NASAL DRUG DELIVERY VIA THE ORAL ROUTE USING A PMDI

In this article, Laurent Vecellio, PhD, Research Engineer, University of Tours, and Scientific Director, Nemera (previously employed by Aerodrug-DTF Medical), Déborah Le Pennec, Research Technician, University of Tours, and Alain Regard, Technology Product Manager, Nemera, discuss a study Nemera has funded into the retronose concept, using a pMDI to deliver to the nasal cavity via the oral route during exhalation through the nose.

INTRODUCTION

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. A recent study in patients with chronic rhinosinusitis has shown how deposition of corticosteroids in the nasal cavities can have an impact on clinical outcomes.[1] This study demonstrated the importance of the delivery device on drug efficacy.

Standard nasal sprays have limitations regarding the reproducibility and the deposition efficacy in the distal region of interest in the nasal cavities. An alternative, the "retronose" concept (Figure 1) has been proposed as a means to reduce variability and improve drug deposition in specific nasal zones, consisting of drug administration through the buccal cavity during the nasal expiratory phase.

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Using this method, a different nebuliser concept has been developed for better drug deposition in the distal region of the nose,[2,3] without lung deposition. Drug particles enter the nasal cavities through the rhinopharynx, which has a significant impact on drug deposition. Additionally, in a recent study, five asthmatics with rhinosinusitis were successfully treated with an aerosol therapy exhaled through the nose[4] using a similar concept.

In the study funded by Nemera presented here, the use of a pressurised metered dose inhaler (pMDI), as an alternative to a nebuliser, for delivering drugs to the nose via the buccal cavity was explored. Specifically, the study focused on the influence of particle size and the expiratory flow rate on particle deposition in an upper airways model using a standard pMDI.

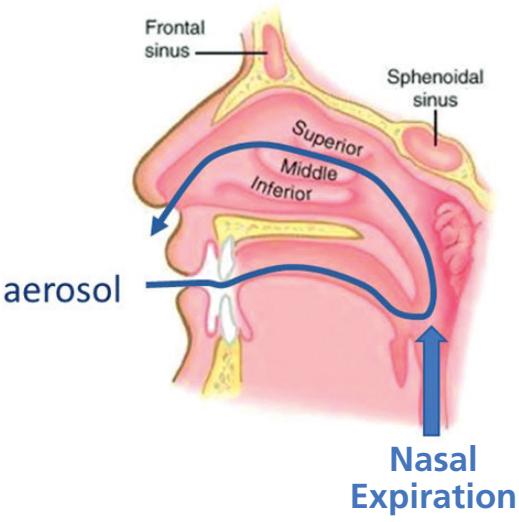

Figure 1: The retronose concept.

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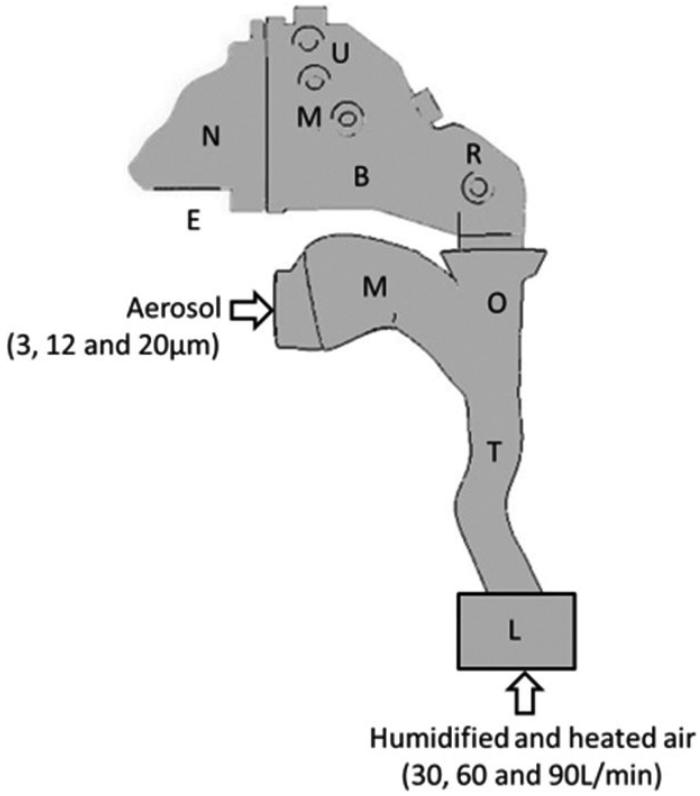

Figure 2: Experimental set up using the VCU upper airways model.

METHOD

A pMDI filled with HFA 134a propellant (no surfactant) was used with a 90 µL valve system (Inhalia®, Nemera) and an actuator (NM200, Bespak, Germany). Three different particle sizes (3, 12 and 20 µm in terms of volume mean diameter) of a model drug were put in the canisters, resulting in three different pMDI suspensions (pMDI-A, pMDI-B, pMDI-C) delivering 100 µg of drug per dose. Aerosol particle size produced was measured using a cascade impactor operating at 30 L/min (Next Generation Impactor, Copley Scientific, UK).

Aerosol deposition in the upper airways (Figure 2) was studied using an anatomical model[5] developed by the Virginia Commonwealth University (Richmond, VA, US). The trachea model was connected to an absolute filter (L) and a humidified air source at three different flow rates: 30, 60 and 90 L/min. A vacuum pump connected to an absolute filter (E) was located near to the nose model for collecting the totality of the exhaled aerosol from the model. Eight regions of interest were defined in the upper airway model:

- Mouth (M)
- Trachea (T)
- Oropharynx (O)
- Rhinopharynx (R)
- Upper part of the nasal cavity (U)
- Middle part of the nasal cavity (M)
- Bottom part of the nasal cavity (B)
- Nostrils (N).

The active compound was assayed by a spectrophotometric method.

RESULTS

The aerosol particle sizes produced by pMDI-A and pMDI-B, measured by cascade impaction, were characterised by a mass median aerodynamic diameter (MMAD) as shown in Table 1. The MMAD produced by pMDI-C could not be calculated due to its high deposition in the induction port of the cascade impactor. Regarding the percentage of particle size lower than 10 µm. The results obtained with pMDI-C are consistent with the particle size put in the canister (Table 1).

	pMDI-A	pMDI-B	pMDI-C
MMAD (µm)	3.7 ± 1.3	14.8 ± 0.4	N/A
Particle size lower than 10 µm (%)	70 ± 17	29 ± 8	3 ± 1

Table 1: Aerosol particle size data for the three pMDIs.

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An increase of drug penetration into the nasal cavity was observed with a decrease of particle size. No active compound was detected depositing into the filter corresponding to the lung model (L). No statistical difference was observed on the influence of expiratory flow rate on aerosol deposition in the oropharynx, mouth or trachea, and drug penetration into the nasal cavity ($p>0.05$, Friedman test, GraphPad Prism V5) for all three flow rates were examined.

The drug deposited homogenously in all regions of the nasal cavity (Figure 3). An exception was the upper part of the nasal cavity, where deposition was relatively low (less than 2%), independent of particle size or expiratory flow rate. An increase in particle size was associated with a decrease in exhaled fraction. An increase in expiratory air flow rate was also associated with a decrease in exhaled fraction. There was no statistical influence of expiratory flow rate on deposition fraction in the other regions of the nasal cavity, N, U, M, B and R ($p>0.05$, Friedman test, GraphPad Prism V5).

CONCLUSION

The concept of nasal drug delivery via the oral route using a 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.

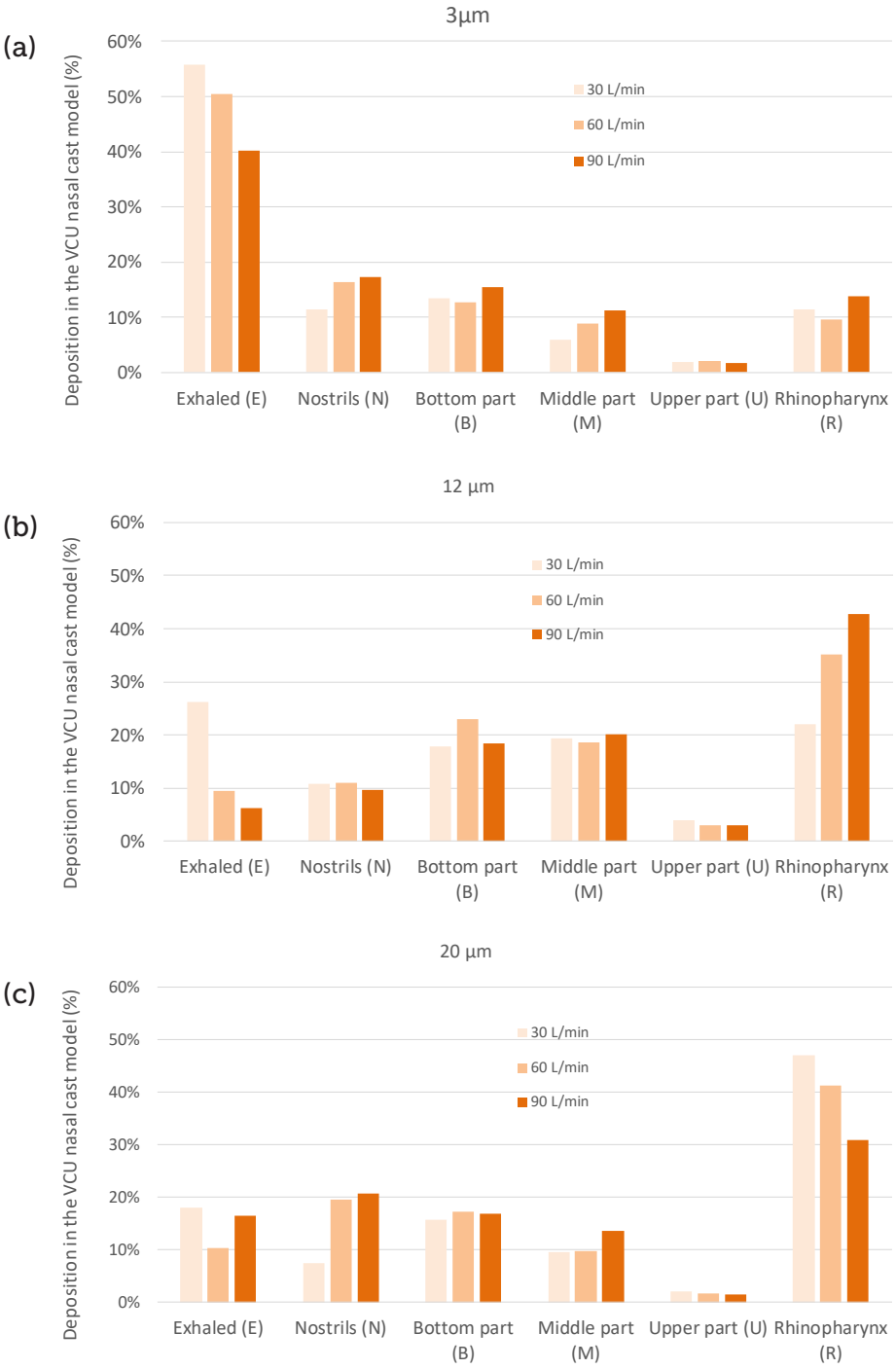

Figure 3: Deposition in the nasal cavity model expressed in term of total drug delivered in the nasal cavity (N+U+M+B+E+R) for 3 µm (A), 12 µm (B) and 20 µm (C) (n=3).

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ABOUT THE COMPANY

Nemera designs, develops and manufactures nasal, buccal, auricular, ophthalmic, pulmonary, parenteral (passive safety devices autoinjectors, pens, and implanters), dermal and transdermal drug delivery devices for the pharmaceutical, biotechnology and generics industries.

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ABOUT THE AUTHORS

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Alain Regard, Technology Product Manager, Nemera, graduated with a degree in Polymer Engineering and Processing from ESP in Oyonnax, France. After a long experience in design and development in the automotive industry, he joined the company in 2010 as a product development leader. Mr Regard, today one of the key technical experts of Nemera's Innovation Center for Devices (ICD), leads the nasal and dermal developments. He drives some of Nemera's own IP projects as well as working on several customer product developments in the field of nasal and dermal applications.

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