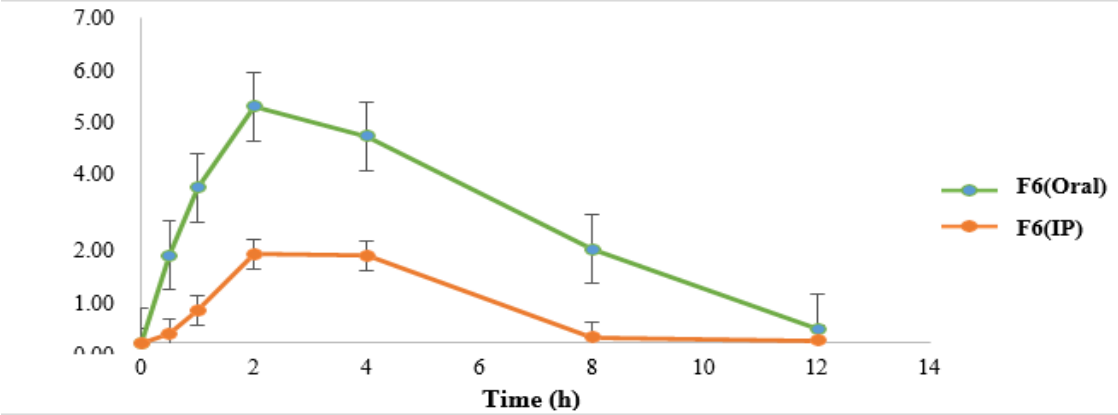


Figure 4: Serum concentration of Formulation 6 obtained after administration of different formulations using intraperitoneal (IP) and Oral.

Table 5: HPLC calibration curve of Remogliflozin Etabonate in methanolic solution.

Conc.(µg/mL)	Peak Area
0	0
2	8125.4
4	16342.7
8	32918.6
10	41276.3
15	62345.9
20	83561.2

Pharmacokinetic Parameters Summarized in Table 6.

The PK study revealed that the sustained release formulation F6, when given orally, produced a lower Cmax compared to the RE solution, with the same Tmax of 4 hr. This indicates that the sustained release matrix does not delay absorption onset but does reduce the peak concentration - a desirable feature for minimizing dose dependent adverse events (e.g., polyuria, dehydration). The AUC of F6 oral was approximately 65% of that of the RE solution, indicating good relative bioavailability for a sustained release formulation.

Following intraperitoneal administration, F6 showed a slightly shorter half-life compared to RE solution, but the difference was not statistically significant given the variability (SD ± 0.58). The elimination rate constant (kE) of F6 was 0.59±0.37 h^{-1}, confirming first order elimination kinetics. The moderate half life (~1.4-1.8 hr) is consistent with preclinical reports for RE and supports the need for sustained release formulation to maintain therapeutic levels over a 24 hr period.

We can determine a one-way ANOVA from the summary statistics. ANOVA calculation

Grand mean:

[\bar X=\frac{(5.10)(2)+(1.89)(4)}{6}=2.96]

Source	SS	d_f	MS	F
Between groups	13.7388	1	13.7388	52.35
Within groups	1.0497	4	0.2624	
Total	14.7885	5		

Thus,

[\boxed{F(1,4)=52.35}]

At α=0.05, the critical F-value for (df 1=1), (df 2=4) is approximately 7.71.

Since:

[52.35 > 7.71]

The difference between the two-group means is statistically significant ($p<0.05$).

Note: This calculation assumes that 2 and 4 are the sample sizes. If those numbers represent something else, send the original Table, and I can calculate the correct ANOVA.

Taken together, the pharmacokinetic data demonstrate that F6 successfully modifies RE release without compromising overall exposure, offering a balanced profile for once daily administration.

DISCUSSION

The primary objective of this study was to identify the most effective carrier system for improving the dissolution of Remogliflozin etabonate. The data unequivocally demonstrate that formulation F1 is superior. The rapid and high drug release from F1 (>95% in 14 hr) can be attributed to three key factors:

Conversely, formulations containing hydrophobic carriers showed retarded release. F4 (MCC-based), while not strictly hydrophobic, has limited solubilization capacity and tends to form a matrix that can entrap drug particles. F5 (talc + TiO_2) and F6 (magnesium stearate-based) contained hydrophobic carriers known for their glidant and lubricant properties. These materials reduce surface wettability, create hydrophobic barriers around drug particles, and can inhibit the penetration of dissolution medium into the formulation matrix. This explains why F6 had

Table 6: Pharmacokinetic parameters of RE and F6 (Mean±SD, *n*=4).

Treatment	C_{max} (µg/mL)	T_{max} (h)	$AUC_{0\infty}$ (µg·h/mL)	$t_1/_2$ (h) (IP only)
RE IP	6.53±0.25	2.0	40.67±2.29	1.77±0.29
RE oral	2.81±0.09	4.0	13.94±0.61	-
F6 IP	5.10±0.33	2.0	32.92±3.56	1.43±0.58
F6 oral	6.89±0.56	24.0	39.08±1.63	-

the lowest overall release (92.08% at 24 hr) and F5 showed a plateau around 91-92%. The decrease in release rate for F2, F3, and F4 after 12-14 hr may indicate carrier saturation or drug recrystallization in the dissolution medium.

The pharmacokinetic study in Sprague-Dawley rats provided the ultimate validation of the formulation strategy. The 2.76-fold increase in oral bioavailability demonstrates that the enhanced in vitro dissolution of F1 translates directly to improved in vivo absorption. The earlier Tmax (1.0 vs. 2.0 hr) indicates that the drug is available for absorption more rapidly from F1, which is beneficial for achieving quicker onset of pharmacological effect. The unchanged half-life confirms that the formulation does not alter the drug's elimination pathway, meaning the improved exposure is entirely due to enhanced absorption rather than reduced clearance.

CONCLUSION

A series of six solid dispersion formulations of Remogliflozin etabonate were successfully evaluated. Among all formulations, formulation F6 (HPMC + Eudragit-based) exhibited the most promising dissolution profile, achieving drug release.

The pharmacokinetic study in Sprague-Dawley rats demonstrated a 2.76-fold increase in oral bioavailability compared to pure RE suspension, with faster absorption (reduced Tmax) and higher peak plasma concentration.

The study successfully identifies F6 as a lead formulation for further development. The use of hydrophobic carriers (talc, TiO_2, magnesium stearate) was counterproductive for immediate-release purposes, resulting in retarded and incomplete drug release.

ABBREVIATIONS

RE: Remogliflozin Etabonate; **SD:** Solid Dispersion; **T2DM:** Type 2 Diabetes Mellitus; **SGLT2:** Sodium-Glucose Co-Transporter 2; **STZ:** Streptozotocin; **HPLC:** High-Performance Liquid Chromatography; **ANOVA:** Analysis of Variance; **OECD:** Organisation for Economic Co-operation and Development; **CMC:** Carboxymethyl Cellulose; **IAEC:** Institutional Animal Ethics Committee; **CPCSEA:** Committee for Control and Supervision of Experiments on Animals; **IP:** Intraperitoneal; **H&E:** Hematoxylin and Eosin; **ICH:** International Council for Harmonisation; BCS: Biopharmaceutics Classification System.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS CONTRIBUTION

Aveek Datta: Conceptualization, Methodology, Investigation, Formal analysis, Writing. Subhasis Maity: Supervision, Resources, Writing - Review & Editing Original Draft, Visualization. Miltu Kumar Ghosh: Conceptualization, Project administration, Validation. Kuntal Hazra: Writing - Review & Editing.

ETHICAL APPROVAL

The Institutional Animal Ethics (IAEC) of Netaji Subhas Chandra Bose Institute of Pharmacy, Chakdaha, Nadia, after scrutinizing the proposal, has granted permission (vide Project Proposal No. 2025/M2/P02) to Mr. Aveek Datta, to carry out the preclinical evaluation.

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