



NEW RESEARCH TOOLS FOR TOPICAL & TRANSDERMAL DEVELOPMENT

MedPharm has developed new research tools to de-risk and expedite the development of topical and transdermal products for its clients. These tools also enable companies to assess the delivery of their molecules to their targets better, in what is a growing area of the pharmaceutical sector. In this article, Marc Brown, PhD, Chief Scientific Officer; Rob Turner, PhD, Director of Performance Testing; and James Gibbons, Commercial Manager, all of MedPharm, provide a view on the current topical and transdermal market and elaborate on some of the common approaches to product development in this area. The authors reveal the company's newest model, the MedFlux-HT™ system, which represents a significant step forwards in the field of skin permeation and penetration assessment; a crucial part of the topical and transdermal product development process, increasing data accuracy, detail and throughput.

GROWTH IN TOPICAL & TRANSDERMAL APPLICATIONS

The topical and transdermal drug delivery market was expected to have reached a size of US\$31.5 billion (£22 billion) in 2015¹ and in recent years there has been an increase in efforts to deliver drugs via these routes. This trend appears to have been driven by a number of factors:

- 2015 saw a continued investment in the field, fuelled by a buoyant, albeit occasionally volatile, investment market. Companies such as Dermira (Menlo Park, CA, US) and Aclaris (Malvern, PA, US) floated on the stock market for values of \$125 million and \$55 million, respectively, both within the last 18 months.²⁻³
- The mergers and acquisitions (M&A) cycle has continued with Kythera (Westlake Village, CA, US) being acquired by Allergan which, in turn, has been acquired by Pfizer thus creating

the world's largest drug developer. One effect of this cycle has been an increase in funds flowing into smaller dermatology companies from increased investor confidence that has led to an increase in product development.

- A number of higher value dermatology products will come off patent in the years ahead, and these include Taclonex (betamethasone and calcipotriene), Picato (ingenol mebutate) and Elidel (Pimecrolimus).⁴ This, combined with a perceived logical adaptability of the regulations created for demonstrating equivalence, particularly in Europe, has encouraged a number of high profile generics companies to grow their portfolio in the dermatology sector.
- Finally, as companies look to bolster their pipelines in the face of patent cliffs or M&A activity, there are a number of companies that are refocusing on the dermatology markets, including Almirall and Novartis. GlaxoSmithKline has decided to continue its commitment to



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dermatology, with four programmes in early clinical development.⁵ Other companies hope to take advantage of the benefits of delivering therapeutics either topically or transdermally. These benefits include enhanced patient compliance, product life cycle management, brand line extension and avoidance of first pass metabolism.

“The current trend among new compounds being developed is that of increasing lipophilicity... yet lipophilic molecules are more challenging to deliver into or across the skin, necessitating the screening of candidates in human skin and making formulation development and optimisation even more important.”

MedPharm, a leader in topical and transdermal formulation development, testing and manufacturing, has developed a new battery of testing and development tools. These tools offer a previously unattainable level of accuracy, speed, efficiency and reliability, enabling MedPharm’s clients to make informed decisions about their projects and giving them confidence in the performance of their products. In the recent past, MedPharm has used these models as a crucial part of a development strategy that ultimately achieved biowaivers for two generic products in the EU, the first time this has happened for topical products of this type.

CURRENT GOLD STANDARD

There is a large number of factors that are taken into consideration when developing and testing topical and transdermal products. Once the process of developing and optimising a formulation that is fit-for-purpose has commenced – a process worthy of an article in its own right – there are several testing models considered essential to the development process.

For both topical and transdermal drug product development, the primary challenge

of delivery is overcoming the intrinsic barrier properties of the skin. Before a medication is tested to ensure it will reach its target, it is important to test that the drug is released from a formulation. In topical and transdermal products this is achieved through *in vitro* release testing (IVRT).

Data from IVRT is increasingly sought by regulators to provide an understanding of product performance and quality. Such information is often requested at certain time-points during stability studies to show that drug release is the same throughout a product’s shelf life.⁶ However, drug delivery to and across the skin is a complex process and it is not enough just to show that the drug releases from a formulation.

Skin permeation and penetration studies are a key aspect of almost all topical and transdermal product development programmes. From an early stage it is important to select the right molecule for the job. The ideal compounds are thought to be within a certain molecular weight (<500 Da) and moderately lipophilic (logP(octanol/water) 1-3.5).⁷ However, there are always exceptions to these rules, thus it is important that a well characterised system is used to assess topical and transdermal delivery. MedPharm has built expertise over the years in formulating and delivering challenging molecules with properties often significantly outside of these indicated ranges. Whilst these parameters can be used to make an initial *in silico* approximate ranking of candidates, additional experimental work is necessary to verify candidate validity as *in silico* models cannot fully replicate *in vivo* complexities.

The current trend among new compounds being developed is that of increasing lipophilicity (log P >3) and greater potency. Yet lipophilic molecules are more challenging to deliver into or across the skin, necessitating the screening of candidates in human skin and making formulation development and optimisation even more important. Once a number of candidate formulations are developed, skin permeation studies can give confidence that a drug is reaching targeted areas within the skin or the systemic circulation. Skin permeation and penetration studies should be performed on *ex vivo* human tissue.

The penetration and permeation model is a well-validated tool for the study of percutaneous absorption and determination of the pharmacokinetics of topically applied drugs. The model uses excised human skin mounted in specially designed diffusion

chambers (static or flow-through) that allow the skin to be maintained at a temperature and humidity that match *in vivo* conditions. The formulation is applied to the surface of the skin and the permeation of the compound is measured by monitoring the rate of permeation into the receiver solution underneath the skin samples. This model also allows the drug and metabolites within the different layers of the skin (i.e. epidermis and/or dermis) to be quantified. It is vital to have a permeation and penetration model that offers good control over the potential variables in topical application such as dosing volumes, humidity, temperature and skin thickness.⁸⁻⁹

Franz Cell

There are several commercially available diffusion cells that can be used for these *ex vivo* skin penetration and permeation studies. The most common is a static cell, known as a “Franz cell” (Figure 1), where a fixed volume of receiver fluid lies directly beneath the skin or other tissue and serves as a reservoir to collect drug that permeates through the skin. The receiver fluid is then assayed at certain time-points so that drug flux across skin can be quantified. If systemic delivery is not the aim, drug penetration within the skin layers can also be quantified.

“MedFlux-HT is a continuous flow system with a carefully designed flow-path to enhance local clearance of the receiver fluid from beneath human skin. This design allows the user to generate more accurate and more detailed flux profiles within a shorter time frame.”

The fixed volume of the Franz cell can cause issues when studying compounds that are highly lipophilic (logP>4). This is because lipophilic compounds are insoluble in the physiological, aqueous-based receiver fluid. In these situations additives such as ethanol, solvents or albumin need to be added to the receiver fluid to allow the drug to partition into the receiver fluid (known as ensuring

“sink” conditions). These solubilisers can artificially modify the barrier properties of the skin and also cause problems when the receiver fluid is assayed by analytical equipment. Unwanted artefacts in the data can occur when solvents migrate from the receiver fluid into the skin and dissolve or breakdown structures such that then leech back into the receiver fluid, contaminating it.

A balance must be struck to ensure the right sink, whilst limiting the potential artefacts in the analytical data. These static cells also require manual sampling making automation and high throughput of samples challenging, if not impossible.

Flow-Through Diffusion Cell

A second type of commercially available diffusion cell is the flow-through diffusion cell. This system incorporates a receiver fluid that is constantly perfused under the skin using peristaltic pumps. These systems can be advantageous as they address some of the permeability challenges of assaying lipophilic molecules static Franz cells. However, these cells have a low flow rate, and the receiver fluid ultimately can collect in a large well under the skin. This can result in a thin, undisturbed layer of static receiver fluid directly under the skin, which limits the partitioning of lipophilic drugs from the skin into the receiver fluid. The net result is that the compound will remain in the tissue, accumulate and not partition into the receiver fluid. In this situation, flux calculations are not possible making comparison of vehicles difficult.¹⁰⁻¹¹

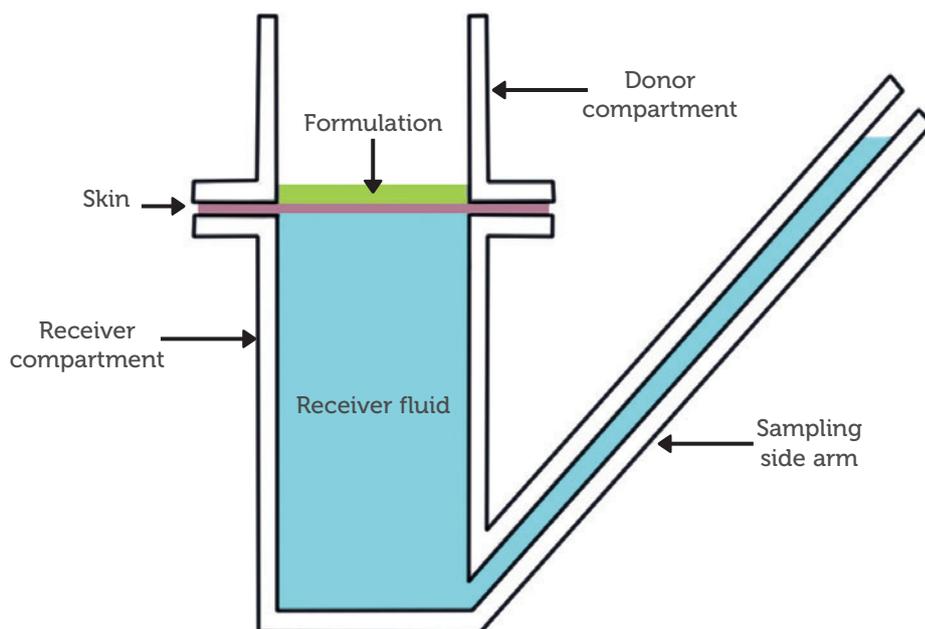
MEDPHARM'S NEW PERMEATION MODELS

MedFlux-HT™

To overcome the limitations of the commercially available diffusion cells, MedPharm’s team of UK and US scientists have developed a proprietary system to assess skin and tissue permeation and penetration; the MedFlux-HT system (Figure 1). By leveraging MedPharm’s years of experience in developing and testing topical and transdermal formulations, this new system generates more valuable data on the performance characteristics of topical and transdermal vehicles.

MedFlux-HT is a continuous flow system with a carefully designed flow-path to enhance local clearance of the receiver fluid from beneath human skin. This design allows the user to generate more

MedPharm’s Static Franz Cell



MedPharm’s MedFlux-HT™ Cell

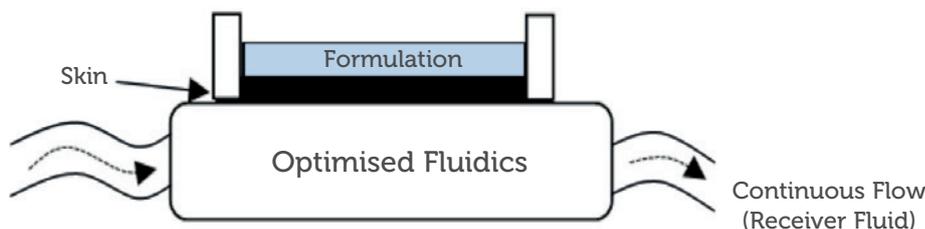


Figure 1: Schematic representation of a static Franz cell (top) and MedFlux-HT™ cell (bottom).

MedPharm’s Static Franz Cell	MedPharm’s MedFlux-HT System
<ul style="list-style-type: none"> • Widely used in the industry • Manual sample collection • Static system • Receiver fluid may have to include additives to ensure sink conditions • Meets IVRT /SUPAC criteria • Ideal for skin penetration studies • Larger dosing areas allows increased exposure of the skin to the formulation • Ideal for regulatory submissions • Study duration 6-8 weeks 	<ul style="list-style-type: none"> • MedPharm’s proprietary high-throughput system • Automated sample collection • Flow-through design with rapid local clearance • Sink conditions easily achieved with biologically relevant receiver fluid • Ideal for skin permeation studies • More accurate permeation profiles and fluxes over more data points • Smaller dosing area allows larger formulation screens • Ideal for early development and screening • Study duration 2-3 weeks

Table 1: Comparison of the different permeation and penetration systems available at MedPharm.

accurate and more detailed flux profiles within a shorter time frame. The increased local clearance from beneath the skin and optimised receiver fluid flow improves sink conditions and facilitates the analysis of lipophilic compounds, eliminating the need for the additives to be present in the receiving fluid. In addition, MedFlux-HT has been engineered with a high-throughput approach to sample collection and analysis in mind. The system is thermostatically controlled so as to maintain constant physiological temperature and the collection of the receiving fluid is automated for higher throughput sample quantification.

The MedFlux-HT system has also been designed specifically to minimise the amount of skin required for dosing. This has the benefit of increasing the repetitions that can be achieved with an often limited tissue supply. A full comparison of permeation and penetration systems is provided in Table 1.

Additional Models

As the leader in field, MedPharm has developed a number of other performance testing models which it uses to assess a variety of formulation and drug characteristics in order to allow its clients to make more informed decisions. These include models to assess drug metabolism in the skin, as well as assays to assess drug binding within the skin.

MedPharm possesses a battery of *ex vivo* human skin efficacy models where, for example, fungal, bacterial and viral skin infections can be replicated. Such systems represent the closest model to the actual disease itself where drug delivery and formulation efficacy can be evaluated and compared without having to perform clinical trials. This provides the ideal opportunity to de-risk the product development process. In addition, these models have been recognised

as validated by the regulatory authorities for use in the assessment of therapeutic bioequivalence.

Further, MedPharm's proprietary skin inflammation models can assess corrosivity and irritation under OECD guidelines 431 and 439, which can all provide a strong indication as to a formulation's viability for the intended target indication and toxicity before programmes progress to the clinic.

CONCLUSIONS

There are a number of challenges that are associated with developing topical and transdermal medications. MedPharm has the expertise to assist in all aspects of the process, from molecule selection through formulation development, testing and clinical trial material manufacture. MedPharm constantly strives to develop new, insightful tools that allow its clients to make informed decisions enabling them to ultimately develop the best product.

The MedFlux-HT system offers more detailed, more accurate as well as higher throughput data generation which, in tandem with MedPharm's other proprietary models, can facilitate quality-by-design approaches for formulation development and thus de-risk the development process by allowing selection of only those formulations with the best efficacy and safety profiles. All of these models are available to MedPharm's clients on a contract service basis together with services in formulation development and GMP manufacturing. The company also develops its own topical and transdermal drug delivery technologies that are available for licensing.

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