Pulmonary drug delivery systems

Lecture 21

(Second hour)

Monday : 9/1/2023

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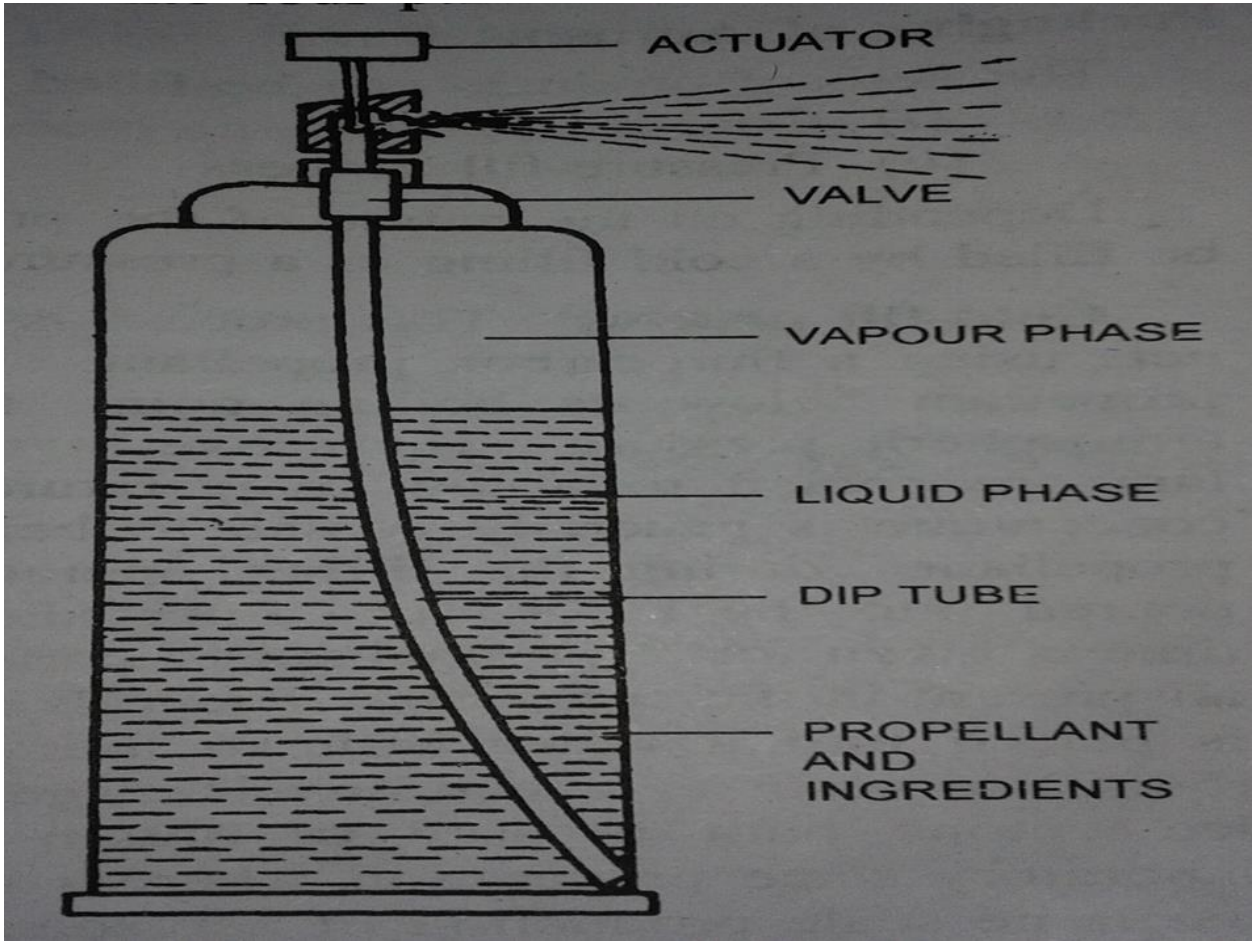
Aerosols materials

- Package/containers: consist of three main parts

1) Container 2) Valve 3) Actuator

- Content formulations



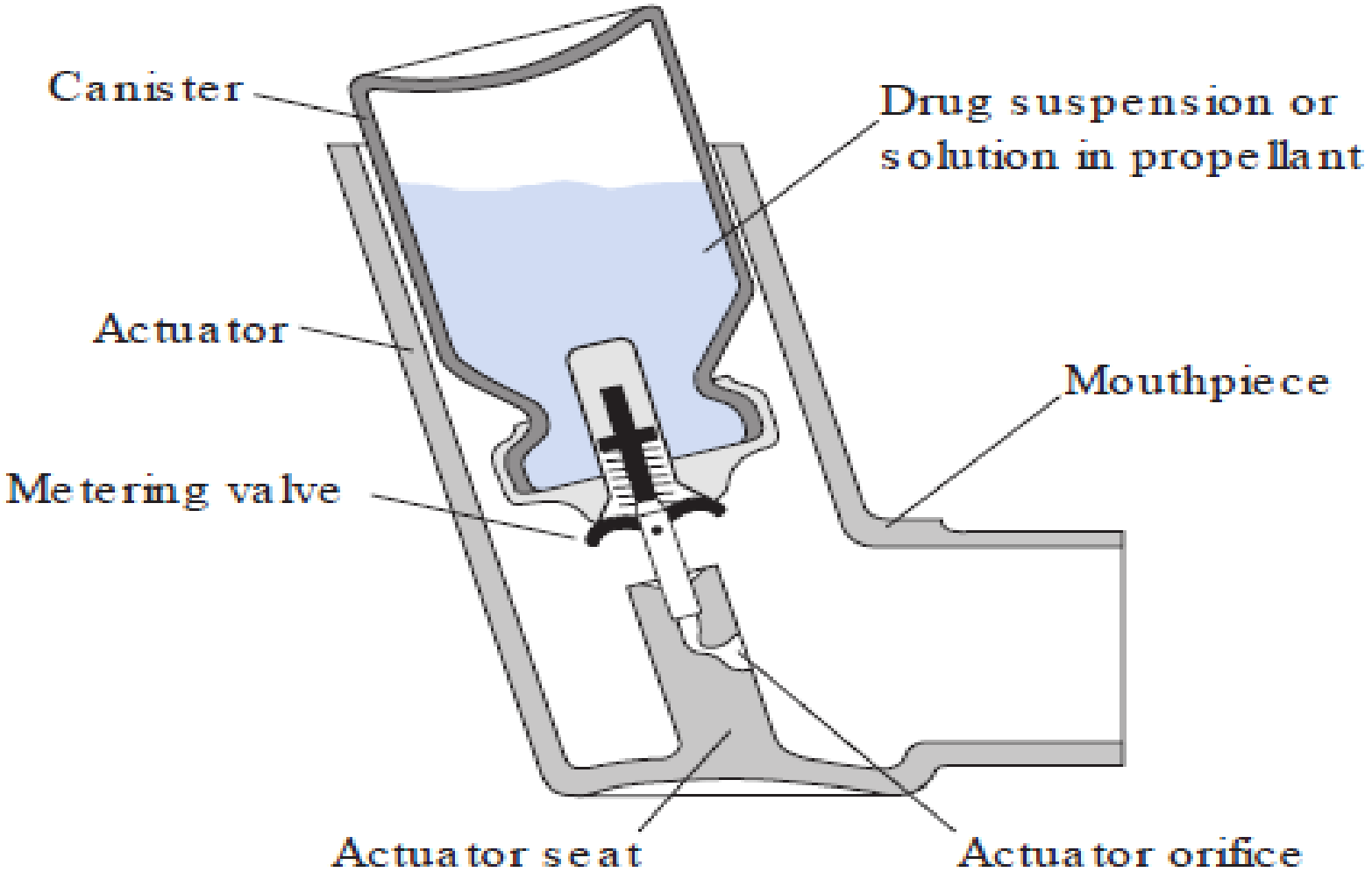


Fig. 37.2 • The pressurized metered-dose inhaler.

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 130ºF or about 54°C.

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

2. Valves:

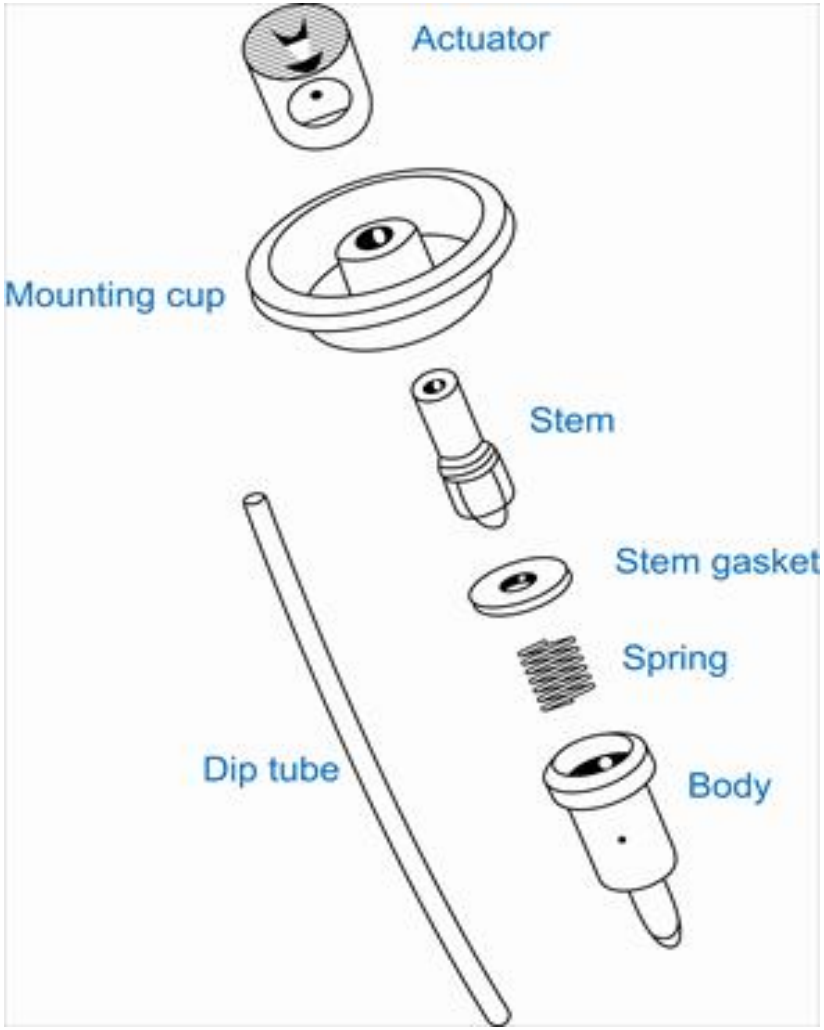
- The valves used should be such that it can be easily opened and closed.
- It should also deliver the content in the desired form.
- So three types of valves are used nowadays:

(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:

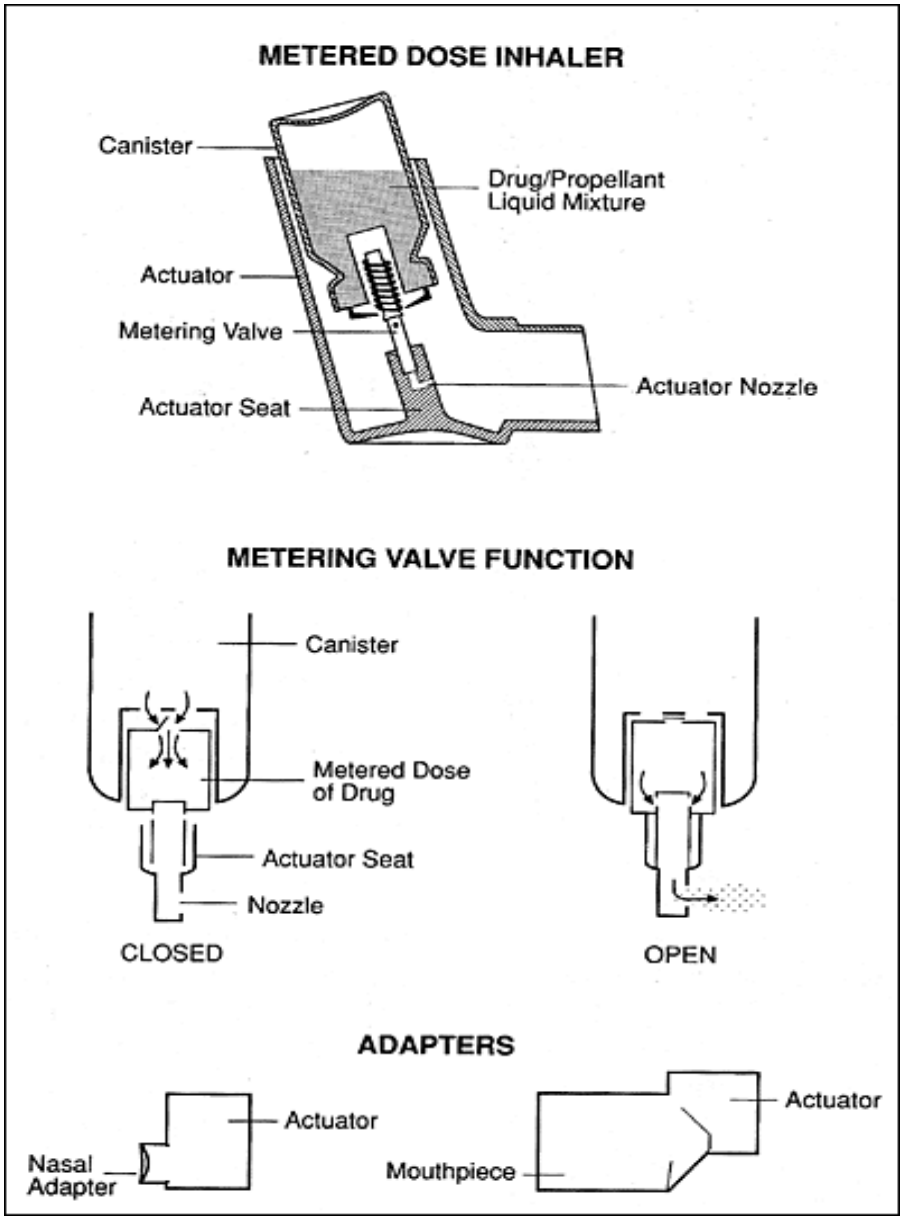
(i) Delivery of the liquid from the bottom of the container to the valve at the top.

(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:

What is the meaning of?:

1- Metering-Dose Inhalers (MDI.s)

2- Spacer device

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 in 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

<u>Liquefied gases:</u> (Hydrocarbons, fluorocarbons, Chlorofluorocarbons, hydrofluorocarbons and hydrochloroflourocarbons)

For many years, the mostly used were **chlorofluorocarbons,** and now prohibited because **they deplete the ozone layer.**

Fluorinated hydrocarbons are gases at room temperature. They may be liquefied by cooling below their boiling point or by compression at room temperature.

- Among the CFCs used as propellants in pharmaceuticals were;
  - dichlorteterafluoroethane (Propellant or Freon 114)
  - trichloromonofluoromethane (Proellant or Freon 011)
  - dichlorofluoromethane (Propellant or Freon 012).

- **The numerical designation system (XYZ);(three digits)**

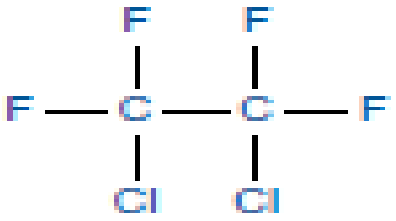
  X = number of carbon atoms +1

  Y = number of hydrogen atoms - 1

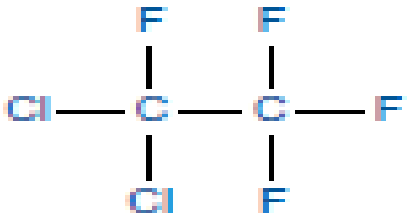
  Z = number of fluorine atoms

  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

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.



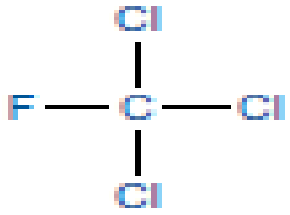
Propellant 114



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- 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 2nd 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:

Active ingredient up to 10-15%

Solvent (ex. ethanol or PG) up to 10-15%

D/W 10-15%

HC propellant 55-70%

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

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)[a]

- 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)[a]

- 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:

Active ingredients, oil waxes, o/w surfactant and water 95-96.5%

HC propellant 3.5-5%

2) Non aqueous stable foams:

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

Glycol 91-92.5%

E.A. 4%

HC prop. 3.5-5%

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%