Quality Control Tests of Aerosols

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CONTENTS

- Anatomy of lung
- Definition
- Advantages of Aerosols
- Components of Aerosols
- Aerosol generating devices
- Quality control tests
- Conclusion
- References
Anatomy of Lung

- Upper respiratory tract
- Lower respiratory tract
Definition

Pharmaceutical aerosols are defined as products containing therapeutically active ingredients dissolved, suspended, or emulsified in a propellant or a mixture of solvent and propellant, intended for:

- topical administration
- for administration into the body cavities
- intended for administration orally or nasally as fine solid particles or liquid mists via the respiratory system
Advantages of Aerosols

- Quick absorption into the blood stream
- A dose can be removed without contamination of the remaining material
- The medication can be delivered directly to the effected area in a desired form, such as spray, stream, quick-breaking foam, or stable foam.
- Irritation produced by the mechanical application of topical medication is reduced or eliminated.
- Exact dose can be delivered.
Uses of Pharmaceutical Aerosols
Topical

- Local anesthetics (e.g. Benzocaine)
- Spray on bandages
- Proprietary burn applications
- Antibacterials (e.g. Neomycin)
- Antifungal sprays (Miconazole)
- Anti-inflammatory steroids (e.g. Dexamethasone)
Uses of Pharmaceutical Aerosols

- Respiratory Bronchodilators (e.g. Albuterol)

- Anti-inflammatory steroids (e.g. Beclomethasone)

- Antiallergics (e.g. Cromolyn sodium)

- Antivirals (e.g. Ribavirin)

- Smoking cessation (e.g. Nicotine)

- Migraine (e.g. Ergotamine tartrate)
Uses of Pharmaceutical Aerosols

Nasal:

- Decongestants (e.g. Phenylephrine)
- Anti-inflammatory steroids (e.g. Beclomethasone)

- Antiallergics (e.g. Cromolyn sodium)
- Moisturizers (e.g. Normal saline)

- Systemic access
  - Antidiuretics (e.g. Desmopressin)
  - Antismoking (Nicotine)

- Ocular
- Contact lens cleaning solutions
Components of an Aerosol

- Propellant
- Container
- Valve and actuator
- Product concentrate
Propellants

- Liquefied gases
- Chlorofluorocarbons (CFC)
- Hydrochlorofluorocarbons (HCFC)
- Hydrocarbons (HC)
- Hydrocarbon ethers
- Compressed gases
CHLOROFLUOROCARBONS
(Used only in inhalation aerosols)

Ex: Propellant 11 (trichloromonofluoromethane)
Propellant 114 (dichlorotetrafluoroethane)

**Advantages**
- Low inhalation toxicity
- High chemical stability
- High purity

**Disadvantages**
- Destructive to atmospheric Ozone
- Contribute to “greenhouse effect”
- High cost
HYDROCARBON Propellants (most common)

Ex: Propane, Isobutane, n-butane.

- **Advantages**
  - Inexpensive
  - Minimal ozone depletion
  - Negligible "greenhouse effect"
  - Excellent solvents

- **Disadvantages**
  - Flammable
  - Aftertaste
  - Unknown toxicity following inhalation
  - Low liquid density
CONTAINERS

- Metal
  1. Tinplated steel
  2. Aluminium

- Glass
  1. Uncoated glass
  2. Plastic coated glass
Figure 50-15. 20-mm metered-dose valve showing the subcomponent parts and metering chamber. It is used in the upright position (courtesy, Bespak).

Figure 50-14. Metering valve—inverted (courtesy, Valois).
VALVES

Continuous (used for most topical aerosols)

- Product is released as long as pressure is maintained on the actuator.

Metered (Used for all inhalation, & some topical aerosols)

- A finite Volume of product is released when the actuator is pressed. No more product is released unless the actuator is returned to its rest position and repressed

  - 25 - 150μl for inhalation aerosols
  - up to 5 ml for topical aerosols
Drug (Active)

- Drug may be **dissolved** in the propellant system

- Smaller spray particle size can be achieved after complete propellant evaporation
- Simplified manufacturing process
- Drug must be soluble
Drug may be **Suspended** in the propellant system

- Can be used to deliver insoluble drugs
- Higher doses can be delivered
- Constant agitation during manufacturing and use is required
- Physical instability may be a problem
Aerosol generating devices

- Metered dose inhalers
- Dry powder inhalers
- Nebulizers
In MDIs, drug is either dissolved or suspended in a liquid propellant mixture together with the other excipients, including surfactants, and presented in a pressurized canister fitted with a metering valve.

A predetermined dose is released as a spray on actuation of the metering valve.

When released from the canister the formulation undergoes volume expansion in the passage within the valve and forms a mixture of gas and liquid before discharge from the orifice.

The high speed gas flow helps to break up the liquid into a fine spray of droplets.
DRY POWDER INHALERS

- DPI systems are the systems in which the drug is inhaled as a cloud of fine particles.

- The drug is either preloaded in an inhalation device or filled into hard gelatin capsules.

Figure 1. spinhaler.
Nebulizers deliver relatively large volumes of drug solutions and suspensions.
Quality Control Tests for Pharmaceutical AEROSOLS

A. Flammability and combustibility
   1. Flame extension
   2. Flash point test.

B. Physicochemical characteristics
   1. Vapor pressure
   2. Density
   3. Moisture content
   4. Identification of propellants

C. Performance
   1. Aerosol valve discharge rate
   2. Spray pattern
   3. Net contents
   4. Uniformity of delivered dose
   5. Particle size determination
   6. Leakage

D. Stability testing
Flame Projection Test

- Flame Extension
- 20cm ------- combustible
- 45cm ------- flammable

- **Flash point test:**
- **Tag open cup apparatus:**
  - Aerosol is chilled to -25°F.
  - Temperature at which the vapor ignites is the **Flash point.**
MOISTURE CONTENT

- Karl Fisher Method:
  - Iodine produced at anode reacts with the water present in the sample. When all has been consumed, excess of iodine is detected electrometrically and that is the indication of end point.
  
- For propellants 10ppm
Spray Pattern

- By TLC
Net Contents

a) Weigh the ten full containers.
b) Empty each container through the valve.
c) Open each container with tube cutters employing any safe technique -- e.g. chill to reduce the internal pressure.
d) Wash and thoroughly dry each container, valve and all associated parts.
e) Weigh the containers, valves and all associated parts.
f) Subtract the weight of the ten empty containers, valves and associated parts.
g) Express the difference in the units of declared on the label.
Mechanisms of particle deposition

- Inertial impaction
- Sedimentation
- Diffusion
- Interception
- Electrostatic precipitation
Particle size determination

- Microscopy
- Cascade Impactor
- Glass Impinger
- Time of flight
- Laser Diffraction
- Phase doppler analysis
- Optical particle counter
Particle size determination by Microscopy

- Membrane filtration apparatus is used.
- It is fitted with an input chamber which is designed to prevent the loss of material when the actuator mouth piece of aerosol is inserted and valve is actuated.
- The pore size of membrane filter is 5 micro meter.
- 50 deliveries are discharged into the input chamber at an interval of 5 secs per each actuation.
- The membrane filter is dried and examined microscopically under a magnification of 40X.
Particle size determination by Microscopy

- Acceptance criteria
- The number of particles larger than 20μm does not exceed 50 & no particle exceeds 100μm in length.
CASCADe IMPACTOR

- **Principle**: The cascade impactor is based on the principle of carrying the particles in the stream of air through a series of consecutive smaller jet impactors.

- The heavier and larger particles get impacted on the slide having the larger opening and as the openings get smaller, the velocity of the air increases and the next larger particles get deposited on the next slide.
CASCADe IMPACtor

- Aerosol deposition on stages 0, 1, and 2 of the cascade impactor corresponds to particles of 5.1-10 μm.

- Aerosol that deposited on stages 3, 4, and 5 of the cascade impactor corresponds to particles of 1-5 μm, a range considered ideal for deposition and retention within the small human airways (bronchi and bronchioles).

- Aerosol collected on stages 6, 7, and in the final filter of the cascade impactor corresponds to particles smaller than 1 μm, a range considered too small for therapeutic use in asthma and one that favors deposition into the respiratory bronchioles and alveoli.
Advantages and Limitations of cascade impactor

**Advantages**
- Wide spread acceptance and use
- Qualitative and quantitative drug analysis with chemical detection methods

**Limitations**
- It lacks precision
- Slow & tedious
- Precautions are required to ensure that particles are collected efficiently
Twin Stage Impinger

- Tests the lung penetration capability of a pressurized metered dose inhaler (pMDI)
Glass impinger apparatus

- A Mouthpiece adaptor
- B Throat
- C Neck
- D Upper impingement chamber
- E Coupling tube
- F Screw thread, side-arm adaptor
- G Lower jet assembly
- H Lower impingement chamber
Multi-stage Glass Impinger

Multi-stage glass impinger
Advantages & Disadvantages of Glass Impinger

**Advantages**
- Liquid collection media, hence no issue with particle bounce and re-entrainment
- Easy/quick to use – only 2 stages (Twin & Metal only)
- Multi-Stage gives wider range of data

**Disadvantages**
- Two stages do not give in-depth particle size distribution (Twin & Metal only)
- Multi-Stage is time consuming
Dose collection apparatus for pressurised metered dose inhaler

Fig. 1: Dose collection apparatus for pressurized metered-dose inhalers
Uniformity of delivered dose

- **Acceptance criteria**
  - Nine out of ten results must lie between 75% & 125% of the average value & all should lie between 65% & 135%.

- If 2 or 3 values lie outside the limits of 75% to 125%, the test is repeated for 2 more inhalers.

- Not more than 3 of the 30 values must lie outside the limits of 75% to 125% & no value should lie outside the limits of 65% to 135%.
Time of Flight Technique

- In TOF technique, a narrow focused beam of laser light explores an area of suspension.
- The size of the particle is measured by the time taken by the laser beam to pass across the fine particle.
- Operates effectively in range 0.3-15μm aerodynamic diameter

Aerosol flow path and TOF detection system for the models 3300 and 3310 APS® aerodynamic particle sizer spectrometer (courtesy TSI Inc.)
Advantages & Limitations of Time of Flight Technique

**Advantages**
- Size distribution pattern based on several thousand particles can be obtained in less than 20 seconds

**Limitations**
- Susceptible to overloading due to particle coincidence in the measurement zone at high aerosol concentrations, leaving particles undetected
- Does not possess ability to discriminate between active drug and excipients/surfactant, and also between actives within a combination product
Laser Diffractometry

Fig. Classical set-up for laser diffractometer-based particle sizing
Advantages and Limitations of Laser Diffractometry

**Advantages**
- Operates over a wide range between 0.5-200μm.
- Fast / highly reliable technique with automated recording

**Limitations**
- No assay for API is performed
- The phenomenon of ‘vignetting’ occurs, in which light scattered at wide angles misses the detector array, and therefore results in bias due to the absence of the finest particles in the distribution
Leak Test

- Leakage rate = \( \frac{365 \times 24}{T} \times (W_1 - W_2) \)
- Net fill weight = \( (W_1 - W_3) \)
- The requirements are met if the average leakage rate of the 12 containers is not more than 3.5 percent of the net fill weight per year & none of the containers leaks more than 5% of the net fill weight per year. If one container leaks more than 5% per year, and if none of the containers leaks more than 7% per year, leakage rate of additional 24 containers is determined.
- Not more than 2 of the 36 containers should leak more than 7% of the net fill weight per year.
# Stability Testing

<table>
<thead>
<tr>
<th>Study</th>
<th>Storage condition</th>
<th>Minimum time period covered by data at submission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long term*</td>
<td>25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH</td>
<td>12 months</td>
</tr>
<tr>
<td>Intermediate**</td>
<td>30°C ± 2°C/65% RH ± 5% RH</td>
<td>6 months</td>
</tr>
<tr>
<td>Accelerated</td>
<td>40°C ± 2°C/75% RH ± 5% RH</td>
<td>6 months</td>
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CONCLUSION

- Pharmaceutical aerosols represent a significant dosage form based on their acceptability to both patient & physician.

- Aerosols require more stringent attention & perhaps more conservative approach.
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Thanks to one & All