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INTRANASAL DELIVERY OF BIOLOGIC THERAPEUTICS AND VACCINES

In this article, David Ward, Formulation and Manufacturing Lead at Intertek Melbourn, looks at how the nasal route of drug administration offers the potential to improve the delivery of biologics, even for very complex molecules such as antibodies – and why strategic formulation is required to make this a reality.

Typically, biologic therapeutics and many vaccines are large, complex molecules with a high molecular weight (MW). However, because intranasal delivery can target both topical and systemic delivery via the different tissue types in the nasal cavity (Figure 1), nasal administration has the potential to address a wide range of diseases. There is currently an increased focus on addressing both prophylactic and therapeutic potential against SARS-CoV-2 infection – but other successes to date include a nasal spray delivering the 3.5 kDa polypeptide hormone calcitonin, which has been used for many years to treat postmenopausal osteoporosis. Table 1 lists a selection of other marketed intranasal biologics, as well as some which are currently in development. Intranasal vaccines also promise multiple benefits, with the successful launch of influenza vaccines – for example, FluMist (MedImmune) – onto the market as far back as 2003.

Biologic drugs are complex molecules; structure is just as fundamental to their function as chemical stability. They are susceptible to a wide range of degradation routes, which can impact the safety and efficacy of the drug.

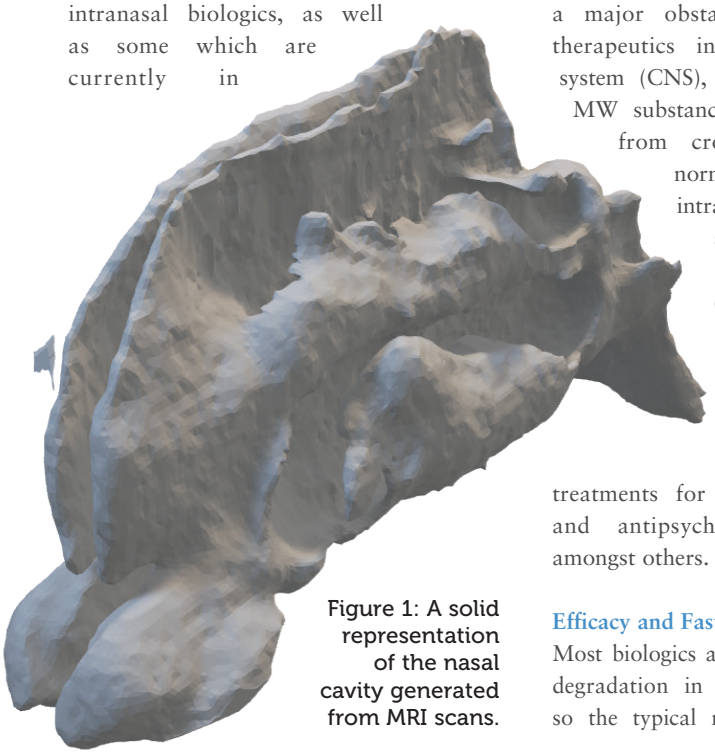

Figure 1: A solid representation of the nasal cavity generated from MRI scans.

ADVANTAGES

Potential Nose to Brain Route

The blood-brain barrier (BBB) presents a major obstacle to the delivery of therapeutics into the central nervous system (CNS), as the majority of large MW substances are severely restricted from crossing the BBB under normal conditions.[1] Successful intranasal delivery of biologics such as peptides, proteins, monoclonal antibodies, oligonucleotides and gene and cell therapies via the nose-to-brain route presents a potential strategy for bypassing the BBB, enabling new treatments for Alzheimer's, Parkinson's and antipsychotic-induced symptoms, amongst others.

Efficacy and Fast Onset of Action

Most biologics are susceptible to enzymatic degradation in the gastrointestinal tract, so the typical route of administration is

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Compound/Product	Molecule	Therapeutic Target	Status
Calcitonin	Peptide	Osteoporosis	Marketed
Desmopressin	Peptide	Diabetes insipidus, Haemophilia A	Marketed
Oxytocin	Peptide	Start or strengthen uterine contractions during labour	Marketed
Nafarelin	Peptide	As part of a fertility programme, endometriosis	Marketed
Cyanocobalamin	Peptide	Deficiency of vitamin B12	Marketed
Live attenuated influenza vaccine	Virus-based vaccine	Influenza	Marketed

Table 1: Examples of marketed nasal biologics.

a subcutaneous injection. When drugs are administrated by the intranasal route, they enter through the respiratory region around the inferior turbinate where the respiratory nasal mucosa is highly vascularised and lined with columnar epithelium cell types, which present a large surface area (>150 cm^2) for drug absorption[2] and are highly permeable.[3] Because the intranasal route avoids enzymatic degradation in the gastrointestinal tract and first-pass hepatic elimination, it therefore reduces the impact of common barriers which limit drug absorption and contributes to a fast onset of action.

Patient Adherence

Good patient adherence is important for treatment efficacy and this is particularly true for intranasal drug products, which must be administered regularly and consistently to ensure continued therapeutic benefit. Patient satisfaction and comfort with administering the drug according to the correct medication regime is therefore important. The intranasal route is both non-invasive and well tolerated, expanding the possibility for patient self-administration,[1] although differences in delivery devices and their handling characteristics can be a factor.[4]

DISADVANTAGES

Mucociliary Clearance

The nasal anatomy, by design, is quick to clear material from entry to the airways via mucociliary clearance – a natural process where the nasal mucosa drag mucus and deposited material from the front of the nose to the throat, where it is swallowed. This means there is typically a short window for absorption of nasally delivered drugs to occur. The natural nasal cycle can also affect absorption rates. This is an approximate two-and-a-half-hour cycle where one side of the nose is more congested than the other, with the process alternating between sides.[5] If your product dose consists of only one shot into the nose, then absorption could vary depending on which nostril is used.

Marketed Drug	Molecular Weight
Desmopressin	1183 Da
Nafarelin acetate	1321 Da
Oxytocin	1007 Da
Calcitonin	3432 Da
Cyanocobalamine	1355 Da

Table 2: Molecular weight of marketed intranasal peptides.

Poor Absorption

Nasal delivery of biologics is limited by the low membrane permeability of large MW protein or peptide drugs. Currently marketed peptides, as shown in Table 2, have a MW in the region of 1000 Da – 3500 Da, with calcitonin having the highest MW of 3432 Da.[2] This low permeability for some drugs means that formulation with absorption enhancers is necessary and, potentially, larger doses of the active are required to reach the appropriate therapeutic dose.

STRATEGIC FORMULATION REQUIREMENTS

Strategic formulation for intranasal biologic delivery is important. Formulation can be used to increase residency time in the nasal cavity using bioadhesives or viscosity adjusters to slow down the rapid mucociliary clearance and increase the amount of drug retained in the nasal cavity to allow sufficient absorption to occur. Absorption is a major factor to understand during formulation development and several strategies can be used to optimise this, including permeation-enhancing agents, mucolytic agents, mucoadhesive agents, *in situ* gelling agents and drug carrier technologies (Table 3).

Mucoadhesive nasal gels are the most prominent non-invasive dosage forms through which a drug can reach systemic circulation directly, avoiding the first-pass effect and enhancing the underlying bioavailability of the drug.[6]

Agent	Action	Examples
Permeation-enhancing agents	Help to increase the transport of proteins and peptides across the nasal membrane by several modes of action	n-dodecyl beta-D-maltoside (Neurelis's Intravail), surfactants e.g. polysorbates and lecithin
Mucolytic agents	Enhance nasal absorption	N-acetyl-L-cysteine (NAC)
Mucoadhesive / bioadhesive agents	Enable prolonged retention at the site of application, providing a controlled rate of drug release for improved therapeutic outcome	HPMC, carbopol 934 and sodium alginate
In situ gelling agents	Non-Newtonian fluids – free flowing when being mixed or sprayed but then forming a thick gel following actuation	Avicel RC591 (DuPont)
Drug-carrier technologies	Agents that enhance absorption through encapsulation or surface modification	liposomes, emulsions, nanoemulsions, nano/micro particles

Table 3: Potential formulation agents.

Making use of drug-carrying technologies, or technologies which modify the inhaled particle surface with agents that enhance their absorption, is a strong formulation strategy, provided that structural integrity can be maintained. For example, spray-dried, polymer-coated liposomes composed of soy phosphatidylcholine and phospholipid dimyristoyl phosphatidylglycerol coated with alginate, chitosan or trimethyl chitosan demonstrate increased penetration of the liposomes through the nasal mucosa compared with uncoated liposomes when delivered as a dry powder.[7] Introduction of agents at the structural level – for example, enzyme-inhibiting agents – should be evaluated for additive activity or enhanced activity over and above the activity of the biologic on its own.

TESTING

In regulatory terms, inhaled and nasal biologics will require characterisation as per ICH Q6B, as well as the specific respiratory testing outlined in documents such as the EMA "Guideline on the pharmaceutical quality of inhalation and nasal products" (June 2006) or the US FDA "Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation" (July 2002). Testing programmes should aim to both fully characterise the biological entity and establish whether the device delivery mechanism (e.g. actuation) has adversely affected parameters, including structure, purity (aggregation, fragmentation, etc.) and the activity (potency), in line with the ICH Q6B guidance. Nasal products also require specific testing to assess delivered dose uniformity from the device and the droplet/particle size of the drug emitted.

Attribute	Characteristics	Analytical Method
Comparative physiochemical & structural characterisation	Primary sequence confirmation	Peptide mapping approach (LC-MS/MS)) covering full sequence confirmation, PTMs information (if applicable) and confirmation of di-sulphide (if peptide contacts cysteine), N/C terminus profiling
	N-terminal sequence	Edman degradation
	Free thiol determination	Ellman's reagent
	Amino acid composition	Amino acid analyser/HPPLC
	Intact mass analysis	MALDI TOF/LCMS/ESI MS
	High order structure	CD (near, far and thermal denaturation), FTIR, DSC, NMR -1D (1H & C13), 2D (TOCSY & NOESY), fluorescence spectroscopy, HDX
	Optical purity	GCMS
	Chiral confirmation (typically for peptides)	GCMS/LCMS
Impurity profiling	Oligomer/aggregation	UV-SEC-MALS, SV-AUC, DLS, SDS-PAGE, CE SDS
	Charge variant profiling	iCIEF/IEX
	Peptide-related impurity profiling	UPLC/HPLC- HR-MS/MS, RP-HPLC
Biological activity	Cell-based assay/immunoassay	*In vitro* cell-based method, based on the intended mode of action of the protein/peptide

Table 4: Analytical methods to be considered in relation to development of a nasal protein or peptide product.

Protein structures have limited stability and can easily unfold under only mild stress. Aggregation, where the protein self-associates, is one of the most common issues, whereas fragmentation, deamidation, hydrolysis, oxidation, isomerisation, succinimidation, deglycosylation, disulphide bond formation/breakage and other crosslinking reactions can all play their role in the stability of the biologic active. Table 4 illustrates the scope of tests required to determine critical quality attributes for protein or peptide therapeutics, which includes mass spectrometry (Figure 2).

Figure 2: Mass spectrometry is a key analytical tool for the characterisation of biologics.

CONCLUSION

Intranasal is a promising route for biologic administration, which is reflected in the growing number of marketed products treating chronic diseases, as well as a large number of clinical trials currently in progress, particularly those focused on development of a treatment for the respiratory illnesses caused by SARS-Cov-2 infection or of vaccines. The nasal route of drug administration offers the potential to improve the delivery of biologics, even for very complex molecules such as antibodies. However, strategic formulation is required to make this a reality.

A FOCUS ON PEPTIDES

As peptides offer greater efficacy, safety and tolerability in humans compared with small molecules, and are also, due to their smaller size, better able to penetrate cell membranes compared with proteins, peptides have emerged as potential drug candidates for both therapeutics and vaccines against covid-19. Overall, the development pipeline is robust, with more than 100 peptides in late-stage clinical development and more than 200 in the preclinical stage, with intranasal delivery being explored for many candidates. Within this pipeline, over 20 peptides are being assessed to address the recent global outbreak of covid-19/SARS-CoV-2 infection, including 15 synthetic peptides.[8] Studies on the intranasal application of peptides have explored these candidates, either pre- or post-challenge with coronavirus, with outcomes that suggest these may have both prophylactic and therapeutic potential against SARS-CoV-2 infection.[9]

INTERTEK SOLUTIONS

The recent expansion at Intertek's Centre of Excellence for Inhaled and Nasal Drug Development in Melbourn (UK) has focused on new, powerful analytical strategies, integrated with formulation, stability and clinical trial material manufacturing to drive understanding of clients' products and processes, enabling clients' key decision-making activities throughout the product development life cycle.

The Intertek team supports the design and optimisation of formulations for biologics or small molecules, powders, capsules, liquids, solids and semi-solids for inhaled, nasal, nebulised, pressurised and topical drug formulations. It delivers focused development strategies from an early stage which can be tailored to new chemical entities (NCEs) or generic products, from feasibility studies through to development support, Phase I and Phase II clinical trials, scale-up and transfer to commercial manufacturing.

Intertek's expertise helps accelerate project timelines and includes pre-formulation, excipient-API compatibility assessment and optimisation, physicochemical testing, formulation screening, lab-scale formulation and accelerated stability studies to achieve the desired product characteristics.

It offers a broad range of analytical capabilities, including protein structure, physico-chemical properties characterisation and potency alongside solubility assessment, dissolution, solid state characterisation, particle morphology (Malvern Morphologi 4 ID), forced degradation and stability screening, in order to select the optimal development candidates.

With a holistic approach to service provision, including raw material quality control, scale-up, pilot-scale batch manufacturing and testing, GMP clinical batch manufacturing, stability storage and impurities testing, as well as release testing with qualified person (QP) release, Intertek offers a one-source solution for material supplies for use in Phase I and II clinical trials. The company understands the need to invest time to establish rugged methodology with a focus on identifying and controlling critical quality attributes as an integral part of product development. Its experienced scientists deliver analytical programmes to support all stages of development for both innovative and generic products, as well as maintaining involvement in the development of new and improved techniques and technologies.

ABOUT THE COMPANY

With nearly 30 years of experience in supporting clients' orally inhaled and nasal drug product development, Intertek Melbourn provides product performance testing, method development/validation, stability, CMC support, formulation development and clinical manufacturing capabilities. Intertek's network of more than 1,000 laboratories and offices and over 46,000 people in more than 100 countries delivers innovative and bespoke assurance, testing, inspection and certification solutions for its customers' operations and supply chains across a range of industries worldwide.

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David Ward is the Formulation and Manufacturing Lead for Intertek Melbourn. He has worked in the pharmaceutical and device development sectors for over 20 years across innovative pharma companies and device design and product development, specialising in formulation, analysis and clinical production approaches for orally inhaled and nasal drug products. He has worked across many device types including pressurised metered dose inhalers, dry powder inhalers, nasal products and nebulisers.