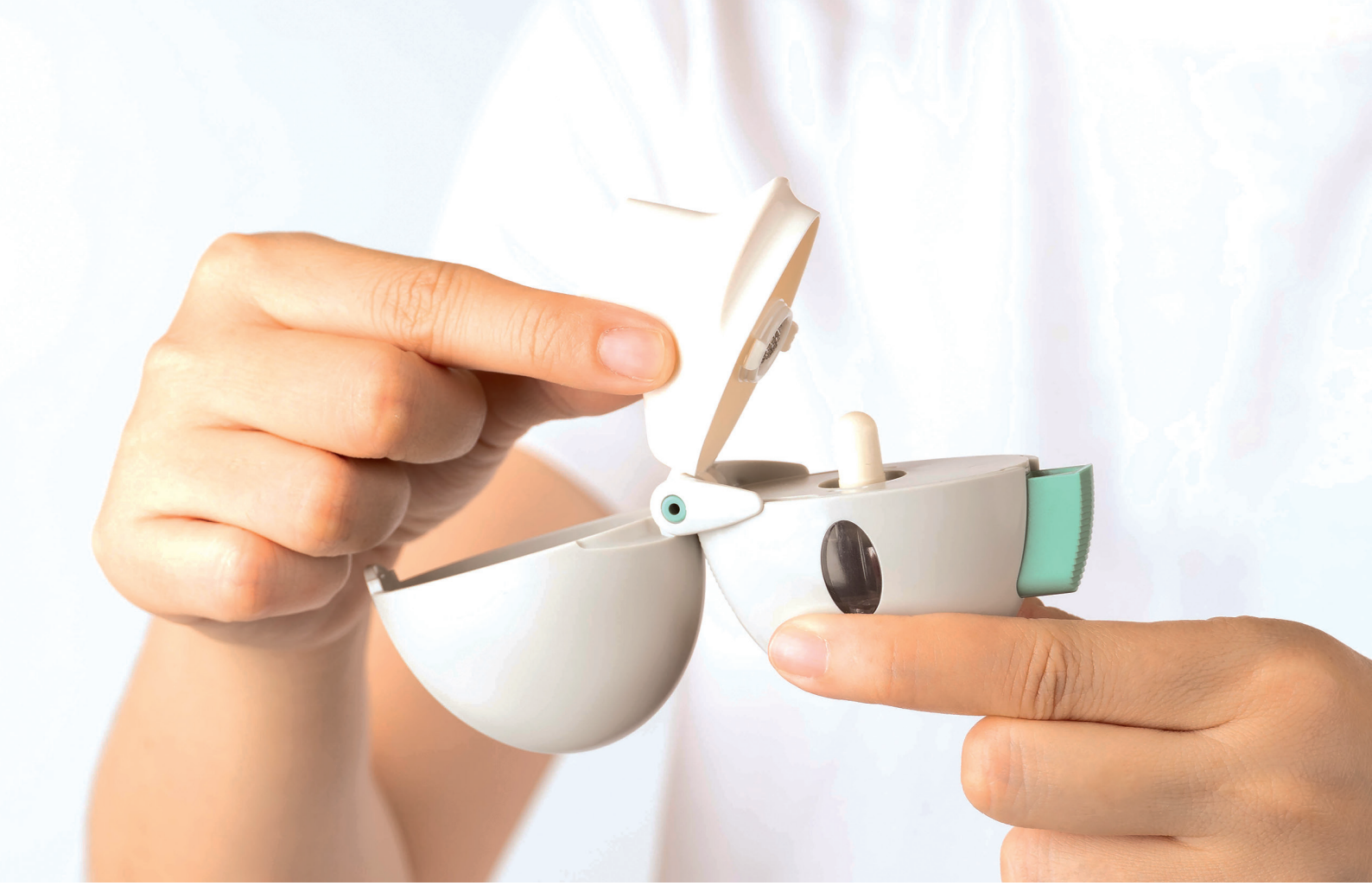

CLEARING THE AIR(WAY): DEBUNKING THREE COMMON MYTHS ABOUT INHALED DRUG DELIVERY

ROQUETTE
Offering the best of nature™

Dr Keat Theng Chow and **Susana Ecenarro** of **Roquette** explore three myths surrounding inhalation as a route of administration, clearing the way for a deeper understanding of one of pharma's most exciting areas for innovation.

The economic potential of inhaled therapies is truly breathtaking – and yet somehow misunderstood. Increasing urbanisation, worsening pollution in some regions and a growing global population mean rates of asthma, chronic obstructive pulmonary disease (COPD) and cystic fibrosis are on the rise.[1–4] As a result, the pulmonary and respiratory drug delivery market is expected to grow at a CAGR of 6.5% over the next four years to reach a value of US$87.7 billion (£65.3 billion) by 2029.[5]

At the same time, an advancing understanding of both pharmaceutical science and the patient experience are ushering in a new era of drug development where there are options beyond the traditional pill or capsule format. Inhalation as a route for drug delivery offers promising potential for broad drug development, both in and outside the treatment of respiratory diseases, yet inhalation remains a lesser-known route of administration compared with oral dosage or parenteral delivery.

WHAT IS INCLUDED IN "INHALATION"?

Before diving fully into the misconceptions surrounding inhaled drug delivery, it is first important to lay out the facts. Inhaled drug administration, at its core, refers to the delivery of drugs to the respiratory tract via inhalation through the use of various devices, such as metered dose inhalers (MDIs), dry powder inhalers (DPIs) and nebulisers.[6] Their value as highly effective

therapies stems from their capacity for rapid systemic absorption and targeted delivery to specific regions of the lung, leading to rapid onset of action with a lower risk of side effects.[7]

While they all share the same end goal, the various technologies that sit under the umbrella of inhaled therapies vary significantly in their approaches, advantages and applicability. MDIs, for instance use an aerosol and propellant system, providing a convenient and portable option, though their effectiveness relies on a patient's individual self-administration technique.[8] Soft mist inhalers (SMIs) generate a fine, slow-moving mist, which can improve drug deposition and reduce the need for precise timing – a notable improvement over MDIs for patients with dexterity or co-ordination difficulties.[9] DPIs, meanwhile, are a range of breath-actuated devices that enable a wide array of drug types to be dispersed solely by the patient's inspiratory effort.[8] DPIs and SMIs only provide a simpler method of administration, but also eliminate the need for propellants.[10,11]

MYTH 1: INHALED ROUTES OF ADMINISTRATION ARE INHERENTLY UNSUSTAINABLE

As with many misconceptions, the perception of inhaled drug delivery as less than sustainable is based on a kernel of truth. Beginning in the late 1980s, efforts to reduce damage to the Earth's ozone layer eventually culminated in the banning of chlorofluorocarbons (CFCs); a class of chemicals that were widely used in refrigeration, air conditioning, and – most importantly for a pharmaceutical discussion – as aerosol propellants in MDIs.[12]

After CFCs were phased out, hydrofluorocarbons (HFCs), which do not contribute to ozone degradation, were introduced as an effective alternative for MDIs, but this switch unfortunately raised a fresh set of concerns.[12] While less harmful to the ozone layer specifically, HFCs are nevertheless potent greenhouse gases with a warming effect of up to 3,800 times that of carbon dioxide. Looking only at these more traditional delivery methods, the assertion that inhaled therapies are inherently harmful to the environment seems reasonable. However, when widening the view to other forms of inhalers, the myth begins to break down.

> "SIMPLY BY MERIT OF THE FACT THAT THEY DO NOT REQUIRE THE USE OF PROPELLANTS, THE AVERAGE DPI IS ESTIMATED TO HAVE A CARBON FOOTPRINT 18 TIMES LOWER THAN THAT OF AN EQUIVALENT MDI."

Since their introduction in the 1990s, DPIs have proven themselves to be an effective, and far more sustainable alternative to aerosol-propelled MDIs.[13,14] In fact, simply by merit of the fact that they do not require the use of propellants, the average DPI is estimated to have a carbon footprint 18 times lower than that of an equivalent MDI.[12]

The power of these propellant-free devices lies in their simplicity and flexibility. Under the wider category of DPIs are several subtypes, each with a unique dose metering and delivery action. Whether designed for single- or multi-unit dosages, pre-metered DPIs feature capsules, blister disks or blister strips that are punctured during use. This allows for the inhalation of pre-measured doses of an API accompanied by a carrier excipient. In contrast, doses delivered by reservoir-based DPIs are metered by the device itself, removing the need for capsules and blisters but also necessitating more complex inhaler designs with less opportunity for reuse.

> "AS A NON-REDUCING SUGAR ALCOHOL, MANNITOL OFFERS SUPERIOR CHEMICAL STABILITY COMPARED WITH REDUCING SUGARS SUCH AS LACTOSE, MAKING IT PARTICULARLY SUITABLE FOR CO-FORMULATING WITH SENSITIVE APIs."

From an environmental perspective – particularly regarding plastic waste – DPIs do not offer a marked improvement over MDIs beyond the elimination of potentially damaging aerosol propellants. The vital point, as is often the case in pharmaceuticals, is balance. Because DPIs require adequate inspiratory effort for effective drug delivery, they may not be suitable for patients with severely reduced lung function. In such cases, MDIs – especially when used with a spacer – or SMIs can offer a more reliable alternative. The task for pharmaceutical producers is therefore to optimise the manufacture of each form of inhaler to allow clinicians to make the right choice for their patients and the planet.[15]

MYTH 2: LACTOSE IS THE ONLY VIABLE EXCIPIENT FOR DPI FORMULATION

Put simply, this misconception is patently untrue. While it can still be argued that lactose is the most dominant excipient in the inhalation market,[16] it is far from being the only carrier that has proven effective in the delivery of APIs to the lungs, nor is it universally suitable. Not only is lactose known to be an allergen, but its dairy origins make it unattractive or even dangerous as an inhalation excipient for some patients.

Considering these drawbacks, pharmaceutical producers have begun to turn to alternatives such as mannitol. Widely used across various pharmaceutical dosage forms, mannitol is universally prized as a safe and effective excipient with broad patient appeal, and this is no different for DPI formulations. As a non-reducing sugar alcohol, mannitol offers superior chemical stability compared with reducing sugars such as lactose, making it particularly suitable for co-formulating with sensitive APIs, including proteins, peptides and drugs with primary amine groups, which are susceptible to Maillard reactions.[17,18]

Mannitol's crystalline and non-hygroscopic nature also ensures better physical stability and lower moisture uptake than lactose, making it the superior choice for maintaining powder flowability, preventing aggregation during storage and achieving consistent dose delivery.[17,19] Furthermore, mannitol's ability to be engineered into various particle sizes and morphologies allows for optimisation of aerodynamic performance, contributing to improved fine particle fraction (FPF) and deep lung deposition of the co-formulated drug.[20,21]

Directly comparing the performance of the two excipients in an exemplary formulation makes mannitol's advantages over lactose clear. In a recent product study, researchers at Roquette assessed the maximum FPF achievable with either a lactose or a mannitol carrier, mixed to form an interactive mixture with the APIs salbutamol sulfate and budesonide. The results showed that the mannitol-based formulations produced a significantly higher FPF than lactose carriers, with the best performance achieved with PEARLITOL® 200 INH mannitol, a specialised grade optimised for use in DPIs.

Whether opting for a lactose or mannitol carrier, in the case of devices such as GSK's Rotadisk or Diskus, the choice of capsule material is equally crucial. As in the world of oral drug delivery, gelatin is the traditional material of choice for encapsulating drugs for inhalation, but here again the tide is turning. A growing body of research points to the unsuitability of gelatin capsules for encapsulating hygroscopic APIs such as salbutamol sulphate, which can draw moisture from surrounding materials, thereby becoming unstable.

"A GROWING BODY OF RESEARCH POINTS TO THE UNSUITABILITY OF GELATIN CAPSULES FOR ENCAPSULATING HYGROSCOPIC APIs SUCH AS SALBUTAMOL SULPHATE, WHICH CAN DRAW MOISTURE FROM SURROUNDING MATERIALS, THEREBY BECOMING UNSTABLE."

Just as mannitol provides an effective alternative to lactose, hydroxypropyl methylcellulose (HPMC) offers a plant-based solution to the drawbacks of gelatin capsules, displaying excellent chemical stability and a low moisture content of between 4.5% and 6.5%, which is ideal for hygroscopic APIs. As found by Roquette's researchers, combining the improved powder flow and aerodynamic performance of high-quality mannitol with the optimal stability and delivery characteristics of HPMC-based capsules results in an inhalation formulation that delivers more lifesaving drug to the lungs. This shows that lactose is far from being the only option for impactful inhaled therapies.[12]

MYTH 3: INHALATION IS ONLY SUITABLE FOR THE TREATMENT OF PULMONARY CONDITIONS

While it is true that inhaled therapies are predominantly employed in the treatment of pulmonary diseases, reflecting their primary clinical application, this does not define the full extent of their therapeutic potential. DPIs in particular are emerging as a promising platform for systemic drug delivery, extending their utility beyond the localised treatment of lung diseases to encompass applications such as vaccine administration and therapies for central nervous system (CNS) disorders.[17,22,23]

For vaccine delivery, DPIs have been shown to trigger local mucosal immunity – which is critical for protection against respiratory pathogens – and systemic immune responses, all without the use of off-putting needles.[24] This approach offers obvious benefits in terms of patient compliance and can also contribute to improved vaccine stability at ambient temperatures, simplifying logistics to give more people access to vital vaccines.[17,24]

In the context of CNS disorders, while direct nose-to-brain pathways are more often associated with nasal delivery, systemic absorption via the lungs can still contribute to drug concentrations in the brain by bypassing peripheral metabolism.[25] Recent research highlights the potential for inhaled delivery to achieve improved pharmacokinetics and rapid onset of action for various neurological drugs, exhibiting once again that the opportunities offered by DPIs extend far beyond respiratory conditions.[25]

Harnessing all this potential relies heavily on the development of advanced excipients.[17] Safe, effective and widely applicable carriers such as mannitol will play a critical role in addressing emerging formulation challenges, such as safeguarding the stability of moisture-sensitive APIs or effectively masking unpleasant flavours or odours to ensure that these exciting new forms of drug delivery do not leave a bad taste in patients' mouths.[17]

A BREATH OF FRESH AIR

The common adage is that progress moves slowly in pharma, but that belies the substantial volume of cutting-edge research and discovery that takes place in labs around the world every day. The evolution of inhaled routes of administration from their aerosol propellant beginnings to DPIs capable of replacing parenteral vaccinations offers a perfect example of this dichotomy – both rapid and decade-spanning, both gradual and seismic. With millions more people each year requiring safe, effective and convenient treatments, no avenue for innovation should be closed to pharmaceutical formulators, particularly not one with as much multifaceted potential as inhaled therapies. So, with some of the more common myths debunked and the air beginning to clear, inhaled therapies could be poised for a whole new era of innovation.

"THE EVOLUTION OF INHALED ROUTES OF ADMINISTRATION FROM THEIR AEROSOL PROPELLANT BEGINNINGS TO DPIs CAPABLE OF REPLACING PARENTERAL VACCINATIONS OFFERS A PERFECT EXAMPLE OF THIS DICHOTOMY – BOTH RAPID AND DECADE-SPANNING, BOTH GRADUAL AND SEISMIC."

Dr Keat Theng Chow

Keat Theng Chow, PhD, is the Head of the Applied Sciences Pharma team for Greater Asia at Roquette Health & Pharma Solutions' Asia Pacific Innovation Centre in Singapore. Alongside her team, Dr Chow supports the strategic management of the centre's pharma innovation portfolio and oversees its operations management. Dr Chow joined Roquette in 2017 as a Pharmaceutical Research Manager following ten years in pharmaceutical product development with Abbott, AbbVie, MSD and A*Star. She holds a BSc in Pharmacy and a PhD in Pharmaceutics from the National University of Singapore and completed a postdoctoral fellowship at The University of Texas at Austin (TX, US).

E: pharma@roquette.com

Susana Ecenarro

Susana Ecenarro is the Vice-President of R&D for Qualicaps EMEA at Roquette Health & Pharma Solutions. In this role, she leads the region's research, development and regulatory strategy, guiding the innovation portfolio and overseeing operational execution across Europe, the Middle East and Africa. Ms Ecenarro joined Qualicaps after nearly two decades with Schering AG in Germany, where she held senior positions in quality, analytical development, technology transfer and operational excellence, followed by leading an Analytical Development R&D unit at Bayer Healthcare in Spain. She holds a bachelor's degree in Pharmacy and an MBA from IE Business School.

E: pharma@roquette.com

Roquette

1 rue de la Haute Loge, 62136 Lestrem, France

www.roquette.com

REFERENCES

1. *"Household air pollution". WHO, Oct 16.*
2. *Bikis A, "Urban Air Pollution and Greenness in Relation to Public Health". J Environ Public Health, 2023, Vol 2023, art 8516622.*
3. *Balch B, "Do seasonal allergies seem to be getting worse? Blame climate change". AAMC, Apr 2024.*
4. *"Occupational exposure and respiratory disease". European Environment Agency, Nov 2024.*
5. *"Dry Powder Inhaler Device Market Forecast, By Type, By Application, and By Region Forecast to 2034". Market Report, Reports and Data, Jun 2024.*
6. *Lumb AB, "Chapter 11: Nonrespiratory Functions of the Lung" in "Nuun's Applied Respiratory Physiology 8th Edition" (Lumb AB ed). Elsevier, 2024, pp 203–214.e1.*
7. *Tokarczyk AJ, Greenberg SB, Vender JS, "Oxygen Delivery Systems, Inhalation Therapy, and Respiratory Therapy" in "Benumof and Hagberg's Airway Management 3rd Edition" (Hagberg C ed). Saunders, 2013, pp 301–323.e2.*
8. *Tony SM, Abdelrahim MEA, "Inhalation Devices and Pulmonary Drug Delivery". J Clin Nurse Res, 2022, Vol 6(3), pp 54–72.*
9. *"Inhalers for COPD". Web Page, Healthline, accessed Oct 2025.*
10. *"The Pros and Cons of Dry Powder Inhalers and How to Use Them Correctly". Web Page, Healthline, accessed Oct 2025.*
11. *Mulpas J, "The Power of Pulmonary: Advances in Inhaled Drug Delivery Expand Respiratory Treatment Options". ONdrugDelivery, Issue 170 (Apr 2025), pp 8–12.*
12. *Ecenarro S, "The Capsule-Based DPI, An Environmentally Friendly & Efficient Dosage Form". ONdrugDelivery Magazine, Issue 72 (Dec 2016), pp 8–11.*
13. *Dolovich MB et al, "Device selection and outcomes of aerosol therapy: Evidence-based guidelines: American College of Chest*

Physicians/American College of Asthma, Allergy, and Immunology". Chest, 2005, Vol 127(1), pp 335–371.

14. *Shepherd J et al, "Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long-acting beta2 agonists for the treatment of chronic asthma in adults and children aged 12 years and over". Health Technol Assess, 2008, Vol 12(19), pp 1–360.*
15. *Panigone S et al, "Environmental impact of inhalers for respiratory diseases: decreasing the carbon footprint while preserving patient-tailored treatment". BMJ Open Respir Res, 2020, Vol 7(1), art e000571.*
16. *Hebbink GA et al, "Recent developments in lactose blend formulations for carrier-based dry powder inhalation". Adv Drug Deliv Rev, 2022, Vol 189, art 114527.*
17. *Ye Y, Ma Y, Zhu J, "The future of dry powder inhaled therapy: Promising or discouraging for systemic disorders?". Int J Pharm, 2022, Vol 614, art 121457.*
18. *Benetti AA et al, "Mannitol Polymorphs as Carrier in DPIs Formulations: Isolation Characterization and Performance". Pharmaceutics, 2021, Vol 13(8), art 1113.*
19. *Rhein N, Birk G, Scherließ R, "Characterisation of particle engineered Mannitol as alternative carriers in dry powder inhalation formulations". DDL 26, 2015.*
20. *Kaialy W et al, "Towards a more desirable dry powder inhaler formulation: large spray-dried mannitol microspheres outperform small microspheres". Pharm Res, 2014, Vol 31(1), pp 60–76.*
21. *Party P, Piszman ZI, Ambrus R, "Development of Mannitol-Based Microparticles for Dry Powder Inhalers: Enhancing Pulmonary Delivery of NSAIDs". Pharmaceuticals, 2025, Vol 18(6), art 923.*
22. *Tronde A, "Pulmonary Drug Absorption". Comprehensive Summaries of Uppsala Dissertations from the Faculty of Pharmacy 275, 2002.*
23. *Gunjal VB et al, "A Review On Novel Excipients". Int J Pharm Sci, 2023, Vol 1(09), pp 304–320.*
24. *Thakur A et al, "Optimizing the design and dosing of dry powder inhaler formulations of the cationic liposome adjuvant CAF®01 for pulmonary immunization". Front Drug Deliv, 2022, Vol 2, art 973599.*
25. *Tai W, Kwok PCL, "Recent advances in drug delivery to the central nervous system by inhalation". Expert Opin Drug Deliv, 2022, Vol 19(5), pp 539–558.*