PRECLINICAL DRUG
DEVELOPMENT TESTING FOR

药明康德
WuXi AppTec

TOPICAL AND TRANSDERMAL DRUGS

Shorten the Development Cycle with WuXi AppTec DMPK

Therapeutic Areas Series

Unique Pharmacokinetics Evaluation System for Topical and Transdermal Drugs

Topical and transdermal drugs are widely used across therapeutic areas thanks to their many advantages, including improved patient compliance, reduced adverse effects, and sustained release. However, compared to oral drugs, research in this field presents unique challenges—diverse formulation types, complex skin tissue separation and analysis, and sophisticated experimental operations—all without clear guidelines. This demands a high level of expertise, making the right research partner crucial for success.

WuXi AppTec DMPK has been conducting dermatological experiments since 2018, providing more than 5 years of preclinical research and development experience. We have developed more than 100 transdermal formulations, and conducted more than 2,000 *in vitro* permeation tests (IVPT) and *in vivo* PK experiments. Our expertise spans various formulation types—including gels, creams, lotions, foams, patches, and nanoparticles—as well as dermal administration techniques such as microneedling. We excel in high-quality isolation of skin tissue, sample processing, and bioanalysis. Our expertise supports a wide range of programs, including conventional small molecules, peptides, antibodies, and other new modalities.

Strengths

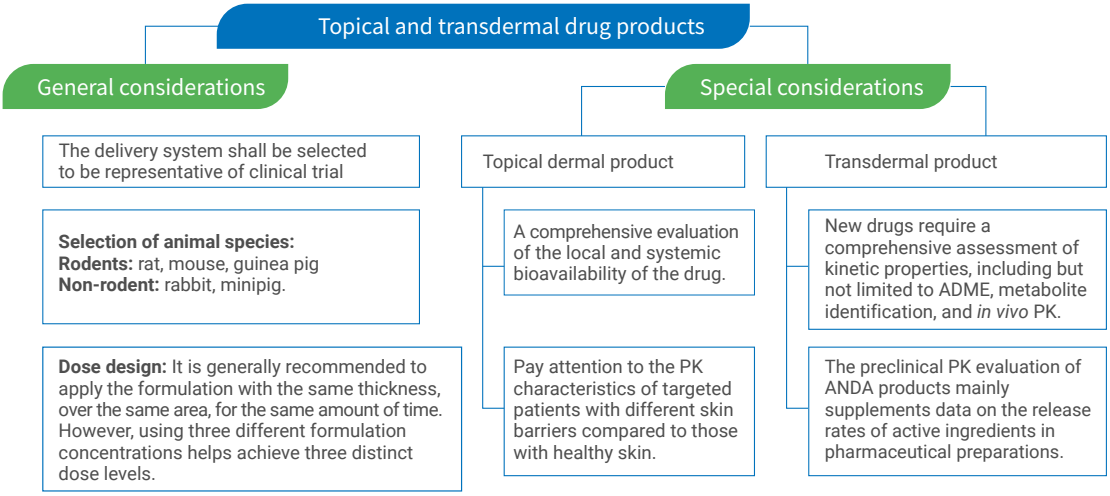
- Rodent and mini pig dermal tissue isolation
- Sample processing and analysis
- Integrated drug discovery services

Features

- Administration capabilities for various formulation types
- Challenges in dermal tissue isolation and analysis
- Meticulous experimental operations
- Lack of appropriate guidelines

WuXi AppTec DMPK Study Strategies

The preclinical development of topical and transdermal drugs should align with non-clinical pharmacokinetic guidance. Unlike systemically administered drugs, these delivery systems exhibit distinct characteristics in prescription composition, dosage form, and administration route.



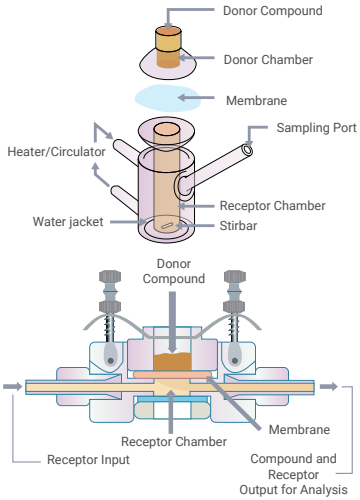
▶Pharmacokinetic studies for IND filing

Research project		Topical administration route	Transdermal administration route
In vitro plasma protein binding		Recommended if there is systemic exposure	Recommended
In vitro cell-based permeation and inhibition			
In vitro substrate and inhibition of transporters			
In vitro metabolic stability			
In vitro metabolic induction and inhibition			
In vitro cytochrome p450 reaction phenotyping			
	Species selection	Two species are recommended: mini pigs and one species of rodent	Two species based on the results of *in vitro* metabolite identification data for small molecules Typically, species are selected based on their efficacy with macromolecules.
	Sample type	Stratum corneum, epidermis, dermis, subcutaneous tissue, muscle, plasma	Plasma
	Sample quantity Time-point design	3 samples/gender/time-point	3 samples/gender/time point
		No less than 5.	10–12, typically 13–15 for macromolecules
	Administration frequency	Single-dose and multiple-doses	Single-dose and multiple-doses
In vivo tissue distribution		Recommended if there is systemic exposure	Recommend radiolabeling experiment
In vivo excretion		Recommended if there is systemic exposure	Recommend radiolabeling experiment
Metabolite identification *in vivo* (skin or plasma)		Recommended if there is systemic exposure	Recommend radiolabeling experiment

WuXi AppTec DMPK Topical and Transdermal Drug Platform

▶*In vitro* release testing (IVRT) and *in vitro* permeation testing (IVPT)

In vitro experiments are used to evaluate skin permeability, including drug release from different formulations and assessment of transdermal formulations by using biological skin or synthetic membranes. This approach provides insights into the clinical effectiveness of formulations and helps investigate factors that affect transdermal drug absorption. The Franz diffusion cell is recognized as the gold standard in the industry for dermato-pharmacokinetics [1]. WuXi AppTec DMPK has successfully established IVRT and IVPT testing platforms.



▶*In vivo* techniques for evaluating penetration of the drug into the skin

The platform provides dermal administration of a wide range of drug formulation types for various animal species (mice, rats, minipigs, etc.), such as gels, creams, lotions, foams, patches, nanoparticles, and microneedles.

***In vivo* skin application and sample processing procedures**


Administration site [2] (rodents and non-rodents)


Administration route


Fixation device


Sample collection


Skin separation


Tissue homogenizer

▶Collectable sample types

Animal species	Type of sample
Mice	Plasma (serum), stratum corneum, epidermis, dermis, subcutaneous tissue, muscle
Rats	Plasma (serum), stratum corneum, epidermis, dermis, subcutaneous tissue, muscle
Mini pigs	Plasma (serum), stratum corneum, epidermis, dermis, subcutaneous tissue, muscle

WuXi AppTec DMPK Topical and Transdermal Drug Platform

▶Mature models to mimic the barrier conditions of different skin diseases

To replicate the barrier conditions of different skin diseases, we use validated tools to develop various models while ensuring animal welfare. The extent of skin damage is assessed following WuXi AppTec DMPK standards to ensure experimental reliability. Hematoxylin and eosin (H&E) staining of Bama mini pig skin reveals a weakened barrier function after epidermal removal, enhancing drug permeability.

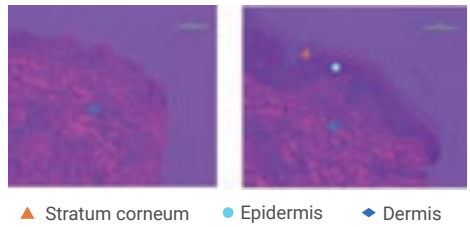


Figure 1. Hematoxylin and eosin (H&E) staining of Bama mini pig skin (left: results of H&E staining of damaged skin model; right: H&E staining of normal Bama mini pig skin)

▶Precise skin integrity testing equipment for *in vitro* permeation studies

Equipped with a professional veterinary team and comprehensive skin testing equipment, we can perform various examinations, including transepidermal water loss (TEWL), hydration status, skin damage assessment (for drug pharmacokinetics evaluation in injured skin models), and skin surface temperature.

▶High-precision dermal tissue separation and bioanalysis instruments

WuXi AppTec DMPK has extensive experience in separating skin tissue from rodents and mini pigs and utilizing high-precision bioanalytical instruments. We have established a dermal tissue stratification platform that integrates a microtome cryostat with a sample homogenization method using low-temperature bead milling to achieve small, uniform particle sizes for dermal tissue. Our team also develops unique methodologies to tackle challenges in bioanalyzing dermal relevant samples, such as detecting low drug concentrations in plasma and extracting drugs from adhesive tapes through specialized stratum corneum processing techniques.

Tissue homogenized by traditional homogenizer

Tissue homogenized by bead milling

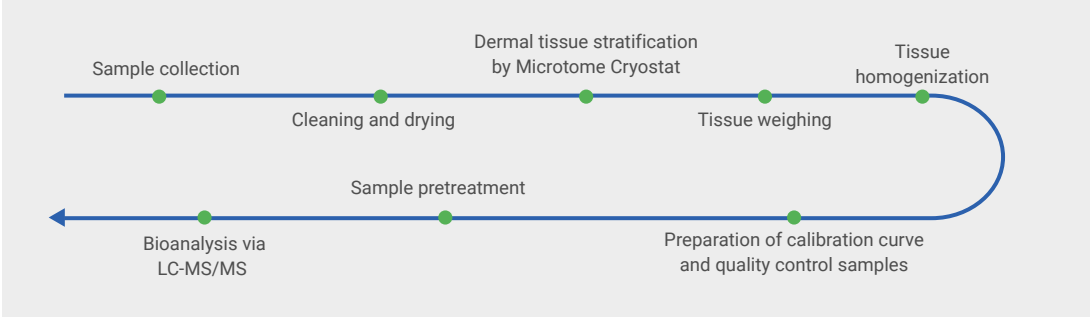


Figure 2. Liquid chromatography-tandem mass spectrometry (LC-MS/MS) analysis workflow for dermal tissue

Case Study

Commercial compound A, a widely used anti-inflammatory nonsteroidal drug with rapid absorption and a short half-life, served as a model drug in this study. Validation experiments were conducted in a vertical Franz diffusion system to evaluate the *in vitro* transdermal characteristics of six formulations, which included a clear solution formulation (group 1), a commercial cream formulation (group 2), and self-made poloxamer formulations (group 3–6).

Before the experiment, the selected Bama mini pig back skin was pretreated for uniform thickness. The prepared skin was placed between the donor and receptor chambers with the stratum corneum facing upward. Only dermal tissues with qualified transepidermal water loss (TEWL) were used. A single dose of the Compound A formulation was applied, and the temperature was maintained at levels typical for normal skin. Samples from the receptor chamber were collected at predetermined time points. Then, the tissue was washed, and the stratum corneum, epidermis, and dermis were carefully collected to analyze the distribution of the compound within the skin. The results are shown in Figures 3 and 4.

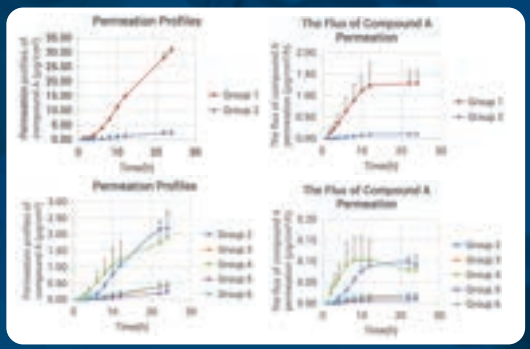


Figure 3. Cumulative permeation (left) and permeation flux (right) -time curve of each formulation

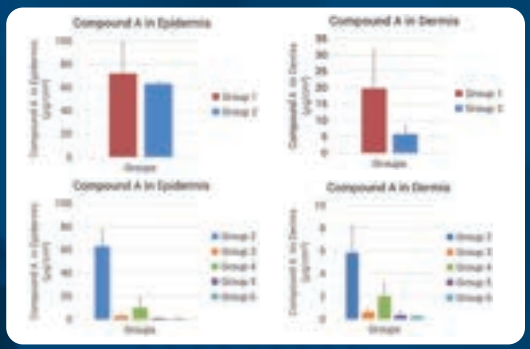


Figure 4. Retention amount of compound A in the epidermis (left) and dermis (right) at 24 hours post-dose

Figure 3 shows the commercial gel formulation (group 2) significantly reduced the drug's permeation flux and permeation amount compared to the clear solution formulation (group 1). Variations in solvent ratios influenced the drug's transdermal characteristics among the four poloxamer formulations. Figure 4 shows the retention amounts of compound A in the epidermis and dermis significantly decreased in four poloxamer formulations (groups 3–6). These findings facilitate the further screening and optimization of compound A formulations and highlight the effectiveness of the vertical Franz diffusion system in distinguishing the transdermal permeation capabilities of different formulations.

References

[1] HEATHER A E. Transdermal and topical drug delivery: principles and practice. Hoboken: Wiley,2011.

[2] Migdadi EM, Courtenay AJ, Tekko IA, et al. J Control Release. 2018;285:142-151.

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