

WHITE PAPER

Nasal Delivery of Spray Dried Biologics: Opportunities and Challenges.

Dr. Richard Johnson
Chief Scientific Officer



Upperton
Pharma Solutions



01

Introduction.

The nasal route offers a number of benefits over some of the traditional routes of administration for biologics. This includes rapid delivery into the bloodstream, the avoidance of first pass metabolism, the ability to self-administer and the added potential of bypassing the blood-brain barrier, achieving direct delivery into the brain/CNS.

In recent years there has been an upsurge in interest in delivering a wide range of different classes of molecules via the nasal route. This interest encompasses not only small molecule API's but also larger biologics such as peptides, proteins, vaccines and oligonucleotides.

Interest in nasal delivery of biologics has been fuelled by the emergence of new dry powder devices and the use of spray drying as the method of choice to engineer stable dry powder products.

These spray dried formulations can create stable, dry powder dosage forms incorporating even the most sensitive biological molecules along with selected excipients needed to enhance delivery to the target regions in the body.

Spray dried nasal formulations have the ability to offer **excellent stability, targeted nasal deposition, enhanced permeation with a tried and tested route to commercial scale manufacture.**

+ Interest in nasal delivery of biologics has been fuelled by the use of spray drying as the method of choice to engineer stable dry powder products.



02

Nasal anatomy and potential delivery targets.

For ease of reference, the nasal anatomy can be broken down into three key delivery target areas shown in Figure 1 and Table 1 below.

- ✔ Turbinates
- ✔ Olfactory Region
- ✔ Nasopharynx

Device manufacturers are now developing next-generation dry powder devices to target different parts of the nasal anatomy to maximise delivery efficiency, depending on the where the drug deposition is most optimal.

Figure 1: Schematic showing nasal anatomy

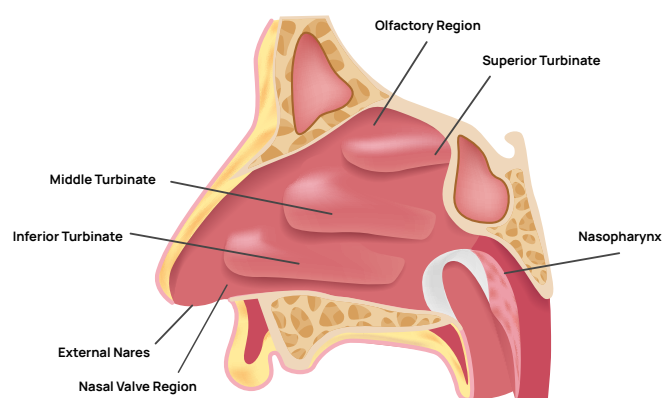


Table 1: Potential nasal targets for nasal delivery of biologics

Target Area	Description	Examples of Candidate Molecules
Turbinates	Largest (approximately 130 cm ²) and most vascularized part of the nasal cavity. Prime site for systemic drug absorption after nasal administration.	Drugs for fast, systemic release eg rescue drugs, pain relief and neurological conditions that require frequent self-dosing.
Olfactory Region	Small fraction ($\leq 10\%$) of the the nasal cavity. Contains olfactory sensory neurons, a potential route for direct-to-brain/CNS delivery.	Biologics that treat conditions in the brain that cannot cross the blood-brain barrier by traditional administration routes.
Nasopharynx	Contains nasopharynx-associated lymphatic tissue (NALT), part of the mucosal immune system, acts to prevent infection.	Vaccines, immune stimulators, typically peptides, oligonucleotide based biologics.



03

Barriers to delivery and pathways into the body.

The surface of the nose offers several barriers that must be overcome if nasal drug delivery is to succeed. These barriers can be summarized as follows:

Mucus Layer

The first barrier on the surface of the nasal epithelium. Primarily composed of mucin polysaccharide, creating a hydrogel layer with intrinsic porosity and a negative charge which can act to slow down drug diffusion.

Mucociliary Clearance

A removal system that uses motile cilia on epithelial cells to constantly sweep mucus and trapped particles out of the cavity.

The cilia beat at a rate of approximately 1000 strokes per minute and it is estimated that the respiratory mucus layer is renewed every 10 to 20 min.

Nasal Epithelium

Once a drug has crossed the surface mucosa, the main challenge to drug absorption is to cross the epithelium.

Extracellular transport across the columnar cells of the epithelium can occur via paracellular diffusion.

Tight junctions are hydrophilic and generally impermeable to many drugs. In its natural state, the epithelium allows passage of molecules up to 1000 Da, with decreasing absorption with increasing molecular weight.

Molecules passing through the epithelium enter the lamina propria where they can then enter the vasculature and systemic circulation.

Intracellular transport via transcytosis is another possible mechanism to reach the lamina propria and is probably more appropriate for larger biologics.

CNS Delivery

Intracellular transport in olfactory neurons begins with internalization of the compound into the neuron and then transportation within the neuron toward the CNS, where it is released.

Olfactory neurons have been shown to use both endocytosis and pinocytosis to transport a range of molecules using receptor-mediated and nonreceptor-mediated mechanisms.

Extracellular pathways in the olfactory epithelium use paracellular mechanisms to allow molecules to cross the epithelium into the lamina propria, similar to mechanisms in the respiratory mucosa.



04

Spray drying to produce particle formulations for successful nasal delivery (UpperNose™).

Spray drying has emerged as the most effective technology for creating dry powder formulations for the nasal delivery of biologics.

Not only does spray drying enable the production of particles of the right aerodynamic size for nasal delivery (Figure 2) but it also enables the production of formulations containing excipients that can enhance delivery performance (Table 2) as well preserving biological structure and function.

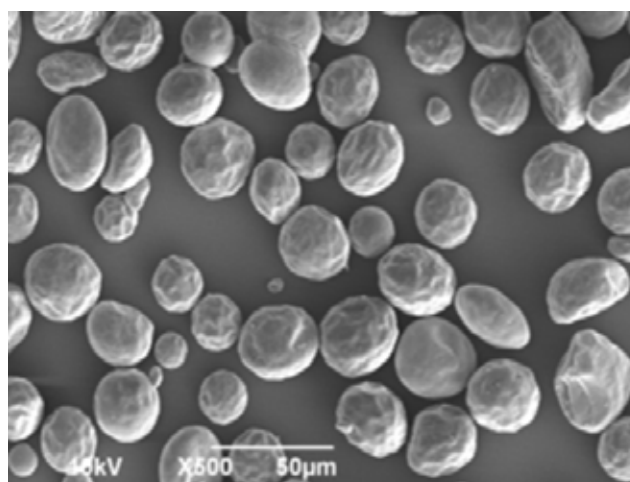
All of these features are captured in the UpperNose™ development platform that utilises the unique features of spray drying to create formulations that are capable of delivering sensitive biologics from a dry powder nasal devices.

Particle Engineering.

Creating particles with the correct size is important for nasal delivery of biologics. It is generally accepted that particles in the 10-100µm range are optimal for nasal delivery (see Figure 2) with drug regulators showing particular interest in reducing particles below 10µm in size to minimize the potential for particles travelling through the nasal airways into the lung.

By optimizing spray drying conditions it is possible to produce gram or kilogram quantities of spray dried nasal powder formulations containing biologics with excellent retention of structure, biological function with ambient storage conditions.

Figure 2: Scanning electron micrograph of spray dried particles produced for nasal delivery.



Excipient Selection.

There are a range of excipients available that can be incorporated into the spray dried formulation to help stabilise the tertiary structure of the biologic, maintain stability on storage and enhance the delivery at the site of deposition.

Table 2 below summaries some of the most widely used excipients and the impact that they might have on biologics and their delivery properties.



Table 2: Categories of excipients for formulating nasal dry powders containing biologics

Excipient Category	Description	Examples
Amorphous stabilisers	Used to stabilize tertiary structure of complex biological molecules	Trehalose, Sucrose, Amino acids
Permeation enhancers	Enhance transport of molecules across epithelia, usually by opening tight junctions	PEG400, Polysorbate 80, fatty acids (eg oleic, palmitoleic acid) Vitamin E (TPGS), Chitosan
Mucoadhesive agents	Retains biologic at surface of epithelium by slowing mucociliary clearance	Chitosan, Hyaluronan, Gellan gum, Pectin

Choice of Device.

There are an increasing number of dry powder nasal devices available for testing prototype nasal formulations. The choice of device is generally dictated by (i) the number of doses required to be delivered (i.e. single dose or multidose) and (ii) the target delivery area in the nose (i.e. general nasal delivery or the use of more specialized devices for targeting powder deposition in the olfactory region for enhanced nose-to-brain delivery).

Images of single-dose and multi-dose devices that can be used for delivering dry powder dosage forms into the nose are shown below in Figure 3.

Figure 3: Examples of single-dose and multidose dry powder nasal devices



05

Testing spray dried nasal formulations containing biologics.

Confirming biological structure has been retained.

As part of the UpperNose™ development strategy, pilot formulations can be produced by spray drying at small scale (typical batch sizes of around 1-2g of spray dried powder). These batches can be analysed using a number of techniques with a particular focus on retention of tertiary structure and biological activity. Typical assays listed below in Table 3.

Table 3: Typical assays used to analyse spray dried powders containing biologics.

Assay	Description
HPLC (size exclusion, reverse phase, ion exchange)	Used to confirm biologics are intact and have retained tertiary structure without aggregation or chemical degradation
Nanosizing (dynamic light scattering)	Can be used to determine any changes in size (post spray drying) of larger globular proteins and nano-sized liposomal structures
Gel Electrophoresis	Determine whether structure is intact under denaturing or non-denaturing conditions
Functional (potency) assays	Required to determine whether activity of the biologic has been retained. Assays include expression based (oligonucleotides), ELISA (mAb) or cell based test systems (peptides, hormones)
Physical/Thermal properties of spray dried powder	Techniques such as DSC, XRPD, DVS can be used to test physical and thermal powder properties that may have a significant impact on handling properties and storage stability

In addition to analysing biologics after spray drying there is also a need for testing stability of early prototype formulations. The UpperNose™ utilises accelerated testing/modelling provided by the ASAPprime® to determine potential shelf life issues in the early stages of development.



Testing Aerodynamic Performance of formulation/device combination.

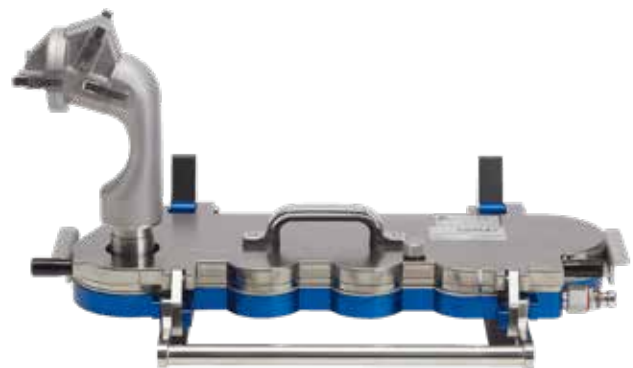
It is hugely important to determine what proportion of the administered dose enters the nose, where it deposits across the nasal passage, and how much might subsequently enter the lung.

This deposition pattern will be dictated by a combination of the aerodynamic properties of the spray dried powder and the device from which it is delivered.

Spray dried formulations can be filled into a nasal delivery device and delivered into one of a number of model nasal/lung systems. The UpperNose™ development platform utilises two impactors representing the nose (Alberta Idealised Nasal Inlet or AINI) and the lung (NGI) as shown in Figure 4 joined in series, down-stream of the device.

Following delivery of the dose from the nasal device, the individual component chambers representing the nose and the lung can be opened, and drug deposition determined using a range of analytical techniques (e.g., HPLC, spectrophotometric methods).

Figure 4: AINI attached to NGI for measuring nasal and lung deposition of dry powders

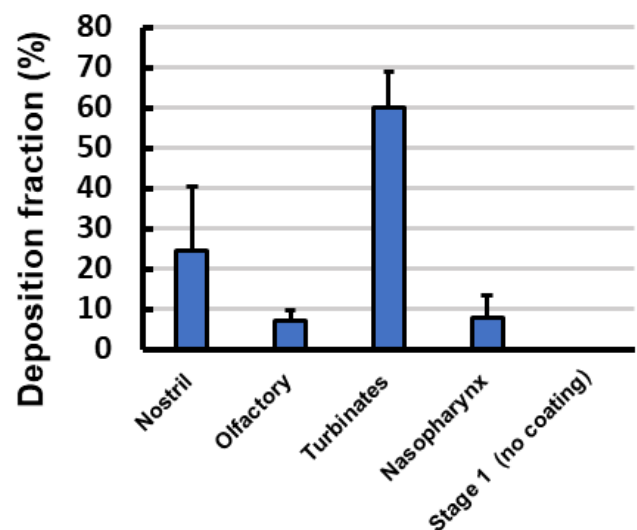


Data generated from both impactors can then be used to calculate (i) where in the nose the drug will be deposited and (ii) how much of the delivered dose might end up in the lung (crucial from a toxicology perspective).

Figure 5 shows the typical dose distribution of a spray-dried powder delivered using an Aptar UniDose® dry powder device in the test system depicted in Figure 4.

Testing of the aerodynamic properties of nasally delivered powders is still very much in its infancy but with the UpperNose™ platform, early stage dry powder formulations can be delivered from a range of selected nasal device to determine dose deposition and reproducibility of manufacture.

Figure 5: Nasal/Lung drug deposition of a spray dried powder delivered by an Aptar UniDose® device



06

Conclusion.

The anatomy and physiology of the nasal cavity offers an attractive delivery route for an extensive range of biologics, from small peptides to larger vaccines and oligonucleotides. Maximising the delivery potential of this exciting new route requires the development of new, stable dry powder formulations that can incorporate a range of excipients to maximise uptake into the body.

Spray drying has now emerged as the method of choice for engineering these dry powder formulations, incorporating the right excipients into the formulation, maintaining structure and function of sensitive biologics during the drying process, optimising particle size to achieve targeted nasal deposition and improving storage stability.

An integral part of developing dry powder biologics for nasal delivery is in the device selection and testing of the delivered dose to ensure maximum delivery of the biologic into the correct areas of the nasal geometry (in a reproducible manner whilst minimising potential lung deposition).

However, these aerodynamic analytical techniques are still in the developmental stage and great care is needed when choosing the correct delivery parameters needed to achieve a robust, reproducible output.

The development of a dry powder nasal dosage form containing a biologic can be seen as challenging with many techniques still in their infancy.

However, utilising end-to-end development platforms like UpperNose™ maximises the chances of success whilst accelerating the pathway into clinical development.

An integral part of developing dry powder biologics for nasal delivery is in the device selection and testing of the delivered dose to ensure maximum delivery of the biologic into the correct areas of the nasal geometry.



About the author



Dr. Richard Johnson is the Founding Director and Chief Scientific Officer at Upperton Pharma Solutions, a UK-based Contract, Development and Manufacturing Organisation (CDMO). Graduating from Warwick University with a PhD Biochemistry he was employed as a protein chemist at Delta Biotechnology. In 1994 he was part of a management buy-out team that founded Andaris Ltd, a research and development company exploiting the use of spray drying technology in the fields of diagnostic imaging and drug delivery. In 1999, Dr. Johnson founded Upperton and has overseen significant growth and expansion over the past 20 years.

upperton.com



Driven by experts, led by science