NEW RESEARCH TOOLS FOR TOPICAL & TRANSDERMAL DEVELOPMENT

TRANSDERMAL DELIVERY INNOVATIONS USING LIQUID SILICONE RUBBER

ADHESIVE SELECTION FOR OPTIMAL TRANSDERMAL DRUG DELIVERY

SKIN DRUG DELIVERY: DERMAL, TRANSDERMAL & MICRONEEDLES
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This edition is one in the ONdrugDelivery series of publications from Frederick Furness Publishing. Each issue focuses on a specific topic within the field of drug delivery, and is supported by industry leaders in that field.

12 MONTH EDITORIAL CALENDAR

Apr Pulmonary & Nasal Drug Delivery

May Injectable Drug Delivery: Devices Focus

Jun Connected Delivery Devices

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Mar Skin Drug Delivery: Dermal, Transdermal & Microneedles

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E: subscriptions@ondrugdelivery.com.

EDITORIAL AND ADVERTISING:

Contact: Guy Furness, Proprietor & Publisher

T: +44 (0) 1273 47 28 28

E: guy.furness@ondrugdelivery.com

MAILING ADDRESS:

Frederick Furness Publishing Ltd
The Candlemakers, West Street, Lewes,
East Sussex, BN7 2NZ, United Kingdom

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MICRO BRISTLE APPLICATORS
THE INNOVATIVE RESPONSE TO THE RISING TRENDS OF PRECISE DRUG APPLICATION

- Combine deposition & application in one system
- Increase precision of application
- Increase dosing precision with simple system
- Avoid the drawbacks of current application systems
- Use proven know-how & technology with pure pharmagrade plastics

BLOW-FILL-SEAL SINGLE DOSE WITH MICRO BRISTLE APPLICATOR

rommelag® and GEKA partner to invent a cost efficient alternative to expensive and complicated existing dosing systems. BFS bottelpack® containers are aseptically formed, filled and sealed in one operation cycle in a close environment. The GEKA dip-in micro bristle applicator (DIP-IN MBA) is inserted during the BFS process.

TWIST’n’BRUSH CONCEPT

- Single-dose tube system based on Neopac’s established Twist’n’use™ closure system with integrated tamper-evident function.
- Nozzle tip is replaced with a Flow-Through Microbristle Applicator (MBA™) developed by GEKA: ultra fine soft pharma grade plastic bristles brush which allows the convenient and gentle topical application of medicinal products, precisely and hygienically.
- For medical applications such as in wound care the entire tube including the brush will be sterilized prior to filling.

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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 2015 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.

• 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). 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

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.

Marc Brown
Chief Scientific Officer

Rob Turner
Director of Performance Testing

James Gibbons
Commercial Manager
dermatology, with four programmes in early clinical development. 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 that ultimately achieved biowaivers for two products. Once the process of developing and testing 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. 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). 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 increases in 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 topicaly 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 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 penetration and penetration model that offers good control over the potential variables in topical application such as dosing volumes, humidity, temperature and skin thickness.

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.”

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“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

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<tr>
<th>MedPharm’s Static Franz Cell</th>
<th>MedPharm’s MedFlux-HT System</th>
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<tr>
<td>Widely used in the industry</td>
<td>MedPharm’s proprietary high-throughput system</td>
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<td>Manual sample collection</td>
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<td>Receiver fluid may have to include additives to ensure sink conditions</td>
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<td>Meets IVRT /SUPAC criteria</td>
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<td>Ideal for skin penetration studies</td>
<td>More accurate permeation profiles and fluxes over more data points</td>
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<td>Larger dosing areas allows increased exposure of the skin to the formulation</td>
<td>Smaller dosing area allows larger formulation screens</td>
</tr>
<tr>
<td>Ideal for regulatory submissions</td>
<td>Ideal for early development and screening</td>
</tr>
<tr>
<td>Study duration 6-8 weeks</td>
<td>Study duration 2-3 weeks</td>
</tr>
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Table 1: Comparison of the different permeation and penetration systems available at MedPharm.

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

REFERENCES
bottelpack® Technology:
- Integrated clean room US-class 100
- Recognized by GMP, FDA, JP …
- Aseptic packaging of liquids, creams, ointments …
- Endless container designs in PE, PP …

Your benefits:
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- Simple to use
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Advanced aseptic packaging in one operation cycle
Reliable – Simple – Cost-Effective

3 in 1

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Patients can today easily find deposition systems for liquid and semi-liquid drugs, but they face a real lack of suitable application systems for these formulations, in particular if looking for precise and hygienic dosing with pharma-applicators.

This is even more the case when a combined deposition and application is required. Current application systems like cotton tips, flocked applicators, spatulas, nail polish brushes or fingers present major drawbacks such as a lack of sterility, application and dosage precision, poor hygiene and fibre detachment.

Therefore, GEKA has adapted its proven technology used in cosmetics to provide systems that combine these two attributes to fulfil pharmaceutical and cosmetic needs. The systems use applicators with extremely delicate microbristles (Figure 1), resulting from many years of expertise in injection-moulding technology and patented processes (EP1465759B1, Method And Device Of The Production Of Brushes). These applicators allow users to uptake formulations under hygienic conditions and to apply these with high precision – even for the most sensitive and pinpoint application areas. As just targeted areas will be touched with the very fine bristles, an increased efficiency and reduced side effects of application are the result.

The benefits of microbristle applicators are:

1. Increased application precision (Figure 2):
   • Track precision: bristles do not spread, but create a precise, continuous track
   • Dot precision: bristles do not spread, but create a precise dot
   • Targeted areas: MBA™ reach several areas with their adjusted rigidity and perfect resilience.

2. Increased dosage precision:
   The MBA™ technology and expertise in topography/design allows us to design applicators with specific shape and geometry for a defined load and release dose of the drug in a consistent and patient-independent way.

IMPROVEMENT IN TOPOCAL & TRANSDERMAL APPLICATION

In this article, Pierre Michelet, Head of Global Sales, Healthcare; Karl Hartstock-Martin, Head of Product Development; and Moritz Beyhl, Project Manager, all of GEKA, present the innovative technology of microbristle applicators (MBA™) for a more precise and hygienic application within topical and transdermal treatment. MBA™ comprises a platform of moulded, pure plastic applicators with very fine bristles to apply liquid and semi-liquid formulations.

CONTRIBUTION TO INCREASED COMPLIANCE & PERFORMANCE

Pierre Michelet
Head of Global Sales Healthcare
T: +33 1 53 53 21 15
M: + 33 6 01 17 01 89
E: pierre.michelet@geka-world.com

Karl Hartstock-Martin
Head of Product Development

Moritz Beyhl
Project Manager
E: moritz.beyhl@geka-world.com

GEKA GmbH
Waizendorf 3
91572 Bechhofen
Germany
www.geka-world.com
GEKA

3. Guarantee of purity and hygiene:

- Pure pharma-grade plastics (e.g. LDPE) are used for production without additives, glues, metal or loose fibers.
- Automated production in one step
- Radio sterilisation at 25 kGy
- Depending on the design of the customised MBA™, a wide range of materials (polyolefin and TPE) can be offered.

4. Guarantee of traceability:

Full traceability up to the raw materials is ensured.

Microbristle systems are not limited to a specific application field and can be used for various market segments (as shown in Figure 3) such as:

- Dermal care (Rx medicated skin care dermatology, OTC skin care, cosmetic skin care)
- Oral health care, e.g. mucus membrane treatment, aphthae
- Dentistry, e.g. easing dentists’ gestures
- Dental for patients, e.g. bleaching treatments, interdental brushes
- Eye care, e.g. drops and ointment, infections, sty, lashes/brow treatments
- Hair/scalp treatments
- Animal health
- Ear/nasal/foot/rectal/vaginal care
- Diagnostics.

TEST METHODS & RESULTS

GEKA Healthcare can provide services such as sharing methods or realising customised tests using its specifically developed Performance Test Method, for example, to evaluate dosage pick-up and release, or calculation of standard deviation to monitor the consistency of application.
Therefore a specific machine with a movement precision of 0.1 mm, including camera system and exact scale is used. This test system was created in collaboration with Ansbach University of Applied Sciences (Figure 4) and allows us to recreate the movement of the applicator during usage by consumer (various positions and angles of the applicator) and to measure uploaded and released quantities of formulations.

**Dosage Precision Increase**

The graph in Figure 5 illustrates the difference between standard polyamide (PA) brushes and the GEKA Healthcare MBA™ for the uploaded dose (dose ‘charged’ on the applicator and ready to be applied on the skin) and for the released dose (dose effectively applied on the skin). The product used is water and the system used is the dip-in applicator 28730.

In conclusion, the difference between uploaded and released quantity is over four times smaller when using an MBA™, rather than the PA brush.

**Dosage Precision Consistency**

Figure 6 illustrates the consistency of dosing for a standard PA brush and for a MBA™ applicator. The product used is water and the system used is the dip-in applicator 28730. The standard deviation is more than ten times smaller for the released quantity with MBA™ compared with a standard PA brush, which means much higher consistency of dose really applied to the patient. The standard deviation for the uploaded quantity is also much smaller for the MBA™.

**DESIGN & PLATFORM NEEDED FOR A SPECIFIC TRANSDERMAL USE**

**Different designs**

GEKA Healthcare offers MBA™ in different shapes and sizes, for example with 4.7 bristles per mm². Figure 7 shows convex and concave applicators, applicators with reservoir zones and comb-, brush-, and paint-type applicators. Upon test methods, the specific applicator topography is designed to perfectly match the drug characteristics (e.g. viscosity, surface tension). The length of bristles, space between bristles, bristle density, entire wettable surface and the surface tension of the applicator material can be defined.

**Different Platforms**

MBA™ can be combined with various packaging systems as Figure 8 shows:

a) Dip-in formats with single usage sticks

The drug is contained in any standard bottle of customer’s choice and the single-stick applicator will be delivered beside the bottle. The quantity of sticks per patient is to be defined by the pharmacopoeia. The patient deposits a drop of drug on the applicator, and then applies it on the target. Once used, the single-usage stick can be thrown away.

b) Dip-in formats with multi-dose packs

A complete multi-use packaging is perfectly adapted for warts, scars and wound care. It can contain a small polyethylene terephthalate (PET) or polypropylene (PP) bottle equipped with a wiper ensuring the removal of excess product before the application and a screw-on cap equipped with an MBA™ applicator. The MBA™ can also be combined with tamper-evident, child-resistant and standard screw caps with thread according to DIN 168.

**Figure 6: Standard deviation.**
GEKA Healthcare shows with its MBA™ technology the answer to the rising trend of precise and hygienic drug application that existing systems aren’t able to fulfil. The ability to mould fine structures with pure plastics and the experience in development of applicators and packaging systems allowed GEKA Healthcare to create a platform for precise and consistent drug application. Within this platform, the MBA™, various shapes and designs of applicators are possible. As shown, there are many possibilities of usage and application fields. Whenever a drug or formulation needs to be applied in a precise, consistent and hygienic way, the MBA™ is the answer.

ABOUT GEKA

Driven by an increasing market demand for innovative solutions improving the way a drug or cosmetic is applied by/to the patient precisely and hygienically, GEKA Healthcare has been created as a division of the GEKA Group.

GEKA is one of the world’s leading manufacturer of brushes, applicators and complete packaging systems for cosmetics industries. The know-how and experience in 1K- and 2K-injection micro-moulding was the basis to create unique microbristle applicators (MBA™). This platform of plastic moulded applicators and the development of solutions for precise and hygienic applications is the core competence of GEKA Healthcare.
## ONdrugDelivery 2016/17 EDITORIAL CALENDAR

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Download the 2016 Media Pack for more information!
Microneedle-based technology is a significant advance in the delivery of vaccines due to its strong stability and greater effectiveness. In this article, Luis Tissone, Director of Life Sciences, Trelleborg, outlines technological developments behind microneedle design including the use of advanced liquid silicone rubber (LSR) and two-component injection technology, and explores the advantages this offers over traditional intramuscular routes.

The transdermal drug delivery market is growing dramatically as a result of the multitude of benefits it provides for administering certain drugs over conventional systems. The rapid evolution of transdermal delivery is especially apparent with microneedle products due to its ability to provide exciting potential improvements for vaccine delivery (Figure 1).

Amongst all the companies involved in developing microneedle products, almost 50% are start-ups receiving support from financial investors. These start-ups, as well as the more established companies such as Pfizer, Roche, Johnson & Johnson, Novartis and Bayer, are looking at all the ways they can gain a competitive advantage. To ensure optimal performance, such companies are taking into consideration all the components used in their microneedle delivery system design. Knowledge of advanced technologies is crucial (Figure 2).

**MICRO NEEDLE PATCH TYPES & MARKET GROWTH**

Advanced liquid silicone rubber (LSR) and two-component injection technology can accelerate the development of transdermal drug delivery devices such as microneedle patches. There are four types of microneedles currently on the market. First is the hollow microneedle, which only requires a liquid drug formulation to be infused through the bores. The solid microneedle punctures holes in the skin where a patch can then be applied. Then there is the dissolving microneedle that is coated with the drug. Lastly, there are polymer microneedles that are made from special polymers offering dissolving, non-dissolving or hydrogel-forming options.

All of these microneedle patch types offer an excellent delivery route to enhance

“Many new studies show that microneedle use for vaccination delivery reveals either comparable or greater immunogenicity, a stronger level of stability and more advantageous dose sparing as compared to the traditional intramuscular routes.”

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Luis Tissone
Director of Life Sciences
T: +1 310 921 4134
E: Luis.Tissone@trelleborg.com
Trelleborg Sealing Solutions
200 N Sepulveda Blvd, Suite 1650
El Segundo
CA 90245
United States
www.tss.trelleborg.com
the vaccination’s effectiveness. This is primarily because microneedles possess the ability to target the rich network of immunologic antigen-presenting cells in the dermis and epidermis layers under the skin. Many new studies show that microneedle use for vaccination delivery reveals either comparable or greater immunogenicity, a stronger level of stability and more advantageous dose sparing as compared with the traditional intramuscular routes.

**VERSATILE LSR TECHNOLOGY FOR MICRONEEDLE COMPONENTS**

Advanced technologies are coming into play in enhancing microneedle components during the design process. For example, product developers and research institutes are looking at the use of LSR technology to enhance the performance of their transdermal delivery systems.

Silicone – and LSR in particular – is becoming an increasingly attractive choice of polymer due to a number of advantages. Silicone is well regarded for its favourable haptic properties and proven generally not to cause skin irritation. In addition, silicone provides biocompatibility and compliance with relevant industry regulations. Most importantly, LSR offers fast, essentially unlimited, processing possibilities for the most complex high-precision technical components in large volumes (Figure 3).

LSR technology is very effective where:

- Customised solutions are needed
- Components with extremely complex, thin, or tiny features are needed, such as a carrier or protective element as part of a microneedle patch
- Multiple materials or layers of materials need to be combined into a composite structure
- The surface texturing and surface enhancements of devices are critical to provide the intended absorption of medicine through the skin
- The highest component precision and consistency of quality are key to provide best possible support to human health.

“Microneedle-based drug delivery has the potential to be a transformative technology for the delivery of biologics and vaccines. It may provide enhanced therapeutic profiles for therapeutics and vaccines.”

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Figure 1: A detail of a transdermal patch using microneedles.

Figure 2: One of Trelleborg’s Class 8 cleanrooms where safety-critical medical LSR components are produced fully automatically to a zero-defect policy.
Advancements in drug delivery systems will be the result of access to newly developed materials, emerging methods of technological delivery and advances in manufacturing capabilities. This is precisely what LSR injection technology is offering. LSR technology can deliver smaller, more robust and stronger polymers to provide more stability, wear and usage. The more demanding requirements of pharmaceutical companies and device manufacturers have led to a more concentrated effort to deliver breakthroughs in LSR technology and microfabrication. This necessitates incorporating the smallest of parts, down to micro- and already nano-gram weights (Figure 4).

MULTIPLE FABRICATION METHODS & USES

Microfabrication manufacturing technology can be of help in delivering innovative microneedle designs. To fully understand microfabrication, it is important first to note that microneedles consist of a plurality of micro-projections, generally ranging from 25–2000 μm in height, of different shapes, which are attached to a base support. There are numerous configurations that can compose a microneedle patch. The flexibility of LSR can assist in achieving those configurations regardless of complexity.

The first microneedle devices were fabricated from silicone but many other materials have also been used in its fabrication; stainless steel, dextrin, glass, ceramic, maltose, galactose and various polymers, for example. In recent years, manufacturing of microneedles has encompassed conventional microelectronic fabrication technologies, replication, and laser drilling. Microneedles have been fabricated with a wide range of designs (different sizes and shapes) and different types (solid, hollow, sharp or flat).

MARKET PROJECTIONS

With silicone and polymer compounds falling within our core area of expertise, the opportunities to enhance transdermal delivery system design is indeed an exciting one. Device manufacturers are investing in R&D and design strategies to support the transdermal drug delivery industry, valued at US$13.5 billion (£9.5 billion) in 2013 and expected to reach $21.7 billion by 2018, according to MicroMarketMonitor (Pune, India). Microneedles are not limited to any specific class of drugs. According to a 2014 Roots Analysis report, “Microneedles for Transdermal and Intradermal Drug Delivery, 2014-2030”, more than 70% of the products in development are patches incorporating solid or dissolvable needles, while the rest are hollow microneedle arrays that employ the use of a syringe. With several new microneedle-based therapeutic product launches expected by the end of this decade, the report concludes that the overall market for microneedle-based delivery devices will reach annual sales of 485 million units by 2030.

LEVERAGING A COMPETITIVE ADVANTAGE

Microneedle-based drug delivery has the potential to be a transformative technology for the delivery of biologics and vaccines. It may provide enhanced therapeutic profiles for therapeutics and vaccines. It allows for the administration of lower levels of drug to achieve the same therapeutic endpoints. Additionally, microneedles provide an alternative to traditional needles. This industry provides a means to overcome one of the biggest barriers to patient compliance for the treatment of chronic diseases and routine vaccination. The variation in the microneedle types could also prove useful in controlling the kinetics of vaccine release. Such complex variations will further support the use of LSR technology and will be instrumental in the further evolution in the effectiveness and use of transdermal delivery systems.
The International Conference on Microneedles provides a unique international forum for academics and industry involved in the design, development, application and clinical translation of microneedle technology. The conference includes keynote presentations from leaders in the field interspersed with poster sessions and numerous opportunities for networking, when researchers at all levels can interact.

The event will take place at GSK House in London from 23-25th May. Registration includes access to both the Conference and Exhibition in addition to the Gala dinner event.

Registration closes on 11th April 2016 and spaces are limited – register now to avoid disappointment.

For more information please visit www.microneedles2016.org or contact the organizers at contact@microneedles2016.org.
Vaccines are widely recognised as one of the greatest achievements in public health, yet incorrect handling and administration can compromise their effectiveness. The process of storage, handling, preparation and administration can be complex, particularly where vaccines are being distributed in developing countries in which security of the cold chain can be difficult to assure. In addition, administration procedures can be a source of error.

For conventional vaccines supplied in vials, there can be contamination and stability risks associated with the advance preparation of syringes (“pre-drawing”). This is why the US Centers for Disease Control & Prevention (CDC) encourages the use of unit dose, ready to administer vaccines.1

It is clear even from the brief discussion above that a vaccine which does not require cold-chain handling and which is single use, unit dose and ready to use, requiring no specialised training to administer, would offer a significant step forwards in maximising the benefits of vaccination.

Microneedle delivery systems have been extensively investigated as a means to address this unmet clinical need. Both removable and biodegradable systems have been evaluated.2 The former were associated with safety concerns because of the perceived risk of needles fracturing and remaining in the skin. This led to greater interest in biodegradable systems. However, these present significant challenges, particularly in terms of their fabrication.2

As an alternative to the microneedle concept, Nemaura has developed a novel solid dose injector device which enables the controlled delivery of solid dose vaccine formulations.2 As an alternative to the microneedle concept, Nemaura has developed a novel solid dose injector device which enables the controlled delivery of solid dose vaccine formulations. This offers similar advantages to microneedle systems in terms of avoidance of cold chain and simplicity of use but, due to its larger size, presents fewer fabrication challenges. In the context of vaccine administration, where only one (or a few) doses are required, the larger size is not considered limiting. Here we present the results of a proof of concept study in mice in which...
A prototype device was used to deliver a tetanus vaccine and a diphtheria, tetanus and pertussis (DTaP) vaccine.

**NEMAURA SOLID DOSE DELIVERY DEVICE**

Figure 1 shows a prototype version of the Nemaura solid dose delivery device. The principle is based upon the initial insertion of a super sharp stainless steel needle to breach the tough outer barrier of the skin followed by delivery of the solid dose formulation in pellet form which is inserted alongside the needle. The needle is subsequently retracted leaving the solid dose formulation in the skin (Figure 2). In this particular prototype, a frustoconical-shaped pellet was used but various pellet geometries are feasible.

The device design can be adapted to allow the solid-dose formulation to be inserted efficiently into the skin either intradermally or subcutaneously depending on the dosing requirements. The device is designed to be easy to administer and includes safety features such as the complete retraction of the needle into the device following insertion of the solid-dose pellet, thus reducing the risk of needlestick injuries.

**IN VIVO PROOF-OF-CONCEPT STUDY**

A proof-of-concept study in mice provided a preliminary evaluation of the immunogenicity of the solid-dose vaccine using a Nemaura prototype solid-dose injector.

**MATERIALS**

Tetanus vaccine was selected for one arm of the study. Freeze-dried inactivated tetanus toxoid was purchased from the National Institute for Biological Standards and Control (NIBSC; Potters Bar, UK).

Infanrix® vaccine (sourced from GSK) was used for the DTaP arms of the study. The DTaP vaccine contains tetanus toxoid, pertussis and diphtheria and is a component of the childhood vaccination programme. This vaccine is supplied as a liquid and was converted to a dry state by freeze-drying with suitable excipients. Pharmacopeia-grade excipients were obtained from reputable excipient suppliers.

**METHODS**

Manufacture & Characterisation of Pellets

An optimised excipient blend was developed which, when compressed, resulted in pellets with physical properties in the desirable range. Excipients were selected based on their suitability for use in parenteral products.

Freeze-dried vaccine formulations were incorporated into the optimised excipient blend using geometric mixing. The solid-dose formulations were individually compressed into pellets using a bespoke direct compression micro-press. The pellets had a base diameter of 1.6 mm, a tip diameter of 0.8 mm and a height of 2 mm (approximate dimensions). The average mass was approximately 4 mg. Compressed solid-dose pellets were mounted on the prototype device and packaged in a nitrogen environment using a moisture-impermeable barrier material.

“The study reported here is an encouraging step forward in developing a vaccine delivery system which is straightforward to manufacture, a low-cost disposable system, easy to use and avoids the problems associated with cold-chain delivery of vaccines, and potentially other biologics.”
Tetanus pellets were formulated at a “high” dose (2.5 Lf units, equivalent to ¼ of a human dose) and a “low” dose (0.625 Lf units). Relatively high doses were selected because of the lack of adjuvant in the tetanus formulations.

DTaP pellets contained all the components of the original Infanrix® vaccine including the adjuvant. Two different freeze-dried formulations, containing different stabilisers, were used in the manufacture of the pellets. Pellets contained approximately 2% of the normal human dose of all components.

Pellet hardness was evaluated using a MultiTest 2.5-i compression instrument (Mecmesin, Slinfold, UK). Friability was evaluated using an in-house friability tester and disintegration time was determined by measuring the time taken for an individual pellet to disintegrate in 1 ml of water.

Immunogenicity Study
The immunogenicity study was conducted at a third-party CRO site. For tetanus arms, pellets were administered to ten mice in each dose group. For DTaP arms, 20 mice per dose group were used as each mouse could only provide sufficient serum for two ELISA assays.

Control groups for the tetanus study were administered reconstituted pellets or an equivalent dose of reconstituted, freeze-dried tetanus toxoid as supplied from NIBSC. Control groups for the DTaP study were administered an equivalent dose of reconstituted freeze-dried vaccine or an equivalent dose of Infanrix®. A constant dosing volume of 500 µL was used for all control groups. Animals were dosed on day 0 (prime) and day 28 (boost). Blood samples were taken on days 21 and 42.

The pellets were inserted into the skin of the lower back of the mouse in a lateral direction to ensure the pellet was administered subcutaneously. Daily physical and general behaviour of the mice throughout the study was monitored including weight, faecal matter and general movement. Body weight and feed intake of all the animals was evaluated weekly. No mortalities occurred during the study.

ELISA kits (GenAsia Biotech, Shanghai, China) were used to determine the antibody response to the administered vaccine solid dose pellets. Samples from all test animals except the naïve (untreated) control group were diluted five-fold prior to assay. The ELISA assays were performed according to kit instructions.
RESULTS

Physical Properties of Pellets

Hardness and disintegration data for sample pellets are shown in Table 1. Previous Nemaura data indicated that a hardness of 3N was sufficient for skin penetration. All tested pellets were sufficiently hard and disintegrated rapidly. Only one pellet was noted to break during the course of the immunogenicity study.

Table 2 provides physical stability data for pellets stored at 25°C and 40°C. Friability testing was also performed and less than 3% weight loss was observed for all tested pellets. This study was conducted using the DTaP Formulation Two pellets and provided assurance that the pellets were sufficiently robust to withstand storage and shipping conditions.

Animal Observations

Basic observations of the animals were determined to be normal. No mortality occurred and the weight gain of the mice was normal. Minor observations of erythema and oedema were noted at the injection site.

a) Immunogenicity: Tetanus Study

Figure 3 shows the anti-tetanus immune response. The results are expressed as an optical density value and are adjusted for the negative control (naïve mouse). Values for blanks, positive and negative assay controls were very similar at both 21 and 42 days enabling the 21- and 42-day data to be directly compared.

The results clearly show that there is an increased effect at day 42 compared with day 21 with all the high-dose groups showing a stronger response than the low-dose groups. The high-dose tetanus pellet gave a stronger response than both positive controls (reconstituted pellets and reconstituted freeze-dried vaccine) which could suggest a dose-sparing effect associated with the solid formulation. However, further studies are required to evaluate this further. All dose groups show a clear response compared with the placebo group.

b) Immunogenicity: DTaP Study

Figures 4 to 7 show the immune responses to the DTaP pellets. As for the tetanus study, the results are expressed as an optical density value and are adjusted for the negative control.

The anti-tetanus signal was weaker for the triple vaccine compared with the tetanus

Figure 4: Tetanus immune response (DTaP Study).

Figure 5: Diphtheria immune response (DTaP Study).
pellets. However, the dose of triple vaccine was significantly lower (approximately 2% of a human dose compared with 25% and 6% for the high- and low-dose tetanus-only groups). The anti-tetanus response was very low at 21 days and no response was seen to diphtheria at this time point. However, a response to both was seen at 42 days after the boost dose. In contrast, the pertussis response was evident at 21 days with no significant increase at 42 days.

DISCUSSION

The purpose of this study was to demonstrate the potential for solid-dose vaccine delivery using the Nemaura proprietary solid-dose injector technology. The data clearly show that solid-dose delivery of tetanus and DTaP vaccines resulted in immune responses. The tetanus study showed a dose-response effect with some indication of a possible dose-sparing effect when delivery was in the solid form. In addition, the DTaP study demonstrated that the freeze-drying process which was used to convert the vaccine to a solid form did not result in any observable loss in potency.

The study reported here is an encouraging step forwards in developing a vaccine delivery system which is straightforward to manufacture, a low-cost, disposable system, easy to use and avoids the problems associated with cold-chain delivery of vaccines and potentially other biologics.

Industrial processes for pellet manufacture are currently in progress and pellets of a significantly smaller size than those used for this preliminary study have also been developed by Nemaura. The technology is currently being evaluated for a number of molecules, and collaboration and business development enquiries should be sent to David Scott: bd@nemaura.co.uk.

REFERENCES

In this piece, Megan Greth, Business Manager, ARx, LLC, and Gozde Karabiyik, PhD, Product Development Scientist, Adhesives Research, discuss why selecting the right adhesive for body-worn drug delivery systems – be they transdermal patches or wearable injection devices or pumps – is critical for a successful outcome.

The adhesive is an integral part of any active transdermal delivery device and passive short- and long-term wear transdermal patch. It is critical that an adhesive is selected or custom developed in consideration of the following key attributes when developing an effective and robust drug delivery system.

**SKIN-FRIENDLY ADHESIVES FOR ADVANCED DRUG DELIVERY SYSTEM PERFORMANCE**

Drug delivery methods have expanded in scope and capability, which has created a need for new adhesive technologies to overcome skin bonding challenges. Development of new active transdermal importance in the delivery of insulin and other biologics to subcutaneous tissue.

Skin adhesives are critical components for both transdermal patches and drug delivery device applications to ensure firm bonding on skin to deliver target therapeutic dose. Adhesive and skin bond must withstand moving and lifting due to physical activity, constant friction from clothing, moisture exposure and varying degrees of skin oil levels. In drug delivery device applications, such as patch pumps and infusion sets, further challenges arise from the weight of the device filled with drug and limited moisture vapour transmission of skin adhesive under the device. It is also important to note that a number of factors including age, race and patient health contribute to skin variations. Likewise, variations of skin surface energy and skin stretching at different body locations affect wear performance.

"It is also important to note that a number of factors including age, race and patient health contribute to skin variations. Likewise, variations of skin surface energy and skin stretching at different body locations affect wear performance."

Drug delivery systems (TDDS) has enabled the delivery of larger compounds through the *stratum corneum*. Additionally, body-worn drug delivery devices have gained
wear performance. All of these factors must be considered by an adhesives expert in order to achieve a consistent delivery profile across a specified patient population.

**ADHESIVE REQUIREMENTS: BIOCOMPATIBILITY & BREATHABILITY**

Adhesive biocompatibility is a significant concern in skin adhesive applications. Presence of any residual monomers and leachable components, particularly acrylics and natural rubber-based adhesives, could potentially cause skin irritation and sensitisation. Skin adhesives should be formulated carefully to provide a biocompatible adhesive system to prevent any adverse skin reaction (see Figure 1). In addition, skin breathability through the adhesive is essential to prevent maceration during wear.

In some applications, maintaining a certain hydration level at skin and adhesive interface is critical for enhancing drug flux. In this case, the skin becomes weak due to maceration and it can result in potential tearing and pain during device removal. Adhesive breathability depends on the moisture vapour transmission rate (MVTR) of the skin patch and body-worn device design as well as the adhesive construction. Breathability of a skin adhesive can be increased via substrate selection, lowering adhesive coat weight and zone or pattern coating.

“Adhesive breathability depends on the MVTR of the skin patch and body-worn device design as well as the adhesive construction. Breathability of a skin adhesive can be increased via substrate selection, lowering adhesive coat weight and zone or pattern coating.”

**SKIN-FRIENDLY, AGGRESSIVE ADHESIVES FOR LONG-TERM WEAR**

Several currently available transdermal patches are designed to be removed within 24 hours of application. However, new applications are designed for longer wear time extending wear duration up to multiple days for continued controlled release. Current seven-day, passive transdermal patches on the market are provided with an adhesive overlay to assist with bonding for the desired time period. In addition, several body-worn drug delivery devices are designed to adhere on the skin beyond seven days.

Adhesives Research has designed a tailorable, pharmaceutical-grade, acrylic-based adhesive technology that provides an aggressive long-term wear (LTW) adhesive platform to secure a drug delivery patch or device on skin for up to seven days. This adhesive platform ensures bonding of the tape to skin with minimal edge lift during the course of wear and removes from the skin cleanly without leaving any residue. This adhesive platform provides high MVTR for breathability and good wear properties with no edge residue or cold flow.

Aggressive adhesion on skin offers a secure bond to prevent lifting or moving of the patch. In spite of the aggressiveness of the LTW, it has a pain index of <2.5 on the Wong-Baker FACES® Pain Rating Scale and pain experienced upon removal of the tape is tolerable. Studies have also shown that removal of the adhesive tape does not cause disruption of stratum corneum. This adhesive formulation can be further tailored to customise the wear time and pain level depending on the wear duration and the delivery application.
SOFTWEAR® LOW-TRAUMA ADHESIVES FOR SHORT-TERM WEAR

There is a growing need for low-trauma adhesives to provide reliable adhesion on different skin conditions and age groups with gentle removal from skin. Moreover, treatments for chronic conditions require repeated application (see Figure 2) and removal of a skin patch on specific skin site. Adhesives Research is addressing the growing need for gentle and repositionable skin adhesives through the development of low-trauma adhesive (LTA) technology.

The adhesive is formulated to release from hair and the top layer of skin cleanly, with a pain index of <2.5 on the Wong-Baker Faces® Pain Rating Scale.

For comparison purposes, a standard skin-friendly adhesive has a pain index rating of 4–5 on this scale, based on Adhesives Research’s studies. In addition, LTA formulations exhibit resistance to radiation sterilisation techniques. This is important in applications such as microneedles and abrasion, providing an advantageous alternative to standard adhesives available on the market.

“Recent years, the US FDA and various journals have discussed mechanisms to characterise cold flow. The FDA also references cold flow as a consideration in the Quality by Design section of its August 2011 guidance, Residual Drug in Transdermal and Related Drug Delivery Systems.”

COLD FLOW CONSIDERATIONS FOR PASSIVE TRANSDERMAL PATCHES

Transdermal patches for passive, controlled-release delivery have been on the market for approximately 35 years. However, the issue of cold flow still exists and has received heightened attention in recent years. As both time from date of manufacture and wear time increase, so does the ability for the adhesive matrix to flow outside of the patch backing layer and seep into the packaging foil or form a ring of residue on the skin. This phenomenon is not only aesthetically displeasing and inconvenient, but it can also impact the drug flux of the patch.

In recent years, the US FDA and various journals have discussed mechanisms to characterise cold flow. The FDA also references cold flow as a consideration in the Quality by Design section of its August 2011 guidance, “Residual Drug in Transdermal and Related Drug Delivery Systems”. As with all Critical Quality Attributes, the minimising of cold flow has to be designed into the patch. Scientists must take careful consideration in selecting the appropriate adhesive chemistry, as well as the interaction with the active pharmaceutical ingredients and any other enhancers. Adhesives Research and ARx scientists have the advantage of over 35 years of foundational expertise in adhesive polymers and the selection thereof when formulating transdermal patches.

For further info, contact Kim: (217) 721-5774, or email us: khubbard@pharmaedresources.com

Register online at: www.pharmaedresources.com
OPTIMISING IN VITRO TESTING FOR TRANSDERMAL AND TOPICAL DRUG PRODUCTS

In vitro testing is an effective, cost-efficient way of assessing the performance and quality of drug products delivered via the skin. This article by Tony Copley, Managing Director, Copley Scientific, examines the regulatory framework for transdermal and topical products and the most popular techniques for quantifying their release characteristics.

Whether for topical action, or as a means of introducing systemically acting drugs into the body, the skin is an important route of administration for a wide range of pharmaceutical products.

Topical products are intended for localised action and offer immediate relief for dermatological conditions, while transdermal drug products (TDPs) are typically designed to release an active ingredient through the skin into the bloodstream, over a prolonged period. This crucial difference directly impacts the in vitro test methods of relevance to each product type, which have been substantially refined over recent years.

This article reviews the regulatory framework associated with testing both TDPs and topicals, most specifically semisolids, and the test methods described in the relatively recently revised United States Pharmacopeia (USP) Chapter <1724>. A key focus is the equipment used for in vitro drug release testing and the factors that must be controlled to ensure the successful, relevant measurements required for regulatory compliance.

WHY USE THE SKIN FOR DRUG DELIVERY?

Topical formulations for the localised treatment of skin conditions enable the delivery of relatively high concentrations of drug directly to the site of action, with minimal risk of systemic exposure and accompanying side effects. Such products include foams, sprays or aerosols, and principally semisolids, a classification that encompasses gels, ointments, pastes, suspensions and lotions, and is a key focus here. All topical products are easy to use and have a high degree of patient acceptance/compliance. Furthermore, semisolids are often formulated to deliver a moisturising effect, which as well as offering immediate patient relief, can enhance efficacy.

Like topical products, TDPs share the attraction of high patient acceptability, but there are additional inherent benefits compared with alternatives such as oral or injected drug delivery. Transdermal drug delivery avoids first-pass metabolism in the gastrointestinal tract, which can damage the efficacy of certain drugs, and enables steady, controlled release over a prolonged period. As a result, TDPs – typically patches – are commonly used for the sustained delivery of, for example, hormones and treatments for smoking cessation.

Skin is a highly efficient barrier against the outside environment. Therefore, ensuring that a transdermally delivered drug reaches the intended site of action – whether that involves penetrating the outer part of the epidermis or reaching the bloodstream – is a defining challenge.

Physical and chemical properties, including liposolubility, molecular weight and electronic structure, have a big effect on the penetration of molecules through skin and influence which drug molecules can be most successfully formulated for transdermal delivery. Because skin is generally non-polar in nature, non-polar carriers with low molecular weight can penetrate it more easily; small lipophilic molecules tend to be optimal drug candidates.

PRODUCT & PERFORMANCE TESTING

There are two categories of test routinely specified for drug products – those for product quality and those which quantify product performance. Quality tests assess general physical attributes, which for a TDP include measurements of tack and
adhesion. Product performance tests, in contrast, focus specifically on the release of the pharmacologically active substance from the formulation matrix – a patch in the case of a TDP, for example, or an ointment or cream in the case of a topical semisolid.

In vitro performance testing strategies for topical semisolids and TDPs are in many ways analogous to dissolution testing for oral formulations, but the additional barrier to diffusion presented by the skin adds a layer of complexity. Methods for testing transdermal drug delivery have consequently been expanded beyond the simple measurement of dissolution rate across a solid-liquid interface to include the kinetics of membrane transfer.

The European Medicines Agency (EMA) does not currently offer specific guidance for semisolids, and there are no specific European Pharmacopoeia (Ph Eur) chapters. However, product quality testing for semisolids is included in USP Chapter <3>,\(^2\) which outlines the need to measure properties such as apparent viscosity and product uniformity over the assigned shelf life.

These methods are complemented by those in USP Chapter <1724>\(^1\) for performance testing via the measurement of drug release, with three different apparatuses specified – Vertical Diffusion (or Franz) Cell (VDC), Immersion Cell and Flow-Through Cell (USP Apparatus 4). There is no US FDA Guidance associated with new submissions for semisolids, but guidance for scale-up and post-approval changes similarly references the Franz Cell.\(^3\)

The EMA offers comprehensive guidance for TDPs, referencing both performance and product quality tests.\(^4\) Guidance for performance testing indicates that the release characteristics of the active substance should be tested with a suitable dissolution method as specified in the Ph Eur.\(^5\)

Proposed techniques based on modified tablet dissolution testing procedures include the Paddle over Disk, Rotating Cylinder and Reciprocating Holder methods. Compendial methods for TDPs in the USP include those specified in USP Chapter <3>\(^2\) for product quality and in USP Chapter <724>\(^6\) for product performance. This latter chapter, like the Ph Eur, references the Paddle over Disk and Rotating Cylinder methods.

**IN VITRO DRUG RELEASE TESTING**

By quantifying product performance, in vitro drug release testing enables the assessment of different formulations/products, along with evaluation of the impact of process changes and QC. The adequate characterisation of drug release from the dosage form requires the generation of a release profile with values being determined as a function of time. The often complex composition and release mechanisms of semisolids and TDPs require multi-point release tests to characterise the drug product robustly and to test for batch-to-batch and shelf-life consistency.

Experimental conditions must be discriminating enough to detect manufacturing variables that may affect product performance, as well as reflecting the physiological conditions at the site of drug administration, and are directly influenced by differences between the dosage forms. Semisolids are typically hydrocarbon-based systems or oil-in-water emulsions, incorporating additional ingredients such as emulsifiers, stabilisers, pH buffers and preservatives. In contrast, TDPs are administered via physical devices that may incorporate multiple polymeric membranes and layered matrices. The test methods and apparatuses specified are designed to produce meaningful and relevant data for these quite different physical forms.

**TDPs**

Of the three compendial methods specified for testing TDPs, Paddle over Disk is increasingly preferred on account of its simplicity. This is described as Method 5 in USP <724> and Method 1 in Ph Eur Chapter 2.9.4. The Rotating Cylinder method shares the advantage of specification in both the USP and Ph Eur (Method 6 and Method 3, respectively) and consequently is the most widely used alternative. The Reciprocating Cylinder method is rarely used and, therefore, is not covered in further detail here.

**Paddle over Disk**

Paddle over Disk (Figure 1) is a modified version of the standard Method 2 (Paddle Method) pharmacopoeial specification for dissolution testing. It makes use of standard dissolution testing apparatus – together

Figure 1: Paddle over Disk is the more popular performance test method for TDPs (images left and centre) but the Rotating Cylinder (image on the right) method also enjoys significant use.
with a disc assembly designed to hold the TDP at the bottom of the test vessel. The standard disc comprises a 35 mm sieve with a pore size of 125 μm mounted in a 41.2 mm diameter stainless steel holder, and is suitable for patches up to a maximum of 16 mm in outside diameter.

The patch for testing is mounted on the disc with its release side uppermost. A second, larger system comprising a 90 mm watch glass-patch-PTFE, is available for larger diameter patches and is often preferred since experimental investigations indicate that this gives results almost identical to those from other more complex apparatus.

Whichever size is used, the disc assembly is placed at the bottom of the vessel parallel to the lower edge of the paddle. Paddle height should be 25 mm from the surface of the disc assembly and a paddle speed of 50 or 100 rpm is typically selected. The dissolution vessel is filled with preheated, degassed media with a pH of 5-6 and held at 32°C to simulate in vivo skin conditions. Samples of dissolution media are extracted for assay at regular intervals over an appropriate test time to generate a release rate profile for the patch.

**Rotating Cylinder**

The Rotating Cylinder method is closely similar to Paddle over Disk but replaces the disc basket assembly with a cylinder stirring element (Figure 1). In this method, the transdermal patch is attached to the exterior of the cylinder using an appropriate adhesive, with a cylinder extension available for testing larger patches. Testing then proceeds in a strictly analogous way as with USP Method 5.

**SEMISOLIDS**

USP <1724> specifies measurement of both the total amount of drug released and the release rate for semisolid performance characterisation. Of the apparatuses specified, the VDC is rapidly emerging as the preferred choice because of its simplicity and reproducibility, although the Immersion Cell remains in widespread use. The less widely deployed Flow-Through Cell (USP Apparatus 4) is not covered here in detail, though, when used in combination with an automatic fraction collector, has claimed advantages, especially for testing formulations with rapid permeation characteristics.

**The Vertical Diffusion Cell**

Three different designs of VDC are included in USP <1724>, but the basic principle of operation is the same in each case. In practice, each design can be assembled with either an open or closed cell top. In the open configuration, a sample is held in a donor chamber as shown in Figure 2, and is separated from the receptor media by an artificial membrane (or skin) designed to act as a conduit for diffusion to take place. An open configuration offers the flexibility to test with just a minimal smear of semisolid, with a full chamber, or with an infinite reservoir, depending on test requirements. A closed configuration consists of a “three-part sandwich”, comprising a support disc, a PTFE sample chamber ring in which the sample is initially placed and the artificial membrane (or skin).

This sample sandwich is placed onto the cell such that the membrane is bathed in the receptor medium. The cell top is occluded to prevent the ingress of air and hence minimise back diffusion from sampling, whilst also providing a sample of defined volume.

Testing is typically conducted over a period of six hours, during which samples of receptor medium are extracted.
periodically for assay, with an equal top up of fresh medium keeping the sample bathed in the receptor medium. The resulting data generates a time-dependent release profile where release is proportional to the square root of time, i.e. the profile should be a straight line with a gradient representing the release rate.

USP <1724> references three different VDC models with ports designed for sample withdrawal and media replacement (Figure 3). The receptor chamber of Model A has two ports while those of Models B and C have just a single port. In the case of Model A, the sample is withdrawn from the upper port by forcing replacement media into the cell via the lower port.

Although this design is well-suited to automation, it is also associated with cell leakage and/or back diffusion because of the upward pressure that operation exerts on the sample holding assembly. The simpler design of Models B and C largely eliminates these problems and is increasingly preferred. These latter two cells differ only in terms of size, with Model C enabling higher volume testing where this is helpful because of the drug concentration/dosage form concerned.

For all cell designs a magnetic stirring bar ensures a homogeneous temperature distribution and adequate mixing of the cell contents. Test temperatures are normally 32°C to reflect usual skin temperature (37°C for vaginal preparations), and may be maintained using a water-jacketed design and appropriate water circulation system. However, a more modern and efficient approach is to use a compact heated block, such as the HDT 1000 Vertical Diffusion Cell Test System from Copley Scientific, which holds ten VDCs and eliminates the excessive tubing associated with jacketed designs (Figure 4).

Since data can be compromised by air collection at the membrane affecting diffusion, accessories such as the Vacuum Deaerating Apparatus Model VDA from Copley Scientific – which degasses the receptor medium ahead of testing – can also be helpful in streamlining and improving the accuracy of routine testing.

**Immersion Cell**

An Immersion Cell can be used to test semisolids with the conventional USP Apparatus 2 for dissolution testing and a small volume conversion kit. Adjustment tools enable the user to vary the volume of the reservoir within the cell.

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**Figure 4:** Using a compact heating block for testing is an efficient approach and eliminates the ‘spaghetti’ of tubing associated with water jacketed designs.

**Figure 5:** An immersion cell (above) is used with the conventional USP Apparatus 2 fitted with a small volume conversion kit, as shown on the right.
SUCCESS OF TESTING SEMISOLIDS

**FACTORS INFLUENCING THE REPRESENTATIVE TESTING:**

The PTFE Immersion Cell, which include:

- The cell body, a variable volume compartment that holds the sample
- The 25 mm diameter membrane or skin sample
- A washer to hold the membrane in contact with the sample
- A retaining ring, which secures the membrane to the cell body.

**In vitro release testing procedures for both TDPs and topical products are now well-defined, robust and reproducible.**

Testing is carried out in an analogous way as with the VDC, over a comparable period of time. Once the sample has been loaded and assembly is complete, the entire cell is immersed in receptor medium at the bottom of the dissolution tester vessel. Samples of receptor medium are then extracted periodically for assay to generate a release profile, with preheated, degassed medium added to top up as required.

**REPRESENTATIVE TESTING: FACTORS INFLUENCING THE SUCCESS OF TESTING SEMISOLIDS**

The *in vitro* drug release testing of TDPs is well documented, whilst that of semisolids less so. *In vitro* release testing does not directly model the behaviour of a product, and is therefore not a complete substitute for bioavailability or clinical studies. However, steps can be taken to enhance its relevance. Apparatus choice and test temperature are important factors but there are a number of other issues involved in testing semisolids to consider.

**Choice of Dissolution/Receptor Medium**

While diffusion is a spontaneous and irreversible process, it is influenced by the balance of intermolecular forces between the solute and solvent. Certain radicals, water and sodium chloride all affect the dissolution characteristics of a drug molecule in a potential receptor/dissolution medium, with the maxim “like dissolves like” providing a good starting point for selection, along with the need to reflect the physiology of the skin. The pH of the medium is usually adjusted to lie in the range 5-6 for this reason.\(^8\)

Dissolution rate depends on the degree of under-saturation in the liquid solvent film immediately adjacent to the solid solute, so it is also important to select a medium with high drug solubility. Low viscosity is also beneficial since this enhances the permeability of the membrane within the test set-up, reducing the resistance it presents to diffusion. Finally, it is essential that the chosen medium does not impact the integrity of the product or the membrane. It should be compatible with any polymers present and, in the case of semisolids, immiscible with the formulation.

**Maintenance of Sink Conditions**

An underlying premise of drug release testing is that it is measured under “sink conditions”\(^1\) to minimise the influence of the experimental set-up on the relevance of the data. Sink conditions means that the concentration of drug dissolved in the receptor or dissolution medium is maintained at such a low level, relative to the concentration in the product itself, that it does not inhibit the diffusional process. This requirement may influence test apparatus choice in extreme cases, or more simply require a modification to the amount of sample used.

**Membrane Choice**

Membrane choice is an important aspect of semisolids testing, since the membrane acts as a support for the sample. Chosen membranes should be chemically inert to both the receptor and the product, and wet easily since complete wetting is essential to eliminate air from the pores of the membrane and enable an accurate measurement of diffusion. In addition, it is important to select a membrane with high permeability, such that the rate-limiting process is diffusion of the drug product from the formulation.\(^1\)

Synthetic membranes in widespread use are made from materials such as cellulose acetate, polycarbonate, nylon, polysulfone and Teflon, but newer transdermal test materials such as Strat-M can offer important advantages. Strat-M delivers data that are highly predictive of diffusion in human skin while avoiding the wetting, lot-to-lot variability, safety and storage limitations associated with real skin.

**CONCLUSION**

*In vitro* release testing procedures for both TDPs and topical products are now well-defined, robust and reproducible. Furthermore, relative to costly and time-consuming *in vivo* methods, *in vitro* drug release testing methods are simple, economical and more open to automation.

Understanding how apparatus works and the factors that affect the resulting data is key to the successful application of the specified performance tests for semisolids and TDPs from development through to QC. Such understanding underpins the valuable use of *in vitro* testing to demonstrate batch-to-batch uniformity, to support the demonstration of *in vivo* bioequivalence or to assess the impact of post-approval changes to excipients, batch size or manufacturing processes.

**REFERENCES**

1. **USP38-NF33 Chapter <1724>.** “Semisolid drug products – performance tests”.
2. **USP38-NF33 Chapter <331.** “Topical and transdermal drug products – product quality tests”.
5. **Ph Eur 8th Edition,** Chapter 2.9.4, “Dissolution Test for Transdermal Patches”.
6. **USP38-NF33 Chapter <724>.** “Drug Release”.
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USE-RELATED HAZARDS

Combination product users, such as patients, professional and lay caregivers, pharmacists and physicians have unique needs that vary from product to product, but all users need all products to be safe and effective. Human factors engineering (HFE) and usability engineering (UE) provide the necessary tools to identify, assess and mitigate use-related hazards. According to the US FDA, the “goal is to eliminate or reduce to the extent possible” anything related to the user-device interface “that could cause harm or degrade medical treatment”. In particular: “Drug development should take into account the user interface and factors that can reduce the risk of medication errors, i.e. features to enhance patient safety.” Note that “the user interface includes all points of interaction between the product and the user(s) including elements such as displays, controls, packaging, product labels, and instructions for use”.

The HFE/UE “processes can be beneficial for optimising user interfaces in other respects (e.g. maximising ease of use, efficiency, and user satisfaction)” but FDA is “primarily concerned that device-containing medical products are safe and effective for the intended users, uses, and use environments”, and the guidance is focused on that singular goal. Therefore, manufacturers interested in other uses of HFE/UE besides risk control should look elsewhere. Some recommended guidance documents for those other goals are ANSI/AAMI HE75 1 and ANSI/AAMI/IEC 62366-1.2

FD A GUIDANCE & DRAFT GUIDANCE

On February 3rd, 2016 the FDA issued three guidance documents describing how they expect industry to address use-related hazards as part of their overall risk-management process. The first document came from the Center for Devices and Radiological Health (CDRH) and is the final version of a draft that was published back in 2011. It is titled: “Applying Human Factors and Usability Engineering to Medical Devices: Guidance for Industry and Food and Drug Administration Staff”.1 The second document also came from CDRH and is a draft titled: “List of Highest Priority Devices for Human Factors Review”.4 The third document came from the Office of
Combination Products (OCP) and is also a draft, entitled: “Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development: Draft Guidance for Industry and FDA Staff”. Together, these guidances provide insight into how the FDA views the risks associated with use-related hazards and their expectations for how manufacturers should follow HFE/UE processes during the development of combination products.

HUMAN FACTORS & USABILITY ENGINEERING

The HFE/UE process can start at any time. However, “user interface design flaws identified during formative evaluation [i.e. early, information-gathering human factors studies] can be addressed more easily and less expensively than they could be later in the design process”. The process is started and scaled appropriately when it is done in relation to the potential for harm as a result of use-related hazards. A typical HFE/UE process includes three steps, which the FDA calls “essential”.

They are:
1. The identification of use-related hazards
2. The elimination or mitigation of those hazards (i.e. the control of the hazards)
3. Demonstration that the hazards have been successfully & sufficiently controlled.

Whilst each product should have a process tailored to its unique characteristics, successful HFE/UE processes conclude with the same statement that the product “has been found to be safe and effective for the intended users, uses, and use environments”.

USE-RELATED HAZARDS UNIQUE TO DRUG DELIVERY SYSTEMS

Drug delivery device use typically exposes users, particularly those self-administering, to at least the following hazards: overdose, under-dose, missed dose, inadvertent needle-sticks (when a needle is involved) and transmission of blood-borne pathogen (when a needle or other sharp is involved). Therefore, users of combination products which are intended for drug delivery must be able to prepare properly and administer the drug safely at the labelled/prescribed dose and assure correct disposal. Also, users must be able to distinguish the product from others of similar appearance such as when medication for other conditions and for “other family member or pets” is “stored in the same location”.

USERS

Professional caregivers (such as nurses and physicians), lay caregivers (friends and family), and patients are all exposed to the use-related hazards associated with combination products. According to the FDA, a determination of user groups examines whether use-related hazards that may affect two or more people can be analysed, controlled and evaluated in the same manner. If there are “meaningful differences in capabilities or use responsibilities between user populations that could affect their interactions with the device (such as lay and professional users who might use the same device to perform different tasks or different types of professionals who might perform different tasks on the device)”, then there are different,
unique user groups. Further, for combination products, users may be grouped as nurses, pharmacists, physicians, emergency medical technicians, home health care providers, lay caregivers and self-administering patients. In addition, since a user’s experience may affect how they use a product, it may be necessary to include groups of users with and without “experience of similar-appearing products with different instructions for use or different hazards”.

Training is only appropriate as a last resort to control a use-related hazard. If training is necessary to control a use-related hazard, FDA says: “It is important to determine what the training is likely to encompass and how it will be performed, who is responsible for conducting the training” and “whether there is an expectation that training will routinely and consistently occur, before the first use of the combination product”.

“Together, these guidances provide insight into how the FDA views the risks associated with use-related hazards and their expectations for how manufacturers should follow HFE/UE processes during the development of combination products.”

**HUMAN FACTORS STUDIES & CLINICAL STUDIES**

According to the draft guidance, the human factors validation study (which is the study intended to “demonstrate that the final finished combination product user interface would maximise the likelihood that the product will be safely and effectively used by intended users, for the intended uses in the intended use environments”) should ideally occur before conducting major clinical studies (i.e. studies intended to “provide the primary support for the safety and effectiveness of a product for a proposed indication”).

If the final finished combination product will be used in major clinical studies, the human factors validation should be conducted on the final finished combination product prior to initiating major clinical studies. However, FDA acknowledges that the “sequencing of the human factors study prior to the clinical study may be less critical to inform our understanding of the product’s safety and efficacy”.

Further, “in some cases it may be appropriate to conduct your human factors studies in parallel to your major clinical studies or after your clinical studies to address modifications to your product”.

While these studies can be conducted sequentially or in parallel, it is nearly impossible to conduct one study to support both objectives. This is due to the fundamental nature of most of these studies – that they are controlled studies in which independent variables are controlled and dependent variables are not controlled.

In clinical studies, use of the combination product is typically one of the independent variables that needs to be controlled and this is the exact opposite in human factors studies in which use of the combination products is the dependent variable and is therefore not controlled. Use in a human factors study should not be controlled because use of the combination product is specifically what is intended to be evaluated.

**SIMULATED VS ACTUAL USE**

Most combination products should be evaluated in a simulated use study but there are some instances in which simulated use is insufficient to assess all aspects of safety and effectiveness. OCP proposes that there are two types of human factors validation studies: 1) simulated use, and 2) actual use. They further divide actual use studies
into two subcategories: 2a) actual use in a simulated environment, and 2b) actual use in a real environment.

When simulated, the simulation should be sufficiently realistic so that the results of the study are representative of aspects of actual use of the product once introduced to the market. OCP states that “there are rare circumstances when it is difficult to simulate the conditions or use, physical characteristics of the product, or environment of use”, and it is therefore necessary to conduct an actual use study.

**LABELS & LABELLING**

“In situations where the understanding of information provided in a combination product’s labels or labelling is a critical task to using a product safely and effectively, a study to assess the user’s understanding of such information (Knowledge Task study) is appropriate,” says FDA. Knowledge assessments focus on the understanding and interpretation of user interface information that will be applied in making use-related decisions. They differ from other types of human factors studies where critical task performance is assessed by observation.

Some of the critical tasks that may be evaluated in a knowledge assessment are: identification of defective/expired product, awareness/understanding of pertinent safety information in the instructions for use, recognition of clinical signs identified in the instructions for use that prompt medical attention and understanding labelling diagrams.

**SUBMITTING HUMAN FACTORS INFORMATION TO FDA**

A use-related risk analysis “should [always] be submitted in an investigation application”, since a “combination product’s specific use-related risk analysis generally informs the Agency’s expectations” for whether additional human factors data should also be submitted. In general, additional human factors data should be submitted to the FDA as part of the application whenever there is potential for serious harm resulting from use error or whenever the FDA specifically requests it either through device specific guidance or while in consultation with an applicant. The FDA encourages applicants to contact them to discuss specific product proposals.

However, regardless of whether additional human factors data must be submitted as part of the application, FDA expects that all applicants are compliant with 21 CFR 820.30 – Design Controls, which mandates the conduct and documentation of human factors activities throughout the design and development process.

The “FDA encourages applicants to submit the following human factors information for feedback before commencing the HF Validation study:

1. Use-related risk analysis and any updated risk analysis of design changes
2. A summary of human factors formative study results and analysis
3. A summary of changes made to the product user interface after the formative studies, including how the results from those studies were used to update the user interface and use-related risk analysis
4. The draft human factors validation study protocol
5. Intend-to-market labels and labelling (including instructions for use if any are proposed) that will be tested in the human factors validation study.

The FDA states that it “intends to provide preliminary comments on the user interface labels and labelling. However, final labelling is determined after review of the entire marketing application that includes information beyond that in the human factors validation study”. Depending on the outcome of its review, final approved labelling may differ from what is tested in the human factors validation study. Therefore, “an additional human factors validation study may be needed to ensure that the labelling changes minimise the use-related risks without creating additional hazards”.

**CONCLUSION**

HFE/UE is a time-proven method for reducing use-related hazards. If products are not developed with awareness and implementation of HFE/UE controls, end-users will be more likely to injure themselves, or fail to receive needed medical treatment. This is why the FDA, which is responsible for regulating safety and effectiveness of drugs, biologics and medical devices, including combination products, has issued these new guidelines to explain its current thinking on what actions are necessary during the development and post-market approval management of new products.

Please visit the Chimera Consulting® website (www.ChimeraConsultingNA.com) for additional analysis of the draft guidance.

**REFERENCES**

5. Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development: Draft Guidance for Industry and FDA Staff.

**THE COMBINATION PRODUCT TRAINING INSTITUTE**

In 2016, the Combination Product Training Institute® will conduct two identical three-day training programs that address quality system and design controls requirements for combination and borderline products in the US and EU, and the conduct of human factors studies. These programs will cover requirements for both newly developed and legacy products as well as quality system obligations of device component manufacturers. The first of the two training programs will take place on March 29-31, 2016 at the Chemical Heritage Foundation Conference Center (Philadelphia, PA, US). The second program will take place on June 14-16, 2016 at the NH Barbizon Palace (Amsterdam, The Netherlands).

Throughout the year, the Combination Product Training Institute will offer other venue-based training programs on various combination product topics. In-house training programs are also available. For additional details please visit the Combination Product Training Institute website at: CombinationProductTrainingInstitute.com
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