MedPharm

INNOVATION AND AUTOMATION IN TOPICAL FORMULATION DEVELOPMENT

In this article, Marc Brown, PhD, CChem, FRSC, Chief Scientific Officer, Jon Lenn, PhD, Chief Technology Officer, and Charles Evans, PhD, Vice-President of Pharmaceutical Development, all of MedPharm, discuss the challenges faced by the pharmaceutical industry during the development of topical delivery formulations, and how MedPharm's performance testing models help identify and mitigate risks during the process.

TOPICAL PRODUCT DEVELOPMENT

Today, the pharmaceutical market is valued at over US$1 trillion (£764 billion), over 90% of which is in oral or intravenous dosage forms. Naturally, this means formulators have a sound grasp of how to develop these medicines.

Nevertheless, for some drugs, this more conventional delivery is not possible due to drug instability, inability to get the drug to the target site, or systemic side effects, so direct topical application to the target site is required. However, such topical dosage forms are complex to develop and rely upon differing drug physicochemical properties. The formulations are applied to complex biological membranes that have evolved to keep such xenobiotics out. In addition, cosmetic and aesthetic properties of these topical formulations are also critical, as patient compliance is often driven by the ease of use and the application experience.

The global topical market was around $93 billion in 2019, and is forecast to reach approximately $123 billion by 2024[1] with the dermatology market being a significant portion of this market. A 2020 BioPharm Insight report, estimated that there are approximately 900 new products in development for dermatology, split between small molecules (65%) and biologics (35%), with a considerable focus on topicals for the treatment of conditions such as psoriasis, atopic dermatitis and acne vulgaris.

This article focuses on the latest innovation, automation and proprietary technologies that are mitigating the risk of product failure with regard to safety, efficacy and quality in the development of topical products, using dermatological medicines as an example.

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MANAGING RISK IN TOPICAL PRODUCT DEVELOPMENT

A company's attitude towards risk fundamentally affects their drug development strategy, which can vary between the development of a simple or prototype formulation (higher risk) or a fully market-ready, commercially viable product (lower risk) to be used in initial preclinical/clinical evaluation. This decision typically

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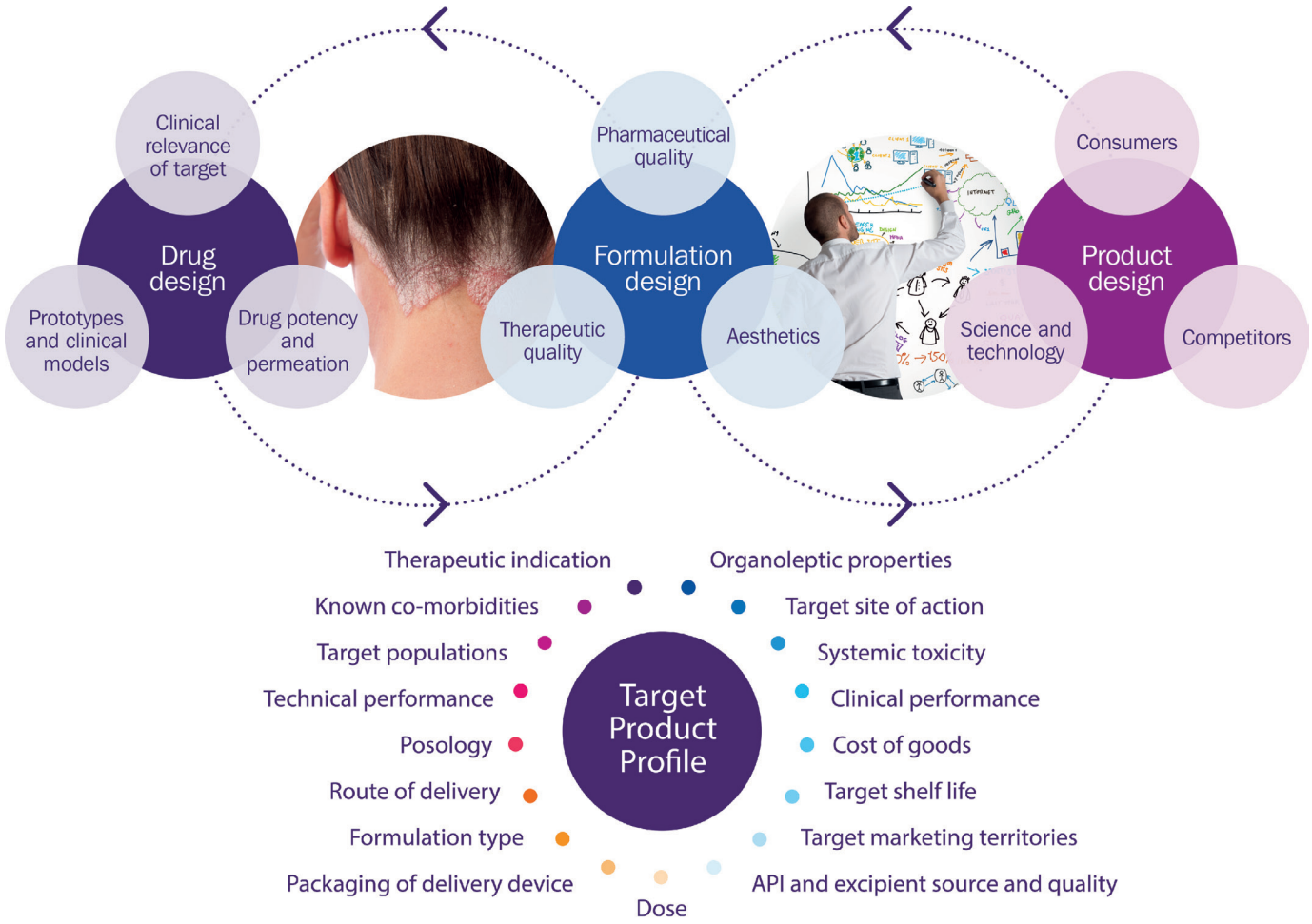

Figure 1: Common considerations for topical product development.

depends on the available funding, target markets and corporate culture. Big Pharma, with many potential drug candidates to prioritise, tends to be more risk-averse, and so generally focuses on entering clinical evaluation with a market-ready formulation that has been developed with risk mitigation considered throughout the development process. For these large companies, early failure is much less expensive than a failure in the clinic.

Conversely, small biotech companies, which may only have a single drug candidate and are typically funded by external investment, often find the development of a prototype formulation more favourable. These small companies tend to be more risk tolerant and prefer to address problems as they arise, in order to evaluate the drug candidate in a clinical proof-of-concept (PoC) study as quickly as possible. In addition, these smaller companies will usually focus on taking their single drug candidate into a formulation development programme for a single geographic market rather than the more universal big pharma approach, e.g. North America, Europe or Japan, which adds a further layer of complexity.

The challenge with this prototype formulation approach is that if the PoC study achieves a positive outcome, further reformulation work is required after the clinical trial to achieve a more patient-friendly and usable product, leading to extensive bridging safety studies. In the worst-case scenario, the formulation development may have to start again in order to proceed to final MAA or NDA. As such, the time and money saved in the early stages is often lost and/or exceeded later in the project. Additionally, any pharma company that is considering in-licensing from, or investing in, a small biotech start-up will always factor in the commercial readiness of the formulation into their due diligence, and the risks of only having a prototype formulation will reduce the market value of their programme.

In MedPharm's experience, the optimal route to success sits somewhere between these two approaches where we leverage our extensive technical and regulatory expertise, proprietary models and state-of-the-art facilities to mitigate the above risks as much as possible, regardless of the financial constraints on the client.

After over 20 years of successfully developing commercial topical products MedPharm emphasises to all its clients that a topical product's 'ease-of-use', aesthetic and cosmetic properties are as important as its efficacy. The selection of a formulation for topical application is influenced by the physicochemical properties of the drug and its potency, the disease to which it is applied and the patient who will use it (Figure 1). As a result, a Quality Target Product Profile (QTPP) should be created to define the key requirements around the quality, safety and efficacy of the drug product. This is an evolving document that is updated as the project progresses where any Critical Quality Attributes influenced by Critical Material Attributes and Critical Process Parameters are identified, monitored, and/or controlled. In parallel, MedPharm always advocates that a risk assessment is performed at these early stages and kept up to date through the entire development process. This inexpensive assessment evolves alongside the project and underpins the ongoing development strategy for the client, regulators and any potential investors.

"MedPharm considers the preformulation stage of a new drug candidate to be the most critical step for topical programmes, upon which the final, optimised, commercially-ready formulation is built."

MedPharm considers the preformulation stage of a new drug candidate to be the most critical step for topical programmes, upon which the final, optimised, commercially-ready formulation is built. For the development of topical drug products, preformulation studies typically involve solubility, stability and compatibility studies with potential excipients to be used in the final dosage form. At MedPharm much of this work is performed using automated and robotic systems. The lowest-risk approach to any submission is to try and keep to excipients, packaging, processes and parameters with which the regulatory authority is familiar. MedPharm always advocates the use of approved and, where possible, compendial excipients, as listed in the Inactive Ingredients Database that are appropriate for use on the disease itself. Once a full understanding of the 'formulatability' of the drug is gained, then a series of formulations can be developed based on the QTPP. Ultimately, for topical products, it is essential that the lead (and any back-up) formulation has been optimised and characterised not only to demonstrate that it will maintain its quality and performance during its entire shelf life, but also to give the formulation the best chance of success in the clinic.

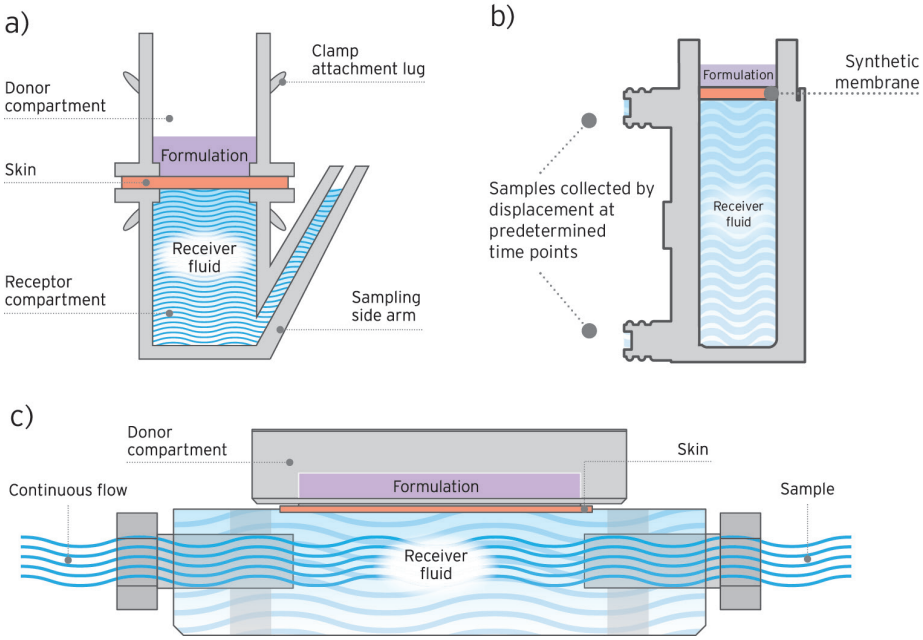

Figure 2: Compared with the industry standard vertical diffusion cells (a) MedPharm's proprietary and fully automated systems, MedStat-HT® (b) and MedFlux-HT® (c) are designed to increase throughput and reduce variability.

PERFORMANCE TESTING: INNOVATION, AUTOMATION AND HIGH-THROUGHPUT SCREENING

Performance testing tools and models provide a way to evaluate new chemical entities, drug delivery, product safety, and the efficacy and quality of topical formulations to reduce their risk of clinical failure, i.e. 'future-proofing'. These tools and models can be divided into four main areas:

1) *ex vivo* pharmacodynamic or disease models
2) *in vitro* (drug) release testing (IVRT)
3) *in vitro* (drug) penetration and permeation (IVPT)
4) product characterisation and stability testing.

As previously stated, one of the major routes of delivery considered for topical medicines is via the skin; some of the biggest advances in dermatology have been with the introduction of biologics for severe skin diseases. These biologics have revolutionised the management of skin disease and have also been instrumental in expanding the basic understanding of inflammatory dermatosis and the discovery of new targets. There is a tremendous amount of effort required to prove that these pathways can be treated with local or topical delivery. This growing interest and understanding in the basic biology of inflammatory dermatosis has led to the development of novel pharmacological disease (PD) models using fresh human skin.

Skin research has a huge advantage in its direct access to large sections of surgical tissue. The latest advances in tissue culture have allowed MedPharm's scientists to keep this surgical skin alive in culture for over a month; thereby creating a living tissue explant. The existing cell population(s) in these explants can be stimulated with specific mixtures to elicit biological responses. MedPharm spends a great deal of time researching specific stimulation conditions (e.g. Th17, Th1/Th2, LPS/PGN, TLRs, etc.), which can be added to these explants to explore different disease states and mechanisms of action, including psoriasis, atopic dermatitis, acne and vitiligo. By combining an increased understanding of immunology, tissue culture and pathway biology these *ex vivo* skin PD models have become critical to the development of new chemical entities and are helping bridge the gap for clinical translation as well as de-risking processes for topical products.

IVRT is used routinely throughout the development process, from the early stages of formulation optimisation and process development, through to scale-up. In addition, regulatory bodies are increasingly requiring its use as a quality tool in release and stability specifications and for demonstrating generic bioequivalence. The majority of industry use comprises an IVRT method based on an open chamber vertical diffusion cell (VDC) system (Figure 2a) fitted with a synthetic membrane as a support for semi-solid dosage forms in order to measure and optimise the drug release from the formulation over time (something akin to tablet dissolution testing). However, MedPharm recently developed a fully automated VDC system (MedStat-HT®) (Figure 2b) that improves on these manual VDCs by providing significant improvements in sample collection, data variation, operator repeatability and study robustness.

Most of the industry uses similar manual VDCs for IVPT studies where the drug is applied to the skin (normally surgically removed), mounted in the VDC (onto which formulation is applied) and the absorption of the drug into and across the tissue is quantified. Such a set-up allows formulations to be optimised and compared, and the risk of not achieving delivery to the pathological site and/or excessive systemic exposure can be evaluated. These systems are notorious for variability and can be challenging for modern lipophilic drugs, making data interpretation difficult. Thus, MedPharm has developed a fully automated flow-through diffusion system called the MedFlux-HT® (Figure 2c) for use in such IVPT studies, which not only dramatically reduces the variability, but more closely mimics the clinical situation compared with the manual static VDCs.[2]

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MedPharm's use of automation, robotics and higher throughput systems reduces the need for manual operation and enables researchers to deliver more accurate, robust and reliable data to accelerate timelines. Through the use of liquid handlers and robots, MedPharm can automate steps in preformulation and formulation development to allow drug solubility and stability to be assessed more accurately within various solvents and solvent systems, reducing the risk in variability when compared with manual procedures. When assessing longer-term physical stability, automated instrumentation such as a LUM (Berlin, Germany) LUMiSizer® helps to provide a more accurate prediction of shelf-life compared with the harsher centrifugation technique, where even products on the market are often observed to phase separate. Within process development and scale-up, MedPharm uses IKA (Oxford, UK) laboratory reactors, which provide the ability to control and perform multiple manufacturing parameters at the same time. Assessment of product microstructure (e.g. rheology/droplet size) is quite often overlooked until much later in the clinical phase of development, however,

ABOUT THE AUTHORS

Professor Marc Brown, PhD, CChem, FRSC, Chief Scientific Officer and co-founder at MedPharm, has been the guiding force behind all of the company's scientific developments and intellectual property. Currently he retains Honorary Professorial positions in the School of Pharmacy, University of Reading (UK), School of Pharmacy, University of Hertfordshire (UK), De Montfort University (UK) and the Institute of Pharmaceutical Science, King's College London (UK). He has over 200 publications and 26 patents describing his work. His research interests lie mainly in drug delivery to the skin, nail and airways. To date, he has been involved in the pharmaceutical development of over 55 products that are now on the market in Europe, America and Japan.

Jon Lenn, PhD, Chief Technology Officer, has direct responsibility for MedPharm's pharmaceutical innovation and technology strategies and is based out of its facility in Durham, NC, US. Since joining in 2015, he has led MedPharm's development of cutting-edge biological models and tools to evaluate drug product candidates for assessing penetration and activity of clients' products targeted towards key biochemical pathways. He has over 15 years' experience within the pharmaceutical industry developing topical medications for dermatology and, as a result, he has been directly involved with the development and approval of eight marketed products. He received his PhD on the topical delivery of macromolecules from the University of Reading (UK).

Charles Evans, PhD, Vice-President of Pharmaceutical Development, has been with MedPharm for over 15 years and has been heavily involved in evolving and refining the company's rigorous approach to formulation development. Dr Evans has many years of expertise in the successful development of robust commercial products across all types of topical, inhalation and transdermal formulations. Moreover, he played a key role in the development of MedPharm's proprietary MedSpray® technology, which is currently under licence to customers to enhance their products' performance. He obtained his PhD at the University of Hertfordshire (UK) for the development of a novel dynamic spray formulation for the treatment of Athlete's foot.

it is not only key in the development of generic products to show sameness, but also during early phase process development to demonstrate that the process is robust. Such an approach mitigates the risk of failure during clinical manufacture and ensures there are no major changes in product microstructure during the different clinical phases that could potentially change product performance. The consistent and reproducible results on a laboratory scale that can be successfully transferred to larger scales have meant MedPharm has not had any clinical batch manufacturing failures in the last 10 years.

CONCLUSION

Whether via the eye, skin, lungs, nail or other mucosal membranes, it is clear that these alternative topical routes offer key advantages alongside presenting unique challenges. MedPharm's development philosophy forces a rigorous analysis of the product requirements to identify these challenges and de-risk them throughout the development process. MedPharm's formulation strategy builds a formulation specific to the compound. This generates a sound formulation foundation that proactively focuses on creating a final product that will be physically and chemically stable and ready for the clinic. This formulation strategy is coupled with MedPharm's state of the art performance testing models to de-risk potential product failure that may result from an inability to deliver the compound to the target site or elicit a biological response prior to the clinic. This ensures that all risks are identified and mitigated as early as possible to give the product the best chance of success.

ABOUT THE COMPANY

MedPharm is a leading contract provider of topical and transdermal product design and formulation development services. MedPharm are experts at reducing risk and accelerating development times for generic and proprietary pharmaceutical customers through their unique, cost-effective and industry-leading performance testing models. Well established as a global leader in dermatology, nail, mucosal membrane, and transdermal product development, MedPharm can also offer innovative solutions for ophthalmic and airway preparations recognised for their scientific rigour by regulators and investors. MedPharm has fully established Centres of Excellence in the US and the UK.

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