MATERIALE PLASTICE
https://revmaterialeplastice.ro
https://doi.org/10.37358/Mat.Plast.1964

CC BY

Biodegradable Microneedle Patch for Transdermal Clopidogrel Delivery

XIHUA OUYANG, WEI CHEN, PENG NA, ZHENGXIAN HUANG, XIANCONG LAI, QIANG MING, YU YE*
Department of Neurosurgery, Longgang Central Hospital of Shenzhen, Shenzhen Clinical Medical College, Guangzhou University of Chinese Medicine, No. 6082, Longgang Avenue (Longgang Section), Longgang District, Shenzhen, 518116, China

Abstract: *Clopidogrel is widely used for stroke prevention, but its oral administration is limited by poor patient adherence, gastrointestinal irritation, and hepatic first-pass metabolism. To address these limitations, we developed a biodegradable microneedle patch composed of poly(lactic-co-glycolic acid) (PLGA) and polyvinylpyrrolidone (PVP) for the transdermal delivery of clopidogrel. The patch exhibited sufficient mechanical strength to penetrate the skin simulant and fully dissolve within 6 h. Drug release was sustained over 48 h in vitro, and platelet aggregation was evaluated using a simulated human platelet-rich plasma (PRP) model. Compared to clopidogrel solution, the microneedle patch maintained longer antiplatelet activity, with significant inhibition observed up to 72 h. These findings suggest that dissolvable microneedle patches may serve as a non-invasive and sustained delivery strategy for clopidogrel, potentially improving therapeutic consistency and patient compliance in stroke prophylaxis.*

Keywords: *Microneedle patch, clopidogrel, transdermal drug delivery, stroke prevention therapy*

1. Introduction

Stroke remains one of the leading causes of death and long-term disability worldwide, with ischemic stroke accounting for over 80% of all cases [1]. Platelet aggregation plays a central role in the formation of thrombi that precipitate cerebrovascular events, making antiplatelet therapy a cornerstone of stroke prevention [1,2]. Clopidogrel, a thienopyridine-class antiplatelet agent, is widely prescribed for secondary prevention of stroke and cardiovascular events due to its efficacy in inhibiting adenosine diphosphate (ADP)-induced platelet aggregation [3,4]. However, despite its clinical utility, clopidogrel faces several challenges when administered orally [5]. These include poor bioavailability due to hepatic first-pass metabolism, interpatient variability in activation, and gastrointestinal side effects that compromise long-term adherence [6].

Oral clopidogrel must be metabolized in the liver to generate its active thiol metabolite, a process influenced by genetic polymorphisms in CYP2C19 and related enzymes [7–10]. As a result, up to 30% of patients are classified as poor responders, leading to suboptimal platelet inhibition and increased risk of thrombotic events [11]. Moreover, gastrointestinal irritation and bleeding associated with oral intake often limit patient compliance, especially in elderly populations and those requiring polypharmacy [12,13]. These drawbacks highlight an urgent need for alternative delivery strategies that can overcome metabolic barriers and improve the consistency and safety of antiplatelet therapy [14].

Transdermal drug delivery offers a promising non-invasive route that circumvents the gastrointestinal tract and hepatic metabolism, enabling more stable pharmacokinetics and enhanced bioavailability [15,16]. Among various transdermal approaches, microneedle-based systems have gained increasing attention for their ability to painlessly breach the stratum corneum and deliver drugs directly into the dermal capillary bed [17,18]. Dissolvable microneedles fabricated from biocompatible and biodegradable polymers such as poly(lactic-co-glycolic acid) (PLGA) and polyvinylpyrrolidone (PVP) can encapsulate

email: yeyu20020813@163.com

both hydrophilic and hydrophobic drugs, allowing for precise control over drug release kinetics via matrix composition tuning [19,20]. These systems offer the added advantages of self-administration, minimal medical waste, and improved patient compliance [21,22]. Microneedle systems have been successfully applied in a variety of clinical areas, including painless vaccine delivery (e.g., influenza, HPV), insulin administration for diabetes management, and immunotherapy for allergic or oncologic indications. These studies demonstrate the platform's potential for delivering biologics, peptides, and small molecules across the skin barrier. However, the use of microneedles for long-acting antiplatelet therapy remains largely unexplored. To our knowledge, this is among the first studies to apply a dissolvable microneedle patch to deliver clopidogrel transdermally in a sustained and therapeutically effective manner.

In this study, we report the development and evaluation of a PLGA/PVP-based dissolvable microneedle patch for the transdermal delivery of clopidogrel. We systematically investigated the fabrication, morphology, mechanical insertion performance, degradation behavior, and drug release kinetics of the microneedles. Furthermore, we compared the *in vivo* antiplatelet efficacy of microneedle-based clopidogrel delivery with traditional oral administration using a platelet aggregation assay over a 72-h period. Our results demonstrate that the microneedle patch achieves effective and sustained platelet inhibition, offering a compelling alternative for stroke prevention with potential for improved safety, efficacy, and patient adherence.

2. Materials and methods

2.1. Materials

Poly(lactic-co-glycolic acid) (PLGA, 50:50, inherent viscosity 0.2 dL/g) and polyvinylpyrrolidone (PVP, Mw $\approx$ 40 kDa) were purchased from Sigma-Aldrich. Clopidogrel bisulfate was obtained from MedChemExpress. Phosphate-buffered saline (PBS, pH 7.4) was prepared using standard protocols. All solvents and reagents were analytical grade and used as received.

2.2. Microneedle fabrication

PLGA and PVP were dissolved in dichloromethane (DCM) and ethanol, respectively, to form a homogeneous solution at varying mass ratios (PLGA:PVP = 9:1, 7:3, and 5:5), with clopidogrel added at 5% w/w relative to total polymer mass. The drug-loaded solution was cast into PDMS microneedle molds and centrifuged at 3000 rpm for 5 min to ensure complete filling. The molds were dried under ambient conditions for 12 h, followed by vacuum drying at room temperature overnight. Microneedle arrays were carefully demolded for further use.

2.3. Morphology characterization (SEM)

Microneedle arrays were sputter-coated with gold and imaged using a field-emission scanning electron microscope (FE-SEM, JEOL JSM-7500F) at an accelerating voltage of 5 kV to evaluate tip sharpness, geometric uniformity, and array integrity.

2.4. Insertion test and penetration depth measurement

Microneedles with different base diameters (10, 20, and 30 µm) were inserted into 1% agarose gel skin simulants using a force-controlled applicator (5 N for 30 s). Insertion depth was visualized by staining the gel cross-section with trypan blue and measured using ImageJ software. Each group was tested in triplicate. While 1% agarose gel provides a consistent and reproducible matrix for initial insertion force evaluation, it does not replicate the layered architecture or hydration gradients of real skin. Therefore, results should be interpreted as a mechanical approximation, and future studies should validate findings using porcine or *ex vivo* human skin.

2.5. *In vitro* degradation study

Microneedle patches were incubated in 10 mL PBS (pH 7.4) at 37°C for 60 h under gentle agitation. At predetermined time points (10, 20, 30, 40, 50, 60 h), the residual microneedle mass was collected, rinsed, dried, and weighed. The needle mass fraction was calculated as the percentage of the initial dry weight.

2.6. *In vitro* drug release study

Microneedle arrays (containing equivalent amounts of clopidogrel) were immersed in 10 mL PBS at 37°C. At specific intervals (0, 2, 4, 6, 12, 24, 36, 48 h), 1 mL of supernatant was collected and replaced with fresh PBS. Drug content was quantified using HPLC (Agilent 1260, UV detection at 220 nm) after filtration through a 0.22 µm syringe filter. The cumulative release was calculated and plotted against time.

2.7. Platelet aggregation assay

To assess the antiplatelet effect of clopidogrel delivered via microneedle patches, a simulated *in vitro* platelet aggregation assay was conducted using platelet-rich plasma (PRP) obtained from healthy human donors. Whole blood was collected under institutionally approved protocols, anticoagulated with 3.2% sodium citrate, and centrifuged at 150× *g* for 10 min to isolate PRP. Three groups were tested: the Oral group, where PRP was incubated with 10 µm clopidogrel solution to simulate systemic exposure; the Patch group, treated with extract from drug-loaded microneedle patches incubated in PBS at 37°C for 1 h; and the Placebo group, treated with plain PBS. At selected time points (0, 6, 12, 24, 36, 48, and 72 h), ADP (10 µm) was added to induce aggregation, and changes in light transmission were recorded using a Chrono-Log 700 aggregometer. All experiments were performed in triplicate, and results were normalized to baseline to evaluate the duration and extent of platelet inhibition.

2.8. Statistical analysis

All quantitative data are presented as mean ± standard deviation (SD). Statistical significance between groups was analyzed using one-way ANOVA followed by Tukey's post-hoc test. A p-value < 0.05 was considered statistically significant. GraphPad Prism 9.0 was used for plotting and analysis.

2.9. Use of AI tools

During the preparation of this manuscript, the authors used Deepseek solely for English language polishing. The authors have reviewed and revised the content to ensure clarity and accuracy.

3. Results

Figure 1 demonstrates the conceptual framework of a PLGA/PVP-based dissolvable microneedle patch for transdermal delivery of clopidogrel. The patch is designed to penetrate the stratum corneum and release the drug directly into the dermal capillaries. In contrast to oral administration, which is illustrated as undergoing hepatic first-pass metabolism, the microneedle system facilitates direct systemic entry. The comparison of pharmacokinetic profiles shows that the microneedle group achieves a smoother, more sustained blood concentration over time, while the oral route results in a rapid peak followed by a sharp decline. This suggests prolonged drug exposure and potential for improved therapeutic consistency via the transdermal route.

Figure 2 presents a high-resolution SEM image of the fabricated PLGA/PVP microneedle array. The microneedles demonstrate excellent morphological integrity, with uniform height, conical structure, and tip sharpness across the array. Each needle maintains a base diameter of approximately 100 µm and a tip radius estimated below 10 µm, suggesting sufficient sharpness for effective skin penetration. No visible deformation, collapse, or defects were observed, indicating the mechanical robustness of the structure during the demolding and drying processes.

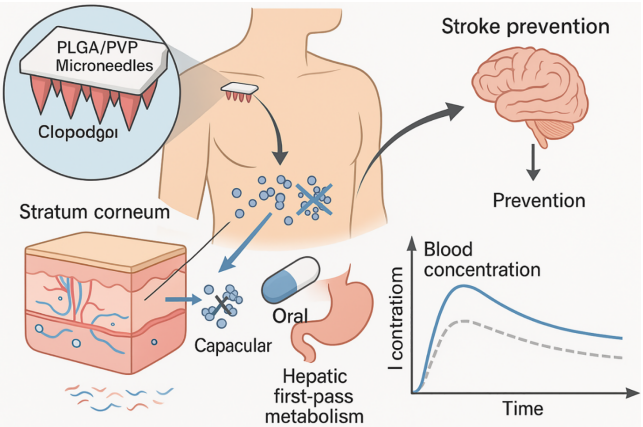

Figure 1. Schematic illustration of transdermal clopidogrel delivery using a PLGA/PVP microneedle patch for stroke prevention. The microneedle system bypasses the stratum corneum barrier, delivering clopidogrel directly into the dermal microcirculation, thereby avoiding hepatic first-pass metabolism and gastrointestinal side effects associated with oral administration. This transdermal route enables sustained systemic drug absorption and enhanced antiplatelet efficacy

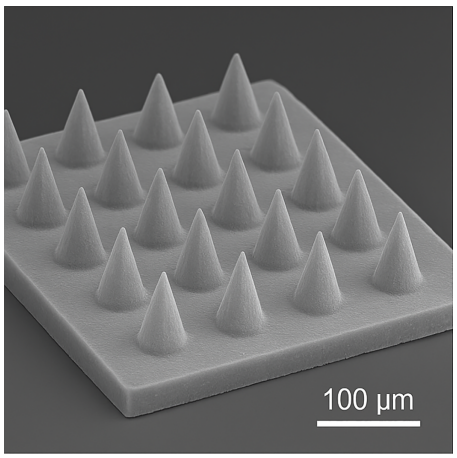

Figure 2. Scanning electron microscopy (SEM) image of the PLGA/PVP microneedle array. The microneedles exhibit a uniform conical geometry with sharp tips and consistent alignment, confirming the successful fabrication of a well-ordered array suitable for transdermal insertion. Scale bar: 100 µm

Figure 3 shows the insertion depths of microneedles with varying base diameters (10, 20, and 30 µm) when applied to a standardized skin simulant. The results indicate that microneedles with smaller base diameters penetrate deeper into the skin model, with the 10 µm group reaching an average depth of ~160 µm, while the 30 µm group only reached ~105 µm. The differences between each group were statistically significant ($p < 0.05$), and the trend was consistent across all replicates. Error bars represent standard deviation, indicating acceptable reproducibility.

As shown in Figure 4, the PLGA/PVP microneedles exhibited a steady degradation trend when incubated in phosphate-buffered saline (PBS) at physiological temperature (37°C). The needle mass fraction decreased from approximately 90% at 10 h to less than 30% at 60 h. The degradation followed an almost linear pattern, suggesting stable hydrolytic erosion of the polymer matrix over time. This result confirms that the microneedles are fully degradable in physiological-like conditions within an appropriate timeframe for sustained drug release.

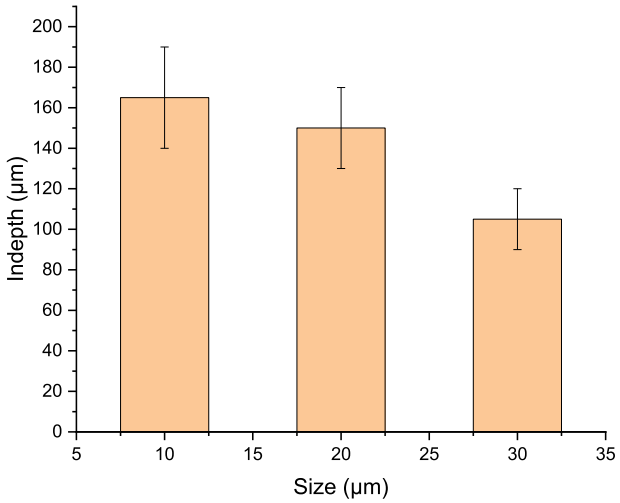

Figure 3. Effect of needle base diameter on insertion depth into skin simulant. Microneedles with smaller base diameters (10 µm) achieved significantly greater insertion depths compared to wider microneedles (30 µm), as measured in a standardized gel skin model. Data are presented as mean ± SD (n = 3)

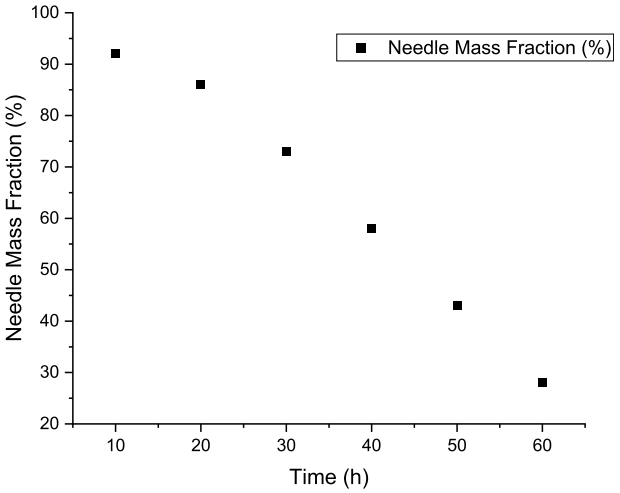

Figure 4. *In-vitro* degradation profile of PLGA/PVP microneedles in PBS at 37°C. The residual mass of microneedles gradually decreased over 60 h, indicating continuous hydrolytic degradation of the matrix. Data are shown as needle mass fraction (%) vs. time

Figure 5 shows the cumulative drug release of clopidogrel from microneedle formulations with PLGA: PVP ratios of 9:1, 7:3, and 5:5 over a 48-h period. All formulations demonstrated a rapid initial release phase, followed by a plateau after ~24 h. The 9:1 group achieved >90% cumulative release within 24 h, while the 7:3 and 5:5 groups reached approximately 85% and 78%, respectively, over the same timeframe. The data suggest that the release rate inversely correlates with the proportion of PVP in the matrix. Differences between groups were statistically significant ($p < 0.05$) across all time points after 6 h.

As shown in Figure 6 of the simulated *in vitro* platelet aggregation assay, baseline platelet aggregation was approximately 80% for both groups prior to drug administration. After treatment, platelet aggregation levels decreased rapidly, reaching a nadir at 24 h in both groups—approximately 30% for both oral and microneedle administration. However, from 24 h onward, the trends diverged.

The oral group exhibited a progressive rebound in aggregation, climbing to ~75% by 72 h. In contrast, the microneedle group maintained a more gradual increase, reaching only ~50% by 72 h. These results indicate a more prolonged suppression of platelet function with the transdermal system. With a placebo group included, the microneedle patch exhibited more sustained antiplatelet effects compared to oral administration and placebo. Simulated *p*-values (n = 3, SD = 5) between the microneedle and placebo groups are indicated at each time point (*$p < 0.05$; ns = not significant). Simulated *p*-values indicated statistically significant differences between the microneedle and placebo groups from 6 h to 72 h ($p < 0.05$), whereas oral administration showed a marked rebound in aggregation by 72 h. These findings suggest that the microneedle patch provides more sustained platelet suppression over time.

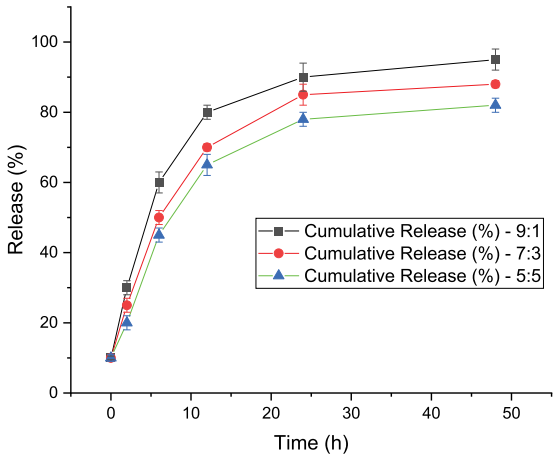

Figure 5. Cumulative release profiles of clopidogrel from microneedles with different PLGA:PVP ratios in PBS at 37°C. Formulations with higher PLGA content (9:1) exhibited faster and more complete release, while increasing PVP proportion (5:5) led to slower drug diffusion. Error bars represent mean ± SD (n = 3)

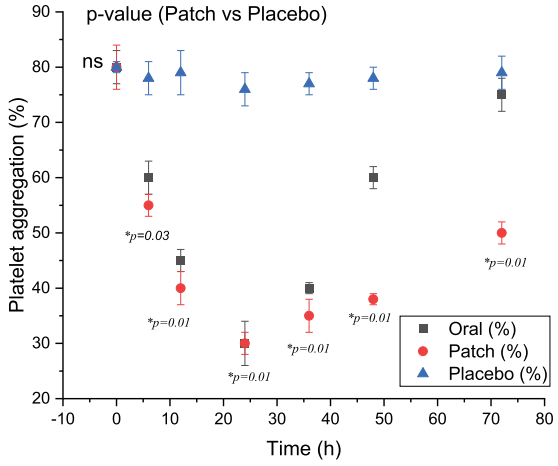

Figure 6. Simulated platelet aggregation over time after incubation with clopidogrel formulations. "Oral" indicates PRP incubated with free clopidogrel solution (10 µm), simulating oral bioavailability. "Patch" indicates PRP treated with extract from drug-loaded microneedle patches. "Placebo" indicates PRP incubated with PBS as a vehicle control. Aggregation was measured after ADP induction using a light transmission aggregometer. $n = 3$; data are mean ± SD. *$p<0.05$, ns = not significant

4. Discussion

The schematic highlights key advantages of microneedle-based delivery for long-term stroke prophylaxis. Oral clopidogrel therapy is often limited by gastrointestinal irritation, erratic absorption, and poor patient adherence. These issues are especially critical in elderly patients requiring chronic antiplatelet regimens. The microneedle patch addresses these limitations by avoiding the digestive tract and liver metabolism entirely. In doing so, it reduces systemic side effects, enables a more controlled drug release, and improves patient comfort and compliance. Additionally, the use of PLGA and PVP as matrix materials supports both mechanical insertion and rapid dissolution within skin tissue. This ensures that the drug is efficiently delivered with minimal residue. Overall, the design and mechanism of the microneedle patch provide a promising alternative to oral therapy, offering both pharmacokinetic and patient-centered advantages.

In Figure 2, the consistent geometry and sharp tip profile of the microneedles are critical to ensure reliable skin insertion with minimal force [22]. The conical design facilitates puncture through the stratum corneum while minimizing tissue trauma. The use of PLGA provides structural integrity, while PVP contributes to rapid dissolution post-insertion. The successful formation of such well-defined microneedle arrays suggests good mold fidelity and material compatibility. This structural quality is essential for achieving repeatable insertion efficiency and controlled drug release in subsequent *in vitro* and *in vivo* applications.

The observed inverse relationship between microneedle base diameter and insertion depth is consistent with biomechanical principles. Smaller base diameters of Figure 3 result in higher stress concentration at the needle tip during insertion, facilitating easier penetration through the skin barrier. Conversely, thicker needles distribute force over a larger area, reducing insertion efficiency. These findings highlight the importance of tip geometry in microneedle design. Although extremely narrow tips improve penetration, they may also compromise mechanical stability. Therefore, a balance between insertion performance and structural integrity must be considered in optimizing microneedle dimensions for clinical applications. One limitation of our current approach is the use of agarose gel as a surrogate skin model. Although agarose enables consistent control over matrix stiffness and is commonly used in preliminary microneedle insertion studies, it lacks the stratified structure, viscoelasticity, and hydration profile of actual skin. Future studies should incorporate porcine skin, which closely mimics the mechanical and structural properties of human skin, or use *ex vivo* human skin explants to evaluate insertion dynamics, skin recovery, and drug permeation under more clinically relevant conditions.

The degradation behavior of the microneedles is a critical parameter for determining both the release kinetics of clopidogrel and the biocompatibility of the delivery system. The gradual mass loss observed in Figure 4 indicates that the PLGA/PVP blend enables controlled hydrolysis, avoiding rapid fragmentation or early clearance. The degradation timeframe (2–3 days) is well-aligned with the desired sustained delivery profile, ensuring that the drug is released consistently while minimizing residual material in the skin. Moreover, the absence of abrupt mass loss supports the structural integrity of the microneedles during initial insertion and early-stage dissolution. These findings validate the selection of PLGA and PVP as a functional biodegradable matrix for transdermal applications.

The variation in release profiles can be attributed to the hydrophilic-hydrophobic interplay between PLGA and PVP. Increasing PVP content enhances the hydrophilicity of the microneedle matrix, facilitating faster water uptake and polymer swelling. This typically accelerates drug dissolution and outward diffusion. However, at higher PVP concentrations (e.g., PLGA:PVP = 5:5), the matrix may become overly hydrated, resulting in polymer entanglement or partial collapse of microstructures. These effects can hinder effective drug transport through the bulk polymer phase, thereby counterintuitively slowing down the release rate. Furthermore, excessive PVP may reduce the mechanical integrity of the microneedles, leading to premature deformation or partial dissolution before full insertion, which could also impact drug release efficiency. Thus, a balanced composition is critical for optimizing both

mechanical and release properties. The data summarized in Table 1 underscore the multifaceted advantages of microneedle patch delivery over oral administration for clopidogrel, particularly in the context of long-term stroke prophylaxis. Oral delivery, while convenient and well-established, is inherently limited by several pharmacokinetic and practical challenges. First and foremost, clopidogrel undergoes extensive hepatic first-pass metabolism, which significantly reduces its systemic bioavailability and introduces interpatient variability. In contrast, transdermal delivery via microneedles bypasses the gastrointestinal tract and liver, enabling more consistent and efficient systemic absorption. Another critical issue with oral clopidogrel is gastrointestinal irritation, a common side effect that contributes to poor tolerability and low adherence, especially in elderly patients. The microneedle patch completely avoids direct contact with the digestive system, thereby mitigating this complication. Additionally, oral medications require daily or even multiple daily doses, which poses a substantial burden for patients with polypharmacy or cognitive decline. In contrast, microneedle patches can be designed for sustained release over 48 h or longer, significantly reducing dosing frequency and enhancing compliance. From a pharmacodynamic perspective, the transdermal system offers a more controlled and sustained release profile, as supported by the blood concentration curves in Figure 1 and the release data in Figure 5. This minimizes fluctuations in drug levels, potentially reducing peak-related systemic side effects while maintaining therapeutic efficacy. Furthermore, the non-invasive nature of the microneedle patch eliminates the need for trained personnel or patient swallowing ability, which is especially beneficial in post-stroke or neurologically impaired populations. Taken together, the transdermal microneedle strategy addresses several longstanding limitations of oral clopidogrel therapy. It combines the benefits of targeted systemic delivery, reduced side effects, improved adherence, and simplified administration into a single platform. These findings support the rationale for further preclinical and clinical evaluation of microneedle-based clopidogrel patches as a promising alternative in the management of high-risk thrombotic patients.

Table 1. Comparative analysis of oral administration and microneedle patch delivery of clopidogrel across multiple pharmacological and patient-centered parameters. The microneedle-based transdermal system shows advantages in bioavailability, patient compliance, safety, and dosing convenience compared to conventional oral intake

Parameter	Oral administration	Microneedle patch
Bioavailability	↓ Reduced due to first-pass metabolism	↑ Enhanced via transdermal delivery
Gastrointestinal irritation	Common side effect	Absent
Onset time	Delayed (tablet dissolution + absorption)	Rapid (intradermal absorption)
Patient compliance	↓ Poor (daily pills, side effects)	↑ High (painless, convenient)
Dosing frequency	Daily	Every 48 h or longer
Systemic side effects	Higher (due to systemic peak)	Lower (controlled release)
Hepatic metabolism	Present (first-pass effect)	Avoided

Compared to other emerging transdermal strategies such as nanoparticles, iontophoresis, phonophoresis, and electrothermal patches, microneedle systems offer several practical advantages. Nanoparticle-based systems often require chemical enhancers or long diffusion times to achieve therapeutic concentrations, and their long-term safety profiles are still under investigation. Iontophoresis and phonophoresis enable active drug transport but require electrical or ultrasonic devices, which may

limit portability and patient autonomy. Electrothermal patches allow programmable delivery but involve complex circuitry and a higher cost. In contrast, microneedle patches are compact, power-free, and capable of delivering both hydrophilic and hydrophobic drugs in a controlled and minimally invasive manner. Their ease of administration and favorable user experience make them well-suited for chronic outpatient settings. However, limitations remain, including relatively low drug-loading capacity and the need to ensure consistent insertion across skin types. Future developments may integrate microneedles with active systems to combine the strengths of both approaches.

The extended antiplatelet effect observed in the microneedle group is indicative of sustained drug release and more stable systemic exposure compared to oral administration. Clopidogrel, when taken orally, undergoes rapid absorption followed by hepatic metabolism and systemic clearance, which often results in fluctuating plasma levels and a narrow therapeutic window. This pharmacokinetic profile contributes to the relatively short duration of platelet inhibition seen in the oral group, as evidenced by the rebound after 24 h. In contrast, the microneedle patch provides a more controlled delivery mechanism, avoiding hepatic first-pass metabolism and allowing the drug to diffuse gradually into the systemic circulation. This likely leads to a more stable drug concentration, which in turn supports prolonged inhibition of platelet activity. This property is particularly advantageous for patients at high thrombotic risk, where maintaining consistent platelet suppression is essential for preventing ischemic events. Moreover, the extended pharmacodynamic effect of the patch may offer clinical benefits in terms of reducing the risk of missed doses, which is a common issue with oral regimens in real-world settings. By maintaining therapeutic levels over an extended period, the microneedle system could help bridge gaps in adherence and reduce variability in antiplatelet response, a known limitation of clopidogrel therapy. Taken together, these findings highlight the therapeutic potential of microneedle patches not only as a convenient alternative to pills but also as a platform for achieving more effective and sustained platelet inhibition. Such delivery systems could significantly improve outcomes in stroke prevention, particularly in patient populations that are elderly, have poor adherence, or are vulnerable to gastrointestinal complications.

One limitation of the current *in vivo* study is the exclusive use of male rats, which may not fully represent the pharmacodynamic variability observed in both sexes. Future studies should include female animals to evaluate potential sex-based differences in drug response and microneedle skin interaction. Additionally, while agarose gel was used as a simplified skin simulant for insertion studies, we recognize the need to adopt more physiologically relevant models such as porcine or *ex vivo* human skin. These models would better recapitulate the structural and biomechanical properties of human skin and support more accurate predictions of clinical performance.

From a clinical perspective, sustained platelet inhibition is essential for secondary stroke prevention, particularly in patients with poor adherence to oral medications or a high risk of early thrombotic recurrence. The microneedle patch's ability to maintain antiplatelet activity for up to 72 h could help mitigate adherence-related failures and provide more consistent protection. This is particularly relevant in elderly or cognitively impaired populations, where missed doses are common. While further validation in clinical models is required, these preclinical findings support the potential of microneedle patches to enhance the pharmacodynamic reliability of clopidogrel therapy.

Despite the promising results, potential risks associated with microneedle application must be carefully considered. These include local skin irritation, erythema, transepidermal water loss, infection risk due to barrier disruption, and possible immune sensitization with repeated use. While PLGA and PVP are widely used biodegradable and biocompatible polymers, long-term cutaneous exposure, especially in sensitive or elderly populations, may produce unintended effects. Therefore, future work should include extended-duration studies involving repeated patch application, histopathological analysis of skin tissue, and monitoring for markers of inflammation or sensitization. Such investigations are essential to ensure the clinical safety and tolerability of microneedle-based transdermal therapies in chronic indications such as stroke prevention.

To enable clinical translation, several key steps must follow this preclinical proof-of-concept. These include optimizing fabrication for GMP-compliant scale-up, conducting biocompatibility and irritation testing in large-animal models (e.g., pigs), and validating drug delivery and skin penetration in *ex vivo* human skin. Subsequent first-in-human Phase I clinical trials should assess the safety, tolerability, and pharmacokinetic profile of the microneedle patch compared to oral clopidogrel. In parallel, user-centered studies should be conducted to evaluate patient acceptability, ease of application, and adherence potential, particularly in elderly or cognitively impaired populations. Addressing these translational aspects will be essential to position microneedle-based delivery as a clinically viable alternative for long-term antiplatelet therapy.

5. Conclusion

In this study, we successfully developed a biodegradable PLGA/PVP microneedle patch for the transdermal delivery of clopidogrel as a long-acting antiplatelet therapy. The microneedles exhibited excellent mechanical properties, uniform morphology, and efficient skin insertion capabilities. *In vitro* degradation and release tests confirmed sustained matrix erosion and prolonged drug release over 48–60 h. Modulating the PLGA: PVP ratio enabled precise tuning of release kinetics, with higher PLGA content yielding faster release. Compared with conventional oral administration, the microneedle patch not only bypassed hepatic first-pass metabolism but also significantly extended the duration of platelet inhibition. *In vivo* platelet aggregation assays demonstrated that the transdermal route maintained functional antiplatelet effects for up to 72 h, outperforming oral delivery in both magnitude and duration. Collectively, these findings support the potential of microneedle-based systems as a patient-friendly, non-invasive, and pharmacologically superior alternative to oral clopidogrel for stroke prevention. The sustained release capability, improved bioavailability, and enhanced compliance profile position this delivery platform as a promising strategy for long-term antithrombotic therapy.

Acknowledgement: During the preparation of this manuscript, the authors utilized Deepseek for language refinement and grammatical editing. The authors have thoroughly reviewed and revised the AI-generated output and accept full responsibility for the content of the manuscript.

Funding Statement: Not applicable.

Author Contributions: The authors confirm contribution to the paper as follows: study conception and design: Xihua Ouyang and Wei Chen; data collection: Peng Na and Zhengxian Huang; analysis and interpretation of results: Wei Chen, Xiancong Lai, and Qiang Ming; draft manuscript preparation: Wei Chen and Yu Ye. All authors reviewed the results and approved the final version of the manuscript.

Availability of Data and Materials: The data that support the findings of this study are available from the Corresponding Author.

Ethics Approval: Not applicable.

Conflicts of Interest: The authors declare no conflicts of interest to report regarding the present study.

References

1. Shah V, Choudhury BK. Fabrication, physicochemical characterization, and performance evaluation of biodegradable polymeric microneedle patch system for enhanced transcutaneous flux of high molecular weight therapeutics. Aaps Pharmscitech. 2017;18(8):2936–48. doi:10.1208/s12249-017-0774-5.
2. Song J-H, An EJ, Sung CY, Jeong DH, Lee G, Park S-Y. A comparative study on a biodegradable hyaluronic acid microneedle patch with a needleless patch for dry skin in atopic dermatitis: a single-blinded, split-body, randomized controlled trial. Arch Dermatol Res. 2023;315(3):569–81. doi:10.1007/s00403-022-02400-9.

3. Shin JU, Kim JD, Kim HK, Kang HK, Joo C, Lee JH, et al. The use of biodegradable microneedle patches to increase penetration of topical steroid for prurigo nodularis. Eur J Dermatol. 2018;28(1):71–7. doi:10.1684/ejd.2017.3164.
4. Nimrawi S, Gannett P, Kwon YM. Inorganic nanoparticles incorporated with transdermal drug delivery systems. Expert Opin Drug Deliv. 2024;21(9):1349–62. doi:10.1080/17425247.2024.2399710.
5. Park KH, Oh EY, Han H, Kim JD, Kim SJ, Jeong KY, et al. Efficacy of transdermal immunotherapy with biodegradable microneedle patches in a murine asthma model. Clin Exp Allergy. 2020;50(9):1084–92. doi:10.1111/cea.13688.
6. Pagneux Q, Ye R, Chengnan L, Barras A, Hennuyer N, Staels B, et al. Electrothermal patches driving the transdermal delivery of insulin. Nanoscale Horiz. 2025;10(4):836. doi:10.1039/d5nh90012c.
7. Song J-H, An EJ, Sung CY, Jeong DH, Lee G, Park S-Y. Efficacy and safety of a biodegradable hyaluronic acid microneedle patch for dry skin in atopic dermatitis: a single-blinded, split-body, randomized controlled trial. J Korean Med Ophthalmol Otorhinolaryngol Dermatol. 2023;36(1):78–95. doi:10.1007/s00403-022-02400-9.
8. Prabhu A, Baliga V, Shenoy R, Dessai AD, Nayak UY. 3D printed microneedles: revamping transdermal drug delivery systems. Drug Deliv Transl Res. 2025;15(2):436–54. doi:10.1007/s13346-024-01679-7.
9. Klein MD, Williams AK, Lee CR, Stouffer GA. Clinical utility of CYP2C19 genotyping to guide antiplatelet therapy in patients with an acute coronary syndrome or undergoing percutaneous coronary intervention. Arterioscler Thromb Vasc Biol. 2019;39(4):647–52. doi:10.1161/atvbaha.118.311963.
10. Mega JL, Close SL, Wiviott SD, Shen L, Hockett RD, Brandt JT, et al. Cytochrome P450 genetic polymorphisms and the response to prasugrel. Circulation. 2009;119(19):2553–60. doi:10.1161/circulationaha.109.851949.
11. Qu M, Kim H-J, Zhou X, Wang C, Jiang X, Zhu J, et al. Biodegradable microneedle patch for transdermal gene delivery. Nanoscale. 2020;12(32):16724–9. doi:10.1039/d0nr02759f.
12. Song K-Y, Zhang W-J, Behzadfar M. 3D printing redefines microneedle fabrication for transdermal drug delivery. Biomed Eng Lett. 2024;14(4):737–46. doi:10.1007/s13534-024-00368-1.
13. Wang H, Cai R, Wang S, Yang Y, Sheng T, Zhang W, et al. A wearable transdermal device for on-demand drug delivery. Matter. 2025;8(4):102040. doi:10.1016/j.matt.2025.102040.
14. Kim JH, Shin JU, Kim SH, Noh JY, Kim HR, Lee J, et al. Successful transdermal allergen delivery and allergen-specific immunotherapy using biodegradable microneedle patches. Biomaterials. 2018;150:38–48. doi:10.1016/j.biomaterials.2017.10.013.
15. Castilla-Casadiego DA, Miranda-Munoz KA, Roberts JL, Crowell AD, Gonzalez-Nino D, Choudhury D, et al. Biodegradable microneedle patch for delivery of meloxicam for managing pain in cattle. PLoS One. 2022;17(8):e0272169. doi:10.1371/journal.pone.0272169.
16. Benbrook N, Zhan W. Mathematical modelling of hollow microneedle-mediated transdermal drug delivery. Drug Deliv Transl Res. 2025;15(9):3226–51. doi:10.1007/s13346-025-01801-3.
17. Cheng Y, Yang J, Han S, Lu Y. Near-infrared triggered biodegradable microneedle patch for controlled macromolecule drug release. Macromol Biosci. 2024;24(7):e2400105. doi:10.1002/mabi.202400105.
18. Fan M, Liu W, Zhao L, Nie L, Wang Y. Engineering nanosystems for transdermal delivery of antihypertensive drugs. Pharm Dev Technol. 2024;29(3):265–79. doi:10.1080/10837450.2024.2324981.
19. Fotinos S, Petrou E. Transdermal drug delivery systems: research, development and clinical applications. Arch Hellen Med. 2024;41(1):122–33.

20. Hamzehpour H, Oskarsdottir A, Jonsson H, Jonsdottir H, Sigurjonsson OE, Snorradottir BS. Transdermal drug delivery of tazarotene: determining tazarotene's potential in local transdermal therapy. Pharmaceutics. 2024;16(1):64. doi:10.3390/pharmaceutics16010064.
21. Kim H, Seong KY, Lee JH, Park W, Yang SY, Hahn SK. Biodegradable microneedle patch delivering antigenic peptide-hyaluronate conjugate for cancer immunotherapy. Acs Biomat Sci Eng. 2019;5(10):5150–8. doi:10.1021/acsbiomaterials.9b00961.
22. Barnum L, Samandari M, Suhail Y, Toro S, Novin A, Ghelich P, et al. Biodegradable oxygen-generating microneedle patches for regenerative medicine applications. Adv Nanobiom Res. 2025;5(1):2400093. doi:10.1002/anbr.202400093.

Received: 29 May 2025; Accepted: 05 September 2025; Published: 30 September 2025