OPTIMISATION OF NASAL DRUG PRODUCTS FOR SYSTEMIC DELIVERY

David Ward
Formulation and Manufacturing Lead,
Intertek Melbourn UK
Global ATIC Business with over 45,000 Employees

- 45,000+ employees worldwide
- £7.8b+ market capitalisation
- FTSE 100 company in the Support Services sector
- 1,000+ laboratories & offices
- 100+ countries
- 130+ years of history
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# INTERTEK PHARMACEUTICAL SERVICES
## OUR REGULATORY LAB LOCATIONS

### Recent Investments
- Stability Footprint Expansion in UK > 250,000L
- Doubled UK Centres of Excellence Laboratory Footprint

### Americas
<table>
<thead>
<tr>
<th>Location</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>San Diego, CA</td>
<td>Small and Large Molecule Bioanalytical - GLP</td>
</tr>
<tr>
<td>Whitehouse, NJ</td>
<td>Analytical with expertise in E/L, elemental impurities and stability – GMP</td>
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</tbody>
</table>

### Europe
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<tr>
<th>Location</th>
<th>Category</th>
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</thead>
<tbody>
<tr>
<td>Basel, CH</td>
<td>Analytical with specialist capabilities for E&amp;L - GLP/ GMP</td>
</tr>
<tr>
<td>Melbourn, UK</td>
<td>Analytical, Formulation &amp; Clinical Manufacturing Special Expertise with Complex Dosage Forms (OINDP) Stability – GMP</td>
</tr>
<tr>
<td>Manchester, UK</td>
<td>Bioanalytical and Analytical with specialist capabilities for Biologics – GLP/ GCP/ GMP</td>
</tr>
</tbody>
</table>

### Asia / Australasia
<table>
<thead>
<tr>
<th>Location</th>
<th>Category</th>
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<tbody>
<tr>
<td>Melbourne, AU</td>
<td>Analytical - GLP/ GMP</td>
</tr>
</tbody>
</table>
CURRENT NASAL PRODUCT USES

Traditionally Only Topical Use

- Seasonal Rhinitis
- Sinusitis
- Systemic absorption undesirable

Recently Gained Interest in Systemic Treatment

- Sumatriptan (Imigran), Naloxone, Flu Vaccinations
- Interest in use of nasal route for treatment of
  - Alzheimer’s
  - Parkinson's
  - Depression
  - Anxiety

Historically nasal sprays have only been used for the treatment of topical conditions such as seasonal rhinitis (hayfever) and sinusitis, and the systemic absorption of these drugs is undesirable due to affects that could occur to the Hypothalamic-pituitary-adrenal axis, bones, eyes or other parts of the anatomy.

More recently there has been an increase in interest in delivering drugs to the nose for systemic conditions.
WHY CHOOSE SYSTEMIC NASAL DELIVERY?

Advantages

- Avoidance of parenteral administration/non-invasive
- Rapid absorption of small molecules, generally 15 – 30 minutes
- Avoidance of hepatic first-pass effect
- Apparent permeability to some peptides
- Ease of administration, good patient compliance

Disadvantages

- Environmental conditions, infection and inter-subject variability can lead to inconsistent absorption
- Short time span for absorption due to rapid clearance
- Poor absorption of larger molecules can reduce bioavailability
- Existing formulations not designed for systemic delivery
- Most commonly used devices do not target optimal regions of nasal cavity
THE NASAL CAVITY

Simplified Sagittal Nasal Anatomy

Turbinates - Have a large surface area of nasal mucosa which allow for systemic delivery

Olfactory region - Could potentially be useful for direct nose to brain delivery of particular treatments, such as treatments for migraine, Parkinson’s or Alzheimer’s or any molecule that cannot pass the blood/brain barrier.

Nasal Associated Lymphoid Tissue - Connected to the lymphatic network and can induce a mucosal and systemic immune response, so is therefore a target for delivery of vaccines and biologics.
THE NASAL CAVITY

MRI Cross Section of Nasal Cavity

Complex structure:
A network of very narrow passage ways, Two narrow slits at the front of the nose, called the nasal valve, where much of a nasal spray is deposited, particularly in the case of aqueous nasal sprays, although some other types of devices can have higher deposition in more posterior areas.
METHODS TO OPTIMISE SYSTEMIC ABSORPTION

Formulation – Increase Residency Time of Active in Nasal Cavity

- **Bio-adhesives and viscosity adjusters**
  - Chitosan
  - CMC, HPMC, HMC
  - CMC/MCC – Avicel® RC591
  - Polyethylene Glycol (PEG)
  - Polyvinylpyrrolidone (PVP)
  - Glycerol
METHODS TO OPTIMISE SYSTEMIC ABSORPTION

Formulation – Enhance Absorption Rate of Active

- Permeability enhancers and solubilisers
  - Neurelis Intravail®
  - Polysorbate 20/80
  - Cyclodextrins
  - Lecithin
  - HPMC
  - Oleic Acid
  - Propylene Glycol
  - Ethanol
Traditional multi dose aqueous spray pumps deposit the drug primarily at the front of the nose. Monodose sprays have a similar performance.

Alternatives:
- Dry powder devices can potentially deliver the drug deeper into the nasal cavity
- pMDIs use a volatile propellant so are less likely to drip out of the nose
- Nebulisers create small droplets that can be inhaled further into the nose
- In development (Nemera) - pMDI devices that can be actuated into the mouth and then exhaled through the back of the nasal cavity giving a greater deposition in the areas of interest.
SUMMARY

• The nasal delivery route offers a good opportunity for systemic drug delivery

• Optimisation of formulation can overcome difficulties in developing a commercialisable product

• This can be achieved by increasing residency time, absorption rate and formulation or device type
FURTHER INFORMATION

Intertek recently presented a series of webinars on the subject of nasal drug delivery, recordings of which are available from the link below

Teresa Iley – Introduction and Background to Nasal Products

Mark Parry – Review of In-Vitro Testing for Bioequivalence of Nasal Drug Products

David Ward - An introduction to the formulation and manufacturing approaches for nasal drug products


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