



Transdermal Drug Delivery Systems: Recent Advances in Nanocarriers, Microneedles, and Controlled Release Technologies

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Abstract

Transdermal drug delivery has progressed from conventional passive patches to increasingly sophisticated systems incorporating nanocarriers, microneedles, smart materials, and controlled-release technologies. Broader clinical use, however, remains limited by the barrier properties of the stratum corneum and by the poor permeability of hydrophilic compounds, macromolecules, and many therapeutically important drugs. This review evaluates recent advances in transdermal drug delivery, with particular emphasis on nanocarrier-based systems, microneedle technologies, integrated nanocarrier-microneedle platforms, and responsive controlled-release approaches. Recent literature was narratively synthesised to assess their mechanisms, formulation characteristics, therapeutic applications, translational potential, and current limitations. The available evidence indicates that nanocarriers can improve drug solubility, stability, cutaneous interaction, and localised deposition, whereas microneedles can transiently bypass the stratum corneum and facilitate delivery of peptides, proteins, vaccines, and other poorly permeable agents. Hybrid systems may further enhance intradermal targeting and prolong drug release, while polymeric matrices, hydrogels, reservoir systems, and stimuli-responsive platforms can provide greater temporal control over dosing. Translation into routine clinical practice remains constrained by manufacturing reproducibility, dose uniformity, skin compatibility, device reliability, sterility, scalability, long-term safety, and regulatory complexity. Overall, these technologies are redefining transdermal delivery as a multifunctional therapeutic platform, but their clinical value will depend on standardised performance testing, scalable manufacturing, and robust human validation.

Keywords: Controlled release, Microneedles, Nanocarriers, Skin permeation, Transdermal drug delivery

1. Introduction

Compared with common medicated patches, transdermal drug delivery systems (TDDSs) have developed into more sophisticated systems that promote skin permeation, drug release, and delivery to the skin. (Jeong et al., 2021) Systemic bioavailability can be higher for appropriate drugs when administered via the transdermal route, due to the avoidance of gastrointestinal degradation and hepatic first-pass metabolism (Alkilani et al., 2022). TDDSs may also offer extended drug exposure and decrease dosing frequency compared to some conventional dosage forms (Jeong et al., 2021). Transdermal treatment can also be stopped by simply removing the transdermal formulation from the skin, thus providing an extra level of dosage control (Wong et al., 2023). These features have helped to make transdermal systems useful for delivering therapeutic drugs over time or at a controlled rate (Xu et al., 2025).

Barrier properties of the skin, especially the stratum corneum (SC), are the main challenge for effective transdermal delivery (Rabiei et al., 2020). This outer layer impedes the passive penetration of many hydrophilic compounds, high molecular weight drugs, peptides, proteins and other biomolecules (Peña-Juárez et al., 2022). Therefore, conventional transdermal patches are still the most appropriate for very potent drugs that have physicochemical properties compatible with passive skin diffusion (Jeong et al., 2021). The limited number of appropriate molecules has led to the emergence of chemical, physical and nanoenhancement techniques (Tapfumaneyi et al., 2022).

Nanocarrier-based formulations have proven to be one of the most significant strategies to overcome some of the disadvantages of traditional transdermal formulations (Kang et al., 2024). The selection of liposomes, ethosomes, transfersomes, polymeric nanoparticles, lipid nanoparticles, and nanoemulsions has been explored as solutions for enhancing the solubility, stability, skin interaction and cutaneous deposition of the drugs (Qu et al., 2022). Additionally, nanocarriers can facilitate the delivery of drugs within specific layers of the skin, as they are crucial for dermatological treatments (Raina et al., 2023). They can also modulate drug distribution and release, leading to increased interest in their use at the nanoscale for topical and transdermal delivery applications (Kang et al., 2024).

The complementary approach is microneedle technology, which involves creating temporary microchannels in the stratum corneum (Qu et al., 2022). It can help with the delivery of compounds that have low passive permeability through intact skin (Alkilani et al., 2022). Peptides, proteins, vaccines and other active macromolecules have been studied with these systems for administration (Peña-Juárez et al., 2022). The development of microneedles and their combination with nanocarriers and polymeric matrices has also led to the localised deposition and better sustained release of a drug into the skin (Qu et al., 2022).

The functional capabilities of TDDSs have also been increased by controlled-release technologies (Dumitriu Buzia et al., 2023). The polymeric matrices, hydrogels and reservoir systems, and responsive materials can control the drug release (Dumitriu Buzia et al., 2023). The smart transdermal platforms can be designed to incorporate electrical, thermal, mechanical, optical, or other physical stimuli to control the drug transport (Zhang et al., 2024). This is because these systems are designed to be more responsive to the skin and to provide precisely controlled transdermal delivery, which is a broader shift from passive drug diffusion (Zhang et al., 2024).

While significant technological advances have been achieved, clinical translation is hindered by safety, skin compatibility, dose reproducibility, scale-up, and regulatory standardization concerns (Alkilani et al., 2022). Nanocarriers, microneedles, and controlled release technologies are often referred to as separate avenues of nanotechnology development instead of being part of the whole of modern TDDSs (Xu et al., 2025). Thus, an integrated evaluation is beneficial for comprehending their complementary mechanisms, therapeutic significance, and translational challenges (Xu

et al., 2025). This review focuses on the recent developments of nanocarrier-based systems, microneedle technologies and controlled-release TDDSs with a particular emphasis on their mechanisms, clinical applications, translational barriers and future perspectives (Xu et al., 2025).

1.1 Objectives of the review

This review aims to summarise recent advances in transdermal drug delivery systems, with particular emphasis on nanocarriers, microneedles, and controlled-release technologies. It evaluates their mechanisms of skin penetration, formulation strategies, and therapeutic applications. It also examines current translational challenges, including safety, scalability, and regulatory considerations, while highlighting emerging directions for smarter and more personalized transdermal delivery.

2. Review

2.1. Skin Barrier and Mechanisms of Transdermal Drug Transport

The skin consists of three layers: the epidermis, dermis and subcutaneous layer, with the stratum corneum being the most resistant to the transdermal passage of the drugs (Ramadon et al., 2022). It is the outermost layer, which consists of corneocytes in an organised lipid matrix that is highly selective of exogenous molecules (Abdul Aziz et al., 2025). The skin can be penetrated by drugs via the corneocyte transcellular pathway, the lipid pathway between corneocytes and appendageal pathway through hair follicles and sweat glands (Ramadon et al., 2022). Diffusion between the cells is especially significant for dealing with many small lipophilic molecules, due to the lipid-rich structure of stratum corneum (Abdul Aziz et al., 2025).

The skin permeation properties depend on both drug properties and formulation properties (Meng et al., 2024). The amount of passive diffusion across the cutaneous barrier (CB) is affected by molecular size, lipophilicity, ionisation, solubility, concentration gradient, and partitioning (Ramadon et al., 2022). The effect of formulations can also be modified by altering the thermodynamic activity of the drug, the hydration of the stratum corneum and interactions with epidermal lipids (Abdul Aziz et al., 2025). All these constraints restrict the passive delivery of hydrophilic compounds, high-molecular-weight drugs and biological macromolecules (Meng et al., 2024). The key drawback of conventional drug delivery systems is that the stratum corneum is extremely dense and impedes the penetration of drugs into deeper layers of the skin. Conventional drug delivery systems have a major disadvantage because the stratum corneum is thick and difficult to penetrate with drugs. It is therefore essential to understand these transport mechanisms to select the right enhancement strategies and design the proper transdermal delivery platforms. Figure 1 illustrates the skin barrier and principal mechanisms of transdermal drug transport.

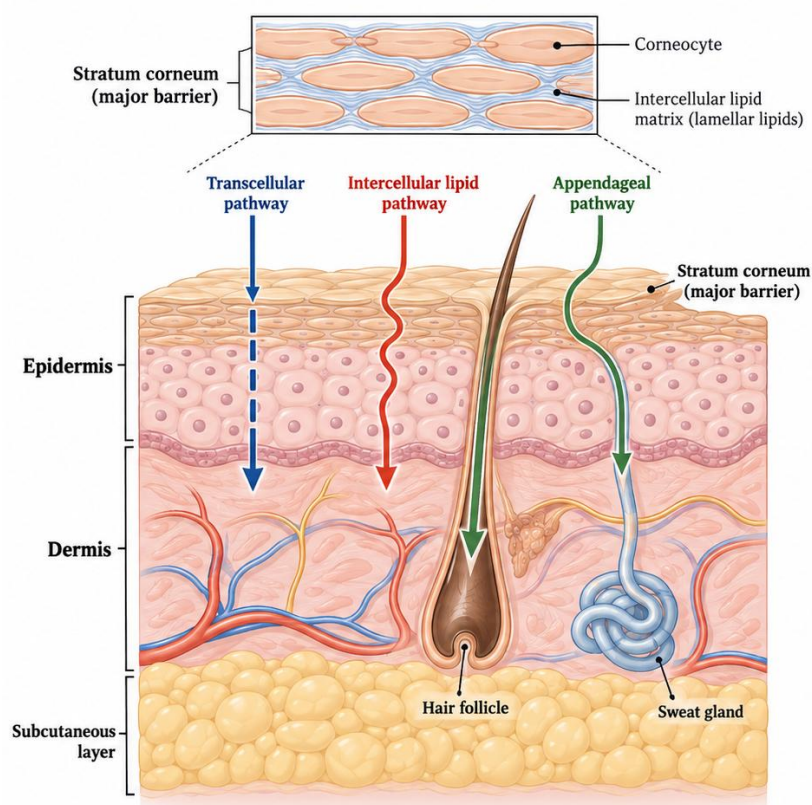


Figure 1. Skin barrier and mechanisms of transdermal drug transport

2.2. Nanocarrier-Based Transdermal Drug Delivery

Nanocarrier-based drug delivery system has been found to be one of the most promising strategies to improve the solubility, stability, interaction with skin, and deposition of the drugs in the targeted skin areas for cutaneous and transdermal drug delivery (Liu et al., 2025). The small size and surface properties that can be manipulated in these nanosize particles can enhance contact with the stratum corneum and affect penetration into specific compartments of the skin (Panda et al., 2025). The most common platforms are liposomes, ethosomes, transfersomes, polymeric nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers and nanoemulsions, which have different compositions, deformability, drug loading capacity, and release properties (Liu et al., 2025).

These systems have the potential to enhance the delivery for unstable drugs by preventing drug degradation, enhancing apparent solubility, changing the partitioning of the drug into the skin, and allowing for sustained or controlled release (Panda et al., 2025). The deformability and membrane-disrupting properties of flexible vesicular carriers like ethosomes and transfersomes can improve their ability to penetrate intercellular lipid domains (Liu et al., 2025). Lipid-based nanocarriers can also hydrate the skin and interact with the lipids present in the skin, thus enhancing skin drug retention and permeation (Panda et al., 2025).

By combining nanocarriers with microneedles, it is possible to further overcome the barrier of the stratum corneum and create transient microchannels to deliver the nanocarriers to deeper skin layers (Ruan et al., 2021). This strategy could be especially beneficial for peptides, proteins, vaccines, and other biopharmaceutical products with low passive permeability (Nguyen & Nguyen, 2023). Although they are promising, the translation requires repeatable manufacturing, formulation stability, safety, and scaling production, all of which require research (Liu et al., 2025).

2.3. Microneedle-Based Transdermal Delivery Systems

The systems based on microneedles are highly adaptable for the transdermal delivery of drugs due to their ability to penetrate the stratum corneum without causing significant discomfort when compared to the hypodermic method of drug administration (Zafar et al., 2025). These micron-sized structures form transient microchannels in the superficial layer of the skin that allow molecules that have low passive permeability to move through the skin (Zarepour et al., 2025). Microneedles are available in various major designs based on the amount of drug they can hold, how the drug is released from the microneedle, the method used to fabricate the microneedles, and the therapeutic application to which they are intended (Singh et al., 2024).

The properties of the material are also key factors in the performance of microneedles, as they affect its biomechanical strength, insertion efficiency, dissolution properties, biocompatibility, and release rate, as reviewed by Zafar et al. (2025). The polymeric and dissolving microneedles are especially appealing because their matrix can contain therapeutic agents which can be released after being inserted into the skin (Zarepour et al., 2025). The additional benefits of integrating with nanocarriers further enable physical barrier disruption with nanoscale drug transport, enhancing intradermal delivery and sustained or controlled release (Zarepour et al., 2025).

Small molecules, vaccines, peptides, proteins, and other therapeutics that are challenging to deliver through intact skin are being explored on microneedle platforms (Singh et al., 2024). AI can also be used to enhance device optimisation, prediction of release, and personalised transdermal dosing strategies (Sabbagh et al., 2025). Clinical translation, on the other hand, demands reproducible manufacturing, dose uniformity, mechanical reliability, sterility, patient acceptability, and clear regulatory standards (Zafar et al., 2025). Figure 2 summarises the major microneedle designs and their transdermal applications.

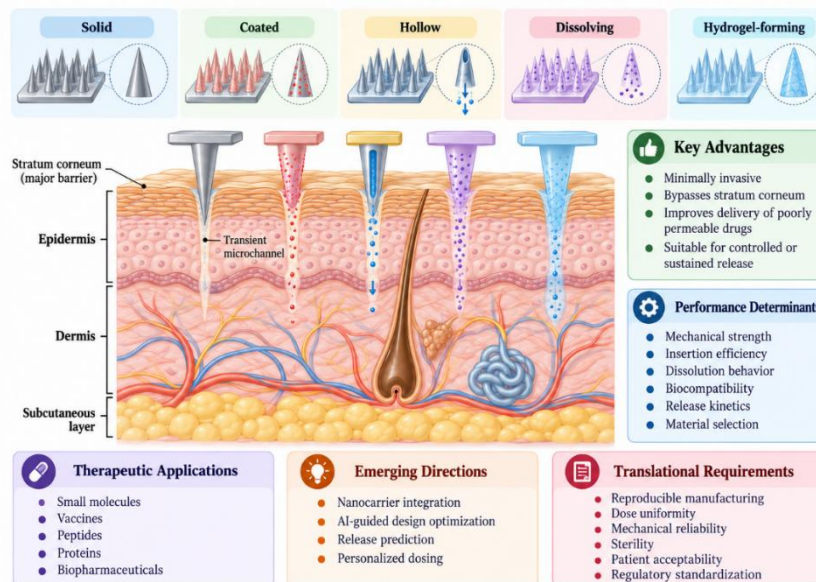


Figure 2. Microneedle-based transdermal drug delivery systems

2.4. Integration of Nanocarriers with Microneedle Platforms

The hybrid approach involves integrating nanocarriers with microneedle systems, offering a combination of nanoscale drug delivery and direct penetration through the stratum corneum (SC) (Wu et al., 2025). This strategy can help to increase the stability of the drugs, better deposition within viable layers of skin, and help delivery for molecules with poor passive permeability (Ahmad et al., 2021). The use of nanoparticles in dissolving or polymeric microneedles can also help to ensure the protection of sensitive therapeutics during processing and provide delayed release after

skin insertion (Wu et al., 2025).

The performance of the polymer depends on various factors, including its composition, which affects the strength of the microneedles, their effectiveness in insertion, the dissolution rate, and the kinetics of the release of the nanocarriers (Wu et al., 2025). The mechanical integrity can be enhanced by the proper modification of polymers, and the release of the drug can be sustained or sequential, depending on the requirement, while maintaining the characteristics of nanoparticles (Buzia et al., 2023). For poorly permeable molecules, macromolecules, and therapies that require local or extended exposure, these properties make the selection of integrated systems even more appealing (Ahmad et al., 2021).

In addition, hybrid platforms can also enable multifunctional applications that involve delivery of the drug with sensing, diagnostic, or responsive functions (Ahmad et al., 2021). The growing number of patents for transdermal technologies reflects a growing interest in transposing these technologies toward application and commercialization (Cammarano et al., 2023). For wider clinical adoption, the ability to manufacture these nanocarriers reproducibly, load the drug uniformly, ensure nanocarrier stability, reliability of mechanical strength, scalability, and regulatory standardisation are necessary (Cammarano et al., 2023).

2.5. Controlled-Release and Smart Transdermal Drug Delivery Technologies

Controlled-release transdermal systems are developed to ensure a controlled release of the drug over time, ensuring a therapeutically relevant exposure with less fluctuation due to repeated dosing (Kathuria et al., 2025). The polymeric matrices, hydrogels, reservoir systems and microneedle-based formulations are at the heart of this approach, as they can be engineered to alter diffusion, swelling, dissolution and degradation-controlled release (Swain et al., 2022). These properties make them suitable for therapies that demand extended or predictable drug administration (Kathuria et al., 2025).

The hydrated polymer networks of hydrogels are especially advantageous for their ability to host multiple therapeutic agents and tune their environment for sustained release (Swain et al., 2022). Moreover, polymeric microneedles have been developed as a means to further sustain a controlled delivery by incorporating matrices that are meant to either swell or dissolve after insertion, or to slowly release the drug. (Roy et al., 2025) They depend on polymer choice, mechanical strength, drug–polymer interaction, dissolution properties, and release kinetics (Avcil & Çelik, 2021).

In recent years, there has been a growing trend to utilise responsive design principles in recent transdermal platforms to help deliver more precise temporal control of drug administration (Kathuria et al., 2025). The delivery of microneedle systems can be tailored to a fast, slow, or staged release profile, which can be customised to meet various therapeutic needs (Roy et al., 2025). The translation to routine clinical use will rely on a reproducible release behaviour, stability of the formulation, biocompatibility, consistency of the manufacturing process, and the regulatory standardisation (Avcil & Çelik, 2021). Table 1 summarises key controlled-release transdermal platforms and their principal release characteristics.

Table 1. Controlled-release transdermal systems and key characteristics

System/a approach	Principal mechanism	Key advantage	Main consideration	Citation
Polymeric matrices	Drug diffusion through or release from a polymer	Sustained and predictable delivery	Polymer properties strongly influence	Swain et al. (2022)

	network		release kinetics	
Hydrogels	Swelling-mediated diffusion from hydrated polymer networks	Tunable sustained release and compatibility with diverse drugs	Hydration and network structure affect release behaviour	Swain et al. (2022)
Reservoir systems	Controlled diffusion from a drug reservoir through a rate-limiting membrane	Maintains prolonged therapeutic exposure	Requires consistent membrane performance and formulation stability	Kathuria et al. (2025)
Polymeric microneedles	Dissolution, swelling, or gradual matrix-mediated release after skin insertion	Combines barrier bypass with controlled drug release	Mechanical strength and insertion efficiency are critical	Roy et al. (2025)
Responsive transdermal systems	Drug release triggered or modulated by system design and external/internal stimuli	Enables greater temporal control of administration	Reproducibility and responsiveness require careful optimization	Kathuria et al. (2025)
Staged-release microneedles	Engineered matrices provide rapid, sustained, or sequential release	Can match different therapeutic dosing requirements	Release profile depends on polymer–drug interactions	Avcil and Çelik (2021)
Translational considerations	Standardised formulation and manufacturing controls	Supports reliable clinical performance	Stability, biocompatibility, manufacturing consistency, and regulation remain barriers	Avcil and Çelik (2021)

2.6. Clinical Applications, Therapeutic Potential, and Translational Progress

The application of microneedle and nanotechnology-based transdermal systems is being explored in various therapeutic fields due to their potential to enhance the dermal absorption of drugs and to achieve local, sustained or systemic delivery (Mdanda et al., 2021). Due to their versatility, there has been an expansion of interest in the delivery of vaccines, peptides, proteins and agents with very limited passive transdermal transport,

such as small molecules (Mdanda et al., 2021). Additionally, drug-loaded microneedles featuring a nanoscale reservoir and a controlled dissolution or diffusion from the microneedle matrix can further extend the drug's duration of action (Oh & Jung, 2022). Cancer therapy is a promising use that could involve delivering anti-cancer drugs directly to the site of the tumour and minimising exposure to healthy tissues (Seetharam et al., 2020). These platforms have also been investigated for the delivery of superficial or accessible lesions for cancer vaccination or immunotherapy, and chemotherapeutic agents to superficial or accessible lesions (Seetharam et al., 2020). Sustained-release microneedle systems can also be designed to provide for longer therapeutic effects and lower administration frequencies if longer exposure is desired (Oh & Jung, 2022).

The technological and commercial interest in microneedle-assisted transdermal delivery has been growing, as evidenced by its increasing level of patent activity (Queiroz et al., 2020). The recently patented devices include various architectures of the device, various materials used in the manufacture of the device, strategies for loading drugs into the device, and therapeutic applications of the device (Queiroz et al., 2020). However, clinical translation requires repeatable manufacture, assurance of sterility, dose uniformity, mechanical reliability, storage stability and regulatory standardisation (Mdanda et al., 2021). Successful fulfilment of these requirements is crucial to the successful translation of promising platforms from the lab to scalable and clinically reliable therapeutics. Table 2 summarises major therapeutic applications and translational considerations of microneedle- and nanotechnology-based transdermal systems.

Table 2. Therapeutic applications and translational considerations of advanced transdermal systems

Therapeutic area/application	Delivery approach	Potential benefit	Key translational consideration	Citation
Vaccines and biologics	Microneedle-assisted transdermal delivery	Enables delivery of peptides, proteins, vaccines, and poorly permeable agents	Requires reliable insertion and dose reproducibility	Mdanda et al. (2021)
Sustained drug delivery	Nanoparticle-loaded microneedles	Extends drug release through nanoscale reservoirs and controlled matrix dissolution or diffusion	Release kinetics must remain predictable and stable	Oh and Jung (2022)
Cancer therapy	Localised microneedle-based	May increase local drug	Tumour accessibility and delivery	Seetharam et al.

	delivery	exposure while reducing exposure to healthy tissues	precision are important	(2020)
Cancer vaccination and immunotherapy	Microneedle-mediated administration	Supports localised immune-targeted delivery to superficial or accessible sites.	Requires validated therapeutic efficacy and safety	Seetharam et al. (2020)
Long-acting therapy	Sustained-release microneedle systems	May prolong therapeutic action and reduce dosing frequency	Formulation stability and controlled release must be maintained	Oh and Jung (2022)
Device innovation and commercialisation	Patented microneedle platforms	Supports diverse architectures, materials, and drug-loading strategies	Scale-up and manufacturing consistency remain essential	Queiroz et al. (2020)
Clinical translation	Advanced microneedle systems	Potential progression from laboratory platforms to clinical products	Sterility, dose uniformity, mechanical reliability, storage stability, and regulation are critical	Mdanda et al. (2021)

2.7. Challenges, Regulatory Considerations, and Future Perspectives

Although the advanced TDS systems have recently been developed, they still have several translation issues such as formulation complexity, skin compatibility, dose reproducibility, manufacturing consistency and stability of the product in the long term (Damiri et al., 2022). The mechanical stability of microneedle platforms is essential for them to penetrate the skin properly, and they should also be biocompatible, have a predictable dissolution and controlled drug release (Damiri et al., 2022). The problems of carrier stability, batch-to-batch variation, tissue interaction and scalability of manufacturing are also a concern with nanotechnology-based systems (Udugade et al., 2025).

The situation of drug–device–nanomaterial combination product in a single platform necessitates regulatory complexity in its assessment (Seetharam et al., 2020). Therefore,

it is necessary to standardise the evaluation of all of the above issues for consistent product development (Damiri et al., 2022). Moreover, the release profile of controlled-release drug products should be reproducible under in vivo conditions to ensure their reliability in clinical use (de Araujo & Padula, 2023).

The development of future systems will continue to be targeted towards multifunctional systems that combine microneedles, nanocarriers, responsive polymers, and sustained release systems in coordinated delivery platforms (de Araujo & Padula, 2023). For infectious diseases, nanotechnology-based transdermal delivery systems could be especially beneficial due to the ability to enhance the penetration of a drug into a particular area of the body while simultaneously minimizing any systemic side effects (Udugade et al., 2025). There are a number of factors that need to be addressed for broader clinical adoption, such as scalable manufacturing, more transparent regulatory avenues, comprehensive safety assessment, and more convincing translational data demonstrating reproducible therapeutic benefit (Seetharam et al., 2020).

3.Conclusion

This current review shows how the utilisation of nanocarriers, micro needle and controlled release systems has expanded the potential applications of transdermal drug delivery, not only by increasing skin penetration but also by enhancing the stability of the drug, its localisation in the skin and the temporal control of its release. The versatility of nanocarriers can be exploited to improve their solubility and their ability to target the skin, while the microneedles are a minimally invasive approach to penetrate the stratum corneum and extend transdermal delivery to macromolecules and poorly permeable drugs. They can be incorporated into polymeric matrices, hydrogels, and responsive materials, which can provide sustained and staged delivery of drugs, and even personalised delivery in certain cases. This transition from passive to multifunctional and intelligent patches is clearly evident in these developments. However, pharmaceutical translation to the clinic is limited by manufacturing reproducibility, dose uniformity, safety of the material, reliability of the devices, storage stability, regulatory complexity, and scalability. Standardised performance testing, clinically relevant models, thorough long-term safety assessments and manufacturable designs that maintain therapeutic consistency should be focused on in future investigations. Incorporating nanotechnology, biomaterials, device engineering and data-driven optimisation could help enable safer, more precise, and clinically adaptable transdermal therapies.

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