SKIN DRUG DELIVERY:
DERMAL, TRANSDERMAL & MICRONEEDLES

ON drugDELIVERY

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ON drugDELIVERY

2021/22 EDITORIAL CALENDAR

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SKIN DRUG DELIVERY: DERMAL, TRANSDERMAL & MICRONEEDLES

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.

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Kindeva
DRUG DELIVERY

MICRONEEDLES FOR INTRADERMAL DELIVERY OF CANCER VACCINES

In this article, John Vasilakos, PhD, Global Head of MTS Business Development and Senior Research Immunologist at Kindeva Drug Delivery, discusses the immuno-oncology market. He examines the role of cancer vaccines in supplementing other immuno-oncology therapies, as well as the value of delivering cancer vaccines intradermally.

Throughout 2020, the pharmaceutical industry received ample public scrutiny around its search for covid-19 vaccines and therapeutics. However, even with so much focus rightfully centred on the race to develop therapies that address the pandemic, covid has not diminished oncology drugs' colossal importance in the industry. This importance can be measured both in research and development spend and in drug sales. Clinical development spend on oncology therapies in the US is estimated to be more than US$80 billion (£59 billion), which is more than a third of total pharma development spend.[1] Meanwhile, drug sales for oncology are expected to exceed $300 billion by 2026, representing roughly a fifth of the total pharma market.[1]

> "A series of studies suggests that patients treated with checkpoint inhibitors are more than twice as likely to experience a durable response."

The sustained investment and opportunity in oncology matters because cancer remains a public health crisis. Existing drugs and treatment regimens still have many gaps and much room for improvement. These gaps should be addressed by not only optimising the drugs that are used to treat cancer, but also optimising the devices that deliver these drugs.

This article focuses on the sizable immuno-oncology subsegment, which is expected to grow to nearly $100 billion by 2026 – growth of over 20% per annum.[1] It discusses a dominant immuno-oncology drug class (checkpoint inhibitors) and their shortcomings, considers the role of cancer vaccines in supplementing other immuno-oncology therapies and the value of delivering cancer vaccines intradermally. Kindeva Drug Delivery's microneedle-based drug delivery platform will be used as an example of how to address many of the industry's unmet needs with respect to intradermal delivery.

THE CURRENT LANDSCAPE OF IMMUNO-ONCOLOGY THERAPEUTICS

In the last decade, immune checkpoint inhibitors, such as pembrolizumab (Keytruda, PD-1 antagonist) and ipilimumab (Yervoy, CTLA-4 antagonist), have emerged as a dominant class of immuno-oncology therapeutics. There is a strong case to be made in favour of checkpoint inhibitors based on the durability of the patient response. In essence, this means that a patient can meaningfully extend their life expectancy when these drugs work.

A series of studies suggests that patients treated with checkpoint inhibitors are more than twice as likely to experience a durable response – and roughly 30% of these patients experienced overall survival (OS) that was more than twice the patient population's median OS.[2] Moreover,

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combination therapies, in which the patient is treated with two or more checkpoint inhibitors, have had an even more promising impact on patient survival.[3]

Among the most prevalent of the checkpoint inhibitors are programmed cell death protein 1 (PD-1) and programmed cell death ligand 1 (PD-L1) inhibitors. PD-1 is a T-cell receptor that helps downregulate or inhibit immune responses. In the normal course of events, PD-1 engages with PD-L1 on antigen-presenting cells – resulting in the inhibition of T-cell function, such as cytotoxicity. Therefore, PD-1 functions as a brake on T-cell activity, thereby preventing overactivation of the immune system, which could result in deleterious effects on healthy tissues. Cancer has found a way to take advantage of this normal regulatory system. Cancer cells can produce PD-L1, which downregulates T-cell function following PD-1 engagement. Therefore, tumour cells that express the ligand PD-L1 block the tumour-killing function of T-cells by engaging T-cell PD-1.

> "The number of T-cell targeted immunomodulators in the pipeline has more than doubled since 2017, with over 200 programmes targeting either PD-1 or PD-L1."

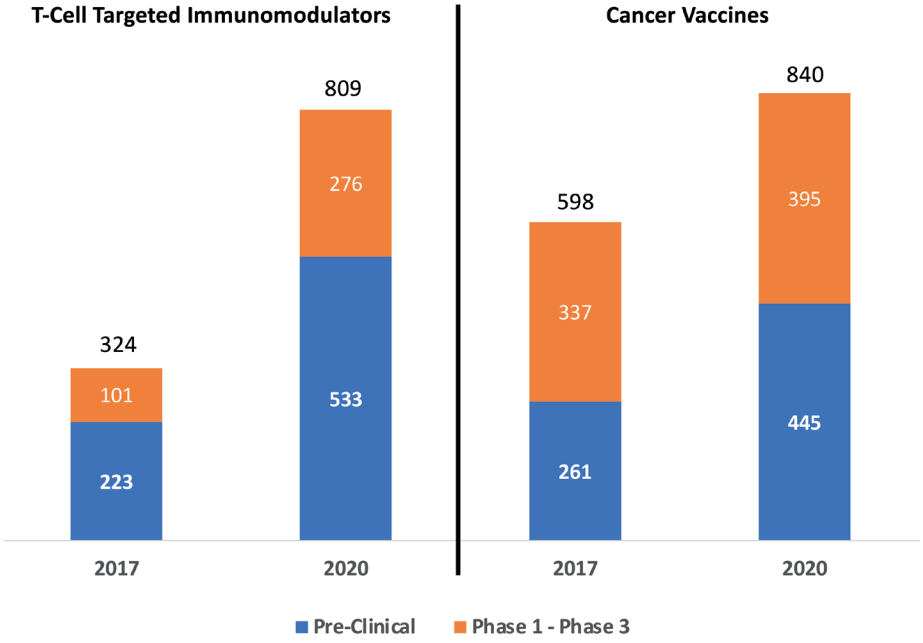

Figure 1: Number of T-cell targeted immunomodulators and cancer vaccines in development globally.

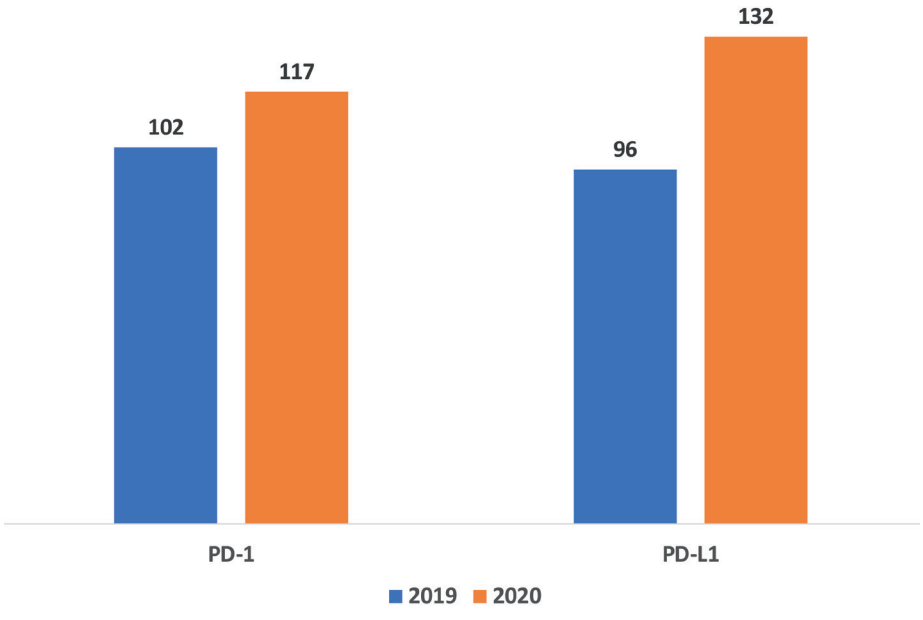

Figure 2: Number of immunomodulators targeting PD-1/PD-L1 in development globally.

As evidence for their durability grows, checkpoint inhibitors have been commercially successful for many types of cancer, and their popularity in clinical trials has continued to grow. Specifically, the number of T-cell targeted immunomodulators in the pipeline has more than doubled since 2017 (Figure 1), with over 200 programmes targeting either PD-1 or PD-L1 (Figure 2).[4] However, despite the promise, there is still a clear need for improvement. The approximately 30% of patients who experience higher OS represent a significant achievement, but approximately 70% of patients require additional therapy.[5] Indeed, combination therapy has become the norm for oncology patients.

Moreover, checkpoint blockade therapies have recently been approved for use for several cancers. For example, the US FDA has approved Keytruda (Merck, Kenilworth, NJ, US) for use with chemotherapy (carboplatin) to treat metastatic head and neck cancer. In addition to chemotherapeutics, other combination strategies are being evaluated with checkpoint blockade therapies, such as kinase inhibitors, anti angiogenics, immune-stimulating cytokines and multiple combinations of checkpoint blockade therapies and vaccines.

THE ROLE OF CANCER VACCINES AND COMBINATION THERAPY WITH CHECKPOINT BLOCKADE

Within the immuno-oncology space, there is lots of energy around cancer vaccines. There are an estimated 840 cancer vaccines currently in development (Figure 1),[4] with up to 600 companies developing them. In most situations, these vaccines are being developed as combination therapies, intended to be delivered to patients in conjunction with checkpoint inhibitors.

Cancer vaccines are compelling because checkpoint blockade therapies are not successful at eliminating all tumours in all patients, especially when used in isolation. These immunotherapeutics are most effective when the tumour microenvironment (TME) contains tumour-infiltrating T-cells (TILs).[6] The TME can be

characterised as cold (non-T-cell inflamed) or hot (T-cell inflamed). Hot tumours are characterised by T-cell infiltration and molecular signatures associated with immune activation, whereas cold tumours exhibit T-cell absence or exclusion. In general, hot tumours present higher response rates to checkpoint blockade therapies. Therefore, various efforts have focused on converting non-inflamed cold tumours into hot tumours to achieve a better clinical response.

To solve the problem of converting cold tumours to hot ones, numerous strategies have been employed, such as targeting tumours with immune stimulators or inhibitors of immune suppressor cells. Another approach currently being evaluated is cancer vaccination in combination with checkpoint blockade. Vaccination makes sense in the context where the patient exhibits minimal cancer-specific T-cell immunity. The idea is to increase the number of tumour-specific T-cells with the vaccine and prevent or inhibit their inactivation, or enhance their proliferation, using checkpoint blockade therapies. In other words, cancer vaccines can induce tumour-specific T-cells in those patients that lack anti-tumour T-cells.

Some of the earliest cancer vaccines available on the market proved to be only marginally effective. Now, the industry has become much wiser about cancer vaccines with respect to antigen selection, patient selection and combination therapies to use with vaccines, which adds to their promise. Regarding patient selection or targeting, a better understanding of the patient's tumour burden and immune status help define which patients may benefit from vaccination. Conducting vaccine trials only on patients with late-stage cancer is not ideal, because those patients often have severely compromised immune systems. For cancer vaccines to work, the patient needs to have a functional immune system. Therefore, cancer vaccines should be delivered to and tested on patients in earlier stages of the disease.

Other improvements in the development of cancer vaccines have resulted from the use of more optimal adjuvants or viral vectors that enhance cytotoxic T-cells and interferon-gamma producing T-helper cells, and the use of cancer antigens that are more commonly expressed on multiple tumour types or antigens that are unique to the patient (neoantigens).

Continued innovation in cancer vaccines and their formulations is essential – but the question of how and where cancer vaccines are delivered to the body should not be overlooked. The route of administration may impact the ultimate success rates of these vaccines.

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INTRADERMAL DRUG DELIVERY OF CANCER VACCINES

As previously discussed, cancer vaccines induce tumour-specific immunity. In an ideal world, cancer vaccines would be delivered directly into immune organs such as the lymph nodes, the spleen or the skin itself. When delivered subcutaneously or intramuscularly, cancer vaccines are deposited into parts of the body where immune cells do not normally reside. By contrast, intradermal delivery would deliver the vaccine directly into the dermis, where immune cells do reside. There is evidence that demonstrates a comparative advantage of intradermal delivery over intramuscular delivery.[7] Of salience to cancer vaccines, intradermal vaccinations have led to enhanced immune responses in many cases.[8]

While intradermal delivery of cancer vaccines seems ideal, its biggest limitation is a practical one: it is difficult to achieve precise and reproducible delivery to the intradermal layer using traditional delivery devices. One challenge is that the dermis is thin – approximately 1,800 µm in depth. To achieve this, the delivery device would need to deliver the vaccine to a depth of 500–1,500 µm and do so reliably. The lack of a reliable delivery method has limited the use of intradermal vaccination.[9]

Kindeva has advanced the development of delivery devices that help overcome the challenge of intradermal delivery. With microneedles, Kindeva's hollow microstructured transdermal system (hMTS) facilitates the reliable and reproducible delivery to the dermis. Kindeva's hMTS device is an injector that includes a drug cartridge to contain the liquid formulation and an array comprised of 12 hollow microneedles (Figure 3). The cartridge can be loaded up-front or at the time of use, depending on the drug's requirement. At the time of use, the applicator delivers the microneedle array into the skin; the liquid formulation will then move through the hollow microneedles and deliver the drug into the dermis. The drug delivery system is intended for the intradermal space, which makes the injection time longer than is typically experienced with standard vaccine injections. Depending on the formulation, the patient and the delivery site, total hMTS injection time is typically less than two minutes per mL.

The two main features that make Kindeva's hMTS platform well suited to deliver cancer vaccines are the depth of delivery and the volume of delivery. For depth, Kindeva has refined the device design to achieve reproducible intradermal

Figure 3: Kindeva's hollow microstructured transdermal system (hMTS).

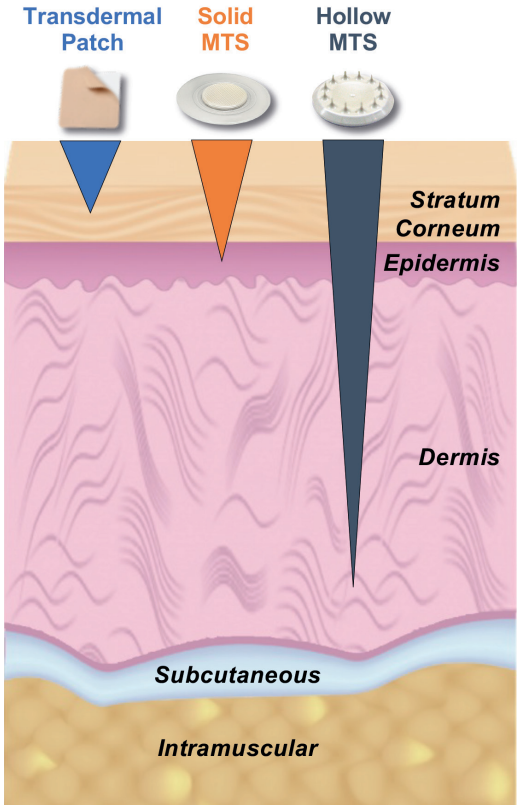

Figure 4: Anatomy of the skin.

"Devices that enable reproducible intradermal delivery should be seriously considered by biopharma companies developing cancer vaccines."

delivery, using microneedles with a length of either 1,000 µm or 1,500 µm. Cancer vaccines administered via hMTS will be delivered to a shallower part of the skin compared with vaccines delivered subcutaneously (Figure 4), thus delivering the vaccine to the immune-cell-rich dermis and elicit a more robust immune response.

In terms of volume, hMTS can deliver up to 2 mL. This is a meaningful increase in capacity compared with other intradermal and non-intradermal delivery devices currently used to deliver vaccines. While the hMTS device is currently in development, it is already well positioned to be the device-of-choice for biopharma companies developing cancer vaccines. Kindeva's device has been used in partners' Phase I and IIa drug clinical studies in the US,[10-13] and the development of a device suitable for Phase III/commercial use is progressing. Moreover, Kindeva's manufacturing capabilities are in place to meet preclinical and clinical needs.

CONCLUSION

Immuno-oncology therapies, such as checkpoint inhibitors, are designed to facilitate the ability of the patient's immune system to effectively attack and kill tumours. Over the last decade, there has been demonstrable success, with blockbuster therapies achieving significant increases in patient survival rates. Cancer vaccines can be used in combination with these checkpoint inhibitors to make cold

tumours hot, thereby increasing the overall success rate. New oncology drug classes continue to crop up and gain momentum, which provides a reason for optimism.

However, innovation in the pharmaceutical industry is not exclusive to the discovery of novel drugs and vaccines. Innovation in drug delivery devices can also play a meaningful role in improving how the medical industry treats cancer. For example, devices that enable reproducible intradermal delivery should be seriously considered by biopharma companies developing cancer vaccines. Devices like Kindeva's hMTS platform are capable of delivering cancer vaccines directly to the dermis, with its relative abundance of immune cells, increasing the potential that the drug is effective in improving patient survival rates.

REFERENCES

1. *"World Preview 2020, Outlook to 2026." EvaluatePharma, 2020.*
2. *Pons-Tostivint E et al, "Comparative Analysis of Durable Responses on Immune Checkpoint Inhibitors Versus Other Systemic Therapies: A Pooled Analysis of Phase III Trials." JCO Precision Oncology, 2019, Vol 3, pp 1–10.*
3. *Larkin J et al, "Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma." N Engl J Med, 2019, Vol 381, pp 1535–1546.*
4. *Upadhaya S, Hubbard-Lucey VM, Yu JX, "Immuno-oncology drug development forges on despite COVID-19." Nat Rev Drug Discov, 2020, Vol 19, pp 751–752.*
5. *Haslam A, Prasad V, "Estimation of the Percentage of US Patients with Cancer Who Are Eligible for and Respond to Checkpoint Inhibitor Immunotherapy Drugs." JAMA Netw Open, 2019, Vol 2(5), e192535.*
6. *Duan Q et al, "Turning cold into hot: firing up the tumor." Trends in Cancer, 2020, Vol 6(7), pp 605–618.*
7. *Teunissen MB, Haniffa M et al, "Insight into the immunobiology of human skin and functional specialization of skin dendritic cell subsets to innovate intradermal vaccination design." Curr Top Microbiol Immunol, 2012, Vol 351, pp 25–76.*
8. *Ogai N, Nonaka I et al, "Enhanced immunity in intradermal vaccination by novel hollow microneedles." Skin Res Technol, 2018, Vol 24(4) pp 630–635.*
9. *Kim YC, Jarrahian C et al, "Delivery systems for intradermal vaccination." Curr Top Microbiol Immunol, 2012, Vol 351, pp 77–112.*
10. *Gramza A et al, "Phase 1/2 Open-Label, Multi-Center Trial of SNS-301 Added to Pembrolizumab in Patients with Advanced Squamous Cell Carcinoma of the Head & Neck." Poster Presentation, 2020 SITC Annual Meeting.*
11. *Algazi A et al, "Early Safety and Efficacy of a Phase 1/2 Open-Label, Multi-Center Trial of SNS-301 Added to Pembrolizumab in Patients with ASPH+ Locally Advanced Unresectable or Metastatic/Recurrent Squamous Cell Carcinoma of the Head and Neck." Poster Presentation, 2020 EMSO Annual Meeting.*
12. *Block MS et al, "Th17-inducing autologous dendritic cell vaccination promotes antigen-specific cellular and humoral immunity in ovarian cancer patients." Nature Communications, 2020, Vol 11(1), Article 5173.*
13. *Gustafson MP et al, "Preliminary manufacturing, safety, and immune monitoring results of an allogeneic tumor lysate-pulsed dendritic cell vaccine for patients with newly diagnosed glioblastoma." Poster Presentation, 2016 SITC Annual Meeting.*

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TRANSDERMAL. MARKETLEADER.

WHY THE CONSISTENT CHALLENGES SURROUNDING MAPS ARE DISSOLVING FAST

In this article, Sebastian Braun, PhD, Head of Formulation Development and Manufacturing for Innovative Injection Systems at LTS, discusses the current state of microneedle-based transdermal drug delivery, covering available microneedle delivery methods, the US FDA's current stance on microneedle technologies and LTS's microarray patch system and the possibilities it represents.

INTRODUCTION

For the past decade, innovation in microneedles has been a focus within the pharmaceutical world. Today, microneedles are seen as a viable option for the delivery of drugs such as biologicals, vaccines and difficult-to-deliver small molecules through the skin, in both immediate-release and long-acting products. The widely recognised benefits of transdermal administration in terms of pain-free delivery, convenience and patient compliance, make microneedles an ideal platform for an increasing number of therapeutic areas.

However, the journey has not been pain-free. The US FDA has clearly struggled with the quality of submissions received from combination products using microneedles, specifically around stability testing, content uniformity, risk analysis, sterility validation and manufacturing.

This article will cover the relative merits in each form of microneedle technology; review the specific requirements set out by the FDA in October 2020; present the case for the specification of dissolvable microarray patch (MAP) technology (Figure 1), which uniquely addresses the FDA's requirements; and finally evaluate the benefits of MAP technology to each stakeholder group, including pharma partners, payers, healthcare professionals (HCPs) and patients.

The skin is an important protective barrier with an innate reactive capability (Figure 2). Its protective, inflammatory and immunological properties make it an attractive target for efficient drug delivery. It has been well documented over the years that, for various drugs, there are many advantages to intradermal delivery compared with the intramuscular and subcutaneous routes. However, the use of a traditional needle mostly requires a relatively sophisticated cold chain supply, as well as the time and effort of an HCP. It also presents issues for the patient as it is quite invasive, particularly

Figure 1: LTS's MAP system.

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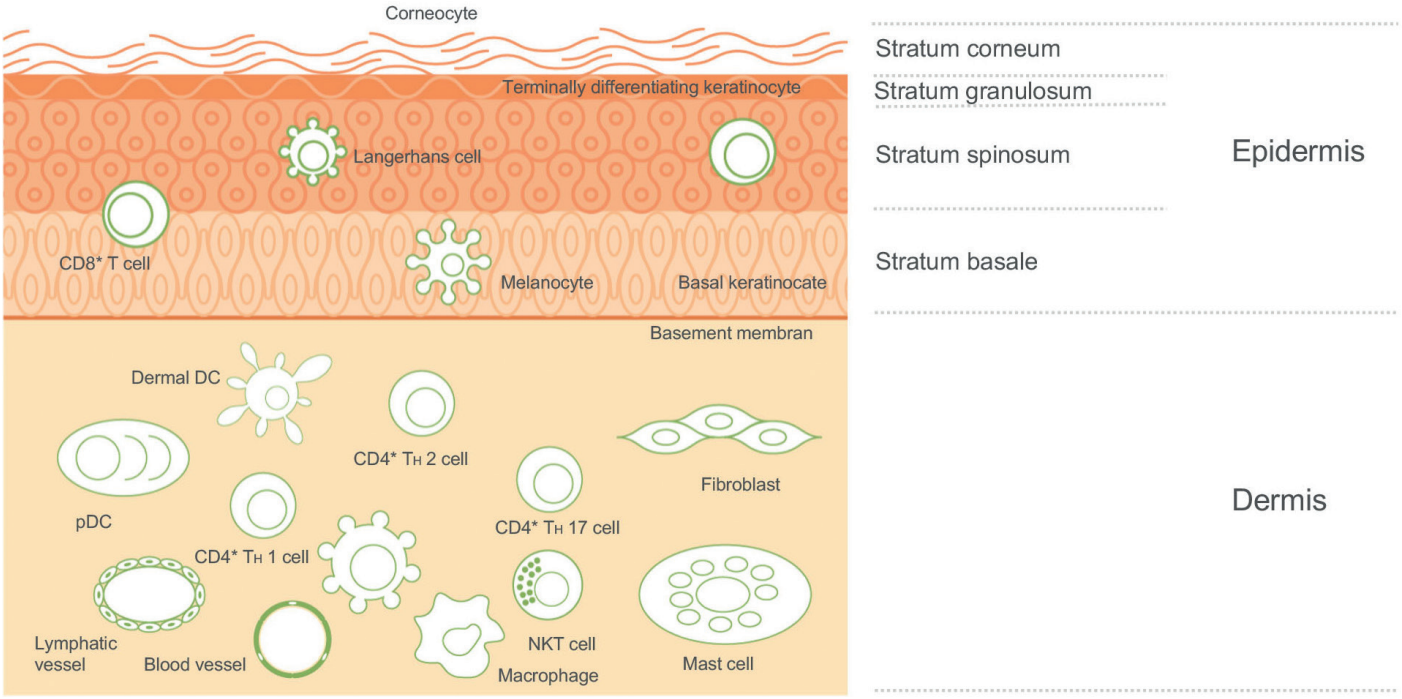

Figure 2: Skin composition.

for the large portion of patients who suffer from needle phobia.

As an alternative approach, MAPs can reproducibly deliver APIs into the dermal and epidermal layers of the skin, which contain high densities of immune cells.[1] Microneedle technology was first conceptualised, and subsequently patented, in the 1950s,[2] but it took some time for the benefits of microneedles to be fully recognised. It was not until 1998 that a paper was published exploring the possibility of using microneedles for vaccination in the future.[3] Since that early work, the WHO has identified microneedles as a potential game-changer for vaccine distribution and coverage in low-to-middle-income countries (LMICs).[4]

> "The pharmaceutical industry is very much aware of the benefits of drug delivery by injection in terms of its capability to deliver to the dermis, subcutaneous tissue and muscle layers under the skin. For a number of drugs, it is, in many ways, an ideal delivery route."

NEED FOR A LESS PAINFUL WAY THROUGH THE SKIN

The pharmaceutical industry is very much aware of the benefits of drug delivery by injection in terms of its capability to deliver to the dermis, subcutaneous tissue and muscle layers under the skin. For a number of drugs, it is, in many ways, an ideal delivery route. However, there are evident issues too, specifically related to patient compliance, usability and safety for HCPs. Aversion to needles, pain and needle size are all very real concerns for many patients.

Needlestick injuries are a source of great concern for HCPs, indeed the WHO stated in its World Health Report 2002 that of 35 million HCPs, two million experience percutaneous exposure to infectious diseases each year. The WHO further noted that 37.6% of Hepatitis B, 39% of Hepatitis C and 4.4% of HIV/AIDS in HCPs globally are due to needlestick injuries.[5] As well as the human cost, there is a financial cost too, with each needlestick injury case costing the local healthcare system around US$350 (£259).[6] Although MAPs do not entirely eradicate the potential for needlestick injuries, they are certainly a big step in the right direction towards protecting HCPs.

THE EVOLUTION OF MICRONEEDLES

Transdermal patches offer a demonstrable improvement in patient compliance, safety and usability, and represent the delivery mechanism of choice for many therapies. The challenge is, of course, that at present the choice of API is limited to small molecules, with today less than 30 APIs having been successfully commercialised for transdermal therapeutic systems (TTSs).

These limitations have been addressed by several microneedle technologies which enable the drug to overcome the skin barrier (Figure 3). Here, the currently available transdermal microneedle options are:

- **Solid removable microneedles** dispense only a limited drug load and deliver a short, sustained release of drug due to the speed of the skin healing.
- **Coated microneedles** deliver an immediate release of API and require only a short application time on the skin. They do, however, only carry a very limited drug load.
- **Hollow microneedles** can carry a higher drug load and be used for immediate or sustained release, but there are limitations in the types of API solution that can be delivered this way.
- **Dissolvable microneedles** offer very little in terms of compromise, and a great deal in terms of benefit. Dissolvable microneedles will be returned to later in this article.
- **Hydrogel-forming microneedles** have the capacity to carry a higher drug load to be delivered over a sustained period. Although they present no sharp-edge waste issues, they are limited by diffusion of the API in the polymer matrix and by the number of polymers that can be used.

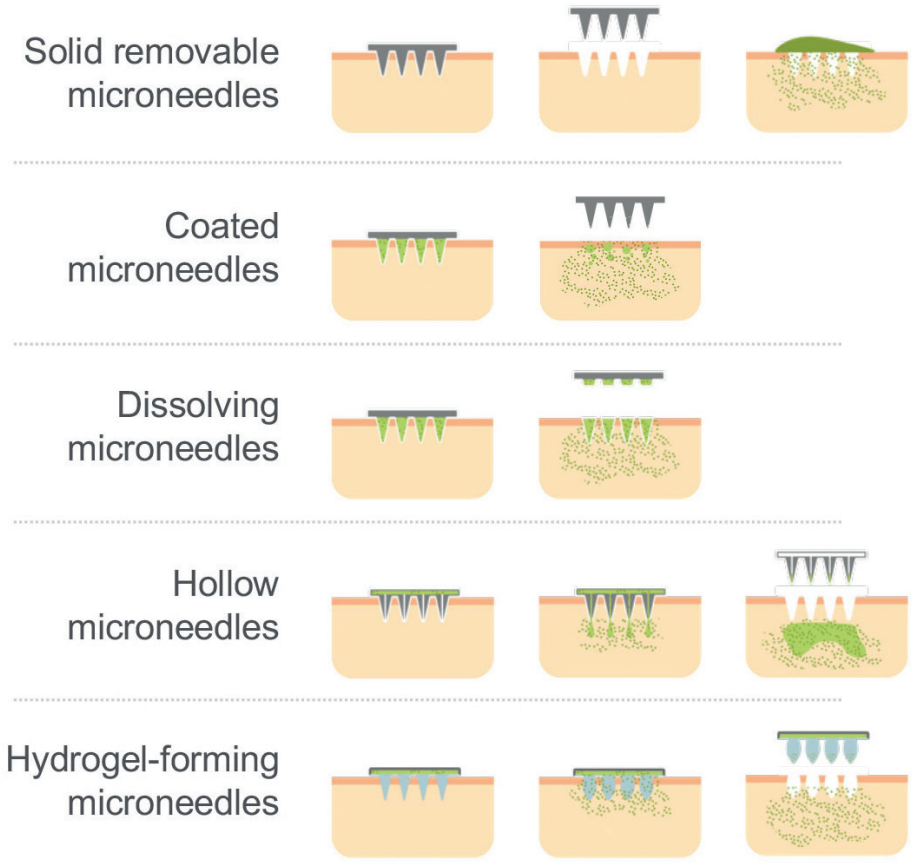

Figure 3: Overview of microneedle technologies.

All these options offer tangible benefits in terms of patient compliance and HCP safety compared with injection-based administration. It is also worth noting that solid removable, coated and hollow microneedles all result in sharps waste, whereas dissolvable and hydrogel-forming microneedles do not.

MICRONEEDLES AND THE FDA

The FDA's experience of submissions relating to microneedles to date could perhaps be described as disappointing, with quite basic failures evident in many fundamental aspects of submission. This increasing level of disappointment manifested itself in an October 2020 presentation from the FDA which sought to set out in very clear terms the criteria for a successful submission.[7] In it, the FDA stated: "Regulation of combination products must take into account the safety and effectiveness questions associated with each constituent part and the product as a whole."

The FDA's presentation sought to clarify the common product, product-use and manufacturing deficiencies, as well as setting out what it needs to see from future applications. In terms of the common product and product-use deficiencies, the headlines related to stability testing in terms of formulation/API migration and continued testing of mechanical attributes.

Content uniformity is fundamental, and there is some work to do for delivery device designers and the pharmaceutical industry more broadly in order to establish the required specification limits and then adequately demonstrate compliance. Some submissions showed that verification and validation testing was not using the final finished combination product in bench-top, clinical or human factors studies, and there was a lack of risk analysis to ensure leaving the system in place longer than prescribed would not result in injury or overdose.

The guidance from the FDA in this regard is clear. Submissions must deliver:

- A comprehensive design control package that identifies risks and hazards
- A clearly defined control strategy for EPR, design verification and validation
- A risk management plan
- An iterative guide to risk management activities throughout the entire product lifecycle.

Common Manufacturing Deficiencies

One particular area of weakness has been incomplete facility responsibility listings on the 356h form. Process parameters and in-process controls are not supported by process development knowledge in the application. There have been significant failures with submitted batches, with no root cause analysis provided. In terms of biologics, there have been incomplete process performance qualifications (PPQs) submitted; the product not being manufactured within the review cycle and inspection times; the sterilisation validation data delivered has been insufficient; and there have been failures with equipment qualification, process simulation and sterility testing methods.

The FDA's unequivocal requirement is for evidence of process development and the bridge to commercial scale. Submission documentation must deliver commercial process descriptions, process flow diagrams, master batch records (MBRs) and a sterilisation validation package for sterile products.

The presentation also highlighted three clear objectives for prior approval inspection (PAI):

- Readiness for commercial manufacturing
- Conformance to application
- Data integrity.

In LTS's opinion, the requirements set out by the FDA are nothing more than would be expected for any regulated drug delivery device, and it is alarming that the quality of some submissions has

> "The requirements set out by the FDA are nothing more than would be expected for any regulated drug delivery device, and it is alarming that the quality of some submissions has been poor enough to necessitate such regulatory guidance, given the immediate and unparalleled opportunities this kind of technology presents."

"LTS's goal was to develop a transdermal delivery method where, if the API can be delivered via an injection, it can be delivered by LTS's transdermal device. LTS has developed such a device with its MAP system."

been poor enough to necessitate such regulatory guidance, given the immediate and unparalleled opportunities this kind of technology presents.

Meeting FDA Guidance

For 40 years, LTS has been regarded as a trusted partner and market leader in innovative transdermal drug delivery systems. The company's mission is to find alternatives for patients where conventional drug delivery presents challenges. As such, LTS constantly creates new technologies that support pharmaceutical development and improve patient outcomes. While LTS is clear about the efficacious benefits of TTSs, it is also aware of their limitations in terms of API fit, and so is committed to research and development towards finding a technology where the compromises inherent in current TTSs were reduced.

Essentially, LTS's goal was to develop a transdermal delivery method where, if the API can be delivered via an injection, it can be delivered by LTS's transdermal device. LTS has developed such a device with its MAP system. This system delivers a range of benefits to the entire healthcare ecosystem in terms of increased patient comfort and better compliance, a faster onset, lower overall healthcare costs through self-administration, lower costs per administration – via reducing the dose ("dose sparing") – and the removal of cold chain distribution challenges.

The LTS MAP system is based on uncoated dissolvable microneedles, which enables optimal API load without relying on liquid reservoirs. There are three key processing requirements for a homogeneous microneedle product:

- Homogeneity of dispensing solution
- Dosing precision
- Precise mould dimensions and geometry.

LTS's MAP technology can provide for improved stability because the API is embedded homogenously in the polymer, ensuring 100% of the drug content is dispensed. The API and polymer are mixed with a solvent, dispensed into the mould and then dried to remove the solvent (Figure 4). The dispensing heads deliver a precise, reproducible volume of solution. Indeed, the dispensing heads are so precise that pharmaceutical partners can even switch formulations and volumes within each MAP. Configured for the API to be delivered and desired release option, each MAP can feature up to 1,000 needles per cm^2, with needle lengths ranging from 200 µm to more than 1,000 µm – 900 µm being the threshold for pain sensation.

RECOMBINANT VACCINE HUMAN STUDY RESULTS

In this study, LTS aimed to investigate the safety and the general and local tolerability of the recombinant vaccine delivered by a microneedle system, as well as the efficacy of vaccination. Four cohorts were established with 12 subjects in each. Three doses of the recombinant vaccine were delivered with the LTS MAP system, according the standard "prime-boost-boost" scheme. One dose level of recombinant vaccination via intramuscular (IM) injection was delivered, with boosts administered after months one and three. The results demonstrated that the recombinant vaccine MAP system is safe and well tolerated, and saw mild and moderate reactions in the subjects, comparable with those who received the vaccine via IM injection.

WHERE NEXT?

MAPs are a novel vaccine delivery methodology that has the potential to become a game-changer for immunisation programmes, especially in LMICs, which mostly rely on vaccine storage and transportation at 2–8°C and trained HCPs to administer injectable vaccines by needle and syringe. Whilst the benefits are most obvious for programmes in LMICs, that does not mean they are irrelevant for the rest of the world. Indeed, much of the development work LTS is undertaking right now is for high-value APIs.

Microneedle technology is considered an advantageous delivery route for existing vaccines, including influenza, tetanus toxoid, measles-rubella, Hepatitis B and inactivated poliomyelitis vaccine (IPV),

"MAPs are a novel vaccine delivery methodology that has the potential to become a game-changer for immunisation programmes, especially in LMICs, which mostly rely on vaccine storage and transportation at 2–8°C and trained HCPs to administer injectable vaccines by needle and syringe."

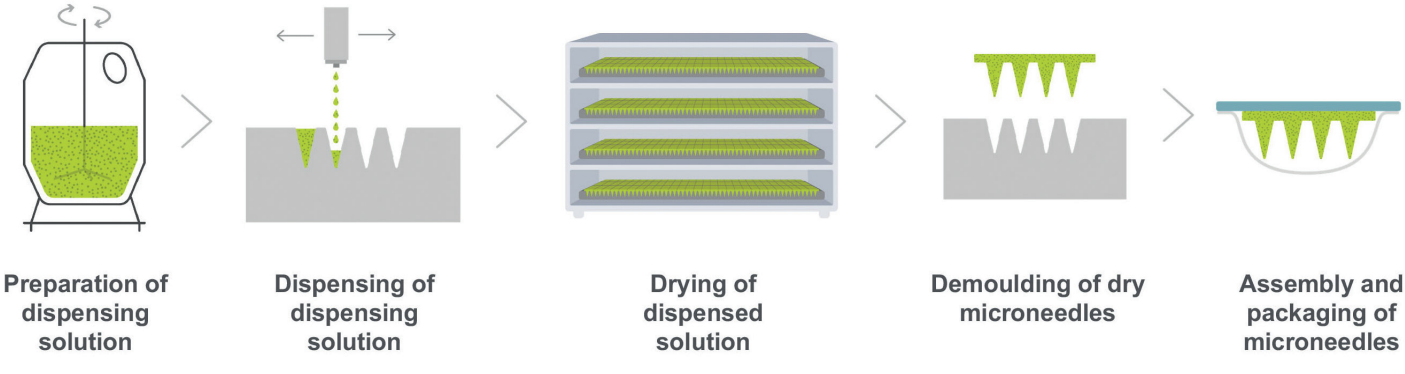

Figure 4: The MAP manufacturing process.

as well as vaccines still in development, such as inactivated rotavirus and dengue. Given the challenges currently surrounding the cold-chain distribution of covid vaccines, a great deal of consideration should be given to MAPs as an efficient method to mass-immunise populations.

CONCLUSION

MAPs have great potential, but it has been untapped to date. The technology has accrued advocates since the 1970s, and today there is a growing weight of evidential data to show the concerns around content uniformity have been largely eradicated. This is now a real and present opportunity for pharma partners to benefit and deliver real value across the healthcare ecosystem.

The technology overcomes the various challenges associated with conventional formulations and offers tangible benefits for pharma partners, payers, HCPs and, of course, patients:

- For pharma partners, there is now the necessary evidence to demonstrate that MAPs are a safe and reliable dosage form and that adequate patient dosing can be achieved. There are several advantages in terms of custom design too, with both sustained and immediate release options available, as well as flexibility in needle design, length, width and composition. There are also real options for patent protection and brand differentiation, as well as lifecycle management and product extension opportunities. There is also a very clear option to repurpose existing products into a more patient-friendly delivery mechanism.
- For payers, there is a real benefit to MAPs in that they can enable patient self-administration, creating the potential for lower healthcare costs.
- For HCPs, they help to reduce the challenges and threats associated with needlestick injuries.
- For patients, the reduced pain and lower psychological challenge of administering microneedle technologies creates the potential for increased patient compliance and adherence.

ABOUT THE COMPANY

LTS Lohmann Therapie-Systeme AG is a leading pharmaceutical technology company that develops and manufactures innovative drug delivery systems such as transdermal therapeutic systems (TTSs) and oral thin films (OTFs) for the pharmaceutical industry. The company's commercial offering encompasses more than 20 marketed products and a diverse pipeline of more than 30 development projects targeting multiple disease indications. LTS's innovation pipeline contains both partner-funded and proprietary LTS-funded projects. LTS maintains its leading position through the continuous refinement of its core TTS and OTF technologies and by advancing emerging drug delivery technologies, including microarray patches (MAPs) for the intradermal delivery of large molecule, biological actives. LTS has an established dedicated state-of-the-art R&D centre for its parenteral and sterile MAP technology platform, including a GMP area for manufacturing of clinical supplies.

Founded in 1984, LTS operates today from two sites in Andernach (Germany) and West Caldwell (NJ, US), and a representative office in Shanghai (China).

REFERENCES

1. *Fernando GJP et al, "Safety, tolerability, acceptability and immunogenicity of an influenza vaccine delivered to human skin by a novel high-density microprojection array patch (Nanopatch™)". Vaccine, 2018, Vol 36(26), pp 3779–3788.*
2. *Gerstel MS, Place VA, "Drug Delivery Device". US Patent No 3,964,482, 1976.*
3. *Henry S et al, "Microfabricated microneedles: a novel approach to transdermal drug delivery". J Pharm Sci, 1998, Vol 87(8), pp 922–925.*
4. *"WHO Microarray Patch (MAP) Product Development Workshop". Geneva, Switzerland, 2015.*
5. *"Needlestick injuries. Protecting health-care workers – preventing needlestick injuries". WHO website.*
6. *Mannocci A et al, "How Much do Needlestick Injuries Cost? A Systematic Review of the Economic Evaluations of Needlestick and Sharps Injuries Among Healthcare Personnel". Infect Control Hosp Epidemiol, 2016, Vol 37(6), pp 635–646.*
7. *Strasinger C, "Product Development and Quality Considerations for Transdermal Systems and Microneedle Systems: A Regulatory Perspective". PharmaEd Resources, Microneedle Drug Delivery Systems Virtual Conference, Oct 27–28, 2020.*

ABOUT THE AUTHOR

Sebastian Braun has worked in the field of transdermal and dermal drug delivery for 15 years. A molecular biologist with a PhD in analytical chemistry and molecular biology, he started his career at a transdermal drug delivery company, building a fundamental understanding of the biological workings of the skin. Spending the last 15 years at different transdermal and dermal drug delivery companies in various positions, including head of formulation development, head of manufacturing and head of science and technology, he is now focused on microneedle development and manufacturing.

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PHARMA LATCH ANGLED **MICRONEEDLE** PATCH FOR ENHANCED DRUG AND VACCINE DELIVERY

Nicky Bertollo, PhD, Co-Founder and Chief Technology Lead, Ronan Byrne, Co-Founder, and Andrew Muddle, PhD, Advisory Board Member, all of Latch Medical, introduce Pharma Latch – a user-centric angled microneedle patch technology. They discuss its key benefits, such as dramatically increased payload potential, precision, low cost and variable patch-wear times, and highlight how Pharma Latch has the potential to overcome many of the limitations of existing routes of administration for therapeutics and vaccines.

Intradermal delivery holds great promise as an attractive alternative to traditional oral and parenteral routes of administration for the delivery of vaccines and therapeutics, including biologics. Systemic uptake of therapeutics via the dermal blood capillaries has a host of benefits, including avoiding the deleterious effects of first-pass metabolism, rapid drug onset and improved bioavailability of APIs, such as biologics, that are not readily absorbed across the mucosal layers of the gastrointestinal tract. Furthermore, the skin is replete with antigen presenting cells (APCs) and therefore represents an optimal location for the delivery of vaccines (both traditional and novel DNA- and mRNA-based vaccines) in order to elicit an enhanced immune response.

Methods employed to deliver or diffuse drugs into the dermis must compete against the skin's excellent barrier function – and are associated with known limitations as a result. Invasive intradermal injections using hypodermic needles, pen injectors and even needle-free injectors are associated with the potential for discomfort and distress for the patient; have significant requirements around infrastructure, training of personnel and sterile settings; and have the ever-present risk of needlestick injuries. Transdermal patches overcome some of these limitations but are confined to a relatively small number of compounds which are known to be able to successfully permeate the intact outer layer of skin – the stratum corneum – either passively or in combination with permeation enhancers.

> "Pharma Latch is a revolutionary MNP technology that unlocks a delivery solution that addresses a wide variety of drug and vaccine delivery challenges faced by both conventional routes of administration and current MNP technologies."

These and other restrictions have motivated the development of minimally invasive microneedle patch (MNP) technologies which not only overcome many of these limitations but – as noted by the World Economic Forum in its list of Top 10 Emerging Technologies of 2020[1] – have the potential to play a role in transforming healthcare. The enhanced intradermal delivery attributes offered by MNPs have the potential to cater for existing, repurposed or new ranges of compounds not suited to the established routes of administration.

Pharma Latch is a revolutionary MNP technology that unlocks a delivery solution that addresses a wide variety of drug and vaccine delivery challenges faced by both conventional routes of administration and current MNP technologies.

INTRODUCING PHARMA LATCH

Pharma Latch is an easily self-administered, self-anchoring, solid-coated MNP optimised

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Figure 1: Pharma Latch microneedle patch technology. (Image courtesy Latch Medical. Reproduced with kind permission.)

for therapeutic and vaccine delivery (Figure 1). Pharma Latch technology exhibits opposing arrays of angled stainless-steel microneedles (MNs) coated using a proprietary process performed at room temperature which dries instantaneously and is compatible with a range of compounds, including biologics.

Pharma Latch is applied to the skin using a simple and intuitive clicking action. This manual clicking moves the opposing angled MNs towards one another, penetrating the outer skin layers and drawing the skin onto the MNs in a controlled, repeatable fashion. Robust, adhesive-free and instantly reversible attachment to skin can be achieved. This, coupled with inherent tailorability in both design and coating, means that Pharma Latch can facilitate both short- and longer-term patch wear and drug elution times (seconds/minutes/days/weeks) across a range of compound types at much higher payloads than are currently achieved by existing solid-coated and dissolvable MNP technologies.

Key features and benefits of Pharma Latch's technology include:

- **Increased MN surface area available for coating.** When compared with the conventional vertical approach taken by MNPs, the angling of the Pharma Latch MNs – specified for a given depth target in the skin – results in greater surface area available for coating with the API.
- **Superior coating concentration across a range of compound types.** The proprietary coating technology produces coatings at room temperature and without the need for linkers or binders, meaning that APIs may be formulated and deposited at relatively higher concentrations. The process deposits API-containing formulations in uniformly even and thin layers, which preserves MN tip geometry to a greater extent than traditional dip-coating techniques..
- **Increased payload potential.** The combination of these geometry and coating factors can elevate the payload potential of the Pharma Latch far beyond what is currently achieved by solid-coated and dissolvable MNP technologies.
- **Stable coatings.** The proprietary coatings can potentially be stable at room temperature, which removes cold-chain and logistics requirements, facilitating global, remote distribution. Pharma Latch has demonstrated with a number of biological APIs that the coating process does not affect its stability.
- **Robust, adhesive-free attachment.** The unique manner in which the angled MNs interdigitate with and anchor to the skin removes the need for chemical-based adhesives. This also opens up the possibility of long-term patch wear from hours and days up to several weeks – a possibility not achievable using existing solid-coated MNP technologies.
- **Highly user-centric design and ease of use.** The Pharma Latch is applied to the skin using a simple and intuitive manual clicking action and is easily removed. Built-in safety mechanisms prevent accidental deployments, whilst visual, tactile and audible feedback is provided to the user on successful attachment. The user-centric and intuitive design has no training requirements, allowing for administration by minimally trained medical personnel or self-administration by patients.
- **Repeatable, reliable penetration and depth targeting.** Uncontrolled and variable skin deformation occurs during the application of conventional MNPs to skin, resulting in partial, incomplete and highly variable embedding of the full MN height.[2,3] In some cases, only a small proportion (up to 30%) of MN height is routinely exposed to skin.[4] Variable, incomplete MN penetration may potentially reduce payload delivery efficiency for both conventional solid-coated MNPs and dissolvable MNP technologies.[3,5] The unique method of engagement applies subtle traction to skin during deployment, drastically reducing deformation and ensuring near full-length (>95%) exposure of the angled

> "The proprietary coating technology produces coatings at room temperature and without the need for linkers or binders, meaning that APIs may be formulated and deposited at relatively higher concentrations."

MNs to skin.[6] The superior penetration efficiency of Pharma Latch's angled MNs could result in reduced dosing variability, which will be observed in drug absorption measured in the pharmacokinetic data of its products.

- **No reliance on pre-energised applicators.** Many MNP solutions looking to deliver higher payloads need a high-density MN configuration. These need a high-velocity impact onto the skin to aid penetration – requiring a pre-energised applicator. This also limits potential patch size. Pharma Latch's controlled mechanism of engagement with skin removes the reliance on pre-energised applicators and increases the range of permissible patch sizes from 4 cm^2 upwards.
- **Configurable to meet treatment objectives.** The Pharma Latch platform can be readily adapted to meet varied treatment objectives, including human factors considerations, with one- or two-part configuration options to facilitate both short- and long-term wear and delivering low-to-high payloads.

ENGINEERING THE PHARMA LATCH

The Pharma Latch is optimised for skin penetration and adhesive-free attachment. The unique solution ensures that each individual angled MN is repeatably inserted to the same depth in the skin every time in every patient.

Mechanism

Subtle traction is applied to the skin by the opposing arrays of angled MNs keeping the skin taut and dramatically reducing skin deformation during insertion. This novel mechanism of insertion is illustrated in Figure 2. Conceptually, the net effect of these attributes results in skin being drawn up onto the Pharm Latch MNs in a controlled, repeatable fashion.

The mechanism of insertion differs fundamentally from many existing MNP technologies and application techniques (including both manual pressing and high-speed impact using pre-energised applicators) which effectively act to push the skin away from the patch as it is being applied. As mentioned prior, the variability in MN penetration across existing MNPs is well reported in the scientific literature. Importantly, the extent of this deformation can be exacerbated by the anatomical location and integrity of the skin, as well as by subdermal fat.[7] The combination of these patient-related and skin biomechanics factors can be expected to give rise to dosing variability across repeated applications on the same patient (i.e. intra-subject variability) and/or between patients across a population (i.e. inter-subject variability) when treated using conventional MNP technologies.

Repeatability

The Pharma Latch deployment mechanism is designed to produce repeatable MN insertion, independent of skin type or anatomical location. This substantially reduces intra-subject and inter-subject dosing variability risks, which may be observed in pharmacokinetic data. The increased penetration efficiency achieved by the Pharma Latch MNs, derived from a combination of the angled MN geometry and skin insertion mechanics, ensures repeatable,

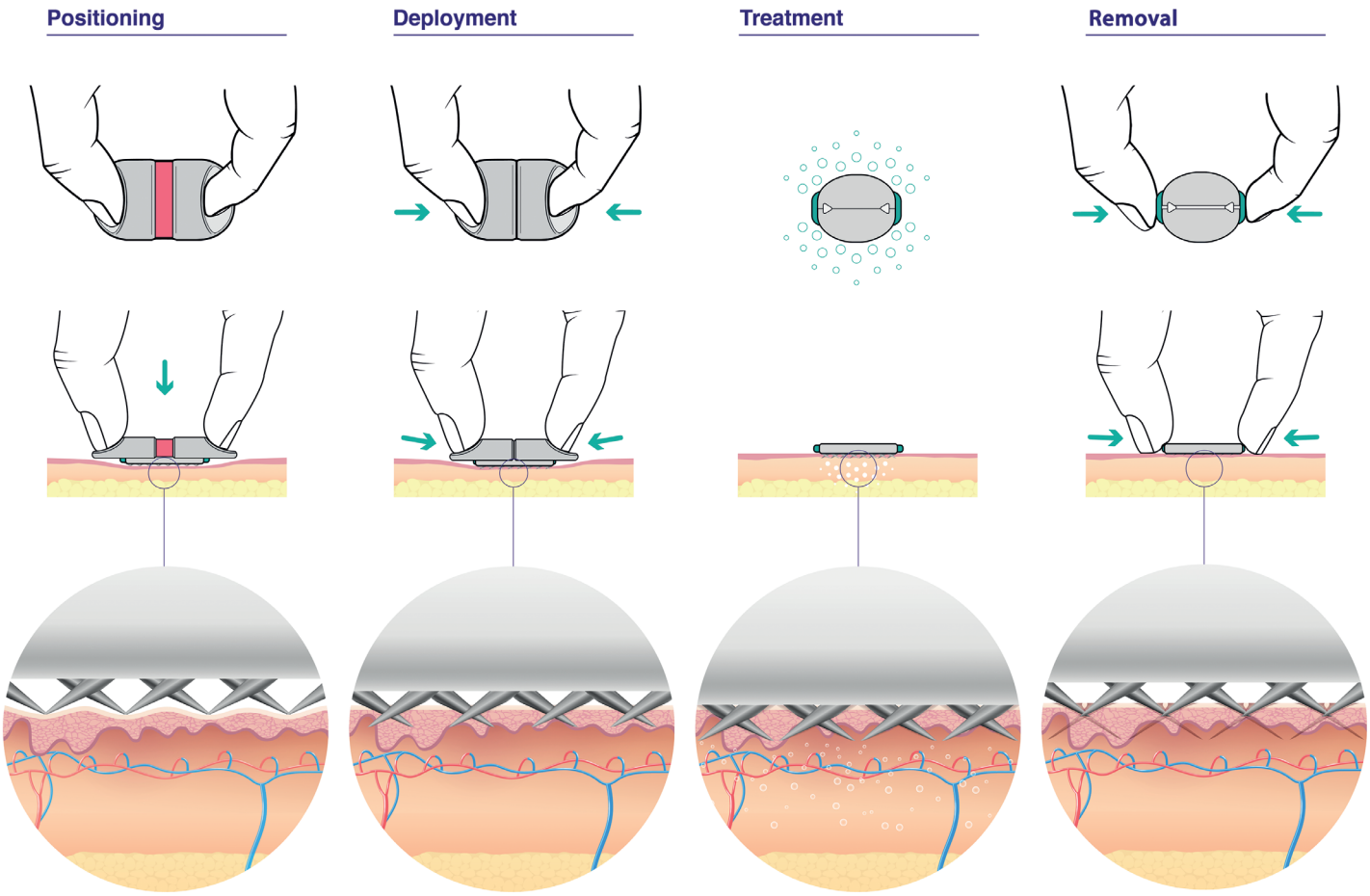

Figure 2: Schematic depicting Pharma Latch's mechanism of engagement, the subsequent release of the API from the fully embedded angled microneedles and the method of removal.

> "The Pharma Latch deployment mechanism is designed to produce repeatable MN insertion, independent of skin type or anatomical location."

near-full-length coated MN exposure and release of API into the interstitial fluid of the skin for systemic uptake.

Manufacturing

The increased MN insertion efficiency of Pharma Latch, coupled with a controlled, manual application action, removes the need to employ costly, high-strength metal alloys. Pharma Latch uses low-cost, surgical-grade stainless steel and can be produced using scalable, low-cost production methods leveraging standard pharmaceutical packaging materials and processes. Coating of the MNs relies on a highly automated process with established high-volume, low-cost techniques.

Tailorability

Pharma Latch is highly configurable and both the core MN platform and coating process can be readily tailored to meet the treatment objectives, in terms of desired payload, release kinetics and wear times. Pharma Latch offers an unsurpassed ability to target specific depths in the skin, owing to its superior penetration efficiency (>95% length penetration),[6] which may be important when treating certain dermatological conditions or administering vaccines. The direct implication of a highly efficient MN insertion is that vertical penetration depth is ultimately governed by the MN geometric parameters and, specifically, the vertical MN tip height from the substrate, which can typically be engineered to be in the range of 250–600 µm or beyond.

The scalable approach to MN fabrication ensures that the Pharma Latch design (i.e. MN geometry, tip height, number and density) is readily customisable to accommodate the desired payload and intended release kinetics of the deposited coating. MN density can be tuned to meet the payload objectives of the specific application, which gives rise to a range of potential Pharma Latch configurations. Pharma Latch makes use of a two-part system (with reloading capabilities) for high-density MN patch configurations supporting high payloads, with the second part increasing the mechanical advantage and promoting usability. A one-part system is available for lower payload, low-MN-density applications.

Coating

Pharma Latch's solid MNs coated with API offer an advantage over dissolvable MNP technologies in that the solid MNs themselves provide the mechanical backbone and requisite strength. This potentially simplifies the mechanical considerations around – and specific requirements of – excipients in a given formulation. This approach, coupled with the method of coating, can simplify the formulation process, whilst simultaneously increasing the range of compound types that can be readily incorporated into the platform.

Payload

The tailorability in the proprietary coating process allows the delivery of payloads far in excess of what is currently being achieved by solid-coated and dissolvable MNP technologies. Combined with the self-anchoring angled MN geometry, this potentially allows Pharma Latch to rival the dosages currently being delivered through more traditional means. As a result, Pharma Latch has the potential to offer a step change in MN-mediated therapeutic and vaccine delivery.

> "Pharma Latch has the potential to offer a step change in MN-mediated therapeutic and vaccine delivery."

FUTURE OUTLOOK

The Pharma Latch technology is technically validated and currently moving towards a number of pre-clinical studies with a range of different compounds and vaccines. The simplicity of Pharma Latch, combined with its payload potential, opens up a variety of new possibilities – both in the MN drug delivery sphere and also in a broader consideration of drug delivery opportunities previously considered out of reach for MNP technologies.

The company is actively seeking collaborations with companies looking to develop novel products which meet currently unmet patient needs – be they existing compounds or vaccines, generic APIs looking to differentiate through the 505(b)(2) route of registration in the US or new compounds or vaccines looking to be delivered intradermally, be they small molecules, vaccines or biologics.

ABOUT THE COMPANY

Latch Medical is a venture-funded company with a platform microneedle technology. The technology is centred on opposing arrays of angled microneedles that can penetrate the outer layers of the skin in a manner ensuring consistent needle penetration and without the use of any adhesive. The platform can be used in a number of different applications, including drug delivery, biosensing and wearables. In 2019, Pharma Latch was awarded a substantial grant by the Irish government. A rapid development plan ensued, allowing the Pharma Latch technology to progress.

REFERENCES

1. *"Top 10 Emerging Technologies of 2020". World Economic Forum, November 10, 2020.*
2. *Römgens AM et al, "Monitoring the penetration process of single microneedles with varying tip diameters". J Mech Behav Biomed Mater, 2014, Vol 40, pp 397–405.*
3. *Donnelly RF et al, "Optical coherence tomography is a valuable*

tool in the study of the effects of microneedle geometry on skin penetration characteristics and in-skin dissolution". J Control Release, 2010, Vol 147(3), pp 333–341.

4. *Nguyen J et al, "Pharmacokinetics and Skin Tolerability of Intracutaneous Zolmitriptan Delivery in Swine Using Adhesive Dermally Applied Microarray". J Pharm Sci, 2018, Vol 107(8), pp 2192–2197.*
5. *Arya J et al, "Tolerability, usability and acceptability of dissolving microneedle patch administration in human subjects". Biomaterials, 2017, Vol 128, pp 1–7.*
6. *In vitro and In vivo preclinical animal model testing data on file with Latch Medical.*
7. *Kochhar JS, Quek TC, Soon WJ et al, "Effect of microneedle geometry and supporting substrate on microneedle array penetration into skin". J Pharm Sci, 2013, Vol 102(11), pp 4100–4108.*

ABOUT THE AUTHORS

Dr Nicky Bertollo, PhD, is the inventor of the Pharma Latch angled microneedle platform technology and a medical device innovator. He has over 15 years' experience in the design, development, preclinical testing and evaluation of medical devices and technologies, publishing more than 40 research articles from this work. He has more than 25 issued or pending patents which have been licensed to multiple start-up companies, including Latch Medical, which he co-founded.

Ronan Byrne is a highly experienced Chief Executive Officer and commercial leader of multiple companies over the last two decades. His speciality is commercialising innovative medical technologies. He founded, built and led the development of an ophthalmic diagnostics company – ClearSight Innovations – which was sold to a global industry leader in 2015. Mr Byrne acts as an evaluator and panellist for organisations such as Enterprise Ireland and is an advisor and mentor to multiple life sciences companies.

Dr Andrew Muddle, PhD, Advisory Board Member at Latch Medical, is a transdermal and topical drug delivery expert who was a founder and Chief Executive Officer of MedPharm, a UK-based contract provider of topical and transdermal delivery solutions. This company was partially acquired in 2018 and Dr Muddle remains on the board. He has spent over 30 years in the pharmaceutical industry in the drug delivery area.

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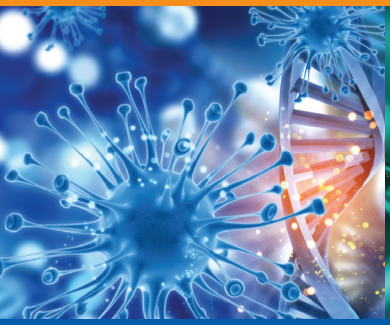


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MEDICSEN: NEEDLE-FREE SMARTPATCH FOR PAINLESS DRUG DELIVERY

In this article, Eduardo W Jørgensen, MD, Chief Executive Officer, Juan César de Mercado, Chief Operations Officer, and José Carlos Montesinos, Chief Technology Officer, all of Medicsen, describe the Smartpatch, a novel technology for subcutaneous delivery of drugs via a comfortable, pain-free patch using sonophoresis, based on Medicsen's patented miniaturised ultrasound technology.

DRUG DELIVERY IS A PROBLEM

There is a clear market trend in drug delivery pointing towards products that deliver greater comfort, control and standardisation. However, the traditional market remains focused on painful and uncomfortable needles and pumps, with new innovations having major drawbacks, such as iontophoresis devices that only work with small, charged molecules or the formulation hurdle of needing to modify the drug for different, less painful methods of administration like inhalation.

There are over 16 billion injections per year, each creating biowaste and over 2,000 needlestick injuries per day in the US, generating over US$3 billion (£3.2 billion) in associated costs every year. The World Health Organization has called for a global effort on smart injectors to reduce the problems associated with traditional needle-based injections, and the transdermal pathway has a promising future as first choice for the delivery of most molecules. However, there have been major challenges in the drive to develop wearable, connected and painless transdermal devices that could be used with virtually any drug.

Figure 1: Medicsen's Smartpatch..

> "Medicsen's research suggests that the only efficient approach towards a universal needle-free device is through sonophoresis, but this technique has traditionally required large devices with significant power demands."

Microneedles offer limited benefits and are hardly controllable, jet-injectors are painful and bulky, and implants can be unsafe for certain drugs. Medicsen's research suggests that the only efficient approach towards a universal needle-free device is through sonophoresis, but this technique has traditionally required large devices with significant power demands. To improve the viability of sonophoresis, Medicsen has centred its R&D efforts on optimising ultrasonic skin stimulation for drug delivery and enclosing the technology in an intuitive and comfortable device.

MEDICSEN´S SMARTPATCH

The Smartpatch is a wearable, needle-free drug delivery device based on Medicsen's patented skin permeabilisation technology (Figure 1). Medicsen's specific combination of ultrasonic waves creates a transitory disorganisation of the stratum corneum of the skin. This allows macromolecules of up to 2,000 kDa (e.g. heparin, insulin, interferon, antibodies, vaccines) to cross the skin barrier without the patient experiencing pain or other abnormal feelings. Permeability is only present while the device is activated, with skin returning to normal shortly after stopping stimulation.

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The specific ultrasound setting is slightly adapted to each patient by the Smartpatch to optimise performance in different skin types. Changes to the ultrasound settings also allow the device to modify the absorption rate and depth reached by the drug. Medicsen's tests have shown absorption rates of 0.05–0.2 mL/minute on a 1 cm^2 pig skin area. Drug penetrates through the skin, reaching the hypodermis, and then diffuses to the capillary vessels and circulatory system following the same pharmacokinetics and pharmacodynamics of the drug with its original delivery method (subcutaneous or intradermal).

In short, the Smartpatch uses sonophoresis, an alternative delivery methodology, for the proven subcutaneous administration route. It could be described as a syringe with no needle or a pump with no catheter. It provides painless, wearable and controllable drug delivery (Figure 2).

Figure 2: Smartpatch and accompanying phone app.

"The specific ultrasound setting is slightly adapted to each patient by the Smartpatch to optimise performance in different skin types. Changes to the ultrasound settings also allow the device to modify the absorption rate and depth reached by the drug."

The device involves two major components:

- A durable, reusable part that contains the electronics and ultrasound generators. Medicsen and its research partners, such as CSIC (Spanish National Research Council, Madrid, Spain), made possible this state-of-the-art technology by reducing the size and power consumption of the ultrasound actuators, which was a necessary step towards a truly wearable device.
- A disposable piece with biocompatible reservoirs for containing the drug and hypoallergenic adhesive that can be replaced in less than two minutes. Reservoirs can be loaded by the patient using traditional drug presentations, such as vials and syringes.

The Smartpatch is designed to last for up to 24 hours in full operation; the drug reservoir can hold 2 mL of drug per cm^2 of skin to be stimulated. This capacity means that Smartpatch is capable of delivering most subcutaneously administered chronic daily treatments, such as insulin or interferon. The device can be operated from a Smartphone app, via a Bluetooth connection, but is also operable using the physical buttons on the device itself.

How It Works

The Smartpatch is operated using four simple steps (Figure 3):

1. **Load:** Users inject their drug into the reservoir using a traditional syringe
2. **Insert:** The disposable piece is inserted in the durable part of the Smartpatch device
3. **Place & Activate:** The device is attached to the body via its adhesive or elastic band. The dose can be selected on the device or on the app
4. **Detach:** The reservoir is ejected by pressing a button and then disposed of for recycling.

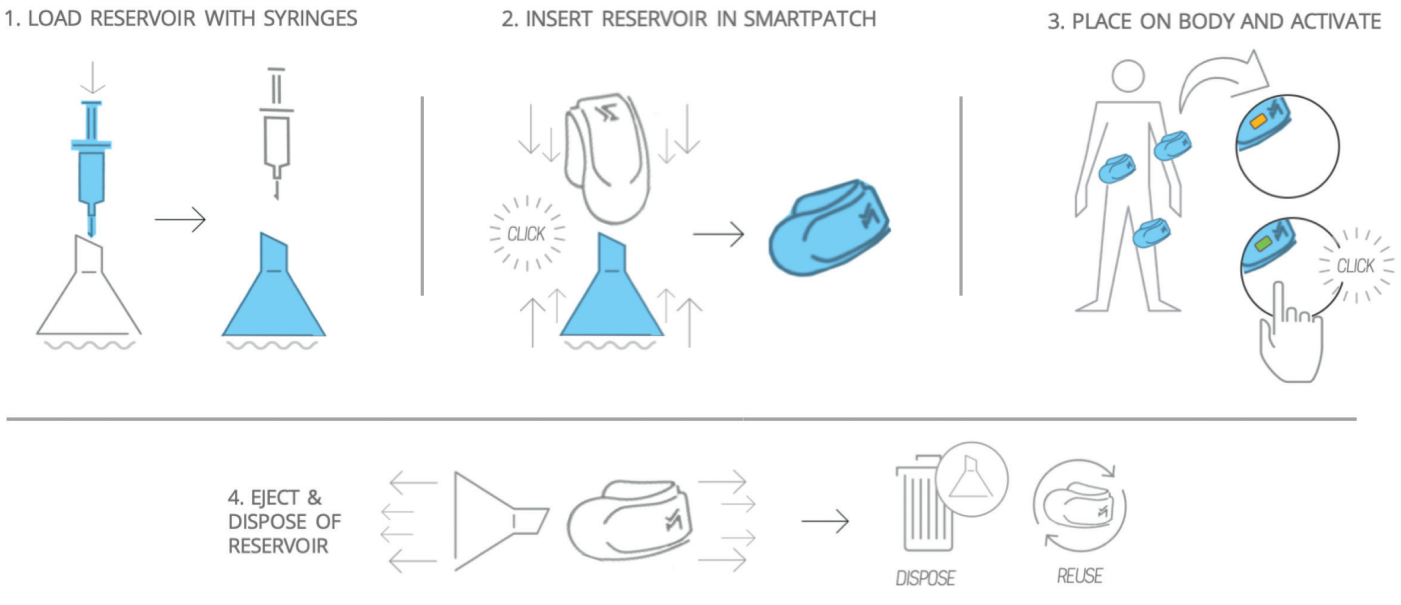

Figure 3: How the Smartpatch works.

CURRENT STATE AND TRIALS

Medicsen's Smartpatch is currently an *in vivo* working prototype undergoing miniaturisation to reach its final version. Getting to this stage has required over three years of trials, moving from the basic science to development of the full prototype.

Medicsen has chosen to focus on insulin as the first molecule to validate with the Smartpatch, since improving treatment for diabetes is core to Medicsen's identity and, given the prevalence of diabetes in society, a successful, pain- and needle-free insulin delivery method will have a huge impact. Medicsen conducted hundreds of *in vitro* trials with insulin and ultrasound on pig skin with the aim of demonstrating:

- **Permeability:** Density of energy, flow rate, conductance, timings, etc
- **Skin Safety:** Absence of damage to the pig skin, tested by electronic microscopy and enzyme-linked immunosorbent assay (ELISA) of tumor necrosis factor alpha (TNF-α) and interleukin-2 (IL-2)
- **Insulin Safety:** High-performance liquid chromatography (HPLC) and circular dichroism studies show conserved bioactivity and structure
- **Replicability:** The ability to replicate the studies with alternative molecules, such as interferon.

Following positive results in the final *in vitro* trials, Medicsen prepared and completed *in vivo* animal trials in 2020 during the global pandemic. The pig trials have projected the optimal parameters for

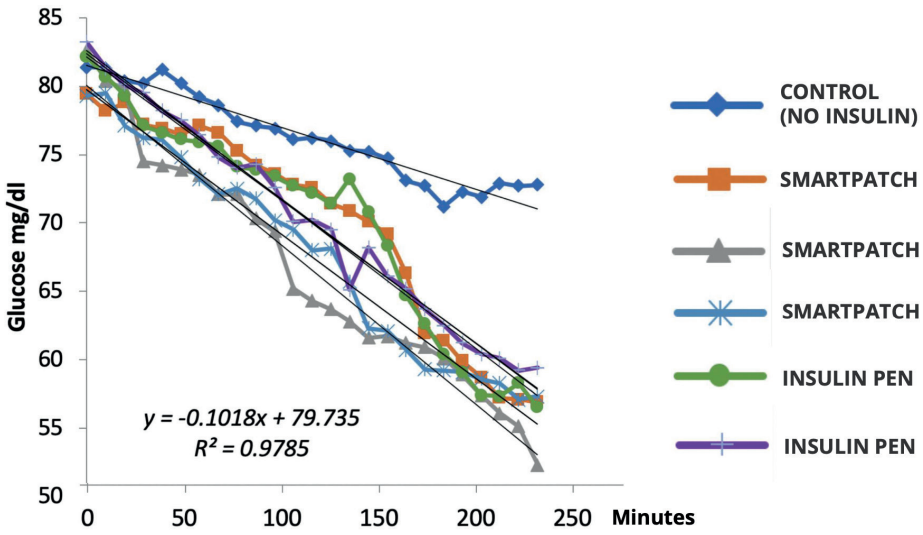

Figure 4: Glucose reduction in pig trials.

device configuration and confirmed the safety, absorption efficacy and correct functionality of the Smartpatch, allowing Medicsen to decrease the risk in upcoming *in vivo* human trials.

Medicsen performed individual pig trials with sus scroffa (landrace) pigs, which had their blood glucose measured before and after administering a controlled dose of insulin (25 units) with both the Smartpatch and a traditional insulin Novorapid® pen (Novo Nordisk, Bagsværd, Denmark). The test results showed an average slope of the glucose reduction curve of -0.09 with the Novorapid® pen and -0.10 with the SmartPatch (Figure 4), which proves that Smartpatch is as effective as an insulin pen when delivering insulin. Safety concerns have also been waived since there was no evidence of conduct alteration on the pigs, no signs of tissue damage upon dermatoscopic examination and no toxic by-products on the analysis of the post-administration skin's exudate.

POTENTIAL APPLICATIONS

As the market moves towards standardisation, Medicsen focused on building a device that could work with as many drugs as possible and as both an injector and an infuser, creating the possibility of reaching agreements with pharmaceutical stakeholders in different verticals. Medicsen envisions the use of the Smartpatch for chronic diseases that require daily or weekly subcutaneous delivery of macromolecules, such as multiple sclerosis, but also for punctual on-site injections, such as vaccine delivery, or even to optimise delivery of cosmetics to the optimal layer of action (Figure 5).

Figure 5: Different Smartpatches for different molecules.

With positive results in animal trials, Medicsen is on the way to succeed in human trials in 2021 and disrupt the drug delivery landscape shortly after. This makes now the perfect time to get in touch and secure a partnership with the Smartpatch.

ABOUT THE COMPANY

Medicsensors SL is a technology start-up, located in Madrid (Spain), founded in 2015. The story of Medicsensors started when a 10-year-old girl with diabetes rejected an insulin pump in a hospital in front of Dr Jørgensen due to the insulin delivery method.

> "Medicsen envisions the use of the Smartpatch for chronic diseases that require daily or weekly subcutaneous delivery of macromolecules, such as multiple sclerosis, but also for punctual on-site injections, such as vaccine delivery, or even to optimise delivery of cosmetics to the optimal layer of action."

Since then, Medicsensors has been committed to shaping the future of drug delivery and chronic disease management, initially oriented towards improving the control of diabetes and patients' quality of life and then moving towards standardising treatment methodology for chronic disease management with a multi-award-winning and patented technology.

ABOUT THE AUTHORS

Eduardo Jørgensen, MD, has led various projects since he studied medicine at university, creating and guiding teams to solve complex tasks through lean start-up-based R&D. Instead of clinical practice, he focused on leadership and technological healthcare innovation with the goal of improving quality of life for millions of patients. He is a passionate and creative problem solver who has persevered through the initial phases of creating businesses and validating technological assets until market entry.

Juan César de Mercado is a telecommunications engineer with experience in databases and signal analysis. Mr Mercado has a desire to make things easier and safer through technology and strives to reach the latest technological methodologies and their practical application. As well as experience as a data analyst and database technician, he has also held management positions that have given him operational experience.

José Carlos Montesinos holds a degree in Telecommunications Engineering from Universidad Politécnica de Madrid (Spain) and a Master's degree in Biomedical Engineering from the same university. Mr Montesinos has experimented with ultrasound on several occasions throughout his career, combines management skills with deep technological understanding, brings five-plus years of experience in the development of combined hardware and software, and has been co-founder of previous award-winning IT companies.

Nemera

ENSURING FORMULATION PROTECTION AND PATIENT CARE WITH AIRLESS DISPENSERS

In this article, Audrey Chandra, Category Project Manager, Manuela Basso, Communications Manager, and Raphaële Audibert, Global Category Manager, Inhalation and Dermal, all at Nemera, consider Nemera's holistic approach to dermal drug delivery, explaining why airless technology is important for dermal pharmaceutical applications.

INTRODUCTION

Dermal application is a non-invasive way to administer solutions, lotions, gels or creams on the skin. It is used as a drug delivery path to target different parts of the body.

The first, and most common, target is the upper layers of the skin itself to treat dermatological conditions such as acne, atopic dermatitis or psoriasis. Acne, as an example, is estimated to affect 9.4% of the global population, making it the eighth most prevalent disease worldwide, according to the British Association of Dermatologists.

The second target is the bloodstream, known as "transdermal systemic delivery", whereby gels or creams are absorbed and circulated into the whole body through the bloodstream. The main examples here are hormone replacement therapy (HRT) for women with menopausal symptoms or men with hypogonadism.

The third target is the underlying tissues below the skin layers for the application of anti-inflammatory treatments directly to the source of the problem, most commonly aching knee, elbow and shoulder joints. Here, the drug is absorbed through the skin into the muscles and tendons below.

DERMAL DELIVERY DEVICES FOR PHARMA APPLICATIONS

Both cosmetics and dermal pharmaceuticals use the skin as their point of access, but there is a world of difference in the way they are regulated and manufactured.

> "For pharmaceutical applications, the dispensers must be suitable to contain drug formulations and ensure that the treatment delivery to the patient is consistent."

For pharmaceutical applications, the dispensers must be suitable to contain drug formulations and ensure that the treatment delivery to the patient is consistent.

Very few can fulfil these requirements. They can be identified by their compliance with regulatory standards specific to packaging of medicinal products and medical devices.

This is essential to ensure that both the formulation and its container are safe and easy to use for patients. Some dermal delivery devices are airless, which ensures the formulation is not in contact with air.

With some of the treatments, the formulations they contain are very sensitive and need to be perfectly protected to remain stable. When you press down on the pump of, for example, a soap dispenser, you have air that enters the bottle when the product is dispensed, but that does not happen with airless devices. This allows patients to use the device in any position, and allows the pharma company to avoid overfilling, as most of the formulation is delivered from the device.

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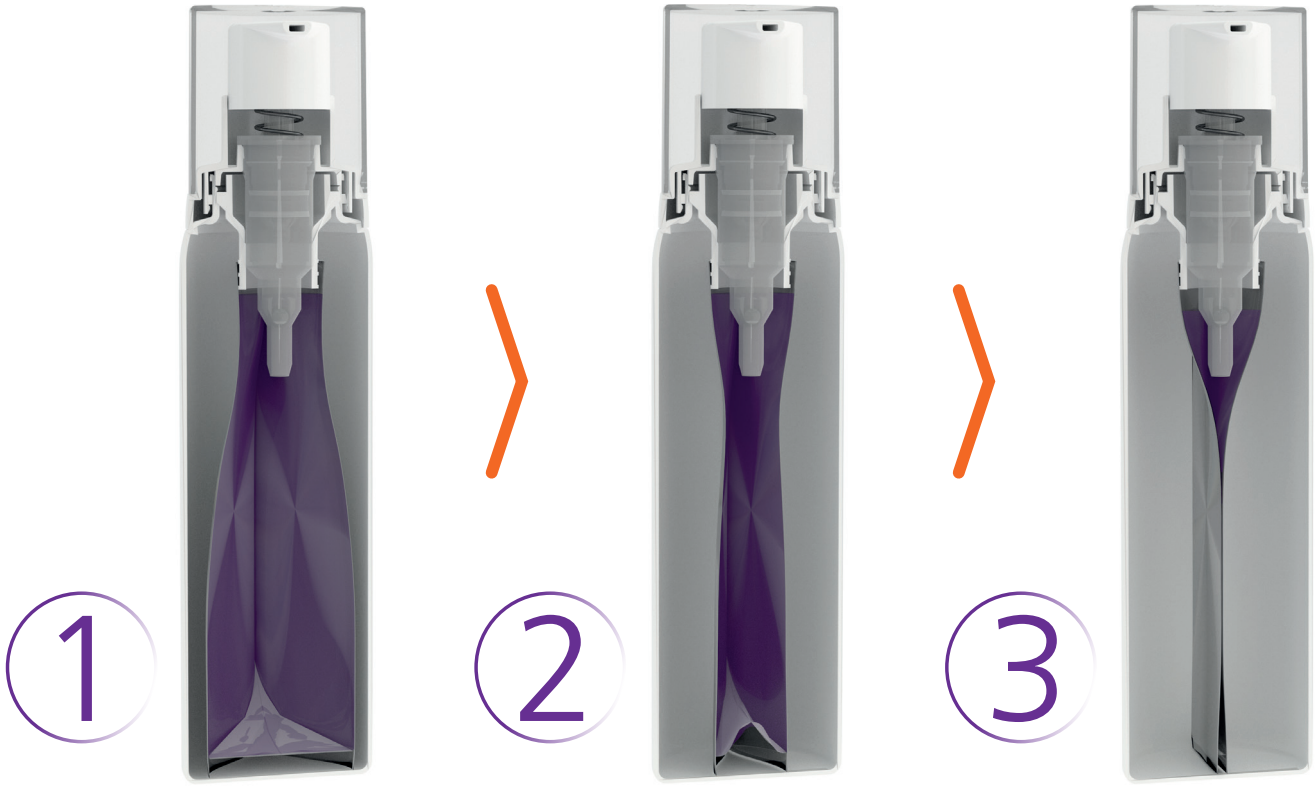

Figure 1: Sof'Bag® pouch collapsing during product life.

NEMERA'S LONG-STANDING EXPERIENCE IN DERMAL

Nemera has been working in the dermal field for the past two decades, producing airless devices used by some of the biggest pharmaceutical companies in the world, and is a leader in the systemic transdermal gel and cream market.

The company provides an end-to-end service, helping customers navigate their device strategy for both novel and platform solutions, including technical support for drug filling, and the submission of registration dossiers to the appropriate regulatory authorities.

This holistic approach and integrated front-to-end services enable Nemera to innovate within every development phase of its products and ultimately deliver solutions to meet patients' needs.

> "This holistic approach and integrated front-to-end services enable Nemera to innovate within every development phase of its products and ultimately deliver solutions to meet patients' needs."

Compliant with the most demanding regulatory standards specific to packaging of medicinal products and medical devices, Nemera's devices are well suited to topical or systemic drugs such as local anaesthetics, anti-inflammatories, hormones, antibiotics, antifungals or counterirritants for the skin.

The first treatment launched with a Nemera device was for cold sores and today millions of patients rely on its precise delivery systems for a wide range of topical and systemic conditions in the dermal drug delivery field alone.

Nemera focuses on addressing patients' needs by developing and producing high-end devices as well as on giving the pharmaceutical companies all the technical support they might need along the way.

The airless device Sof'Bag® was developed in the same spirit.

SOF'BAG®: THE AIRLESS POUCH-IN-BOTTLE TECHNOLOGY FOR SENSITIVE FORMULATIONS

Sof'Bag® was designed to ensure that patients receive a consistent treatment as a result of precise and reliable dosing, which is especially critical when applying formulations for systemic treatments.

It is an airless packaging solution for prescription (Rx) and over-the-counter (OTC) formulations for dermal and transdermal applications composed of an aluminium-based collapsing pouch encased inside a rigid bottle surrounded by a metered pump dispenser (SP943).

> "Sof'Bag® is suitable for solutions, lotions, gels and creams, even the most sensitive ones. Thanks to its multi-layer, collapsible, aluminium pouch technology, formulations are highly protected from oxidation, light and moisture."

Each actuation delivers a precise metered dose of formulation, which is dispensed out of the pouch as shown in Figure 1. No air enters into the pouch during this process.

Sof'Bag® is suitable for solutions, lotions, gels and creams, even the most sensitive ones. Thanks to its multi-layer, collapsible, aluminium pouch technology, formulations are highly protected from oxidation, light and moisture.

With 360° delivery due to its airless property, the Sof'Bag® makes treatment administration more convenient for patients. In addition, very little of the product is wasted – more than 95% of the contents of this "pouch-in-a-bottle" can be extracted.

Figure 2: A patient using Sof'Bag®.

Figure 3: A patient using Sof'Airless XS.

Sof'Bag® is also fully customisable and it is possible to modify cap and bottle colours, shapes and sizes, or to add new functions (dose counter, electronics features, etc.) (Figure 2).

SOF'AIRLESS XS: THE AIRLESS PISTON TECHNOLOGY

Sof'Airless XS is the solution for trial sizes or local treatments with very little skin surface to cover: a protective mini-airless system for small dose applications and sampling.

Sof'Airless XS targets Rx and OTC dermal gels and creams. It is compact and portable (2 mL size) and can be used in any position. The airless piston technology allows the formulation to be dispensed out of a rising piston upon pump actuation.

Sof'Airless XS is already used for the treatment of cold sores (Figure 3).

ABOUT THE COMPANY

As a world-leading drug device combination solutions specialist, Nemera's purpose of putting patients first enables it to design and manufacture devices that maximise treatment efficacy.

Nemera is a truly holistic partner that helps its customers succeed in the sprint to market. From early device strategy to state-of-the-art manufacturing, the company is committed to the highest quality standards.

Agile and open-minded, Nemera works with its customers as colleagues, going the extra mile together to fulfil their mission.

ABOUT THE AUTHORS

Audrey Pamila Chandra is the Category Project Manager at Nemera. She joined Nemera in 2019. Ms Chandra graduated from the Faculty of Medicine Universitas Atma Jaya Indonesia and pursued her Master's degree in Strategy and Business Development at Toulouse School of Management, France. With her dual competence asset, she is in charge of providing strategic support for various targeted marketing projects and working on diverse content along with communication activities coordination.

Manuela Basso is an experienced communications professional, with a journalism and marketing background. Ms Basso holds a European Master in Management and specialised in International Marketing. She has been working at Nemera for six years, developing effective communications to support Nemera's overall vision and mission: to put patients first.

Raphaële Audibert holds a Biomedical Engineering degree from ISIFC (Besançon, France). Ms Audibert has worked in the medical device industry as a project manager for five years, where she led the development of a surgical instrument set for neurosurgery. Ms Audibert joined Nemera in 2016 as Category Manager for Inhalation and Dermal. Since then, she has helped identify the needs of tomorrow and in building the franchise strategies.

Nemera

Sof'Bag®

The airless solution for your sensitive formulations

We are the utmost **holistic partner** and help our customers succeed in the **sprint to market.**

From **early device** strategy to **state-of-the-art manufacturing,** we're committed to the highest **quality standards.**

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Logan Instruments' Transdermal Testing Portfolio

Logan Instruments is a leading provider of laboratory instrumentation to the global pharmaceutical and cosmetics industries, with a focus on physical, dissolution and transdermal testing systems.

Its pioneering transdermal testing system offering includes:

- System 913-12 (Figure 1), an automated 12-position transdermal diffusion cell system that contains two FDC-6TA vertical transdermal diffusion testers, an SCR-DL sample collector, dual SYP-12L-10mL syringe pumps and a DSC-800 system controller.
- FDC-6TA (Figure 2), a water jacket vertical transdermal diffusion cell system.
- C&D 360 (Figure 3), a patch coating and drying system that can evenly apply a patch ingredient on release liner by using a dual-peak-blade.
- System 914-12 (Figure 4), an automated dry heating transdermal system that contains two DHC-6T dry heat transdermal diffusion testers; a SCR-DL sample collector; dual SYP-12L-10mL syringe pumps and DSC-800 system controller.
- DHC-6TD (Figure 5), a dry heat transdermal diffusion system that is designed to test *in vitro* permeation rate for semi-solid dosage and topical drug formulation.

"Logan Instruments is a leading provider of laboratory instrumentation to the global pharmaceutical and cosmetics industries, with a focus on physical, dissolution and transdermal testing systems."

Figure 1: System 913-12 automated transdermal diffusion cell system.

Figure 2: FDC-6TA vertical transdermal diffusion cell system.

Figure 3: C&D 360 patch coating and drying system.

VALUE ADDED SERVICES

Technical Services

To reduce the downtime of faulty machines and ensure consistent daily operations, Logan Instruments offers annual or biannual preventative maintenance, and troubleshoots and repairs instruments as required. Other technical services include: new instrument installation; upgrading and modification; customisation.

Compliance Services

To meet the stricter requirements of the US FDA 21 CRF Part 11, CFDA and GMP of the EU regarding data storage, security, consistency and audit tracking, Logan Instruments' customers benefit from software that provides database management functions. Compliance services include: installation qualification (IQ); operation qualification (OQ); performance confirmation (PVT); and associated bespoke services.

Training

Logan Instruments has experts within its service teams in the US and Asia/Pacific who provide customers with instrument operation training, customer sample testing, and experimental methodology application services.

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Figure 4: System 914-12 automated dry heat transdermal system.

Figure 5: DHC-6TD dry heat transdermal diffusion system for semi-solid formulations.

AIRLESS DRUG DELIVERY: WIDELY ACCEPTED, ACCESSIBLE AND AVAILABLE

In this article, Stefan Hellbardt, PhD, Vice-President Business Development and Scientific Affairs at Aptar Pharma, reflects on the role of Airless technology in the dermal drug delivery market and the benefits it offers.

For those closest to the dermal drug delivery market, using Airless devices to dispense dermal therapies is not a new concept. Although a widely recognised device technology with clear benefits around safety, reliability, convenience and patient experience, Airless has not yet witnessed the universal adoption one would have expected.

In this article, we will review the current state of the dermal market in terms of dispensing solutions and offer a macro environmental view, both from a consumer and regulatory perspective.

We will then discuss the benefits of Airless technology, specifically regarding dermal drug delivery, and consider the perceived challenges associated with this delivery technology. We will look to dispel the concerns around complexity, development time and cost by demonstrating the capability Aptar Pharma offers to support pharma clients through the drug development pathway to regulatory approval, customer product launch and lifecycle management, including the potential for differentiation for legacy therapies.

Finally, we will consider the connected technologies that are available to enhance patient adherence and support a vision of digital health for pharmaceutical companies, healthcare providers and consumers in the dermal space.

> "Dermal drug delivery provides many obvious advantages over other routes of delivery, including an improved patient experience, reduced risk of error during self-administration and flexible dosing in response to symptom variation and flaring, both of which are common in most dermal conditions."

Dermal and transdermal drug delivery has been an attractive area for some time, with an increasing number of drugs being delivered via this route, including conventional small-molecule drugs, macromolecules and, more recently, products associated with microbiome therapy.

Dermal drug delivery provides many obvious advantages over other routes of delivery, including an improved patient experience, reduced risk of error during self-administration and flexible dosing in response to symptom variation and flaring, both of which are common in most dermal conditions. When supported by premium product design and a quality user experience, these combined benefits may result in improved patient compliance, especially for long-term treatments.

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Furthermore, dermal administration introduces the possibility of local (dermal) and systemic (transdermal) delivery, enabling the drug to be targeted to the area of disease, while avoiding drug peaks and systemic side effects, or preventing hepatic first-pass metabolism and gastrointestinal tract problems, respectively.

PREMIUM BRAND DIFFERENTIATION AND SUSTAINABILITY ARE DRIVING GROWTH IN AIRLESS APPLICATIONS

The overall Airless packaging market is expected to reach a market size of *circa* US$5.66 billion (£4.16 billion) by 2025, with 34.55% of that share attributable to Europe.[1] North America will represent 29% and Asia-Pacific just under 23%. While the personal and home-care sectors command the lion's share of the market, pharmaceutical applications are growing in size, with the sector forecast to be worth *circa* $1.59 billion (£1.17 billion) by 2025. Topical medicines will represent nearly 50% of that total, with an average compound annual growth rate (CAGR) of 4.29%.

The same market report also predicts that Airless packaging for pharmaceutical applications will grow by 3.7% between 2019 and 2025, however, this growth rate is well below the anticipated growth in cosmetics and skincare. Why is that?

The rise in demand for Airless drug delivery devices is fuelled by increased research and development activity, with companies looking to exploit the protection that Airless technology provides against environmental influences, safeguarding the quality and integrity of the packaging during storage, shipment and delivery. In addition, Airless devices present an appealing choice for pharmaceutical brand owners seeking drug delivery and packaging options that deliver differentiation, premium brand appeal and patient-centric design – while also addressing the challenge of sustainability by avoiding content wastage.

THE IMPORTANCE OF CUSTOMER CHOICES

As a leader in Airless dispensing technology, with an unrivalled number of pharmaceutical customer references, Aptar Pharma is deeply invested in dermal drug delivery. As part of its ongoing efforts to understand patient concerns for treating skin disease, whilst also aiming to leverage the benefits of Airless drug-delivery technology, the company commissioned proprietary consumer research to investigate this subject.[2] Designed to establish the issues and concerns of target consumers regarding current packaging, the focus groups were made up of regular users of both prescription and over-the-counter tube-packaged topical treatments for acne, dermatitis and psoriasis. All candidates were presented with a choice of Airless dispensing systems and tube-packaged products and asked to provide feedback on how the differing methods compared for everyday dermal drug administration.

Acknowledging that tubes are the most common way of administering dermal drugs, the lack of choice in packaging noted by participants was one stark finding from the research. While evaluating tubes as a delivery mechanism, the group also found it was hard to fully evacuate the product; it was often messy (with leaks and dried-out product), it seemed unhygienic and it was difficult to control the amount dispensed. In addition, attendees highlighted their fear of spillage and leakage from tubes when stored in bags or luggage – a concern that compelled many users to add an additional layer of secondary packaging to avoid unintentional damage.

In contrast, Airless systems were favoured due to their apparent robustness, dosing convenience and differentiating appearance. At first, the group was unsure of how to fully empty the airless system – a real frustration for consumers of premium products and medicines packaged in tubes. However, once this was explained, there was unanimous agreement that Airless dispensing was the preferred option due to the complete bottle evacuation. Appreciating the benefits of Airless dispensing products, the majority of our research participants were open to considering premium priced products, if given the choice.

"Airless devices present an appealing choice for pharmaceutical brand owners seeking drug delivery and packaging options that deliver differentiation, premium brand appeal and patient-centric design – while also addressing the challenge of sustainability by avoiding content wastage."

"Candidates in the study said: I like pumps better than the tube. I've had medication in a pump before, and I just find it's less messy. And more convenient. And quicker. Usually when I'm in a rush. I have kids, I'm on the run, you know? I pump psh-psh-psh and go. I like that [the Airless system] gets every drop."

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THE PRINCIPLES AND BENEFITS OF AIRLESS TECHNOLOGY

While Airless technology is necessarily sophisticated, the principle is actually very simple: it ensures that after filling and closing the system, there is no air contact with the drug product until it is dispensed. It is the moving piston or collapsing pouch/tube that compensates for the evacuated content, rather than incoming air (Figure 1). This makes Airless systems ideal for both liquid and semi-solid formulations. Both metered and non-metered Airless systems are available.

By preventing air from entering the packaging, Airless drug delivery systems protect against a variety of environmental influences, including oxygen, light, moisture and dirt, supporting a longer shelf-life for sensitive drug formulations. Critically, the robust nature of the plastic container mitigates the risk of leakage during transport.

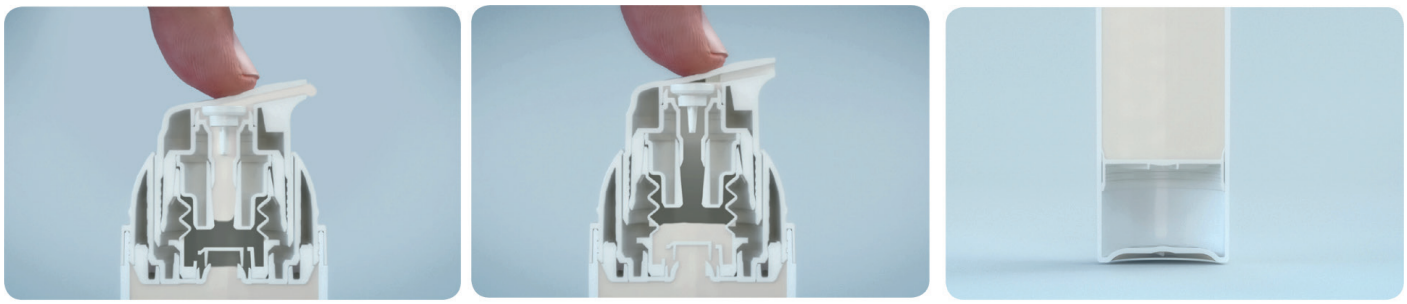

Figure 1: The principles of Airless piston technology.

REGULATORS ARE SHAPING THE AIRLESS LANDSCAPE

The implementation of the new US Pharmacopeia (USP) <661>, "Plastic Packaging Systems and their Materials of Construction", dated November 2020, will have an impact on all current and future drugs on the US market. Discussions between Aptar Pharma and pharmaceutical packaging experts concur that it makes perfect sense for the packaging of topical dermal drugs to transition from food-grade to medical-grade resins, supporting pharmaceutical partners with a compendial test package and increased documentation. With the EU Medical Device Regulation (MDR) coming into force in early 2021, similar requirements are expected to be introduced in Europe and it is not unreasonable to expect future guidance to become increasingly robust, bringing dermal drug delivery packaging in line with drug delivery systems for other administration routes. As recent experience shows, medication delivered via Airless systems are designated as drug-device combination products, requiring additional device-related documentation and testing as demanded by the 21 Code of Federal Regulations 820.30 in the US and the EU MDR.

> "Aptar Pharma has embraced the changing regulatory and market landscape to deliver Airless+: a new product and service portfolio that is redefining dermal drug delivery."

This reshaping of the landscape requires delivery device manufacturers not just to engineer products from new materials, but also to provide a whole new level of support, including design development records, analytical testing, regulatory support, GMP-related and additional manufacturing traceability. Increasing levels of expertise and service are required from drug delivery device partners so that they can effectively address the very specific demands of pharmaceutical companies in their effort to gain market access in different regions.

MEETING THE GROWING MARKET AND REGULATORY NEEDS HEAD ON

While the overall Airless market demands premium brand differentiation and consideration of issues relating to environmental sustainability, Aptar Pharma's pharmaceutical partners have some additional, more specific demands of dermal delivery technologies, primarily around safety, reliability and convenience.

And so, as a market leader, Aptar Pharma has embraced the changing regulatory and market landscape to deliver Airless+: a new product and service portfolio that is redefining dermal drug delivery (Figure 2). The Airless+ range is made up of devices engineered entirely from medical-grade resins complemented by a comprehensive set of services and documentation. With the addition of the company's deep understanding of the evolving regulatory and consumer landscape in different regions, Aptar Pharma is able to de-risk and accelerate the drug development projects led by its pharmaceutical partners in the Airless device space.

When it comes to safety, we know that pharma partners want protection for their formulation and for their patients. To answer this, Airless+ employs the moving-piston principle, in combination

Figure 2: Airless technology is suitable for various purposes, formulations and applications.

with Aptar Pharma's proprietary bellows-pump technology, to ensure reliable and convenient dosing even with high-viscosity bulks. In addition, a large variety of actuator designs and container sizes support brand differentiation and premium shelf appearance. Products requiring special packaging can choose from a variety of child-resistant and senior-friendly options, including MiniCR+ and NanoCR+.

Drawing on the findings of Aptar Pharma's own proprietary research with dermal drug users, the Airless range has been developed with convenience at its core, answering the demand for ease-of-use and no-mess application. The robust nature of the container, and the fact that the pump system remains closed while not in use, prevents leakage and spillage when the device is being transported. For convenient use on different body locations, the technology also allows reliable 360° dispensing.

Beyond issues of practicality, consumers are also concerned with measures to address sustainability and waste. Airless systems answer this through effortless emptying, which results in unsurpassed low amounts of residual product when the empty pack is discarded.

Aptar Pharma's piston-based airless systems are also unique in that they are up to 96% recyclable, using only plastic moulded components with no metal parts. As it is processed in existing recycling streams, the Airless system meets Cyclos requirements.[3] Furthermore, the Airless system is manufactured within Aptar facilities that have achieved ISO 14001 and ISO 50001 certifications.

ADDRESSING THE PERCEIVED CHALLENGES ASSOCIATED WITH AIRLESS DRUG DELIVERY

In the topical dermal drug market, in both the US and Europe, semi-solid formulations (lotions, creams, gels and ointments) account for around 80% of all products. Compared with liquids, these higher-viscosity bulks present their own challenges. For instance, they do not flow easily and tend to stick to the bottle wall, meaning evacuation is compromised when using dip-tube-based pumps. This has led to tubes becoming the most common method for dispensing semi-solid products, which, although well-established, come with several drawbacks. In the case of dosing for dermal drugs, tubes are considered uncontrolled, given that it is dependent on patient judgement, and when it comes to the end of a tube's lifetime, users often have to deal with leakages from degrading packaging while also struggling to remove the remaining product.

Figure 3: Aptar add-on solution for Airless systems and platform for digital ecosystems. (Image courtesy DCA Design International Limited.)

As discussed in this article, Airless drug delivery systems address most of these issues. Any perceived challenges can be mitigated or removed when partnering with Airless device experts, such as Aptar Pharma. There is no doubt that experts in formulation development and filling will be aware about the impact of entrapped air in semi-solid formulations. For example, air bubbles conflict with fluid functionality and dose consistency in pump systems. As it is hard to remove bubbles from viscous bulks, careful consideration must be taken during mixing and transporting to the filling site.

Aptar Pharma is in worldwide partnership with contract organisations specialised in semi-solid formulation and filling of Airless systems. The company is also able to recommend filling line providers, should clients choose to establish their own filling capacity, providing valuable input on key areas to ensure that the filling and closing of Airless systems is achieved with success. Aptar Pharma also provides support for partners at the initial stages of a development project for dermal drug delivery, with solutions for bench-size filling and closing.

CONNECTING IT ALTOGETHER

Prior to the covid-19 pandemic, digital health was an area slowly building momentum, with many sharing Aptar Pharma's vision of a connected future where technology is increasingly integrated into intelligent patient care. In the space of just a few short months, this trend has shifted several gears, with early adoption accelerated by the need to continue to provide high-levels of patient care, while also limiting person-to-person contact as much as possible.

Among Aptar Pharma's digital healthcare solutions for various routes of administration, connected Airless systems are an appealing offering to the pharmaceutical industry. The company's add-on solution and digital platform provides an entire digital ecosystem to existing Airless systems (Figure 3). With the company's solutions, existing products

"Among Aptar Pharma's digital healthcare solutions for various routes of administration, connected Airless systems are an appealing offering to the pharmaceutical industry. The company's add-on solution and digital platform provides an entire digital ecosystem to existing Airless systems."

and developments can, with minimal effort and cost, be transformed into complete digital offerings that enable a wealth of tracking information to be recorded, from actuation events to relevant disease and therapy information and interactions with healthcare providers.[4] Audible reminders for drug intake, and visual feedback on improvement of a patient's disease, could help improve adherence, especially with long-term or chronic diseases. Through partnerships with leading pharmaceutical companies, Aptar Pharma is continuing to design connected solutions that will be a key feature of the digital healthcare environment at the heart of the future of patient care.

AIRLESS+ BY APTAR PHARMA – WIDELY ACCEPTED, ACCESSIBLE AND AVAILABLE

In summary, skin diseases are among the most common diseases worldwide, with around one third of us affected with a pathological skin problem during our lifetime. As a result, dermal drug delivery has, for many years, been regarded as an efficacious option, one that only continues to grow in relevance and popularity as more therapies are developed. The benefits of dermal drug delivery are also well recognised – for both users and pharmaceutical partners – particularly regarding convenience and patient adherence.

Airless drug delivery in the dermal space has perhaps been overlooked, primarily because of the perceived challenges around complexity, development and cost. As discussed in this article, those challenges are comparatively easy to overcome and are far outweighed by the clear benefits of Airless delivery when it comes to premium brand differentiation, recyclability, safety, reliability and convenience.

Aptar Pharma, as a leader in the Airless drug delivery market, is encouraging a re-evaluation of this perspective through the combination of product innovation and market expertise that is wrapped into its Airless+ range. It enables pharmaceutical companies to de-risk and accelerate dermal drug development projects by designing and delivering products that answer the various challenges set out by each stakeholder group, all of whom are demanding more from Airless. Regulators can be assured of device safety, and users can be presented with a premium device that is not only more convenient to use, but more sustainable than alternative options. It is only true Airless device specialists however – those with a track record in mastering the technology and navigating the regulatory pathway – who will be able to respond to such challenges.

ABOUT THE COMPANY

For pharma customers worldwide, Aptar Pharma is the go-to drug delivery expert, providing innovative drug delivery systems, components and active packaging solutions across the widest range of delivery routes including nasal, pulmonary, ophthalmic, dermal and injectables. Aptar Pharma Services provides early stage to commercialisation support to accelerate and derisk the development journey. With a strong focus on innovation, Aptar Pharma is leading the way in developing connected devices to deliver digital medicines. With a global manufacturing footprint of 14 manufacturing sites, Aptar Pharma provides security-of-supply and local support to customers. Aptar Pharma is part of AptarGroup, Inc. (NYSE:ATR).

ABOUT THE AUTHOR

Stefan Hellbardt is Vice-President Business Development and Scientific Affairs at Aptar Pharma. As a trained biologist, he earned his PhD at the German Cancer Research Center (Heidelberg, Germany). Having held various positions in the pharmaceutical industry, Dr Hellbardt gained more than 15 years of experience in clinical development. He joined Aptar Pharma in 2011 to lead the global business development of the application field of Dermal Drug Delivery, Wound Care and Analgesics. In this role, he has been instrumental in delivering the expertise and services of Aptar Pharma to both new and existing customers, developing pharmaceutical products for topical dermal, transdermal, topical analgesic and wound applications. With a deep knowledge in drug development, a broad understanding of the market and therapies, and a clear view on the role of an expert drug delivery partner for successful medication development, Dr Hellbardt is a recognised go-to person in the industry for skin and wound-related drug dispensing.

REFERENCES

1. *"Global Airless Packaging Report – Forecast to 2025". Research Report, Market Research Future, 2019.*
2. *Airless Technology, US Consumer Research, Proprietary Research for Aptar Pharma, June 2018.*
3. *Institute Cyclos-HTP (Institute for Recyclability and Product Responsibility), Report and Certificates on File. 2020.*
4. *"Interview with Sai Shankar, Adam Shain and Marcus Bates, Aptar Pharma". ONdrugDelivery, June 2020, Issue 108, pp 29–34.*

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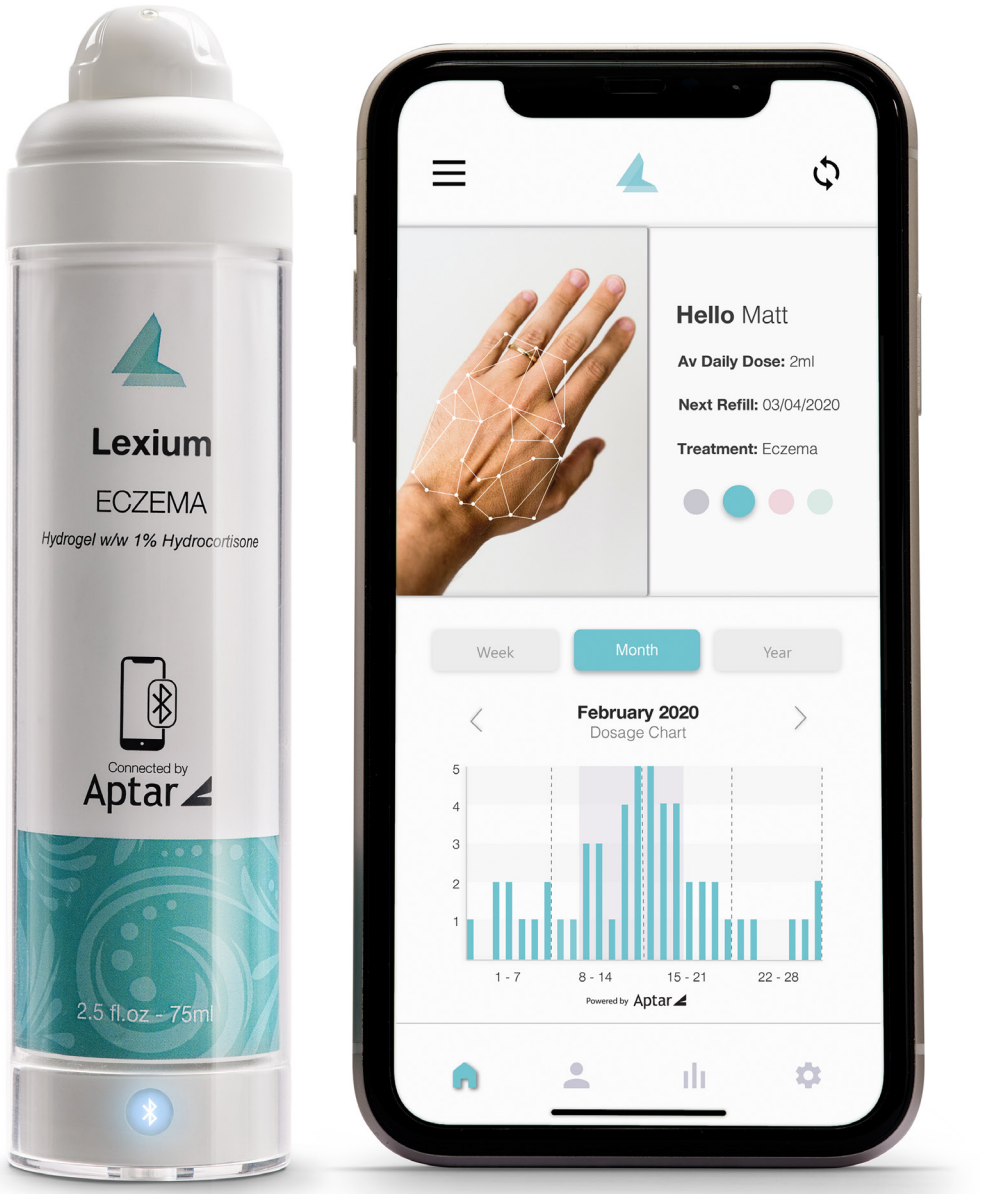

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