2022/2023

Fifth Stage

First Semester/ Industrial Pharmacy II

Pulmonary drug delivery systems

Lecture 22

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Methods and Equipment:

1) Selection of appropriate package and formulation system to be prepared depending on the type of aerosol.
2) Filling of concentrate and propellant inside the package at certain conditions (temperature and pressure).
3) Placing of valve, and sealing.
4) Testing of filled package.
5) Labeling, coding and storage

Filling

The aerosol products can be filled into several ways depending on the nature of the product concentrate :

1. Cold-fill process.
2. Pressure-fill process
3. Compressed gas filling process

1. Cold-fill process

- This process is used to fill metered aerosol products using **a fluorocarbon propellant.**
- By lowering the temperature of a propellant below its boiling point, the propellant becomes liquid at atmospheric pressure.
- The product concentrate and propellant are cooled to a low temperature of about

  (-30^0 to -40^0F).
- The concentrate is generally cooled to below 0^0 in order to reduce loss of propellant during the filling operation.

- The chilled concentrate is poured (metered) into the equally chilled container and propellant is added.
- Sufficient time is given for the propellant to partially vaporise, in order to expel the air present in the container.
- The valve is fitted on to the container which is placed into a water bath so that the contents are heated to 130^0F (54^0C) in order to check any leakage and strength of container.
- A dry ice-acetone bath is used to obtain the desired low temperature for laboratory scale preparation whereas refrigeration equipment is used for the large scale production of aerosols.

Notes:

- Because of the low temperature is required, aqueous systems cannot be easily filled by this process, since the water turns to ice.
- In the process, some of the propellant vapors are also lost.

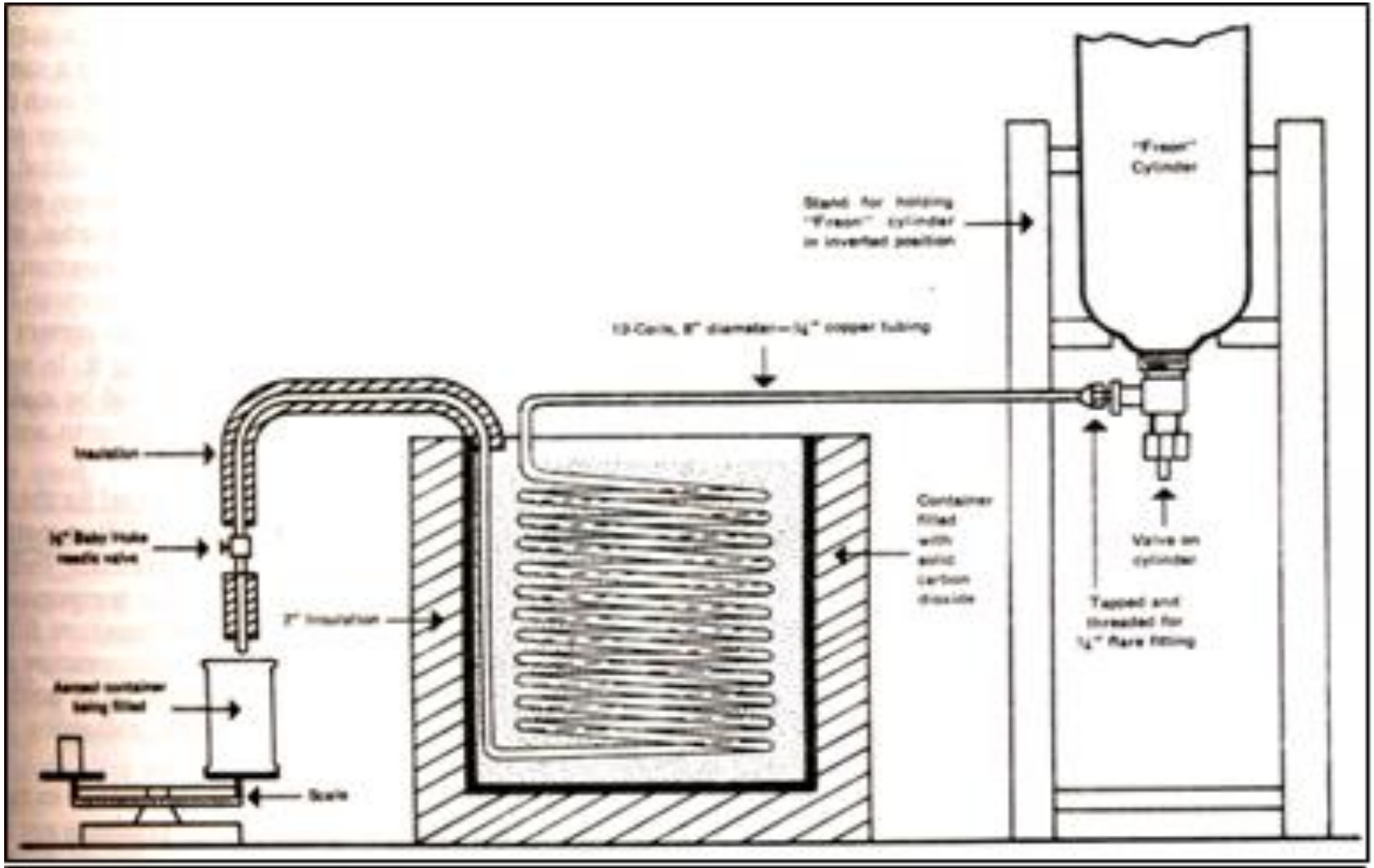


Fig. 16. Aerosol Cold filling process Apparatus [1]

2. Pressure-fill process

- This process is used for filling aerosols containing **liquified propellant** using pressure filler.
- The product concentrate is placed into the container and the valve is sealed.
- The propellant is forced through the valve under pressure at room temperature followed by leakage test as before.
- It is essential that the air present in the container must be expelled before filling the contents into the aerosol container.

It has advantages over the cold filling method:

- Less danger of moisture contamination of the product.

- Less propellant is lost in the process.

3- Compressed gas filling process

Used for compressed gases which are stored under high pressure in certain bottles with a pressure- reducing valve.

Other methods and equipment

Valve placing

Using valve placer, either manually or automatically, can orient the valve and place it in position prior to the crimping operation.

Purging and Vacuum crimping

May be occurred in one equipment (dual function), like single-head or multiple-head crimpers.

Testing of aerosol

- The aerosol container is tested under various environmental conditions for leaks or weakness in the valve assembly or container.
- The valve discharge rate is determined by discharging a portion of the contents of a previously weighed aerosol during a given period of time.

Aerosols may be tested:

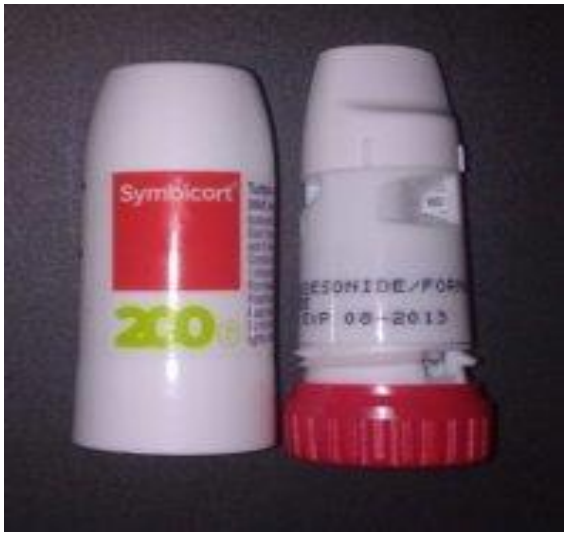
- For particle size distribution of the spray: (5-10µm)
- For accuracy and reproducibility of dosage when using metered valves.
- Propellant properties (V.P., B.P. and density)
- Toxicity, biologic testing and therapeutic activity.

Dry powder inhalers

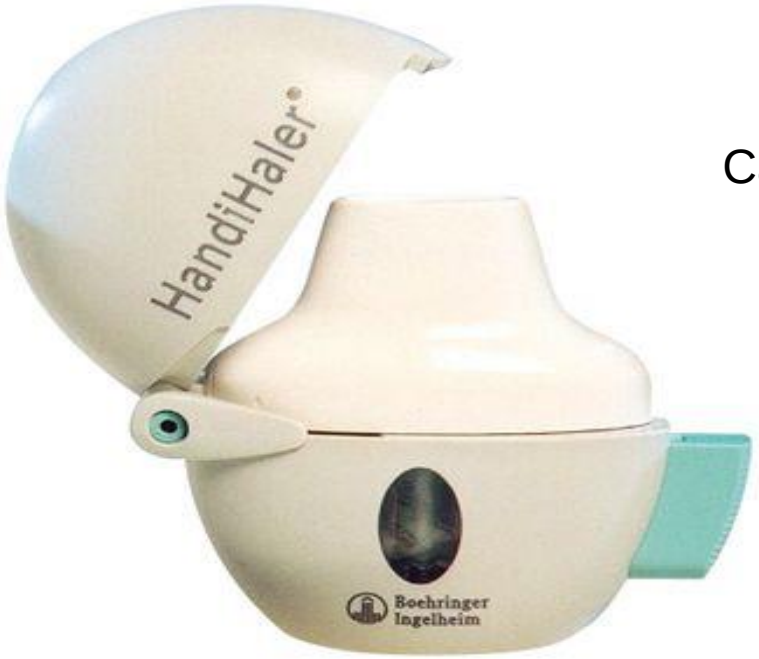
- Are devices that deliver medication to the lungs using an inhalation device in the form of a dry powder.
- These devices are commonly used for drug delivery for local action.
- Powder properties required for their use in DPIs include good flow, lack of adhesion to the material of package, low and uniform particle size for deposition in the appropriate region of the lung, and an adequate low drug dose.

- With solid powder fill without propellant or **spacer?**.
- The fill may enclosed within capsules or sachets ready to be inhaled using a special device or the powder may be filled inside chamber found within a metered device (Turbohaler) or (Diskus).
- The powder is containing micronized drug (less than 5 µm) and solid coarse (30-150 µm) excipient as diluent, carrier or bulking agent (ex. lactose and other sugars), leucine and Mg stearate.
- The inhaled powder is tasteless powder

Diskus inhaler



Turbohaler



Capsule-based Device

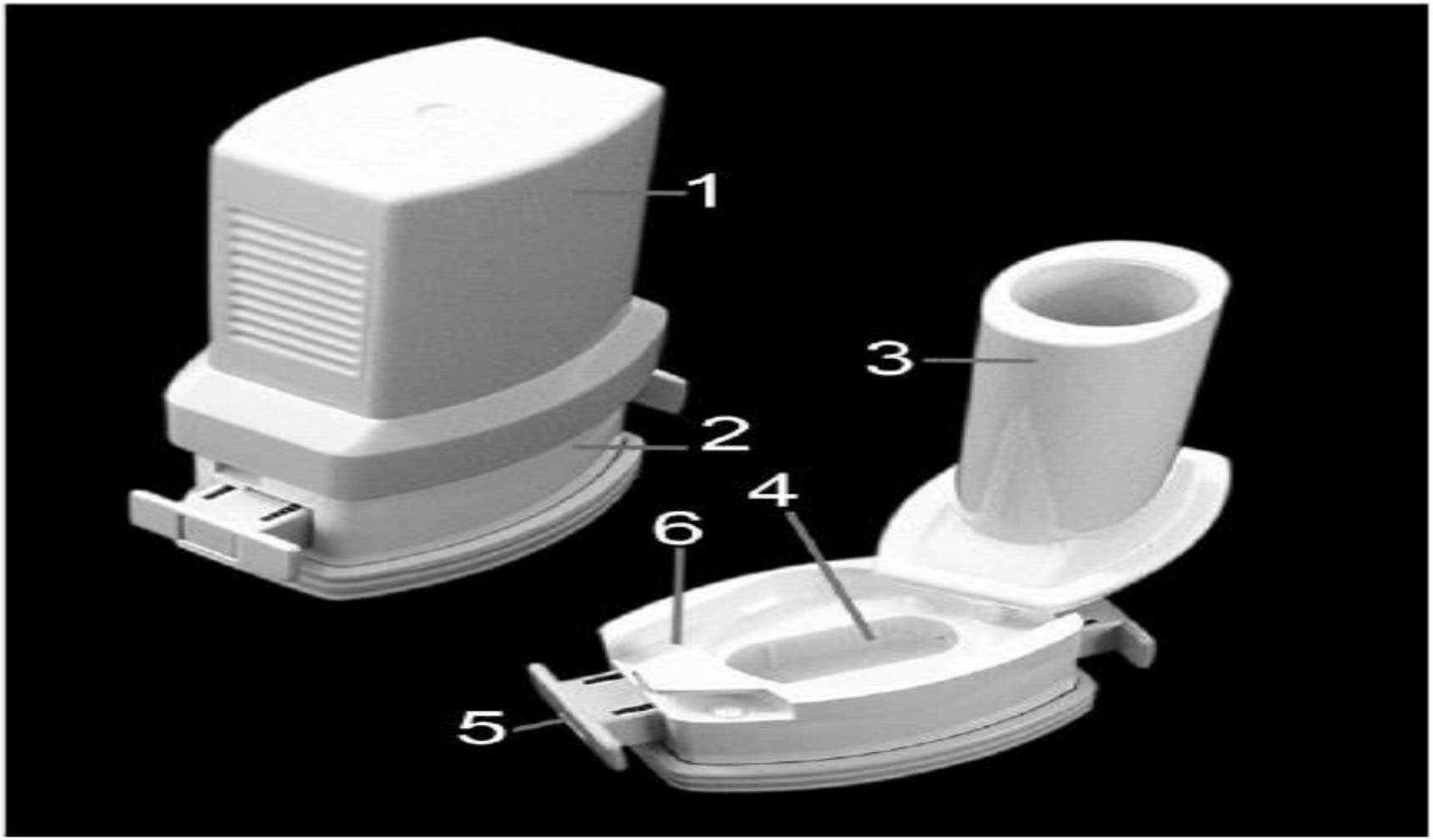
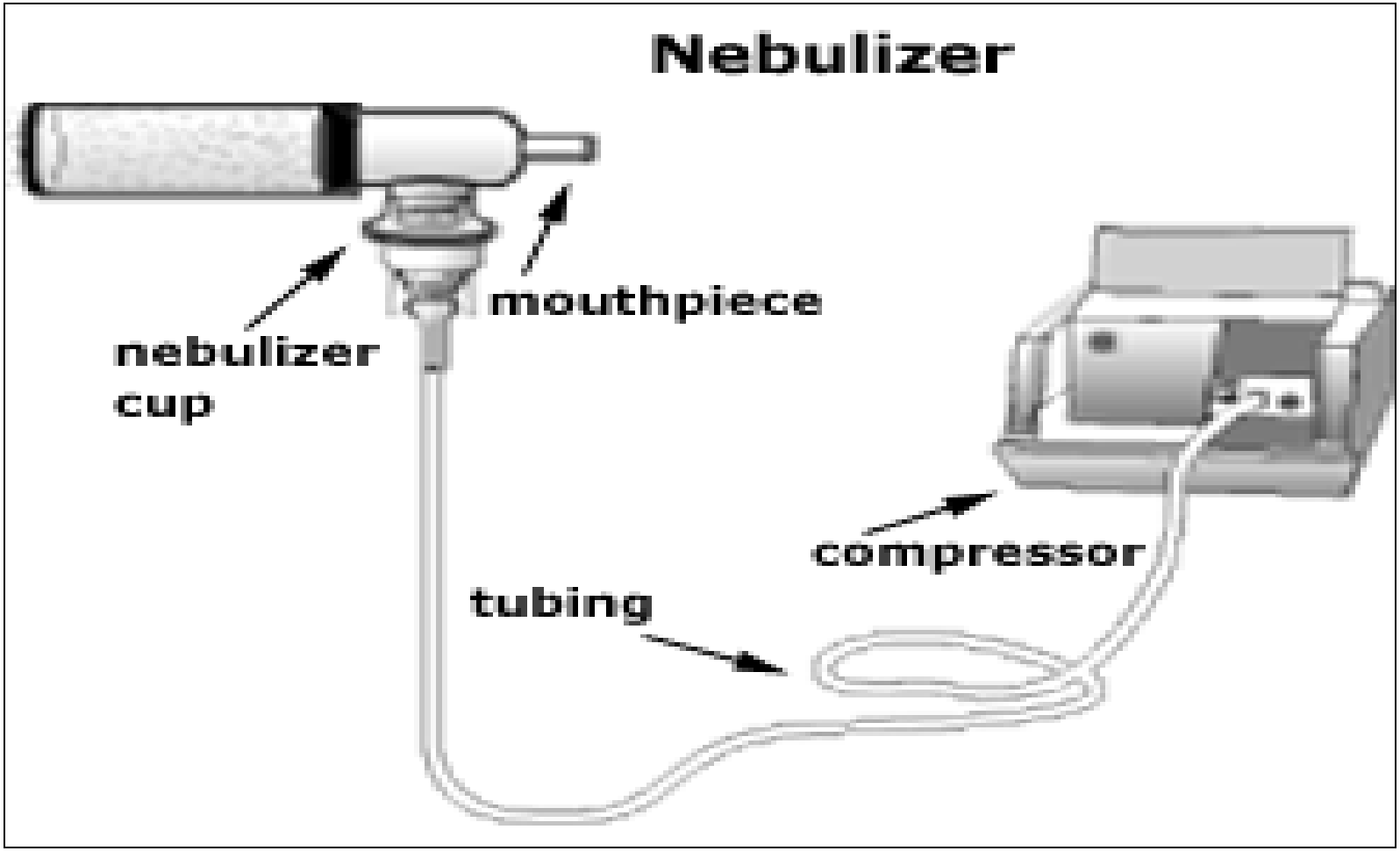


Fig. 37.5 • The Aerolizer/Cyclohaler® dry powder inhaler. Comprising: 1 cap; 2 base; 3 mouthpiece; 4 capsule chamber; 5 button attached to pins for piercing capsule; 6 air inlet channel

Nebulizer: (electric device + Solution for nebulization???)

- Uses forced air to turn asthma medication into a fine mist so that it can easily be breathed into the lungs.
- It delivers relatively large volumes of drug solutions and are frequently used for drugs that cannot be conveniently formulated into MDIs or DPIs, or where the therapeutic dose is too large for delivery with these alternative systems.

It is useful for patients who experience difficulties with MDIs.


Nebulizer
mouthpiece
nebulizer
cup
compressor
tubing

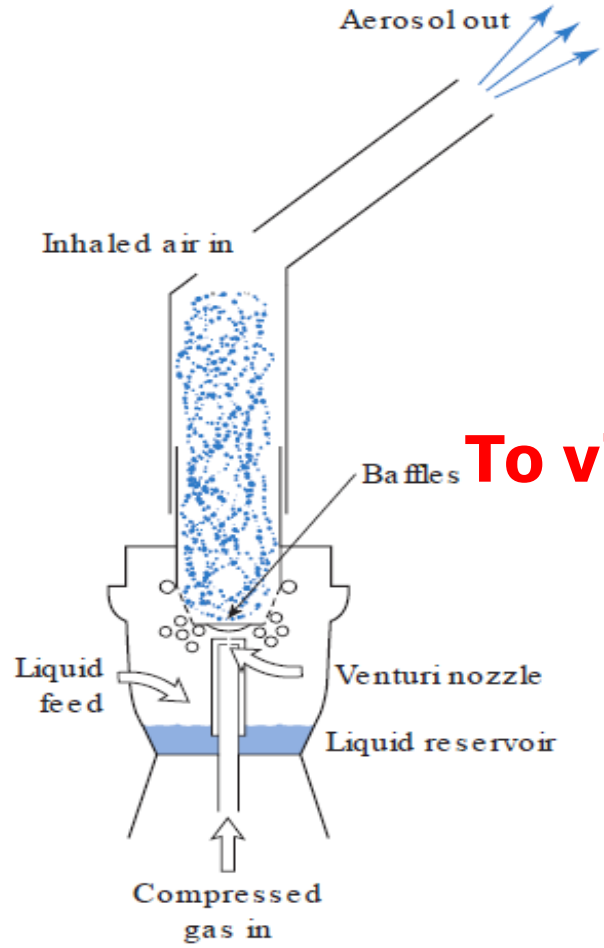


Fig. 37.10 • Schematic diagram of a jet nebulizer. Compressed gas passes through a Venturi nozzle, where an area of negative pressure is created. Liquid is drawn up a feed tube and is fragmented into droplets. Large droplets impact on baffles, and small droplets are carried away in the inhaled air stream.

Formulation of nebulizer fluids

- They are formulated in water, co solvent may be used (like ethanol), surfactant, isotonicity modifiers, buffers, stabilizers (for multiple use containers).
- Nebulizer formulations are generally presented as sterile, isotonic unit doses (usually 1 –2.5 mL) without a preservative.

Suggest, we have the following aerosol formulation:

Material	Weight %
Beclomethasone dipropionate (within 1-5 micrometers)	**q.s.**
Sorbitan trioleate	**0.25**
Mineral oil	**0.25**
Propellant 114	**49.5**
Propellant 12	**49.5**

1. What is the expected:
a) Aerosol type
b) Formulation type
c) Valve type and why?
d) Container type and why?
e) Filling method and why?
2. Give the cause(s) behind the use of drug derivative (dipropionate) and its particle size.
3. What are the chemical names of the involved propellants?
4. Give the cause (s) behind the use of propellants combination.
5. Give the cause(s) behind the use of mineral oil in the formulation.