Expert View

TRANSDERMAL DRUG DELIVERY: ENHANCING PERMEABILITY AND *IN VIVO* TRANSLATION

Dr Leo Pan of WuXi AppTec provides insights into the field of transdermal drug delivery and investigates the two primary approaches being taken to advance the sector – enhancing the ability of drugs to permeate through the skin barrier and translating *in vitro* data to an *in vivo* reality.

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Transdermal drug delivery is among the oldest methods of administering medications in human history. The Ancient Egyptians used oils, fats, perfumes and other ingredients to make cosmetic and dermatological products; in Ancient Greece, the physician Galen developed something similar to modern cold cream; and precursors of modern transdermal patches were found in Ancient China.

Today, these drugs, which are administered through the skin rather than via injection, inhalation or oral ingestion, offer many benefits to drug developers. This form of drug delivery enables the API to enter the bloodstream for systemic distribution, with developers constantly seeking ways to improve their delivery further. To this end, researchers tend to focus on two areas in particular: enhancing permeability and *in vivo* translation.

THE BENEFITS OF TRANSDERMAL DRUG DELIVERY

Transdermal drug delivery products include transdermal patches, creams, sprays, gels, ointments, foams, films, microneedle systems and more. Transdermal patches are the most established format, the first of which, a three-day patch to treat motion sickness, was approved in the US in 1979.[1] Since then, the transdermal drug delivery market has expanded to the fields of pain management, hormonal applications, central nervous system disorders, cardiovascular diseases and other applications, such as nicotine patches to help patients quit smoking.

Transdermal drug delivery offers several advantages over other methods. It avoids the first-pass effect in the liver and degradation in the gastrointestinal tract, which reduces the interindividual variability in the drug response and improves the effective bioavailability for some drugs. This also means there is reduced formation of toxic or inactive metabolites. Also, doses can be lowered, which is especially valuable for drugs that are primarily metabolised orally.

Transdermal drug delivery also maintains a constant, effective blood drug concentration, so that patients do not suffer from fluctuations in blood drug levels which can occur with oral administration, reducing adverse effects and peak-trough fluctuations. This feature makes transdermal patches widely suited for pain reduction, hormone therapy and cardiovascular drugs.

Above all, transdermal drug delivery is a convenient route of administration for patients. It is non-invasive, straightforward and often requires less frequent dosing. This makes this form of delivery particularly useful for treating chronic conditions and even essential for patients who struggle with swallowing or managing injections. It is also often the best option for long-term treatments due to their ease of use.

The sustained-release properties of this type of delivery make it suitable for drugs with short biological half-lives that require frequent oral or non-gastrointestinal administration. This can reduce dosing frequency, extend the duration of delivery, enable flexible administration and improve patient compliance, particularly for those who struggle with oral medications. For developers, transdermal delivery can also extend product lifecycles and differentiate existing drugs, as well as enable reformulation of drugs with poor oral tolerability.

"CHEMICAL METHODS ARE THE MOST COMMONLY EXPLORED MEANS OF ENHANCING TRANSDERMAL DRUG PERMEATION, AS THEY ARE RELATIVELY AFFORDABLE, EASY TO PRODUCE, OFFER DESIGN FLEXIBILITY AND ALLOW PATIENTS TO SELF-ADMINISTER THEIR DRUGS."

ENHANCING THE PERMEABILITY OF TRANSDERMAL DRUG DELIVERY

To be effective, transdermal drugs must penetrate the skin's outermost layer: the stratum corneum. This is the skin's primary barrier and is composed of dead cells surrounded by a lipid matrix. It is highly lipophilic and extremely resistant to diffusion. The structure of the stratum corneum resembles a brick wall and is around 10–20 µm thick. Only very small lipophilic molecules, such as nicotine, can naturally cross this barrier.

By increasing the permeability of the skin before or as the drug is delivered, researchers can raise the flux – the rate at which it passes across the skin. This enables therapeutically meaningful doses to reach systemic circulation or local tissues and expands the range of drugs suitable for transdermal delivery.

Chemical and physical permeation enhancers are frequently used to improve drug permeability. Chemical methods are the most commonly explored means of enhancing transdermal drug permeation, as they are relatively affordable, easy to produce, offer design flexibility and allow patients to self-administer their drugs.

TOXICOLOGICAL RISKS OF PERMEABILITY ENHANCERS

The toxicological risks associated with high solvent concentrations are numerous. Developers must avoid certain pitfalls when aiming to increase permeability; for example, harsh penetration enhancers, such as dimethyl sulfoxide (DMSO), can damage the skin, and chronic use of enhancers can disrupt the skin barrier and increase the risk of infection. To evaluate the toxicological liabilities of permeability enhancers, developers should assess acute irritation, sensitisation, phototoxicity and systemic toxicity using *in silico*, *in vitro*, *ex vivo* and *in vivo* models. Early screening can help to avoid costly late-stage failures.

Irritation and Barrier Disruption

High concentrations of solvents can cause skin erythema, oedema and desquamation, while chronic exposure can lead to hyperkeratosis, dermatitis or eczema. Some ionic liquids may disrupt keratinocyte membranes at high doses. To address this issue, developers should define and respect no-observed-effect levels (NOELs) using dose-response irritation data, demonstrate the reversibility of barrier effects, use repeated-dose toxicity studies and structure toxicity optimisation for ionic liquids.

Sensitisation and Allergic Reactions

Solvents can promote contact dermatitis, and ionic liquids may trigger T-cell-mediated hypersensitivity. To address this, researchers can exclude or strictly limit skin sensitisers, apply a weight-of-evidence sensitisation strategy and use conservative exposure margins.

Phototoxicity

Some solvents are photo-reactive, causing oxidative stress under UV exposure. Phototoxic hazard identification can identify whether solvents or ionic liquids generate reactive oxygen species (ROS) under UV or visible light. Developers should set toxicological thresholds that consider worst-case UV exposure and apply risk-based exclusion to the development strategy.

Systemic Toxicity

Solvents can also increase the penetration of drugs and toxins, such as residual impurities and leachables. High concentrations and doses of solvents or ionic liquids (if absorbed) may result in specific organ toxicity. To mitigate the risk of systemic toxicity, researchers should apply strict toxicology thresholds, evaluate co-transport risks and perform organ risk assessments.

IMPROVING *IN VIVO* TRANSLATION

In vivo translation is essential for transdermal drug development because it relies on dynamic, living skin physiology that cannot be fully captured *in vitro*. Without effective translation, developers risk misjudging dose, efficacy, safety and regulatory acceptability. Key gaps between *in vitro* permeation and irritation models and living organisms include the lack of physiological complexity and homeostatic regulation, simplified tissue architecture and limited cell-to-cell interactions. *In vitro* models also lack systemic and immune response mechanisms, which are crucial for predicting whole-body toxicity.

In vitro systems also often fail to accurately predict long-term or chronic effects because of their static, short-term nature. In contrast, *in vivo* studies offer advantages such as dynamic homeostasis, complete detoxification and clearance mechanisms, fully layered tissue structures with functional barriers and the ability to capture immune responses and systemic effects.

"*IN VIVO* STUDIES OFFER ADVANTAGES SUCH AS DYNAMIC HOMEOSTASIS, COMPLETE DETOXIFICATION AND CLEARANCE MECHANISMS, FULLY LAYERED TISSUE STRUCTURES WITH FUNCTIONAL BARRIERS AND THE ABILITY TO CAPTURE IMMUNE RESPONSES AND SYSTEMIC EFFECTS."

To improve translation, developers should focus on integrating *in vivo* and *in vitro* data into project disciplines and design experiments. They should also use predictive pharmacokinetic and pharmacodynamic models, ensure that they are using the most useful biomarkers and surrogate endpoints, and place emphasis on collaboration and data sharing.

Ex vivo models, such as reconstructed skin, can act as a bridge between *in vitro* and *in vivo* testing. However, they have variable reliability in predicting human safety, depending on the endpoint assessed. Models such as EpiDerm (Mattek, Ashland, MA, US) and SkinEthic (EPISKIN, Lyon, France) show high reliability, exhibit correlations with human data and are validated for regulatory use.

To enhance physiological relevance, full-thickness reconstructed human skin models incorporate a collagen dermal layer containing human fibroblasts, thereby better mimicking the structure and function of natural skin. However, in practice, reconstructed skin models often underestimate permeation, particularly for lipophilic and small molecules, owing to the absence of a functional dermis and skin appendages.

NAVIGATING REGULATORY CONCERNS

Regulators focus primarily on the following items when evaluating the safety of transdermal drug delivery systems:

- Local skin toxicity
- Systemic exposure and toxicokinetics
- Enhancer and excipient safety
- Long-term and cumulative effects.

Global regulation of transdermal drug products is only partially harmonised through ICH guidelines and OECD test methods. Some of the core scientific principles apply across multiple regions, but implementation, evidentiary thresholds and review emphases differ between agencies, including product classification, local tolerability expectations and evidentiary thresholds for combination products and novel excipients.

As such, sponsors must design transdermal programmes to a globally conservative standard, using harmonised scientific principles while anticipating region-specific regulatory interpretation. Developers should treat transdermal systems as combination products. For example, in the US, patches must comply with both device and drug regulations.[2] Regulators assign the primary mode of action to these products, which determines which centre reviews them.

One of the more common mistakes when assessing the toxicology of a transdermal drug candidate for submission is only to evaluate acute irritation and not the long-term barrier impairment. This can be avoided by conducting repeated-dose studies with histopathological evaluation. Another mistake is failing to consider that while the API may not be phototoxic, the enhancer may be. This can be managed by conducting phototoxicity studies with the full formulation.

A FINAL WORD ON TRANSDERMAL DRUG DELIVERY

The global transdermal drug delivery system market size is projected to reach more than US$136 billion (£101 billion) by 2030, rising from $62 billion in 2023, according to a report from Grand View Research.[3] This is partly due to the increasing incidence of chronic diseases, but also because these systems are improving through research on permeability and *in vivo* translation.

"FURTHER ADVANCES IN TRANSDERMAL TECHNOLOGY HOLD GREAT PROMISE, INCLUDING TECHNOLOGICAL INNOVATIONS AND 3D BIO-PRINTED SKIN WITH IMMUNE COMPONENTS."

Further advances in transdermal technology hold great promise, including technological innovations and 3D bio-printed skin with immune components. Advanced microneedle technologies are also being explored, with the hope that they will enable routine transdermal delivery of biologics, while smart and connected transdermal systems could move the field towards precision medicine. As with many medical research areas, machine learning is being touted as a possible accelerant to progress.

As these technologies move forwards, the number of applications for transdermal drug delivery will increase dramatically, providing new treatment options for patients around the world. Developers seeking to carve out a share of that expanding market can significantly increase the impact of their products by focusing on enhancing both permeability and *in vivo* translation, thereby changing the lives of countless patients.

ABOUT THE COMPANY

WuXi AppTec is a partner and contributor to the pharmaceutical and life sciences industries, providing R&D and manufacturing services that help advance healthcare innovation. With operations across Asia, Europe and North America, WuXi AppTec offers integrated, end-to-end services through their unique CRDMO platform. WuXi AppTec works alongside nearly 6,000 partners across over 30 countries, supporting their efforts to bring breakthrough treatments to patients. Guided by a vision that every drug can be made and every disease can be treated, they are committed to advancing breakthroughs for patients – one collaboration at a time.

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Leo Pan, PhD, is the Senior Director of Toxicology at WuXi AppTec. He earned his PhD in developmental biology and, since graduating in 2008, has dedicated his career to chemical and drug safety evaluation. Prior to joining WuXi AppTec, Dr Pan served as a Study Director at Intertek, where he specialised in reproductive toxicity testing for chemicals. Throughout his career, he has contributed to a wide array of preclinical programmes for pharmaceuticals, many of which have been submitted to regulatory agencies such as the US FDA and NMPA for Investigational New Drug and New Drug Application approvals.

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REFERENCES

1. *Pastore MN et al, "Transdermal patches: history, development and pharmacology". Br J Pharmacol, 2015, Vol 172(9), pp 2179–2209.*
2. *"Transdermal and Topical Delivery Systems – Product Development and Quality Considerations". Draft Guidance for Industry, US FDA, Nov 2019.*
3. *"Transdermal Drug Delivery Systems Market (2024 - 2030)". Market Report, Grand View Research, Feb 2024.*