ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 18, Issue 9, 2025

Online - 2455-3891
Print - 0974-2441

Research Article

AN INSIGHT INVESTIGATION ON STEADY-STATE PHARMACOKINETICS OF LOBEGLITAZONE-LOADED DISSOLVING MICRONEEDLES IN RATS

SUKANTA ROY[1], DIBYA DAS[2], JAYANTA KUMAR CHAUDHURY[2], KAMALAKANTA RAY[2], SOUMIK LAHA[3], SUBAS CHANDRA DINDA[4]*, ANIRBANDEEP BOSE[5]

[1]Department of Pharmaceutics, School of Pharmacy, The Neotia University, West Bengal, India. [2]Department of Pharmaceutical Technology, JIS University, Kolkata, India. [3]Department of Pharmaceutical Technology, School of Health and Medical Sciences, Adamas University, Barasat, Kolkata, West Bengal, India. [4]Department of Pharmaceutics, School of Pharmacy, The Neotia University, West Bengal, India. [5]Department of Pharmaceutics, BCDA College of Pharmacy and Technology, Hridaypur, Barasat, Kolkata, West Bengal, India. *Corresponding author: Subas Chandra Dinda; Email: subaschandra.dinda@tnu.in

Received:10 July 2025, Revised and Accepted: 21 August 2025

ABSTRACT

Objectives: This study aimed to investigate the steady-state pharmacokinetics of lobeglitazone administered through a dissolving microneedle array (DMNA) compared to conventional oral delivery in rats, addressing limitations such as first-pass metabolism and fluctuating plasma concentrations associated with oral therapy.

Methods: Lobeglitazone-loaded DMNAs were fabricated using a micromolding technique with polyvinylpyrrolidone K90 and hyaluronic acid. Structural characteristics were confirmed through SEM. Male Wistar rats were divided into two groups (n=6): oral and DMNA (0.5 mg/day for 7 days). Plasma samples were collected over a period of 216 h and analyzed using a validated liquid chromatography–mass spectrometry/mass spectrometry method. Pharmacokinetic parameters, including C_{min},ssC_{max}, T_{max}, AUC, k_{el}, $T_{1/2}$, and mean residence time (MRT), were determined by non-compartmental analysis.

Results: DMNA administration resulted in significantly enhanced systemic exposure ($AUC_{168–216:}$ 26072.26±1510.30 ng·h/mL vs. 13658.04±1659.16 ng·h/mL, p<0.00001), prolonged half-life (10.05±0.68 h vs. 6.16±0.55 h), and a higher MRT (14.51±0.98 h vs. 8.88±0.80 h). The DMNA group maintained stable plasma concentrations with reduced fluctuation between peak and trough levels, indicating effective steady-state achievement and sustained drug release compared to oral delivery.

Conclusion: Dissolving microneedle-based transdermal delivery of lobeglitazone offers a superior pharmacokinetic profile over oral administration, supporting its potential in improving long-term glycemic control. Further studies are warranted to confirm efficacy and safety in clinical settings.

Keywords: Dissolving microneedles, Lobeglitazone, Steady-state pharmacokinetics, Transdermal delivery, Type 2 diabetes mellitus.

 DOI: http://dx.doi.org/10.22159/ajpcr.2025v18i9.55996. Journal homepage: https://innovareacademics.in/journals/index.php/ajpcr

INTRODUCTION

Lobeglitazone, a potent agonist of the peroxisome proliferator-activated receptor gamma, is an antidiabetic agent classified as a thiazolidinedione. In persons with type 2 diabetes mellitus, it has demonstrated significant efficacy in improving insulin sensitivity and glycemic regulation [1,2]. Conventional oral administration of lobeglitazone is associated with variable bioavailability due to first-pass hepatic metabolism, inconsistent gastrointestinal absorption, and potential food-drug interactions, despite its therapeutic promise. These factors affect alterations in plasma medication concentrations, thereby compromising treatment efficacy and increasing the risk of dose-dependent adverse effects such as weight gain and fluid retention [3-6].

Alternative delivery strategies that enhance patient adherence and provide more predictable pharmacokinetic profiles have garnered increasing interest to address these limitations. Dissolving microneedles represent a promising transdermal platform among novel approaches capable of delivering therapeutic agents directly into the skin microcirculation while gently piercing the stratum corneum. Dissolving microneedles, composed of water-soluble, biocompatible polymers, rapidly decompose upon insertion into the skin, delivering the therapeutic payload without generating sharps waste [7]. This approach has several advantages over conventional transdermal patches or parenteral administration, including enhanced patient adherence, precise dosing, reduced invasiveness, and the potential to circumvent first-pass metabolism, hence improving systemic bioavailability [8,9].

While the efficacy of administering small therapeutic agents and peptides using microneedles has been demonstrated in several studies, there is less understanding regarding their capacity to achieve and maintain steady-state plasma concentrations across extended dose regimens. In chronic therapies such as diabetes management, where consistent medication administration is essential to sustain therapeutic effectiveness and mitigate the risks of hypoglycemia or disease advancement, steady-state pharmacokinetics are particularly critical [10,11].

The primary objective of this study was to evaluate the steady-state pharmacokinetic profile of lobeglitazone administered to rats by dissolving microneedles. The study aimed to develop and characterize lobeglitazone-loaded dissolving microneedle arrays (DMNAs) for transdermal application, assess plasma concentration–time profiles following multiple doses, and compare key pharmacokinetic parameters with those obtained from conventional oral administration. The results are anticipated to provide essential insights into the feasibility and potential advantages of this novel delivery technique for long-term antidiabetic therapy.

MATERIALS AND METHODS

Materials

Lobeglitazone was procured from a certified supplier (please specify vendor and batch details in your final manuscript). Polyvinylpyrrolidone K90 (PVP K90) and hyaluronic acid (HA, pharmaceutical grade) were purchased from Sigma-Aldrich (St. Louis, MO, USA). All other chemicals and solvents were of analytical or high-performance liquid chromatography grade and used as received.

Preparation and characterization of lobeglitazone-loaded dissolving microneedles

Dissolving microneedles were fabricated using a micromolding technique. Briefly, a polymeric solution was prepared by dissolving PVP K90 and hyaluronic acid in deionized water under constant stirring until a clear, homogenous mixture was obtained. 0.5 mg of lobeglitazone was dispersed uniformly into the polymer solution to achieve the desired drug concentration. The resulting mixture was carefully poured into silicone microneedle molds and centrifuged at 3000 rpm for 10 min to ensure complete filling of microcavities and removal of trapped air. Molds were dried under vacuum at ambient temperature for 24 h. After drying, microneedle arrays were gently demoded and stored in desiccators until further use [12,13]. The mechanical strength and morphology of the microneedles were evaluated using a TA.XT texture analyzer and scanning electron microscopy (SEM) to confirm their uniform shape and dimensions. Drug content and encapsulation efficiency were determined by dissolving known quantities of microneedles in phosphate buffer (pH 7.4) and quantifying Lobeglitazone through ultraviolet visible spectroscopy at 248 nm [14].

Animals and ethical considerations

Male Wistar rats weighing 200–250 g were obtained from the institutional animal facility. All animal procedures were approved by the Institutional Animal Ethics Committee under the protocol number PK (R) DMNA 093 dated 01.08.2022 from IAEC Registration No. 1938/PO/Rc/S/17/CPCSEA and carried out in compliance with the CPCSEA guidelines for the care and use of laboratory animals. Rats were acclimatized for 1 week before the start of the study under controlled conditions (temperature 22±2°C, 12-h light-dark cycle) with free access to standard diet and water [15].

Study design and dosing regimen

Animals were randomly divided into two groups (n=6 per group): Group 1 (oral control): Received daily oral administration of 0.5 mg lobeglitazone suspension at an equivalent dose. Group 2 (DMNA Group): Received daily transdermal application of 0.5 mg Lobeglitazone-loaded dissolving microneedles. Treatments were administered once daily for seven consecutive days to attain steady-state conditions. For microneedle application, the dorsal skin was carefully shaved and cleaned before administration. Microneedles were manually applied with gentle thumb pressure for 1 min to ensure complete insertion and retained in place for approximately 30 min to allow complete dissolution [15] (Fig. 1).

Blood sampling and sample processing

Approximately 0.3 mL of blood was collected from the retro-orbital plexus under light anesthesia at predetermined time points to evaluate drug accumulation and steady-state pharmacokinetics. Sampling was performed at the following time points: 0 (pre dose),12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 168.25, 168.5, 169, 170, 171, 172, 174, 176, 184, 192, 204, and 216 h' post-initiation of dosing. Blood samples were transferred into heparinized tubes and centrifuged at 4000 rpm for 10 min. Plasma was separated and stored at–80°C until liquid chromatography–mass spectrometry/mass spectrometry (LS-MS/MS) analysis [15].

Bioanalytical method for lobeglitazone quantification

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 was rat plasma with K_2EDTA as an anticoagulant, purchased from precision laboratories. The analytical approach was positive ionization LC-MS/MS with a Sciex Triple Quad 4500 system and multiple reaction monitoring. Instrument control and data processing was performed using analyst software version 1.7.3. The method used a peak area ratio for measurement, with a weighting factor of $1/x^2$ to ensure linearity over the calibration range. Chromatographic separation was done at room temperature using a Thermo Scientific Hypersil GOLD C18 column (50 × 4.6 mm, 5 µm particle size). The mobile phase was 70:30 (v/v) acetonitrile, 2 mM ammonium acetate, and 0.2% formic acid. System flow was 0.600 mL/min. Purified extracts and increased sensitivity were obtained through liquid-liquid extraction (LLE). Each sample was processed with 200 µL plasma volume. After extraction, materials were reconstituted and analyzed in LC-MS/MS. MRM transitions m/z 482 → 258 for lobeglitazone and m/z 357.1 → 134.1 for pioglitazone were chosen, ensuring high specificity and sensitivity. The lobeglitazone calibration curve, spanning 0.200-101.788 ng/mL, is highly linear with correlation coefficients (r^2) above 0.999. Lobeglitazone was accurately quantified in rat plasma samples following oral and transdermal therapy using the optimized method [16-18].

Pharmacokinetic analysis

Pharmacokinetic analysis was performed to characterize the steady-state profile of Lobeglitazone following repeated transdermal administration through dissolving microneedles. Plasma concentration–time data were analyzed using non-compartmental methods with Phoenix WinNonlin software (Certara, USA). The primary parameters determined included the maximum plasma concentration at steady state (C_{max},ss), minimum plasma concentration (C_{min},ss), time to reach maximum concentration (T_{max},ss), area under the plasma concentration–time curve over the dosing interval ($AUC_{0-\tau}$), and the area under the first moment curve ($AUMC_{0-\tau}$). Mean residence time (MRT) was calculated as the ratio of AUMC to AUC, whereas the elimination half-life ($t_{1/2}$) was estimated from the terminal log-linear phase of the concentration–time profile. To evaluate attainment of steady state, pre-dose (trough) concentrations collected over consecutive dosing days were compared. All data were expressed as mean±standard deviation, and statistical comparisons between the microneedle-treated group and the oral control group were performed using an unpaired Student's t-test, with $p<0.05$ considered statistically significant [18,19].

RESULTS

Characteristics of the microneedle

The optimized dissolving microneedles were successfully fabricated using a micromolding approach and subsequently demolded without visible structural compromise. As illustrated in Fig. 2a and b, the front and backing layers of the Lobeglitazone-loaded microneedle array demonstrated uniform distribution, intact alignment, and well-defined geometry across the patch surface. The digital images confirm that the microneedles retained their conical structure post-demolding, with no evidence of warping, breakage, or polymer delamination. The backing layer appeared smooth and consistent, suggesting optimal mold filling and polymer solidification. These observations reflect the effectiveness of the formulation and drying process in preserving microneedle architecture during scale-up and handling. SEM analysis (Fig. 2c and d) demonstrated that the fabricated dissolving microneedles possessed well-defined, conical architectures with smooth, uniform surfaces, indicating a high degree of fabrication precision. The microneedles exhibited consistent geometric dimensions, with an average base diameter of approximately 300–350 µm, a tip diameter ranging from 5–10 µm, and an overall height of 350–400 µm. These structural features, including sharp tips and minimal tip radii, are indicative of their capacity to facilitate efficient transdermal penetration with reduced insertion force. High-magnification and cross-sectional SEM images revealed a homogenous distribution of the polymer-drug matrix throughout the microneedles, with no observable cracks, voids, or fabrication defects, thus affirming their mechanical robustness and structural integrity. A mild surface porosity and roughness were

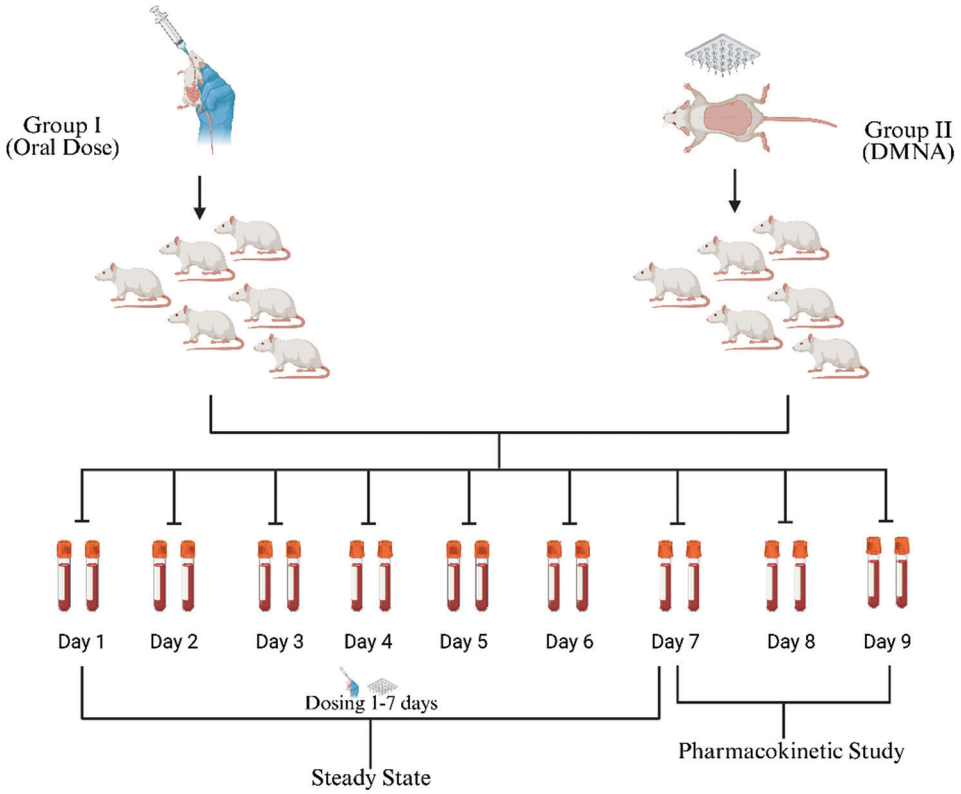

Fig. 1: Schematic representation of the experimental design for steady-state and pharmacokinetic evaluation of lobeglitazone in rats. Group I received lobeglitazone through oral suspension, while Group II was administered lobeglitazone through dissolving microneedle array patches. Blood samples were collected on days 1–7 for steady-state assessment, followed by intensive pharmacokinetic sampling from day 7–9. The study aimed to compare systemic exposure and drug disposition between the two delivery systems. Publication License: Created in BioRender. https://BioRender.com/ykswhof

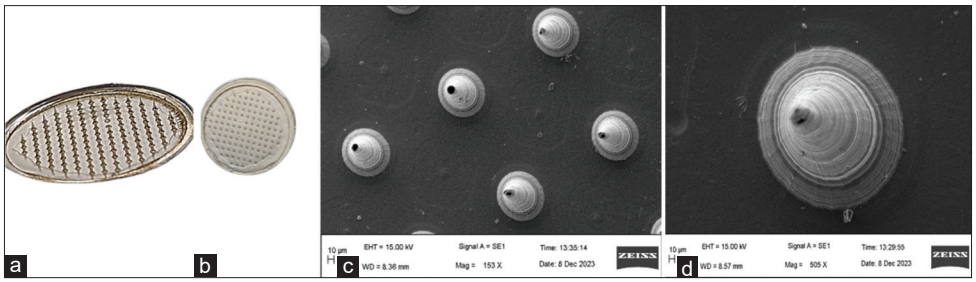

Fig. 2: Morphological evaluation of Lobeglitazone-loaded dissolving microneedle array patches. (a) Digital image showing the front view of the fabricated microneedle array patch containing uniformly arranged needle tips. (b) Backing layer of the microneedle patch illustrating the structural base that supports needle alignment and integration. (c) Scanning electron microscopy (SEM) image of the microneedle array at low magnification (×150), revealing uniform conical geometry and consistent spatial distribution of individual microneedles. (d) High-magnification SEM image (×500) of a single microneedle displaying a well-defined apex and concentric surface pattern indicative of precise molding and material deposition. The images confirm structural integrity and reproducibility essential for transdermal delivery applications

observed, which may be beneficial for enhancing drug adherence and facilitating controlled release. Mechanical strength analysis revealed a tip deformation force of more than 0.24 N, suggesting successful insertion while maintaining sufficient mechanical strength to ensure reliable performance during transdermal delivery.

Plasma extraction, method validation, and sample processing

Plasma samples were processed using a LLE method to ensure optimal analyte recovery and minimal matrix interference. A 200 µL aliquot of rat plasma was spiked with 50 µL of internal standard solution (pioglitazone) and extracted with 2 mL of tert-butyl methyl ether. After vortexing for 10 min at 2500 rpm, the samples were centrifuged at 4500 rpm for 5 min at 4°C. The upper organic layer was carefully transferred into pre-labeled vials and evaporated to dryness under nitrogen at 40°C. The residues were reconstituted with 1 mL of the mobile phase, vortexed briefly, and transferred to autosampler vials for LC-MS/MS analysis.

A sensitive and robust LC-MS/MS method was developed and validated for the quantification of lobeglitazone in rat plasma, using pioglitazone as the internal standard. Chromatographic separation was performed on a Hypersil GOLD C18 column (50 × 4.6 mm, 5 µm), using a mobile phase composed of acetonitrile and 2 mM ammonium acetate containing 0.2% formic acid in a 70:30 ratio, at a flow rate of 0.6 mL/min. The system operated under positive electrospray ionization using multiple reaction monitoring (MRM), monitoring transitions of m/z 482 → 258 for

lobeglitazone and m/z 357.1 → 134.1 for pioglitazone. The calibration curve was linear over the range of 0.200 to 101.788 ng/mL (r^2>0.999), with an LLOQ of 0.200 ng/mL. Method validation, performed according to ICH M10 guidelines, confirmed high selectivity, accuracy (87–101%), and precision (CV<7%). Mean analyte recovery was approximately 96.2%, with minimal matrix effects (normalized matrix factor CV<9%). The method demonstrated excellent stability under bench-top conditions, and negligible carryover was observed, confirming its reliability for pharmacokinetic assessment.

Blood sampling was conducted at defined intervals to capture systemic exposure and evaluate steady-state kinetics. Approximately 0.3 mL of blood was collected through retro-orbital plexus under light anesthesia at various time points up to 216 h post-dosing. Blood was collected into heparinized tubes and centrifuged at 4000 rpm for 10 min at 4°C. Plasma was separated promptly and stored at –80°C until further analysis. The validated sample processing and analytical method ensured high sensitivity and reproducibility for evaluating lobeglitazone concentrations in rat plasma following both oral and microneedle-based transdermal delivery.

Steady-state pharmacokinetic evaluation (0–168 h)

Steady-state plasma concentrations were evaluated over a 7 days repeated dosing schedule for both oral and DMNA-administered lobeglitazone. The data demonstrated that steady state was reliably achieved by approximately the 3rd day in both groups, as evidenced by the consistent recurrence of trough and peak levels in subsequent time points as shown in Fig. 3. In the DMNA group, plasma concentrations remained markedly stable, with peak concentrations (C_{max},ss) observed at 684.0 ng/mL (84 h), 682.7 ng/mL (108 h), and 682.5 ng/mL (156 h), and corresponding trough concentrations (C_{min},ss) at 411.9–422.5 ng/mL. The relative fluctuation between peaks and troughs was minimal, supporting the sustained-release behavior of the transdermal microneedle system.

In contrast, the oral administration group exhibited significantly lower and more fluctuating plasma concentrations. The oral C_{max},ss was approximately 136.6 ng/mL (156 h), while C_{min},ss values consistently dropped to around 41–42 ng/mL, indicating pronounced peak-to-trough variability. Such fluctuations are typical of oral delivery, where rapid absorption is followed by hepatic metabolism and clearance, resulting in more erratic systemic exposure.

The smoother pharmacokinetic profile in the DMNA group confirms its ability to maintain steady-state levels within a narrower concentration range, potentially reducing the risk of peak-related side effects and enhancing therapeutic consistency.

Comparative pharmacokinetic profile: Oral versus DMNA administration (steady-state phase)

A comprehensive pharmacokinetic evaluation between oral and DMNA administration routes during the steady-state phase (168–216 h) revealed statistically significant differences across all key parameters ($p<0.05$), as shown in Table 1. The maximum plasma concentration (C_{max}) was notably higher in the oral group (1648.38±107.05 ng/mL) compared to the DMNA group (1367.28±43.48 ng/mL, p=0.00007), reflecting the typical rapid absorption associated with oral dosing. However, the time to reach C_{max},T_{max} was comparable between groups, with only a slight delay in the DMNA group (172.67±1.03 h) relative to oral (171.33±0.52 h, p=0.00895), suggesting similar timing of peak drug accumulation under repeated dosing conditions.

The area under the concentration-time curve (AUC), a critical indicator of systemic exposure, was significantly greater in the DMNA group. $AUC_{168-192}$ and $AUC_{168-\infty}$ were 25046.02±1509.97 ng·h/mL and 26072.26±1510.30 ng·h/mL, respectively, for DMNA, versus 13588.03±1658.60 ng·h/mL and 13658.04±1659.16 ng·h/mL for oral administration (both $p<0.00001$). These findings indicate that the microneedle delivery system achieved nearly double the systemic exposure compared to oral administration, largely attributed to avoidance of first-pass hepatic metabolism and sustained transdermal absorption.

The elimination rate constant (k_{el}) was significantly lower in the DMNA group (0.0692±0.0048/h) compared to the oral group (0.1134±0.0106/h, $p<0.00001$), resulting in a prolonged elimination half-life ($T_{1/2}$) of 10.05±0.68 h for DMNA versus 6.16±0.55 h for oral administration. This indicates slower systemic clearance and extended retention of lobeglitazone in circulation following transdermal delivery.

The steady-state concentration between 120–168 h (Css) was markedly higher for DMNA (420.52±1.37 ng/mL) than oral (41.84±0.16 ng/mL, $p<0.00001$), confirming superior maintenance of therapeutic levels with less fluctuation. In addition, the AUMC and MRT were significantly elevated in the DMNA group (AUMC: 377984.93±30036.87 ng·h^2/mL, MRT: 14.51±0.98 h) relative to oral (AUMC: 121039.78±16160.10 ng·h^2/mL, MRT: 8.88±0.80 h, both $p<0.00001$), indicating prolonged systemic exposure and a sustained release profile, as shown in Fig. 4.

Collectively, these pharmacokinetic findings underscore the enhanced bioavailability, prolonged retention, and sustained systemic release afforded by the DMNA delivery. This delivery system offers a pharmacologically advantageous profile over oral administration, making it a promising strategy for chronic therapy in type 2 diabetes mellitus.

DISCUSSION

The present study systematically evaluated the steady-state pharmacokinetic (PK) profile of lobeglitazone delivered through DMNAs compared to conventional oral administration in a rat model. The data indicate that transdermal microneedle-based delivery offers considerable pharmacokinetic advantages, including sustained

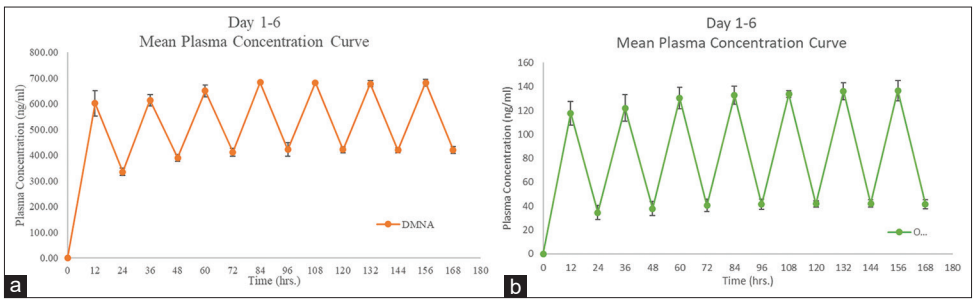

Fig. 3: Mean plasma concentration-time profiles of lobeglitazone during repeated dosing from day 1 to day 6 following transdermal and oral administration in rats (n=6 per group). (a) dissolving microneedle array (DMNA) group: Mean plasma concentrations of lobeglitazone following daily application of DMNA (0.5 mg/day). The profile demonstrates consistent peak and trough levels, indicative of steady-state attainment with minimal inter-dose fluctuation. (b) Oral group: Mean plasma concentrations of lobeglitazone following daily oral suspension dosing (0.5 mg/day). The curve reveals higher variability in peak and trough levels compared to the DMNA group, suggesting less stable systemic exposure. Error bars represent standard deviation

Table 1: Summary of steady-state pharmacokinetics

PK parameters	Treatment arms		
	Oral	**DMNA**	**p-value**
C_{max} (ng/mL)	1648.38±107.05	1367.28±43.48	0.00007
T_{max} (h)	171.33±0.52	172.67±1.03	0.00895
$AUC_{168-192}$ (ng·h/mL)	13588.03±1658.60	25046.02±1509.97	<0.00001
$Auc_{168-\infty}$ (ng·h/mL)	13658.04±1659.16	26072.26±1510.30	<0.00001
k_{el} (h^{-1})	0.11±0.011	0.07±0.005	<0.00001
$T_{1/2}$(h)	6.16±0.55	10.05±0.68	<0.00001
$C_{min}SS_{120-168}$ (avg.) (ng/mL)	41.84±0.16	420.52±1.37	<0.00001
AUMC (ng·h^2/mL)	121039.78±16160.1	377984.93±30036.87	<0.00001
MRT (h)	8.88±0.80	14.51±0.98	<0.00001

C_{max}: Maximum plasma concentration, T_{max}: Time to reach maximum concentration, $AUC_{168-192}$: Area under the plasma concentration–time curve from 168 to 192 h, $Auc_{168-\infty}$: Area under the curve from 168 h to infinity, k_{el}: Elimination rate constant, $T_{1/2}$: Elimination half-life, $C_{min}SS_{120-168}$: Average minimum steady-state plasma concentration between 120 and 168 h, AUMC: Area under the first moment curve, MRT: Mean residence time, DMNA: Dissolving microneedle array, h: hours, ng/mL: Nanograms per millilitre, ng·h/mL: Nanogram hour per millilitre, ng·h^2/mL: Nanogram hour squared per millilitre. *P* value is significant at<0.05

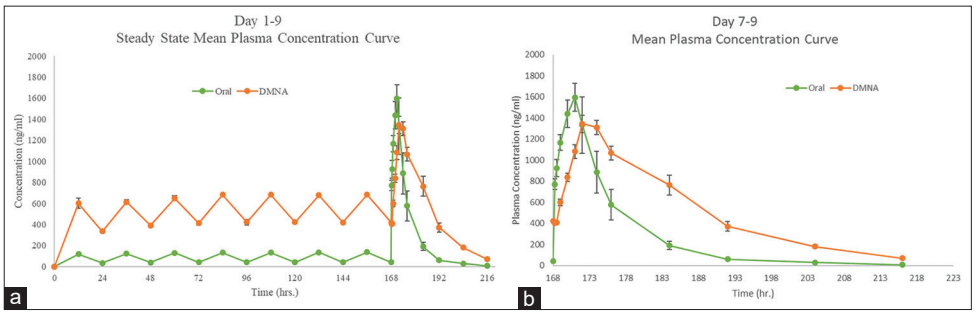

Fig. 4: Steady-state and post-dosing plasma concentration-time profiles of lobeglitazone in rats (n=6 per group) following repeated administration through oral and dissolving microneedle array (DMNA) routes. (a) Composite steady-state profile from day 1 to day 9, comparing mean plasma concentrations between oral (green) and DMNA (orange) administration of lobeglitazone (0.5 mg/day). The DMNA group exhibited consistent plasma levels with attenuated fluctuations, while the oral group showed lower systemic exposure and pronounced variability between peaks and troughs. (b) Post-final dose pharmacokinetic profile (day 7–9) depicting drug elimination kinetics. DMNA-treated animals showed a slower decline in plasma concentration, indicating prolonged systemic retention compared to the oral group. Error bars represent standard deviation

drug release, enhanced systemic exposure, reduced peak–trough fluctuations, and prolonged retention in circulation. These outcomes align with the proposed hypothesis that microneedle-mediated delivery can bypass hepatic first-pass metabolism and offer controlled drug absorption through the dermal microcirculation.

The microneedle patches fabricated using a PVP-hyaluronic acid polymer matrix exhibited excellent structural and mechanical integrity. SEM imaging confirmed the uniformity and conical geometry of the needles, ensuring efficient skin penetration without breakage or polymeric distortion post-demolding or post-application. Previous investigations have shown that geometric fidelity and mechanical strength are key determinants for effective transdermal drug delivery using dissolving microneedles [8,20]. The partial deformation of microneedle tips observed after application further substantiates successful skin insertion, while their subsequent dissolution remains a critical prerequisite for effective intradermal drug deposition.

Pharmacokinetic comparisons between oral and DMNA routes revealed critical differences in systemic exposure and drug disposition. While the oral group exhibited higher Cmax values (1648.38±107.05 ng/mL), the DMNA group demonstrated superior systemic exposure as evidenced by significantly elevated AUC168–216 and AUC168–∞ values (25046.02±1509.97 and 26072.26±1510.30 ng·h/mL, respectively) compared to oral (13588.03±1658.60 and 13658.04±1659.16 ng·h/mL). These findings are consistent with reports where microneedle-mediated drug delivery increased bioavailability of low-solubility compounds by bypassing the gastrointestinal tract and hepatic metabolism [9,21,22].

Moreover, the DMNA group exhibited a lower elimination rate constant (kel=0.0692±0.0048/h) and longer half-life ($t_1/_2$=10.05±0.68 h), indicating a slower and more sustained drug clearance relative to the oral route (kel=0.1134±0.0106/h; $t_1/_2$=6.16±0.55 h). These parameters suggest that microneedles facilitated a depot-like intradermal release, gradually maintaining therapeutic plasma levels and improving (MRT=14.51±0.98 h). A similar phenomenon was observed in studies involving transdermal delivery of other small-molecule drugs such as insulin and levonorgestrel, using microneedles [22,23].

A critical advantage of the DMNA system was its ability to maintain higher minimum steady-state concentrations (Cmin,ss=420.52±1.37 ng/mL) over the dosing interval (120–168 h), as opposed to 41.84±0.16 ng/mL for oral administration. This substantial difference reflects a more stable and controlled release profile that could minimize dose-dependent toxicity associated with high plasma spikes and avoid sub-therapeutic levels that occur with conventional oral regimens. In line with this, prior studies have reported improved glycemic control in diabetic models when drug plasma levels are maintained within a tight therapeutic window [19].

In addition, the visualized mean plasma concentration-time curves further reinforce the pharmacokinetic trends, where the DMNA group displayed consistent oscillatory peaks and troughs suggestive of steady-state attainment by the 3rd day, whereas the oral group experienced erratic plasma levels. The post-dose washout phase (day 7–9) showed a more gradual decline in plasma concentrations in the DMNA group, confirming the extended release and prolonged systemic availability even after cessation of dosing. The observed PK behaviors are consistent

with the pharmacotechnical premise of controlled intradermal drug diffusion and depot formation [24,25].

Collectively, these findings underscore the potential of dissolving microneedle technology as a patient-friendly, efficacious alternative to oral therapy for chronic conditions like type 2 diabetes. The ability to sustain therapeutic concentrations with reduced dosing variability supports its translational relevance, particularly in populations with poor oral bioavailability or adherence concerns. Nevertheless, while the preclinical outcomes are promising, further validation in larger animal models and human subjects is warranted to confirm pharmacodynamic efficacy and dermal tolerability over prolonged use.

CONCLUSION

The present study demonstrates that DMNAs offer a promising alternative to oral delivery for lobeglitazone, providing enhanced systemic exposure, prolonged half-life, and sustained plasma concentrations with reduced pharmacokinetic variability. The formulation showed excellent mechanical integrity and reproducibility, while pharmacokinetic analysis confirmed steady-state achievement with superior therapeutic levels compared to oral administration. These findings support the potential of DMNA-based transdermal delivery systems for improving treatment outcomes in chronic diseases such as type 2 diabetes mellitus. However, the use of a small animal model limits direct clinical translation. Long-term safety and pharmacodynamic outcomes were not assessed. Future studies should explore large-animal or human trials, evaluate repeated application safety, and optimize design for scalable, patient-friendly use in chronic disease management.

ACKNOWLEDGMENT

The authors would like to acknowledge ABS Clinical Solutions, Kolkata-152, and TAAB Biostudy Services for the technical support and all other kinds of help provided for this study. Authors would like to extend acknowledgement to Senjuti Bhattacharjee and Sudeepto Biswas, who performed formal analysis and statistical analysis.

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sector.

AUTHORS CONTRIBUTIONS

Sukanta Roy (S.R.) contributed to conceptualization, methodology design, data curation, formal analysis, and original draft preparation. Dibya Das (D.D.) participated in formal analysis, investigation, and manuscript review and editing. Soumik Laha (S.L.) contributed to data curation and formal analysis. Jayanta Kumar Chaudhury (J.K.C.) supervised the overall study design, project administration, and critically reviewed and edited the manuscript. Kamalakanta Ray (K.R.) supervised the overall study design, project administration, and critically reviewed and edited the manuscript. 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.

REFERENCES

1. Jang JY, Bae H, Lee YJ, Choi YI, Kim HJ, Park SB, *et al*. Structural basis for the enhanced anti-diabetic efficacy of lobeglitazone on PPARγ. Sci Rep. 2018;8(1):31. doi: 10.1038/s41598-017-18274-1, PMID 29311579
2. Lee HW, Kim BY, Ahn JB, Kang SK, Lee JH, Shin JS, *et al*. Molecular design, synthesis, and hypoglycemic and hypolipidemic activities of novel pyrimidine derivatives having thiazolidinedione. Eur J Med Chem. 2005;40(9):862-74. doi: 10.1016/j.ejmech.2005.03.019, PMID 15908051
3. Jung JA, Lee SY, Kim TE, Kim JR, Kim C, Huh W, *et al*. Lack of the effect of lobeglitazone, a peroxisome proliferator-activated receptor-γ agonist, on the pharmacokinetics and pharmacodynamics of warfarin. Drug Des Dev Ther. 2015;9:737-43. doi: 10.2147/DDDT.S76591, PMID 25767371
4. Kim JW, Kim JR, Yi S, Shin KH, Shin HS, Yoon SH, *et al*. Tolerability and pharmacokinetics of lobeglitazone (CKD-501), a peroxisome proliferator-activated receptor-gamma agonist: A single- and multiple-dose, double-blind, randomized control study in healthy male Korean subjects. Clin Ther. 2011;33(11):1819-30. doi: 10.1016/j.clinthera.2011.09.023, PMID 22047812
5. Davit B, Braddy AC, Conner DP, Yu LX. International guidelines for bioequivalence of systemically available orally administered generic drug products: A survey of similarities and differences. AAPS J. 2013;15(4):974-90. doi: 10.1208/s12248-013-9499-x, PMID 23821352
6. Park MK, Kim TE, Kim J, Kim C, Yoon SH, Cho JY, *et al*. Tolerability and pharmacokinetics of lobeglitazone, a novel peroxisome proliferator-activated receptor-gamma agonist, after a single oral administration in healthy female subjects. Clin Drug Investig. 2014;34(7):467-74. doi: 10.1007/s40261-014-0197-y, PMID 24802657
7. Mdanda S, Ubanako P, Kondiah PP, Kumar P, Choonara YE. Recent advances in microneedle platforms for transdermal drug delivery technologies. Polymers (Basel). 2021;13(15):2405. doi: 10.3390/polym13152405, PMID 34372008
8. Donnelly RF, Raj Singh TR, Woolfson AD. Microneedle-based drug delivery systems: Microfabrication, drug delivery, and safety. Drug Deliv. 2010;17(4):187-207. doi: 10.3109/10717541003667798, PMID 20297904
9. Prausnitz MR, Langer R. Transdermal drug delivery. Nat Biotechnol. 2008;26(11):1261-8. doi: 10.1038/nbt.1504, PMID 18997767
10. Jung JH, Jin SG. Microneedle for transdermal drug delivery: Current trends and fabrication. J Pharm Investig. 2021;51(5):503-17. doi: 10.1007/s40005-021-00512-4, PMID 33686358
11. Zhang J, Li H, Albakr L, Zhang Y, Lu A, Chen W, *et al*. Microneedle-enabled therapeutics delivery and biosensing in clinical trials. J Control Release. 2023;360:687-704. doi: 10.1016/j.jconrel.2023.07.023, PMID 37442203
12. Moawad F, Pouliot R, Brambilla D. Dissolving microneedles in transdermal drug delivery: A critical analysis of limitations and translation challenges. J Control Release. 2025;383:113794. doi: 10.1016/j.jconrel.2025.113794, PMID 40319916
13. Oliveira C, Teixeira JA, Oliveira N, Ferreira S, Botelho CM. Microneedles' device: Design, fabrication, and applications. Macromol. 2024;4(2):320-55. doi: 10.3390/macromol4020019
14. Mudaliar S, Sharma S. Quantification of lobeglitazonesulfate in bulk and tablet dosage form by a validated UV spectroscopy method: A new thiazolidinedione antidiabetic drug. Drug Metab Bioanal Lett. 2024;17(2):49-55. doi: 10.2174/0118723128319462240614111627, PMID 40296487
15. Mukherjee K, Roy S, Giri TK. Effect of intragranular/extragranulartara gum on sustained gastrointestinal drug delivery from semi-IPN hydrogel matrices. Int J Biol Macromol. 2023;253(5):127176. doi: 10.1016/j.ijbiomac.2023.127176, PMID 37783254
16. Lee JH, Yang SH, Oh JM, Lee MG. Pharmacokinetics of drugs in rats with diabetes mellitus induced by alloxan or streptozocin: Comparison with those in patients with type I diabetes mellitus. J Pharm Pharmacol. 2010;62(1):1-23. doi: 10.1211/jpp.62.01.0001, PMID 20722995
17. King MJ, Badea I, Solomon J, Kumar P, Gaspar KJ, Foldvari M. Transdermal delivery of insulin from a novel biphasic lipid system in diabetic rats. Diabetes Technol Ther. 2002;4(4):479-88. doi: 10.1089/152091502760306562, PMID 12396742
18. Das D, Halder D, Bose A, Shaw TK, Saha C, Kumar De P, *et al*. Determination of metformin and sitagliptin in healthy human volunteers' blood plasma and its bioequivalence study under fasting condition. Int J Appl Pharm. 2022;14(6):42-50. doi: 10.22159/ijap.2022v14i6.45140
19. Ng LC, Gupta M. Transdermal drug delivery systems in diabetes management: A review. Asian J Pharm Sci. 2020;15(1):13-25. doi: 10.1016/j.ajps.2019.04.006, PMID 32175015
20. Ita K. Transdermal delivery of drugs with microneedles-potential

and challenges. Pharmaceutics. 2015;7(3):90-105. doi: 10.3390/pharmaceutics7030090, PMID 26131647

21. Sullivan SP, Koutsonanos DG, Del Pilar Martin M, Lee JW, Zarnitsyn V, Choi SO, *et al*. Dissolving polymer microneedle patches for influenza vaccination. Nat Med. 2010;16(8):915-20. doi: 10.1038/nm.2182, PMID 20639891
22. Kim YC, Park JH, Prausnitz MR. Microneedles for drug and vaccine delivery. Adv Drug Deliv Rev. 2012;64(14):1547-68. doi: 10.1016/j.addr.2012.04.005, PMID 22575858
23. Ripolin A, Quinn J, Larrañeta E, Vicente-Perez EM, Barry J, Donnelly RF. Successful application of large microneedle patches by human volunteers. Int J Pharm. 2017;521(1-2):92-101. doi: 10.1016/j.ijpharm.2017.02.011, PMID 28216463
24. Larrañeta E, Lutton RE, Woolfson AD, Donnelly RF. Microneedle arrays as transdermal and intradermal drug delivery systems: Materials science, manufacture and commercial development. Mater Sci Eng R Rep. 2016;104:1-32. doi: 10.1016/j.mser.2016.03.001
25. Zhang Y, Yu J, Kahkoska AR, Wang J, Buse JB, Gu Z. Advances in transdermal insulin delivery. Adv Drug Deliv Rev. 2019 Jan 15;139:51-70. doi: 10.1016/j.addr.2018.12.006, PMID 30528729