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CONTENTS
Aqueous Agenda - Navigating Nasal Knowledge Space

Speaker Articles

Poster Articles

Intranasal Vaccination: Rationale, Progress and Challenges

Julie D. Suman

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KEYWORDS: vaccines, respiratory virus, nasal spray, nasal drug delivery, NALT, COVID-19

SUMMARY

Interest in intranasal vaccination development accelerated due to the COVID-19 pandemic. The nasal cavity is ideally suited to tackle respiratory viruses as the nose is the first port of entry into the body. In addition, nasal vaccinations induce both mucosal and systemic immunity. Mucosal immunity can prevent viral shedding, which is key to halting disease spread.

Nasal vaccine formulations are now in development for SARS-CoV-2, influenza and Respiratory Syncytial Virus (RSV). As opposed to intramuscular injection, a particulate is needed to interact with immunocompetent cells in the nasal mucosa. In addition, the vaccine will need to overcome mucociliary clearance. Therefore, careful formulation development is needed to advance effective nasal vaccine.

The deposition target for most nasal vaccines in the nasal associated lymphoid tissue (NALT) located in the nasopharynx. Device performance and use in the hands of the patient also become important considerations for nasal vaccines. In addition, developers should also consider delivery aspects to children in pediatric populations.

INTRODUCTION

Respiratory viruses such as SARS-CoV-2, influenza, RSV, continue to dominate the news. The COVID-19 pandemic bolstered awareness of the critical importance of vaccines to the health and wellbeing of people around the world. To date, over 13.37 billion coronavirus vaccine doses have been administered worldwide [1]. In parallel, there has been significant growth in vaccine programs with more than 3,300 vaccines, covering over 400 indications in development for both prophylaxis and treatment [2]. While intramuscular injection remains the dominant route of administration for vaccines, the respiratory nature of SARS-CoV-2 has resulted in increased interest in intranasal vaccine development. Intranasal vaccines have several advantages over other routes of administration. Nasal vaccination results in both mucosal and systemic immunity and mucosal immunity plays a key role in preventing viral shedding and subsequent disease spread.

The nasal route also has the advantage of avoiding enzymatic degradation of the antigen, ease of administration, and eliminates the use of needles. Needle phobia should not be underestimated. A review of needle fear estimated that 20–50% of adolescents exhibited a fear of needles [3]. While that fact may not be surprising, analysis also indicated that one in 13 workers in hospital-based healthcare avoided the influenza vaccine due to needle phobia [3].

INTRANASAL VACCINE MECHANISMS

The nasal cavity contains important immunocompetent cells making it an ideal target for vaccine delivery. The primary target is the NALT located in the nasopharynx (Figure 1). The NALT consists of subepithelial B-lymphocytes, CD4+ and CD8+ T-lymphocytes, phagocytic antigen presenting cells (APC) such as macrophages and dendritic cells (DC) [4]. DCs are also present throughout the nasal epithelia. Local adaptive immune responses are triggered when a pathogen or antigen interacts with APCs triggering B and T lymphocytes within the NALT. B cells activate the formation of immunoglobulin A (IgA) antibodies triggering a localized mucosal immunity. DCs also transport antigens to draining lymph nodes initiating a systemic immune response. The NALT can illicit both local and systemic immunity, which is not always the case for oral or vaginal mucosal tissues [4].

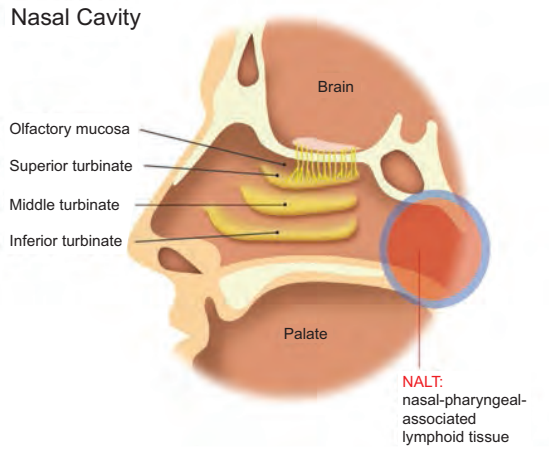

Figure 1. **Side view of the nasal cavity representing key components for drug delivery. The turbinates increase the surface area of the nose, making them a target for systemic absorption. The olfactory region has the potential to transport molecules in the cerebrospinal fluid. The NALT, located in the nasopharynx, remains the key target of nasal vaccination.**

Nasal vaccines have been approved as the primary defense for influenza (FluMist® Quadrivalent, AstraZeneca) and COVID-19 (iNCOVACC®, Bharat Biotech, India), and Convidecia Air TR delivered via inhalation (CanSino BIO, China). RSV nasal vaccines are also currently in clinical trials. In addition, using nasal vaccines as a COVID-19 booster is being explored to address waning antibody levels and manage spreading of more transmissible SARS-CoV-2 variants. The 'prime and spike' concept utilizes existing immunity generated injection ('prime') to elicit mucosal immune memory within the respiratory tract by using unadjuvanted intranasal 'spike' booster [5].

FORMULATION CONSIDERATIONS

Nasal vaccine platforms in development utilize similar formats to injectable vaccines including live attenuated, subunit, viral vectors and inactivated forms as well as DNA and mRNA forms. Injectable mRNA vaccines have proven to be a promising alternative to conventional vaccine approaches because of their high potency, capacity for rapid development and potential for low-cost manufacture and safe administration. Currently marketed nasal vaccines utilize live attenuated platforms. For a nasal vaccine to be effective, it must be delivered in particulate form [6] which differs from injectable strategies. The antigen itself is the particulate in live attenuated vaccines. However, nanoparticle formulations that encapsulate the antigen such as in the case of mRNA are routinely used. Studies have shown that the optimal particle size for DC update is between 200–300 nm [6]. Particulate systems smaller than 5 microns can stimulate both local and system immune responses in the nose. Adjuvants are used to help potentiate the antigen response. Selection of an appropriate adjuvant for nasal vaccines has been limited to bacterial, cytokine, particulate systems such as chitosan, and nucleic acids. A case study reported Bell's Palsy in 46 patients that received an influenza nasal vaccine which included the bacterial adjuvant, *E. coli* heat-labile toxin (LT) [7]. It was hypothesized that LT entered the brain via the olfactory region resulting in this adverse event. The product was subsequently withdrawn from the market. As a result, it is advisable to avoid deposition in the olfactory region with a nasal vaccine, particularly with a live vaccine or formulations with adjuvants.

Mucociliary clearance must also be considered. Movement of the mucus layer is rapid such that the nose can clear itself in 15 to 30 minutes. Depending on the size and surface charge of vaccine formulations [8], the mucus layer may trap particulate systems and prevent uptake into immunocompetent cells. Therefore, cationic nanoparticles should be considered as they may improve retention time in the nasal cavity. In addition, the positively charged particles may also enhance the immune response.

Optimization of the formulation and device is essential for nasal administration. A Phase I clinical trial reported intranasal vaccination with ChAdOx1nCoV-19 (AstraZeneca, UK) in healthy adults [9]. The study used the same formulation of ChAdOx1nCoV-19 as that licensed for intramuscular use in the United Kingdom. The vaccine was administered in a semi-recumbent position using a MAD300 intranasal mucosal administration device (Teleflex Medical, Penn, USA) [9]. While the results indicated tolerability of the formulation, the intranasal vaccine failed to reach its immunogenicity targets. The authors acknowledged that the lack of response was likely due to a lack of formulation and device optimization for nasal administration. This highlights the needs to address the specificities of the nasal cavity and NALT when developing an intranasal vaccine.

INTRANASAL VACCINE DELIVERY SYSTEMS

The deposition site in the nasal cavity has always been linked to response and this is also the case for intranasal vaccines. Therefore, the device (Figure 2) plays a key role to produce droplets in the correct size range. The device should also not impact the integrity of the antigen. Aqueous nasal sprays designed for vaccination typically produce droplets in the 20 to 90 μm range (Figure 3). That range allows for deposition in the turbinate region and prevents lung deposition. To target the NALT, the ideal droplet size is in the 7 to 17 μm range [10]. However, a nasal spray cannot generate a considerable amount of droplets in this size range. Therefore, it is believed that deposition in the turbinate region will allow the formulation to eventually be transported to the NALT region by mucociliary clearance mechanisms.

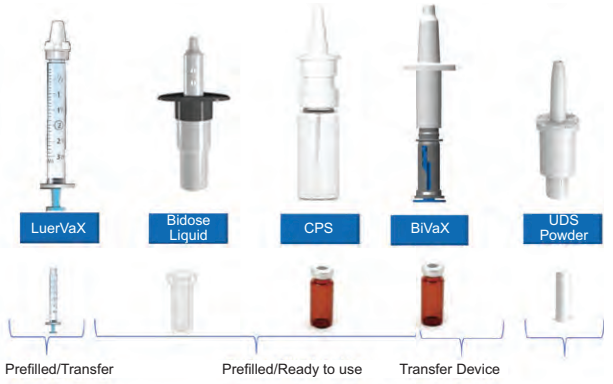

Figure 2. **Examples of aqueous and powder nasal vaccine platforms (Aptar Pharma, France). To accommodate existing injectable vaccine manufacturing prefilled and transfer devices were developed. Transfer devices allow the formulation to be withdrawn directly from the vial. The Bidose Liquid and CPS pumps are based on approved nasal platforms and can be adapted for vaccines.**

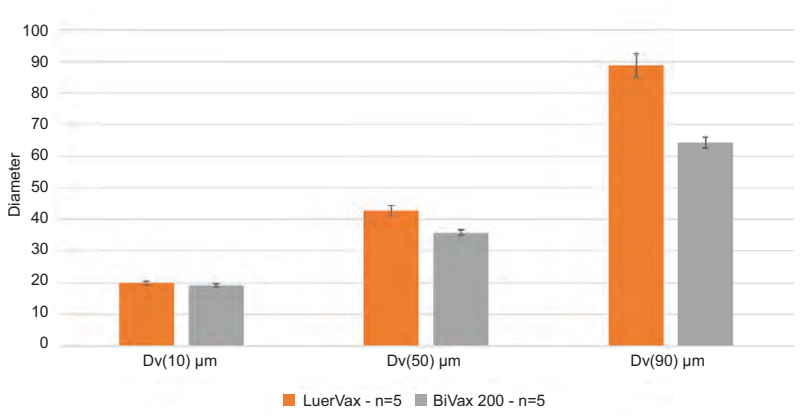

Figure 3. **Droplet size distribution measured by laser diffraction of two intranasal vaccine systems, LuerVax and BiVax (Aptar Pharma, France). Both devices were filled with water and positioned 4 cm from the laser beam (n = 5, Mean ± SD).**

Instructions for use may also play an important role in vaccine delivery. An *in vitro* nasal cast (AeroNose™, Aptar Pharma) was used to quantify deposition of the BiVax device (Figure 4). The BiVax device is a complete assembled transfer unit for aqueous or reconstituted formulations. The device is available in 200 or 500 µL and an integrated dose divider simplifies dosing to each nostril. Three angles of insertion from the horizontal were utilized with water filled into the 200 µL device. This study demonstrated that a 30° angle produced a higher percent deposition in both turbinates and nasopharynx.

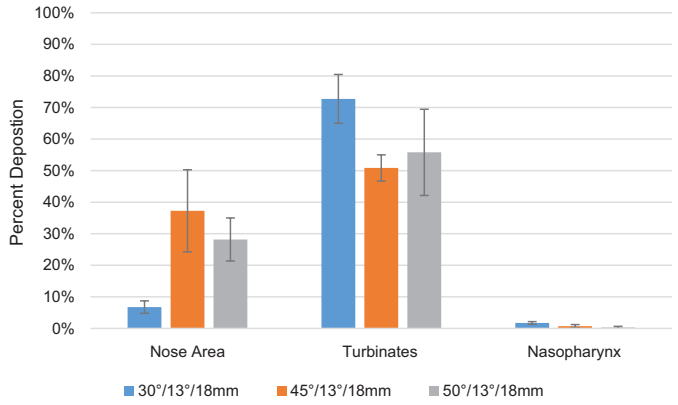

Figure 4. **Percent deposition of a 2 centipoise (cP) placebo formulation consisting of 7.5% fluorescein in water using the BiVax device. The nasal spray was inserted into the *in vitro* nasal cast at 30°, 45° and 50°. The insertion depth (18 mm) and coronal angle (13°) were held constant.**

Nasal powder formulations are gaining interest as a platform for vaccine administration because of their improved stability for sensitive biologic formulations and their potential to avoid cold chain storage. Furthermore, nasal powders have the ability to deliver a larger dose compared to aqueous platforms. Nasal powders can be formulated to include mucoadhesive and stabilizing excipients as well. Spray drying is common practice for producing powders for inhalation but may not be suitable for all biologic products. The feasibility of thin-film freeze-drying (TFF Pharmaceuticals, USA) was evaluated with a model antigen formulation delivered using a Unit Dose Nasal Powder device (UDSp, Aptar Pharma) [11].

In this study, ovalbumin (OVA) was formulated with a liposomal adjuvant, which is being assessed for nasal administration [12]. Thin-film freeze-drying was used to convert the liquid vaccine containing sucrose at a sucrose to lipid ratio of 15:1 (w/w), in the presence or absence of carboxymethyl cellulose sodium salt (CMC) as a mucoadhesive agent. Characterization of the formulation indicated that antigen integrity was maintained during processing as well as after spraying from the nasal powder device. *In vitro* deposition was assessed in a child and adult nasal cast (Figure 5) using a Taguchi L8 orthogonal array to identify the optimal administration parameters. The results indicated that the nasal powder formulation was suitable for intranasal administration. The optimal parameters for the nasal powder were no inhalation flow rate with 45° sagittal and 20° coronal angles, respectively.

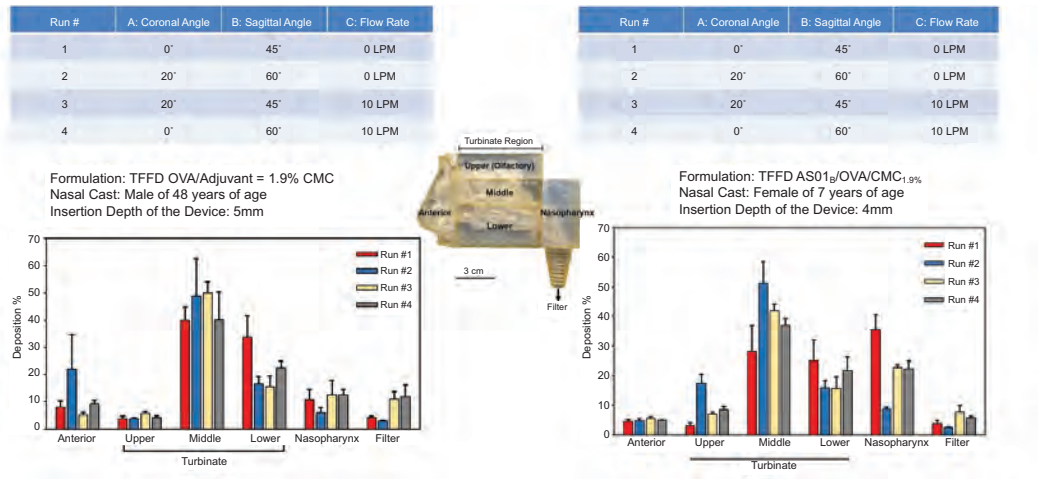

Figure 5. **Coronal angle, sagittal angle and inhalation flow rate were evaluated using an adult and child nasal cast. A model OVA vaccine containing a liposomal adjuvant and CMC were delivered using an UDSp nasal powder device. Deposition in the target regions (middle turbinate, lower turbinate and nasopharynx) was optimal with 0 LPM inhalation, 45° sagittal and 20° coronal angles.**

INTRANASAL VACCINES FOR CHILDREN

There is a growing interest to understand device usability between adults and younger populations. Therefore, there is value in understanding delivery in children and pediatrics for intranasal vaccination. An *in vitro* nasal cast study evaluated nasal deposition in 2-, 5- and 18-year-old models [13] using a mucosal atomizer. The study also assessed head position: supine, supine with head backwards at 45°, and sitting with head backwards at 45°. The results indicated that head position did significantly influence posterior deposition in the 2- and 5-year-old nasal casts. Limited nasal spray deposition and performance exists in the pediatric population. Another recent study attempted to understand the impact of device performance using *in vitro* nasal casts in infants [14]. Four nasal spray devices were evaluated in five nasal airway replicas (three to 24 months). The nasal casts were positioned head leaning backwards at 45°. The results indicated that delivery efficiency was affected by either the spray droplet size distribution or the distance between the nozzle tip and the internal nasal valve.

CONCLUSIONS

Intranasal vaccination offers clear advantages compared to injectable and other mucosal delivery systems. Ease of use, avoidance on injection and both mucosal and systemic immunity being key. The last few years have rapidly advanced clinical trials in this growing area, in which there has been little historical data. Formulation optimization, selection of the delivery system, and instructions for use all play a key role in targeting immunocompetent cells.

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Dual Nasal and Pulmonary Targeting to Optimize Mucosal Absorption: Exploring Methods, Devices and Formulations

O. Lastow, M. Viklund, S. Karlsson, V. Åkerberg and M. Ekström

Iconovo AB, Lund, Sweden

KEYWORDS: Dry powder inhalers (DPIs), dual targeting, nasal, pulmonary, nasal cast, vaccines

SUMMARY

Dual nasal and pulmonary targeting offers the potential to maximize mucosal absorption in the respiratory tract which may result in more efficacious vaccines and treatments against respiratory viruses. Tests of commercially available dry powder inhaler (DPI) products suggest that it is feasible to simultaneously deliver drug to the nasal cavity, to the oropharyngeal region and to the lung. An effective deggregation mechanism, capable of producing an aerosol optimized for pulmonary delivery, is most likely the best strategy for combined nasal and pulmonary dry powder delivery.

INTRODUCTION

Similar to COVID-19, future pandemics are expected to be caused by airborne virus infecting the respiratory tract. Several studies have shown that mucosal IgA can provide immunity against respiratory viruses [1, 2]. A future vaccine, treatment or prophylactic drug could, therefore, be more efficacious using combined nasal and pulmonary delivery by providing maximal mucosal absorption in the entire respiratory tract. A non-invasive method to simultaneously administer drug or vaccine to both the nose and the lung could be an important first line of defense against the next pandemic. Several liquid nasal spray vaccines are under development, but sprays have inherent limitations in terms of short shelf-life and coordination issues. Droplets in the spray are designed to coat the nasal cavity, and therefore the pulmonary fraction is negligible. A passive dry powder delivery system could potentially address the limitations of wet sprays. A nasal dry powder inhaler (DPI) is driven by the inspiratory flow, eliminating all coordination issues. Dry powders are stable at room temperature eliminating the need for expensive and complicated cold storage and preservatives. The dry powder formulation can also be optimized to produce maximal combined nasal and pulmonary deposition. The purpose of this work is to investigate the prospect of dual nasal and pulmonary delivery using a nasal DPI. A range of commercially available DPI

products will be characterized using two different nasal casts. In addition, the different formulations from the commercial DPI products will also be tested using an independent nasal DPI device. Data from the many different combinations of devices, formulations and test parameters are expected to generate an understanding of the requirements of an efficient system for combined nasal and pulmonary dry powder delivery. This will provide valuable guidance for future development of an ultra-low-cost dry powder nasal inhalation platform for improved global health and access to treatment everywhere.

NASAL CAST MODEL

Liu *et al*. at the Department of Mechanical and Aerospace Engineering, Carleton University, Ottawa, Canada, created a digital model of a three-dimensional (3D) novel, standardized geometry of human nasal cavity [3]. Thirty healthy subjects were scanned using computed tomography (CT). Both sides of the nasal airways were scanned producing 60 3D geometries. A novel image processing algorithm was used to generate idealized two-dimensional (2D) images from which a digital original 3D standardized median human nasal cavity was created. In this paper, the geometry developed by Liu *et al*. [3], will be referenced to as the Carleton nasal cast. A 3D computational mesh (Figure 1) of the Carleton nasal cavity model was generated to visualize the air flow in the nasal cavity using computational fluid dynamics (CFD).

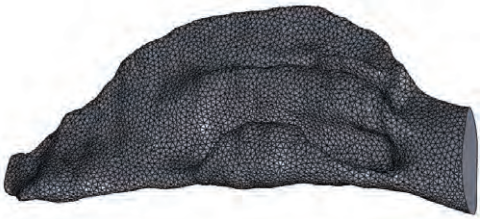

Figure 1. Mesh model of nasal cavity.

A model was built in Autodesk CFD (Autodesk, USA) and included an inlet geometry, a nasal device, the nasal cavity and an exit geometry (Figure 2).

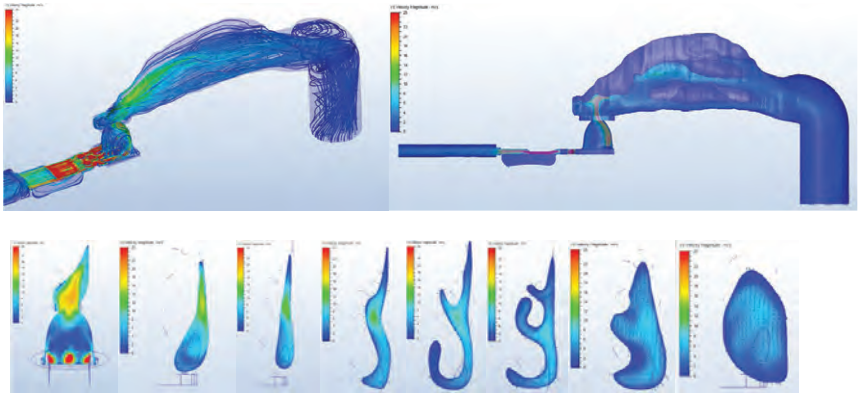

Figure 2. Computational fluid dynamics visualization of the flow (upper) in the nasal cavity and (lower) in different cross-sections of the nasal cavity.

The flow paths suggest a high flow velocity both around the middle turbinate and the superior turbinate. It can be assumed that micron-sized particles will follow the flow paths to reach deep onto the nasal cavity where they ultimately can be deposited. Due to high exit velocity and large droplet size, aqueous nasal sprays follow a straight line, and the deposition is highly dependent on the direction of the spray [4]. Delivering micron-sized particles that are expected to follow the air flow path could be advantageous compared to liquid sprays.

The Carleton model was used to 3D print a cast of the nasal cavity with a circular inlet port and a circular outlet port for easy connection to devices and instrumentation (Figure 3). The inlet port was then equipped with soft silicone rubber adapters for a tight fit to the mouthpiece of the tested DPI devices. The outlet port was connected to either a filter or a Next Generation Impactor (NGI), (Copley Scientific, UK).

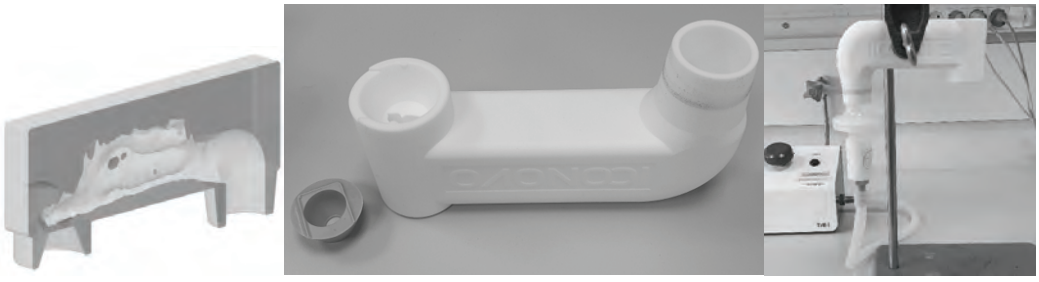

Figure 3. Cross-section of a 3D print of a Carleton nasal cavity with inlet and outlet ports (left). 3D print of a Carleton nasal cavity with inlet and outlet ports (center). Experimental setup with filter (right).

As a reference and comparison to the Carleton model, the Alberta Idealized Nasal Inlet (AINI), (Copley Scientific, UK) [5, 6] was used in some complementary tests together with the NGI, see Figure 4 and Figure 5.

Figure 4. Alberta Idealized Nasal Inlet.

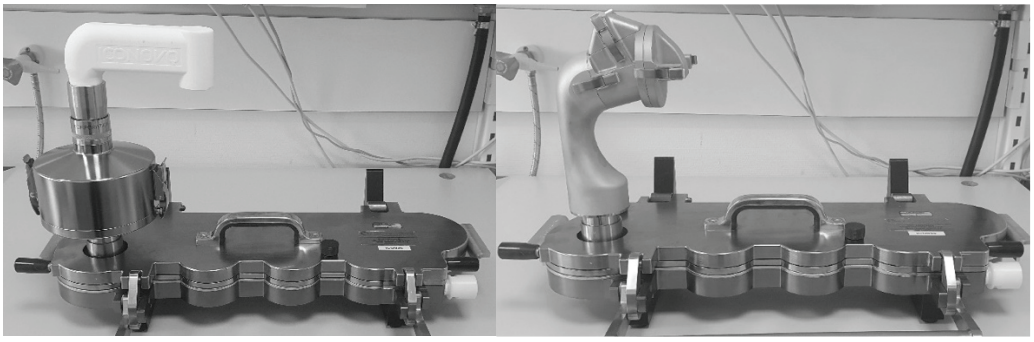

Figure 5. Carleton nasal cast with NGI (left) AINI with NGI (right).

Passive nasal dry powder inhalation is not very well researched and understood. Consequently, the relationship between flow resistance and flow was initially investigated. Seven volunteers were selected based on gender, height and age and inhaled against different flow resistances (see Figure 6). Based on these findings, it was concluded that a flowrate of 30 L/min was possible to achieve over a range of flow resistances. All NGI testing in this study were performed using 30 L/min. Tests with a filter only, were performed using 30 L/min and 45 L/min.

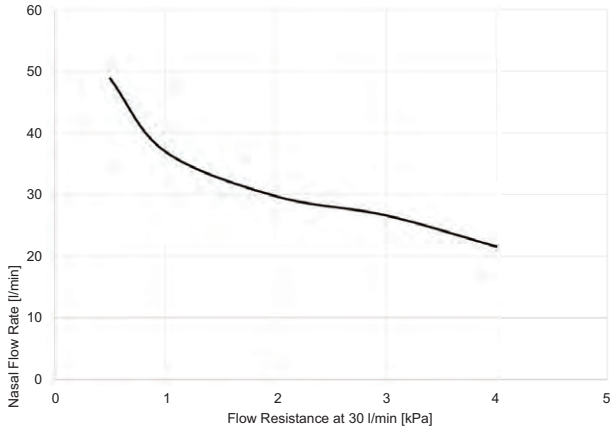

Figure 6. Nasal flow rate vs. flow resistance following inhalation against different flow resistances by seven healthy volunteers.

Table 1 summarizes the commercial dry powder inhalation products selected for testing. These products are used for the treatment of asthma and chronic obstructive pulmonary disease (COPD) by oral inhalation and are not intended for nasal inhalation. Furthermore, these commercially available DPIs are designed for inhalation flow rates higher than 30 L/min. It is important to note that these products were tested at a suboptimal flow rate, and the reported *in vitro* performance cannot be expected to be equivalent to the expected performance at the recommended inhaled flow rate.

Table 1.
Commercial DPI products tested in this study.

Product	Dose	Drug
PULMICORT© Turbuhaler©	200 µg	Budesonide
SYMBICORT© Turbuhaler©	160 µg/4.5 µg	Budesonide/Formoterol
BUFOMIX© Easyhaler©	160 µg/4.5 µg	Budesonide/Formoterol
FOSTAIR© NEXThaler©	100 µg/6 µg	Beclomethasone/Formoterol
ULTIBRO© Breezhaler©	85 µg/43 µg	Glycopyrronium/Indacaterol
SPIRIVA© HandiHaler©	18 µg	Tiotropium
DUORESP© Spiromax©	160 µg/4.5 µg	Budesonide/Formoterol

The commercial DPIs use many different types of inhalation devices and can be grouped based on their flow resistance. Handihaler is considered to be a high resistance device. Turbuhaler, Easyhaler and NEXThaler are medium high resistance. Spiromax is medium resistance, and Breezhaler is a low resistance device. A possible connection between the flow resistance and nasal performance will be investigated.

To provide better understanding of the individual role of the devices and the formulation, an additional group of tests was included. The commercial products were opened, and the formulation was harvested. The formulations were then filled into the Iconovo ICOone Nasal device to serve as an independent test device, see Figure 7.

Figure 7. ICOone Nasal unit dose device.

RESULTS AND DISCUSSION

It is not common practice to quantify both the nasal and pulmonary fraction during nasal inhalation. No agreed terminology is available and the size fractions of the particles reaching the different regions are not well understood. In this paper a terminology and definition are proposed to help describe and understand the results. The respiratory fractions are defined as: nasal fraction (NF): > 20 µm, oropharyngeal fraction (OPF): 10–20 µm and fine particle fraction (FPF): < 10 µm.

Traditionally, 5 µm is used as the cut-off for the FPF for pulmonary delivery. The higher particle size of 10 µm was selected based on the shift towards larger particle sizes at lower flowrates and slower inhalation. Stevens *et al.* [7] show a shift when comparing a 30 L/min inhalation to 60 L/min. The deposition in the oropharyngeal region moved from about 4.5 µm to about 8 µm. A similar trend was observed for the pulmonary deposition. In this study, the FPF is defined as less than 10 µm, the cut-offs provided by the NGI at 30 L/min. The term postnasal fraction (PNF) is

also used and is defined as: PNF = OPF + FPF. When the tests were performed with nasal cast and filter only, everything passing the cast and collected on the filter is the PNF. This fraction can either be deposited in the oropharyngeal region or in the lung.

All tested products showed a significant PNF. Even though the products are optimized to produce a high fraction of respirable particles, when inhaled orally, they performed well, even when inhaled nasally, see Figure 8 and Figure 9.

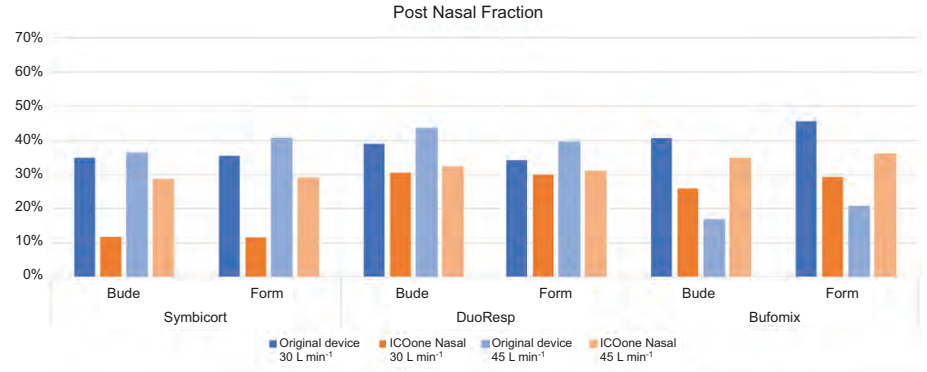

Figure 8. PNF at 30 L/min and 45 L/min for budesonide/formoterol 160 µg/4.5 µg formulations delivered via Symbicort, DuoResp, Bufomix and ICOone Nasal.

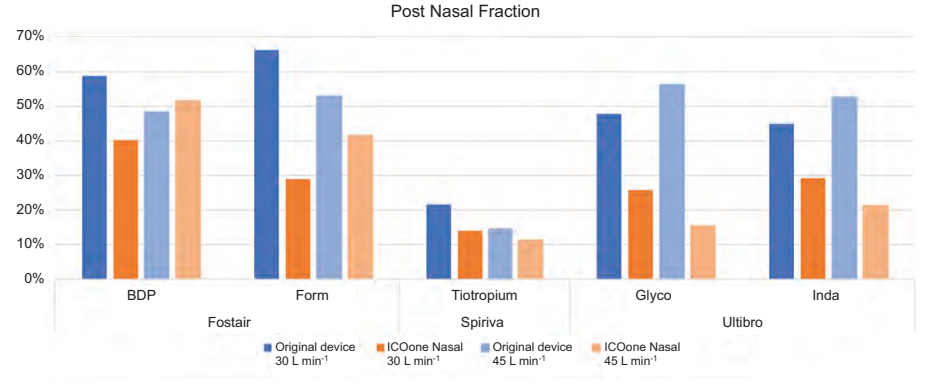

Figure 9. PNF at 30 L/min and 45 L/min delivered via Fostair, Spiriva, Ultibro and ICOone Nasal.

One of the products with the lowest PNF was Symbicort Turbuhaler. This could be expected as the Turbuhaler is recognized for reduced deaggregation and reduced performance at lower flow rates. The Symbicort formulation also performed very poorly in ICOone Nasal. This can be attributed to the spheronized formulation used in the Turbuhaler platform which requires a higher deaggregation force, which is not supplied in ICOone Nasal. The other budesonide/formoterol (DuoResp and Bufomix) products use carrier-based formulations, requiring much less deaggregation energy. These products performed better, and the formulations performed better in ICOone Nasal. The results show, however, little difference between 30 L/min and 45 L/min which was unexpected and cannot presently be explained.

The results shown in Figure 9 include both the best and the worst performing products. The high resistance Spiriva Handihaler proved not to be suitable for combined nasal and pulmonary delivery. Both the results from original device and the formulation in ICOone Nasal, showed clearly inferior results compared to the other products. The other capsule based product, Ultibro Breezhaler showed a high PNF even though it is a low resistance/high flowrate device. The Ultibro formulation was, however, not suitable for ICOone Nasal. This suggests that the formulation requires the deaggregation force generated when the capsule rotates in the device. Fostair NEXThaler was the best performing product. The PNF was around 60% and the formulation also performed well in ICOone Nasal, suggesting that the product both has an efficient device and a formulation well suited for combined nasal and pulmonary delivery. Both Fostair and Ultibro formulations contain magnesium stearate to improve deaggreagtion.

The results from the commercial products using the Carleton cast provided valuable information on the requirements of the device and formulation to achieve combined nasal and pulmonary delivery. The requirements proved to be similar to those needed when developing only for oral inhalation and pulmonary deposition. To better understand the differences and similarities between the Carleton nasal cast and the AINI, additional tests were performed. Based on the knowledge obtained, a model budesonide/formoterol formulation with magnesium stearate was produced and tested together with two ICOone Nasal device variants in the Carleton nasal cast and the AINI (Figure 5). Although it was a budesonide/formoterol formulation, only budesonide was analyzed.

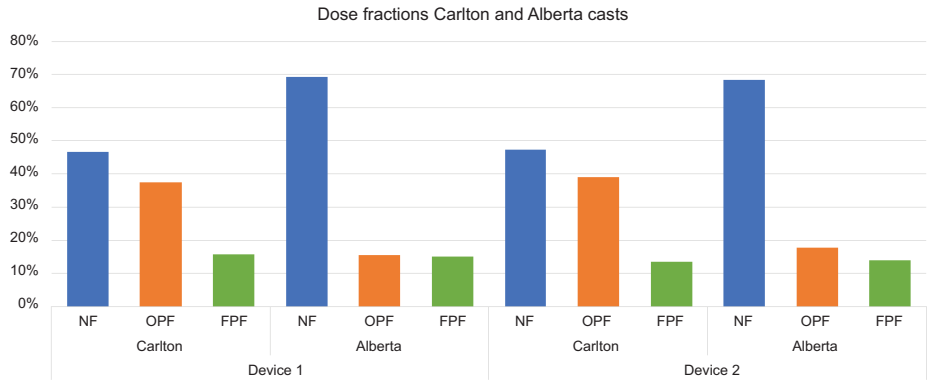

Figure 10. Nasal (blue), oropharyngeal (orange) and FPF (green) for budesonide delivered via two variants of the ICOone Nasal device in the Carleton Nasal Cast and the AINI.

Figure 10 shows that the nasal fraction is significantly higher in the AINI, whereas the oropharyngeal fraction is smaller. Additional testing is required to understand what drives the different deposition. It should be noted that the fine particle fraction is very similar. While the split between the nasal fraction and oropharyngeal fraction is clearly different, the combined nasal fraction and oropharyngeal fraction is similar.

CONCLUSIONS

The results presented suggest that it is feasible to use nasal dry powder inhalation to simultaneously deliver drug to the nasal cavity, the oropharyngeal region and the lung. The results show that even the most efficient DPI, with a high FPF, results in significant nasal deposition. There is, therefore, no need to have a bi-modal particle size distribution with a larger nasal fraction. It is believed that the best approach to achieve dual nasal and pulmonary targeting is to develop a product producing an aerosol with a small mass median diameter; i.e., less than 3 μm. Furthermore, a DPI product with strong deaggregation and a particle size distribution optimized for pulmonary delivery is most likely the best strategy.

ACKNOWLEDGMENTS

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Development of a Novel Device Targeting Drug Delivery into the Olfactory Region of the Nasal Cavity

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KEYWORDS: nasal cast, nose-to-brain delivery, aqueous nasal spray, regional deposition

INTRODUCTION

Nasal drug delivery offers major opportunities for introducing new therapies targeting the central nervous system via the nose-to-brain pathway [1]. However, the potential for direct access to the brain via the olfactory region presents new challenges from a formulation and device development perspective. The success of a targeted nasal drug delivery device relies on having a consistent (user independent) and a high percentage of the drug product being delivered to a certain area of the nasal cavity (e.g., olfactory region for nose-to-brain pathway). While a high deposition in the olfactory region of the nasal cavity has been observed for powder devices, there is still a lack of options for aqueous nasal sprays [2, 3]. For liquid nasal sprays, reducing the plume angle by changing the swirl chamber dimensions on the device and increasing the formulation viscosity have been the main strategies considered [4]. However, the dependency of these nasal pump spray performances on actuation velocity and force are well known [5]. Furthermore, it has been demonstrated that the insertion angle and depth of the device into the nose have an impact on the drug product regional deposition [6, 7]. The effect of patient-specific administration parameters in the regional deposition of drug products remains a major drawback for targeted nasal delivery, hence, new technologies are required. Herein, we present a novel concept to deliver aqueous nasal formulations that include an off-the-shelf syringe, which is prefilled with a formulation and inserted into the device. The user will then operate the device (Figure 1) by pressing the operating button, which will release a pressurized Y-shaped jet-spray (Figure 2). The Y-shape of the jet spray, characterized by a low angle jet that opens into smaller jets at a certain distance from the nozzle tip, is expected to optimize the nasal delivery into the olfactory region in a user independent manner.

Figure 1. **(A) The device used during this study with a syringe and schematics of the Y-shaped spray. (B) The ergonomic concept being developed.**

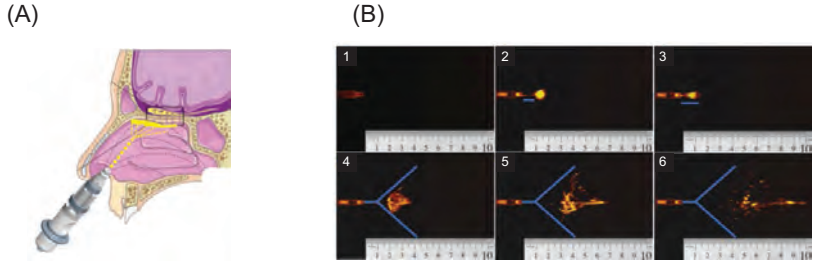

Figure 2. **(A) Schematics of the Y-shaped spray targeting the olfactory region. (B) Video frames of the Y-shaped jet-spray being originated.**

METHODS

Nasal solutions of water, glycerol and fluorescein sodium (for nasal cast studies) were prepared as described previously [7] with different viscosities of 2 cP, 23 cP and 80 cP, respectively. Prior to testing, the syringes were filled with 50 or 200 μL of the previously prepared formulations and placed into the devices (Aptar Pharma, Le Vaudreuil, France).

The spray performance was characterized by evaluating the spray droplet size distribution (DSD) and spray pattern (SP). DSD was measured using a Spraytec® (Malvern Panalytical, Worcestershire, UK) equipped with a 300 mm lens at 3 and 6 cm from the laser. SP was determined by using a SprayVIEW® (Proveris Scientific, Hudson, USA) at 5 cm from the laser. Both tests were conducted with a Proveris Vereo® actuator at 10 mm/s. Spray impact force was measured with a Spray Force Tester Model SFT 1000 (Copley Scientific, Nottingham, UK) at 3 cm.

In vitro deposition of liquid nasal sprays was characterized in an adult male nasal cast (Aeronose™, courtesy of Aptar/DTF/University of Tours) and chemical quantification of the different regions of interest was performed with a spectrophotometer (Light Wave II, Bioserv). The nasal cast model used was designed from computed tomography images of a plastinated head model [8], previously validated as a predictive model for nasal aerosol deposition [3]. One device per nostril was manually actuated into the nasal cast with a combination of different actuation angles (Figure 3). The analysis was performed in triplicate for each configuration. All statistical analysis was performed using SOS Stat 3.5.0.6 (EDC, Doussard, France).

Figure 3. **(A) Schematics showing the different configurations tested by varying the horizontal plane angle and (B) vertical plane angle from the center wall.**

RESULTS AND DISCUSSION

The spray performance of this nasal product was evaluated via DSD and SP with water. As presented in Table 1 and expected from visual and video observations, either at 3 or 6 cm distance from the laser, the spray does not fully micronize into droplets. Although the spray plume angle opens at a certain distance, it opens into smaller jets, which cannot be measured by laser diffraction. Attempts were made to measure the spray pattern; however, the presence of multi-jets and the absence of a clear spray center of gravity did not allow a consistent successful integration of the nasal spray. For the few sprays that the software was able to integrate, a spray area between 400–500 mm^2 and ovality ratio values greater than two were observed. Both commonly used techniques to characterize nasal spray performance do not seem appropriate to use with this device. The spray impaction force presented in Table 1 is well within values previously reported in the literature; hence, no discomfort for the patient is expected with this concept [9].

Table 1.

DSD characterization with 50 µL of water and spray impaction force with 50 µL of 2 cP formulation. Mean values and standard deviations in parenthesis (n = 5).

Distance	DSD_{d10}/µm	DSD_{d50}/µm	DSD_{d90}/µm	Impaction Force /g
3 cm	379 (45)	583 (12)	781 (13)	1.7 (0.6)
6 cm	399 (24)	581 (19)	793 (8)	–

The olfactory region deposition comparing the device with different insertion positions, 50 µL and 200 µL dosage, and formulations with different viscosities are presented in Figure 4. A consistently high deposition in the olfactory region was observed with an average deposition for the different configurations between 24% and 39%. A statistical difference was only observed between the configuration with the highest deposition in the olfactory region (45°/5°/15 mm) and the configuration with a lower insertion depth (10 mm, student's t-test $p = 0.03$) and a larger vertical angle (20°, student's t-test, $p = 0.03$). When comparing 50 and 200 µL dosages with different angles, a slightly higher deposition in the olfactory region was observed for the 200 µL, which is only statistically different when the vertical angle is 0° (student's t-test $p < 0.01$). Lastly, no statistical difference was observed for the olfactory region deposition when comparing formulations with viscosities between 2 and 80 cP (ANOVA, $p = 0.2$).

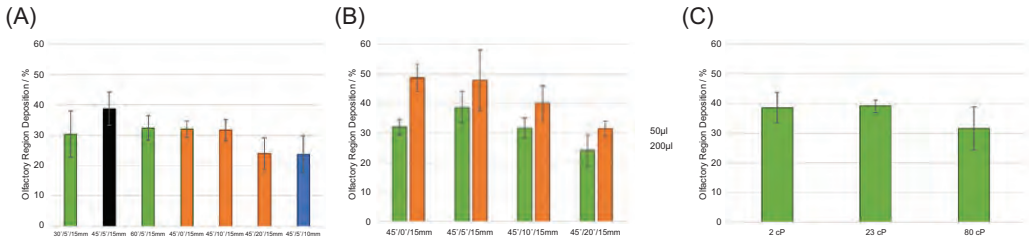

Figure 4. **Comparison of the nasal cast regional deposition in the olfactory region (n = 3 ±SD). At (A), a comparison of insertion configurations with 2 cP formulations: horizontal angle (green), vertical angle (orange), insertion depth (blue) and central configuration 45°/5°/15 mm (black). In (B), a comparison of two different volumes with 2 cP formulations: 50 µL (green) and 200 µL (orange). (C), a comparison of formulations with different viscosities: 2, 23 and 80 cP.**

CONCLUSIONS

In conclusion, a promising new device has been designed for targeting nose-to-brain delivery via the olfactory region. Unlike the currently available data reported in the literature for aqueous nasal sprays where a large dependency in device positioning [6], formulation and actuation parameters are observed, this study demonstrates that this novel technology allows a consistently high delivery into the olfactory region. A minimal effect of patient-specific administration parameters is expected due to its operating mechanism and low variability with different insertion angles, however, testing further nasal cast models and a human factors study to confirm the different angles and insertions that users might use is desirable. The *in vitro* data presented in this study shows its low dependency on formulation viscosity, which might solve some of the formulation challenges observed in the development of drug-device combination products. This aspect still needs to be further evaluated with more complex formulations. Lastly, current *in vitro* tools applied to evaluate nasal spray performance are not fully adapted to characterize this novel device.

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Chemical Imaging by Raman Spectrometer for Particle Characterization of an Aqueous Nasal Spray

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KEYWORDS: chemical imaging, Raman spectroscopy, surface properties, particle statistics, homogeneity

INTRODUCTION

Nasal sprays are widely used to treat allergic rhinitis [1]. This experimental study evaluates a commonly used nasal spray, Beconase® 0.05% (GlaxoSmithKline, UK) indicated for treating hay fever, using a Raman spectrometer [2]. Raman spectroscopy has previously been used for investigating nasal formulations. However, most formulations delivered by the nasal route are very small in size or even micronized. Therefore, in this study Raman chemical imaging (CI) has been employed as a characterization tool for identification and quantification of the nasal product components and for analyzing their particle size distribution (PSD) to further explore this powerful characterization technique and its use in product development.

METHOD

A method was developed for analyzing the nasal formulation using RA802 Raman Pharmaceutical Analyser (Renishaw, UK). Three experiments were carried out from the same formulation to ensure repeatability. The sample preparation was done by spraying the Beconase formulation two times in an upright position onto a mirror slide, held 10 mm above the nozzle. The two sprays represented the dose as per the product labelling. The samples were air-dried before analyzing as depicted in Figure 1. Air drying provided better spectral acquisition compared to a wet sample. CI was used for acquiring data from three areas, identified as maps, of Beconase using LiveTrack focus-tracking. Streamline Image Acquisition (Table 1), Renishaw's fast mapping technique, was used with LiveTrack to acquire Raman images of the formulation. CI by Raman employs collection of data in response to the incident monochromatic laser light which generates images that provide spectral and spatial information. This software feature facilitates evaluation of sample under analysis while generating data, enabling real-time monitoring which is crucial in data acquisition.

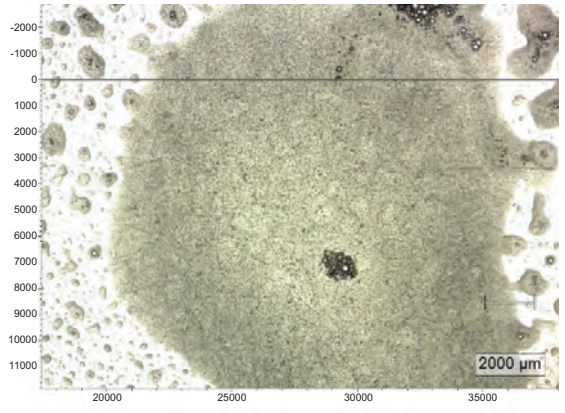

Figure 1. Sample on slide post-air drying. The blacked areas represent air bubbles.

The formulation was assessed using multivariate data analysis to obtain the spectrum dataset. The software WiRE© was used for baseline correction by applying third polynomial function and cosmic ray removal from the mapped spectra using the Cosmic Ray Removal feature. The Non-negative Least Squares (NNLS) component analysis was used to generate the chemical images and perform characterization of the formulation. A reference library was generated for the components present within the formulation for data analysis. Images acquired from the mapped regions correlated with the analyzed reference spectra of Beconase and the excipients present.

Table 1.

Streamline Image Acquisition configuration.

Laser Wavelength	785 nm
Laser Power	100%
Grating	1500 L/mm
Objective	HiMag (x50)
Focus-tracking	LiveTrack
Spectral range	86.77 cm^{-1} to 1974.3 cm^{-1}
Mapped area	350 µm (x) by 350 µm (y)
Step size	1 µm (x) by 1 µm (y)
Total spectra	122,500 each map

RESULTS AND DISCUSSION

The data analyzed from the mapped images detected the various components present in the formulation.

The spectrum shown in Figure 2 depicts a Raman shift peak at 1664 cm^{-1} which is within the acceptable range of the Raman shift reported for the Beclometasone dipropionate (BDP) in literature [3]. The slight variation in Raman shifts observed in comparison to literature cited values are imparted by the difference in wavelength, internal corrections, and detector type which are unique to the instrument [4].

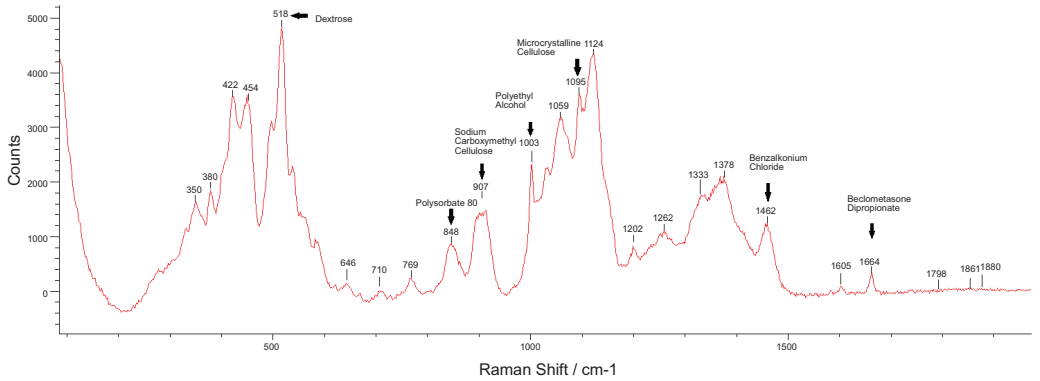

Figure 2. **Spectra of analyzed Beconase formulation (based on the analyzed data, some components present could be identified as Beclometasone dipropionate (BDP) at 1664 cm^{-1}, dextrose at 518 cm^{-1}, microcrystalline cellulose (MCC) at 1095 cm^{-1}, sodium carboxymethyl cellulose (CMC) at 907 cm^{-1}, polysorbate 80 at 848 cm^{-1}, phenylethyl alcohol (PEA) at 1003 cm^{-1} and benzalkonium chloride at 1462 cm^{-1}).**

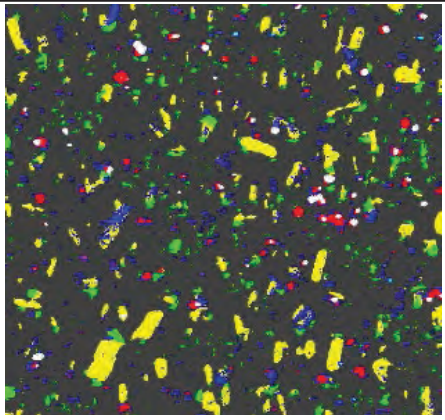

Figure 3. **Chemical image-based particle statistics of the formulation representation (color representation: white: Beclometasone dipropionate, red: Benzalkonium chloride, green: Dextrose, blue: Sodium carboxymethyl cellulose, yellow: Microcrystalline cellulose, aqua blue: Phenylethyl alcohol, and magenta pink: Polysorbate 80).**

Figure 3 shows a chemical image of the analyzed formulation. The CI based on particle statistics shown in Figure 3 represents different components present in the formulation, suggesting a dispersion of active pharmaceutial ingredient (API) with various excipients within the formulation on spraying twice to represent a single dose in each nostril. The PSD and concentration estimate (CE) are represented in Table 2. CE is a software feature that gives the percentage of estimated concentration in sample. The results show a relatively higher concentration for MCC, which may be due to the similar spectral shifts observed with sodium CMC at 1095 cm^{-1} and 1124 cm^{-1}, in addition to the overlap with other components. The CE of 0.5% for the BDP, higher than the expected values, could be explained by the sensitivity of Raman for picking up highly intense spectral signals. These may also be observed due to the spectral overlap from other components present in

the multiphasic formulation. The remainder 1.95% of CE may be contributed by polysorbate 80 and PEA, which are present in liquid state, hence particle statistics were not established. Knowing accurate concentration used in the formulation by the manufacturer would enable scientists to understand more insights into this technique to quantify each component in confidence.

Table 2.

PSD and CE for the analyzed sample.

Components	Partical Size Distribution	Average Value of three samples (μm)	Concentration estimate (percentage)
Beclometasone dipropionate	D10	4.60	0.53±0.11
	D50	6.99	
	D90	10.60	
Dextrose	D10	4.60	27.89±1.94
	D50	7.48	
	D90	11.27	
Benzalkonium chloride	D10	4.60	16.71±3.41
	D50	7.89	
	D90	13.70	
Microcrystalline cellulose	D10	7.48	50.66±0.61
	D50	14.47	
	D90	24.17	
Sodium carboxymethyl cellulose	D10	4.60	2.26±1.71
	D50	8.38	
	D90	14.27	
Polysorbate 80	NA	NA	0
	NA	NA	
	NA	NA	
Phenylethyl alcohol	NA	NA	0
	NA	NA	
	NA	NA	

NA: Not applicable.

CONCLUSION

This study shows that Raman spectrometer, RA802, can be effectively used as a characterization technique for analyzing an aqueous nasal spray formulation. Thus, data generated from Raman provide detection of each component, concentration estimate and size distribution. Based on this study, it can be inferred that the technique is powerful in characterizing formulations containing particles of small sizes of less than 1 μm and in low concentrations, which are often used in respiratory drug delivery. Additional studies will be performed to demonstrate the translational application of the technique to efficiently investigate and characterize other respiratory formulations like nebulizers, dry powder inhalers and other nasal products [5, 6].

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Using a Physiologically Based Pharmacokinetic Model to Investigate the Relationship between Device, Orientation, Deposition Pattern and the Systemic Exposure of Sumatriptan Nasal Solutions

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KEYWORDS: physiologically based pharmacokinetic (PBPK) model, nasal spray, nasal cast deposition, *in vitro/in silico* approach, sumatriptan

INTRODUCTION

When designing new drug devices or formulations, target product profiles are often based on a broad understanding of the disease indication and delivery device, which is good, in general, but not optimal for any single product. With recent advances in realistic *in vitro* testing for nasal drug products and the wider adoption of computational methods for their development, product specific and clinically relevant understanding of development prototypes can be generated. These development product profiles allow for optimization of *in vivo* targets early in the process. This study combined *in vitro* nasal cast deposition with a bespoke physiologically based pharmacokinetic (PBPK) model to understand the relationships between device angle and depth, nasal deposition pattern and systemic pharmacokinetics. The result was an understanding of how to maximize systemic exposure of nasally administered sumatriptan solution delivered from three nasal spray devices.

METHODS

Nasal solutions of fluorescein sodium were prepared as described previously [1] at a fixed viscosity of 2 cP and filled into three devices: the Aptar unidose UDS1 std, VP7+CB18 nasal pump and an experimental device named Device 1. All devices had a metering volume of 100 µL. The *in vitro* nasal cast deposition of the solutions delivered from each device at vertical angles ranging from 30°–60°, horizontal angles from 0°–15° and depths of 10 and 15 mm in the Aptar Aeronose™ cast (courtesy of Aptar/DTF/Univ. of Tours).

Briefly, the Aptar Aeronose cast is a 3D printed cast of a single adult Caucasian male that has been sectioned into nasal valve, olfactory region, turbinates, nasal floor and rhinopharynx regions. The nasal solutions were sprayed into the cast manually, the cast section separated, rinsed with water and the fraction of deposited fluorescein in each region of the cast quantified using a spectrophotometer (Light Wave II, Bioserv).

The nasal cast deposition data was used to predict the systemic pharmacokinetics of nasally administered sumatriptan solution using a whole body PBPK model. The model represented mass transport due to permeation, perfusion, protein and blood binding and clearance in the liver and blood. The nasal section of the model was split into five compartments representing the five sections of the Aeronose cast including the surface areas of each region, allowing direct input of the *in vitro* data to the model. Each section of the nasal cavity was further split into a mucus layer, epithelium and subepithelium.

The model structure followed previous PBPK models aimed at representing orally inhaled and nasal administration [2, 3] and was parameterized from standard literature sources. Parameters with a large degree of uncertainty were optimized following standard procedures allowing the model to match clinical pharmacokinetic data [4]. The boundary conditions of the model were the total emitted dose of sumatriptan (20 mg) multiplied by the *in vitro* nasal cast deposition fraction in each region of the nose. The PBPK model equations were solved using Python version 3.10.4 and SciPy 1.8.1 and principal component analysis was conducted using JMP 15.1.

RESULTS AND DISCUSSION

The predicted systemic pharmacokinetics of sumatriptan for each of the devices at a range of vertical angles (horizontal angle and depth were fixed at 5° and 15°, respectively) are presented in Figure 1. The maximum plasma concentrations (C_{max}) for each of the devices are all maximal at 35° and appear to go through a maximum rising from 30° to 35° and then falling as the vertical angle increases further.

The exact dependence of C_{max} on vertical angle varies between the devices, indicating differences in spray pattern, but the overall dependence is common across all devices. What is striking about this finding is that the vertical angle, which can vary both between and within human subjects, results in shift of C_{max} from 2.8 ng/mL to 11.0 ng/mL.

To understand the relationships between vertical angle, nasal cast deposition pattern and systemic pharmacokinetics a principal component analysis (PCA) was conducted on all deposition fractions and the predicted C_{max}, area under the plasma concentration vs. time curve (AUC) and time to C_{max} (T_{max}). Strong linear correlations between predicted C_{max}, AUC and *in vitro* turbinates plus floor deposition were observed. Turbinates deposition correlated with predicted T_{max} and there was little correlation between floor deposition and any of the predicted systemic pharmacokinetic parameters. The relationship between vertical angle and predicted pharmacokinetics observed for all devices in Figure 1 therefore follow the relationship between vertical angle and *in vitro* turbinates plus floor deposition.

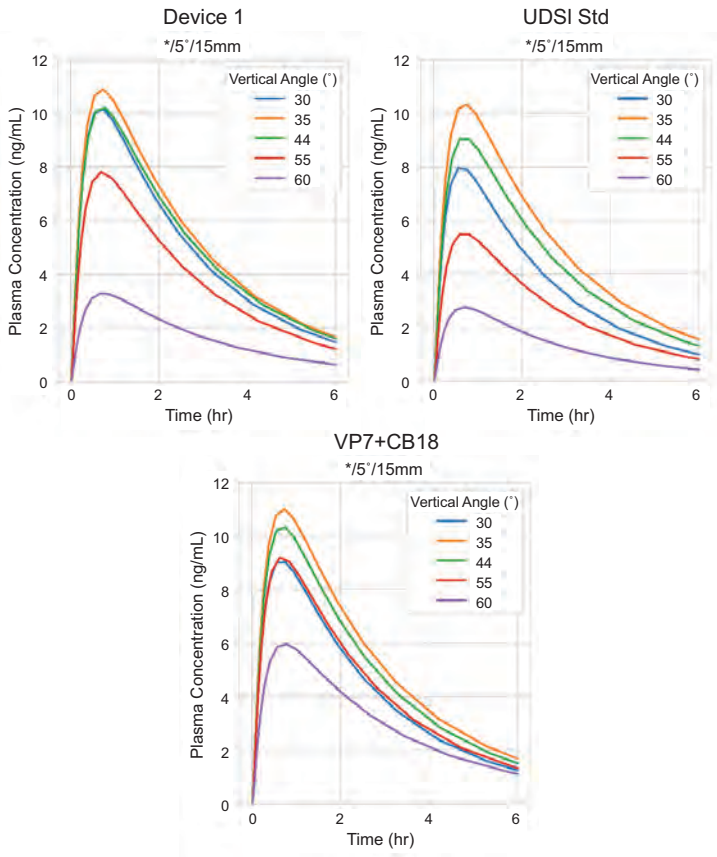

Figure 1. **Predicted systemic pharmacokinetics of sumatriptan solution delivered from Device 1, UDSl std and VP7+CB18 at a range of vertical angles.**

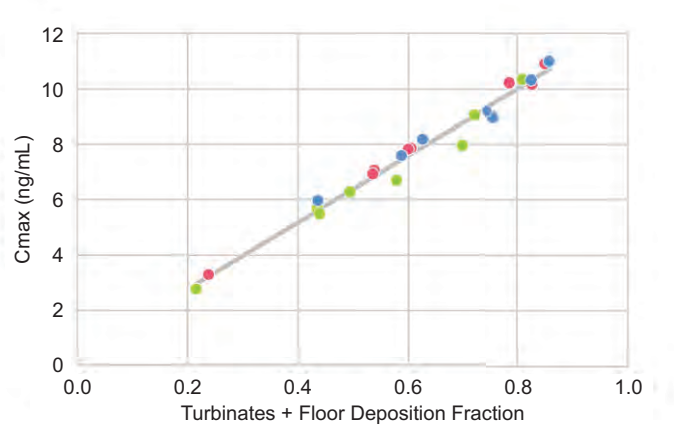

Figure 2. **Relationship between predicted systemic C_{max} and *in vitro* nasal cast deposition fractions in the turbinates and nasal floor. Points show Device 1 (red), UDSl std (green) and VP7+CB18 (blue), line shows linear regression line.**

The result presented in Figure 2 can be explained on physiological grounds. The olfactory region of the nose has a large epithelial tissue depth [5] meaning molecules must diffuse larger distances before they meet blood vessels, the nasal valve is not significantly perfused by blood vessels, and there was little deposition in the rhinopharynx. This leaves the large surface area and well perfused turbinates and floor regions which are therefore the target for the systemic delivery of drugs via the intranasal route.

CONCLUSIONS

In conclusion, a combined *in vitro/in silico* approach was used, combining nasal cast deposition data with a PBPK model, to understand the relationships between insertion angle and depth, nasal deposition pattern and the predicted systemic pharmacokinetics of sumatriptan solution delivered from three nasal spray devices. The model was specifically designed to be directly informed by the *in vitro* data. The results indicated that the combined floor and turbinates deposition correlated strongly with predicted systemic C_{max} and AUC and that this went through a maximum at a vertical insertion angle of 35°. The importance of the turbinates and floor were understood in terms of surface areas, tissue depths and blood flows to the various nasal regions. This approach gave a device and drug specific target to maximize systemic exposure and an understanding of why the target applies.

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Formulation Technologies Assessment for the Development of Intranasal Powders Comprising a Peptide

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KEYWORDS: intranasal powder, peptide, formulation, spray drying, freeze drying

INTRODUCTION

Traditionally, drugs delivered to the nose have been formulated as liquids. However, delivering a powder to the nose can improve chemical and microbiological stability, prolong residence time in the nasal cavity and enhance systemic bioavailability by increasing drug diffusion and absorption due to an extended contact between powder and mucosa and the higher concentration gradient generated across the mucosa [1]. Moreover, nasal powders allow for a wide range of doses, facilitate the formulation of poorly water-soluble compounds, can target the brain by exploiting neuronal pathways to bypass the blood brain barrier and avoid incompatibility issues between drug and excipient since the product is in a solid state. Powders allow for room temperature storage avoiding cold chain, which is especially advantageous for proteins and peptides [2]. An example of this is Baqsimi® (Eli Lilly and Company, USA) where formulating glucagon, a 29 amino acid peptide, as a freeze-dried powder, overcame stability issues of the liquid injectable formulation. The addition of enhancing excipients [3] improved glucagon bioavailability by intranasal delivery to 28% from negligible bioavailability with glucagon alone [4], without being affected by congestion associated with a common cold [5]. In this study, leuprolide, a 9-residue peptide analogue of gonadotropin-releasing hormone that is used to treat central precocious puberty, was reformulated from its injectable form to an intranasal powder. Freeze drying and spray drying were assessed as manufacturing processes, following a similar strategy to that used to produce Baqsimi.

METHODS

Baqsimi feedstock solution was prepared by substituting glucagon with leuprolide acetate (Bachem Americas, USA). Leuprolide, N-dodecylphosphocholine (DPC, MAPCHO-12, Avanti Polar Lipids, USA) and beta-cyclodextrin (β-CD, Carvamax® W7 Pharma, Wacker Chemical Company, USA) in ratio 10:10:80% w/w were dissolved in 1 N acetic acid and powders were produced as follows:

1. Powder 1 was manufactured from a product solution of [2.5% w/v] using a SP Scientific (USA) Virtis Advantage Plus freeze dryer (FD).

2. Powder 1A was prepared by subjecting Powder 1 to 40 minutes of Resonant Acoustic Mixing (RAM) at 90 g-forces.

3. Powder 2 was spray dried (SD) using a 4M8-TriX (Procept, Belgium). The feed solution [2.5% w/v] was atomized by an ultrasonic nozzle at a feed rate of 1.5 g/min. The nitrogen flow rate was 0.30 m^3/min, and the outlet temperature was 90–105 °C.

Assay and related substances (RS) were analyzed by reverse phase high performance liquid chromatography (RP-HPLC) as well as acetic acid content for all powders. Water content was measured by Karl Fischer's coulometric titration (Mettler Toledo, USA). Powders morphology was assessed by Scanning Electron Microscopy (SEM) with a JSM-6490LV (Jeol, Japan) and specific surface area (SSA) by the Brunauer–Emmett–Teller method was collected with a TriStar II Plus (3020) (Micromeritics, UK). Particle size distribution (PSD) was measured for bulk powders by pressure titration (Mastersizer 3000 equipped with an Aero S dry dispersion unit, Malvern Panalytical, UK). The PSD of the powders emitted from the Unidose Nasal Powder device (UDS-P, Aptar Pharma, France) filled manually (20 mg) or semi-automatically by dosator (Minima, IMA, Italy) or drum (Omnidose TT, Harro Höfliger, Germany), both at 30 mg, was measured by Spraytec (Malvern Panalytical, UK) set in an open bench configuration and equipped with a Vereo automated actuator (Proveris Scientific, USA).

RESULTS AND DISCUSSION

Bulk characterization

The powders assay was 96–102% of the theoretical value (Table 1), confirming that all processes were suitable to produce a leuprolide powder without degrading the peptide. The spray drying process was more effective in drying the feedstock, evidenced by the lower water content for Powder 2, similar to Baqsimi; while Powders 1 and 1A had lower acetic acid content, comparable to Baqsimi.

Table 1.

Powders physico-chemical characterization results (n = 1 for assay, RS, water and acetic acid content and n = 3 ± standard deviation for bulk and tapped density).

Formulation	Baqsimi*	Powder 1	Powder 1A	Powder 2
Assay (%)	–	102	98	96
RS (%)	–	0.10	0.09	0.21
Water Content (%)	1.7	5.2	4.6	2.2
Acetic Acid Content (%)	2.7	3.0	3.0	8.8
SSA (m^2/g)	7.47 ± 0.08	11.19 ± 0.31	12.71 ± 0.10	0.81 ± 0.02
Bulk Density (g/cm^3)	–	0.037 ± 0.001	0.176 ± 0.007	0.438 ± 0.032
Tapped Density (g/cm^3)	–	0.051 ± 0.002	0.236 ± 0.006	0.590 ± 0.024
Compressibility Index	–	27.33 ± 5.03	25.33 ± 1.15	25.75 ± 2.47
Hausner Ratio	–	1.38 ± 0.10	1.34 ± 0.02	1.35 ± 0.05

*Basqimi comprises a different peptide, therefore assay and RS were not performed. Moreover, bulk and tapped density analyses were not performed, due to the high volume of powder required.

FD produced powders with higher SSA and pore volume (Powder 1A ≥ Powder 1 > Baqsimi > Powder 2). Bulk and tapped density were very low for Powder 1 before the RAM, which was employed to densify the powder without impacting particle size.

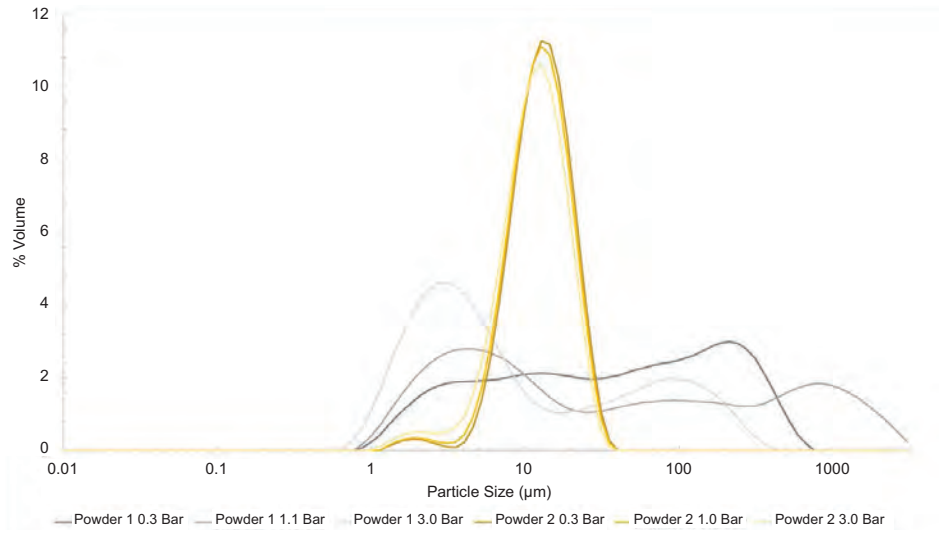

Figure 1. PSD of bulk powders by pressure titration (n = 1).

The PSD of the bulk powder (target mean volume diameter 100 µm) was too small for Powder 2 (Figure 1) independently of the air pressure employed, indicating a too high risk of unwanted lung deposition. Therefore, optimization of SD parameters and feedstock properties would be necessary to improve the PSD. Powder 1 reported larger multimodal PSD dependent on the pressure applied (smallest PSD at 3.0 bar), suggesting a higher friability which may result in a more variable aerosol performance.

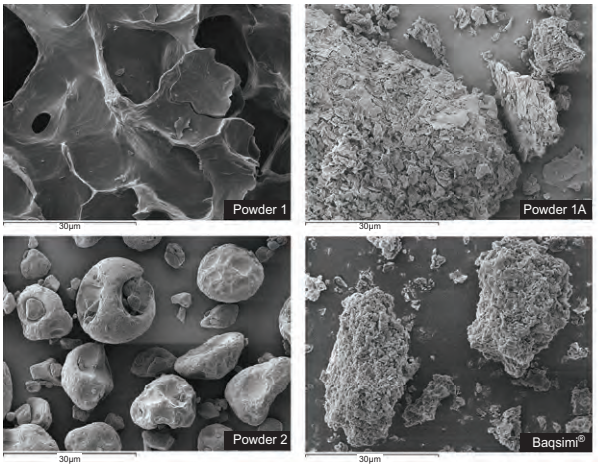

Figure 2. SEM images of powders produced compared to Basqimi bulk formulation.

Results from the SEM showed Powder 1A had similar morphology to Baqsimi (Figure 2) even though with larger caked particles. Powder 2 presented more homogenous and rounded particles, typical for SD, whereas Powder 1 displayed very large flaked particles, typical for a FD cake.

Product performance

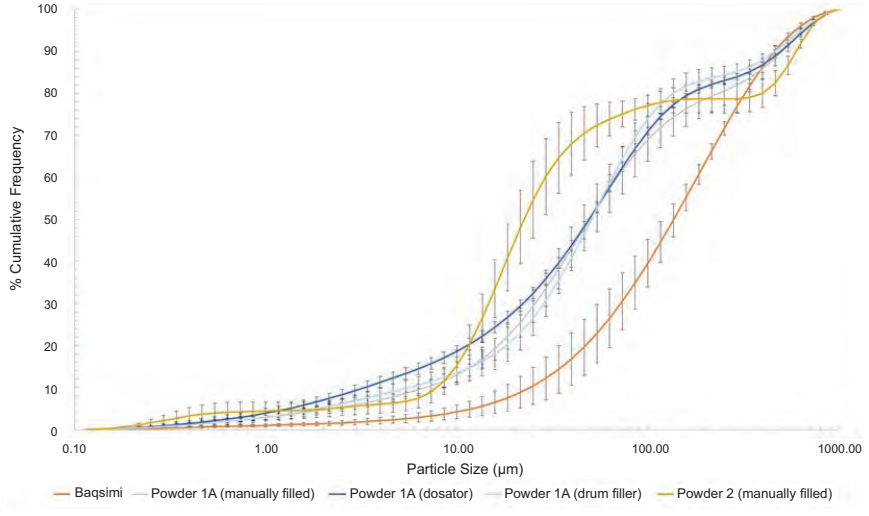

Figure 3. Emitted PSD from UDS-P of powders versus Baqsimi (n = 3, bars represent standard deviation).

Flow properties were poor for all powders; however, they were successfully aerosolized with UDS-P (Figure 3). The bulk PSD results showed Powder 2 to have a smaller PSD compared to Powder 1, 1A and Baqsimi. However, Powder 1 and 1A showed a different emitted PSD compared to the bulk, confirming a higher friability of powders produced by FD. Moreover, Powder 1A had an emitted PSD independent of the technology used for semi-automatic filling, suggesting that the RAM

process stabilized the powder sufficiently to avoid unwanted changes through the filling. Both drum and dosator allowed to reach the target fill weight (30 mg), not achievable by manual filling for the FD powders (20 mg maximum).

CONCLUSIONS

FD coupled with RAM proved to be a more suitable process to obtain a nasal powder similar to Baqsimi, even though optimization of the FD process and post-drying steps will be required to fully match the marketed product performance. In the future, it will be important to ascertain the longer term stability of the different formulations, including the impact on the activity of the peptide, as well as the *in vivo* performance with regard to systemic bioavailability.

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Usability Evaluation of a Novel, User-Independent Unit Dose Nasal Spray via Human Factors Studies

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KEYWORDS: user-centric nasal spray design principles, intuitive actuation, handling comfort, user-independent device performance, reliable and reproducible nasal drug delivery

INTRODUCTION

Most nasal sprays deliver liquid drug formulations without the need for administration by a healthcare professional (HCP) [1]. All currently marketed unit dose devices are user-driven, in the sense that a force must be applied continuously by the user to move the dose through the device and atomize into a spray. As such, the force, maximum displacement and associated velocity, applied by the user – as well as formulation viscosity and other factors – determine both the dispersion parameters and the delivered dose [2–4].

Single dose nasal drug delivery devices are intended for use by a wide range of people, of different backgrounds and varying abilities, and in a wide range of use scenarios. User interaction and patient compliance with these devices can be impacted by factors such as user dexterity [1]. In circumstances where a user has not previously interacted with the device, its use should be intuitive to reduce the risk of delivering no dose or an incomplete dose [2, 5]. The US Food and Drug Administration (FDA) provides guidance for nasal spray performance specifications, including target metered shot weight (MSW) [6]. In parallel, the application of human factors engineering throughout the design process is a prerequisite to ensure the correct use of a device, with minimal effort required from the user. The aim of the work reported here was to enable further device development though understanding of user interaction.

METHODS

In a formative usability study, 23 participants (aged 12–61 years) – including those with limited manual dexterity – were each provided with four of Recipharm's water-filled proprietary development device (PD) samples (example shown in Figure 1) and minimal instructions (Table 1). They were asked to hold, position and actuate them – into the air or a mannequin's nose – and

provide a qualitative review of use characteristics, including ease of use and comfort. The four devices had different build configurations, giving rise to the range of features described in Table 1. The study was conducted by Empathic Mind at their usability laboratory (Cambridge, UK), on behalf of Recipharm (King's Lynn, UK).

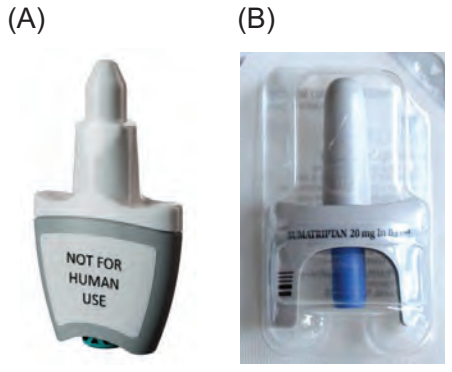
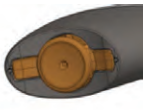


Figure 1. **Example of (A) PD samples used in the formative evaluation and hand actuation study, and (B) reference device (RD) samples; all PDs were externally identical, except for the button, for which there were two designs.**

Table 1.

Practical differences between device samples and use instructions. Actuation force was measured separately on a NSx actuator. (*Patient mannequin.)

	PD sample 1	PD sample 2	PD sample 3	PD sample 4
Actuation Force	Optimal (mean 23 N)	Optimal (mean 23 N)	High (mean 36 N)	High (mean 36 N)
Button Design				
Gloves	Yes	No	No	Yes
Administered to	Self	Third party*	Third party*	Self (close to ear)
Position	Participant chooses	Sitting	Supine	Sitting

Various samples of Recipharm's PD were used in a hand actuation study at Proveris Scientific® Corporation (Hudson, MA, USA), recording stroke length, actuation velocity and acceleration. The results were transferred to NSx actuators at Proveris and Recipharm, for laboratory-based measurements of actuation force, to replicate human use (n = 76 PDs, n = 18 RD samples for benchmarking – these were currently marketed, single dose nasal spray pumps). In parallel, the effect on PD actuation force, of changing the spring and orifice, was investigated. MSW was also measured to assess variability in device performance when actuated by hand, using samples filled with sumatriptan (n = 13, five adult participants), nalmefene (n = 19) or water (n = 25). Nalmefene- and water-filled samples were tested by a single investigator. This was repeated using the NSx actuator and additional samples.

RESULTS AND DISCUSSION

In the formative usability study, participants provided useful feedback on their interactions with the PD, as shown in Table 2 and Figure 2. Rating scores from two participants were excluded from the data presented due to technical difficulties with the audio recording for the session.

Table 2.

Participant feedback from formative usability study.

Positive findings	Negative findings
100% correctly used device, identifying and pressing button → therefore concluded to be intuitive for use by design	28% found edges of finger pad too 'sharp' → device design was updated (blend radius increased to 2 mm from 0.2 mm) and retested in follow-up session, showing discomfort reduced to <5%
100% were able to actuate device at forces tested (25 N and 35 N on average)	
100% understood when device had been used, based on auditory feedback and retracted button	Excessive flexion and radial deviation of wrist caused discomfort when administering dose to supine 3rd party → not a device design-related issue
Wearing gloves did not hinder, or substantially alter, device use	

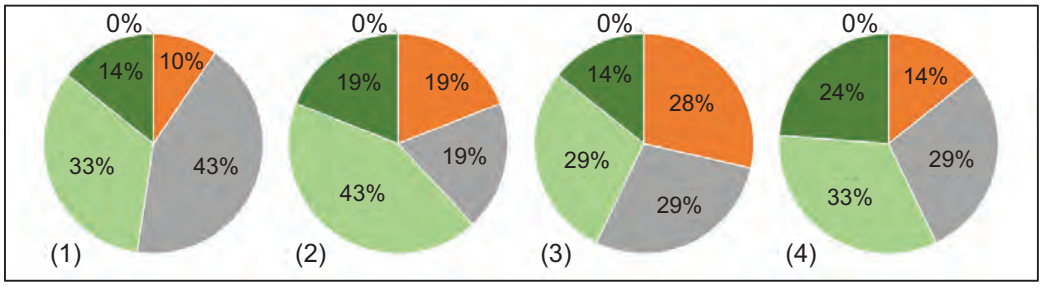


Figure 2. **Feedback on actuation pressure from PD samples (A) (far left) to (D) (far right). Participant ratings: dark green = very comfortable; pale green = comfortable; grey = neutral; orange = uncomfortable; red = very uncomfortable.**

The expected range of forces experienced by the device user, which would be required to dispense a full dose of drug formulation, were consistent for the PD (Figure 3). There was minor difference in measured force between PDs actuated at different speeds, particularly relative to the larger range experienced in the formative evaluation. Data for the RD (Figure 3) show that a broad range of forces can be experienced by users of approved, marketed user-driven products, depending on their interaction with them.

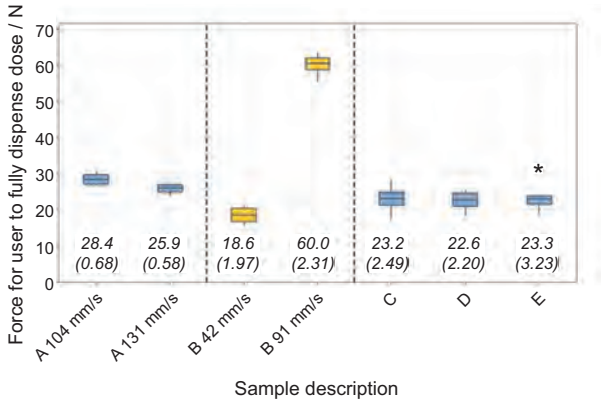


Figure 3. **Peak force applied by a device user as required to dispense a full dose. A = PD with nominal orifice and strongest spring; B = RD; C = PD with nominal orifice and weakest spring; D = PD with large orifice and weakest spring; E = PD with nominal orifice and mid-strength spring. The four plots on the left show data for different actuation speeds, which were recorded in user studies. Mean and standard deviation (SD) values shown in italics, underneath boxplots.**

The MSW data (Figure 4) demonstrate that the PD performed consistently for all formulations and remained within FDA limits, whether actuated by hand or laboratory apparatus. This is further supported by previously reported data on droplet size distribution with this PD [7]. It is important to note that the devices evaluated were not assembled to manage dispersion of the specific formulations contained within them.

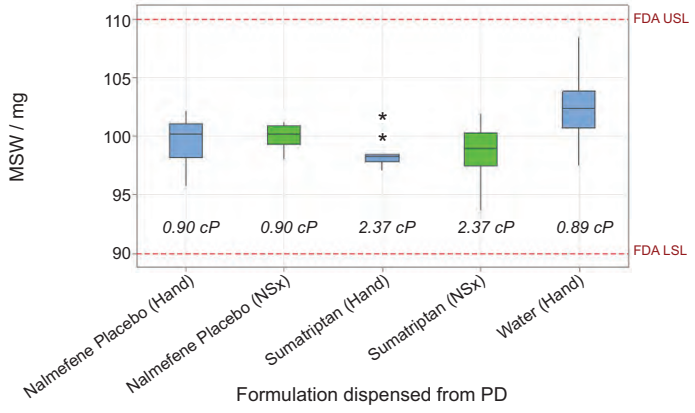


Figure 4. **MSW for PD actuated by hand (blue plots) and by the NSx actuator (green plots). Mean dynamic viscosity values (at 25°C) for each formulation are shown below their respective boxplots; water [8].**

CONCLUSIONS

The use of human factors studies to inform device design, has facilitated the development of a device that is considered comfortable in the hands of the user and intuitive to use. The combination of consistent MSW delivery and consistent actuation forces experienced by the user, contributed to ease of use, with no prior experience required. Method of drug administration to a patient in the supine position should be investigated further, with the intention of providing guidance to the device user on how to position their hand to avoid excessive wrist deviation. This will be particularly relevant for patients who cannot self-administer and might be in an unconscious state.

ACKNOWLEDGEMENTS

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Benchmarking of Particle Engineering Strategies for Nasal Powder Delivery: Characterization of Nasal Deposition Using the Alberta Idealized Nasal Inlet

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KEYWORDS: nasal powder, spray dried microparticles, chimeral agglomerates, aerodynamic performance, Alberta Idealized Nasal Inlet

INTRODUCTION

Powder formulations of a drug and mucoadhesive polymer have increased residence time in the nasal cavity and can be manufactured by blending, spray-drying or agglomeration of primary particles into chimeral agglomerates (CA) [1]. While spray-drying allows particle size control and generation of amorphous solid dispersions, blending is simpler and CA should allow faster dissolution after breakup into smaller particles. The objective of this study was to characterize nasal deposition and benchmark nasal powders manufactured by different particle engineering strategies, namely spray dried microparticles (SDM), CA and blends, using the Alberta Idealized Nasal Inlet (AINI). The AINI method conditions were first optimized by selecting appropriate angle of actuation and flow rate. Then, six different formulations prepared with distinct polymers and particle engineering strategies were evaluated.

METHODS

Piroxicam (abcr GmbH, Karlsruhe, Germany) was selected as model drug for systemic delivery, and polyvinylpyrrolidone/vinyl acetate (PVP/VA) (Ashland Specialties, Beveren, Belgium) and hydroxypropyl methylcellulose E3 (HPMC) (Dow Europe, Horgen, Switzerland) as polymers. Spray-drying was performed using ultra-sonic (USN) and two-fluid nozzle (TFN) to produce microparticles within the nasal size range of 10 to 45 μm [2] and primary particles for agglomeration, respectively, in a Büchi model B-290 unit. Chimeral agglomerates were produced by vibrating primary particles in a sieve shaker equipped with 106 μm and 710 μm mesh size sieves. Agglomerates retained on top of the 106 μm sieve were collected. Physical blends were obtained by mixing neat polymer microparticles with piroxicam raw material in a Turbula blender. All formulations were produced at 20% (w/w) drug load.

Particle size of the powder formulations was assessed by laser diffraction. Powders (20 mg) were filled in QUALI-V®-I capsules size 3 which were placed on the active device Miat nasal insufflator. The delivered dose during insufflation was determined using a Dosage Unit Sampling Apparatus, applying a 15 L/min flow rate for 2 seconds in three actuations. The formulation with the highest and most reproducible delivered dose was used to optimize nasal deposition method.

Nasal deposition was evaluated using the AINI. To mitigate particle bounce, the AINI was coated with Brij solution (0.15 g/mL Brij in ethanol) in glycerol (1 mL Brij solution for 5 g glycerol) [3]. For method optimization, the AINI was coupled with a Fast Screening Impactor (FSI), and the impact of angle of actuation (45° and 70°) and inhalation flow rate (7.5 L/min and 15 L/min) were evaluated in three actuations of 2 seconds each. Absence of airflow could not be tested since the large tip of the device could not be fully inserted in the nostril, and great losses of powder were observed. For formulation deposition evaluation, the AINI was coupled with Next Generation Impactor (NGI). Drug quantification was performed by high performance liquid chromatography (HPLC) with absorbance detector. Experiments were carried out in triplicate.

RESULTS AND DISCUSSION

Physicochemical characterization and delivered dose

SDM and blends presented a Dv50 within the nasal size range of 10 to 45 μm [2] (Table 1).

Table 1.

Particle size of powder formulations.

Formulation	Dv10 (μm)	Dv50 (μm)	Dv90 (μm)
SDM PVP/VA	13.10±0.39	28.40±0.62	50.31±0.61
SDM HPMC	17.43±0.47	44.60±0.33	82.92±0.29
Primary particles for CA PVP/VA	0.50±0.01	2.01±0.03	4.97±0.03
Primary particles for CA HPMC	0.61±0.01	2.86±0.12	6.74±0.41
Blend PVP/VA	2.98±0.02	20.72±0.05	47.29±0.73
Blend HPMC	3.95±0.03	16.42±0.05	33.66±0.13

CA – chimeral agglomerates; HPMC – hydroxypropyl methylcellulose; PVP/VA – polyvinylpyrrolidone/vinyl acetate.
SDM – spray dried microparticles.

Delivered dose was high and reproducible for SDM of HPMC (97.5 ± 1.6%). For the remaining formulations, it was lower (51.6 to 75.1 %) and highly variable (standard deviations of 12.3 to 35.5%). Consequently, SDM of HPMC was the formulation used for AINI method optimization.

AINI method optimization

Two method variables were studied, namely administration angle and inhalation flow (Table 2). The lower administration angle of 45° resulted in consistently lower vestibule deposition and higher turbinates deposition (Table 2), which is in agreement with a study by Chen *et al*. [4] using other nasal devices. These results indicate that a 45° angle has better suitability for drug systemic delivery.

Regarding the inhalation flow, a 15 L/min flow led to higher mass balances (percentage of mass of drug recovered on AINI, FSI and capsule) (Table 2), indicating better suitability of the analytical procedure. Accordingly, a 45° angle and 15 L/min inhalation flow were the experimental conditions selected for nasal deposition studies.

Table 2.

Mass balance and deposition profile of SDM HPMC formulation under the experimental conditions tested.

Administration angle	Inhalation flow (L/min)	Mass Balance (%)	Dose fraction (%)				
			Vestibule	Turbinates	Olfatory region	Naso-pharynx	Preseparator + Filter
45°	7.5	89.6±6.0	16.9±4.0	50.2±1.5	5.5±2.4	9.5±2.8	6.2±0.5
45°	15	96.6±3.2	11.0±0.9	55.3±7.0	1.3±0.7	20.7±1.5	4.8±0.4
70°	7.5	82.8±3.9	33.7±4.3	27.5±5.8	5.7±1.4	7.3±4.4	4.7±1.7
70°	15	103.5±4.9	35.3±6.8	41.3±0.8	6.8±1.8	14.5±7.6	4.0±1.0

Nasal deposition profile of powder formulations

The results show that the particle engineering strategy has an impact on nasal deposition profile (Figure 1). The average deposition on the vestibule and turbinates was higher for SDM, followed by blends and CA, with statistically significant differences between SDM and CA on the turbinates ($p < 0.05$, two-way ANOVA) except between SDM HPMC and CA HPMC ($p = 0.077$), evidencing SDM as an advantageous particle engineering strategy for nasal targeted systemic delivery. HPMC-based CA showed high deposition on the NGI stages (24.0 ± 9.5%), suggesting that the agglomerates may break into fragments that can reach the lungs (Figure 1).

The polymer also showed impact on powder deposition (Figure 1). For the same particle engineering strategy, PVP/VA based formulations had higher average deposition on the vestibule and lower average deposition on the nasopharynx, compared with HPMC-based formulations. Even though no statistically significant differences were observed, there is a tendency for higher deposition of PVP/VA based formulations on the anterior part of the AINI, possibly as a result of the higher particle agglomeration and cohesion. Due to low dose fraction retained in the capsule (1.6 ± 0.6 %) and high dose deposited on the turbinates region (38.9 ± 6.5%), HPMC-based SDM would be the lead formulation candidate for further studies.

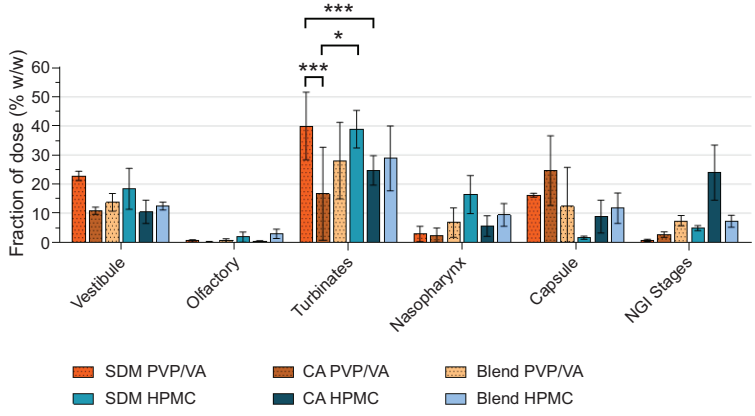

Figure 1. **Nasal deposition profile of powder formulations using AINI coupled with NGI. CA – chimeral agglomerates; HPMC – hydroxypropyl methylcellulose; PVP/VA – polyvinylpyrrolidone/vinyl acetate; SDM – spray dried microparticles. $^{*}p < 0.05$ $^{***}p < 0.001$ was considered as statistically significant.**

CONCLUSIONS

The present work aimed to develop and characterize nasal deposition of nasal powders manufactured by three different particle engineering approaches. SDM within the nasal size range were successfully produced and exhibited higher deposition on the turbinates area, evidencing spray-drying as an advantageous technology for nasal targeted systemic delivery. CA required an extra manufacturing step and presented higher risk of lung deposition since the size of primary particles is in the inhalation size range.

Due to the high delivered dose and high turbinates deposition, HPMC-based SDM seems to be the lead candidate for further performance studies as *in vitro* release and permeation. To the best of our knowledge, this is the first study benchmarking manufacturing strategies regarding nasal powder deposition.

ACKNOWLEDGEMENTS

This research was funded by FCT (Fundação para a Ciência e Tecnologia), Portugal and Hovione under the doctoral fellowship PD/BDE/150298/2019. The authors thank MIAT® S.p.A for providing the nasal insufflator and Qualicaps for the kind donation of QUALI-V®-I capsules.

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In Vitro Methodologies for the Screening of Polymer-Based Nasal Powders

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KEYWORDS: nasal powders, intranasal delivery, amorphous solid dispersions, chimeral agglomerates, spray drying, mucoadhesion

INTRODUCTION

Intranasal delivery is an attractive non-invasive route of administration allowing for local, systemic, and central nervous system drug delivery [1]. Key features for nasal delivery formulations include particle/droplet size that minimizes lung deposition (10–45 μm [2]) and the adequate mucoadhesion properties to delay mucociliary clearance. Nasal powders are more effective in improving residence time and stability than liquid forms [3]. Specifically, polymer-based formulations offer the opportunity to increase the residence time due to their mucoadhesive properties while increasing the dissolution of poorly soluble drugs by formation of amorphous solid dispersions (ASDs) [4, 5]. Particles can be engineered by spray-drying, or, alternatively, agglomerates of smaller primary particles can be produced with the goal of attaining faster dissolution [3]. Currently, there is a need for standardized *in vitro* methods to assess the success of a powder formulation at early development stages. The goal of this work is to provide insight in the use of rheology and *in vitro* dissolution techniques for the screening of nasal powder formulations.

METHODS

Powder formulations

ASDs of 20% (w/w) piroxicam (PXC) with hydroxypropyl methylcellulose (HPMC E3) and polyvinylpyrrolidone/vinyl acetate (PVP/VA) were produced using a Büchi laboratory scale spray-dryer, after dissolving the materials in DCM:MeOH 80:20 (w/w). Feed solutions were atomized by either a two-fluid (2FN) or an ultrasonic (USN) nozzle to generate different size distributions. Chimeral agglomerates (CA) were produced by vibrating the primary particles obtained with the 2FN in a sieve shaker (106 μm/710 μm) with an amplitude of 2.5 mm for two steps of 15 minutes.

Characterization

Solid-state and particle size distribution (PSD) characterization was performed by X-ray powder diffraction (XRPD) and by laser diffraction (Sympatec dry dispersion), respectively. For PSD characterization, two lenses with different measuring ranges were used: R2 (0.45–87.5 μm) and R4 (1.8–350 μm). In the dispersing method, the feed velocity was set to 18 mm/s and the considered pressure was 1 bar.

Mucoadhesion

Mucoadhesion potential was studied by the rheological analysis (HAAKE MARS 60 6000, Thermo Scientific) at 32 °C of the powders dispersed for 1 min in simulated nasal fluid (SNF; 8.77 mg/mL NaCl, 2.98 mg/mL KCl, 0.78 mg/mL $CaCl_2.2H_2O$, pH = 6.0) or simulated nasal mucus (SNM; 8% w/v mucin in SNF, pH = 6.0), at 32 °C. Rotational tests were performed using a cone geometry (C35/2°/Ti) with 0.1 mm gap, from 5.15 to 150 s^{-1}. The viscosity synergism caused by the polymer and mucin interactions, at a specific shear rate, was calculated by $\Delta\eta = \eta_t - \eta_m - \eta_p$, where η_t is the total viscosity (formulation in SNM), η_m is the viscosity of SNM only and η_p is the viscosity of the formulation in SNF [6]. Oscillatory measurements were performed using a plate geometry (P35/Ti) with 0.1 mm gap over a frequency sweep between 0.1 and 10 Hz (within the linear viscoelastic region). The synergy between the polymer and mucin, at a specific frequency, was calculated by $\Delta G' = G'_t - G'_m - G'_p$, where G'_t is the viscoelastic values of the formulation in SNM, G'_m is the viscoelastic components of SNM only and G'_p is the viscoelastic component of the formulation in SNF [7].

In vitro release

Release studies were performed using static vertical Franz diffusion cells (PermeGear, Inc., USA) with a 5 mL receptor compartment (600 rpm, 37°C) with SNF medium and a diffusion area of 0.636 cm^2. Powders (5 mg) were deposited on cellulose membranes (molecular weight cutoff (MWCO) ~14 k), using the Miat® nasal insufflation device. At predetermined timepoints (up to two hours), the receptor compartment was sampled (400 μL) for analysis by high performance liquid chromatography (HPLC).

RESULTS AND DISCUSSION

ASDs of PXC (20% w/w) with HPMC and PVP/VA were successfully produced by spray-drying (Table 1).

Table 1.

Yield and physicochemical characterization of powder formulations.

Analysis		ASDs (USN)		Primary particles for CA (2FN)	
		PVP/VA PXC = 20%	HPMC PXC = 20%	PVP/VA PXC = 20%	HPMC PXC = 20%
Particle size (μm)	Dv10	13.10 ± 0.39	17.43 ± 0.47	0.50 ± 0.01	0.61 ± 0.01
	Dv50	28.40 ± 0.62	44.60 ± 0.33	2.01 ± 0.03	2.86 ± 0.12
	Dv90	50.31 ± 0.61	82.92 ± 0.29	4.97 ± 0.03	6.74 ± 0.41
Assay (% w/w)		101.90 ± 0.93	101.39 ± 0.73	91.53 ± 0.61	102.01 ± 0.25
Agglomeration Yield (%w/w)		NA	NA	80.3	90.6
XRPD		Amorphous	Amorphous	Amorphous	Amorphous

2FN – two-fluid nozzle; ASD – amorphous solid dispersion; CA – chimeral agglomerates; HPMC – hydroxypropyl methylcellulose; PVP/VA - polyvinylpyrrolidone/vinyl acetate; PXC – piroxicam; USN – ultrasonic nozzle; XRPD – X-ray powder diffraction.

Both polymers generated particles within the acceptable range for nasal delivery with Dv10 > 10 μm [8], minimizing the inhalable fraction, and with Dv90 of 50 ± 0.6 μm (PVP/VA) and 83 ± 0.3 μm (HPMC). The formation of 106–710 μm CA was achieved by the shake-sieving method of small particles (Dv90 < 7 μm) produced with a two-fluid nozzle, with agglomeration yields above 80%.

Rheology was used to assess the mucoadhesive potential of formulations, assuming that cumulative changes in polymer-mucin rheology are an indication of interaction due to chain interpenetration, and therefore, would improve residence time [9]. All formulations displayed a shear-thinning behavior (Figure 1A), which is typical of mucins and some polymers, although this was more evident for the powders dispersed in SNM. Physiologically, this effect allows for quicker and more efficient mucus clearance during high shear processes such as sneezing [9]. A synergistic effect was observed for the mucin-polymers mixtures, which was expressed as $\Delta\eta$ (Figure 1B) for low and high shear rates. At a rest state, synergistic effects in viscosity induced by mixtures were similar for all formulations, whereas for high shear rates (e.g., sneezing) HPMC showed enhanced increase in viscosity, indicating its potential to improve the residence time by delaying the mucociliary clearance.

Oscillatory measurements on the same formulations showed a dominant gel-like behavior ($G' > G''$) over the frequency range tested (Figures 2A and B). Similarly, changes in elastic modulus attributed to polymer-mucin interactions were expressed as $\Delta G'$ at 1 Hz (Figure 2C), showing the highest increment to be induced by HPMC. However, contrary to the viscosity, the viscoelastic behavior seemed to be more affected by the morphology rather than by polymer type ($G'CA > G'ASD$). The observed gel-like behavior strongly suggests a build-up in viscoelastic properties of the formulations upon contact with nasal fluid or mucus, thus reducing the mucociliary clearance [10].

PXC release profile (Figure 2D) showed that powders composed of HPMC showed higher percentages of drug release regardless the morphology, which may be related with its ability to maintain PXC supersaturation.

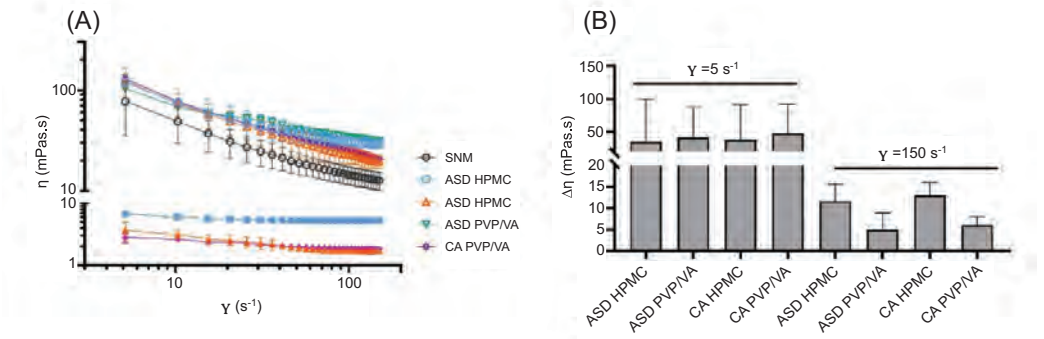

Figure 1. **Viscosity (A) and synergistic viscosity (B) curves of formulations dispersed in SNF (filled symbols) and SNM (open symbols) at low and high shear rates. Results are expressed as mean ± standard deviation (n = 3).**

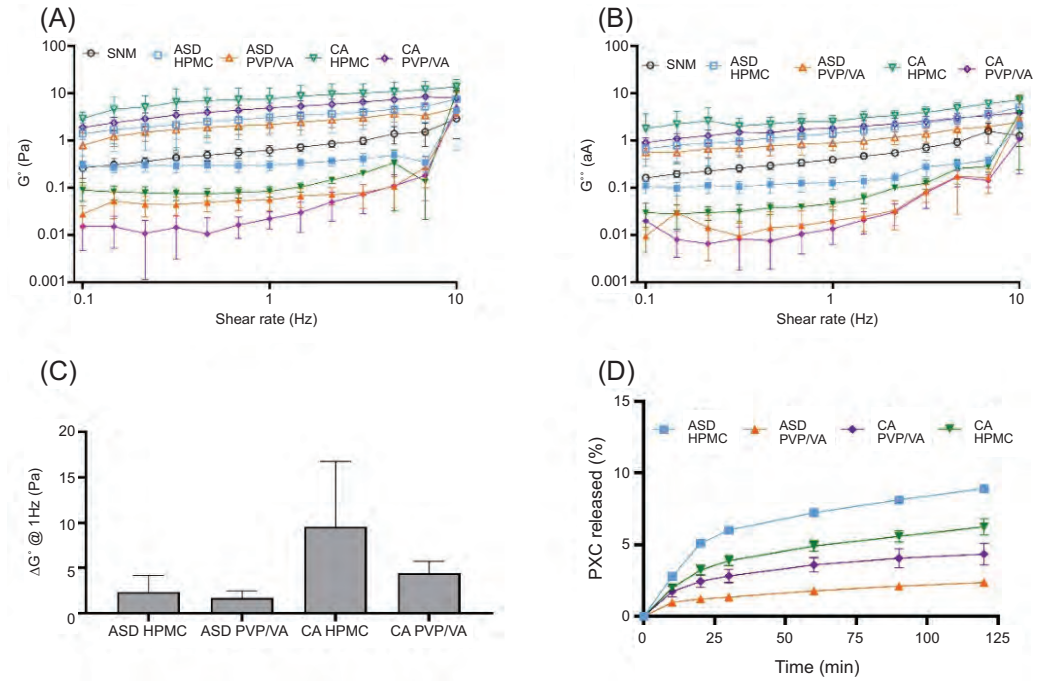

Figure 2. **(A) Storage, G′, and (B) loss, G″, moduli of formulations dispersed in SNF (filled symbols) and SNM (open symbols) and synergistic viscoelastic modulus (C) at 1 Hz. (D) *In vitro* PXC release profile of powder formulations in SNF. Results are expressed as mean ± standard deviation (n = 3).**

CONCLUSIONS

Overall, rotational measurements showed higher discriminatory capacity among different polymer-based formulations, when compared to oscillatory profiles. Ideally, both methodologies should be applied when using rheology measurements for mucoadhesion testing. Formulations composed of HPMC exhibited superior rheological properties and higher drug release profiles.

ACKNOWLEDGEMENTS

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Investigations into the Relationship Between Spray Dried Powder Particle Size and Deposition in Nose and Lung Analogues when Actuated from a Nasal Device

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Upperton Pharma Solutions, Nottingham, UK

KEYWORDS: Alberta Idealized Nasal Inlet (AINI), nasal deposition profile, spray dried powders, particle size distribution, active nasal devices, *in vitro* testing

INTRODUCTION

The administration of therapeutics by nasal delivery is a growing area of pharmaceutical development, due to the ease of administration and large, vascularized surface area available in the nose. However, there is a risk of pulmonary administration if powders are within the respirable range. Inhalable particles are defined by several industries as those with a particle diameter of 10 µm or less [1], however the method of defining powder particle diameter is not clear. There is currently limited pharmacopeial guidance on the testing of nasal powders delivered from a single dose nasal device.

Whilst laser diffraction is commonly used by the pharmaceutical industry to define particle diameter and included as part of target product profiles for nasal products, a more biorelevant test method is required that evaluates the combination of formulation and device.

In this work, we actuated spray dried powders of varying diameters (volume mean diameter (VMD) of 3.5 to 40 µm determined by laser diffraction, aspirated 15 mm from the laser beam) from an Aptar Unidose nasal powder device (UDSp) into an Alberta Idealized Nasal Inlet (AINI), designed to simulate the nose [2], attached to a Next Generation Impactor (NGI), to simulate the lungs. This work aimed to understand if determining particle diameter by laser diffraction is an appropriate test for the development of nasal powders, or if a more physiologically relevant test method can be developed.

METHODS

Spray dried formulations

Three feed solutions consisting of 69:30:1 (%w/w/w) HPMC:Mannitol:Caffeine (Formulations 1 and 2) and 95:5 (%w/w) Trehalose:Caffeine (Formulation 3), were spray dried with either a two-fluid nozzle or ultrasonic nozzle. Spray drying parameters were altered to produce particles of different diameters.

Coating solution preparation and application to AINI and NGI collection cups

The coating solution was prepared by combining 12 g of Brij-35, 20 g of glycerol and 80 mL of ethanol. Internal surface of the AINI and the NGI collection cups were coated. When dried, all components were assembled, with the addition of a pre-separator with 10 mL of water in the reservoir, positioned in between the AINI and NGI.

Deposition profile of caffeine spray dried material by AINI/NGI

The UDSp loaded with 20 ± 3 mg of formulation was positioned at a 45° angle and inserted 1 cm into the nostril orifice of the AINI. A 7.5 L/min airflow was applied for 15 seconds upon actuation of UDSp. After actuation, the configuration was disassembled and 10 mL of water used to rinse and dissolve all spray dried powder on the exterior of the UDSp, deposited in the AINI and the NGI collection cups. An additional dilution was required when analyzing Formulation 3. Each formulation was analyzed in duplicate.

RESULTS AND DISCUSSION

The correlation between geometric particle diameter and nasal deposition was investigated by producing three spray dried formulations with varying particle diameter and therefore, differing percentage of particles with a diameter of < 10 μm (Table 1).

Table 1.

Comparison of percentage of particles with a diameter less than 10 μm analyzed geometrically by laser diffraction and aerodynamically by NGI deposition of spray dried material. Volume mean diameter = VMD.

Formulation	Geometric particle size analysis by laser diffraction		Percentage of Sample in NGI
	VMD (μm)	%≤ 10 μm	(Assumed) %≤ 10 μm
1	39.62	1.52	2.31 ± 1.53 (non-detectable in pre-separator)
2	28.42	17.74	Non-detectable (12.24% in pre-separator)
3	4.22	94.64	1.87 ± 0.02 (19.43% in pre-separator)

Existing literature suggests that coating of the AINI components and NGI collection cups is recommended to simulate the nasal mucosa, to reduce the internal bounce of the particles, and be more representative of *in vivo* conditions [3, 4]. A coating solution inspired by literature was added to the AINI and NGI collection cups [5]. The effectiveness of the coating was assessed by quantifying the deposition profile of Formulation 1 in a coated and uncoated AINI when discharged from a UDSp. Formulation 1 was chosen as an 'idealized nasal formulation' with a VMD of 39.62 μm and only 1.52% of particles with a diameter of < 10 μm by laser diffraction, therefore minimal deposition would be expected in the NGI. It is evident from Figure 1 that coating the AINI significantly changed the deposition profile observed. In the coated AINI, most of the spray dried powder was deposited in the AINI (nostril to nasopharynx) with only 2.31 ± 1.53% of the spray dried powder reaching the NGI (Stage 1). Over 60% of the spray dried powder was deposited in Stage 1 for the uncoated AINI, therefore testing without a coating solution being applied would not represent a good comparator to an *in vivo* nasal environment.

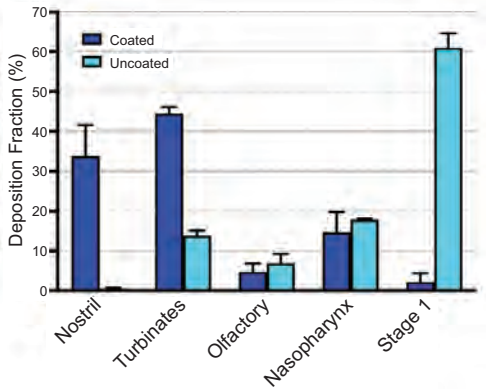

Figure 1. Deposition fraction of Formulation 1 emitted into the uncoated and coated AINI.

The relationship of geometric particle diameter analyzed by laser diffraction and AINI nasal deposition was compared in Figure 2 and Table 1. Laser diffraction showed Formulation 1 to have 1.52% of particles within the theoretical respirable range (particles with a diameter 10 μm or below) which was comparable to the deposition observed in the NGI/lung analog. Although Formulations 2 and 3 showed 17.74% and 94.64% of particles within the theoretical respirable range by laser diffraction, minimal powder was deposited in the NGI. Deposition profiles in Figure 2 of all three formulations were predominantly deposited within the nasal region (AINI). Deposition within specific regions of the AINI differed between formulations; smaller particle diameter produced a lower turbinate delivery. Geometric particle diameter may have minimal correlation on total nasal deposition when discharged from an active nasal device such as the UDSp. Specific nasal deposition profiling may be more heavily influenced by various factors outside of particle diameter, such as plume geometry and particle density.

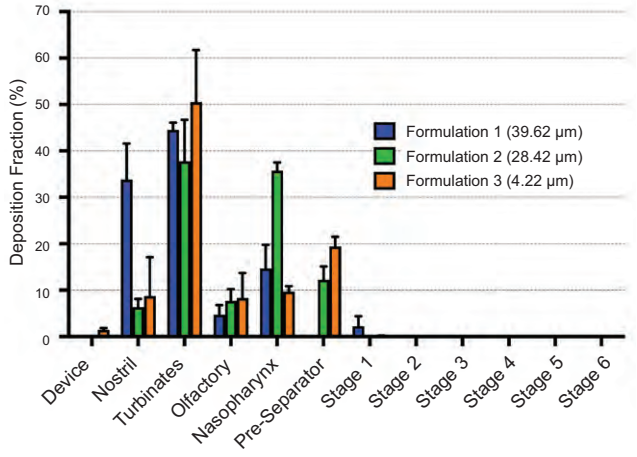

Figure 2. Deposition fraction of spray dried powders of 3.5 µm, 28 µm and 39 µm volume mean diameters in a coated AINI and NGI.

CONCLUSION

In conclusion, we investigated the relationship between particle diameter of spray dried powder and nasal deposition when actuated from an active device. The results from our study have shown that particle size of the delivered powder, ranging from 4.22 to 39.62 µm, did not have a significant impact on the quantity of the delivered dose depositing in the lung (NGI). We conclude that the precedent for nasal formulations where no more than 10% of the particles can have a diameter less than 10 µm as measured by laser diffraction may not be as important as current literature suggests, specifically when actuated from the device that was used in these experiments. Aerodynamic particle diameter, measured with the device intended, is required to understand the possible respirable fraction and thus development targets. Further collaborative work is required with the regulatory agencies to define best testing practices for single-dose nasal powders.

ACKNOWLEDGEMENTS

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Synergies of Inhalation Product Development and Nasal Spray Characterization

Mark Ignaczak, David Wilcox, and Maria Smith

Introduction:

The way in which a device is actuated remains a crucial aspect in determining the deposition profile and, ultimately, the effectiveness of a drug product delivered to the respiratory tract. In general, nasal spray devices are designed to deliver a metered volume of liquid with specific and reproducible spray characteristics upon manual actuation by a user. The spray produced by many orally inhaled products is similarly generated, but more dependent on the patient's breathing cycle than the manual actuation characteristics of the user. For either class of product, the use of suitable automated actuation parameters derived from manual user actuations are suggested in FDA guidance documents.

Workshop Content:

This workshop will investigate how automated actuation parameters have a strong effect on release parameters, such as dose weight, droplet size distribution, spray pattern, and plume geometry; and how each product (formulation, device, and user combination) requires a unique set of parameters in order to ensure reproducible product performance that keeps human usage in mind. The importance of actuating a device in the intended manner to guarantee optimal output will be discussed, along with tips on determining and setting these actuation parameters, and the effect of those settings on expected deposition. In addition, the workshop will highlight how these measurements can provide key insights to accelerate the development process with the goal of getting products to market most efficiently.

Outcome for Participants:

Participants will be provided with an overview of development approaches for determining human actuation profiles and setting actuation parameters based upon various formulation and device combinations to ensure proper actuation of newer devices. They will learn how upfront formulation design, expelled droplet size, and correlated deposition areas can assist in setting these parameters to ensure optimal actuation of the device in a laboratory setting. They will also learn how the above relates to real-world product development strategies.

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Bringing the Respiratory World Together

MedPharm

Breaking through boundaries

In Vitro Epithelial Models to Aid Nasal and Pulmonary Product Development

Jon Volmer and Lynn Allen

Introduction:

Development of new drug products for delivery via the respiratory route for local or systemic effect can be difficult and risky due to complications in deposition, permeation, penetration, clearance, and efficacy. In order to support the development of respiratory therapeutics, MedPharm is developing new *in vitro* model systems and formulation testing systems with the aim of de-risking drug products prior to the start of clinical trials.

Workshop Content:

This workshop will provide an in-depth review of a suite of respiratory epithelial models. This includes current models, such as the MedCast nasal cavity model for assessment of nasal formulation delivery and the reconstituted nasal epithelial model for performance testing and irritation assessment.

Model systems currently in development will also be presented. The first of these is an active reconstituted primary epithelial model of mucociliary clearance where a well differentiated primary airway epithelium is prepared in a linear culture system. This can then be induced to form a mucociliary elevator, which can be used to determine the potential drug product clearance rate from the airways. The second is an induced pulmonary fibrosis model in which primary alveolar or bronchial epithelial cells are co-cultured with certain stromal and inflammatory cells to generate a reconstructed epithelium. These constructs can then be induced to a fibrotic state, which can be used to evaluate the activity of drugs potentially useful to treat fibrosis.

Outcome for Participants:

Participants will learn about unique model systems for nasal delivery and respiratory drug performance testing that can mitigate risk throughout drug development. These models can be useful tools for assessing mucociliary drug product clearance and for testing the efficacy of drugs aimed at the treatment of pulmonary fibrotic disease.

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