Inhalation & Nasal Device Overview

September 29, 2015
Learning Objectives

- To understand rationale for nasal and pulmonary drug delivery
- To differentiate between device attributes for inhalation and nasal platforms
- To list the important components of a MDI
- To describe the metering mechanisms for DPIs
- To understand effects of formulation on nasal spray performance
Rationale for Pulmonary Drug Delivery

- Large surface area
- Gas exchange
- Blood supply
- Particle trapping and removal
Targeting the Lung

- Upper Respiratory Tract
  - Bronchodilators
  - Corticosteroids
  - Anti-infectives

- Lower Respiratory Tract
  - Surfactant Replacement
  - Systemic Drug Delivery
    - Insulin

- Size Matters!
  - Particle size
Inhalation Delivery Platforms

- Metered Dose Inhalers (MDI)
- Soft Mist Inhalers (SMI)
- Nebulizers
- Dry Powder Inhalers (DPI)
Metered Dose Inhalers (MDIs)

- Solution or suspension
- Propellant (HFA-134a or HFA 227)
  - All US drug products will use HFA propellants
  - CFC’s lagging in developing markets
- Excipients
  - Co-solvent (ethanol)
  - Surfactant
  - Taste masking
  - Moisture control
pMDI - Basic Design & Function

Standard pMDIs include three fundamental components:

1. Canister
   - Single component
   - Contain and protect drug formulation

2. Valve
   - Multi-component
   - Multi-function

3. Actuator
   - Single component
   - Easy to hold in hand
   - Direct drug product spray to patient’s mouth
Dose Delivery from the Valve

**Basic principle:**

**At rest**
Free flow of drug formulation between the bulk contents in the can and the Valve Metering Chamber. The drug product formulation is a pressurised liquid.

**Beginning of Actuation**
The patient pushes on the bottom of the can. The Valve Stem is pushed into the Valve. The drug formulation in the Metering Chamber is isolated. This is the dose that will be delivered to the patient.

**End of actuation**
The patient continues pushing until the Stem is fully pushed into the Valve. The drug formulation in the Metering Chamber is exposed to exterior (ambient) pressure and changes from liquid to gas vapour. The vapour exits the Valve.
MDI Features

- Dose counters*
  - New drug products in US must utilize dose counters

- Spacers
  - Add on device
  - Marketed separately from MDI
  - Common use in pediatric and geriatric populations
  - Sometimes specified or listed in product labeling in US
    - Required to be described and tested in EU

Dry Powder Inhalers (DPIs)

- Drug
  - Micronized or spray dried

- Carrier
  - Lactose

- Additional excipients
  - Taste masking
  - Stability

- Dose counter often present
Dry Powder Inhaler (DPI)

- DPI schematic adapted from Telko and Hickey, 2005
- Drug - Micronized or spray dried
- Carrier - Lactose
Passive Dry Powder Inhalers

- A micronized or spray dried powder is:
  - Inhaled
  - Deaggregated
  - Entrained
  - Metered

- Using energy from only the patients inhalation

Astra Turbuhaler
Active Dry Powder Inhalers

- A micronized or spray dried powder is:
  - Inhaled
  - Deaggregated
  - Entrained
  - Metered

- Using energy from a patient independent source

Nektar
DPI Device Metering

- Capsule
- Blister
- Reservoir

Spiriva

Foradil

Aerolizer
Capsule Selection

- Size 3 is a standard capsule format suitable for high speed filling technology
- Size 3 capsule can be easily filled for development & clinical purposes
- HPMC or gelatin
- Filling range between typically between 5-30mg
- Off the shelf solutions available
  - Customization may be required
Capsule Considerations

- Should not fragment if pierced
- Shell should be retained in device during use
- Capsule should be easily inserted and removed
- Capsules from other devices should not be usable
- Capsule should be protected from high and low humidity during storage e.g. capsules in blister packs
DPI Blisters Systems

Glaxo Wellcome
Accuhaler / Diskus
Blister Considerations

:: Advantages

- Protect powder formulation from humidity
- Multiple dose pack possible
- Less chance to inhale fragments from blister

:: Disadvantages

- Non-conventional filling
- Double dosing potential
- Difficult for patient to clean
DPI Reservoir Systems

Asmanex Twisthaler
Mometasone furoate
(Merck)
Reservoir Considerations

- Non-conventional filling and assembly
- Protection of reservoirs against environment and exhalation by patient into reservoir itself
- Dose variance between batches, users, modes of use, and through device lifetime
- Effects of transport
Device Resistance

- Low
  - Aerolizer
  - Diskus
  - Novolizer

- High
  - Turbuhaler
  - Clickhaler
  - Twisthaler

Increasing Resistance
Device Resistance

Output Is Dependent On Air Flow Rate?

Effect of Flow Rate

- **Flow rate**: effect on Delivered Dose

Flow Rate has minimal impact on delivered dose values.

- **Flow rate**: effect on Fine Particle Fraction (FPF)

FPF values increase with increased flow rate.
Single Breath Atomizers

- “Soft Mist Inhalers”
- Solution based
- Drug delivered in a single inhalation
- Example: Respimat
  - Reservoir holds up to 200 doses in a hand-held unit
  - Drug solution specific to device

Respimat (Mechanical break-up)
Nebulizers

- Inhalation Solutions and Suspensions
  - Ampoules or vials marketed independent of device

- Mechanisms
  - Compressed air
  - Ultrasonic
  - Vibrating membrane

- Device typically approved by 510(k) FDA application

MicroAir by Omron
Rationale for Nasal Drug Delivery

- Large surface area
- Highly vascularized
- High permeability limits effect of high enzymatic activity
- Enables immunization (NALT-nasal associated lymphoid tissue)
- Traps particles as a defense mechanism
Targeting the Nose

• Local Indications
  – Allergic rhinitis
  – Sinusitis
  – Polyps

• Systemic Indications
  – Pain
  – Migraine
  – Osteoporosis

• Immunization
  – FluMist
  – H1N1

Side View of Nasal Cavity: Nostril (a), Turbinates (b-d), Olfactory region (blue area), Nasopharynx (e)
Deposition Mechanisms

- Impaction (primary factor)
- Sedimentation
- Diffusion (related to olfaction)

- Droplet size and velocity of droplets key factors
Intranasal Formulations

- **Solutions**
  - Buffered
  - Isotonic

- **Suspensions**
  - Polymers

- **Gels**

- **Powders**

- **HFA Nasal Aerosols**

<table>
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<th>Product</th>
<th>Reported pH</th>
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<tbody>
<tr>
<td>Beconase</td>
<td>4.5 - 7.0</td>
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<tr>
<td>Flonase</td>
<td>5.0 - 7.0</td>
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<tr>
<td>Nasacort</td>
<td>4.5 - 6.0</td>
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<tr>
<td>Nicotrol NS</td>
<td>7.0</td>
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<tr>
<td>Desmopressin</td>
<td>3.5 – 6.0</td>
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<tr>
<td>Product</td>
<td>CMC</td>
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<tr>
<td>Beconase AQ, Nasacort AQ, Rhinocort Aqua, Flonase</td>
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<tr>
<td>Astelin Nasal Spray</td>
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<tr>
<td>Nasonex</td>
<td>X</td>
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<tr>
<td>Nascobal Nasal Gel</td>
<td></td>
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<tr>
<td>Zicam Nasal Gel</td>
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</table>

CMC = Carboxymethyl cellulose  
MCC = Microcrystalline cellulose  
HPMC = Hydroxypropylmethyl cellulose  
Gly = Glycerin  
MC = Methyl cellulose
Preservatives

- Benzalkonium Chloride (BKC), EDTA, phenylethylalcohol, potassium sorbate, benzyl alcohol

- BKC
  - Possible changes to ciliary beat frequency, ciliary morphology, mucociliary clearance, epithelial thinning and/or destruction
  - Marple, et. al. conclude safe and well tolerated for both long- and short-term clinical use
  - FDA still approving nasal spray products with BKC
  - People still ask if BKC is safe → popularity of preservative free systems

Formulation Effects

- Viscosity
  - Direct correlation to droplet size
  - Inverse correlation to plume geometry

- Surface tension
  - Affects droplet size

- Thixotropic suspensions
  - Extent of shaking affects viscosity

What does this mean for Bioequivalence (Reference = Generic)?
Nasal Delivery Platforms

- Multi-dose Metered Spray
- Unit Dose Spray
- Bi-Dose Spray
- Pressurized Aerosol
- Gels

(US Market)
Mechanical Nasal Sprays

Multi-dose

- Up to 240 doses
- Mechanical metering by volume
- 50 to 100 ul per actuation
- Glass or plastic containers
- Require priming / Assembly
- Solutions or suspensions
- Preservative free formulations popular for OTC applications and some countries

Multidose Pumps & Actuators

Actuator:
- Direct the spray into the nasal cavity
- Spray/atomize the liquid
- Essential to ensure the Droplet size Distribution (DSD) & Spray Pattern (SP)

Pump function:
- Meter the dose to be delivered in the nasal cavity of the patient
- Seal the container
Mechanical Nasal Sprays

Unit Dose

- Single spray (on market, examples Imitrex or FluMist)
- Bi-dose (two doses)
- Mechanical metering by volume
- No priming or repriming
- Not for suspensions

Unit Dose Systems for A) Powders & B) Aqueous Sprays
Pressurized Nasal Sprays

- Utilize HFA-134a propellants
- Use in patients with runny nose
- Slower clearance
- Deposition primarily in anterior regions of nose (front of nose)

Nasal Powders-In Development

Applications

- Capable of delivering large doses
- Good for drugs with limited solubility or aqueous instability
- Platform for vaccines

Example

- Sumatriptan powder
  - Phase III clinical trials
- Locemia

Opt-Powder Device by Optinose