NANOTECHNOLOGY: A NEXT-GENERATION TOOL FOR PULMONARY AND NASAL DELIVERY

Here, Frédérique Bordes-Picard, Vice-President of Business Development, Europe, at Nanoform, looks at the role of nanotechnology in the nasal and pulmonary routes of drug delivery and explains how nanoparticle solutions could transform patient comfort and compliance.

The nasal and pulmonary routes present exciting opportunities for localised treatment of respiratory disorders, such as asthma and chronic obstructive pulmonary disease (COPD). Drugs delivered directly to the site of action through local delivery can generate fewer side effects and more rapid onset – a significant patient benefit.

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However, the full potential of inhaled therapies does not end there. Drug delivery to the periphery of the lung and into the bloodstream could facilitate rapid systemic delivery of drugs, including those unsuitable for oral administration due to poor absorption in the gastrointestinal (GI) tract. Meanwhile, drugs delivered through the nasal route with the correct size and aerodynamic properties may be able to cross the blood-brain barrier (BBB), creating exciting possibilities for the treatment of central nervous system (CNS) disorders.

While drug delivery devices can help to target drugs for either local or systemic action, few inhaled drugs for systemic delivery have reached the market to date.[1] This is, in part, due to the challenges associated with respiratory delivery. Powerful new technologies, such as nanoparticle engineering, could provide the means to increase the accessibility of pulmonary and nasal delivery, paving the way for a new wave of revolutionary treatments to reach the market.

THE IMPORTANCE OF PARTICLE SIZE

A significant driver for the development of inhalation therapies is increased patient-centricity. For example, the industry is working to move away from the intravenous (IV) route for biologics – drugs derived from biological sources, such as proteins and lipids – to enhance patients' quality of life and adherence to medication. By repurposing biological drugs as inhalation therapies, it may be possible to avoid the inconvenience associated with injections. Equally, bypassing systemic delivery through local administration can help avoid first-pass metabolism and reduce side effects, for both small molecules and biologics.

To tailor a dry powder drug formulation for local or systemic delivery through the pulmonary or nasal route, a number of factors must be considered. In particular, the aerodynamic diameter of drug particles – the diameter of a sphere of unit density that behaves the same aerodynamically as the particle of the test substance – is of paramount importance. Particle size, morphology and density are key contributors to the aerodynamic diameter. Particles less than 1 µm in size tend to be exhaled from the lung due to low inertia, while particles greater than 5 µm in size are too large to reach the deep lung and thus be absorbed into the bloodstream.[2] The size of particles, among other properties, can also impact residence time in the lung, with larger particles remaining in the lung for longer, which can be beneficial for local delivery.

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Meanwhile, drugs designed for local nasal delivery typically need to be larger than those designed for pulmonary delivery. This prevents them being inhaled into the lung, if this is not desirable. Particles in the 10–15 µm range typically are better suited to nasal delivery. As such, by carefully controlling particle size, it is possible to tailor drug particles for the target delivery route – whether nasal or pulmonary.

PRODUCING DRUG PARTICLES FOR NASAL AND PULMONARY DELIVERY

Historically, dry powder inhalation approaches for nasal and pulmonary delivery involved milling, mixing with a carrier/excipient and then filling into the drug delivery device. More specifically, adhesive mixtures composed of micron-sized API are adsorbed onto 50–200 µm carrier particles, such as lactose, often with the addition of fine milled or micronised lactose. The blend is then filled into a drug delivery device, typically reservoir, blister or capsule-based. However, such approaches involving milling to reduce particle size can result in an undesirable change in surface properties, such as cohesion and the generation of amorphous domains, which can lead to instability over time.

More modern approaches include spray drying to generate APIs with relatively large geometric diameters (a parameter used to quantify the size and shape of irregularly sized particles), with a low density and small aerodynamic diameter. Alternatively, spray drying can be used to produce light, porous particles of API co-processed with an excipient. An example of the former is Inbrija (levodopa inhalation powder) (Accorda Therapeutics, NY, US), while the antibiotic Tobi (tobramycin) (Novartis, Basel, Switzerland) is an approved version of the latter.

Inbrija is administered via a breath-actuated inhaler. It enables levodopa to bypass the GI tract and enter the bloodstream rapidly through the lungs instead. It has been shown to be effective in improving Parkinson's disease symptoms in patients experiencing "off" periods, where routine medication is not sufficient.[3] As a non-intrusive, convenient treatment option, Inbrija highlights the possibilities for creating patient-centric therapeutics by repurposing drugs for inhalation. However, spray-drying formulations, as in the case of Inbrija, while effective, often results in amorphous material and may require more complex formulations to ensure stability.

CREATING NEW POSSIBILITIES WITH NANOPARTICLE ENGINEERING

Advanced nanoparticle engineering techniques offer a means to reduce the size of drug particles to as small as 10 nm as part of a controlled process. While this is too small for direct delivery to the lung, nanoparticles can potentially be prepared as clusters. In this case, the small size of the nanoparticles could make faster absorption possible, while the cluster is prepared/generated at the ideal size for optimal delivery, retention time and release to the lungs or nose upon deposition.

This opens up a number of intriguing prospects. For example, fibrotic scarring observed in fibrotic respiratory diseases typically blocks particles in the 200 nm – 1 µm range. Particles smaller than that could potentially pass through, which could facilitate different treatment approaches.

Meanwhile, for nanoparticle engineering approaches to work successfully on biologics, care must be taken not to expose them to high temperatures or shear stress, which could impact biological activity negatively. Gentle nanoparticle engineering technologies that can produce stable biological nanoparticles as small as 50 nm, potentially alongside co-processing with the excipients to help maintain a uniform particle size and stability, hold enormous potential to facilitate delivery of biologics through the nasal and pulmonary routes.

DELIVERY TO THE BRAIN: FOLLOW YOUR NOSE

In addition to facilitating localised treatment of respiratory or nasal disorders, the nasal route may also represent a gateway for nanoparticles to reach the brain. Direct delivery to the brain is a major issue for drugs targeted at CNS disorders, such as Parkinson's or Alzheimer's disease. Designed to effectively block outside agents from entry, the BBB is impassable to approximately 98% of small molecules and almost all biologics.[4] Transport across the olfactory nerves and respiratory epithelium or trigeminal nerve in the nose could allow drugs administered nasally to bypass the BBB, solving a long-standing challenge in the industry.[5]

In combination with a purpose-built delivery device, nanoparticle clusters could provide a means to leverage this pathway. In this case, particles of carefully controlled size would be potentially rapidly absorbed intranasally and, subsequently, reach target areas in the brain, which could facilitate life-changing new treatments for currently incurable brain disorders.

A NEW FRONTIER IN PULMONARY AND NASAL DELIVERY

While further research is needed to confirm the many ways that nanoparticles could transform nasal and pulmonary delivery, the possibilities are multifold. From empowering a shift to a more patient-centric, localised route of administration for respiratory disorders to potentially overcoming the obstacle created by the impassable BBB, the opportunities to improve patients' lives through technological innovation make it an exciting time to be working in the field. In the future, there may be many more patient-centric therapeutics delivered through the nasal or pulmonary routes, aided and enhanced by nanoparticle engineering.

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ABOUT THE COMPANY

Nanoform is an innovative nanoparticle medicine enabling company that works together with pharma and biotech partners globally to provide hope for patients in developing new and improved medicines using Nanoform's platform technologies. The company focuses on reducing clinical attrition and on enhancing drug molecules' performance through its nanoforming technologies and formulation services. Nanoform's capabilities include GMP manufacturing, and its services span the small-to-large molecule development space with a focus on solving key issues in drug solubility and bioavailability and on enabling novel drug delivery applications.

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ABOUT THE AUTHOR

Frédérique Bordes-Picard is a biochemist engineer by training (Bordeaux Polytechnic Institute, France) and also holds an MBA from KEDGE Business School (Bordeaux, France). Ms Bordes-Picard has nearly 25 years' experience in the pharmaceutical industry, gained first at AstraZeneca, UK, working on the analytical development of therapeutic proteins and antibodies. She subsequently worked within the CDMO Bertin Pharma (now Eurofins), focusing mainly on generic product development and licensing. Ms Bordes-Picard then spent over 10 years at Capsugel, now Lonza, as Pharmaceutical Business Development Manager, providing technical and regulatory guidance in encapsulation solutions for new drug products for oral or pulmonary administration. She recently joined Nanoform as Vice-President of Business Development, Europe.