THE PRESSURIZED METERED DOSE INHALER

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DEVELOPMENT OF THE pMDI

- First half of twentieth century: Squeeze-bulb nebulizer
  - Fragile, inconvenient, inconsistent dose
- April 1955: “Susie’s question”
- March 1956: first pMDIs marketed
  - Epinephrine (Medihaler-Epi™)
  - Isoproterenol (Medihaler-Iso™)
- Benchmark inhaler device for asthma and COPD
  - 50th birthday of pMDI in 2006
  - Now 500 million sold annually

COMPONENTS OF THE pMDI

- Container
- Actuator
- Propellants
- Formulation
- Metering Valve

pMDI FORMULATIONS: SOLUTIONS VERSUS SUSPENSIONS

- To achieve a stable formulation, drugs should be either totally soluble or totally insoluble in propellants
- Early pMDIs:
  - Drug in solution, with ethanol as a co-solvent
  - Low fine particle dose
- Solution formulations have come into favour again recently
- Suspension formulations:
  - Became the standard formulation approach
  - Usually need a surfactant (oleic acid, sorbitan trioleate, lecithin)
  - Need shaking to disperse the suspension

CFC PROPELLANTS

- Chlorofluorocarbons (CFCs)
  - Non-toxic, non-flammable
  - Acceptable taste
  - Compatible with other components
  - Suitable boiling points and vapor pressures
- CFCs -11, -12 and -114 met these criteria
- CFCs are liquefied compressed gases
  - Maintain constant vapor pressure inside canister

PROPERTIES OF CFC PROPELLANTS

<table>
<thead>
<tr>
<th>Propellant</th>
<th>Structure</th>
<th>Boiling Point (degrees C)</th>
<th>Vapor Pressure (kPa at 20 degrees C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFC-11</td>
<td>CCl_3F</td>
<td>23.7</td>
<td>89</td>
</tr>
<tr>
<td>CFC-12</td>
<td>CCl_3F_2</td>
<td>-29.8</td>
<td>566</td>
</tr>
<tr>
<td>CFC-114</td>
<td>C_2Cl_3F_4</td>
<td>3.6</td>
<td>182</td>
</tr>
</tbody>
</table>

- CFCs have ozone depletion potential and greenhouse warming potential
CFC PROPELLANTS IN pMDIs

- CFC-12 is major component in pMDI
  - Low boiling point, high vapor pressure
- CFC-11 and/or CFC-114 used to modify vapor pressure and to allow laboratory handling
- Formulation prepared in CFC-11 or CFC-114
  - Cold-filling: CFC-12 added at low temperature and valve crimped in place
  - Pressure-filling: CFC-12 added via previously crimped valve
- Vapor pressure inside canister typically 300 to 500 kPa

TYPICAL pMDI: SCHEMATIC

OPERATION OF A METERING VALVE

1. At rest
2. Start of actuation
3. Dose release
4. End of actuation
5. Chamber refills

KEY
- Open
- Closed
- Propellant and drug

HOW THE SPRAY IS FORMED

- Patient presses can: opens channel between metering chamber and atmosphere
- Propellant droplets formed at actuator nozzle: “two phase gas-liquid air-blast”
- Propellants start to boil in expansion chamber
- Shearing forces produce ligaments
- Evaporation
- Cooling

CHARACTERISTICS OF CFC pMDI SPRAY

- Short duration plume
  - Typically 0.1 to 0.2 sec
- Rapidly moving
  - Velocity at actuator nozzle may be 30 m/sec
  - Reduction in velocity due to air resistance
- Forceful impaction on back of throat
- Feels cold
- Large propellant droplets containing drug
  - Initial droplet mass median diameter may be 30 µm
  - Reduction in droplet size due to evaporation

ERRORS IN pMDI TECHNIQUE

- Many patients cannot use a pMDI correctly
- Crucial error: may result in zero lung dose
- Non-crucial error: may result in low lung dose

- Poor coordination: Failure to “press and breathe”
  - One-third of patients may have this problem
  - “Cold Freon” effect
**CLINICAL SIGNIFICANCE OF POOR INHALER TECHNIQUE**

- Questionnaire assessment of almost 4000 adult asthmatics taking inhaled corticosteroids via pMDI in primary health care*
  - Asthma instability score (AIS)
  - AIS higher in patients with poor technique
  - AIS highest in poor coordinators
- Strange errors in pMDI technique sometimes reported
- Importance of patient education
- Knowledge about inhalers amongst health care professionals also needs improvement


**CFC pMDI: LOW LUNG DEPOSITION AND HIGH OROPHARYNGEAL DEPOSITION**

- Most of the dose is deposited in the oropharynx and swallowed
- Predicted by early pharmacokinetic studies
- Only 10 - 20% of dose deposited in lung, even with good technique

**CORRECT pMDI TECHNIQUE**

- Little evidence before 1980
- Then data obtained from systematic scintigraphic, pharmacokinetic and bronchodilator response studies

**PROPERTIES OF CFC AND HFA PROPELLANTS**

<table>
<thead>
<tr>
<th>Propellant</th>
<th>Structure</th>
<th>Boiling Point (degrees C)</th>
<th>Vapor Pressure (kPa at 20 degrees C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFC-11</td>
<td>CCl₃F</td>
<td>23.7</td>
<td>89</td>
</tr>
<tr>
<td>CFC-12</td>
<td>CCl₂F₂</td>
<td>-29.8</td>
<td>566</td>
</tr>
<tr>
<td>CFC-114</td>
<td>C₂Cl₂F₄</td>
<td>3.6</td>
<td>182</td>
</tr>
<tr>
<td>HFA-134a</td>
<td>C₃H₇F₄</td>
<td>-26.1</td>
<td>572</td>
</tr>
<tr>
<td>HFA-227</td>
<td>C₃HF₇</td>
<td>-15.6</td>
<td>390</td>
</tr>
</tbody>
</table>

- CFCs have ozone depletion potential and greenhouse warming potential
- HFAs have greenhouse warming potential only

**TRANSITION TO HFA PROPELLANTS**

- CFCs predicted in 1974 to destroy stratospheric ozone
- Not proved until 1980s
  - British Antarctic Survey scientists discovered ozone hole over Antarctica
- CFCs banned under Montreal Protocol of 1987 and other agreements
- CFCs in pulmonary pMDIs granted an essential-use exemption
- HFA-134a and HFA-227 identified as non ozone-depleting propellants
- IPAC collaborations for safety testing
- First HFA product (Proventil®/HFA)® introduced in 1994
- Transition process on-going

* Airomir® in Europe

**PROPELLANT TRANSITION PROCESS**

- Technical challenges:
  - HFA-134a and HFA-227 are direct replacements for CFC-12, but neither replace CFC-11 or CFC-114
  - Established surfactants insoluble in HFAs
  - Existing valve elastomers incompatible with HFAs
- Therefore propellant transition is not just a question of replacing propellants
- Clinical issues:
  - Clinical trials program needed to demonstrate safety and efficacy of reformulated products
PROPELLANT TRANSITION PROCESS

- Make HFA spray properties comparable to CFC
- Recognize need to change propellants and other components
- Same efficacy at same dose
- "Seamless transition"

HFA TRANSITION EXAMPLE: COMPARABLE PRODUCTS

<table>
<thead>
<tr>
<th>Active</th>
<th>Ventolin®CFC*</th>
<th>Ventolin®HFA*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug form</td>
<td>Suspension</td>
<td>Suspension</td>
</tr>
<tr>
<td>Excipients</td>
<td>Oleic acid</td>
<td>None</td>
</tr>
<tr>
<td>Propellants</td>
<td>CFC-11 / 12</td>
<td>HFA-134a</td>
</tr>
</tbody>
</table>

* GlaxoSmithKline
Ventolin® HFA is known as Ventolin® Evohaler® in Europe

HFA TRANSITION EXAMPLE: DISSIMILAR PRODUCTS

- Solution formulation of beclomethasone dipropionate (BDP) in HFA-134a (QVAR™, Ivax)
  - Ethanol co-solvent; no other excipients
  - Mass median diameter 1 µm, versus 4 µm for CFC pMDI
  - Lung deposition: 50 to 55% of delivered dose*
  - Compared with CFC pMDI, maintains asthma control using around half the daily dose of BDP**

Other similar products include:
- Ciclesonide (Alvesco®, Altana)

** Busse, W.W. et. al. (1999), J. Allergy Clin. Immunol., 104, 1215-1222

PRIMING THE pMDI

- Priming: firing doses to waste
- After storage for only a few hours, albuterol CFC pMDIs shown to have erratic first dose content—usually low, but occasionally high*
- Improvements in valve design in some HFA pMDIs have reduced this problem, but have not yet eliminated it
- Priming requirements may vary, and any manufacturers' instructions should be followed


PLUME CHARACTERISTICS OF SELECTED pMDI SPRAYS

From Gabrio, B.J. et. al., (1999), Int. J. Pharm., 186, 3-12

<table>
<thead>
<tr>
<th>Maximum Impact Force</th>
<th>Minimum Plume Temperature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flixotide HFA</td>
<td>Fluticasone HFA</td>
</tr>
<tr>
<td>Primolut HFA</td>
<td>Prierarin HFA</td>
</tr>
<tr>
<td>QVAR HFA</td>
<td>Mucosol CFC</td>
</tr>
<tr>
<td>Maxair CFC</td>
<td>Ventolin CFC</td>
</tr>
<tr>
<td>Flixotide CFC</td>
<td>Primolut CFC</td>
</tr>
<tr>
<td>Beclotide CFC</td>
<td>Fluticasone CFC</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Force (mN)</th>
<th>Temperature (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-60</td>
</tr>
<tr>
<td>50</td>
<td>-40</td>
</tr>
<tr>
<td>100</td>
<td>-20</td>
</tr>
<tr>
<td>150</td>
<td>0</td>
</tr>
</tbody>
</table>

SPRAY VELOCITY AND PLUME DURATION OF SELECTED pMDIs


Spray Velocity

<table>
<thead>
<tr>
<th>Velocity (m/sec)</th>
<th>Flixotide HFA</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>0.4</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Plume Duration

<table>
<thead>
<tr>
<th>Duration (sec)</th>
<th>Flixotide HFA</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>0.2</td>
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</tr>
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<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>0.4</td>
<td>0.4</td>
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</table>
DOSE TAIL-OFF AT END OF CANISTER LIFE FOR A CFC pMDI AND AN HFA pMDI
Expressed as % of mean shot weights

EFFECT OF AMBIENT TEMPERATURE ON FINE PARTICLE MASS FROM A CFC pMDI AND AN HFA pMDI
Expressed as % of values at 20 degrees C

DESIGNING pMDIs
- Spray characteristics of pMDI depend mainly on formulation and actuator nozzle design
- Fine particle fraction (FPF) of solution formulation containing ethanol and HFA-134a predicted by:
  \[
  \text{FPF}(\%) = 2.1 \times 10^{-5} \times A^{-1.5} \times V^{-0.25} \times C^3
  \]
  \[
  A = \text{Actuator nozzle diameter (mm)}
  \]
  \[
  V = \text{Metered volume (µL)}
  \]
  \[
  C = \text{HFA-134a content (%)}
  \]
- Example
<table>
<thead>
<tr>
<th>Product</th>
<th>A</th>
<th>V</th>
<th>C</th>
<th>FPF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product 1</td>
<td>0.4</td>
<td>50</td>
<td>90</td>
<td>23</td>
</tr>
<tr>
<td>Product 2</td>
<td>0.25</td>
<td>50</td>
<td>98</td>
<td>60</td>
</tr>
</tbody>
</table>
- Data are scientific basis of Modulite® formulations (Chiesi)
  * Lewis, D.A. et. al. (2004), Respiratory Drug Delivery IX, 109-115

HOW MANY DOSES LEFT IN YOUR pMDI?
- It is not usually possible to see the contents of the pMDI
- FLOAT IT IN WATER
- ADD A DOSE COUNTER

ADVANTAGES OF pMDI (1)
- Useful practical features:
  - Compact
  - Portable
  - Convenient
  - Unobtrusive
- Advantages over nebulizer:
  - Multi-dose
  - Short treatment time versus several minutes by nebulizer
  - Easier to prepare

ADVANTAGES OF pMDI (2)
- Advantages over DPIs:
  - Superior moisture protection
  - High internal pressure prevents ingress of pathogens
  - Better dose content uniformity than many DPIs
  - Aerosol formation independent of inhalation effort
  - Probably same handling and inhalation technique can be used for all pMDIs
  - Generally cheaper to manufacture in bulk
  - Average regulatory review time shorter
DISADVANTAGES OF pMDI

- Contains propellants
- Press-and-breathe device (not breath-actuated)
- Many patients cannot use correctly:
  - Variable lung dose
  - May give low lung dose even with correct technique
  - Technical issues limit amount of drug per dose
  - Valve-clogging in suspension pMDIs
  - Drug solubility issues in solution pMDIs (current limit on fine particle dose approximately 1.5 mg)
- Sometimes viewed as mid twentieth-century technology

ADDITIONAL pMDI TECHNOLOGY

- Main limitation of “press-and-breathe” pMDI: variable lung dose associated with poor inhaler technique
  - Tolerated for asthma and COPD drugs
  - But some patients get zero lung dose
- Alternatives to “press-and-breathe” pMDI
  - Breath-actuated devices - predicted to be used more widely
  - Reduced-velocity spray devices
  - Spacers and holding chambers - already established

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AUTOHALER® BREATH-ACTUATED DEVICE

(Image provided by courtesy of 3M Pharmaceuticals)

Triggering Mechanism

pMDIs: FUTURE DEVELOPMENTS

- Competition from dry powder inhalers
- Combination inhalers (bronchodilator plus corticosteroid) likely to become even more common
- Potential to widen use beyond asthma and COPD drugs
  - Development of pMDIs containing fewer than standard 100+ doses
- Potential to increase upper limit on fine particle dose
- HFAs are greenhouse gases: will another round of reformulation be necessary?

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pMDIs: ANOTHER 50 YEARS?

- Viewed in 1990s as difficult to use correctly, inefficient, environmentally unfriendly and outdated
- But has proved popular, durable, adaptable and inexpensive
- Limitations of pMDI have been addressed via formulation and hardware improvements, and continue to be addressed
- Survival of pMDI to its 100th birthday is a distinct possibility

Articulate Quizmaker Quiz Placeholder - Metered Dose Inhalers