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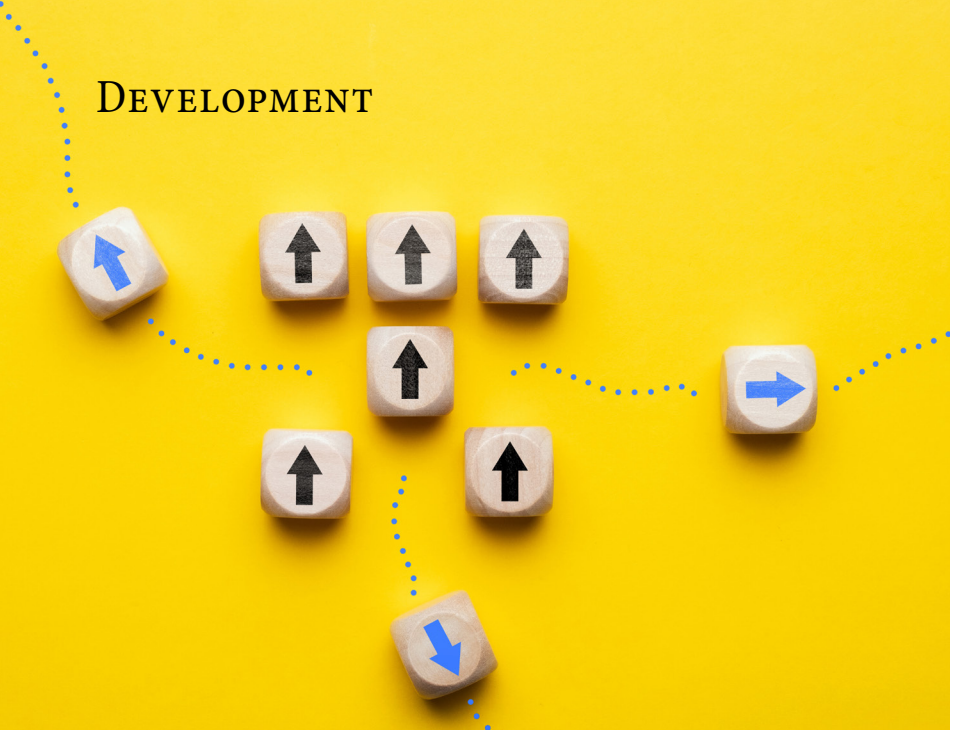

Taking an Alternative Approach to Drug Delivery

Felicity Thomas

Alternative drug delivery approaches are promising, but due to their complexity, they need to be sufficiently justified.

The oral route of administration of medicines remains the most popular due to convenience and ease of administration. However, more complex compounds are being developed for therapeutic applications, which are not so simple to formulate as an oral dosage form, giving rise to an increased demand for alternative drug delivery solutions.

To learn more about alternative drug delivery trends, approaches, and challenges, *Pharmaceutical Technology* spoke with Gemma Keenan, principal scientist, Formulation and Process Innovation, Vectura; and Lynn Allen, vice-president Business Development, and Jon Lenn, chief technology officer, both from MedPharm.

Key drivers

PharmTech: What are the main drivers for alternative drug delivery formulation and how have the drivers evolved?

Allen (MedPharm): Some of the drivers in developing alternate formulation approaches are a result of the development of novel drugs and biologics, and a focus on improving patient compliance while minimizing safety concerns. The development of these new and often highly potent therapeutics can have limitations in some indications. This is where the alternative delivery routes such as topical and transdermal delivery to skin and other epithelium play an important role.

Keenan (Vectura): The main driver is the range of therapies being considered for drug delivery. These therapies, which include biologics such as antibodies and oligonucleotides, and small molecules such as anti-infectives and cytotoxics, require formulations that enable deposition within the respiratory tract, but also control characteristics post-deposition. This may include a requirement for enhanced lung retention, mucus/biofilm penetration, or intracellular delivery.

With the COVID-19 pandemic, there has been a particular focus on the delivery of vaccines, which must be formulated to provide a sufficient immune response. This may also be a contributing factor to the increasing number of products targeting nasal drug delivery. In this case, formulations may be more focused on increasing retention and permeability of the nasal mucosa.

Additionally, there seems to be renewed interest in systemic drug delivery, which will drive formulation strategies for increased absorption. Increased awareness of the carbon footprint associated with pharmaceutical products and the replacement of high global warming potential (GWP) constituents used in the final product, or within the manufacturing process, may drive further diversification of formulation approaches in the future.

Promising approaches

PharmTech: Could you run through some of the alternative drug delivery formulation approaches that you believe are most promising at the moment?

Keenan (Vectura): Formulation approaches remain centered around the use of micronized dry powders, solutions, and suspensions, but these may not always be appropriate to achieve the desired target product profile. Liposomes are a proven formulation approach in parenteral drug delivery, which is increasingly being applied in lung delivery. These formulations are often well-tolerated in the lung and have been shown to increase lung retention and minimize systemic exposure, increasing the safety and efficacy of the product. Importantly, they have been successfully delivered into the lung using nebulization technology. Other formulation approaches are likely to offer similar benefits, including lipid-based and polymer-based nano-carriers. Additional functionality may be afforded through ligand tar-

geting, enabling efficient uptake into target cells. What is particularly encouraging for these systems is that they can be readily translated into a liquid or powder dosage form for inhalation.

Lenn (MedPharm): One of the most promising areas for alternative formulation approaches is nasal drug delivery. This mucosal membrane, the entry way for the rest of the respiratory system, is appealing for many reasons. The nasal cavity is easily accessible offering an opportunity for local, systemic, and even direct to the brain drug delivery. Compared to systemic delivery, there are distinct advantages which include a relatively large surface area for drug absorption, convenience for patience compliance, avoidance of first-pass metabolism and harsh gastrointestinal conditions. Nasal delivery is also an ideal opportunity for vaccines, especially respiratory disorders like COVID.

Potential beneficiaries

PharmTech: Are there specific diseases/therapeutic areas or patient populations that would significantly benefit from alternative drug delivery approaches to formulation?

Allen (MedPharm): Patient compliance will always be an area of focus for pharmaceutical and biotechnology companies. Patient populations where easy-to-use and non-invasive self-administration is required, or where there is hesitancy for needles, are ideal target markets for alternative drug delivery approaches such as the nose and other mucosal membranes.

Intranasal vaccination will be an area of intense research as we continue to struggle with the pandemic and appearance of new variants. Infection with SARS-CoV-2 initially attacks the upper respiratory tract; therefore, it's interesting to explore vaccines or protective treatments of the nasal passage. This could be a potential opportunity to block infection or, at the very least, improve protection of the mucous membranes of the nose and throat. It also presents an opportunity for self-vaccination and/or an easier way to introduce mass vaccinations by less skilled persons.

Localized nasal delivery has been and continues to be an area of development for conditions such as congestion, rhinitis, sinusitis, and other allergic conditions. In addition, the nasal cavity is highly vascularized offering opportunities to exploit rapid onset of action for analgesic effects (e.g., morphine and ketamine).

Finally, the nose offers an opportunity to deliver drugs directly to the brain or central nervous system (CNS) via the olfactory pathway. Two relatively recent commercializations for intranasal delivery are naloxone nasal spray to treat suspected opioid overdose emergencies and diazepam nasal spray for short term rescue treatment of seizure clusters.

Keenan (Vectura): Alternative drug delivery approaches may benefit therapies that need to overcome significant barriers resulting from the disease itself. For example, in cystic fibrosis, the overproduction of mucus and alteration of mucus properties, represents a challenge for effective drug delivery by inhalation alone. The treatment of infections within the lung may also be improved by the use of alternative formulations, particularly when coupled with an inhalation device that can achieve efficient lung deposition. Maintaining an elevated local dose above the minimum inhibitory concentration for anti-infectives is likely to result in better treatments while minimizing the risk of bacterial resistance, as well as limiting systemic exposure. Treatments that specifically target cancerous cells within the lung may also show significant benefits, particularly in light of the number of nano-therapeutic formulations already approved for the treatment of cancer by the parenteral route. Therapies that are used in an acute setting, such as pain relief, may benefit not only from delivery to the peripheral lung, which can be achieved using efficient delivery devices, but through rapid systemic uptake achieved by alternative drug delivery formulations.

It is far more likely that the nature of the therapeutic and the target disease drives consideration of alternative formulation strategies than the patient group. However, selection of an inhaled drug delivery approach over more invasive options, such as by injection, may be preferred by some patients. Examples include severe asthmatics requiring antibody therapy or Parkinson's patients receiving treatment for "off" periods.

Formulation challenges

PharmTech: What are the challenges facing formulators when developing an alternative drug delivery formulation? How are these challenges overcome? Are some challenges insurmountable at the moment?

Keenan (Vectura): There must be a clearly demonstrable benefit for implementing an alternative formulation strategy over a conventional approach because of the increased complexity. The number of excipients approved for lung delivery is particularly limited; therefore, there may be additional requirements to demonstrate safety and tolerability in the lung. If the excipient is novel, then qualification is likely to further increase both costs and timelines, although this must be considered against the potential benefits associated with new intellectual property. In many cases, alternative formulations are not suitable for direct delivery to the lung and must first be translated into a respirable powder or liquid that is compatible with an inhalation device. At each stage, it is essential that the stability, integrity, and functionality of the formulation is preserved, which requires implementation of an appropriate testing strategy. Justifying the investment required to translate a novel formulation approach that has shown promise at bench scale into a marketed product remains a significant challenge.

Lenn (MedPharm): There are some unique challenges associated with developing an intranasal topical, transdermal, or vaccine formulation. These types of medications are unique in that

they require the formulator to think about the physiochemical properties of the drug, the vehicle, and the device throughout product development. In addition, targeted delivery to the different regions of the nasal cavity and the biology of the nasal epithelium present opportunities and challenges.

The nasal epithelium is composed of mucus secreting, ciliated, non-ciliated, and basal cells, thus the formulation needs to be designed for this type of epithelium. The general formulation approach of prioritizing drug solubility and stability remain paramount and should be developed while keeping in mind the anatomy of the nose and the engineering of the device. To aid in the development and optimization of intranasal formulations, MedPharm has developed a testing model that uses regrown human nasal epithelia cells to recreate a 3D living nasal epithelium. The model allows prototype formulations to be applied topically to measure the permeation of the drug from either active or passive transport. To account for the influence of the device, MedPharm has developed a nasal cast model that allows the device to spray the formulation and measure the concentration of the drug to the different compartments of the nose.

Regulatory pathways

PharmTech: Are there clear regulations for alternative drug delivery approaches currently? If not, what should be done in your opinion to rectify this situation?

Allen (MedPharm): MedPharm's formulation approach would be to use excipients that have been used in approved products for the route of delivery that are listed on the FDA Inactive Ingredient Database (IID).

Keenan (Vectura): The regulatory pathways are well documented and when coupled with a continual dialogue with the regulators, alternative drug delivery formulations can be successfully implemented. Even in cases where the approach is truly novel, building this relationship with the regulators will help ensure agreement between both parties provided there is a strong rationale that is supported by robust scientific data. Regulators consider hazards relating to lung exposure as different to those via other administration routes and, therefore, unless safety in the lung has been previously demonstrated, the registering company will be expected to provide a robust preclinical and Phase I inhaled safety package. These additional studies significantly increase the cost and complexity for any alternative drug delivery development pathway. In addition to the increased cost and time, large preclinical studies can create ethical concerns unless sufficiently justified.

Ultimately, it is the cost and impact of alternative formulation approaches on the development timelines, together with the additional risks, that limit their implementation. Only in cases where a novel approach has the potential to be truly product-enabling, or transformative in terms of unmet medical need, can alternative formulations be sufficiently justified. **PT**

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"It is not uncommon for preclinical data to not reflect the human situation, which can lead to the wrong formulation strategy being selected, or sub-optimal formulation performance," emphasizes Lewis. At Quotient Sciences, integrated adaptive clinical trials are used to guide formulation development and selection in human subjects, which, Lewis confirms, accelerates development. "These Phase I trials in healthy volunteers can be used to compare technological approaches head-to-head and select formulations for later dosing periods (e.g., multiple ascending dose) based on their performance," he says. "We have also used these [trials] to bridge from a simple first-in-human formulation to a proof-of-concept ready formulation within study with a single regulatory approval."

Furthermore, it is possible to obtain regulatory approval to dose any formulation within a design space that has been defined through the identification of a critical-to-performance formulation variable, Lewis continues. "The formulation to be manufactured and dosed can be modified, informed by the emerging clinical data (e.g., pharmacokinetic parameter) to ensure the target product profile is achieved," he states. "This is all enabled by real-time adaptive manufacturing—products being manufactured immediately prior to dosing rather than months in advance of the clinical trial, accelerating development."

Final thoughts

"Drug development is a balance between minimizing time to clinic and developing a promising formulation that meets pharmacokinetic targets," reveals Mueller-Albers. "However, risk of failure of a molecule is not only related to its pharmacological and pharmacokinetic properties or its toxicity, but also to its manufacturability."

A thorough understanding of the target product profile is necessary to be able to build a robust formulation strategy, emphasizes Lewis. Additionally, referring to the objectives and end-goals of a program is critical in order to ensure that the formulation developed meets the needs of each stage of development, he stresses.

"Formulators need to engage earlier, to overlap with the medicinal chemistry strategies, to partner with the medicinal chemists themselves in order to make decisions about API and drug product, and using formulation with API-sparing techniques that resolve any liabilities that the medicinal chemist cannot quickly fix without having to necessarily invest in a final formulation, but all the while collecting data that moves the project forward. Formulators also need to address all bioavailability factors and not just solubility," concludes Tindal.

References

1. Statista, "Total Global Spending on Pharmaceutical Research and Development from 2012 to 2026," *statista.com*, July 2021.
2. Therapeutics Research Institute, "Pharmaceutical Predictivity," *tri-institute.org*, March 2021. **PT**