Formulation Considerations for Inhaled Products
Formulation Considerations of Inhaled Products

Inhalation Therapy

Nebulizers and Formulations

Dry Powder Inhalers and Formulations

Metered Dose Inhalers (MDI) and Formulations

Conclusions
Inhalation Therapy

- **Inhalation Therapy Refers to Direct Delivery of the Medications to/via the Lungs by Inhalation**
  - Regional Therapeutic Effect
    - Respiratory Disease
      - Asthma and Chronic obstructive pulmonary disease (COPD)
    - Pulmonary Hypertension
  - Systemic Therapeutic Effect
    - Migraine
      - Ergotamine Tartrate
    - Parkinson’s Disease
      - Apomorphine Hydrochloride
    - Diabete Mellitus
      - Inhaled Insulin

- **Advantages of Inhalation Therapy**
  - Delivery of the Medications Directly to the Action Site
  - Rapid Onset
  - Enhanced Bioavailability by Avoiding First Pass Effect
Challenges in Inhalation Drug Delivery

Dealing with small particles

- Less than 5 µm, majority 2-3 µm in order to reach bronchial regions
Impact of Small Particles on Inhalation Formulations

Formulation Challenges

- Formulation uniformity, e.g. dry powder inhaler, suspension MDI and nebulizer formulations
- Cohesive forces
  - Re-dispersion and aerosolization of drug particles
  - Powder flow
- Physical stability and impact on product performance, e.g.
  - Aggregation
  - Bridging
  - Östwald ripening
- Batch-batch variability (drug & excipients)
  - Size
  - Shape
  - Morphology
  - Amorphous content
  - Etc
Impact of Formulations on Inhaler Performance

Consistent Delivered Dose Through Inhaler Life

Consistent Aerodynamic Particle Size Distribution (Fine Particle Dose / Fraction)

Chemical and Performance Stability
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Conclusions
Nebulizers

**Jet Nebulizers**
- Operating principle

  ![Jet Nebulizers Diagram](image)

  *Respir Care 2000;45(6):609–622*

**Ultrasonic Nebulizers**
- Operating principle

  ![Ultrasonic Nebulizers Diagram](image)

  *Expert Opin. Drug Deliv. (2010) 7(6)*
Nebulizers

Vibrating Mesh Nebulizers

- Operating principle

- Pari, Aerogen, Phillips Respironics

New Designs

- Small volume, soft mist, plug and play...
- Various licensable or proprietary design
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**Dry Powder Inhalers and Formulations**

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Conclusions
Dry Powder Inhalers (DPI) and Formulations

- Delivery of dry powder aerosol to the lungs for local or systemic treatment
- Dry Powder Inhaler = Dry powder formulation + Inhaler device

**Product**

- Size reduced API (< 5µm)
- Pre-formulated API size reduced by micronization, spray dry or other technology
- Loose agglomerates of pure API/API diluent
- API/Carrier (Lactose monohydrate) blend

**Process**

- Blending/blender
  - Low shear: Turbula® shake mixer, Pharmatech® blender
  - “High shear” (high impact): Pharmx®, KG5, Glatt®, Hosokawa® GEA Niro Pharma (PMA), DIOSNA

**Active and passive devices**

- Factory metered and device metered device

Quantos is a trademark of Mettler-Toledo AG Corp., Turbula is a registered trademark of Willy A. Bachofen AG Corp., Pharmx is a registered trademark of Spraying Systems Co., Glatt is a registered trademark of Glatt GmbH, Hosokawa is a registered trademark of Hosokawa Micron Corp., Xcelodose is a registered trademark of Capsugel Belgium BVBA Corp, Omnidose is a trademark of Harro Hoefliger
Dry Powder Inhaler Formulations

Three Types of Formulation

1. **Pre-formulated Small Particles**
   - Present in the DPI Device
   - Aerosolized into individual particles when delivered from the device

2. **Loose Agglomerates of Drug and excipient Particles**

3. **Drug Particles Carrier (Lactose) Blend**
   - Present in the DPI Device
   - Aerosolized into individual particles when delivered from the device
Key Formulation Considerations

Interactive blend formulations
- Drug particles evenly attached to the lactose surface.
- Improved drug content uniformity
- Improved Dose Uniformity

Balanced drug carrier interactions
- “Strong” binding to improve physical stability; No segregation during device filling and subsequent storage
- “Weak” binding to improve aerosolization performance when delivered from the device

Free flowing powders
- Easy for device filling
- Accurately metered
- Improved dose uniformity
Particle-Particle Interaction and Force Balance

Static and dynamic properties of the dry powder formulation can be manipulated by controlling particle-particle interaction through selection of proper formulation and process conditions.

**Weak interactions**
- Poor flow ability – poor delivered dose consistency
- Enhanced aerosolization performance
- Fine lactose; Low shear force blending process; smoother particle surface

**Strong interactions**
- More condensed powder, better flow ability – better delivered dose consistency
- Compromised aerosolization performance
- Large carrier lactose; High shear force blending process; less smooth particle surface

Good formulation means Sophisticate balance in particle-particle interaction.
Summary on the DPI Formulation Development

Selecting and controlling input drug particles, carrier and excipients are important factors in successful DPI formulation development.

DPI formulation and process conditions are equally important in achieving a good drug content uniformity and aerosolization performance.

Device matters, and must be considered iteratively during formulation screening and optimization.

Emerging particle engineering technology provides a new way of streamlining process and improving DPI formulation performance.

**SUCCESS IN THE FORMULATION RELIES ON ALL ABOVE FACTORS**
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Conclusions
Metered Dose Inhalers (MDI)

Formulation
- Drug
- HFA Propellant
- Surfactant
- Co-solvent &/or excipient

Container closure system
- Can
- Metering valve

Actuator

Dose compliance device
MDI Formulations – Suspension and Solution

**Suspension Formulation**
- Micronized drug particles suspended in the liquefied propellant (HFA134a or 227)
- May contain surfactant and co-solvent to aid suspension.
  - Irregular particles
  - Polydispersed (0.5-10µm)
  - Amorphous/crystalline
- Chemically stable
- Physical stability
  - Sedimentation/creaming
  - Drug deposition
    - Coated packaging materials
  - Particle growth
    - Östwald ripening*
    - Aggregation

**Solution Formulation**
- Drug dissolved in the liquefied propellant
- May contain surfactant and co-solvent to dissolve the drug.
  - Solubility
- Excellent dose reproducibility
- ‘Fine’ spray/high throat deposition
- Limited to high potency (ie. low dose products) or highly soluble drugs
- Prone to chemical degradation

*http://pssnicomp.com/definitions/ostwald-ripening/
Key Formulation Considerations

- Consistent product performance on stability and through the labeled number of doses
- Uniform formulation upon shaking to ensure metering and delivery of accurate and consistent doses
- Drug suspension stabilized by forming loose agglomerates and readily re-dispersed upon shaking after storage
- No particle growth due to aggregation or crystal growth to ensure aerosolization performance (Fine Particle Dose/Fine Particle Fraction)
- No drug loss due to deposition on can to ensure consistent doses through inhaler life
- Protection from moisture ingestion to ensure long term stability
Excipients and Additives

- **Co-solvents can be used as formulation aids in HFA systems**
- **Purpose**
  - Solubility enhancement in HFA
    - Drug, e.g.
      - Qvar® (HFA-134a/EtOH)
    - Surfactants, e.g.
      - Proventil® (HFA-134a/EtOH/Oleic Acid)
      - Symbicort® (HFA-227/PEG/PVP)
    - Excipients, e.g.
      - Atrovent® (HFA-134a/EtOH/Water/Citric Acid)
  - Wetting
    - Improved suspension behaviour, e.g.
      - ProAir® (HFA-134a/EtOH)
    - Reduced drug deposition onto the container closure system
  - Valve function & reduced friction
- **Ethanol and PEG 1000 are reported as co-solvents in marketed products**
Container

Considerations

- Chemical compatibility
- Physical compatibility, e.g. drug deposition onto the can wall

Material selection or coating helps resolve both issues

- Aluminum
  - Bare aluminum
  - Anodized aluminum
  - Coated aluminum
    - Polymer coating
      - Heat Cured, e.g. fluoropolymers – PTFE, FEP, PFA, etc
    - Plasma
      - Gaseous monomer, e.g. fluoro, carbon, etc

- Stainless steel
- Glass
Metering Valves

Valve function
- Sealing mechanism to retain volatile formulation
- Barrier to moisture ingress
- Accurate and reproducible metering, i.e. delivered dose

Type of valves
- Retention valves
- Primeless valves, i.e. Fast fill/fast drain

Metering volume
- Typically 25 µl, 50 µl, 63 µl, 100 µl

Materials of construction
- Elastomeric seals, e.g.
  - EPDM (Ethylene propylene diene monomer); Nitrile; Bromobutyl; Chlorobutyl
- Plastic/metallic body & chamber

Considerations
- Drug/surface interaction
- Extractables and leacheables
- Valve friction
  - Metering function
  - Selection of materials
  - Surfactant/lubricant
- etc
### Actuator

**Purpose**
- Mechanism to fire the inhaler
- Mouthpiece/patient interface
- Control aerosol spray behavior, e.g.
  - Spray pattern
  - Plume geometry

**Materials of construction**
- Typically polypropylene

**Actuator geometry**
- Expansion chamber
- Spray orifice, e.g. 0.1 – 0.5 mm

**Requirement for all new MDI products to have a dose compliance device**
- Dose counter
- Dose indicator
Summary for MDI Formulation Development

All formulation components, ie. API, surfactant, co-solvent, propellant, as well as device components ie. can and valve affect formulation performance and stability.

Judicious choice of surfactants or co-solvents can stabilize suspensions, improve solubility, and minimizes drug deposition on the components.

Selecting an appropriate can or can coating minimizes drug deposition on the can and drug-can interaction.

Selecting an appropriate valve gasket minimize moisture ingestion and drug-valve interaction.

Nozzle orifice size is critical for the aerosol spray pattern and plume geometry.

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Concluding Comments

- Inhalation drug delivery deals with delivery of small drug particles into the lung
- Formulation and process design must focus on ensuring an even and controllable distribution of drug particles for the labeled number of doses throughout shelf-life
- A successful formulation relies on a combination of factors including the formulation composition, container closure system, and delivery device
- Research efforts continue to focus on improvements through formulation science, process science, delivery device technology...
more products. better treatments. reliably supplied.™

Catalent Pharma Solutions
14 Schoolhouse Road, Somerset NJ 08873 USA

(866) 720 3148  info@catalent.com  www.catalent.com