PULMONARY & NASAL DRUG DELIVERY

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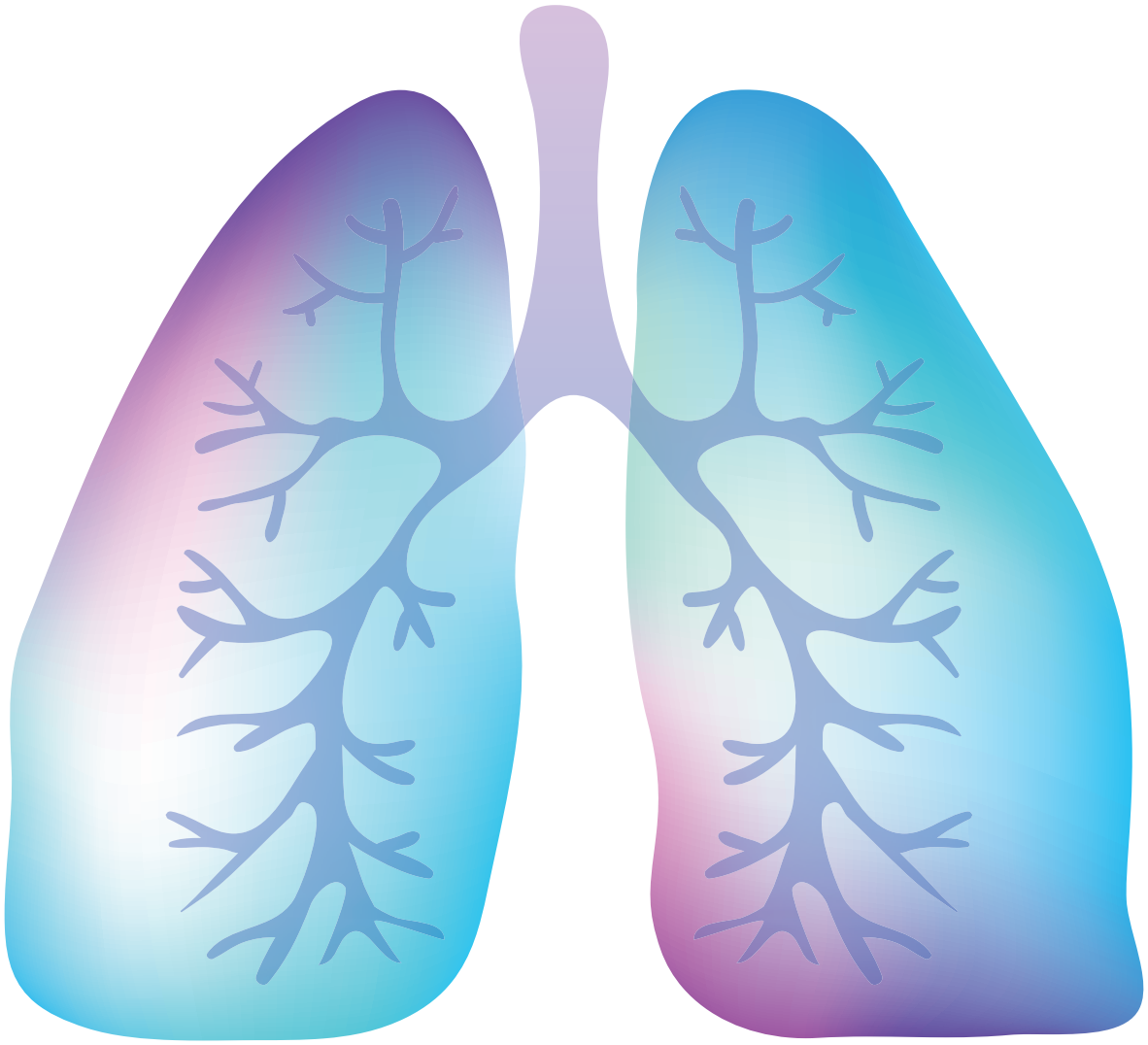

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RETRONOSE: IMPROVING NASAL DELIVERY THROUGH A NEW AND IMPROVED DEVICE

Here, Laurent Vecellio, PhD, Research Engineer, CEPR, INSERM U1100, University of Tours, and Scientific Director, Nemera; Déborah Le Pennec, Research Technician, CEPR, INSERM U1100, University of Tours; Guillaume Grevin, Senior Design Engineer, Nemera; and Alain Regard, Technology Product Manager, Nemera; evaluate the performance of the RetroNose nasal drug delivery device.

The clinical efficacy of a nasal treatment depends on how it is deposited in the nose. Since the pharmaceutical target (local, systemic, brain) is directly related to a specific nasal anatomical site, it is becoming increasingly important for device manufacturing experts to support new drug development in this therapeutic area.

Nasal drug delivery is a non-invasive method that allows for a rapid, high and local therapeutic effect. It offers significant opportunities for new drug development looking to deliver systemic drugs, vaccines and treatments for the central nervous system. The number of applications using the nasal route for local and systemic treatments is on the rise.

At Nemera, integrating early stages of drug development and translating the work into impactful product designs aligns perfectly with our purpose – we put patients first. Furthermore, our ultimate goal is to produce improved drug administration devices that in turn increase therapeutic efficacy. To achieve this objective, it is critical to get input and feedback across the various stages of development to ensure we avoid eventual deficiencies and use time and resources optimally.

> "The main objective of our study was to evaluate the influence of the mouthpiece design on deposition in the upper airways using a nasal cast."

With this in mind, three years ago we initiated a collaboration with the Research Center for Respiratory Diseases (CEPR) of Inserm and the University of Tours (France) to develop a different and portable delivery technology called RetroNose. CEPR's know-how in respiratory preclinical and clinical research joining forces with Nemera's expertise in the development of drug delivery devices made for a powerful partnership. The resulting technology, RetroNose, enables better drug deposition in the distal region of the nose without lung deposition.

The first outcomes of our collaboration with CEPR were presented in 2018, to demonstrate the advantages of RetroNose – resulting in improved particle deposition in an upper airways model for local, vaccine and systemic drugs delivery.

RETRONOSE AT A GLANCE

The concept of nasal drug delivery via the oral route using a pressurised metered dose inhaler (pMDI) in an upper airways model has been demonstrated *in vitro*, with promising results. All anatomical regions, except for the upper part of the nasal cavity, were successfully targeted, with relatively homogenous deposition. This nasal drug delivery system could be of interest for both local and systemic drug delivery, and for the delivery of vaccines.

RetroNose is a completely new drug delivery concept to dispense drug formulation to the nasal cavity. The principle of this concept is to deliver a spray through the oral cavity to deposit the drug in the nasal cavity from rear to front. To avoid aerosol penetration in the lung and to ensure deposition efficacy, the

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Figure 1: RetroNose concept.

aerosol drug is automatically delivered during the nasal expiratory phase. The drug particles are driven by the expiratory flow through the oropharynx, then the rhinopharynx finally entering the nasal cavity where they are deposited on all nasal surfaces. Figure 1 summarises the process.

In vitro deposition studies performed in nasal casts have shown a homogeneous deposition of drug in the rhinopharynx and the nasal cavity, where a standard nasal spray would offer a proximal deposition localised in the front of the nasal cavity (Figure 2).[3] The deposition profile can be tweaked through the adjustment of some key design parameters of the drug-device combination product. For example, RetroNose also delivers drug into the sinuses, where a standard nasal pump will not.

The RetroNose concept can be compared to the retro nasal olfaction when you eat or drink. Odour molecules can easily travel from the mouth to the nasal cavities via this connection in the throat to reach the olfactory receptors and evoke a smell perception. This is why patients with chronic rhinosinusitis (CRS) often complain of alterations in the "taste" or "flavour" of food and drink. They have deficits in retro nasal olfaction, with worse scores in patients with nasal polyposis.[1]

CLINICAL EVIDENCE

A recent study on CRS patients has shown how corticosteroid deposition distribution in the nasal cavities can have an impact on clinical outcomes.[2] It demonstrated the importance of homogeneous deposition in the different target regions of the nasal cavity to improve treatment efficacy.

Additionally, in another recent study, five asthmatics with rhinosinusitis were successfully treated with an aerosol therapy exhaled through the nose using a similar concept.[4] Hence the use of a pMDI as an alternative to a nebuliser for delivering drugs to the nose via the buccal cavity is relevant.

INFLUENCE OF SPACER & MOUTHPIECE ON RETRONOSE PERFORMANCE

We have used a nasal cast to study the influence of a spacer and different mouthpiece designs on deposition in the upper airways from RetroNose delivery.

Spacer

A range of materials was used in the design of this study, such as a canister filled with HFA 134a propellant (no surfactant) with a 90 µL valve and a pMDI actuator (NM200, H&T Presspart, Germany). Another canister with three particle sizes (3, 12 and 20 µm in terms of volume mean diameter) has also been tested.

The doses used were 100 µg delivered by three pMDI suspensions. The mouthpieces used for the study were: an actuator used with a standard mouthpiece without spacer; and an actuator used with a mouthpiece including a spacer.

The aerosol deposition in the upper airways was then studied using the VCU anatomical model (Virginia Commonwealth University, Richmond, VA, US). The regions of interest to the model being:

- Nasal cavities
- Mouth
- Oropharynx
- Trachea
- Lungs.

The trachea model connected to an absolute filter, a humidified air source

"RetroNose also delivers drug into the sinuses, where a standard nasal pump will not."

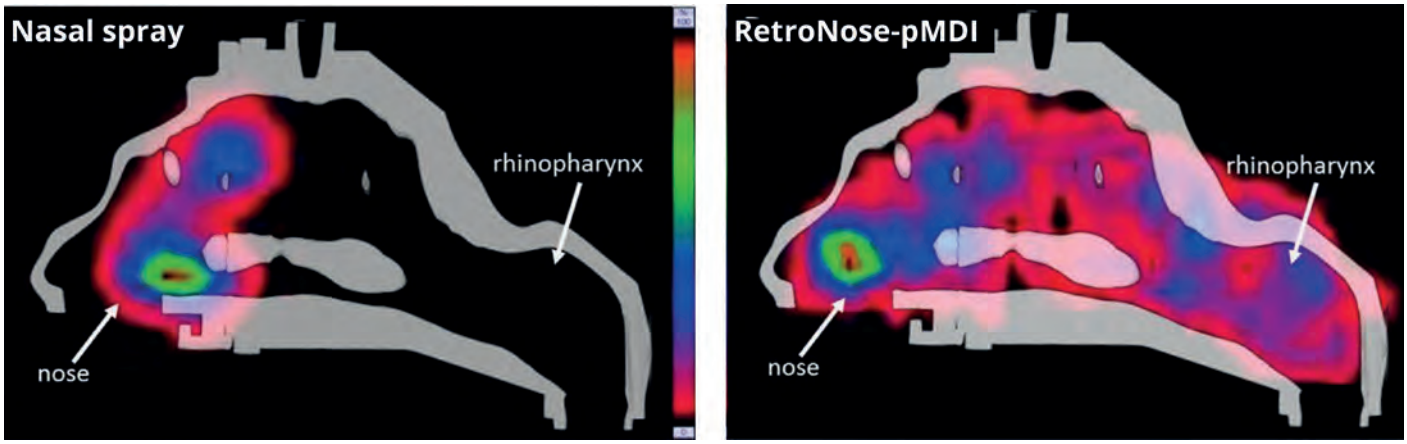

Figure 2: Scintigraphy deposition in nasal cast models using a nasal spray pump and the RetoNose pMDI.

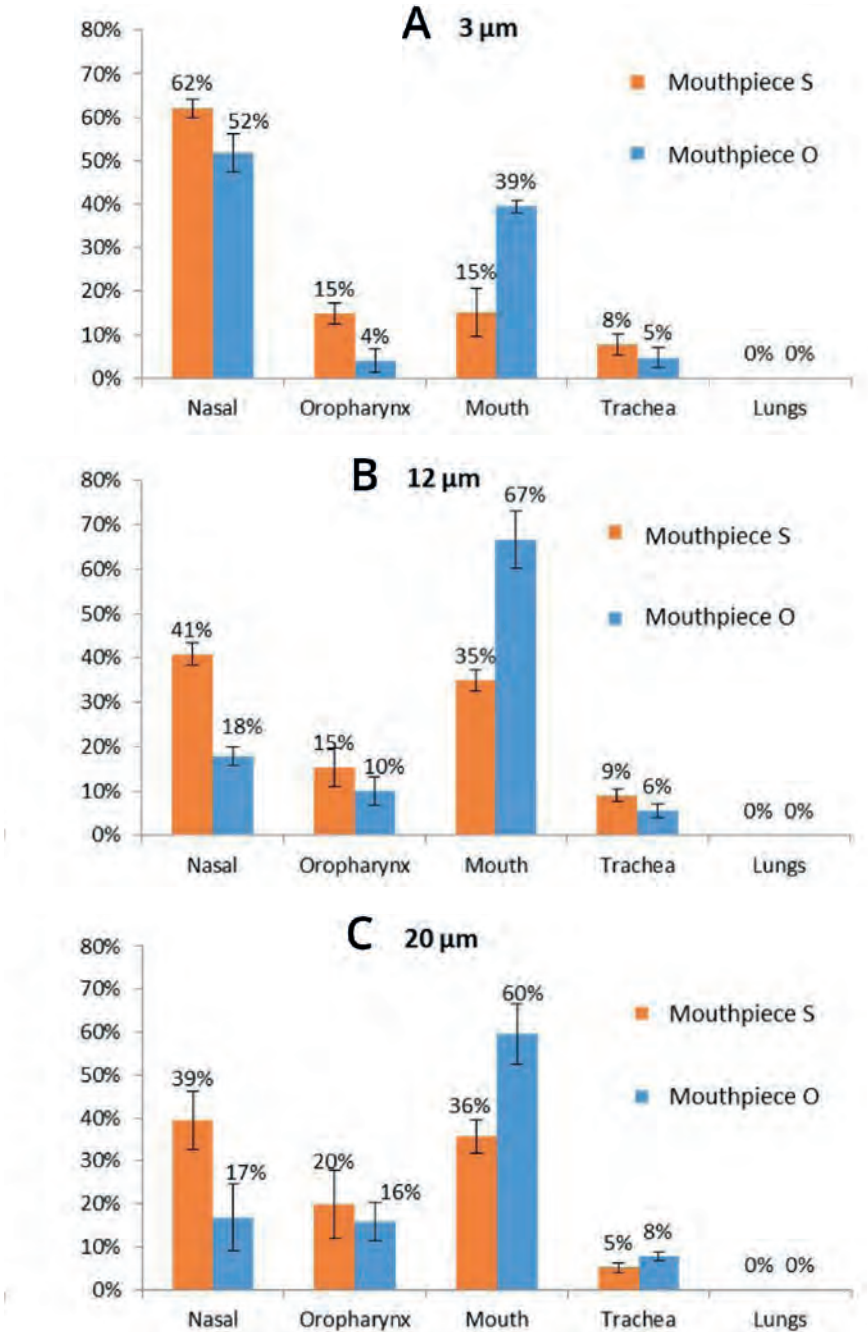

Figure 3: Influence of spacer on deposition in the different regions of an upper airway VCU cast model using RetroNose.

at a flow rate of 60 L/min studied the expiratory flow rate and a vacuum pump connected to an absolute filter located near to the nose model collected the totality of the exhaled aerosol. The active compound was assayed by a spectrophotometric method (Figure 3).

Results of the study showed the following:

- No active compound was detected in the filter (lung model)

The below observations were drawn using mouthpiece-S in comparison with mouthpiece-O:

- A reduced deposition in the mouth was observed
- An enhanced deposition in the nasal cavities
- A decrease of emitted dose (-32% for pMDI-A, -52% for pMDI-B, -15% for pMDI-C).

These results can be explained by the spacer effect for the optimised mouthpiece decreasing the particle velocity, collecting larger particles and consequently reducing the particle impaction in the mouth. Comparison between particle sizes shows an increase of nasal penetration when there is a decrease of particle size.

Mouthpiece Design

The design development also included work around the tongue position to open the oropharynx and make an easier aerosol pathway to the nasal cavities. A specific mouthpiece has been designed and evaluated on six healthy volunteers. As opposed to a standard mouthpiece that doesn't provide easy access to the oropharynx, the RetroNose optimised mouthpiece gives direct access to the oropharynx through the soft palate and the tongue (Figure 4).

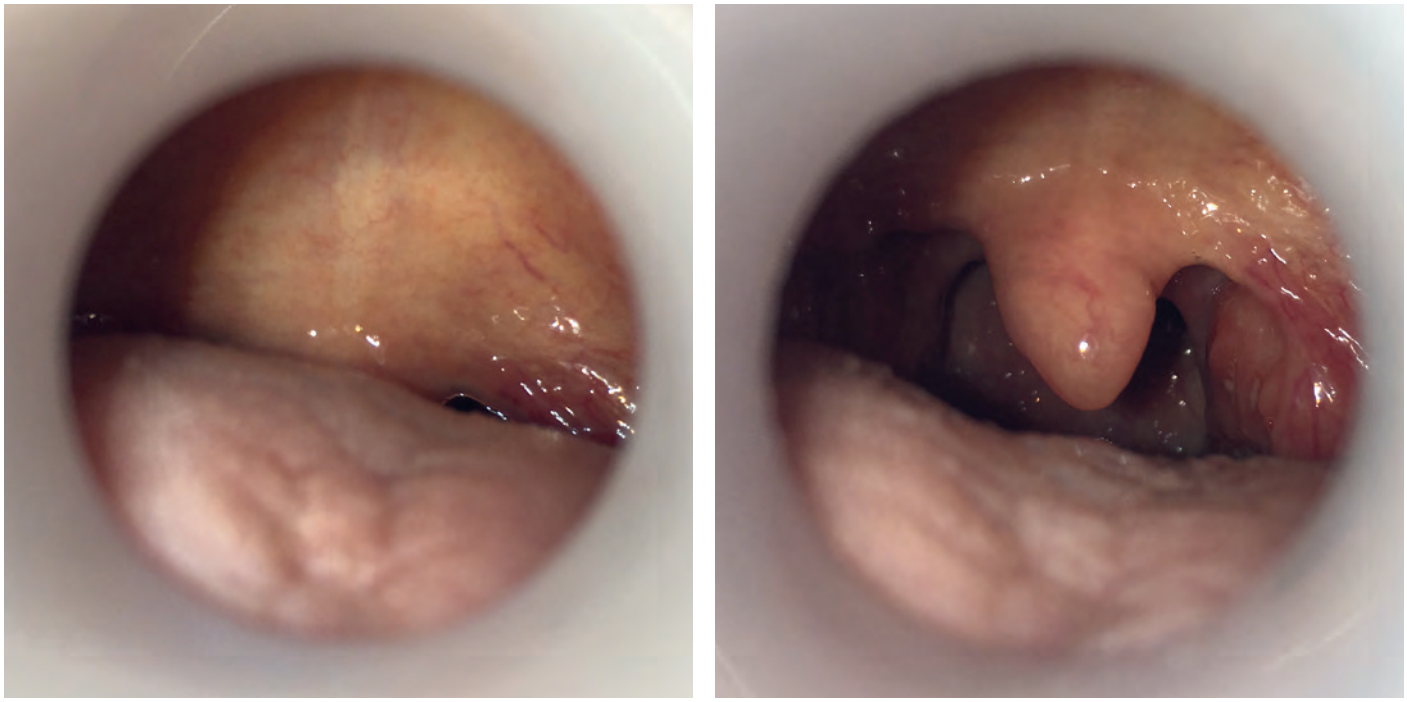

Figure 4: Images of the soft palate with mouthpiece O (left) and mouthpiece S (right) showing the open aerosol pathway through the oral cavity, giving access to the oropharynx. RetroNose mouthpiece to help the aerosol pathway through the oral cavity.

In order to evaluate the influence of the anatomical mouthpiece on drug deposition, we developed two different upper airway cast models. Both have the same nasal cavities but with two different oral cavity models: one corresponding to the anatomy when using a standard mouthpiece and the other corresponding to the anatomy when using the anatomical RetroNose mouthpiece. We measured the deposition distribution with the RetroNose pMDI (12 µm of VMD, 60 L/min) using these models and we observed a fourfold difference in terms of deposition in the mouth when using the anatomical mouthpiece compared with the standard mouthpiece. Mouthpiece design helped to improve the RetroNose pMDI device performances in terms of deposition reduction in the oral cavity.

MAIN BENEFITS OF RETRONOSE

The results of this study reinforce the benefits of the RetroNose technology.

RetroNose improves drug efficacy via a wide and homogeneous deposition:

- applicable to local treatment (e.g. corticosteroids for CRS)
- applicable to systemic treatments
- low deposition distribution variability versus nasal sprays.

RetroNose technology allows a deposition in the back of the nasal cavity and the rhinopharynx, presenting opportunities:

- to treat nose and throat in one go
- for vaccines (lymphatic system)
- to reduce patient-to-patient variability by avoiding the nasal valve passage.

The RetroNose pMDI concept involves device operation steps similar to breath-actuated pMDIs. Triggering upon positive pressure in the mouth from nasal expiration is possible with a mechanical trigger. and also possible with electronics.

CONCLUSION

Nemera understands how vital it is to continue exploring customised solutions for nasal delivery treatments to address unmet medical needs. RetroNose targets nasal disorders through the oral cavity.

An optimised mouthpiece including a spacer reduces the mouth deposition when using the RetroNose technology with a pMDI to target the nasal cavities. This conclusion is aligned with similar studies conducted with pMDIs for lung delivery. Spray triggering upon positive pressure in the mouth seems a good path to ensure drug delivery in the nasal expiratory phase. In the future, a potential next step would be to test the clinical efficacy of RetroNose and its acceptance by patients through the human factors perspective.

ABOUT THE COMPANY

Nemera is a world leader in the design, development and manufacture of drug delivery devices for the pharmaceutical, biotechnology and generics industries. Nemera offers a comprehensive portfolio of products and services across ophthalmology, nasal, inhalation, dermal, transdermal and parenteral delivery. Nemera's vision is to be the most patient-centric drug delivery device company. Nemera always puts patients first, providing high-quality solutions that have a demonstrable impact on patients' health.

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