



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.

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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.

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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

“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.”

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.

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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.



Press actuator to dispense product from dosing chamber

Release of actuator fills dosing chamber from container

Lower piston moves up to balance any pressure in container

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.

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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

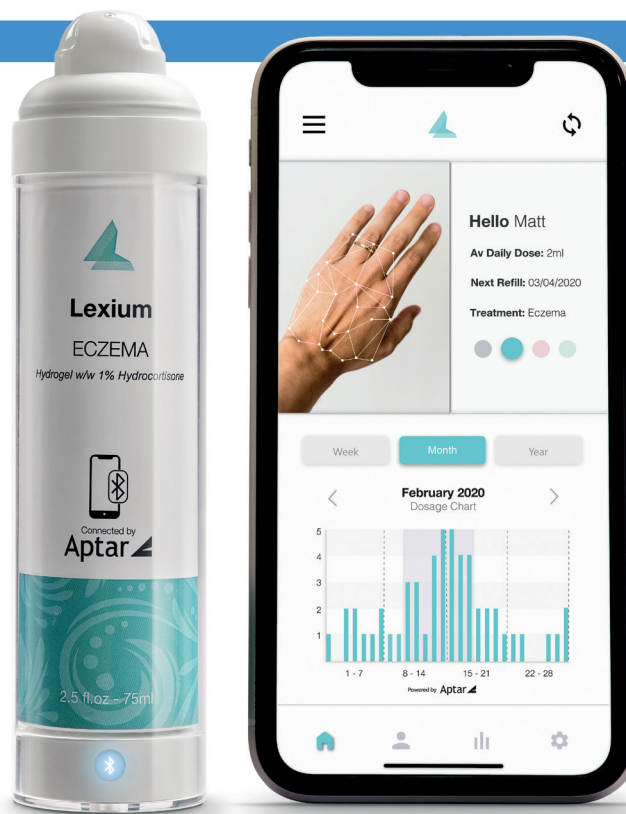


Figure 3: Aptar add-on solution for Airless systems and platform for digital ecosystems. (Image courtesy DCA Design International Limited.)

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.

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

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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).

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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.

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To partner with Aptar Pharma on your next dermal project, contact **Dr Stefan Hellbardt**, Vice President Business Development and Scientific Affairs, at stefan.hellbardt@aptar.com



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