

# Pharmaceutical Aerosols



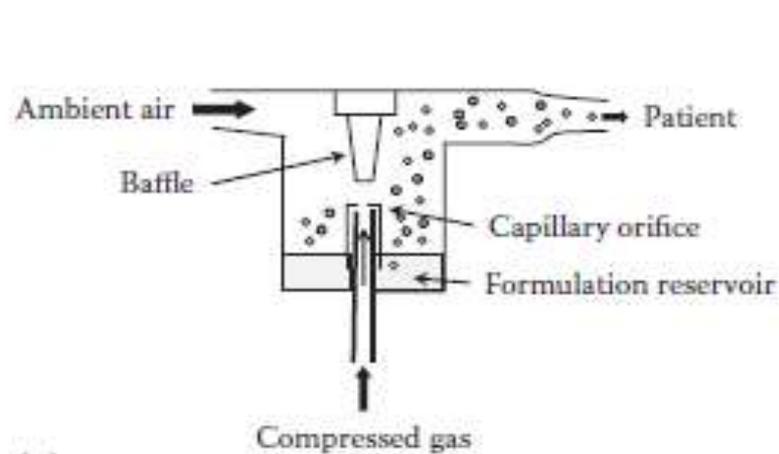
# Outlines

- **Introduction**
- **Advantages and disadvantages**
- **Types**
- **Materials**
- **Methods and equipment**
- **Evaluation**

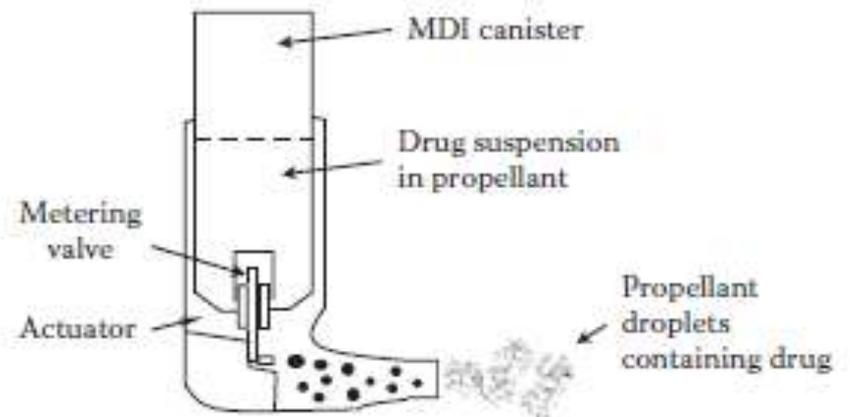
# Introduction

- Are pressurized formulations or systems that depends on the power of a compressed or liquefied gas to expel the contents from the container.
- Factors affecting the deposition of drug inside lungs are: drug-related (particle size, shape, density , charge, hygroscopicity ), device-related , in addition to the physiological factors like the thickness of absorption barriers, muco-cilliary clearance, breathing pattern, presence of macrophages and blood supply.

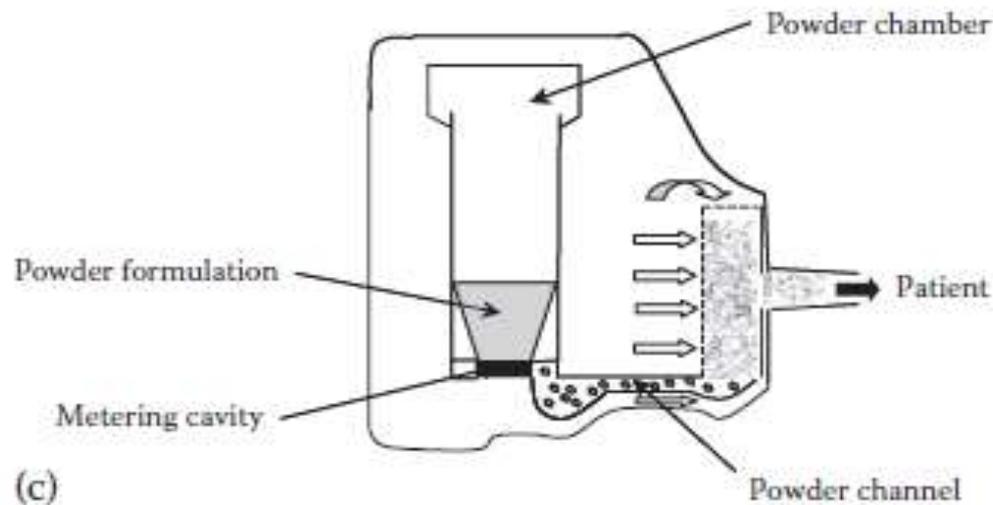
- advantages, such as : less contamination upon doses application, more stability, a proper delivery of medication with less irritation problems.
- Their disadvantages are mainly related to manufacturing difficulty and cost.
- Found into different types:
  - Aerosols (MDI, continuous) , dry powder inhalers and nebulizers.
  - Topical, pulmonary and intranasal.



(a)



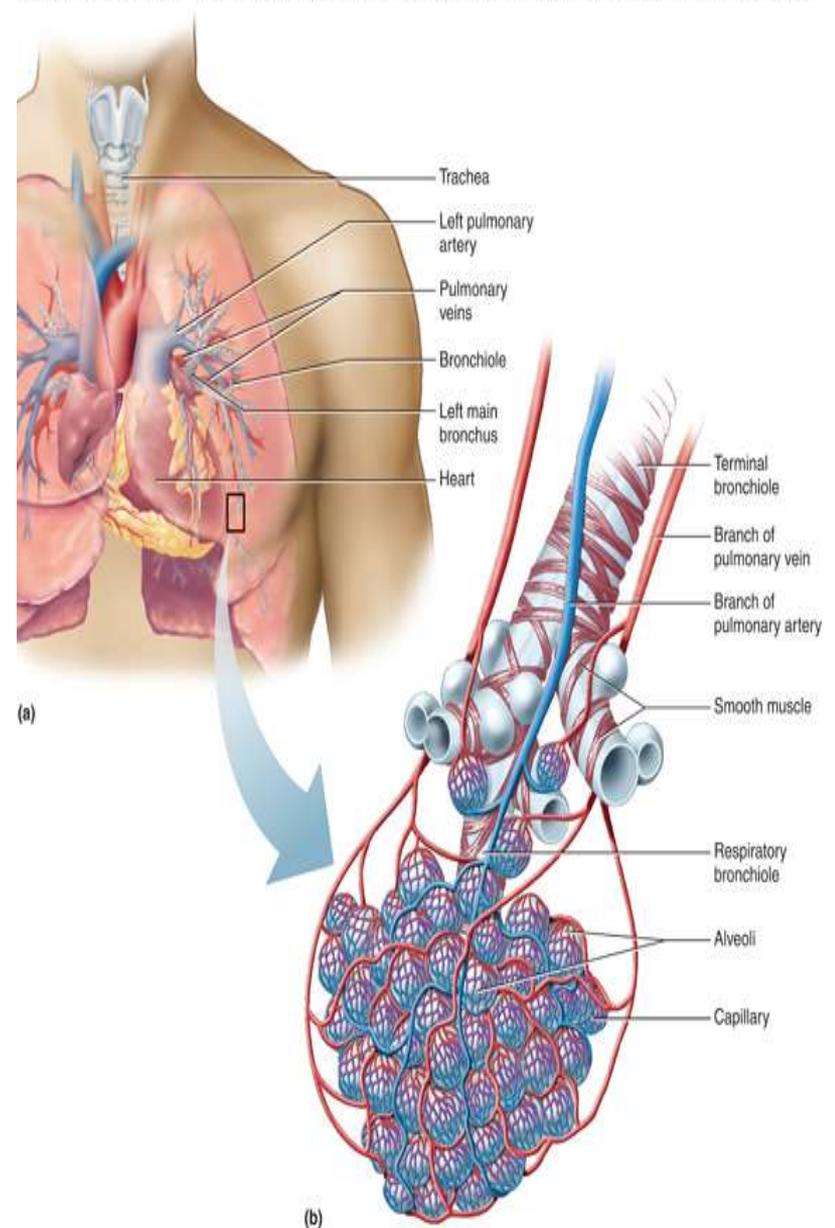
(b)

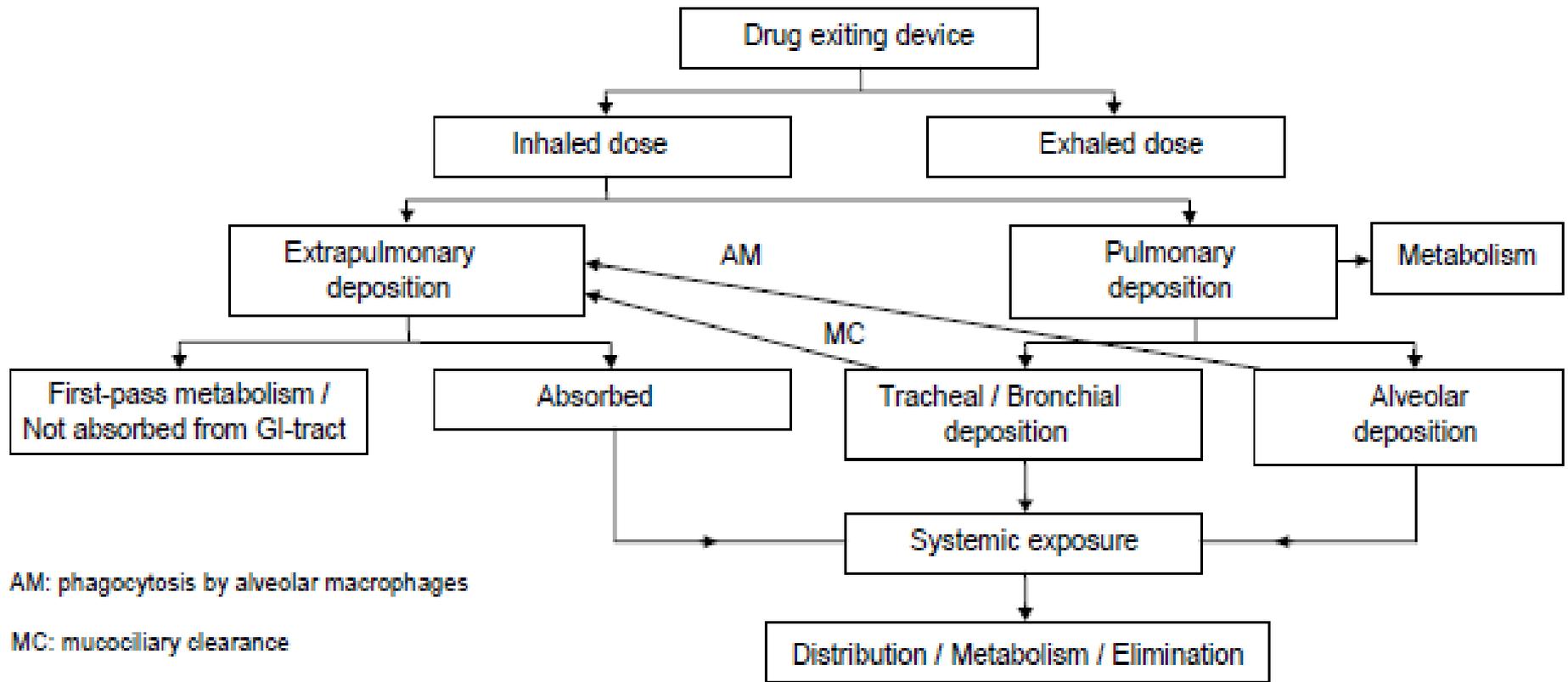


(c)

**Figure 24.3** An illustration of design elements of inhalation devices: (a) nebulizer, (b) metered-dose inhaler, and (c) dry powder inhaler.

	Name of branches	Number of tubes in branch
Conducting zone	Trachea	1
	Bronchi	2
		4
		8
		16
	Bronchioles	32
Terminal bronchioles	$6 \times 10^4$	
Respiratory zone	Respiratory bronchioles	$5 \times 10^5$
		Alveolar ducts
	Alveolar sacs	

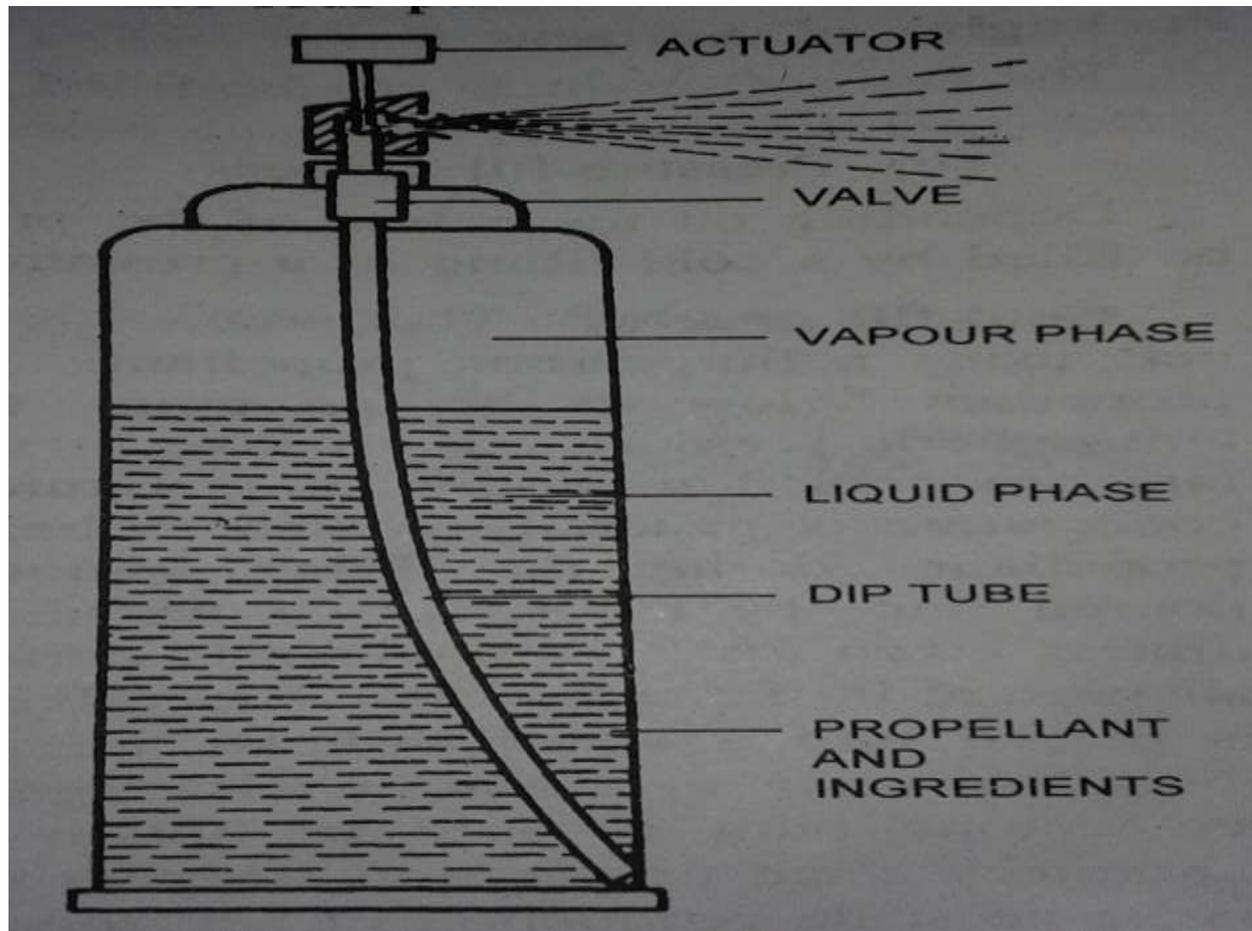


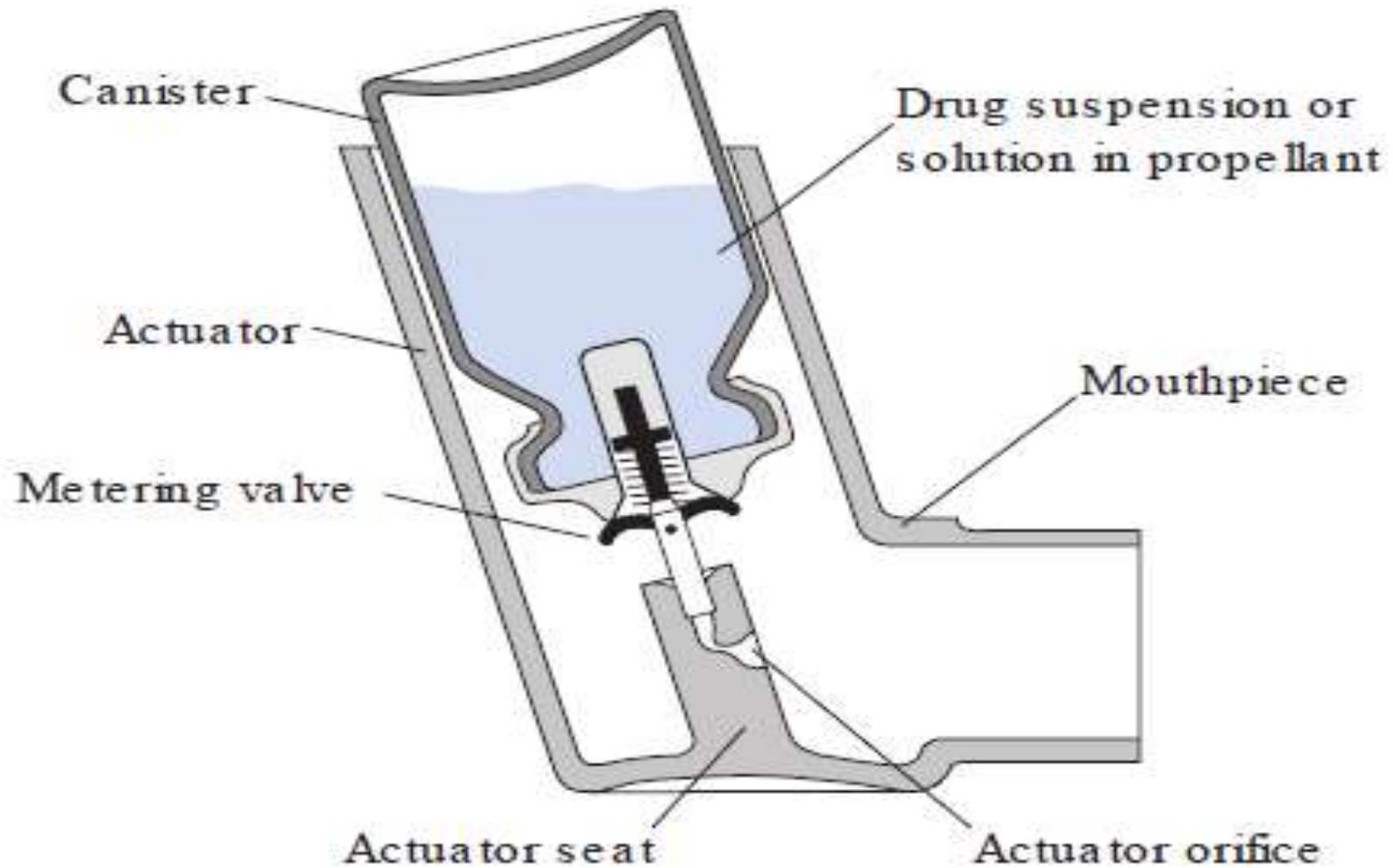


*Figure 6. Schematic illustration of the fate of an inhaled drug.*

# Aerosols materials

- Package/containers: consist of three main parts
  - 1) Container
  - 2) Valve
  - 3) Actuator
- Content formulations





**Fig. 37.2 • The pressurized metered-dose inhaler.**

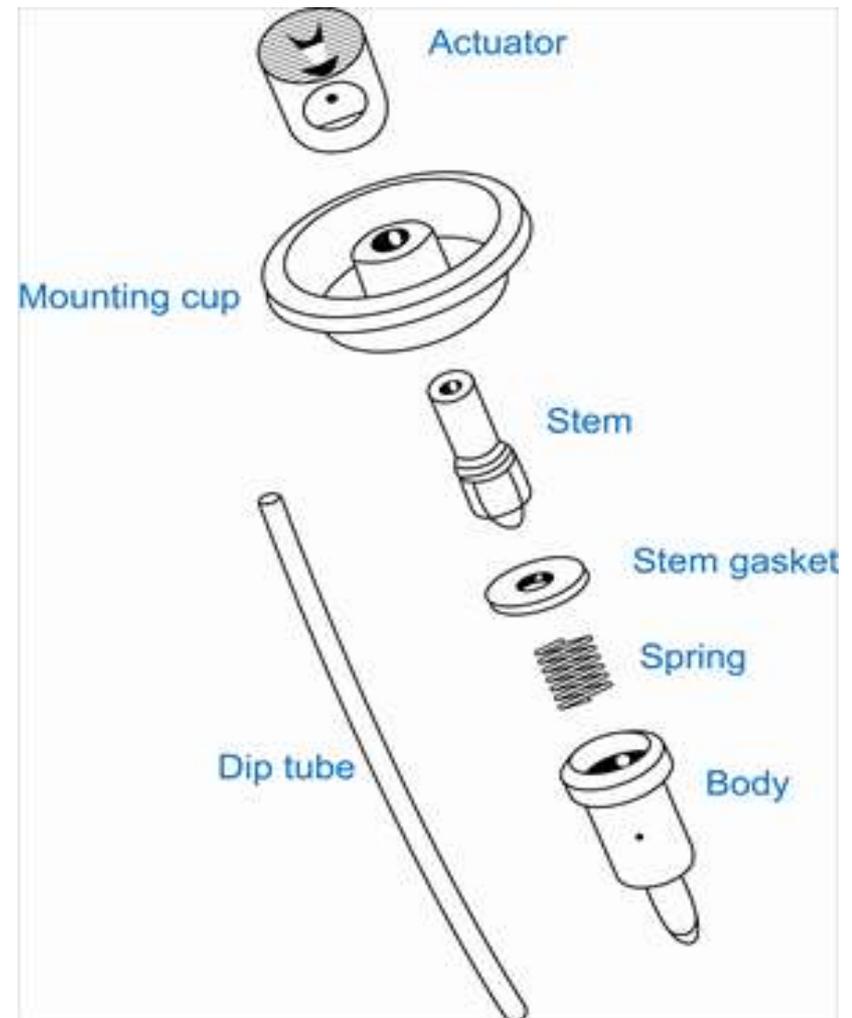
# 1. Container:

- Are made from metal (such as tin-plated steel, aluminum and stainless steel), glass (uncoated and plastic coated) or plastic.
- found into different sizes, weights, lengths and thickness.
- These containers can withstand high pressures in range of 140-180 psig at 130°F or about 54°C.

Metal	Glass	Plastic
More difficult in manufacturing	less	Least
More costly	less	Least
Strong mechanical Properties	Less with danger of breakage	More soft
Tolerate more pressures	Less	least

## 2. Valves:

- The valves used should be such that it can be easily opened and closed.
- It should also deliver the content in the desired form.
- So three types of valves are used nowadays:
  - (i) Continuous spray valve
  - (ii) Metering valve
  - (iii) Foam valve
- By using continuous spray valve, the medicament is expelled continuously as long as pressure is applied on the actuator. But by using metering valve, only a definite quantity of medicament is expelled when actuator is pressed.



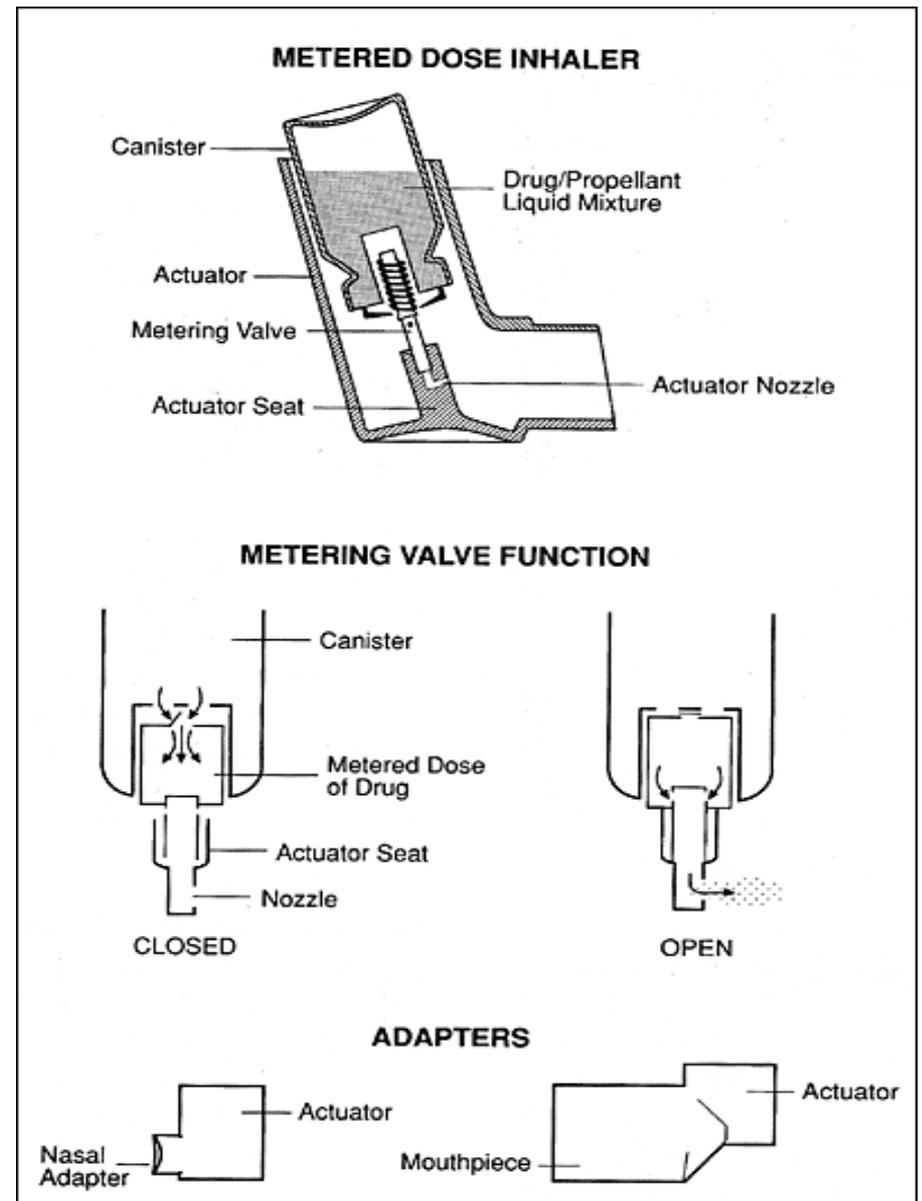
## Composition of valve

- Ferrule: used to attach the valve properly to the container.
- Stem: made from Nylon or metal containing 1-3 orifices.
- Dip tube: is made from polyethylene or polypropylene used for:
  - (i) Delivery of the liquid from the bottom of the container to the valve at the top.
  - (ii) Preventing the propellant to come out without dispensing the contents of the package.

If the dip tube is touching the bottom of the container, it will block the passage of liquid.

# Metering valves

- Are applicable to the dispensing of potent medication, using a chamber whose size determines the amount of medication dispensed.



# 3. Actuator:

- Used to ensure that the aerosol product is delivered in the proper and desired form.
- It is fitted on the valve stem.
- It helps in the easy opening and closing of the valve, whenever it is required.
- There are various types of actuators:
  - ❖ Spray: can be used for topical aerosols
  - ❖ Foam: larger orifices, topical
  - ❖ Solid stream : large orifice, for semisolid
  - ❖ Special actuator: Medicinal aerosols, deliver the drug to nose, eye, throat and other routes



# Questions:

Q1: What is the meaning of?:

**1- Metering-Dose Inhalers (MDI.s)**

**2- Intranasal sprays      3- Spacer device**

Q2: What are factors affecting the selection of materials in the pharmaceutical aerosols?

# Aerosol Content formulation

An aerosol formulation basically consists of

- ❑ Propellant :(one or mixture)
- ❑ Product concentrate: to be propelled and expelled, contains active medication (one or more) and other materials.

## Propellant:

- Is regarded as **the heart** of the aerosol package.
- It supplies the necessary force to expel the product.
- Act as solvent and diluent (The medication may be soluble or insoluble in the propellant).
- The various additives such as solvents, antioxidants, surface, active agents and flavoring agents are also included in the formulation.
- The propellants, medicaments and additives are filled into an aerosol container.

# Types of propellants

➤ Liquefied gases and Compressed gases

**Q/ What are the properties of ideal propellant?**

**Liquefied gases: (Hydrocarbons, Chloroflourocarbons and Fluorocarbons , hydroflourocarbons and HCFC.s)**

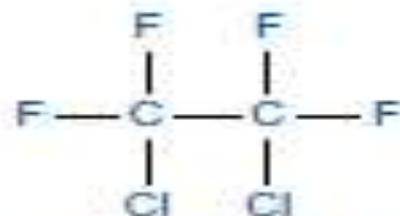
For many years, the liquefied gas propellants most used in aerosols products were **the chlorofluorocarbons (CFCs)**, however, these propellants are being phased out and will be prohibited because **they deplete the ozone layer, which results in an increase in the amount of UV radiation reaching the earth which may increase the incidence of skin cancer.**

But in case of unavailability of other alternative propellant or the product provides a substantial health benefit unobtainable without the use of CFCs. they can be used.

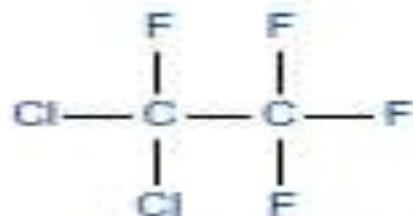
- Among the CFCs used as propellants in pharmaceuticals were;
  - dichlorotetrafluoroethane (Propellant or Freon 114)
  - trichloromonofluoromethane (Propellant or Freon 011)
  - dichlorofluoromethane (Propellant or Freon 012).
- **N.B the numerical designation system (XYZ);(three digits)**
  - X = number of carbon atoms +1
  - Y = number of hydrogen atoms - 1
  - Z = number of fluorine atoms
  - Example: propellant 113 has 2 C + no H + 3 F
- For CFC.S, the rest of atoms required for saturation represents no. of chlorine atoms
- Fluorinated hydrocarbons are gases at room temperature. They may be liquefied by cooling below their boiling point or by compression at room temperature.

Propellant 114 is an ethane derivative, has no hydrogens, and contains 4 fluorine atoms.

Since 6 atoms are required to saturate the carbon chain, of necessity there must be 2 chlorine atoms. These can be arranged in two different ways; however, since there is no letter following the numerical designation, the symmetrical structure refers to Propellant 114.



Propellant 114



Propellant 114a

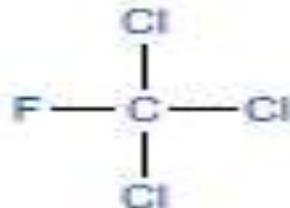
For CFC 11-Trichloromonofluoromethane

The designation is 0 for methane (first digit)

1 for number of fluorine atoms (third digit)

1 for one more than number of hydrogen atoms (second digit)

3 chlorine atoms required to saturate molecule.



Propellant 11

## **Notes:**

**1- Propellants can be used in mixtures (50:50, 60:40, 70:30.....) depending on different factors like (the required pressure, the required density, the type of formulation and type of medication).**

**2- The vapor pressure of a mixture can be calculated according to Dalton's law (Pt=P1+P2...)**

**3- Addition of a solute (which may be second propellant) can decrease V.P. of solvent.**

**Depression is proportional to the mole fraction of solute (Raoult's law) then:**

$$P_1 = (\text{Mole fraction})_1 * P^0 \quad (P^0 = \text{pure propellant pressure})$$

$$(\text{Mole fraction})_1 = n_1 / n_1 + n_2$$

**4- Hydrocarbon like propane, butane and isobutane are mainly used in topical aerosols**

# Compressed gases

- Such as nitrogen, nitrous oxide and carbon dioxide.
- With little expansion power.
- Used in dental creams, hair products, ointments and aqueous antiseptics

# Product concentrate

- We have different formulations or systems with different dispensing forms and selected depending on many factors like:
  - 1) The physical, chemical and pharmacologic properties of active ingredients

2) Site of application

So we have: (2-phase or 3-phase systems) or exactly

**1- Solution system**

**2- Water based system**

**3- Suspension or dispersion systems**

**4- Foam systems**

# **Solution system: (two-phase system)**

- It consist of a vapor and liquid phases
- Co-solvent may be used like 2<sup>nd</sup> propellant, ethanol, PG, ethyl acetate, glycerin and acetone depending on solubility properties of active ingredient or the desired pressure.
- The amount of propellant used may vary from 5% (for foams) to 95% ( for inhalation products).
- The general formula is

**Active ingredient                    to 10-15%**

**Propellant 12/11(50:50)   to 100%**

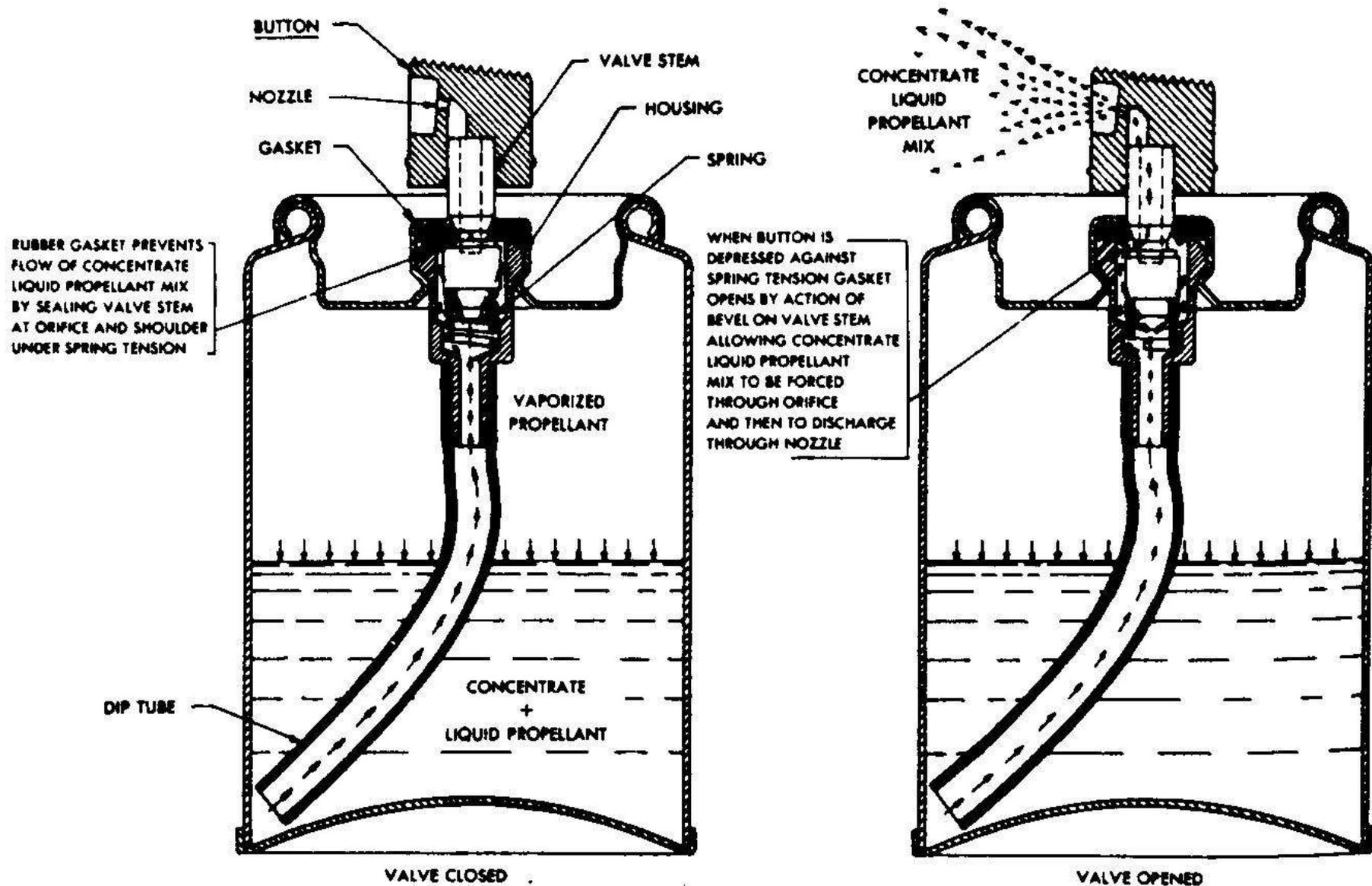
other combinations can be used (30:70) or propellant 12/114 (45:55) and (55:45) for oral inhalations.

- Co-solvent, antioxidant like ascorbic acid may be involved

- Hydrocarbons (HC.s) are used in topical aerosols as in:

<b>Active ingredient</b>	<b>up to</b>	<b>10-15%</b>
<b>Solvent (ex. ethanol or PG)</b>	<b>up to</b>	<b>10-15%</b>
<b>D/W</b>		<b>10-15%</b>
<b>HC propellant</b>		<b>55-70%</b>

Depending on amount of water, the system may be converted into 3-phase system



**Fig. 13-2.** Cross section sketches of contents and operation of a typical two-phase aerosol system. (Courtesy of Armstrong Laboratories, Inc., Division of Aerosol Techniques, Inc.)

## **Water-based system: (three phase system)**

- Relatively large amount of water can be used to replace all or part of the non-aqueous solvents .
- Ethanol has been used as a co-solvent (for solubilizing some of the propellant).
- Surfactant (lipophilic like spans) in 0.5-2%
- Propellant content is about 25-60% but can be as low as 5%, depending on the nature of product.
- There is development (Aquasol valve) which is not typical 3-phase system, because of small amount of propellant used, with no chilling effect after application, and dispenses a fairly dry spray with very small particles (there is no liquefied propellant).

## **Suspension or Dispersion systems : (three phase system)**

- Used for oral inhalations containing active ingredient dispersed into propellant(s) in presence of surfactant or suspending agent like oleic acid, sorbitan trioleate and myristyl alcohol.
- The physical stability can be increased by:
  - 1) Control of moisture content (less than 300ppm) using desiccants.
  - 2) Used of derivative of active ingredient having minimum solubility in propellant(s).ex. Epinephrine bi-tartrate rather than sulfate or hydrochloride salts
  - 3) Reduction of particle size to less than 5 microns.
  - 4) Adjustment of density of dispersed and dispersion phases to be equalized.
  - 5) Use of suspending agent (non-ionic) and lubricant like mineral oil (for valve orifices).

### Table 33-7. Metered-Dose Inhalants (Solution and Suspensions): Prototype Formulation

#### Solution (CFC, HFC)<sup>a</sup>

Active ingredient(s): solubilized antioxidants: ascorbic acid

Solvent blends: water, ethanol, glycols

Propellants: 12/11, 12/114 or 12 alone; 134a, 227, 134a/227

#### Suspensions (CFC)

Active ingredient(s): micronized and suspended

Dispersing agent(s): sorbitan trioleate, oleyl alcohol, oleic acid, lecithin, etc.

Propellants: 12/11, 12/114, 12 or 12/114/11 suspensions (HFC)<sup>a</sup>

Active ingredient(s): micronized and suspended solvent: ethanol

Dispersing agent(s): sorbitan trioleate, oleyl alcohol, oleic acid, lecithin, etc.

Propellants: 134a, 227, 134a/227

or

Active ingredient(s): micronized and suspended propellants: 134a, 227, 134a/227

# Foam or emulsion systems : (three phase system)

- It consist of active ingredient, aqueous or non aqueous vehicle, surfactant, and propellant.
- Dispensed as foams to be applied to a limited area with less irritating.
- Depending on foam stability (which depend on the nature of ingredients and the formulation), can be subdivided into:

## 1) Aqueous stable foams:

With formula like:

<b>Active ingredients, oil waxes, o/w surfactant and water</b>	<b>95-96.5%</b>
<b>HC propellant</b>	<b>3.5-5%</b>

## 2) Non aqueous stable foams:

- Formulated using various glycols such as PEG, as follow:

<b>Glycol</b>	<b>91-92.5%</b>
<b>E.A.</b>	<b>4%</b>
<b>HC prop.</b>	<b>3.5-5%</b>

### 3) Quick-breaking foams:

- The propellant is the external phase, so upon dispensing, foam is emitted which then collapse into a liquid.
- No rubbing after application.
- Can be formulated as:

Ethanol 46-66%

Surfactant 0.5-5% (non ionic or ionic type)

Water 28-42%

HC prop. 3-15%

## **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 addition of propellant inside the package at certain condition (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

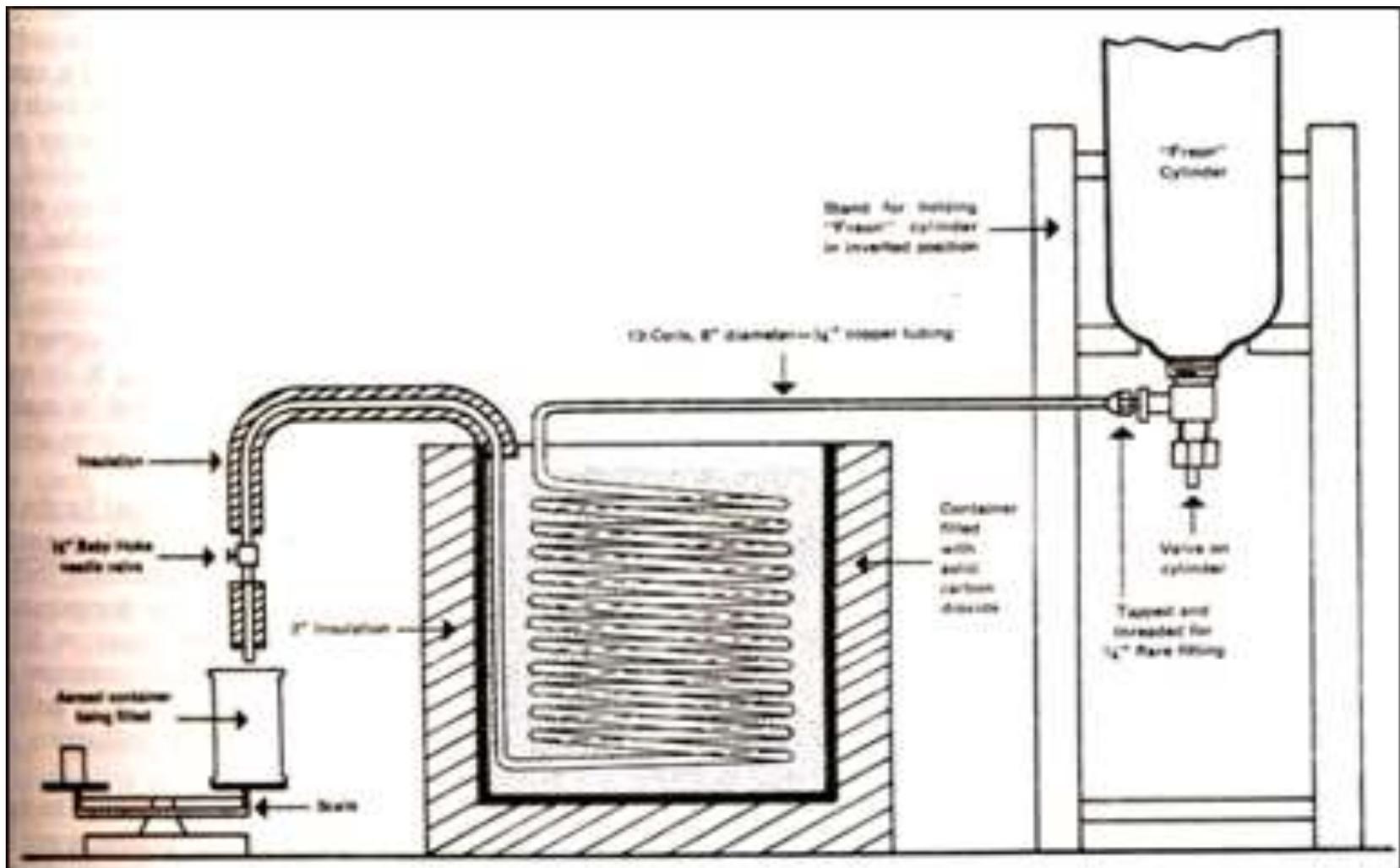
# 1. Cold-fill process

- 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 active ingredients or concentrate and propellant are cooled to a low temperature of about  $-30^{\circ}$  to  $40^{\circ}\text{F}$ .
- The concentrate is generally cooled to below  $0^{\circ}$  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<sup>0</sup>F (54<sup>0</sup>C) 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.

## ❑ Notice

- because of the low temperatures required, **aqueous systems cannot be 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 <sup>1</sup>**

## 2. Pressure-fill process

- This process is used for filling aerosols containing hydrocarbon 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 the advantage over the cold filling method in that there is less danger of moisture contamination of the product, and also less propellant is lost in the process.**

### **3- Compressed gas filling process**

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

## **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, and calculating.

# **Aerosols may be tested:**

- for their spray patterns and discharge rate**
- for particle size distribution of the spray: (5-10 $\mu$ m)**
- 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.

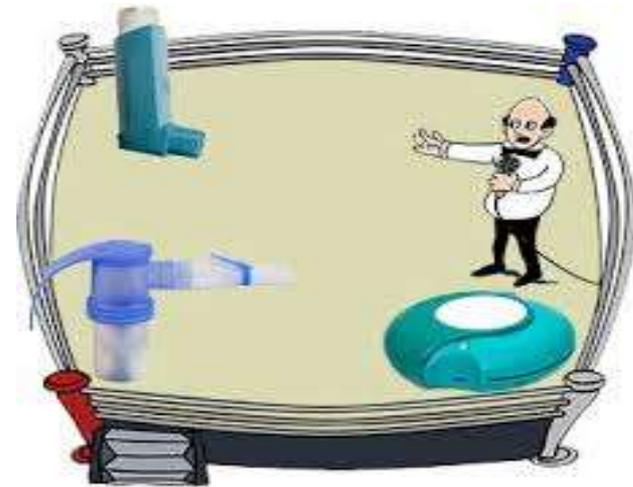
- With solid powder fill without propellant or **spacer?**.
- The fill may enclosed within capsules ready to be inhaled using a special device or the powder may be filled inside chamber found within a metered device (Turbohaler) or (Diskus).
- The powder is containing micronized drug (less than 5  $\mu\text{m}$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

# As questions??

- Compare between MDI and DPI systems depending on formulation materials, stability, administration and efficiency.
- What are the functions of carrier?
- What are the factors affecting drug-carrier mixing?



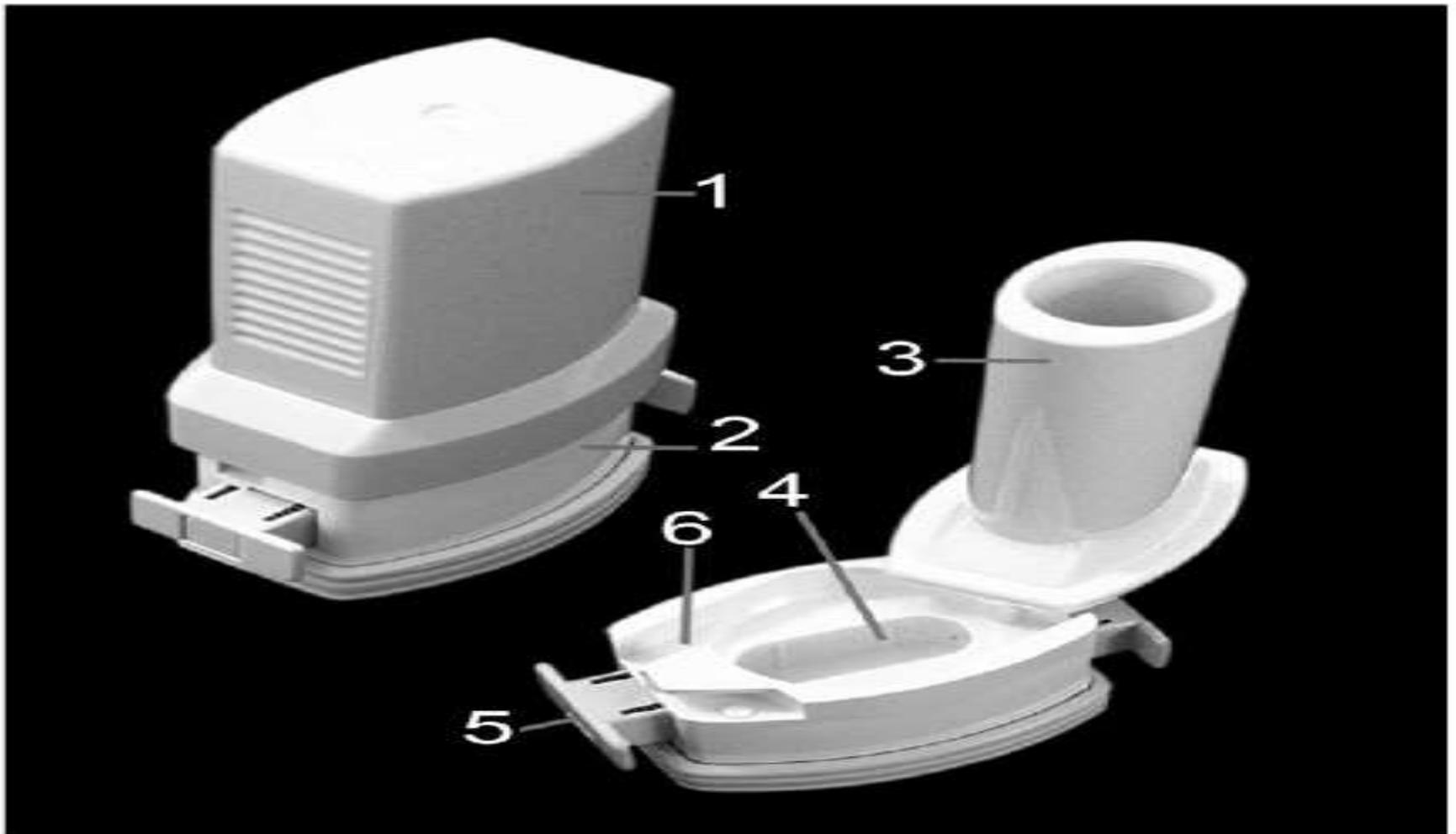
**Diskus inhaler**



**Turbohaler**



**Capsule-based Device**



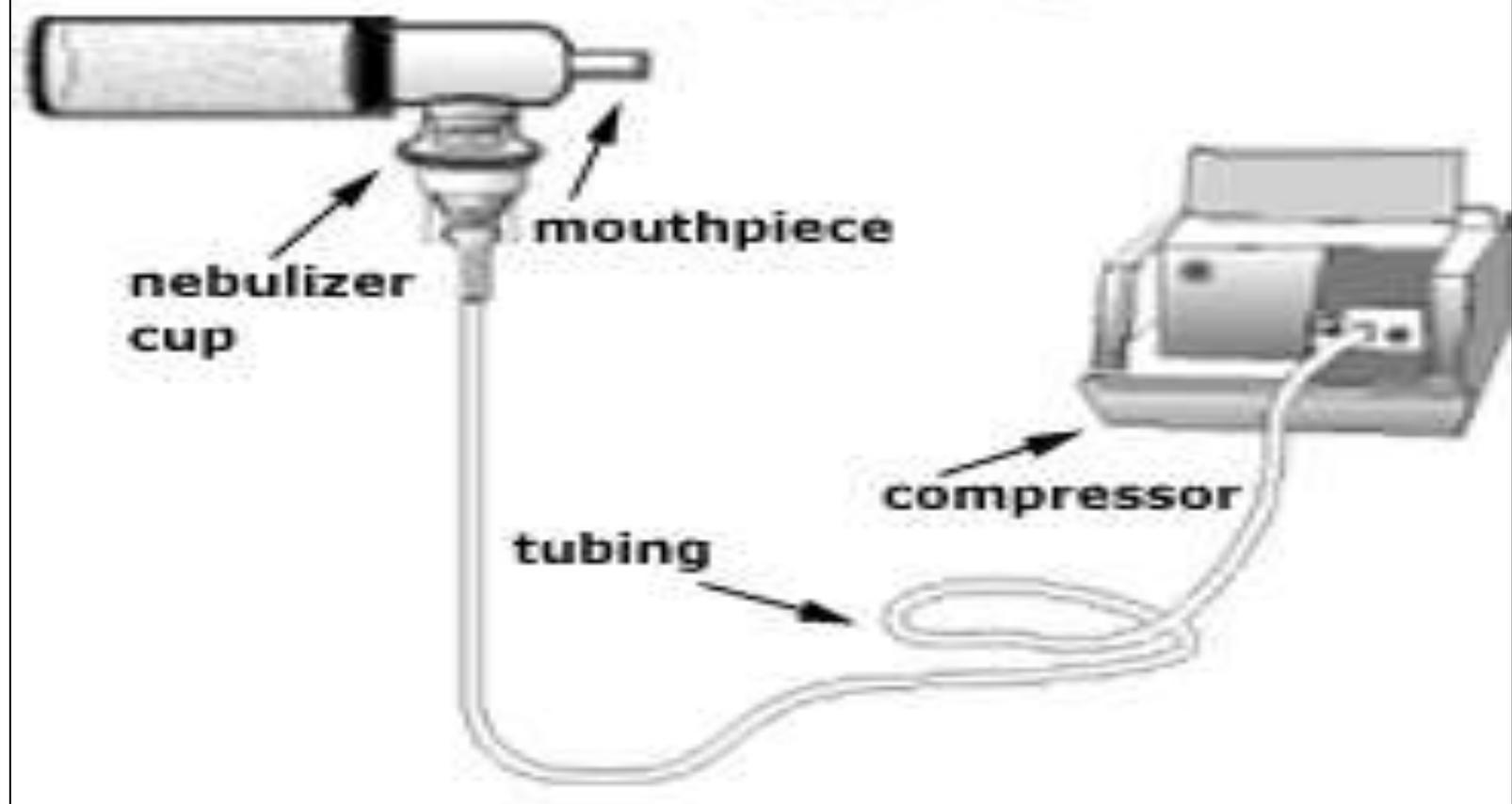
**Fig. 37.5 • The Aerolizer/Cyclohaler® dry powder inhaler. Comprising: 1 cap; 2 base; 3 mouthpiece; 4 capsule chamber; 5 button attached to pins for piercing capsule; 6 air inlet channel**

## **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



# 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.