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Original Article

Fabrication of Polymeric Matrix Type Transdermal Patch Containing Glimepiride for Therapeutic Management of Type-2 Diabetes

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ABSTRACT

Aim: This study aims to enhance Glimepiride's (GMP) solubility and transdermal permeability by developing a matrix-type transdermal patch to improve systemic bioavailability, circumvent first- pass metabolism and decrease dosing frequency. **Materials and Methods:** Matrix-type transdermal patches were developed using the solvent-casting method. Initially, formulations were prepared with varying concentrations of polymers and GMP. Formulations were optimized using a quality-by-design approach using response surface methodology (Box-Behnken Design) via Design of Expert (DoE) software, version 8.0.4. Final formulations included Glimepiride in two forms: (a) solid dispersions of GMP (F4) and (b) pure GMP (F7). These formulations were characterized using various analytical techniques. Quantification of Glimepiride from the Transdermal Drug Delivery System (TDS) patches was conducted using the HPLC technique. **Results:** *In vivo* experiments such as hypoglycaemic effect, Skin sensitization and irritations test were performed on adult C57BL6/J mice. Other hand, the *in vitro* drug release to be fond 99.7±0.99 % and 93.7±1.2 % respectively. Similarly, permeability rates for patch (F4 and F7) of 0.141±0.02 and 0.120±0.04 mg/cm^2/hr were recorded respectively. The results demonstrated that the solid dispersion formulation of GMP (F4) exhibited superior permeation and physicochemical properties compared to the pure GMP formulation (F7). **Conclusion:** In conclusion, the proposed transdermal formulation may serve as an alternative to solid oral formulations, effectively bypassing first-pass metabolism and minimizing the frequency of dosage administration.

Keywords: Glimepiride, Matrix-type patch, Solid dispersion, Transdermal drug delivery, Type-2 Diabetes.

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INTRODUCTION

Diabetes remains a significant global health challenge, exacerbated by modern lifestyle changes and reduced physical activity. According to a World Health Organization survey, approximately 422 million people globally have diabetes, with the majority residing in low- and middle-income countries. Each year, diabetes directly causes 1.5 million deaths.[1] Over the past few decades, both the number of diabetes cases and its prevalence have been steadily rising. The prevalence of diabetes continues to rise, partly due to inadequacies in current drug delivery systems. Diabetes is a metabolic disorder characterized by impairing pancreatic β-cells, disrupting glucose regulation in the bloodstream.[2,3] This condition can progressively affect the nervous and immune systems. Specifically, type II diabetes is marked by insufficient insulin production and poor cellular response to insulin, resulting in imbalanced glucose metabolism. Reduced insulin secretion heightens the risk of mortality, morbidity and diminished quality of life. The discovery of insulin by Frederick Banting and Charles Best in 1921 highlighted the connection between diabetes and pancreatic β-cell dysfunction, categorizing the disease into type I and type II.[4,5]

The oral administration of Glimepiride, a sulfonylurea medication for type 2 diabetes, presents several challenges, including variable absorption in the gastrointestinal tract, potential gastric irritation and fluctuations in plasma concentration, which can result in inconsistent therapeutic effects. Furthermore, oral dosing may lead to hepatic first-pass metabolism, consequently lowering the drug's bioavailability. These issues highlight the need for alternative delivery methods. Transdermal administration emerges as a viable option, as it bypasses both the gastrointestinal tract and first-pass metabolism, thereby ensuring a more stable

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drug release and enhanced bioavailability. This method also reduces systemic side effects, improves patient adherence by lessening the frequency of doses and offers a non-invasive solution for individuals who experience difficulty swallowing or have gastrointestinal disorders.

This study focused on enhancing GMP's solubility and transdermal permeability by employing a matrix-type transdermal patch. The solvent-casting method prepared patch formulations with different polymer concentrations and GMP variants. Response surface methodology was employed by the Design of Experiments (DoE) software to optimize the formulations, which guided the selection of optimal conditions for GMP incorporation. The formulations included solid dispersions containing drug and Polyvinylpyrrolidone (PVP 90) at a 1:10 ratio and pure GMP, which were thoroughly characterized using High-Performance Liquid Chromatography (HPLC). The significant advantage of transdermal drug delivery is avoiding first-pass metabolism and reducing kidney burden by avoiding excipient consumption compared with the oral route of administration. It also improves transdermal bioavailability and reduces dose frequency.[6,7]

The experimental results, including *in vitro* drug release and transdermal permeability studies, demonstrated that the solid dispersion of GMP (F4) significantly outperformed the pure GMP formulation (F7). The F4 patch exhibited superior drug release and permeability, highlighting the potential of solid dispersion techniques in improving the transdermal delivery of poorly soluble drugs. More in-depth, we performed an *in vivo* animal study on C57BL6/J mice to check the safety and efficacy of the transdermal drug delivery system. These findings are crucial for developing more effective and patient-compliant transdermal systems for managing chronic conditions like diabetes.

In summary, developing a matrix-type transdermal patch containing Glimepiride has shown significant promise in enhancing drug delivery and systemic bioavailability. Solid dispersions within the patch matrix improved the transdermal permeability and overall physiochemical profile compared to pure GMP. This approach offers a viable strategy for optimizing the delivery of poorly soluble drugs and could improve therapeutic outcomes in patients requiring long-term medication.

MATERIALS AND METHODS

Materials

Glimepiride, Eudragit® RLPO and HPMC K100M were obtained from Yarrow Chem Pvt. Ltd., Mumbai, India. Streptozotocin (STZ), glycerin, PVP KTween 80 and Dichloromethane (DCM) were sourced from Sigma. Glucometer (Accu-Chek, @B07RMYD9SC) was purchased from a local vendor. All chemicals and reagents were used in this study in high purity grade. Oral sustained-release tablets containing Glimepiride and Metformin (2 mg / 500 mg) were acquired from the market (Danavish). Protocols for Animal experiments were approved by the Institute Ethical Committee at Birla Institute of Technology and Sciences Pilani Hyderabad Campus, under registration number BITS-HYD-AICE-2024-044. Animals were procured from registered vendors at CPCSEA.

Methods

Preparation of solid dispersion

The solid dispersion was prepared using a solvent evaporation method. The drug and polymer (PVP K90) were mixed into various ratios such as 1:1, 1:2, 1:4 and 1:6. Further, it was transferred into a 50 mL volume crucible disc and added 10 mL of methanol and mixed well. The mixture was soluble properly. The resulting crucible disc was kept under a vacuum desiccator for 24 to 48 hr till dry.[8]

Solubility enhancement study for GMP

A solubility enhancement study was conducted to circumvent the poor aqueous solubility of GMP, where the drug was mixed with a water-soluble polymer polyvinylpyrrolidone PVP K90 in various concentration ratios (1:1, 1:5, 1:10, 1:20). Further solubility enhancement ratio calculated by HPLC method.

Quantitation technique

A sensitive reversed-phase High-Performance Liquid Chromatography (RP-HPLC) method was developed to quantify Glimepiride in transdermal patches. The analysis used a Shimadzu binary HPLC system, model SIL-30AC, equipped with a C18 reverse-phase column. All system suitability parameters were within acceptable limits. The HPLC analysis was performed on a PDA detector with detection at a wavelength of 227 nm.[9]

Fabrication of transdermal patch

The matrix-type transdermal patch was prepared using the solvent casting method. Eudragit® RLPO (440 mg) and HPMC K100M (300 mg) were added to a 100 mL beaker, followed by 5 mL ethanol and 5 mL dichloromethane. The mixture was then stirred on a magnetic stirrer for 1 hr. Tween 80 and glycerin were added after 30 min during the stirring process. In a separate 100 mL beaker, Glimepiride (10 mg), glycerin (237 mg), oleic acid (100 mg) and tween 80 (25 mg) were dissolved in 10 mL of dichloromethane. This solution was then transferred to the first beaker containing the polymeric mixture and the combined solution was stirred continuously for an additional 15 min to ensure homogeneity and to remove any entrapped air bubbles. The resulting solution was poured into a petri dish and placed under vacuum in a desiccator at ambient conditions for 24 hr to allow drying. After the drying period, the patch was carefully removed from the petri dish using a sharp blade, 2 cm^2 was cut into uniform shapes with a drug loading of 1 mg/cm^2 and an adhesive backing layer was applied to one side. A representative

formulation is illustrated in Figure S1. The same procedure was followed for the solid dispersion of Glimepiride.[10]

Experiment design (DoE) and optimization

The TDS formulation was optimized using a Quality by Design (QbD) approach through a Surface Optimization Model, specifically, the Box-Behnken Design (BBD) implemented via Design Expert software (version 8.0.7.1), as detailed in Table S4. The experimental design involved three factors: Eudragit RLPO (X1), HPMC K100M (X2) and glycerin (X3), each evaluated at two levels. The software suggested seventeen experimental runs, with three central points selected for further experimentation. Seventeen distinct formulations were prepared, each characterized by three response variables: permeability (Y1), tensile strength (Y2) and Folding endurance (Y3). The results from all seventeen runs were incorporated into a model table for subsequent analysis. A quadratic model was chosen to analyze the data, which was statistically evaluated using ANOVA. A desirability function (numerical optimization procedure) was employed to obtain the optimized formulation and the formulation with a desirability value closest to 1 was selected. Additionally, we prepared two different formulations: one with pure API and another with modified API (solid dispersion) using the same optimized formula.[7]

Morphological analysis

Field Emission Scanning Electron Microscope (FE-SEM)

Morphological analysis of the transdermal patch was conducted by FE-SEM; initially, samples were sectioned into small pieces and affixed to a sample holder using adhesive carbon tape. The resulting formulations, F4 and F7, were then sputter-coated for 45 min. Subsequently, the prepared samples were introduced into the Scanning Electron Microscope (SEM) chamber. The SEM was operated at optimized voltage and magnification settings to acquire detailed images of the surface morphology of the patches. The resulting images were analyzed to assess the transdermal patches' texture, uniformity and structural characteristics.[11]

Fluorescence microscope

The morphological evaluation was done using a fluorescence microscope, Make-Nikon model No. eclipse TS100. A transdermal patch of size 2×2 cm was subjected to a microscope and the clear image was captured with a Nikon camera integrated with a microscope.

FTIR study

Infrared spectra were recorded with an FT-IR spectrometer, Spectrum 2 (Perkin Elmer, France) and a high-performance DTGS (Deuterated Triglycine Sulfate) MIR detector. The I.R. spectra were collected by performing 16 scans over 450-4000 cm^{-1} with a spectral resolution of 4 cm^{1}. The samples were prepared using the KBr press method. Each excipient was scanned individually and the final formulation was analyzed as a transdermal patch.[12]

Thermal analysis

Differential Scanning Calorimeters (DSC) measure thermal transitions in a material. This technique determined a possible interaction between excipients and the drug. The study was conducted on (T.A. instrument DSC-250 US), individuals and the physical mixture. The physical mixture containing Eudragit RLPO, HPMC K100M and GMP was subjected to DSC. Finally, the samples were scanned using defined instrument parameters, such as temperature range 0 to 300°C and scan type ramp. Following instrument protocols.[13]

Physicochemical evaluation of transdermal patch

Visual inspection was initially done for the patch's colour, clarity, flexibility and smoothness.

Measurement of patch thickness

A digital vernier calliper (Electrolab India Pvt. Ltd.,) was used to measure the thickness of the patches loaded with a drug at 3 points from the left corner, right corner and the centre of the patches. The experiment was performed (n=3) and calculated mean and S.D. in mm.[14]

Weight uniformity test

Randomly selected patches (n=3) were weighed on an analytical balance (make: Mettler Toledo, model No. ME204) and their weight variation from average weight was calculated.

Folding endurance

This test determined strength and plasticizer efficiency. The film (2×2 cm) (n=3) was repeatedly folded manually many times from the same place until it broke where the number of times the patch could be folded from the same place and ensure the endurance of the patch.[15]

Percentage moisture content

A desiccator containing approximately 500 g of fused anhydrous calcium chloride was utilized to maintain controlled humidity and temperature conditions (30°C±2°C, 75% relative humidity) for the transdermal films, each having a uniform area. The films were weighed at 24, 48 and 72 hr. The percentage moisture content was calculated using equation 1.[15]

$$\text{Moisture Content (\%)} = \frac{\text{(Initial weight)} - \text{(Final constant weight)}}{\text{The initial weight of the patch}} \times 100 \quad ----- (1)$$

Flatness study

The film's per cent flatness was evaluated by measuring variations in thickness and uniformity. The presence of constrictions or irregularities in the strips was assessed, with zero per cent constriction indicating perfect flatness. The per cent constriction

was determined using equation 2, where (L^i) represents the initial length of each strip and ($L2^f$) denotes the final length of each strip.[15]

$$(L^i - L2^f)/L1^i \times 100 - - - - - - - - (2)$$

Surface pH

The patches were tested with a pH meter from Hanna Instruments, model HI5222. A surface pH electrode was used to measure the surface pH of the patches. The electrode was positioned just above the surface of the patch, with a gentle touch to ensure accurate readings.

Rheological study (Tensile Strength)

A rheometer (Anton Paar MCR 302) assessed the tensile strength. This measurement was performed using a rotational drum assembly. The 4×4 cm patches were placed in the rotating drum and their tensile strength was recorded. The experiment was conducted for both formulations to compare results.[16]

In vitro characterization

In vitro drug release

The dissolution study was carried out by USP apparatus 5, Paddle over disc (Electrolab India, Model: EDT-08LX). A 2 cm^2 patch was placed in a vessel containing 900 mL Phosphate Buffer Medium (PBS pH 7.4) at a temperature of 37°C±0.5°C and 50±2 rpm up to 48 hr with a predefined time interval (4 hr±10 min). Aliquot 5 mL was withdrawn and replaced with the fresh buffer solution. HPLC analysis was carried out on the collected samples. Drug release kinetics was assessed with the help of D.D. solver software and determined r2 for each kinetic model like zero-order, First order, Higuchi, Korsmeyer-Pappas, Hixson -Crowell.[17,18]

Drug content

A GMP-loaded patch with an area of 1 cm^2 and a 1 mg/cm^2 drug concentration was placed into a 10 mL calibrated volumetric flask. To this, 5 mL of diluent, composed of acetonitrile and methanol in a 2:1 ratio, was added. The flask was subjected to vortex mixing on a mechanical shaker for 1 hr. Following this, the volume was adjusted to 10 mL with the same diluent and the solution was sonicated for 10 min using a batch sonicator, with intermittent shaking, while maintaining a temperature of 25±2°C. The

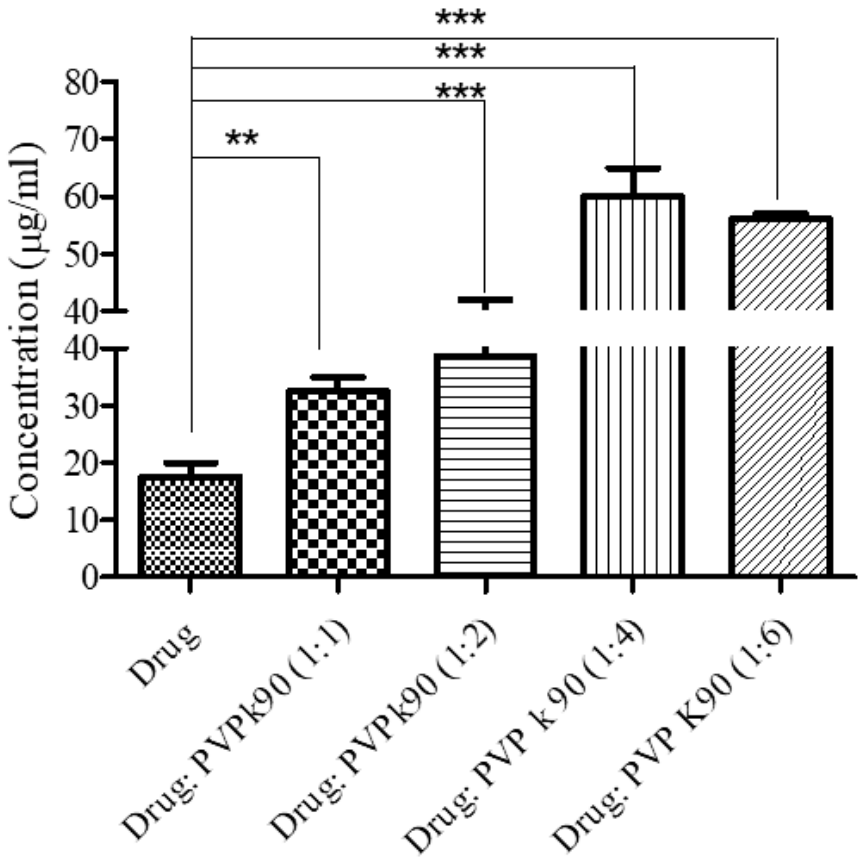

Figure 1: This graph illustrates the significant increase in solubility of Glimepiride when combined with various polymers at different concentrations. The x-axis represents the polymer-drug ratio, while the y-axis indicates the solubility enhancement (µg/mL). The maximum solubility enhancement was observed at a 1:4 ratio, reaching a ~3.5-fold increase compared to the solubility of the drug without the polymer.

resulting solution was then analyzed Using High-Performance Liquid Chromatography (HPLC).

Ex vivo characterization

Skin permeation studies

Male C57BL6/J mice (18-22 g) were sacrificed by excessive ether anaesthesia and the hairs were removed from the dorsal portion using a Philips hair trimmer. The skin was harvested and fat adhering to the dermis side was removed using a scalpel and isopropyl alcohol. Finally, the skin was washed with milli-Q-water and subjected to Franz diffusion cell diffusion (Make electro lab, Model No EDC 07, India) to estimate the penetration of the drug through mice skin. The skin was subjected to Franz diffusion cell apparatus, which maintained a temperature of 32°C±2°C by placing the skin in a phosphate buffer of pH 7.4 for 1 hr. Followed by instruments run with 750 rpm, outer jacket temperature 37°C±0.5°C. The diffusion apparatus comprises two compartments: a donor and a receiver. 7.5 mL of phosphate buffer pH 7.4 was added to the receiver compartment and skin was fixed between the donor and receiver compartment using clips. The medium was kept for equilibration for 30 min until the temperature of the medium reached 32±2°C. Subsequently, a patch of 2 cm^2 was placed above the skin and tightened with the help of a clip. When the skin and buffer solution's pH equalled the iso-electric point, the drug's permeation from the skin to the phosphate buffer solution was measured and the study continued for 48 hr. Aliquots (1 mL) at a predefined time interval of 4 hr±10 min were analyzed by HPLC. Diffusion was calculated as per the equation 3.[19]

$$\% \text{ Diffusion} = \frac{\text{Total Flux mg/cm}^2\text{/48 hr}}{\text{Patch Label Claim}} \times 100 \quad ------3$$

In vivo characterization (Animal Studies)

Induction of diabetes type-2

Diabetes mellitus was induced by streptozotocin using multiple low dosages of 25 mg /kg in adult male C57BL6/J mice by intraperitoneal (i.p) injection. In 0.1 M citrate buffer pH 4.5, previously kept at refrigerator temperature. The control group received an equivalent amount of citrate buffer. A blood glucose monitoring system measured the plasma glucose collected in blood samples using the tail vein puncture method. A blood glucose level of 220-250 mg/dL is considered type-2 diabetes after 72 hr.[20]

Pharmacological evaluation

The anti-hypoglycemic efficacy of TDS patches was tested on male C57BL6/J mice with bodyweight 180-220 g. The experiment was broadly divided into two significant categories: diabetic and non-diabetic. The non-diabetic section involved the negative normal control and a diabetic section called positive control. The animals were divided into five subgroups according to treatment protocols, i.e., *negative control (normal), positive control, Control (STZ) (Control+Treatment F7), (Control+treatment F4), (Control+treatment placebo), (Control+treatment oral (APIs))*. Each Group contained six healthy animals. Two best-optimized transdermal formulations (F4 and F7) were chosen for animal study with 5 mg/kg drug for animal experiments. The skin hair was removed with a Philips trimmer and the transdermal formulations were applied to an abdominal area of the skin. A single dosage was administered using a topical route of administration and the subsequent experiments were performed as per protocol. Further blood glucose was monitored at multiple time points (e.g., 30 min, 1, 4, 12, 24 and 48 hr) after post-treatment. F4 consisted of solid dispersion-bearing GMP and F7 pure GMP.[21]

Skin irritation and sensitization test

Toxicological studies were performed per OECD guidelines TG-420,402 and 406. Toxicological studies were conducted to check the limit and extant toxicity the drug can produce in an animal or human being. This study confirms the skin irritation and sensation after applying a transdermal patch on rat skin. Healthy male C57BL6/J mice (n=12) were taken, their hairs were removed from the stomach and their stomach was nicely cleaned with water and alcohol. Mouse were divided equally into three groups: 1st Group applied a placebo, 2nd and 3rd applied to optimize formulation (F4 and F7), respectively.[22] The experimental protocols followed the method reported by Banerjee *et al*. Animal groups were divided into different groups such as positive control, negative control and third treatments (each group number of animals present n=4). In contrast, positive control was treated with 1% w/v 1-chloro-2,4-dinitrobenzene in 10% propylene glycol, second free drug or placebo and third treated with TDS formulations, i.e., F4 and F7). Before initiating the experiment, the hairs from the lower part of the abdomen of mice were shaven and washed with a hydroalcoholic solution. Skin sensitization was monitored by a score of 0 to 3, with 0 indicating no reaction, 1 indicating scattered mild redness, 2 indicating moderate and diffuse redness and 3 representing an intense skin reaction that included erythema and oedema with eventual more profound skin damage.[22]

Statistical Analysis

The statistical analysis was analyzed and calculated with the help of software GraphPad Prism software version 5.0., USA and All the calculated numerical values were displayed as mean±SEM and p-value. A comparison was made between the normal, control and treated groups by applying a One-Way Analysis of Variance (ANOVA), where $p<0.05$, the difference level was considered statistically significant.

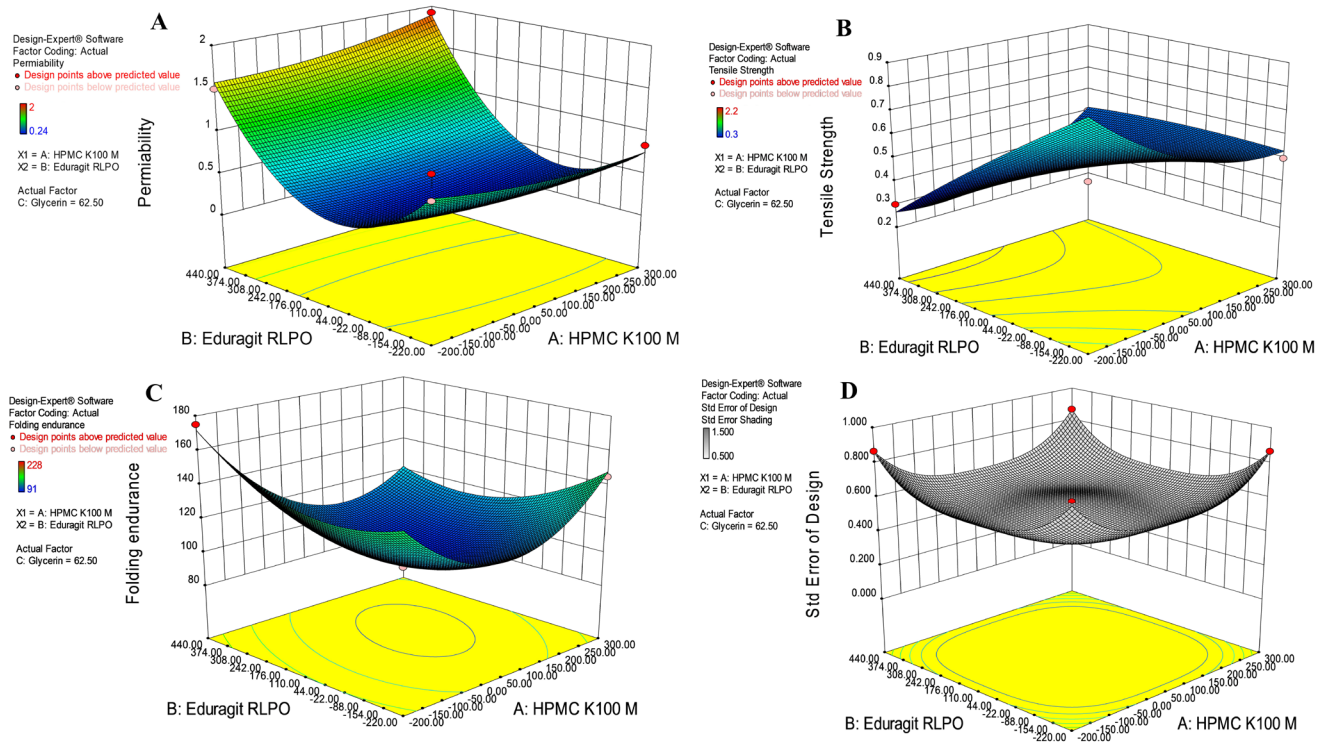

Figure 2: 3D surface model graph of response factors such [A] permeability mg/cm²/h [B] Tensile Strength [C]folding endurance and [D] Design matrix evaluation for response surface quadratic 3D model graph. The graphs show a relationship between the response factor and the concentration of independent variables. The lower concentration is considered as (-) and higher (+).

Table 1: (a) QbD experiment design at two different lower and higher levels (b) final Optimized formulation after successful QbD implementation.

Box-Behnken design								
Independent variables			Concentration Range					
			Low level (-)		High Level (+)			
Factor A: Eudragit RLPO(mg)			50		300			
Factor B: HPMC K100M(mg)			110		440			
Factor C: Glycerin (mg)			62.5		250			
Optimized formulations								
Formulation Code	GMP containing S.D. (mg)	Drug mg	HPMC K100M (mg)	Eduragit RLPO mg	Glycerin mg	Oleic acid mg	Tween-80 mg	DCM: Ethanol (1:1) mL
F4	10	-	300	440	237	100	25	10
F7	-	10	300	440	237	100	25	10

RESULTS

Solid dispersion and solubility enhancement

As anticipated, solubility increased with the amount of the polymer PVP K90. Notably, solubility improved by ~1.8-fold at a 1:1 ratio, about 2-fold at a 1:2 ratio, ~ 3.5-fold at a 1:4 ratio and saturated at a 1:6 drug-to-polymer ratio with 3.2-fold. The maximum solubility was achieved at a 1:4 drug-to-polymer ratio. However, our results indicated that solubility was notably enhanced at the 1:4 ratio, with no further significant increase observed beyond this point (Figure 1).

Analytical Quantitation technique

A validated analytical HPLC method was used to estimate GMP from the transdermal patch. A suitable diluent was used for the extraction of the drug from the TDS patch. The correlation of coefficient R^2 observed is 0.999. Glimepiride's Retention Time (R.T.) was recorded at 4.7±0.47 min and all the system suitability parameters were recorded well within the acceptance limits. The HPLC area was recorded at λ_{max} 227 nm wavelength. The representative chromatograms are depicted in Figure S1.

Fabrication of TDS Patch

The matrix-type transdermal patch was prepared using the solvent casting method. All the physicochemical parameters were initially evaluated and the results were satisfactory. The image of the transdermal formulations is depicted in supplementary Figure S2.

Formulation optimization

The proposed formulation was optimized through the Box-Behnken Design (BBD) using Design Expert software (version 8.0.4). Initially, all the required parameters were fed into the software and run, followed by including dependent variables and response factors in the software program and analyzed using a quadratic equation model (Tables 1 and 2). Accordingly, the model manifested significantly and the lack of fit was non-significant with r^2 0.998±0.003. The resulting proposed model was found to be statistically significant (p>0.05) for all dependent variables and lack of fitness was found to be non-significant (0.500±0.100) with r^2 0.913±0.035. The final formulation was selected based on the desirability value closer to 1 (Tables S1-S4). The 3D model graphs are depicted in Figure 2. All the response factors fit with Equations 4-6, respectively. Additionally, the desirability pareto graph for final optimization formulation is mentioned in supplementary Figure S3.

Permeability=0.33+0.031×A +043 × B-0.049 ×C+0.1255 ×A×B-0.125×B+0.084 ×A^2+0.87×B^2+C^2……(4)

Folding endurance=9566-12.25×A-0.375 ×B+39.87 ×C-12 .5×A×B+4×A×C+3.75×34.04×A^2+17.79 ×B^2+57.79 ×C^2----------(5)

Tensile Strength=0.46-0.025×A0.15 ×B+0.43×C+0.15×A×B+ 0.05×B×C+0.099×A^2-0.015×B^2+1.08×C^2……..(6)

Formulation development and physical appearance

The transdermal patch was developed using solid dispersion followed by solvent evaporation. The amounts of excipients (Eudragit, HPMC, glycerine) were chosen from the prior QbD outputs and the lowest and highest concentrations of excipients were identified. The physical appearance of the TDS patch was shown as transparent, clear, flexible and smooth. 1 mg/cm^2 glimepiride was loaded on the TDS patch Figure S2 A-B.

Morphological analysis

The developed TDS patches were examined using FE-SEM and fluorescence microscopy, which revealed that the polymers and drug were well-distributed. The FE-SEM images (F4) at a 5 µM scale showed the cohesive nature of the polymers, while Formulation (F7) exhibited similar characteristics at a 2 µM scale. Both formulation's morphology is satisfactory. Additionally, fluorescence microscopy provided consistent results, confirming the findings observed with FE-SEM. The image is depicted in Figure 3.

Fourier Transform Infrared Spectroscopy (FTIR) study

FTIR analysis was performed to identify the major functional groups in the drug and excipients: (A) Glimepiride: The Carbonyl Group (C=O) was confirmed at 1700-1720 cm^{-1}, the Hydroxyl Group (O-H) at 3300-3500 cm^{-1} and the Aromatic Group (C-H) at 3000-3100 cm^{-1}. (B) Eudragit RLP: The Carbonyl Group (C=O) was detected at 1730 cm^{-1}, indicative of an ester functional group characteristic of Eudragit RLPO. The presence of aromatic rings in the polymer structure was confirmed by multiple peaks around 3000-3100 cm^{-1}, while a peak at 2850-2950 cm^{-1} indicated the presence of aliphatic hydrocarbon chains. (C) HPMC K100M: An intense peak at 3200-3600 cm^{-1} revealed the/ presence of hydroxyl groups, which are abundant in cellulose ethers like HPMC K100. The ether group (C-O-C) was confirmed by a peak at 1000-1200 cm^{-1}, indicating the presence of ether linkages typical of cellulose ethers. Additionally, peaks at 2850-2950 cm^{-1} and around 3000-3100 cm^{-1} confirmed the presence of alkyl and aromatic groups, respectively. (D) Final Formulation: The FTIR spectra showed no significant interactions between the drug and polymers. The functional groups of Glimepiride were present in the formulation, confirming that the drug was successfully incorporated into the polymers without degradation. The spectral results are detailed in Figure S4 (a-d). Supplementary NMR results of Glimepiride were summarized and the test parameters were characterized, i.e., ^{1}H, ^{13}C, ^{1}H,^{13}C-HSQC and DEPT-135^o Figure S5.

Differential Scanning Calorimetric Analysis (DSC)

Pure GMP and HPMC K100M showed endothermic peaks at 214. 47^{o}C (an enthalpy of 69.528 J/g) and 69.04^{o}C (an enthalpy of 81.117 J/g) respectively. On the other hand, Eduragit RLPO showed two endothermic peaks at 74.01^{o}C and 188.85^{o}C (an enthalpy of 55.986 J/g and 28.868 J/g respectively). Besides that, the physical mixture showed a characteristic endothermic peak at 198.89^{o}C (an enthalpy of 31.319 J/g). The thermograms are reported in Figure 4.

Physicochemical evaluation

The physicochemical parameters of the Transdermal Systems (TDS) were evaluated. The patches were visually inspected for colour, clarity, flexibility and smoothness and all were satisfactory for their intended use. A representative image of the TDS patch is shown in Figure S2. The thickness measurements for formulations F4, F7 and placebo were 0.52±0.07 mM, 0.50±0.05 mM and 0.49 ±0.01 mM, respectively. The solid dispersions notably impacted the patch thickness, with formulation F4 demonstrating superior thickness uniformity. Additionally, formulation F4 exhibited better tensile strength, as illustrated in Figure S5. Folding endurance data, provided in Table 2, showed that formulation

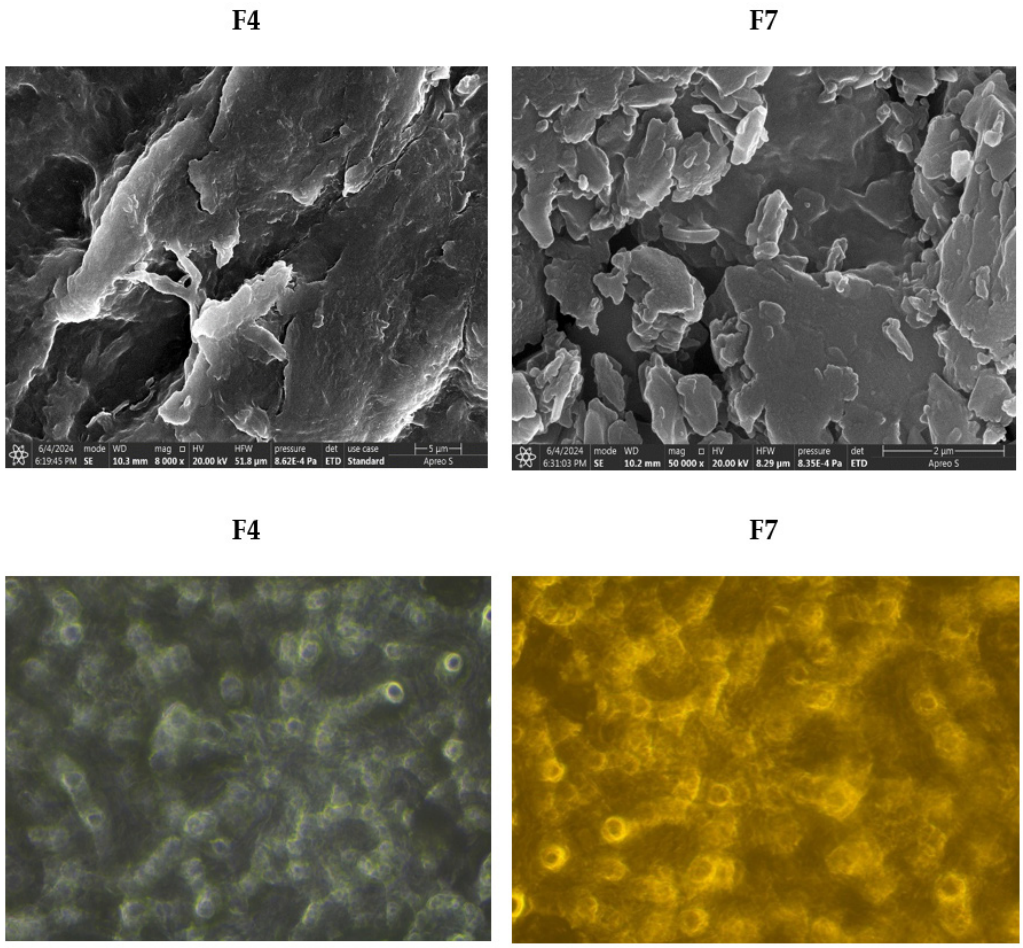

Figure 3: FE-SEM and fluorescence microscope examined transdermal patch morphology and drug dispersion, while drug dispersion was found uniformly inside the transdermal matrix, Both formulations showed that the drug and excipient dispersed uniformly in the TDS patch.

Table 2: In this experiment design table, the total numbers of runs are predicted by software of 15 using three independent variables: viz. A: Eudragit RLPO (mg); B: HPLC K100M (mg) and C: glycerine (mg) and three response factors: viz. R1: permeability (mg/cm²/hr) R2: tensile strength (kg/cm²) and R3: folding endurance (no. of folds).

Std.	Run	A	B	C	R1	R2	R3
12	F1	50	440	250	1.57	1.8	225
3	F2	200	440	62.5	1.5	0.3	175
2	F3	300	220	62.5	0.84	0.5	145
13	F4	50	110	62.5	0.24	0.4	93
15	F5	50	110	62.5	0.256	0.5	91
11	F6	50	220	250	0.896	2	202
14	F7	50	110	62.5	0.498	0.5	103
5	F8	200	110	125	0.587	1.2	155
1	F9	200	220	62.5	0.922	0.9	167
9	F10	50	220	125	0.823	1.4	125
8	F11	300	110	250	0.523	2.2	228
10	F12	50	440	125	2	0.94	133
4	F13	300	440	62.5	1.92	0.5	103
6	F14	300	110	125	0.489	1.1	145
7	F15	200	110	250	0.511	2.1	222

F4 outperformed F7, with F4 exhibiting a folding endurance of >170±5 cycles, compared to F7 at >150±5 cycles and the placebo at >140±5 cycles. Additionally, moisture content was present in TDS patch 6±0.08%, 5±0.05% and 7%±0.07% and flatness 100%, respectively. The patch surface pH is 6.02±0.002, 5.83±0.003 and 5.7±0.006, respectively. Tensile strength was recorded by rheometer analysis and it was found that the F4 formulation is better than F7 (Figure S6). All physicochemical parameters were within the acceptable range of the same TDS patch.

In vitro drug release

Experimental results demonstrated that initial drug release from formulations F4 and F7 was 7% and 5%, respectively, after 2 hr. In contrast, the marketed oral formulation exhibited nearly 30% drug release within the same period. After 10 hr, formulation F4 released 33% of the drug, while formulation F7 released 25%. At the same time, approximately 95% drug release was observed from the oral marketed formulation. After that, at 48 hr, results demonstrated that 99±5% of the drug was released for F4 and 92±5% for F7. However, the F4 and F7 formulations followed the Hixson-Crowell release kinetics model with correlation coefficients (r^2) of 0.994 and 0.996, respectively. Conversely, the marketed Sustained-Release (S.R.) oral tablet followed first-order kinetics, with an r^2 of 0.990, achieving a cumulative drug release of 99±2% after 12 hr (Figure 5).

Skin penetration studies

The drug permeation rate from F4 and F7 formulations was 0.42±0.4 and 0.32±0.3 mg/cm^2/h, respectively. The result shows that the F4 formulation shows a better skin penetration profile than the F7 formulation. Both of these formulations showed a linear permeation profile for a rate of drug penetration (Figure 6).

Hypoglycemic test

Blood glucose levels were tested on rat blood plasma and found that the optimized TDS patch Formulation (F4) was significantly superior (p>0.05) to the F7 formulation. Comparatively, a marked oral formulation showed more significant results at 30 min, 1 hr, 4 hr and 12 hr blood sampling. After that, the TDS patch showed a better hypoglycemic effect of up to 48 hr. However, formulation F4 showed a better glucose control effect up to 48 hr than F7 TDS formulation. The results are summarized in Figure 7.

Skin sensitization and irritation test

The skin sensitization and irritation study was performed and no reaction was observed in treatment groups such as placebo (F4) and (F7), respectively. While in positive control, we found intense sensitization and redness in skin irritation. The detailed results are summarized in Table 3.

DISCUSSION

Pro-inflammatory genes play a critical role in the pathogenesis of metabolic disorders, including diabetes and cancer. Chronic inflammation, driven by these genes, contributes to insulin resistance and β-cell dysfunction, leading to type 2 diabetes. In cancer, pro-inflammatory cytokines promote tumor growth and metastasis by enhancing angiogenesis and immune evasion.[23-25] Straightforward, various types of transdermal drug delivery

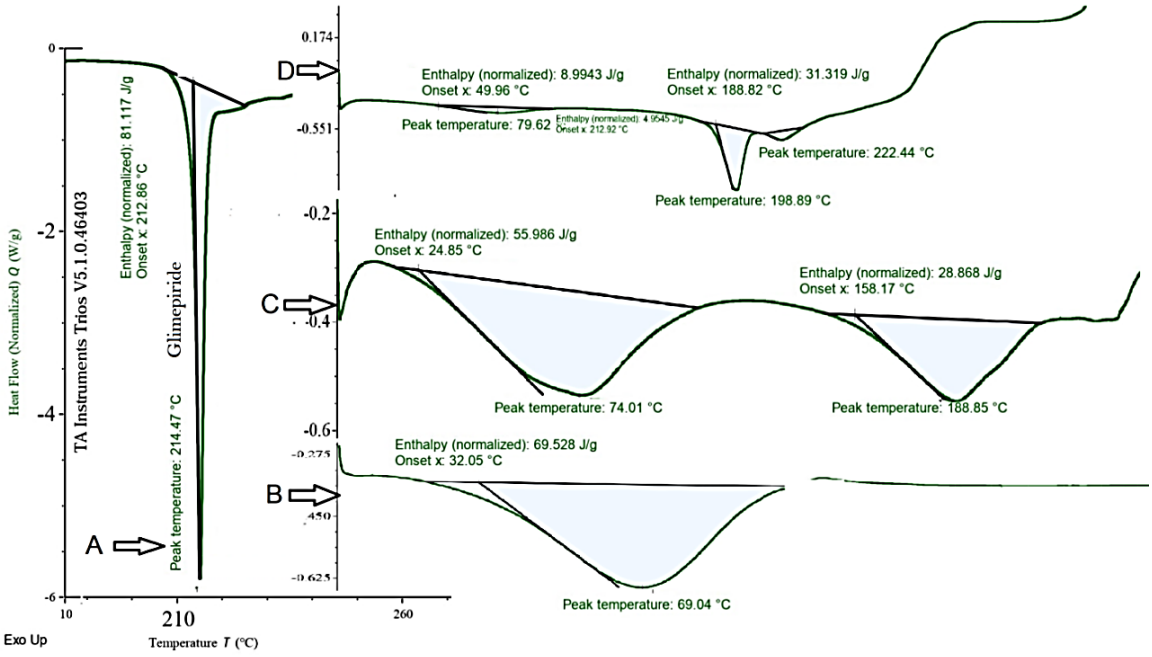

Figure 4: DSC thermograms for drug and excipients. A: GMP, B: HPMC K100M, C: Eudragit® RLPO and D: a physical mixture of excipients and GMP.

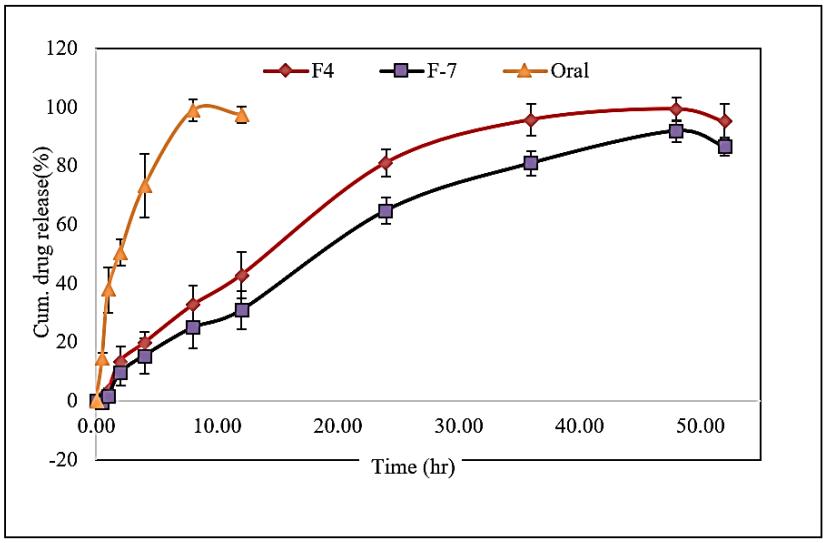

Figure 5: The cumulative drug release profile of the marketed formulation and transdermal patch while the light green solid line represents the marketed sustained (S.R.) tablet, red solid (F4) and black solid line (F7), respectively.

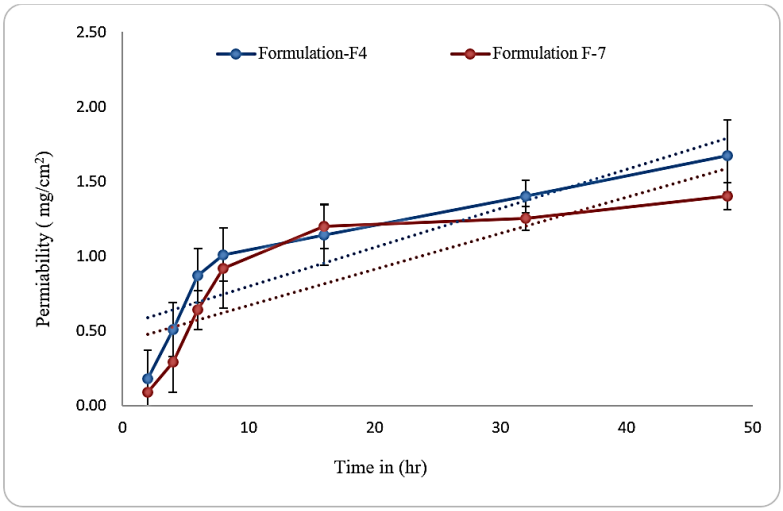

Figure 6: The depicted solid line graph represent rate of permeation of GMP across rat skin from drug loaded transdermal patches. Whereas the dotted line indicates the linear degradation of the drug.

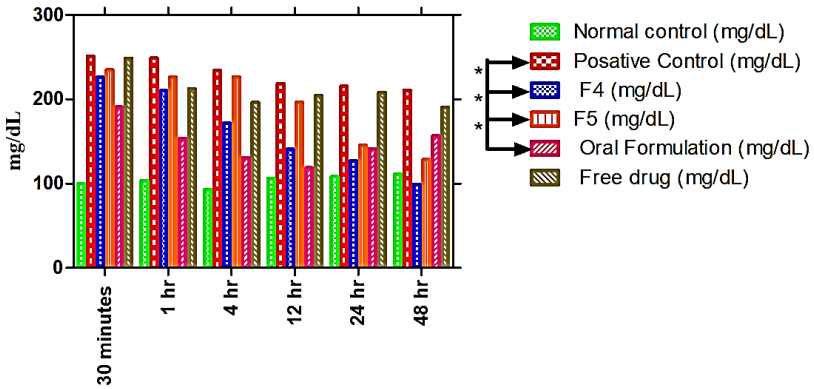

Figure 7: The hypoglycemic effect of Glimepiride was tested with different routes of administration, such as oral marketed formulation and TDS formulations, while TDS-F4 showed little better results compared with TDS-F7. Marketed oral formulation shows better hypoglycemic effect in blood plasma up to 12 hr. (While the p-value was considered ≤ 0.05 and (*) 0.01, (**) 0.001 and (***) 0.0001 respectively.

Table 3: Summarized results of TDS formulations. (+) No skin irritation was considered and (-) was considered skin irritation. A *p*-value> 0.005 is considered as significant.

Toxicity Studies								
Animal Group	Skin sensitization				Skin Irritation			
	Sensitization Rate (%)	Sensitization grade	Sensitization Classification	Reaction	Parameter	Placebo (*n*=5)	Formulation (F4) *n*=5	Formulation (F7) *n*=5
(+) Control, N=4	100(5/5)	V	Extreme	Intense	Redness	+	+	-
(-) Negative Control Placebo, N=4	0 (0/5)	I	Weak	No	Edema	+	+	+
Treatment (F4), N=4	0 (0/5)	I	Weak	No	Irritation	+	+	+
Treatment (F7), N=4	0 (0/5)	I	Weak	No	Inflammation	+	+	+

systems are available, but the existing technology in TDS has a few advantages and limitations. For instance, hollow microneedles can deliver drugs to compressed dermal tissue, compromising the drug's therapeutic efficacy. In contrast, our proposed polymeric matrix-type patch utilizes a cellular transport mechanism to penetrate the skin and quickly reach the epidermis and dermis. Once in the dermis, the drug is absorbed through dermal microcirculation, which stimulates pancreatic β-cells.[26,27] The physicochemical parameters of our formulations- such as physical appearance, tensile strength and folding endurance- were within acceptable ranges. Notably, formulation F4 outperformed F7 in both physical appearance and tensile strength (Figure S5). Formulation F4 demonstrated significantly better overall results due to the modification by the solid dispersion technique, which improved the solubility of Glimepiride. Some nano formulation like liposome are also showing potential role for therapeutics management of type-2 dibeties.[28]

Additionally, the inclusion of oleic acid played a crucial role in enhancing the permeation efficacy of the Transdermal Delivery System (TDS), which we incorporated into the final formulation. This current TDS formulation showed notably better drug release and hypoglycemic control.[29] The research findings suggest that F4 has superior physicochemical properties and permeability compared to F7 (Figure S5). Our TDS formulation bypasses first-pass metabolism and protects the drug from the gastric environment, potentially enhancing therapeutic efficacy. Additionally, the proposed drug delivery could reduce the excipient toxicity, provide sustained drug release, improve systemic bioavailability and prevent alcohol-induced dosage dumping.[30] We employed analytical techniques like HPLC to estimate GMP from the TDS patches. The HPLC chromatographic techniques offer better resolution and understating of pharmaceutical drug products in contrast to quality control, while the U.V. spectroscopy technique has some limitations at the industrial scale, such as the 21 CFR compliance peak purity index at 3D. However, HPLC methods are preferable for industrial applications due to automation and fast analysis. The separation of Glimepiride from the HPLC column was a little better compared to the existing reported method.[31,32] The chromatograms and instruments method has been reported in a supplementary file (Figure S1).[33]

The TDS formulation demonstrated sustained drug release for up to 48 hr. However, our study showed that 99% of the drug was released within this period, significantly outperforming previous research where 100% release was achieved in 25 hr.[10] The formulations adhered to USP Chapter 711, with F4 and F7 displaying similar drug release profiles and following Hixson-Crowell kinetics, with r^2 values of 0.994 and 0.996, respectively.[46] Both formulations reached a Q value of 80% at 39 hr. Although F4 and F7 showed comparable release profiles overall, F4 exhibited a superior drug release profile after 24 hr (Figure 5). Regarding skin irritation, no significant redness, oedema, or inflammation was observed except for mild redness. The permeation rate of the modified Glimepiride (S.D.) transdermal patch showed a relatively better flux profile (Figure 6). Hypoglycemic test indicated that F4 performed better than F7, with significant results (p<0.005) across all parameters. This finding aligns with similar studies reported by Pandey *et al.*[34] Compared to the marketed oral formulation, which shows therapeutic effects for up to 12 hr, the same TDS formulations offer extended efficacy for up to 48 hr. This extended-release minimizes dosage frequency, offers a better choice for a short biological half-life, prevents alcohol-induced dosage dumping and enhances patient compliance for chronic diabetic patients.

Thus, TDS provides better patient compliance by maintaining effective drug plasma concentrations for extended periods while minimizing dose frequency. Additionally, TDS reduces first-pass metabolism and minimizes excipient-related gastrointestinal tract issues, potentially decreasing liver hepatotoxicity. F4 and F7 formulations showed positive outcomes in skin irritation and sensitization tests. However, our proposed drug delivery system could be used for the intended therapeutic management of Type-2 diabetes.

CONCLUSION

A successful transdermal formulation was developed using the QbD (Quality by Design) concept. This approach has the potential to reduce research time and streamline R and D efforts. The efficacy of the transdermal patch was evaluated on C57BL6/J mice, yielding satisfactory results. Consequently, we can conclude that the proposed drug delivery system shows promise for delivering medication via the transdermal route. Additionally, this system could reduce reliance on oral formulations, bypassing first-pass metabolism and enhancing systemic bioavailability. Among the two optimized formulations developed (F4 and F7), F4 demonstrated slightly better permeation and hypoglycemic control performance in C57BL6/J mice. Overall, our proposed drug delivery system could be a viable option for managing chronic type 2 diabetes.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

T2DM: Type 2 Diabetes Mellitus; **GMP:** Glimepiride; **DoE:** Design of Expert; **TDS:** Transdermal drug delivery system; **PVP:** Polyvinylpyrrolidone; **HPMC K100:** Hydroxypropyl Methylcellulose K100; **STZ:** Streptozotocin; **DCM:** Dichloromethane; **CPCSEA:** Committee for the Purpose of Control and Supervision of Experiments on Animals; **RP-HPLC:** Reversed-Phase High-Performance Liquid Chromatography; **FE-SEM:** Field Emission Scanning Electron Microscope; **DSC:** Differential Scanning Calorimeters; **USP:** United State of Pharmacopoeia; **OECD:** Organization for Economic Co-operation and Development; **BBD:** Box-Behnken Design; **CSIR-CDRI:** Council of Scientific and Industrial Research-Central Drug Research Institute.

AUTHOR CONTRIBUTIONS

Mr. Abhiram Kumar: Manuscript drafting and experimentation, Dr. Priyanka Maurya: Review and editings, Dr. Kumar Parnav Narayan: Concept building and supervision.

SUMMARY

The study focused on transdermal drug delivery via the tropical route of administration. A polymeric matrix type transdermal was formulated to overcome the challenges associated with oral formulation, like first-pass metabolism and enzymatic degradation. Overall, we developed a safe and effective transdermal drug delivery system via topical administration and offer a better alternative for type 2 diabetes Mellitus (T2DM). Overall, the matrix-type transdermal patch is presented as a workable alternative to oral formulations, effectively bypassing first-pass metabolism and enhancing patient compliance in chronic diabetes management.This innovative approach shows the potential to address current drug delivery systems' limitations poorly soluble antidiabetic drugs.

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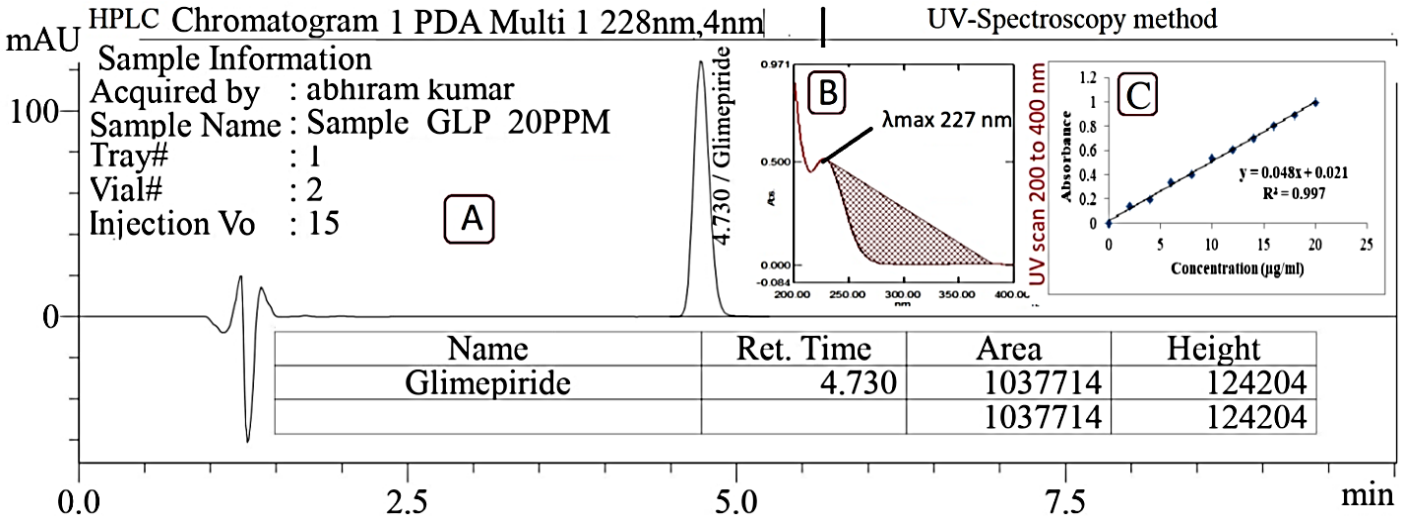
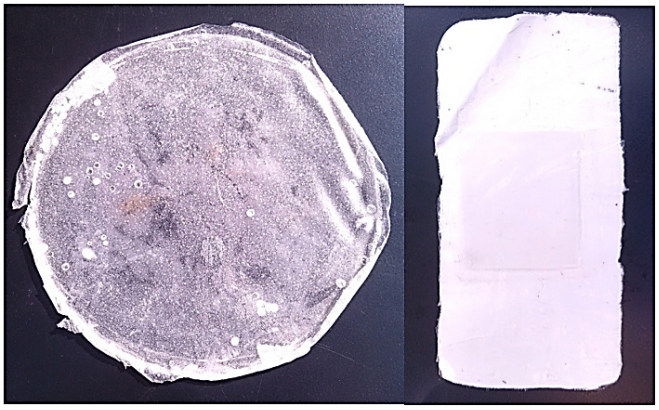


Figure S1: This figure presents the development of analytical methods for quantifying glimepiride in transdermal patches using two techniques (A) Reverse-Phase High-Pressure Liquid Chromatography (RP-HPLC): The analyte peak was eluted at a retention time of 4.7 min. (B) Lambda max scan graph between 200 to 400 nm, The maximum absorbance (λmax) of glimepiride was found to be at 227 nm (C) calibration plot was constructed using phosphate buffer (pH 7.4) and exhibited a strong linear correlation (r^2 = 0.997). Both methods demonstrated their ability to accurately quantify glimepiride from the transdermal patches.

Table S1: ANOVA model table for permeability.

Response	1	Permeability	f			
ANOVA for Response Surface Quadratic Model						
Analysis of variance table [Partial sum of squares - Type III						
	Sum of		Mean	F	*p*-value	
Source	Squares	d_f	Square	Value	Prob > F	
Model	4.5599	9	0.507	31.15	0.0007	Significant
A-HPLC K100 M	0.007938	1	0.008	0.49	0.5160	
B-Eduragit RLPO	1.539135	1	1.539	94.63	0.0002	
C-Glycerin	0.0199	1	0.020	1.22	0.3190	
AB	0.063001	1	0.063	3.87	0.1062	
AC	0.003025	1	0.003	0.19	0.6842	
BC	0.063252	1	0.063	3.89	0.1057	
A^2	0.026494	1	0.026	1.63	0.2579	
B^2	2.855804	1	2.856	175.58	< 0.0001	
C^2	0.045869	1	0.046	2.82	0.1539	
Residual	0.081326	5	0.01626518			
Lack of Fit	0.039531	3	0.013177	0.6305	0.661	not Significant
Pure Error	0.041795	2	0.020897333			
Cor Total	4.641234	14				



[A] [B]

Figure S2: [A] Systematic representation of matrix type transdermal patch without backing layer and [B] Final formulation containing backing layer with 1 mg/cm^2 drug loaded in a patch.

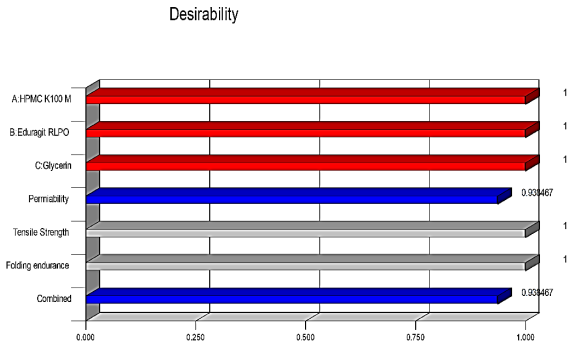


Figure S3: Desirability pareto graph for final optimization formulation.

Table S2: ANOVA model table for tensile strength.

Response	2	Tensile Strength				
ANOVA for Response Surface Quadratic Model						
Analysis of variance table [Partial sum of squares - Type III]						
	Sum of		Mean	F	*p*-value	
Source	Squares	d_f	Square	Value	Prob > F	
Model	6.195	9	0.688	70.87	< 0.000	Significant
A-HPLC K100 M	0.005	1	0.005	0.51	0.505	
B-Eduragit RLPO	0.198	1	0.198	20.43	0.006	
C-Glycerin	1.496	1	1.496	154.06	< 0.000	
AB	0.09	1	0.090	9.27	0.028	
AC	0.01	1	0.010	1.03	0.3568	
BC	0.0169	1	0.017	1.74	0.2443	
A^2	0.036	1	0.036	3.74	0.1110	
B^2	0.000	1	0.001	0.10	0.7700	
C^2	4.340	1	4.340	446.81	< 0.0001	
Residual	0.048	5	0.0097			
Lack of Fit	0.041	3	0.0139	4.19	0.1987	No. Significant.
Pure Error	0.006	2	0.0033			
Cor Total	6.243	14				

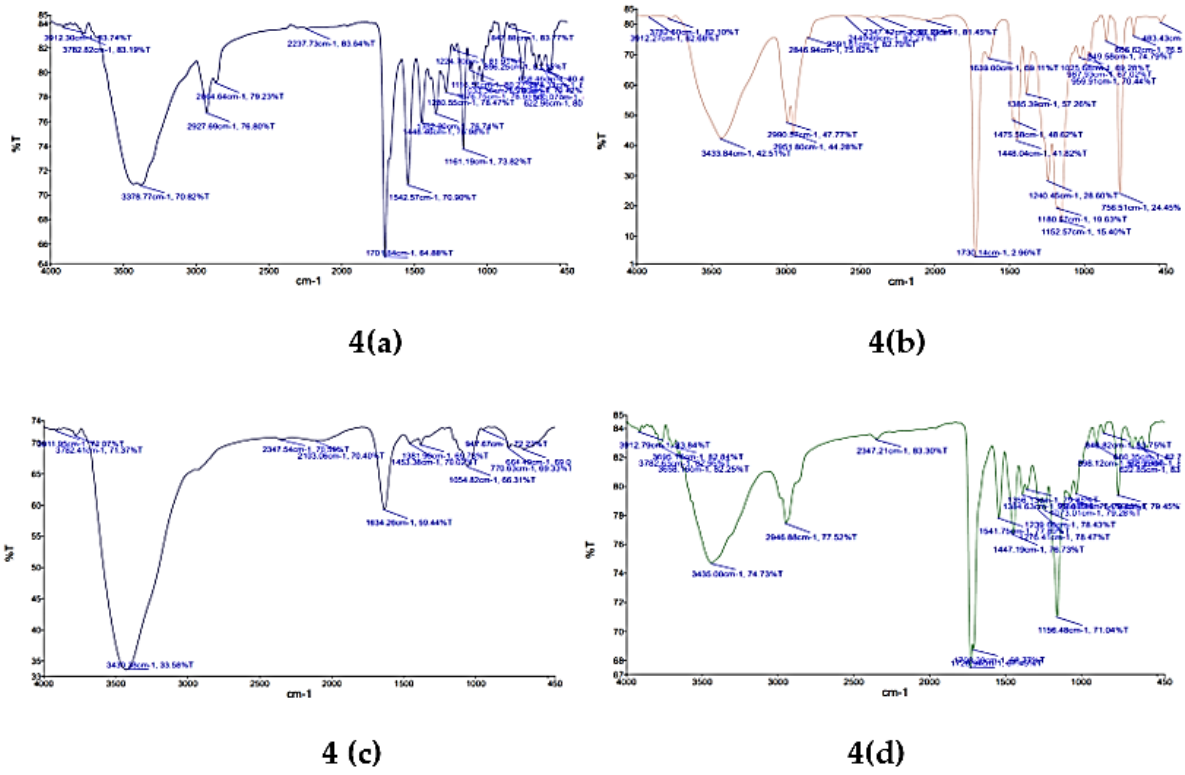


Figure S4: FTIR spectra for (a) GMP, (b) Eudragit® RLPO, (c) HPMC K100M, (d) Formulation.

Table S3: ANOVA model table for Folding endurance.

Response	3	Folding endurance				
ANOVA for Response Surface Quadratic Model						
Analysis of variance table [Partial sum of squares - Type III]						
	Sum of		Mean	F	*p*-value	
Source	Squares	d_f	Square	Value	Prob > F	
Model	30723.	9	3413.	10.230	0.0098	Significant
A-HPLC K100 M	1200.5	1	1200.	3.598	0.1163	
B-Eduragit RLPO	1.125	1	1.1	0.003	0.9559	
C-Glycerin	12720.	1	12720	38.120	0.0016	
AB	625	1	625.0	1.873	0.2294	
AC		1	64.0	0.192	0.6797	
BC	56.25	1	56.2	0.169	0.6984	
A^2	4278.7	1	4278.	12.823	0.0159	
B^2	1168.7	1	1168.	3.503	0.1202	
C^2	12331.	1	12331.	36.957	0.0017	
Residual	1668.4	5	333.6			
Lack of Fit	1585.7	3	528.58	12.78831	0.0734	not significant
Pure Error	82.66	2	41.333			
Cor Total	32391.1	14				

Table S4: Final Optimization formulation table.

Optimization						
Number	**Eduragit RLPO**	**HPMC K100**	**Glycerin**	**Folding Endurance**	**Tensile strength**	**Desirability**
1	440.00	280.00	300.48	238.053	1.86758	0.902829
2	439.73	280.00	299.74	238.018	1.86338	0.90252
3	438.26	280.00	295.55	237.838	1.83985	0.900904
4	438.09	280.00	295.04	237.817	1.837	0.900718
5	437.50	280.00	293.33	237.75	1.82755	0.900119
6	419.17	280.00	230.00	237.564	1.52297	0.898436
7	435.27	280.00	286.71	237.525	1.79167	0.898087
8	420.34	280.00	234.65	237.438	1.54292	0.897297
9	421.41	280.00	238.83	237.341	1.56116	0.896427
10	430.63	280.00	271.95	237.207	1.71572	0.895206
11	424.38	280.00	250.07	237.17	1.61149	0.89487
12	440.00	280.00	303.57	237.986	1.87644	0.894832
13	429.50	280.00	268.17	237.164	1.69705	0.894819
14	429.32	280.00	267.55	237.159	1.69402	0.894769
15	425.28	280.00	253.35	237.144	1.62656	0.894632
16	428.64	280.00	265.23	237.142	1.68274	0.894614
17	426.34	280.00	257.19	237.127	1.64443	0.894479
18	312.31	280.00	370.00	219.067	1.29874	0.691213
19	311.06	280.00	368.85	218.868	1.29078	0.688328
20	310.51	279.11	370.00	218.767	1.28909	0.683927
21	308.81	278.46	369.65	218.49	1.27973	0.677734
22	306.17	280.00	364.44	218.11	1.26038	0.677117
23	315.63	279.27	370.00	219.388	1.3105	0.67495
24	301.68	280.00	360.45	217.437	1.23335	0.666875

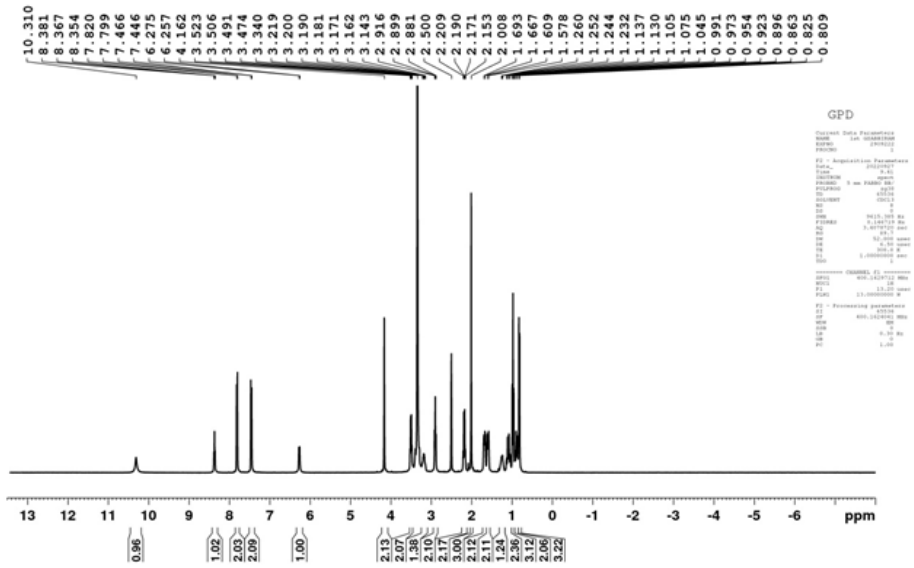


Figure S5: (a) ^{1}H NMR Spectrum of GPD.

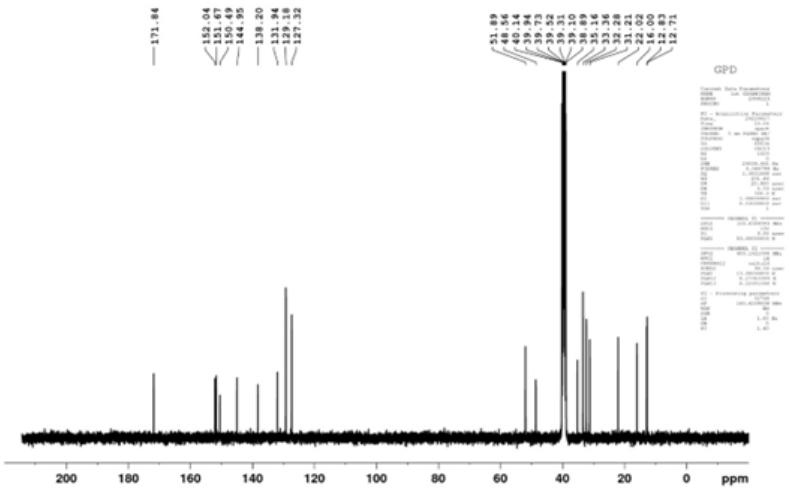


Figure S5: (b) ^{13}C NMR Spectrum of GPD.

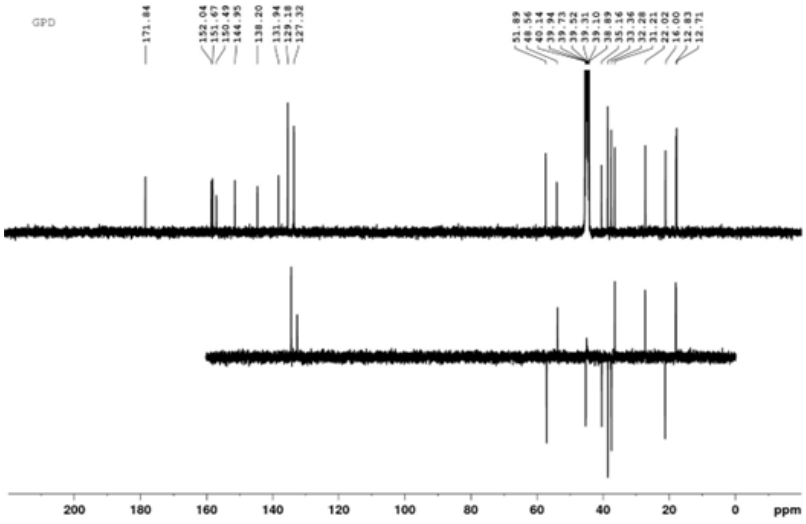


Figure S5: (c) 13C and DEPT-135o NMR Spectrum of GPD.

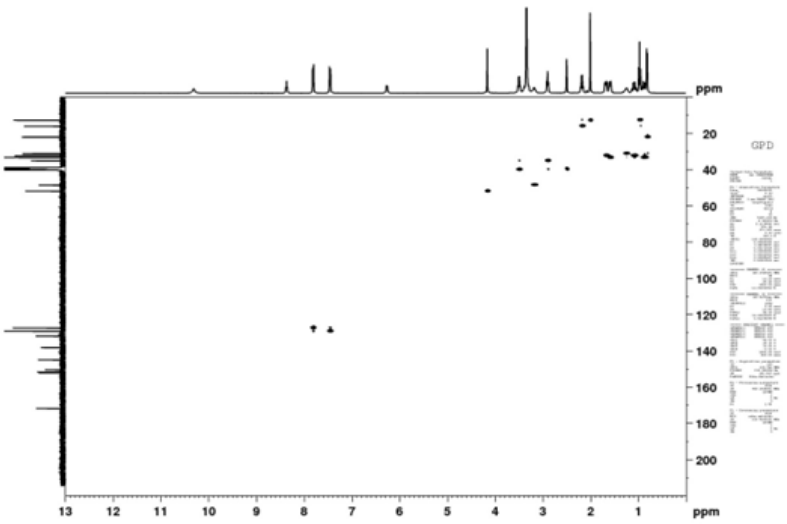


Figure S5: (d) $^{1}H,^{13}C$-HSQC NMR Spectrum of GP

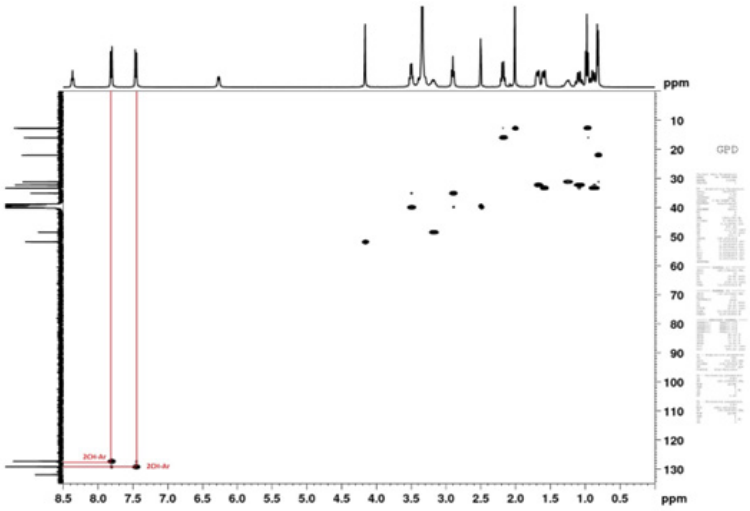


Figure S5: (e) ^{1}H, ^{13}C-HSQC NMR Spectrum of GPD Expansion-1.

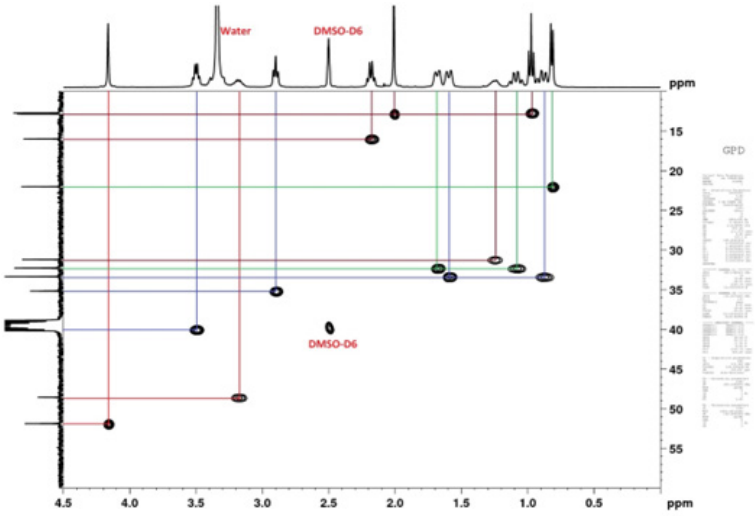


Figure S5: (f) ^{1}H, ^{13}C-HSQC NMR Spectrum of GPD Expansion-2.

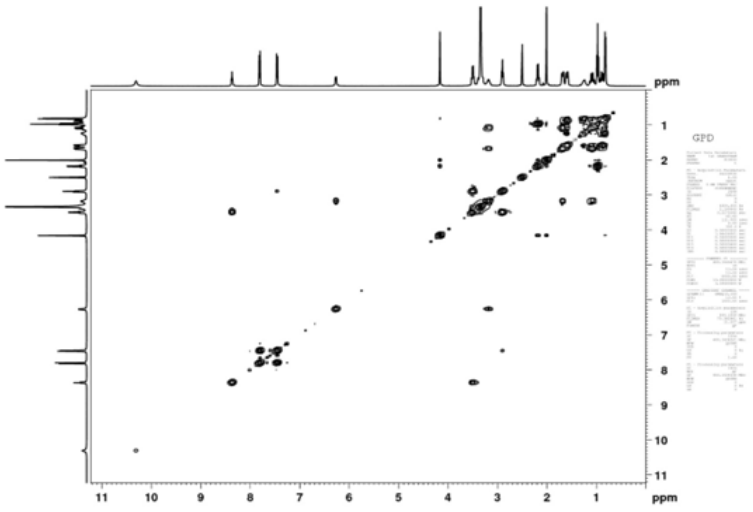


Figure S5: (g) ^{1}H, ^{1}H-COSY NMR Spectrum of GPD.

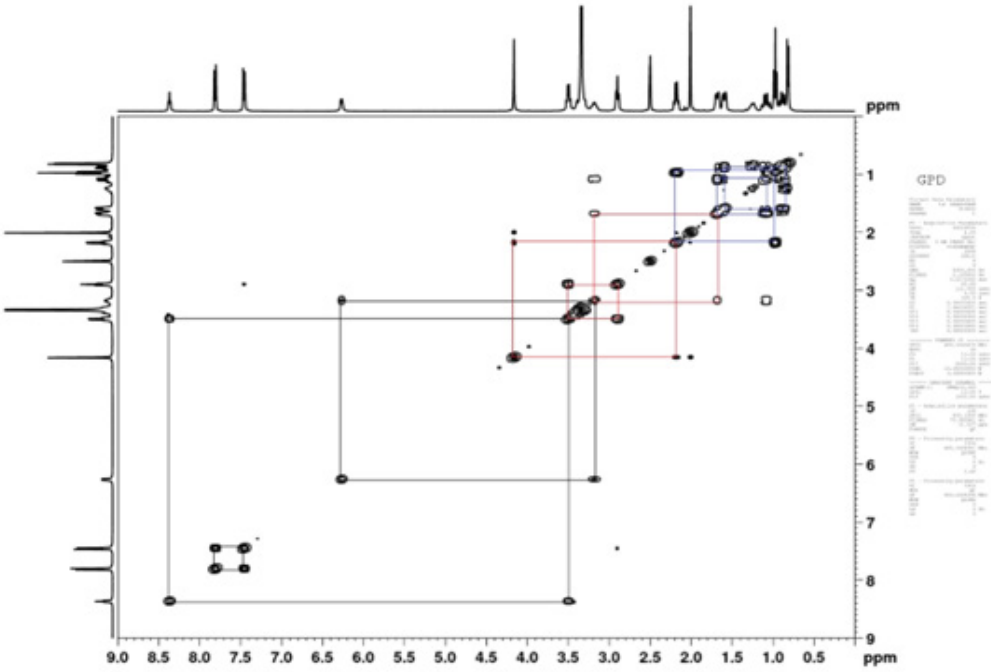


Figure S5: (h) ^{1}H, ^{1}H-COSY NMR Spectrum of GPD Expansion.

Figure S5: The purity and identity of the drug (Glimepiride) were evaluated in 400 MHz, DMSO-d6 using NMR technique, and the results are summarized as follows: 1H NMR (400 MHz, DMSO-d6) δ 10.31 (s, 1H), 8.36 (t, 1H, J = 5.6 Hz), 7.81 (br d, 2H, J = 8.1 Hz), 7.45 (br d, 2H, J = 8.4 Hz), 6.26 (d, 1H, J = 7.2 Hz), 4.16 (s, 2H), 3.49 (q, 2H, J = 6.7 Hz), 3.22-3.14 (m, 1H), 2.89 (t, 2H, J = 7.0 Hz), 2.18 (q, 2H, J = 7.4 Hz), 2.0 (s, 3H), 1.68 (d, 2H, J = 10.3 Hz), 1.59 (d, 2H, J = 12.1 Hz), 1.26-1.23 (m, 1H), 1.13-1.04 (m, 2H), 0.98 (t, 3H, J = 7.4 Hz), 0.92-0.86 (m, 2H), 0.81 (d, 3H, J = 6.5 Hz). 13C NMR (100 MHz, DMSO-d6) δ 171.8 (C), 152.0 (C), 151.6 (C), 150.5 (C), 144.9 (C), 138.2 (C), 131.9 (C), 129.1 (2CH), 127.3 (2CH), 51.8 (CH2), 48.5 (CH), 39.9 (CH2), 35.1 (CH2), 33.3 (CH2), 32.3 (CH2), 31.2 (CH), 22.0 (CH3), 16.0 (CH2), 12.8 (CH3), 12.7 (CH3). The below NMR spectra dipicted (a) ^{1}H NMR Spectrum of GPD (b) ^{13}C NMR Spectrum of GPD (d) ^{13}C and DEPT-135o NMR Spectrum of GPD (d) ^{1}H,^{13}C-HSQC NMR Spectrum of GP (e) ^{1}H,^{13}C-HSQC NMR Spectrum of GPD Expansion-1 (f) ^{1}H,^{13}C-HSQC NMR Spectrum of GPD Expansion-2 (g) ^{1}H,^{1}H-COSY NMR Spectrum of GPD and (h) ^{1}H,^{1}H-COSY NMR Spectrum of GPD Expansion.

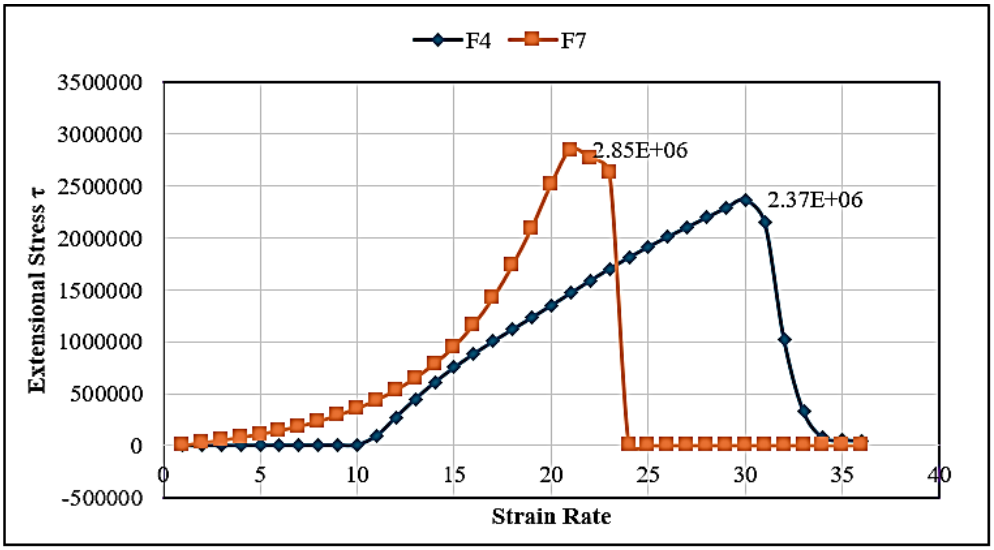


Figure S6: Rheological experimental graph for tensile strength (kg/cm^2) measured graph was plotted between strain rate vs extensional stress ε. However, formulation F4 shown better tensile strength compared to F7.