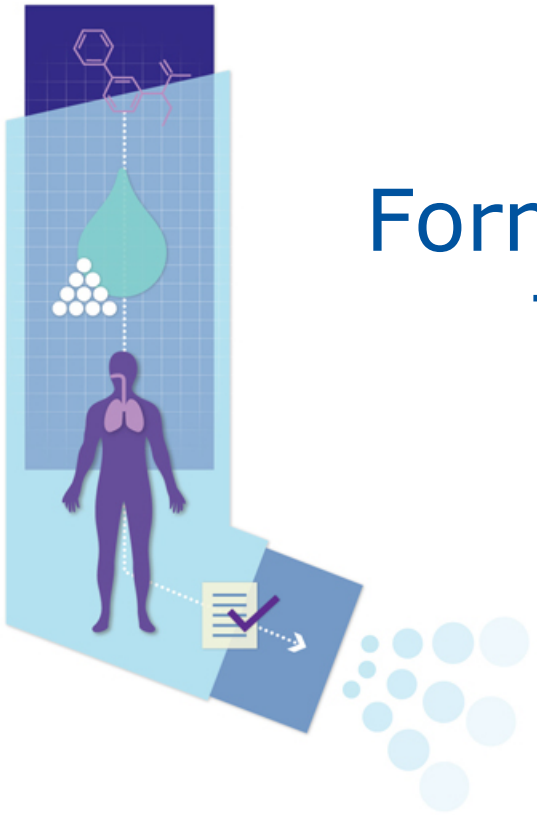

Formulation Considerations for Inhaled Products

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Formulation Considerations of Inhaled Products

Inhalation Therapy

Nebulizers and Formulations

Dry Powder Inhalers and Formulations

Metered Dose Inhalers (MDI) and Formulations

Conclusions

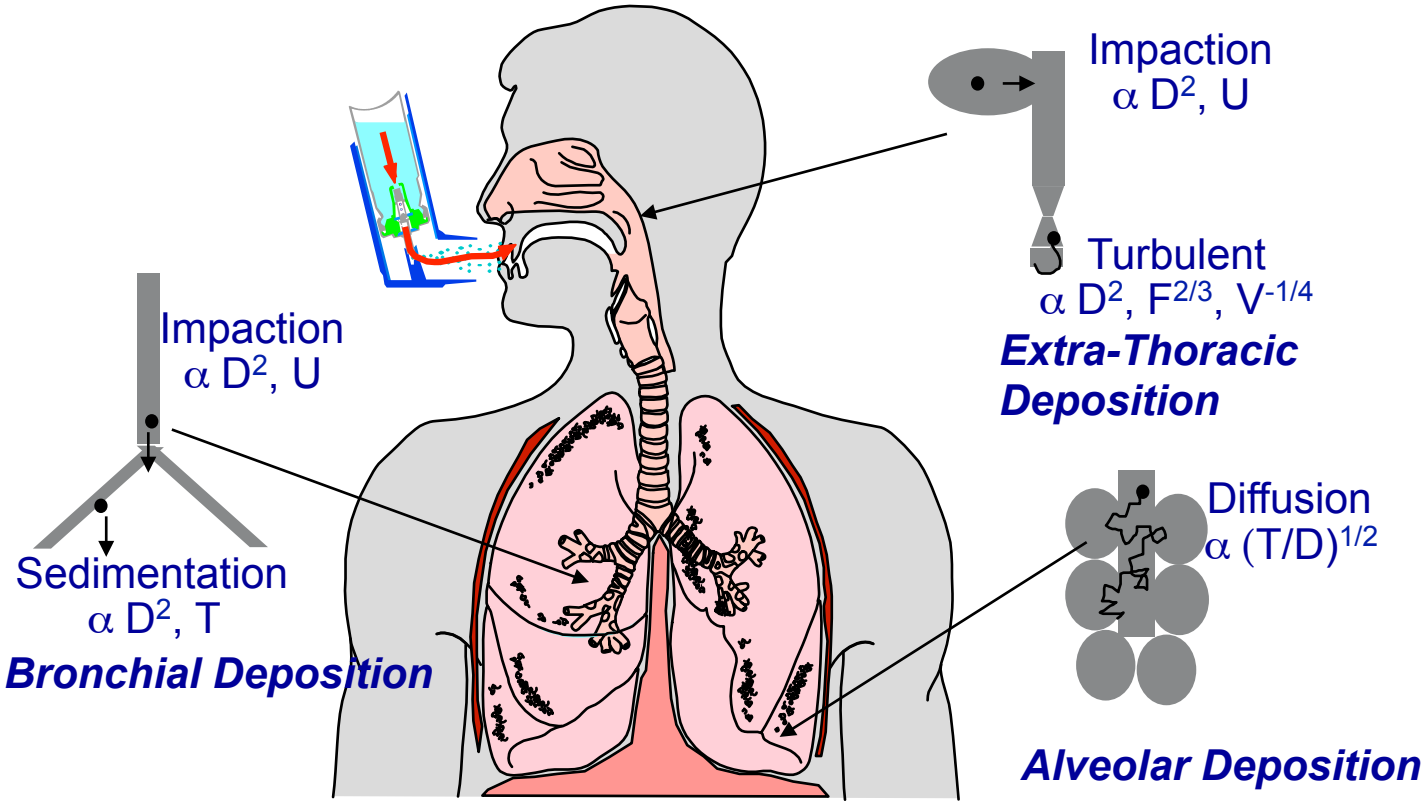
Inhalation Therapy

- **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

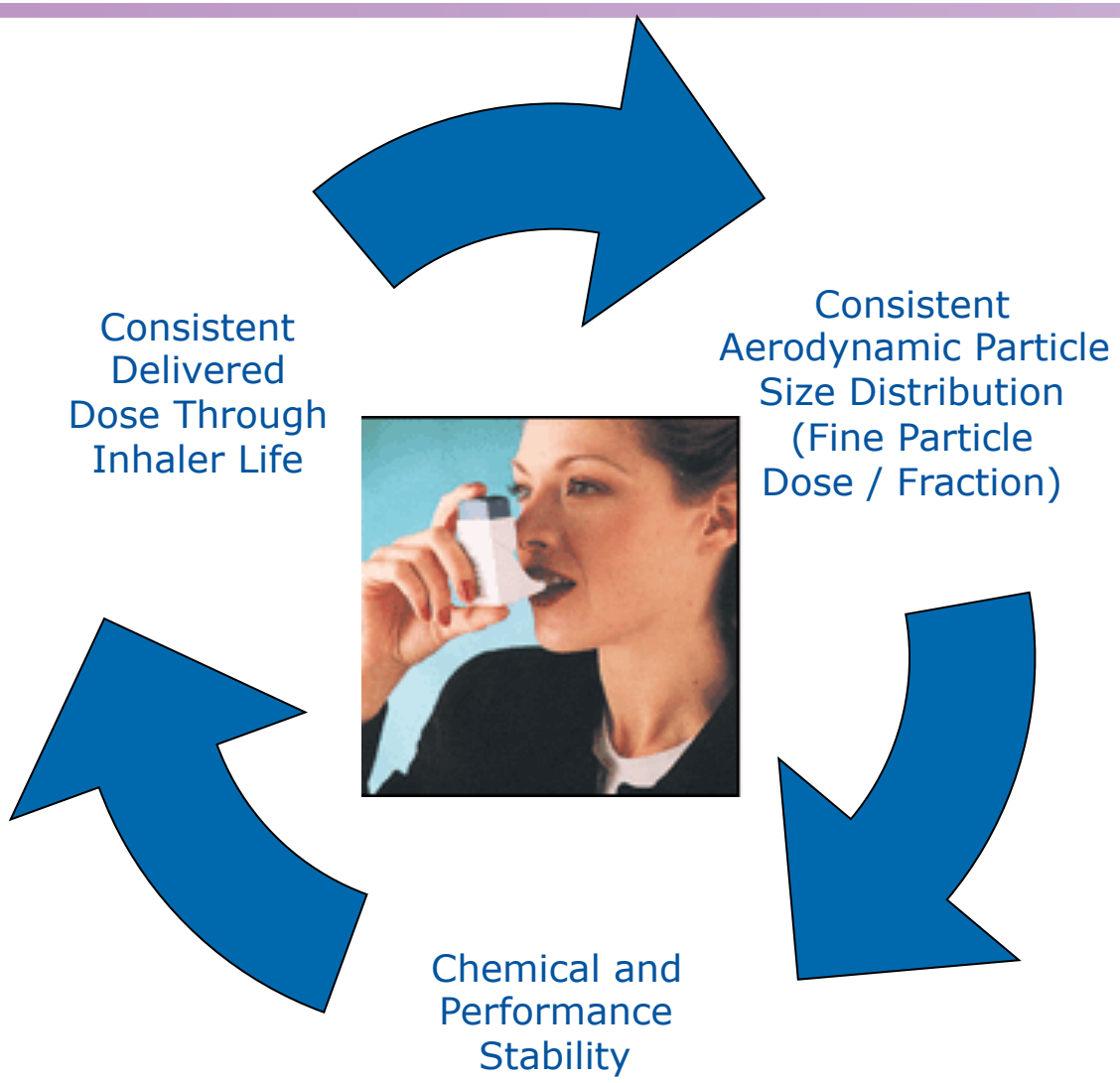


Impact of Small Particles on Inhalation Formulations

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



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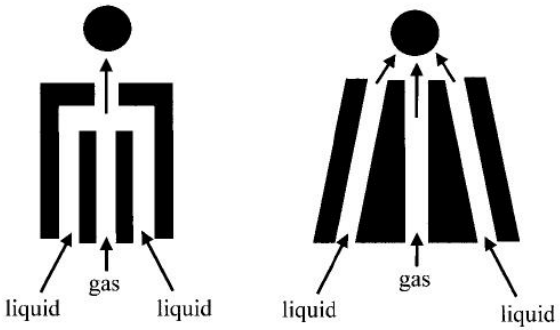
Nebulizers

Jet Nebulizers

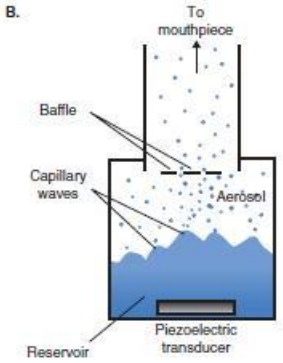
- **Operating principle**



Respir Care 2000;45(6):609–622

Ultrasonic Nebulizers

- **Operating principle**

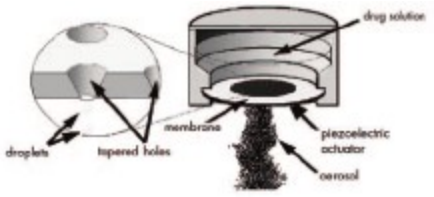


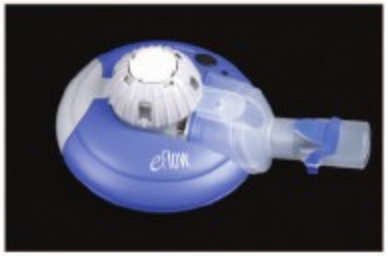
Expert Opin. Drug Deliv. (2010) 7(6)

Nebulizers

Vibrating Mesh Nebulizers

- **Operating principle**





- **Pari, Aerogen, Phillips Respironics**

New Designs

- **Small volume, soft mist, plug and play…**
- **Various licensable or proprietary design**

Formulation Considerations of Inhaled Products

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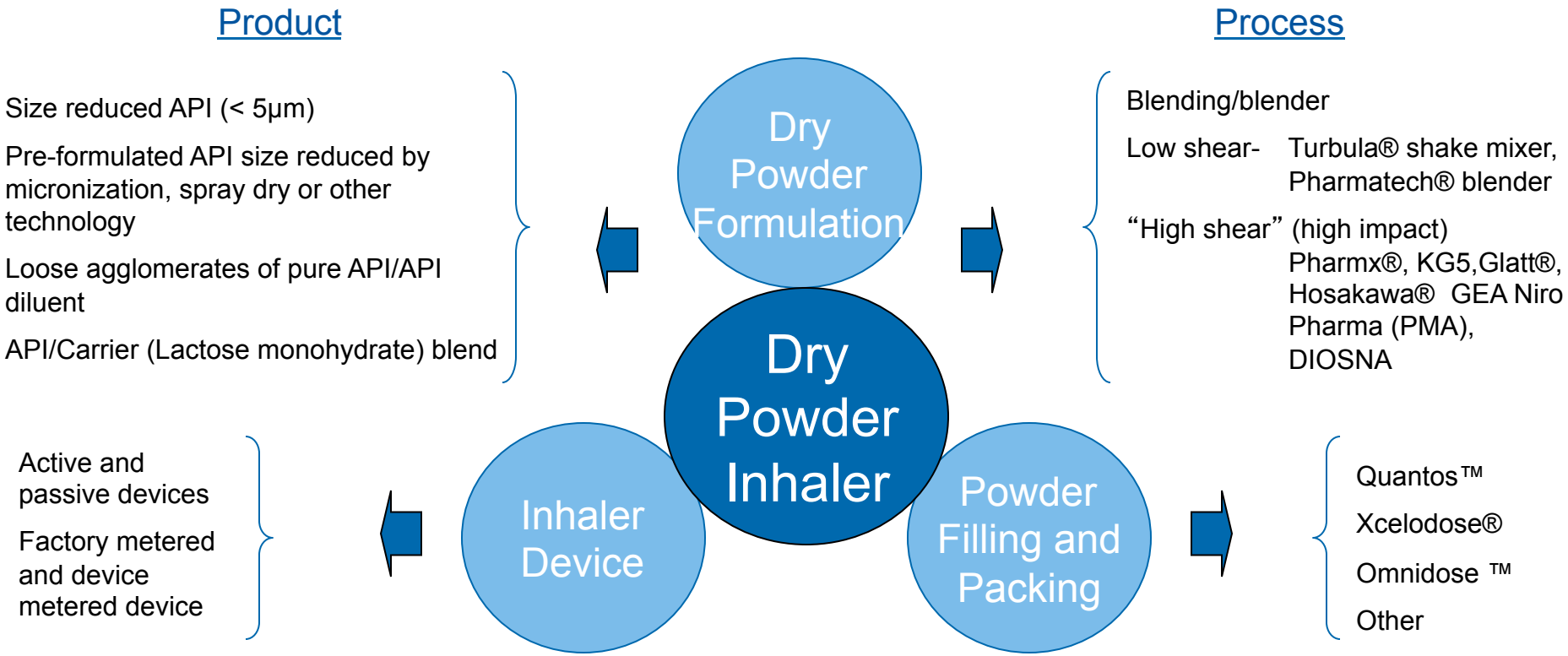
Dry Powder Inhalers (DPI) and Formulations

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



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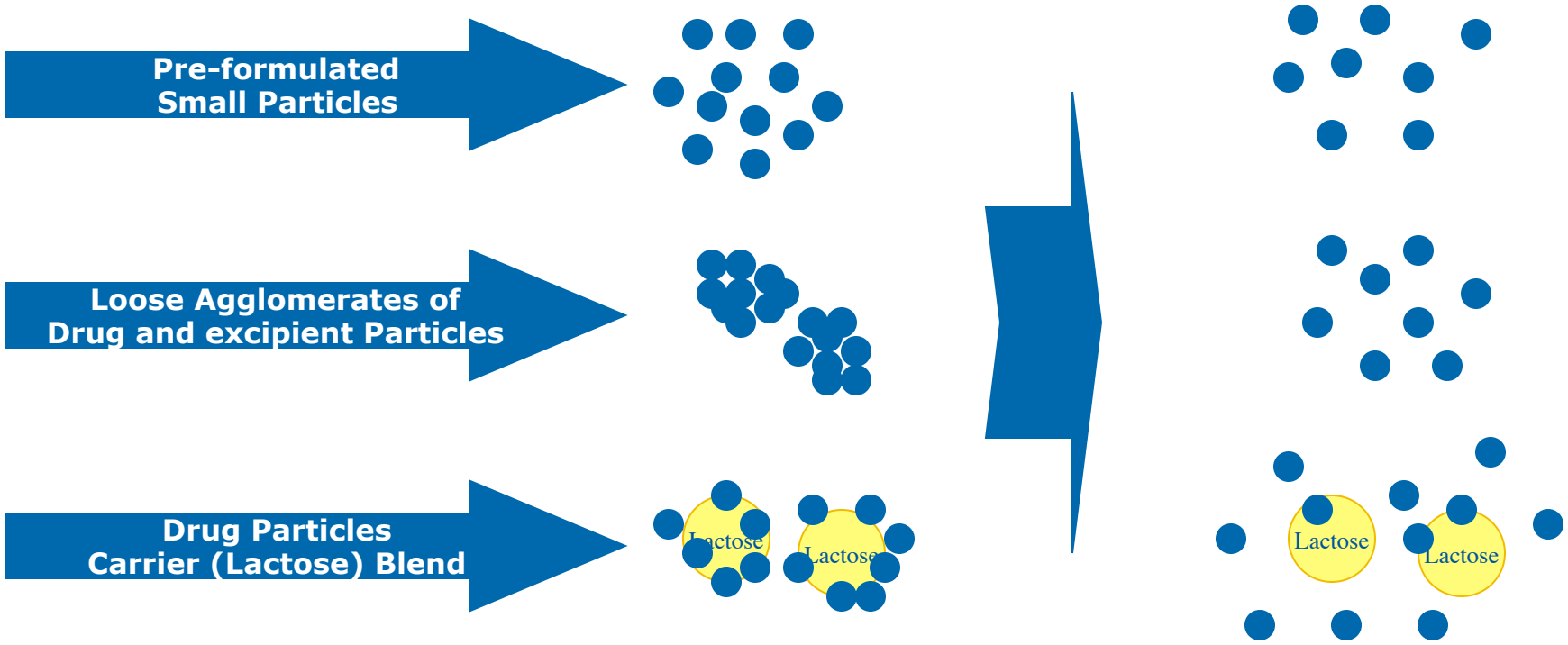
Dry Powder Inhaler Formulations

Three Types of Formulation



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

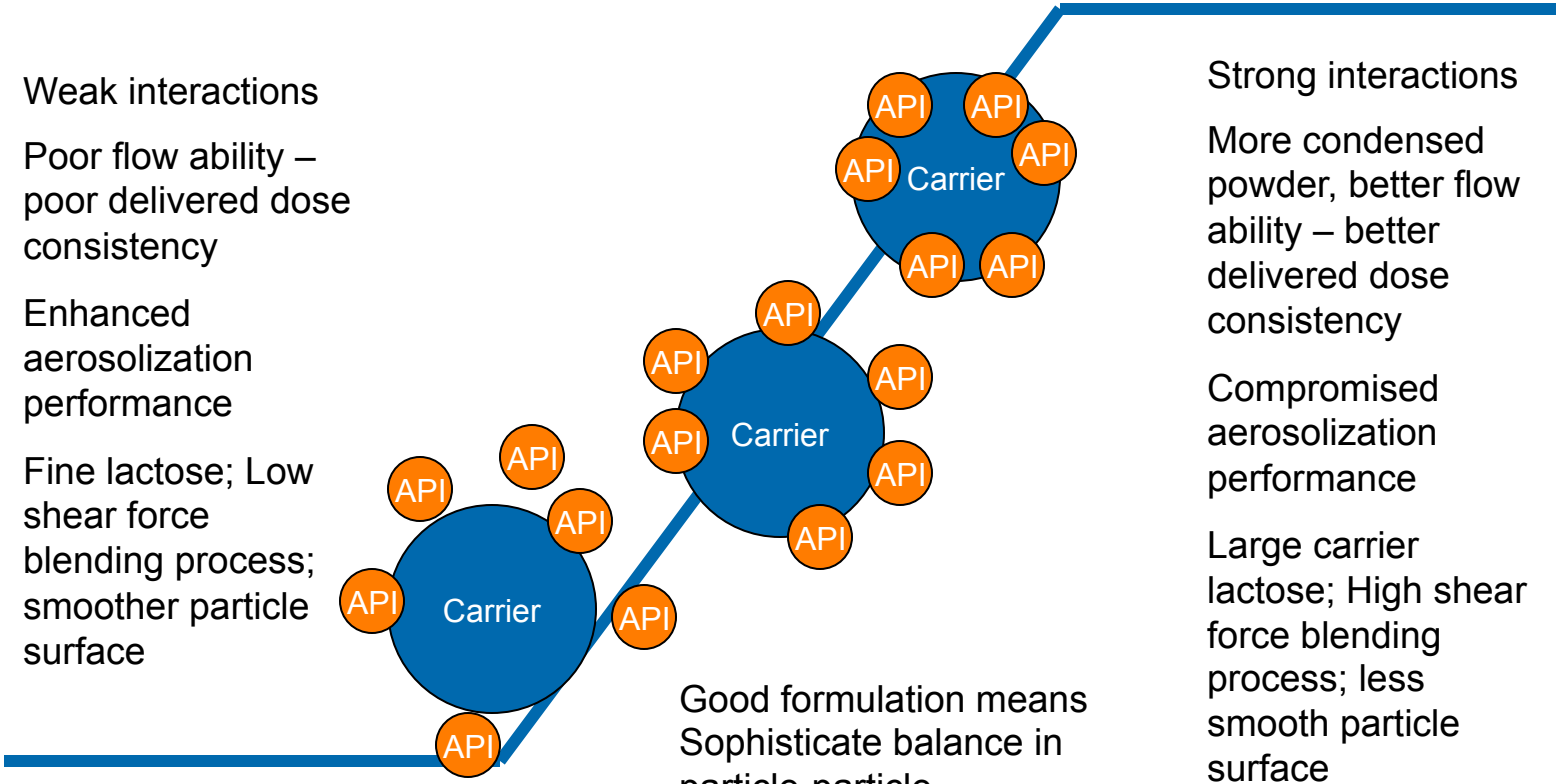
- Easy for device filling

- 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



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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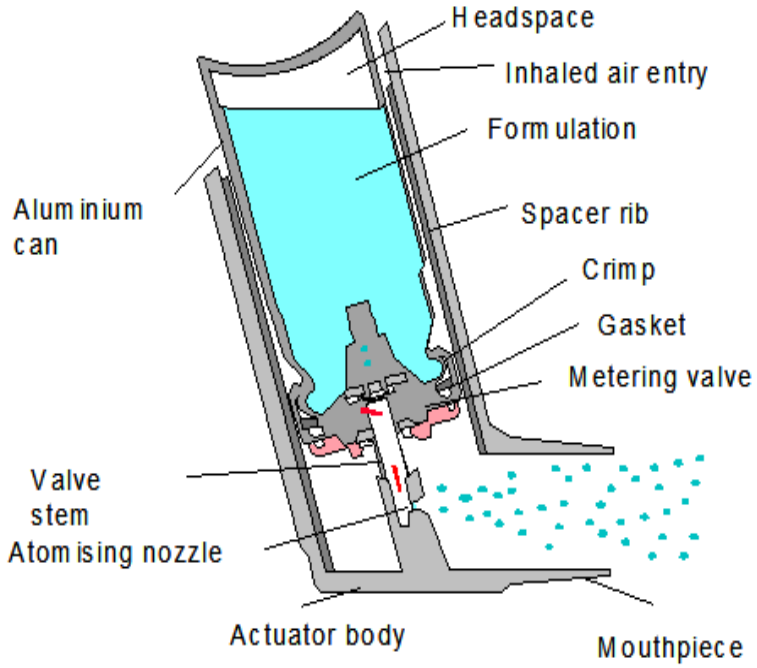
Metered Dose Inhalers (MDI)



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 ingression 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

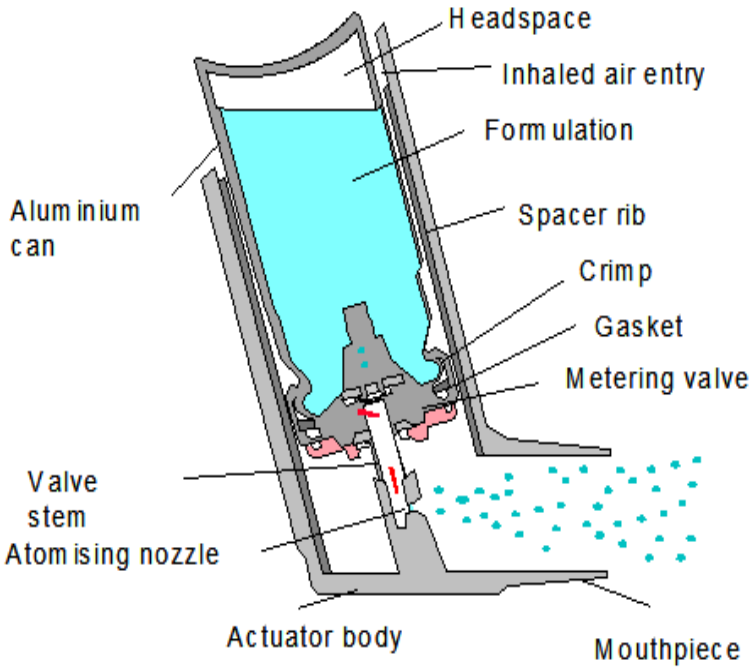
- Typically polypropylene

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 ingression 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…

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