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Original Article

ENHANCED BIOAVAILABILITY OF LOBEGLITAZONE VIA DISSOLVING MICRONEEDLE PATCHES IN RATS

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ABSTRACT

Objective: To compare the pharmacokinetics of lobeglitazone administered via oral suspension and transdermal dissolving microneedle array (DMNA) patch in rats using a validated LC-MS/MS method.

Methods: Male Wistar rats were administered a single 0.5 mg/kg dose of lobeglitazone either orally or via a DMNA patch. Plasma samples were collected at predefined intervals up to 48 h. Lobeglitazone concentrations were analyzed using a validated LC-MS/MS method. Pharmacokinetic parameters, including Cmax, Tmax, AUC_0–t, AUC_0–∞, elimination rate constant (Kel), and half-life ($T_1/_2$) were calculated and statistically compared between the groups.

Results: Oral administration resulted in a higher Cmax (1786.25 ± 66.68 ng/ml) and a shorter Tmax (2.67 ± 0.52 h), while DMNA delivery produced a lower Cmax (1207.69 ± 25.70 ng/ml) and a delayed Tmax (5.33 ± 1.03 h). However, systemic exposure was significantly higher in the DMNA group (AUC_0–∞: 24,250.57 ± 650.92 ng·h/ml) compared to the oral group (12,036.84 ± 860.47 ng·h/ml; $p < 0.00001$). The DMNA group also exhibited an extended half-life (10.13 ± 0.34 h) relative to oral administration (4.85 ± 0.60 h). The calculated relative bioavailability of the DMNA formulation was 201.47%, indicating enhanced systemic exposure.

Conclusion: Transdermal DMNA delivery of lobeglitazone significantly enhances bioavailability and prolongs systemic retention compared to oral administration. These findings suggest that DMNA patches represent a promising, patient-friendly alternative for the sustained delivery of lobeglitazone in the chronic management of type 2 diabetes mellitus.

Keywords: Lobeglitazone, Dissolving microneedles, Pharmacokinetics, Transdermal delivery, LC-MS/MS, Type 2 diabetes

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a progressive metabolic disorder characterized by insulin resistance, β-cell dysfunction, and chronic hyperglycemia, posing a significant global health burden [1-3]. Among the therapeutic targets, peroxisome proliferator-activated receptor gamma (PPAR-γ) agonists have demonstrated potent insulin-sensitizing effects. Lobeglitazone, a novel thiazolidinedione derivative, exhibits high PPAR-γ affinity, offering improved glycemic control at lower doses compared to its predecessors, thus minimizing the adverse cardiovascular outcomes often associated with the class [4-8].

Despite the clinical promise of oral lobeglitazone, its systemic bioavailability is subject to first-pass hepatic metabolism, fluctuating plasma concentrations, and patient non-compliance associated with chronic oral therapy at lower dose [9-12]. To overcome these limitations, transdermal drug delivery systems, particularly dissolving microneedle (DMN) arrays, have gained significant interest. DMNs can bypass hepatic first-pass metabolism, provide controlled release, improve pharmacokinetics, and enhance patient compliance through minimally invasive, pain-free administration [13].

Advancements in microneedle technology have allowed for the formulation of dissolving polymer-based patches capable of delivering therapeutic agents intradermally. Unlike conventional oral routes, microneedle-mediated delivery ensures direct absorption into systemic circulation via dermal capillaries, offering a promising alternative for drugs like lobeglitazone, where maintaining consistent plasma levels is critical for therapeutic efficacy [14-16].

While several pharmacokinetic studies have characterized oral lobeglitazone administration, the comparative pharmacokinetic behavior of lobeglitazone when delivered via a transdermal dissolving microneedle platform remains unexplored. Such an investigation is pivotal to ascertain the feasibility of microneedle patches as a next-generation delivery modality for lobeglitazone, particularly in the context of chronic diabetes management [17-20].

In this study, we aimed to perform a detailed comparative pharmacokinetic evaluation between oral lobeglitazone administration (0.5 mg/kg) and a transdermal dissolving microneedle patch delivering an equivalent dose (0.5 mg/kg) in a rat model. Plasma concentrations of lobeglitazone were quantitatively analyzed using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method, characterized by high sensitivity, selectivity, and reproducibility. Pharmacokinetic parameters, including C_{max}, T_{max}, AUC, and half-life ($T_{1/2}$), were calculated to assess differences in absorption kinetics, bioavailability, and systemic exposure between the two routes of administration [17, 18].

This comparative analysis is expected to provide foundational pharmacokinetic insights into the potential advantages of transdermal dissolving microneedle systems over traditional oral dosing for lobeglitazone, thereby advancing the prospects of patient-centric, non-invasive, and controlled delivery platforms in diabetes therapeutics.

MATERIALS AND METHODS

Chemicals and reagents

Lobeglitazone (>98% purity) was provided by Akums Drugs and Pharmaceuticals Ltd. and Pioglitazone (internal standard, IS) were

obtained from Shubham Bio Pharma certified sources. Acetonitrile (HPLC grade), formic acid, and LC-MS grade water were purchased from J. T. Baker (USA) and Merck (Germany). Blank heparinized rat plasma was procured from healthy male Wistar rats. Dissolving microneedle patches containing lobeglitazone were fabricated by micromolding technique using pharmaceutical-grade polymers like Hyaluronic acid and Polyvinylpyrrolidone K-90 (PVP K-90) and evaluated for dose uniformity. Prior to initiating the study, ethical approval was obtained from the Institutional Animal Ethics Committee (IAEC) under the protocol number PK (R) DMNA 093 dated 01.08.2022 from IAEC Registration No. 1938/PO/Rc/S/17/CPCSEA, in compliance with the CPCSEA guidelines.

LC-MS/MS analytical conditions

Quantitative analysis of lobeglitazone was performed using an AB Sciex, Triple Quad-4500 system coupled with a triple quadrupole mass spectrometer equipped with an electrospray ionization (ESI) source operated in positive mode summarized in table 1. Calibration curves were linear over the range of 0.200–101,788 ng/ml ($r^2 > 0.999$). Quality control samples at low, medium, and high concentrations were included to verify accuracy and precision throughout the analysis [17].

Table 1: Chromatographic parameters

Chromatographic conditions	
Column	Thermo Scientific, Hyersil Gold, 50*4.6 mm,5µm
Mobile phase	Acetonitrile: 2 mmol Ammonium Acetate Containing 0.2% Formic Acid: (70:30).
Flow rate	0.6 ml/min
Column temperature	30 °C
MS/MS	Triple Quad-4500
Make	Sciex
HPLC	Shimadzu LC-20AD
Auto sampler	SIL-HTC
Ionization Mode	Electro Spray Ionization
Detection Mode	MRM (Positive Mode)

Bioanalytical method validation

The developed LC-MS/MS method for the quantification of lobeglitazone in rat plasma was validated following regulatory guidelines. Validation parameters included selectivity, linearity, precision, accuracy, dilution integrity, matrix effect, recovery, and stability assessments [21, 22].

Selectivity

Selectivity was evaluated by analyzing six different lots of blank rat plasma to confirm the absence of significant interference at the retention times of the analyte and the internal standard (IS). Plasma samples analyzed included matrix blanks, zero samples (blank plus IS), and LLOQ samples. Acceptance criteria required that the area response at the analyte's retention time in matrix blanks be less than 20% of the area response at LLOQ, and for the internal standard, less than 5% of the average IS response in the LLOQ samples. Signal-to-noise (S/N) ratio for LLOQ samples was required to be greater than 5.

Linearity

The linearity of the method was assessed by analyzing calibration standards over the concentration range of 0.200 to 101.788 ng/ml. Calibration curves were generated by plotting the analyte to internal standard peak area ratios versus nominal analyte concentrations, using a weighted ($1/x^2$) linear regression model. A minimum of six non-zero calibration points was required. Acceptance criteria included a correlation coefficient (r^2) ≥0.999 and back-calculated concentrations of standards within ±15% of their nominal concentrations, except for the LLOQ, which was within ±20%.

Precision, accuracy, and dilution integrity

Precision and accuracy were evaluated at four QC levels: LLOQ QC, low QC (LQC), middle QC (MQC), and high QC (HQC), each analyzed in six replicates. Intra-day and inter-day precision were assessed by calculating the coefficient of variation (%CV) across replicate analyses. Accuracy was determined by comparing back-calculated concentrations to their nominal values. Acceptance criteria required that the %CV be ≤15% for all QC levels, except for LLOQ QC, where ≤20% was acceptable. The mean accuracy at each level was required to be within ±15% of the nominal value (±20% for LLOQ). Dilution integrity was assessed by preparing samples at concentrations above the calibration range, diluting them appropriately with blank plasma, and analyzing them to confirm acceptable precision and accuracy.

Matrix effect and recovery

Matrix effect was evaluated by comparing the peak responses of post-extracted plasma samples spiked with analyte to those of neat standard solutions at equivalent concentrations at LQC and HQC levels. The internal standard normalized matrix factor was calculated, and the %CV across different plasma lots was required to be ≤15%. Recovery was determined by comparing the peak areas of analyte spiked before extraction to those spiked after extraction at LQC, MQC, and HQC levels. Consistent and reproducible recovery across the concentration range was required, with an acceptable %CV for recovery values within 15% [20].

Stability

Stability of lobeglitazone was assessed under bench-top stability QC samples were kept at room temperature for 24 h before analysis. Stability was evaluated by comparing the measured concentrations to freshly prepared calibration standards. Acceptance criteria required that a minimum of 67% of stability QC samples and 50% at each QC level should be within ±15% of their nominal concentrations. Additionally, the mean % change between stability and comparison samples had to be within ±15%, with %CV also ≤15% at each level.

Animal study design

Male Wistar rats (200–220 g) were housed under controlled conditions (22 ± 2 °C; 55% ± 10% RH; 12 h light/dark cycle) with ad libitum access to food and water. Institutional Animal Ethics Committee (IAEC) under the protocol number and PKPD(Rat) DMNA0159 from IAEC Registration No. 1938/PO/Rc/S/17/CPCSEA, in compliance with the CPCSEA guidelines. Rats were randomized into two groups (n = 6 per group): Oral Group: Received a single oral suspension of lobeglitazone (0.5 mg/kg) in purified water. Transdermal Group: Received a dissolving microneedle patch delivering lobeglitazone (0.5 mg/kg) applied to the dorsal skin. Prior to patch application, hair was removed from the dorsal area using a depilatory cream. Microneedle patches were applied with gentle manual pressure for 2 min and retained in place for 30 min to ensure complete dissolution.

Blood sampling

Serial blood samples (~250 µl) were collected via retro-orbital puncture at pre-dose (0 h) and post-dose at 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36, and 48 h. Plasma was separated by centrifugation (4000 rpm, 10 min) and stored at −80 °C until analysis.

Plasma sample preparation

Liquid-liquid extraction (LLE) was selected as the plasma sample preparation technique for the quantification of lobeglitazone in rat plasma. LLE offers several advantages, including higher analyte recovery, reduced matrix effects, and cleaner extracts compared to protein precipitation methods. These features are particularly important for achieving the sensitivity and specificity required for low-concentration analytes like lobeglitazone. Therefore, LLE was considered the most suitable method to ensure accurate and reproducible results in this pharmacokinetic study.

An aliquot of 200 µl* plasma sample was taken and added 50µl* of internal standard dilution solution and vortex to mix, except in blank sample in which 50 µl* of diluent was added. Added 2.000 ml of Tert Butyl Methyl Ether and cap all samples. Vortexed all the samples on a multitube vortexer for 10 min at 2500 rpm. Kept all samples for

Centrifugation for 5 min at 4.0°Cand 4500 rpm in a refrigerated centrifuge. Transfer about 1.600 ml Supernatant in to pre-labelled ria vials. Kept the samples for drying in Nitrogen Evaporator at 40 °C till the dryness. Reconstitute all the samples with 1.000 ml of Mobile phase and vortex for few seconds. Transferred the samples into pre labelled autosampler vials.

Pharmacokinetic and statistical analysis

Pharmacokinetic parameters were calculated using a non-compartmental model (Phoenix WinNonlin, Certara, USA). The following parameters were estimated: maximum plasma concentration (C_{max}), time to C_{max} (T_{max}), area under the concentration-time curve from time zero to the last measurable concentration (AUC_{0-t}), extrapolated area under the curve ($AUC_{0-\infty}$), terminal half-life ($T_1/_2$), and Elimination Constant (k_{el}). All results are expressed as mean ± standard deviation (SD). Comparative pharmacokinetic profiles between the oral and transdermal groups were analyzed descriptively.

RESULTS AND DISCUSSION

Method development

Method development and optimization

A sensitive and robust LC-MS/MS method was developed and optimized for the quantification of lobeglitazone in rat plasma using pioglitazone as an internal standard. The biological matrix consisted of rat plasma collected with K_2EDTA as an anticoagulant, sourced from Precision Labs. The analytical technique employed was liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) using a Sciex Triple Quad 4500 system, operated under positive ionization mode with multiple reaction monitoring (MRM). Analyst software version 1.7.3 was used for instrument control and data processing. The method utilized a peak area ratio for quantitation with a weighting factor of $1/x^2$ to ensure linearity across the calibration range. Chromatographic separation was achieved on a Thermo Scientific Hypersil GOLD C18 column (50×4.6 mm, 5 µm particle size) maintained at ambient temperature. The mobile phase consisted of acetonitrile and 2 mM ammonium acetate containing 0.2% formic acid in a 70:30 (v/v) ratio. The system was operated at a flow rate of 0.600 mL/min. Sample preparation involved a liquid-liquid extraction (LLE) method, which provided clean extracts and improved sensitivity. A plasma volume of 200 µl was processed for each sample. Following extraction, the samples were reconstituted and injected into the LC-MS/MS system for analysis. The MRM transitions selected were m/z 482 → 258 for lobeglitazone and m/z 357.1 → 134.1 for pioglitazone, shown in fig. 1, ensuring high specificity and sensitivity. The calibration curve for lobeglitazone was established over a concentration range of 0.200 to 101.788 ng/ml and demonstrated excellent linearity with correlation coefficients (r^2) consistently above 0.999 shown in fig. 2. The optimized method provided robust performance, allowing for the reliable quantification of lobeglitazone in rat plasma samples following oral and transdermal administration.

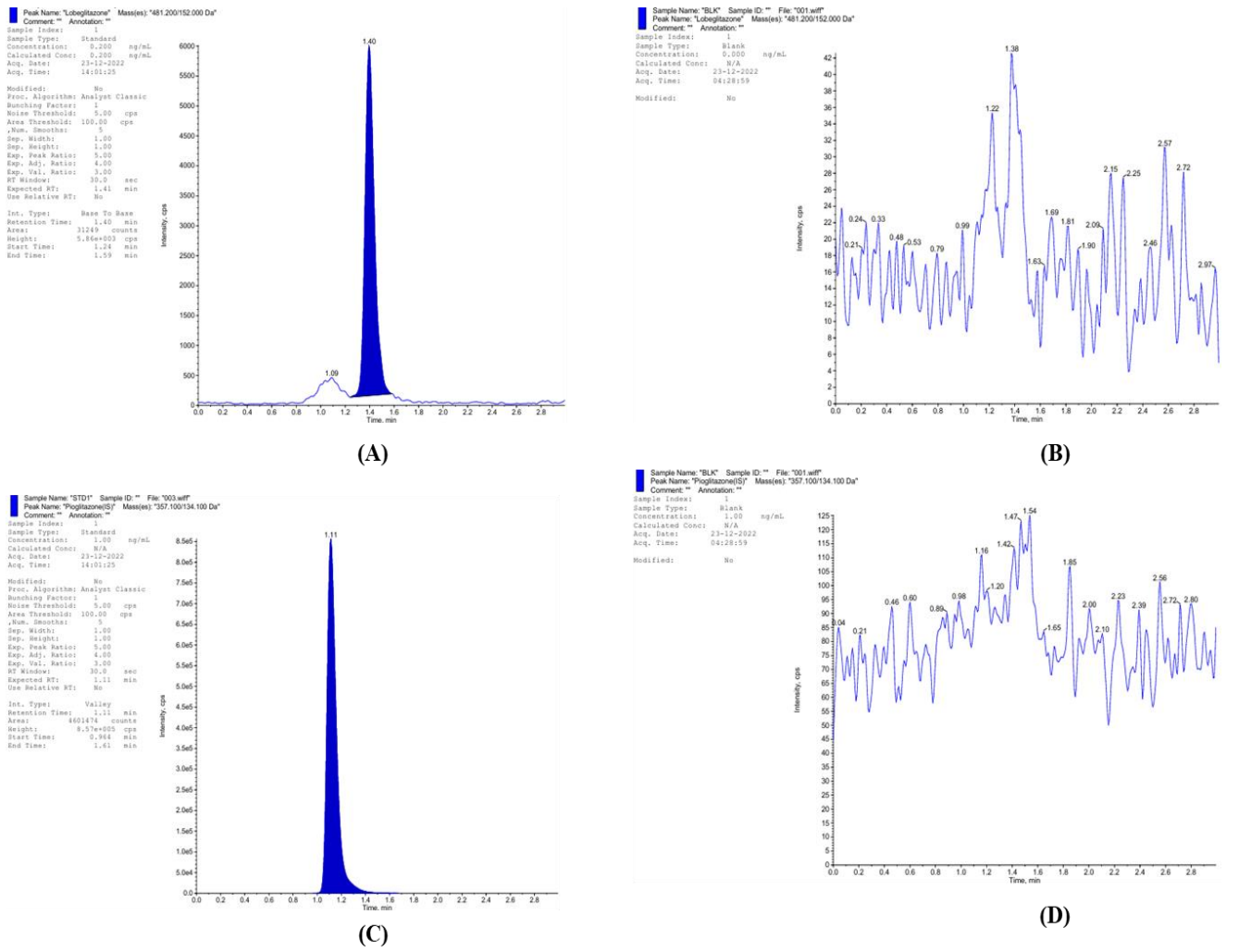

Fig. 1: MS2 Scan of (A) Lobeglitazone MRM transitions m/z 482 → 258, (B) Blank Plasma with Lobeglitazone, (C) Pioglitazone (IS) m/z 357.1 → 134.1, (D) Blank plasma with pioglitazone

Method validation

The bioanalytical method validation was performed for the quantification of lobeglitazone in rat plasma using LC-MS/MS, following regulatory guidelines.

Selectivity and sensitivity

The criteria were evaluated as part of the method validation. The area response of interfering peaks at the analyte's retention time in matrix blank samples was required to be less than 20% of the analyte peak area in the LLOQ sample processed in the respective blank matrix, while the area response of interfering peaks at the internal standard's retention time was required to be less than 5% of the internal standard peak area response at LLOQ. The signal-to-noise (S/N) ratio for the LLOQ sample was mandated to be greater than 5. All matrix blanks (100%) were expected to meet these acceptance criteria. In addition, a minimum of 67% of LLOQ samples had to be within ±20% accuracy of their respective nominal concentrations, including at least one LLOQ sample from haemolysed and lipemic plasma lots. The mean % nominal value for the LLOQ should be within ±20% of its nominal concentration, and the coefficient of variation (CV) for the back-calculated LLOQ concentration should not exceed 20%. Furthermore, a minimum of 67% of bracketing quality control (QC) samples had to fall within ±15% accuracy of their respective nominal concentrations, and at least 50% of QC samples at each concentration level were required to meet the ±15% accuracy criterion. Selectivity was confirmed, with no significant interference observed at the retention times of the analyte (≤0.00%) and internal standard (≤0.04%) across six different blank plasma lots (table 2).

Autosampler carryover

Carryover was assessed during method validation to ensure reliability of the assay. For the analyte, the carryover observed after injection of the highest standard should not exceed 20.00% of the area response of the analyte in the extracted LLOQ sample. For the internal standard (ISTD), the carryover should not exceed 5.00% of the area response of the internal standard in the extracted LLOQ sample. The study shows negligible, with no detectable interference at the analyte and IS retention times after injection of the highest standard (≤0.00% and ≤0.01%, respectively) (table 3).

Sensitivity

Sensitivity and LLOQ performance were evaluated as part of the method validation criteria. A minimum of 50% of LLOQ samples was required to be within ±20% accuracy of their respective nominal concentrations. Additionally, the coefficient of variation (CV) of the back-calculated LLOQ concentrations was required to be ≤20%, and the mean % nominal value had to be within ±20% of the nominal concentration. Furthermore, the signal-to-noise (S/N) ratio for the LLOQ samples was mandated to be greater than 5 to ensure sufficient assay sensitivity. It was established with a lower limit of quantitation (LLOQ) at 0.200 ng/ml, demonstrating a coefficient of variation (CV) of 1.62% and a mean accuracy of 94.583% (table 4).

Table 2: Selectivity

Blank matrix ID	Interfering peak area response at Analyte RT in Blank	Analyte area response in LLOQ	S/N ratio	Area response of interfering peak at IS RT in Blank	IS area response in LLOQ	% Interference at analyte RT	% Interference at IS RT	Back calculated Conc. (ng/ml)	% Accuracy
PL\893\0522	0	5395	217.804	0	2175134	0.00	0.00	0.194	97.079
PL\1457\1122	0	5325	175.911	0	2196344	0.00	0.00	0.189	94.695
PL\1498\1122	0	5439	203.743	0	2213396	0.00	0.00	0.192	96.092
PL\1499\1122	0	5575	209.608	0	2191143	0.00	0.00	0.200	99.795
PL\1500\1122	0	2380	83.767	0	999256	0.00	0.00	0.186	92.873
PL\1505\1122	0	1134	65.063	0	523762	0.00	0.00	0.167	83.692
PL\1388\1022 (HAE)	0	1466	45.826	0	661980	0.00	0.00	0.172	85.790
PL\1389\1022 (HAE)	0	2387	117.700	0	1089308	0.00	0.00	0.170	84.769
PL\1390\1022 (LIP)	0	1068	51.561	216	493194	0.00	0.04	0.167	83.673
PL\1391\1022 (LIP)	0	1151	49.410	0	489727	0.00	0.00	0.183	91.538
N								10	10
Mean								0.1820	90.9996
SD								0.01215	6.06215
%CV								6.67	6.66

Abbreviations: ID – Identification, RT – Retention Time, LLOQ – Lower Limit of Quantification, S/N Ratio – Signal-to-Noise Ratio, IS – Internal Standard, % Interference – Percentage Interference, Back Calculated Conc. (ng/ml) – Back Calculated Concentration in nanograms per milliliter, % Accuracy – Percentage Accuracy, SD – Standard Deviation, %CV – Coefficient of Variation, HAE – Hemolyzed Aqueous Extract, LIP – Lipemic Sample.

Table 3: Autosampler carryover test

Sample ID	Analyte area response	Internal standard area response	% Carry over at analyte RT	% Carry over at IS RT
Blank	0	162	0.00	0.01
STD1 (LLOQ)	3556	1649343	NA	NA
STD8 (ULOQ)	1950533	1533254	NA	NA
BLANK	0	392	NA	NA
BLANK	0	430	NA	NA
Carry over in Ist blank	0	230	0.00	0.01
Carry over in IInd blank	0	268	0.00	0.02

Abbreviations: Sample ID – Sample Identification, Analyte – Analyzed Substance, Area Response – Detector Response for Analyte, Internal Standard Area Response – Detector Response for Internal Standard, % Carry over at analyte RT – Percentage Carryover at Analyte Retention Time, % Carry over at IS RT – Percentage Carryover at Internal Standard Retention Time, LLOQ – Lower Limit of Quantification, ULOQ – Upper Limit of Quantification, NA – Not Applicable, RT – Retention Time, IS – Internal Standard.

Linearity

Calibration curve acceptance criteria were established to ensure method accuracy and reliability. The correlation coefficient (r) of the calibration curve was required to be ≥0.99. The area response observed at the retention time of the analyte in blank and STD0 samples had to be less than 20% of the area response of the STD1 sample, while the area response at the internal standard's retention

time in blank samples had to be less than 5% of the average internal standard response of accepted calibration standards and quality control samples. The percentage nominal values of the calibration standards were required to be within ±15% of their respective nominal concentrations, except for STD1 (LLOQ), which was allowed within ±20%. At least 75% of the calibration standards had to meet the acceptance criteria for curve evaluation, and both the lowest and highest standards were required to be acceptable to validate the calibration curve. Two consecutive calibration standards were not permitted to be excluded from the curve, and in the case of exclusion, standards with the greatest deviation were to be excluded first, considering the acceptance criteria from STD1 to STD8/STD9. If any calibration standard did not meet its acceptance limits, it was excluded, and the calibration curve was re-evaluated without it. Furthermore, the %CV of all acceptable calibration standards was required to be<15%, except for STD1, where it was allowed up to 20%, and the mean % nominal for all acceptable calibration standards had to be within ±15% of the nominal value, except for STD1, which had a limit of ±20%. The study shows excellent linerity across the calibration range of 0.200–101.788 ng/ml, with a correlation coefficient (r) ≥ 0.999 (fig. 2). The percentage nominal values for the calibration standards ranged from 96.191% to 102.515% (table 5 and 6).

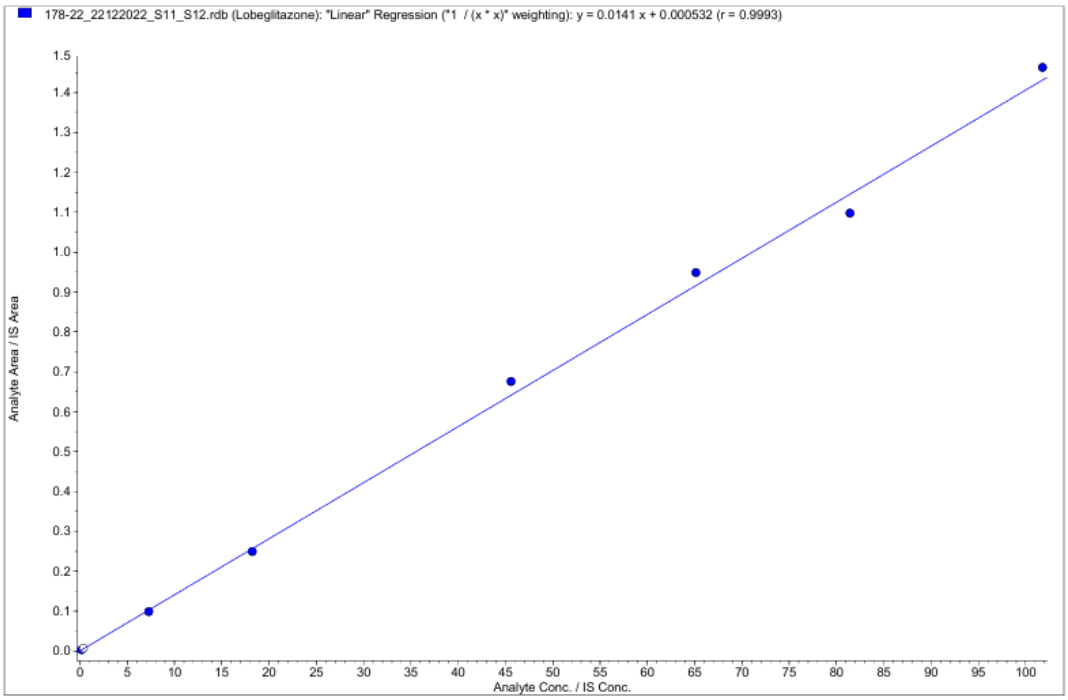

Fig. 2: Liner curve of lobeglitazone between the calibration range of 0.200–101.788 ng/ml (r2≤0.999)

Precision and accuracy

Accuracy and precision acceptance criteria for quality control (QC) samples were established to ensure assay reproducibility. A minimum of 67% of QC samples across all levels was required to be within ±15% of their respective nominal concentrations, except for LLOQ QC samples, where an acceptance limit of ±20% was applied. Additionally, at least 50% of QC samples at each concentration level had to meet the same accuracy criteria, with ±15% for regular QCs and ±20% for LLOQ QCs. The coefficient of variation (%CV) for QC samples at each level was required to be ≤15%, except for LLOQ QC samples, where a %CV of ≤20% was acceptable. Furthermore, the mean % nominal value of analyzed QC samples at each level was required to be within ±15% of the nominal concentration, except for the LLOQ QC samples, where the limit was set at ±20%. The results demonstrated acceptable intra-and inter-batch variability. The QC samples showed CVs between 1.06% and 6.78% and accuracy values between 87.235% and 101.146% across low, medium, and high QC levels (table 7).

Table 4: Within-run sensitivity

	LLOQ (ng/ml)		
Nominal conc.	0.200		
Range	0.160	0.240	
Result table ID	Conc. found	% Nominal	S/N ratio
PMV_20122022_PA01_SEN_01	0.186	93.126	129.836
	0.187	93.591	192.118
	0.194	97.194	222.831
	0.190	95.050	189.121
	0.191	95.307	255.052
	0.187	93.744	272.610
N	6		
Mean	0.1892		
SD	0.00306		
%CV	1.62		
%Nominal	94.583		

Abbreviations: ID–Identification, LLOQ (ng/ml) – Lower Limit of Quantification (nanograms per milliliter), Nominal Conc. – Nominal Concentration, Conc. Found – Concentration Found, % Nominal – Percentage of Nominal Concentration, S/N Ratio – Signal-to-Noise Ratio, N – Number of Replicates, mean – Arithmetic Mean, SD – Standard Deviation, %CV – Coefficient of Variation (expressed as a percentage).

Table 5: Summary of calibration curve parameters

Result table ID	Slope	Y-Intercept	Correlation coefficient (r)
PMV_21122022_SEL	0.0118	0.000198	0.9995
PMV_20122022_PA01_SEN01	0.0124	0.0000407	0.9995
NA	2	2	2
Minimum	0.01	0.00004	0.9995
Maximum	0.0124	0.000198	0.9995

Abbreviations: Result table ID – Result table Identification, Slope – Calibration Curve Slope, Y-Intercept – Intercept on the Y-Axis of the Calibration Curve, Correlation Coefficient (r) – Statistical Measure of Linearity (r-value), NA – Not Applicable.

Table 6: Concentration summary of calibration standards

Calibration standards	STD1	STD2	STD3	STD4	STD5	STD6	STD7	STD8
Nominal Conc.(ng/ml)	0.200	0.400	7.296	18.240	45.601	65.144	81.431	101.788
Range(ng/ml)	0.160	0.340	6.202	15.504	38.761	55.372	69.216	86.520
	0.240	0.460	8.390	20.976	52.441	74.916	93.646	117.056
Result table ID	Conc. Found	Conc. Found	Conc. Found	Conc. Found	Conc. Found	Conc. Found	Conc. Found	Conc. Found
PMV_21122022_SEL	0.196	0.415	7.641	18.212	45.726	64.076	81.130	97.066
PMV_20122022_PA01_SEN01	0.199	0.404	7.318	18.714	45.666	61.249	80.187	105.788
N	2	2	2	2	2	2	2	2
Mean	0.1975	0.4095	7.4795	18.4630	45.6960	62.6625	80.6585	101.4270
SD	0.00212	0.00778	0.22840	0.35497	0.04243	1.99899	0.66680	6.16739
%CV	1.07	1.90	3.05	1.92	0.09	3.19	0.83	6.08
% Nominal	98.750	102.375	102.515	101.223	100.208	96.191	99.051	99.645

Abbreviations: Result table ID – Result table Identification, Calibration Standards – Reference Standards Used for Calibration, STD1–STD8 – Standard Samples 1 through 8, Nominal Conc. (ng/ml) – Nominal Concentration in nanograms per milliliter, Range (ng/ml) – Acceptable Concentration Range in nanograms per milliliter, Conc. Found – Measured Concentration, N – Number of Replicates, mean – Arithmetic mean of Replicates, SD – Standard Deviation, %CV – Coefficient of Variation (expressed as a percentage), % Nominal – Percentage of Nominal Concentration.

Recovery

Recovery and matrix effect evaluations were conducted to ensure consistency of the assay. The coefficient of variation (%CV) of the mean % recovery at each QC level was required to be ≤15%. Additionally, the %CV of the area response of the analyte at low, medium, and high QC levels, both in extracted and post-extracted samples, was mandated to be ≤15%, confirming acceptable reproducibility and minimal variability during the extraction process. Lobeglitazone was consistent across concentration levels, with mean recoveries of 100.735%, 93.047%, and 94.679% at LQC, MQC, and HQC levels, respectively. The overall mean recovery of the analyte was 96.15%, with a CV of 4.21%. The internal standard showed a mean recovery of 92.71% with a CV of 0.85% (table 8 and 9).

Matrix effect

Matrix effect evaluation was performed to assess the impact of endogenous plasma components on ionization efficiency. The coefficient of variation (%CV) of the internal standard (ISTD) normalized matrix factor (MF) across different plasma lots was required to be ≤15%, ensuring consistency and reliability of the assay in various biological matrices. Study evaluated by normalized matrix factor, indicated minimal ion suppression or enhancement. The normalized matrix factor was 1.158 at LQC and 1.077 at HQC with CVs of 8.70% and 2.87%, respectively (table 10), supporting the robustness of the method across different plasma sources

Table 7: Within and between-run precision and accuracy

Nominal Conc.	LLOQQC (ng/ml) 0.201		LQC (ng/ml) 0.598		M1QC (ng/ml) 10.308		MQC (ng/ml) 39.645		HQC (ng/ml) 79.290	
Range	0.161	0.241	0.508	0.688	8.762	11.854	33.698	45.592	67.397	91.184
Result table ID	Conc. found	% nominal	Conc. found	% nominal	Conc. found	% nominal	Conc. found	% nominal	Conc. found	% nominal
	0.199	98.816	0.516	86.228	10.739	104.180	34.257	86.410	69.553	87.719
PMV_2012	0.211	104.916	0.512	85.645	10.457	101.444	34.909	88.054	66.641	84.047
2022_PA01	0.216	107.401	0.534	89.328	10.345	100.361	35.058	88.429	69.996	88.278
_SEN_01	0.183	90.968	0.536	89.705	10.449	101.370	34.492	87.002	69.178	87.247
	0.189	94.209	0.516	86.353	10.385	100.750	34.744	87.637	70.934	89.461
	0.188	93.450	0.516	86.280	10.182	98.773	34.139	86.111	69.744	87.960
N	6		6		6		6		6	
Mean	0.1977		0.5217		10.4262		34.5998		69.3410	
SD	0.01341		0.01046		0.18289		0.36546		1.44849	
%CV	6.78		2.01		1.75		1.06		2.09	
% Nominal	98.342		87.235		101.146		87.274		87.452	

Abbreviations: Result table ID – Result table Identification, Nominal Conc. – Nominal Concentration, LLOQQC – Lower Limit of Quantification Quality Control, LQC – Low Quality Control, M1QC – Middle-1 Quality Control, MQC – Middle Quality Control, HQC – High Quality Control, Range (ng/ml) – Acceptable Concentration Range in nanograms per millilitre, Conc. Found – Measured Concentration, % Nominal – Percentage of Nominal Concentration, N – Number of Replicates, mean – Arithmetic Mean, SD – Standard Deviation, % CV – Coefficient of Variation (percentage).

Table 8: Recovery of analyte from biological matrix

Recovery of analyte						
	LQC (ng/ml)		**MQC (ng/ml)**		**HQC (ng/ml)**	
Nominal conc.	**0.296**		**6.076**		**12.401**	
S. No.	**Area of extracted samples**	**Area of post extracted samples**	**Area of extracted samples**	**Area of post extracted samples**	**Area of extracted samples**	**Area of post extracted samples**
1	10079	9155	636175	863079	1226464	1725117
2	12903	13026	634563	823278	1345550	1692069
3	9822	12756	606334	837220	1342424	1781018
4	9109	14081	618803	820595	1361642	1794486
5	8944	12695	602464	845961	1391016	1802967
6	9738	13478	595417	772075	1396758	1850621
N	6	6	6	6	6	6
Mean	10099.2	12531.8	615626.0	827034.7	1343975.7	1774379.7
SD	1441.11	1733.16	17081.85	31103.98	61846.17	57061.66
%CV	14.27	13.83	2.77	3.76	4.60	3.22
% Recovery	100.735		93.047		94.679	
% Recovery of LQC				100.735		
% Recovery of MQC				93.047		
% Recovery of HQC				94.679		
Mean				96.1537		
Standard Deviation				4.05059		
% CV				4.21		

Abbreviations: LQC – Low Quality Control, MQC – Middle Quality Control, HQC – High Quality Control, Nominal Conc. – Nominal Concentration, Sr. No. – Serial Number, N – Number of Replicates, SD – Standard Deviation, %CV – Coefficient of Variation (percentage), % Recovery – Percentage Recovery, ng/ml – nanograms per millilitre.

Table 9: Recovery of internal standard from biological matrix

Recovery of internal standard						
	LQC		**MQC**		**HQC**	
S. No.	**Area of extracted samples**	**Area of post extracted samples**	**Area of extracted samples**	**Area of post extracted samples**	**Area of extracted samples**	**Area of post extracted samples**
1	1165584	1560104	1189717	1591713	1154058	1522035
2	1096077	1578525	1180215	1576278	1160722	1520128
3	1190729	1605525	1159328	1558877	1157242	1567879
4	1217198	1603824	1182858	1597836	1184261	1574573
5	1147424	1615433	1167301	1566520	1144999	1569847
6	1212386	1605005	1148632	1518561	1134913	1574899
N	6	6	6	6	6	6
Mean	1171566.3	1594736.0	1171341.8	1568297.5	1156032.5	1554893.5
SD	45679.28	20952.25	15655.02	28460.93	16685.16	26336.49
%CV	3.90	1.31	1.34	1.81	1.44	1.69
% Recovery	91.831		93.361		92.935	
% Recovery of LQC				91.831		
% Recovery of MQC				93.361		
% Recovery of HQC				92.935		
Mean				92.7090		
Standard Deviation				0.78964		
% CV				0.85		

Abbreviations: LQC – Low Quality Control, MQC – Middle Quality Control, HQC – High Quality Control, Sr. No. – Serial Number, Area of Extracted Samples – Detector Response for Extracted Samples, Area of Post-Extracted Samples – Detector Response for Spiked Extract After Extraction, N – Number of Replicates, mean – Arithmetic Mean, SD – Standard Deviation, %CV – Coefficient of Variation (percentage), % Recovery – Percentage Recovery of Internal Standard.

Stability studies

Stability assessments were conducted to evaluate the integrity of lobeglitazone under various conditions. A minimum of 67% of comparison and stability quality control (QC) samples was required to be within ±15% accuracy of their respective nominal concentrations, and at least 50% of stability QC samples at each concentration level also had to meet the ±15% accuracy criteria. The percentage change between the mean back-calculated values of stability samples and their corresponding nominal and comparison sample concentrations was required to be within ±15%. Furthermore, the mean % nominal value for stability samples at each level had to be within ±15% of the nominal concentration, and the coefficient of variation (%CV) at each level was required to be ≤15%, ensuring assay precision and reliability under stability testing conditions. The study demonstrated that lobeglitazone was stable in plasma under benchtop conditions at room temperature for at least 6 h. The percentage change from nominal concentrations was −2.118% for LQC and −3.959% for HQC, with CVs of 2.94% and 1.13%, respectively (table 11).

Table 10: Matrix effect

S. No.	LQC (ng/ml)							
	Concentration				0.598			
	Aqueous Sample		Matrix Sample			Matrix Factor		Internal Standard norma-lized matrix factor
	Analyte area response	Internal standard area response	Blank matrix ID	Post extracted analyte area response	Post extracted internal standard area response	Analyte	Internal stand-ard	
1	9227	1681513	PL\893\0522	15605	1581790	1.2726	0.9113	1.3965
2	14703	1724960	PL\1457\1122	12325	1608184	1.0051	0.9265	1.0848
3	12185	1751865	PL\1498\1122	12692	1603479	1.0351	0.9238	1.1204
4	12645	1750919	PL\1499\1122	12602	1605246	1.0277	0.9248	1.1113
5	12603	1753215	PL\1500\1122	12502	1598509	1.0196	0.9210	1.1071
6	12209	1751808	PL\1505\1122	13361	1586813	1.0896	0.9142	1.1919
7			PL\1388\1022(HAE)	13292	1609738	1.0840	0.9274	1.1688
8			PL\1389\1022(HAE)	12341	1638722	1.0064	0.9441	1.0660
9			PL\1390\1022(LIP)	14307	1620820	1.1668	0.9338	1.2495
10			PL\1391\1022(LIP)	12597	1639807	1.0273	0.9447	1.0874
N	6	6	NA			10	10	10
Mean	12262.0	1735713.3				1.07343	0.92718	1.15837
SD	1757.35	28673.14				0.085963	0.011131	0.100823
%CV	14.33	1.65				8.01	1.20	8.70
S. No.	**HQC (ng/ml)**							
	Concentration				**79.290**			
	Aqueous sample		**Matrix sample**			**Matrix factor**		**Internal**
	Analyte area response	**Internal standard area response**	**Blank matrix ID**	**Post extracted analyte area response**	**Post extracted internal standard area response**	**Analyte**	**Inter-nal stand-ard**	**stand-ard norma-lized matrix factor**
1	1685586	1741211	PL\893\0522	1768341	1640665	1.0504	0.9483	1.1076
2	1705063	1749890	PL\1457\1122	1652527	1626817	0.9816	0.9403	1.0439
3	1688346	1739068	PL\1498\1122	1640273	1619971	0.9743	0.9364	1.0405
4	1675723	1730364	PL\1499\1122	1718113	1644793	1.0206	0.9507	1.0735
5	1670305	1710790	PL\1500\1122	1760935	1637903	1.0460	0.9467	1.1049
6	1675997	1709123	PL\1505\1122	1721632	1640600	1.0226	0.9483	1.0784
7			PL\1388\1022(HAE)	1687261	1577007	1.0022	0.9115	1.0995
8			PL\1389\1022(HAE)	1623225	1593332	0.9642	0.9210	1.0469
9			PL\1390\1022(LIP)	1637617	1600551	0.9727	0.9251	1.0515
10			PL\1391\1022(LIP)	1726653	1575643	1.0256	0.9107	1.1262
N	6	6	NA			10	10	10
Mean	1683503.3	1730074.3				1.00603	0.93391	1.07729
SD	12519.45	16783.92				0.031467	0.015600	0.030968
%CV	0.74	0.97				3.13	1.67	2.87

Abbreviations: S. No. – Serial Number, standard, Blank Matrix ID – Identification code of the blank matrix lot, LQC – Low Quality Control, HQC – High Quality Control, ng/ml – nanograms per millilitre, Aqueous Sample – Analyte prepared in solvent, Matrix Sample – Analyte spiked into biological matrix, Matrix Factor – Ratio of analyte response in matrix to that in solvent, Internal Standard Normalized Matrix Factor – Matrix factor corrected by the internal standard, Analyte Area Response – Detector response for the analyte, Internal Standard Area Response – Detector response for the internal HAE – Haemolysed Sample, LIP – Lipemic Sample, IS – Internal Standard, N – Number of Replicates, SD – Standard Deviation,%CV – Coefficient of Variation (percentage).

Table 11: Benchtop stability

	Bench top (Room temperature) stability							
	Bench top stability samples				Fresh QC Samples			
	LQC (ng/ml)		HQC (ng/ml)		LQC (ng/ml)		HQC (ng/ml)	
Nominal concentration	**0.598**		**79.290**		**0.598**		**79.290**	
Range	0.508	0.688	67.397	91.184	0.508	0.688	67.397	91.184
S. No.	% Stability calculated with nominal concentration				% Stability calculated with fresh QC samples			
	Conc. Found	% Nominal	Conc. Found	% Nominal	Conc. Found	% Nominal	Conc. Found	% Nominal
1	0.565	94.526	77.095	97.231	0.579	96.810	75.973	95.816
2	0.586	97.966	76.582	96.584	0.557	93.200	75.319	94.991
3	0.578	96.666	76.535	96.526	0.563	94.195	75.062	94.668
4	0.617	103.180	76.141	96.029	0.584	97.721	73.091	92.182
5	0.582	97.400	75.967	95.809	0.563	94.118	74.756	94.281
6	0.584	97.609	74.585	94.067	0.576	96.271	75.773	95.565
N	6		6		6		6	
Mean	0.5853		76.1508		0.5703		74.9957	
SD	0.01722		0.86147		0.01076		1.03475	
%CV	2.94		1.13		1.89		1.38	
% Nominal	97.882		96.041		95.373		94.584	
% Change	-2.118		-3.959		2.630		1.540	

Abbreviations: S. No. – Serial Number, LQC – Low Quality Control, HQC – High Quality Control, ng/ml – nanograms per millilitre, Nominal Concentration – Target Concentration of the Analyte, Range – Acceptable Concentration Range, % Stability Calculated with Nominal Concentration – Percentage of Stability based on Nominal Concentration, % Stability Calculated with Fresh QC Samples – Percentage of Stability compared to freshly prepared quality control samples, Conc. Found – Measured Concentration of Analyte, % Nominal – Measured concentration expressed as a

percentage of the nominal value, % Change – Percentage Change from Reference (either nominal or fresh), N – Number of Replicates, mean – Arithmetic Mean, SD – Standard Deviation, %CV – Coefficient of Variation (percentage).

Overall, the validation parameters confirmed that the developed LC-MS/MS method was selective, sensitive, precise, accurate, reproducible, and suitable for the pharmacokinetic evaluation of lobeglitazone following oral and transdermal microneedle administration.

Pharmacokinetic evaluation

A comparative pharmacokinetic evaluation was performed following a single 0.5 mg/kg dose of lobeglitazone administered via oral suspension and transdermal dissolving microneedle array (DMNA) in rats. The pharmacokinetic parameters are summarized in table 12 and visualized in fig. 3. The oral group exhibited a significantly higher C_{max} of 1786.25±66.68 ng/ml, with a T_max of 2.67±0.52 h, indicating rapid systemic absorption. In contrast, the DMNA group showed a significantly lower C_{max} of 1207.69±25.70 ng/ml (p<0.00001) and a delayed T_{max} of 5.33±1.03 h (p = 0.0001), consistent with sustained release via transdermal delivery. Despite the lower peak concentration, systemic exposure was markedly enhanced in the DMNA group. The AUC_{0-t} and $AUC_{0-\infty}$ were significantly higher than in the oral group (23195.36±527.74 and 24250.57±650.92 ng·h/ml vs. 11926.71±803.83 and 12036.84±860.47 ng·h/ml, respectively; p<0.00001). Furthermore, the Kel for the DMNA group was significantly lower (0.0685±0.0023 h^{-1}) compared to the oral group (0.1446±0.0179 h^{-1}, p<0.00001), resulting in a longer $T_{1/2}$ of 10.13±0.34 h for DMNA versus 4.85±0.60 h for oral administration shown in fig. 3. The relative bioavailability (%RB) of the DMNA formulation was calculated as 201.47%, indicating more than a two-fold enhancement in systemic availability.

In summary, while the DMNA patch produced a lower peak concentration and delayed onset, it significantly enhanced the overall bioavailability and extended the systemic exposure of lobeglitazone, supporting its potential utility as a controlled and sustained delivery system.

Table 12: Summary pharmacokinetics parameters

Summary of pharmacokinetic parameters					
Pk-parameters	**Oral dose**		**DMNA**		**p-Value**
	mean	**SD**	**mean**	**SD**	
C_{max} (ng/ml)	1786.25	66.68	1207.69	25.70	<.00001
T_{max} (h)	2.67	0.52	5.33	1.03	.000105
Auc_{0-t} (ng*h/ml)	11926.71	803.83	23195.36	527.74	<.00001
$AUC_{0-\infty}$ (ng*h/ml)	12036.84	860.47	24250.57	650.92	<.00001
Kel (h^{-1})	0.14	0.02	0.07	0.00	<.00001
T ½ (h)	4.85	0.60	10.13	0.34	<.00001
% RB	100%				

Abbreviations: PK – Pharmacokinetics, Cmax (ng/ml) – Maximum Observed Plasma Concentration (in nanograms per millilitre), Tmax (hr) – Time to Reach Maximum Plasma Concentration (in hours), AUC_0–t (ng·hr/ml) – Area Under the Plasma Concentration–Time Curve from Time Zero to Last Measurable Concentration (in nanogram hours per millilitre), AUC_0–∞ (ng·hr/ml) – Area Under the Curve from Time Zero to Infinity, Kel (h^{-1}) – Elimination Rate Constant (per hour), T½ (hr) – Elimination Half-Life (in hours), %RB – Relative Bioavailability (percentage), SD – Standard Deviation, p-Value – Probability Value (statistical significance), n – Number of Subjects in Each Group. *n=6 in each group, significant at p<.05.

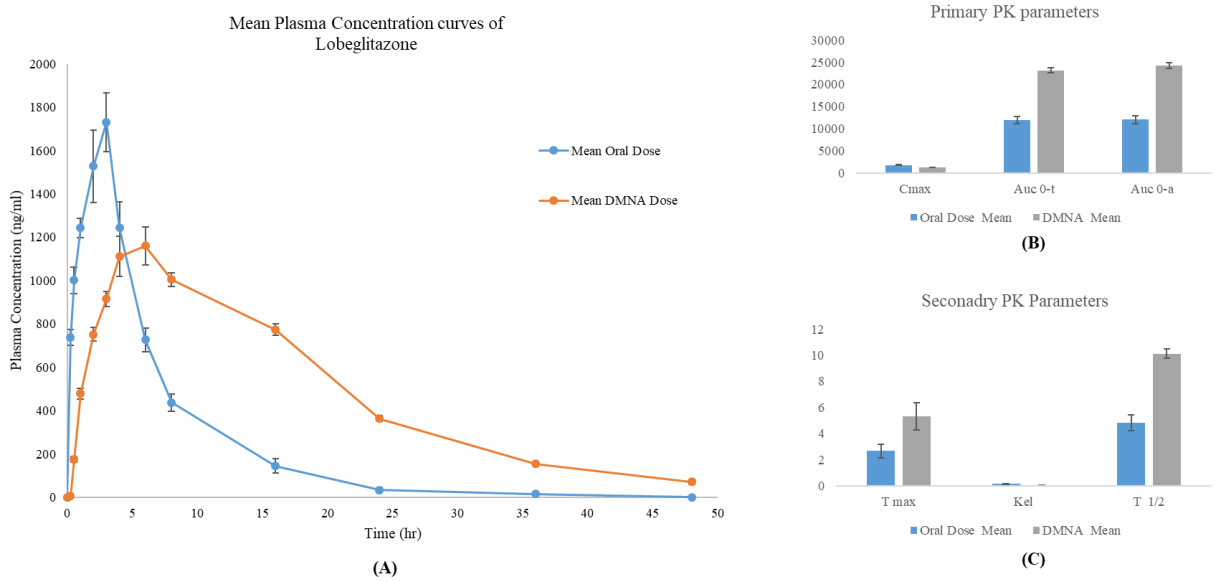

Fig. 3: (A) mean plasma concentration-time profiles of lobeglitazone following a single 0.5 mg/kg dose administered via oral suspension and dissolving microneedle array (DMNA) patch in rats (n = 6 per group). (B) Comparison of primary pharmacokinetic parameters: Cmax, AUC_0–t, and AUC_0–∞ between oral and DMNA administration routes. (C) Comparison of secondary pharmacokinetic parameters: Tmax, elimination rate constant (Kel), and half-life ($T_{1/2}$) between the two groups. Data are presented as mean ± SD. DMNA administration results in delayed Tmax, lower Cmax, and significantly enhanced systemic exposure compared to oral dosing, demonstrating improved pharmacokinetic stability

DISCUSSION

This study presents the first comparative pharmacokinetic evaluation of lobeglitazone delivered via a dissolving microneedle array (DMNA) versus the conventional oral route in a rat model. The findings demonstrate that DMNA-based transdermal delivery significantly alters the pharmacokinetic behavior of lobeglitazone, offering several potential advantages over oral administration.

The lower Cmax and delayed Tmax observed in the DMNA group suggest a sustained release profile, which is consistent with drug delivery via dissolving microneedles. Previous studies have shown that such platforms enable gradual systemic absorption through dermal microcirculation, reducing peak-related toxicity and supporting therapeutic consistency [12, 13]. These pharmacokinetic characteristics are particularly advantageous in chronic conditions like type 2 diabetes mellitus (T2DM), where stable plasma concentrations help mitigate glycemic fluctuations and reduce the risk of side effects such as fluid retention and weight gain known complications associated with thiazolidinedione therapy, including lobeglitazone [8].

Beyond delayed absorption, the significantly enhanced $AUC_0{-}\infty$ and relative bioavailability (201.47%) observed in the DMNA group indicate markedly improved systemic exposure. These improvements likely result from the bypassing of hepatic first-pass metabolism, a key pharmacokinetic barrier in oral thiazolidinedione therapy [14, 15]. As lobeglitazone undergoes extensive hepatic metabolism following oral administration [16], direct dermal delivery via DMNA represents a mechanistically sound strategy to increase bioavailability and improve therapeutic consistency.

The extended elimination half-life ($T_1/_2$) with DMNA administration (10.13 ± 0.34 h vs. 4.85 ± 0.60 h for oral) further supports its potential as a sustained-release platform. This prolongation may enable reduced dosing frequency, which in turn can promote better patient adherence. Similar findings have been reported in previous microneedle-based studies with other small molecules, where extended pharmacokinetic profiles improved treatment outcomes and patient satisfaction [13, 14].

In addition to pharmacokinetic enhancements, DMNA systems offer substantial patient-centric benefits. Their minimally invasive, pain-free application improves user experience, especially for chronic disease management, where long-term oral therapy is associated with compliance challenges [15]. Furthermore, the use of biodegradable polymers like hyaluronic acid and PVP K-90 in patch fabrication minimizes safety concerns related to residual materials.

However, some challenges remain. Transdermal absorption variability influenced by skin thickness, hydration, and regional blood flow can affect drug delivery efficiency. While animal models like rats offer a controlled setting for evaluating pharmacokinetics, human skin presents greater inter-individual variability [10]. Microneedle geometry, dissolution kinetics, and formulation composition must therefore be optimized for clinical application. Future studies should assess these factors in human skin models or early-phase clinical trials.

A further limitation of the present study is its single-dose design, which does not account for long-term pharmacokinetic behavior or potential drug accumulation. Repeated-dose studies are warranted to evaluate chronic safety, therapeutic durability, and real-world feasibility. Previous LC-MS/MS-based pharmacokinetic investigations with antidiabetics, such as those conducted by Das *et al.* (2022) and Halder *et al.* (2020), provide a strong precedent for extending such work into human trials [18, 19].

This study provides compelling preclinical evidence supporting the use of DMNA patches for lobeglitazone delivery. By enhancing bioavailability, prolonging systemic retention, and offering a more convenient and tolerable administration route, DMNA technology may address several limitations of oral thiazolidinedione therapy [17, 8]. From a translational perspective, the DMNA platform holds promise not only for lobeglitazone but also for other PPAR-γ agonists and therapeutics that benefit from sustained systemic exposure. Realizing this potential, however, will require careful clinical evaluation and regulatory validation to ensure consistent performance and safety in human populations.

CONCLUSION

The present study Concludes that transdermal delivery of lobeglitazone via a dissolving microneedle array (DMNA) significantly enhances systemic bioavailability and prolongs drug exposure compared to conventional oral administration in a rat model. While the oral route achieves faster absorption, the DMNA system provides a more controlled release profile, characterized by a delayed Tmax and sustained plasma concentrations. These pharmacokinetic advantages, combined with the minimally invasive and patient-friendly nature of microneedle patches, position DMNA as a promising alternative for the chronic management of type 2 diabetes mellitus.

By circumventing hepatic first-pass metabolism and improving pharmacokinetic stability, the DMNA platform addresses key limitations associated with oral thiazolidinedione therapy, such as variable absorption and suboptimal patient adherence. Nevertheless, interspecies differences and the single-dose design of this study underscore the need for further investigation. Future studies should focus on multiple-dose pharmacokinetics, long-term safety evaluations, and clinical trials to confirm the therapeutic potential of DMNA-based lobeglitazone delivery in humans.

In conclusion, this study provides foundational evidence supporting the development of dissolving microneedle patches as a viable, patient-centric delivery system for lobeglitazone, offering the potential to enhance therapeutic outcomes and adherence in diabetes care.

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AUTHORS CONTRIBUTIONS

Sukanta Roy (S. R.) contributed to conceptualization, methodology design, data curation, formal analysis, and original draft preparation. Balaram Ghosh (B. G.) was involved in methodology development, validation, investigation, and resource acquisition. Ananya Chandra (A. C.) contributed to software handling, data management, and visualization. Dibya Das (D. D.) participated in formal analysis, investigation, and manuscript review and editing. Parag Ghosh (P. G.) contributed to supervision, project administration, and manuscript review. Sangeeta Choudhury (S. C.) was responsible for validation, investigation, and data curation. Anirbandeep Bose (A. B.) contributed to conceptualization, supervision, project administration, funding acquisition, and manuscript review and editing. Subas Chandra Dinda (S. C. D.) supervised the overall study design, project administration, and critically reviewed and edited the manuscript. All authors have read and approved the final manuscript and agreed to be accountable for all aspects of the work.

CONFLICT OF INTERESTS

The authors hereby declare that they have no conflict of interest either to disclose

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