

STRESS-TESTING INHALED MEDICINE SO PATIENTS CAN BREATHE EASIER

Dr Yannick Baschung discusses the benefits and challenges of orally inhaled and nasal drug products and examines how drug developers can stress test their products to improve regulatory success and patient safety, as well as how partnering with an expert CRO can provide an efficient way of performing critical characterisation testing.

Orally inhaled and nasal drug products (OINDPs) have long been a familiar sight on pharmacy shelves. From asthma inhalers to allergy relief nasal sprays, these devices provide patients with a comfortable option for fast-acting drug administration. Over the last decade, drug developers have become increasingly innovative in their use of the respiratory route, designing nasal flu vaccines for at-home administration and inhaled insulin to reduce reliance on needles when managing diabetes.^{1,2} However, despite their apparent ease of use, OINDPs are challenging to manufacture behind the scenes. Ensuring consistent dosage and proper airway distribution of aerosolised compounds can pose a significant challenge.

CHALLENGES AND OPPORTUNITIES FOR OINDPs

Administration via the respiratory route offers an impressive range of advantages. The most apparent use case for OINDPs is for the treatment of respiratory conditions, where medicines can travel through the airways and coat affected tissues to treat respiratory conditions such as seasonal allergies, asthma or chronic obstructive pulmonary disease (COPD). Intranasal administration also provides an attractive route for drug delivery to brain tissues, as the unique physiology of the sinuses allows certain compounds to bypass the blood-brain barrier, which would otherwise filter them out.³ Inhaled compounds are also rapidly absorbed, providing immediate benefits and saving lives, as seen with naloxone's ability to rapidly reverse an opioid overdose.

But that does not mean that inhaled medicines are not without their challenges. The anatomy and mucosal tissues of the respiratory tract have evolved to filter and

trap dust and contaminants in the air that we breathe, and OINDP designs must account for this protective mechanism. Additionally, OINDPs are self-administered, so carefully measured spray patterns in the lab may look entirely different when a patient is using these devices at home. To ensure safety and efficacy, developers must design robust formulations and thoroughly evaluate device-formulation performance to achieve consistent dose delivery and distribution.

Creating the right formulation in which to suspend a drug product is a much more involved process than many people realise. To guide the formulation design, scientists can use solid state characterisation to develop a deep knowledge of the drug's properties. This can inform selection of the right excipients – molecules that are added to the drug formulation to stabilise the API, modulate viscosity or otherwise improve the formulation. To function as a spray, the final formulation needs to maintain a certain viscosity, but without aggregation, which can compromise dosing uniformity. The formulation must also protect the API from degradation to ensure the drug's efficacy remains unaffected.

STRESS-TESTING OINDPs

For OINDPs, formulation and device development must be approached as an integrated process. The performance of an aerosolised therapy depends on how effectively the formulation interacts with its delivery system, whether that's a pressurised metered dose inhaler (pMDI), dry powder inhaler (DPI), soft mist inhaler (SMI), nebuliser or nasal spray. Throughout development, specialised analytical studies are used to characterise critical performance attributes of the combined drug-device system.

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For spray-based platforms such as pMDIs, SMIs and nasal sprays, parameters including spray pattern and plume geometry are evaluated to ensure consistent dose delivery. Additionally, aerodynamic particle size distribution is measured, typically using cascade impactors, to determine the fine particle dose and to assess how effectively and likely the aerosol is to reach the target regions of the respiratory tract. Together with emitted dose uniformity, these tests consider critical quality attributes, reflecting the influence of formulation properties and patient inhalation profiles on drug delivery.

To complement these tests, drug developers are increasingly employing anatomically realistic *in vitro* airway models that mimic the geometry of the human nasal passages or upper respiratory tract. These models help predict regional deposition and provide valuable insights into how a given drug-device combination product will perform under real-world conditions.

Alongside performance studies, developers assess whether impurities can migrate from the container closure system or delivery device into the drug product. OINDPs are considered to be among the highest risk dosage forms for extractables and leachables (E&L), as even trace amounts of foreign compounds can pose a major risk when inhaled directly into the lungs or nasal

passages. Effectively analysing E&L requires multidisciplinary expertise in materials science, analytical chemistry and toxicology, combined with advanced instruments capable of detecting and characterising impurities at very low concentrations. This robust E&L testing is critical for both patient safety and compliance with stringent regulatory guidelines.

Many drug developers find that partnering with a CRO is the most efficient way to perform these important characterisation experiments. The right CRO partner has the appropriate facilities and equipment, along with the scientific personnel to interpret the results. Beyond these practical considerations, a high-quality CRO partner can help smooth out the drug development journey by finding creative solutions to formulation issues that are revealed during rigorous stress testing. With the right CRO partner, drug developers can feel confident in their product as they move from concept to commercialisation.

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CONFIDENCE WITH EVERY BREATH

OINDPs will continue to play an important role in the effective administration of therapies. They provide easy, effective and speedy means of delivering drugs locally to the respiratory system and hold promise for systemic delivery. However, good science rarely occurs in a silo. By partnering with CROs skilled in characterising and designing safe and reliable OINDPs, drug developers can be confident that their product will fulfil the promise of inhaled medicine.

ABOUT THE COMPANY

Solvias is a global provider of chemistry, manufacturing and control analytics to the life sciences industry. Its expert team combines decades of experience with regulatory expertise across small molecules, biologics, and cell and gene therapies. Solvias offers end-to-end solutions from raw material testing to drug product release and API development for small molecules. Headquartered near Basel, Switzerland, Solvias operates six global Centers of Excellence, all adhering to the highest ISO, GMP, GLP and FDA standards.

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