# Aerosols

Dr. Isra Dmour

Credit: Prof. Nizar Al-Zoubi



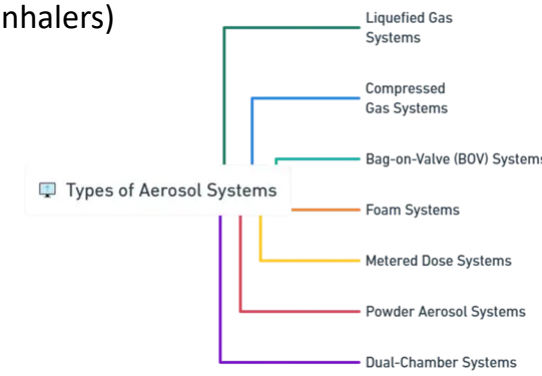


## Aerosols

- Pharmaceutical aerosols are pressurized dosage forms that upon actuation emit a fine dispersion of liquid and/or solid materials containing one or more active ingredients in a gaseous medium.
- Pharmaceutical aerosols differ from most other dosage forms in their dependence upon the function of the container, its valve assembly, and an added component—the propellant—for the physical delivery of the medication in proper form.

# Aerosols

- The term pressurized package is commonly used when referring to the aerosol container or completed product.
- Pressure is applied to the aerosol system through the use of one or more liquefied or gaseous propellants.
- Pharmaceutical aerosols can be administered through different routes like:
  A. Pulmonary (metered dose inhalers)
  B. Nasal
  C. Topical
  D. Rectal
  E. Vaginal




3

3

# Aerosols

- Also there are many cosmetic and household aerosol products, including:
  - personal deodorant sprays
  - hair lacquers and sprays
  - perfumes and colognes
  - shaving lathers
  - toothpaste
  - surface pesticide sprays
  - paint sprays
  - spray starch
  - waxes
  - polishes
  - cleaners
  - lubricants
- A number of veterinary and pet products have been put into aerosol form.

4

4

## Advantages of the Aerosol Dosage Form

1. Easy use and application.
2. Aerosol application is a clean process, requiring little or no wash-up by the user.
3. The aerosol container protects medicinal agents from oxygen, moisture, contamination and light (if opaque container).
4. Sterility may also be maintained during the shelf life of the product.

metered valves

5

5

## Advantages of the Aerosol Dosage Form

5. Topical medication may be applied without anything else touching the affected area.

This method of application may reduce the irritation that sometimes accompanies mechanical (fingertip) application of topical preparations

5. The rapid volatilization of the propellant also provides a cooling, refreshing effect.

6

6

## Advantages of the Aerosol Dosage Form

7. By proper formulation and valve control, the physical form and the particle size of the emitted product may be controlled, which may contribute to the efficacy of a drug, (e.g. inhalant aerosol).
8. Through the use of metered valves, dosage may be controlled.
9. The medicament can be delivered directly to the affected area. This may have advantages like:
   - Rapid onset of action (e.g. asthma treatment)
   - Avoidance of first pass effect
   - Avoidance of degradation by GIT
   - Lower dose is needed and side effects are minimized



7

## Aerosols

- Aerosol products may be designed to expel their contents as:
  - ➢a fine mist
  - ➢a coarse wet or dry spray
  - ➢a steady stream
  - ➢a stable or a fast-breaking foam
  - ➢ointment-like product
- The physical form in which the contents are emitted depends on:
  - the formulation of the product
  - the type of valve.
- The physical form selected for a given aerosol is based on intended use.
- For instance, the particle size is critical for aerosols for inhalation therapy (asthma or emphysema), while it is less critical in aerosols for dermatologic spray



8

# Aerosols

Surface sprays (surface coatings)

- Example: dermatologic aerosols
- the particles range in size from 50 to 200 μm

Space sprays

- Examples: Room disinfectants, room deodorizers, and space insecticides.
- particle size usually below 50 μm

9

9

# The Aerosol Principle

An Aerosol product consists of the following component parts:

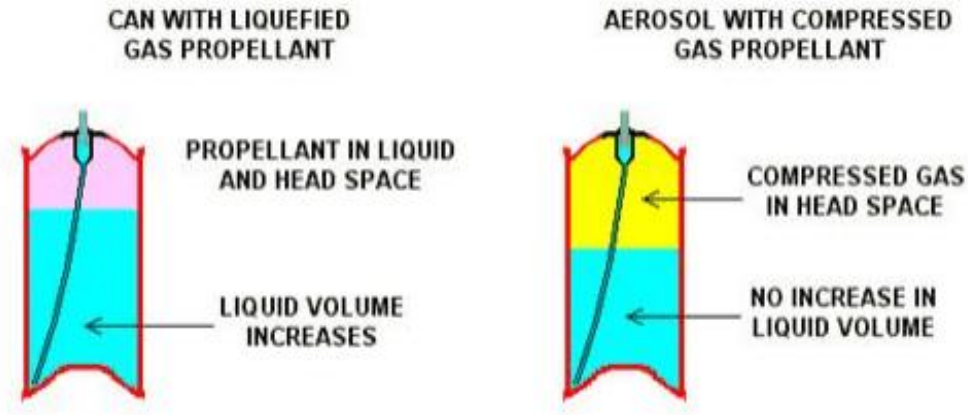
1) Product concentrate
   - active ingredient &
   - Additives (such as, antioxidants, surface- active agents, and solvents)
2) Propellant
   - liquefied gas or a mixture of liquefied gases or
   - compressed gases (carbon dioxide, nitrogen, and nitrous oxide $N_2O$)

➢ When the propellant is a liquefied gas or a mixture of liquefied gases, it frequently serves the dual role of propellant and solvent or vehicle for the product concentrate.

3) Container
4) Valve and actuator

10

10




1) Liquefied gases

2) Compressed gases

11

11

# Propellant

The propellant is responsible for

- developing the proper pressure within the container
- expelling the product when the valve is opened
- the atomization or form production of the product

Types of propellants:

**1) Liquefied gases**

a. Fluorinated hydrocarbons
b. Hydrocarbons

**2) Compressed gases**

12

12

# Propellant

**Fluorinated hydrocarbons**

- Non-inflammable
- The include chloroflurocarbons (CFCs) and Hydrofluroalkanes (HFAs) {= Hydroflurocarbons (HFCs)}.
- They have low toxicity, although some individuals might be sensitive and develop cardiotoxic effect.
- The requirement of the Montreal Protocol in 1989 for the replacement of chlorofluorocarbon (CFC) propellants in pressurised metered-dose inhalers with hydrofluoroalkanes (HFAs), because of the **ozone-depleting properties of CFCs.**



13

# Propellant

**Fluorinated hydrocarbons**

- The FDA has the authority to exempt from the prohibition of CFCs when there is sufficient evidence showing that:
  - (a) there are no technically feasible alternatives to the use of a CFC propellant in the product;
  - (b) the product provides a substantial health or other public benefit unobtainable without the use of the CFC;
  - (c) the use does not involve a significant release of CFCs into the atmosphere or, if it does, the release is warranted by the benefit conveyed.

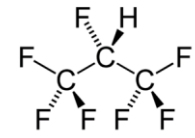


14

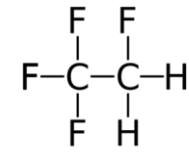
# Propellant

**Fluorinated hydrocarbons**

- The most commonly used CFCs are:
  - Trichloromonofluoromethane ($CCl_3F$ propellant 11)
  - Dichlorodifluoromethane ($CCl_2F_2$ propellant 12)
  - Dichlorotetrafluoroethane ($C_2Cl_2F_2$) propellant 114)
- The most commonly used HFAs are:
  - Tetrafluroethane ( $CH_2FCF_3$ propellant 134a)
  - Heptafluoropropane ($C_3HF_7$ propellant 227)



(propellant 227)



(propellant 134a)

15

15

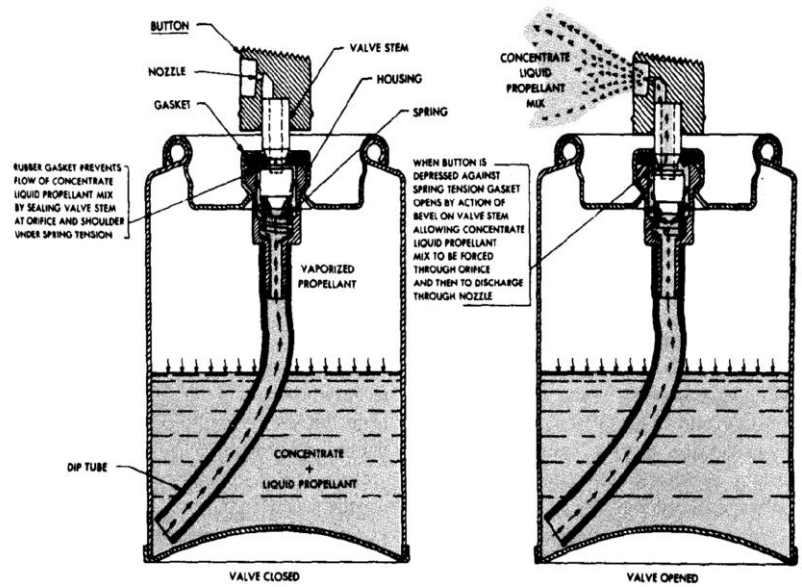



**FIGURE 14.12** Cross-section sketches of contents and operation of a typical two-phase aerosol system. (Courtesy of Armstrong Laboratories, , Division of Aerosol Techniques.)

16

16

# Propellant

## Fluorinated hydrocarbons

- The numerical designation which is explained as follows:
  - Saturated propellant are designated by three digits except when the first digit would be zero, then only two digits are used.
  - The first digit is one **less** than the number of carbon atoms in the molecule.(C-1)
  - The second digit is one **more** than the number of hydrogen atoms in the molecule (H+1)
  - The third digit represents the number of flourine atoms in the molecule.(no. of F)
  - Isomers of a compound have the same number, the most symmetric being indicated by the number alone and degrees of asymmetry are designated by the letters a, b, c, and so on., following the number.

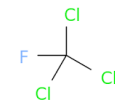
17

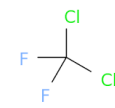
17

**TABLE 14.5 PHYSICAL PROPERTIES OF SOME FLUORINATED HYDROCARBON PROPELLANTS**

| CHEMICAL NAME | CHEMICAL FORMULA | NUMERIC DESIGNATION | VAPOR PRESSURE[a] 70°F | BOILING POINT (1 ATM) °F | LIQUID DENSITY (g/mL) 7( |
|---|---|---|---|---|---|
| Trichloromonofluoromethane | $CCl_3F$ | 11 011 | 13.4 | 74.7 | 1.485 |
| Dichlorodifluoromethane | $CCl_2F_2$ | 12 012 | 13.4 | 74.1 | 1.485 |
| Dichlorotetrafluoroethane | $CClF_2CClF_2$ | 114 | 21.6 | 38.4 | 1.468 |
| Chloropentafluoroethane | $CClF_2CF_3$ | 115 | 17.5 | −37.7 | 1.29 |
| Monochlorodifluoroethane | $CH_3CClF_2$ | 142[b] | 43.8 | 15.1 | 1.119 |
| Difluoroethane | $CH_3CHF_2$ | 152[b] | 76.4 | −11.2 | 0.911 |
| Octafluorocyclobutane | $CF_2CF_2CF_2CFM_2$ 12 | C318 | 40.1 | 21.1 | 1.513 |

[a]Pounds per square inch absolute, equal to psig + 14.7.



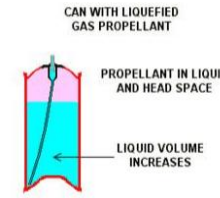




The first digit is C-1)
The second digit is (H+1)
The third digit is flourine atoms in the molecule.(no. of F)
Degrees of asymmetry are designated by the letters a, b, c,

18

18

# Propellant



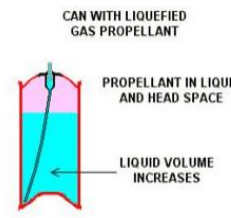

- Fluorinated hydrocarbons are gases at room temperature.
- They may be liquefied by:
  - cooling below their boiling point or (temperature)
  - compression at room temperature. (pressure)
- Both of these methods for liquefying gases are employed in aerosol manufacturing.
- Equilibrium is established between the portion of propellant that remains liquefied and that which vaporizes and occupies the upper portion of the aerosol container.
- The vapor phase exerts pressure that upon actuation of the aerosol valve forces the liquid phase up the dip tube and out of the orifice of the valve into the atmosphere.

19

19

# Propellant

- As the liquid phase is removed from the container, equilibrium between the propellant remaining liquefied and that in the vapor state is reestablished.
- Thus, the pressure within the aerosol package remains virtually constant, and the product may be continuously released at an even rate and with the same propulsion (force).
- However, when the liquid reservoir is depleted, the pressure may not be maintained, and the gas may be expelled from the container with diminishing pressure until it is exhausted.




20

20

# Propellant

- Blends of the various liquefied gas propellants are generally used in pharmaceutical aerosols:
  - to achieve the desired vapor pressure
  - to provide the proper solvent features for a given product.
- Some propellants are eliminated from use in certain products because of their reactivity with other formulative materials or with the proposed container or valve components.
- For instance, trichloromonofluoromethane tends to form free hydrochloric acid (HCl) when formulated with systems containing water or ethyl alcohol, the latter a commonly used cosolvent in aerosol systems.
- The free HCl not only affects the efficacy of the product but also corrodes some container components.



21

# Propellant

**Hydrocarbons**

- The most commonly used are Propane, butane, and isobutane.

**Advantages**:

- Low toxicity in comparison with haloginated hydrocarbons
- Lower cost
- Ability to dissolve wide range of medicaments
- Lack of odor

**Disadvantages**:

- Flammable



22

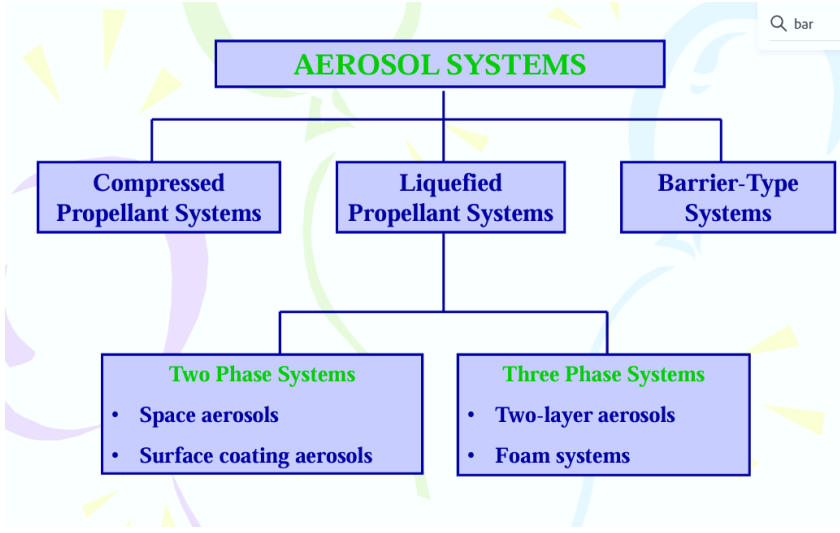
# Propellant

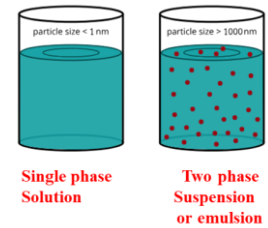
## Compressed gases

- These include: Carbon dioxide, nitrogen and nitrous oxide ($N_2O$).
- They possess little expansion power
- They are used in the gaseous rather than liquefied state.
- A drop of pressure is noted during the use of compressed-gas aerosols.



23






24

## Aerosol Systems

- The pressure of an aerosol is critical to its performance.
- It can be controlled by
  - the type and amount of propellant
  - the nature and amount of product concentrate.
- Thus, each formulation is unique unto itself, and a specific amount of propellant to be employed in aerosol products **cannot be firmly stated**



25

## Aerosol Systems

- Space sprays generally are released with greater pressure and operate at 30 to 40 psig at 21°C and may contain as much as 85% propellant.
- **Pounds per square inch (PSI)g pressure gauge at ambient pressure gauge**
- Surface aerosols commonly contain 30 to 70% propellant with pressures between 25 and 55 psig at 21°C.
- Foam aerosols usually operate between 35 and 55 psig at 21°C and may contain only 6 to 10% propellant.



26

## Aerosol Systems -Foam

- Foam aerosols may be considered to be emulsions, because the liquefied propellant is partially emulsified with the product concentrate.
- Because the fluorinated hydrocarbons are nonpolar, they do not dissolve in the aqueous formulation.
- The use of surfactants or emulsifiers in the formulation encourages the mixing of the two components to enhance the emulsion.
- Shaking of the package prior to use further mixes the propellant throughout the product concentrate.
- When the aerosol valve is activated, the mixture is expelled to the atmosphere, where the propellant globules vaporize rapidly, leaving the active ingredient in the form of a foam.



27

## Aerosol Systems

- The physiologic effect of the propellant must also be considered in formulating an aerosol to ensure safety of the product in its intended use.
- Even though an individual propellant or propellant blend and the active ingredient of a formulation are nontoxic when tested individually, the use of the combination in aerosol form may have undesirable features.
- For instance, when an active ingredient ordinarily used in a nasal or oral spray is placed in a fine aerosol mist, it may reach deeper into the respiratory tract than desired and result in irritation.
- The influence of the aerosol form of the drug on the recipient tissue membranes must be evaluated for irritating effects and changes in the absorption of the drug from the site of application.



28

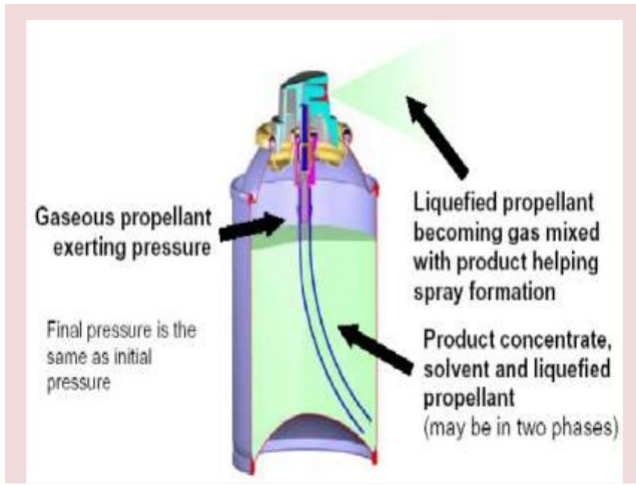
# Aerosols systems and formulation

**1) Liquefied Gas system: Two Phase systems**

- The simplest aerosol system
- It consist only of a vapor phase and a liquid phase
- The liquid phase is a solution of the active ingredient in the liquid propellant, or liquid propellant plus solvent if the drug is not soluble in the propellant alone.
- The particle size is affected by
  1. Types and ratios of propellants used
  2. The concentration of nonvolatile components
  3. Initial droplet size
  4. Rate of droplet evaporation



29



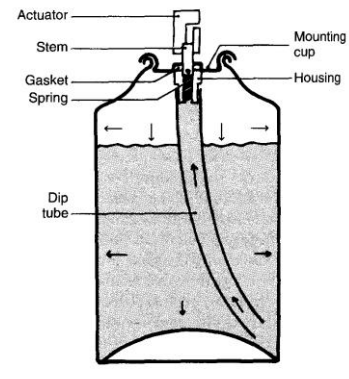




**FIGURE 14.13** Valve assembly components.



30

# Aerosols systems and formulation

**1) Liquefied Gas system: Two Phase systems**

- Increasing the proportion of a relatively low-boiling-point propellant (such as propellant 12 ) will produce a rapidly evaporating dry spray, and consequently fine particles of sizes as low as 1 micrometer.

1. Increasing the proportion of propellants with relatively high boiling point (such as propellant 11) and introducing solvents such as ethanol, propylene glycol, glycerol, acetone or ethyl acetate (which decrease the vapor pressure) or
2. increasing the proportion of active ingredient will result in spray much wetter and coarser (particle size 50 –200 micrometer)

31

31

# Aerosols systems and formulation

**2) Liquefied Gas System: Three Phase systems**

- A three-phase system results when some of the components of aerosol are immiscible with, or insoluble in, the liquefied propellant.

- The non-vapor phases can be
  - two liquid layers,
  - a dispersion or suspension,
  - an emulsion.

32

32

# Aerosols systems and formulation

**Two layer systems:**

- These systems typically comprise three layers: an aqueous solution of the active ingredient, the liquid propellant and the vapor propellant.
- When the valve is opened, the pressure of the vapor forces the aqueous liquid up the dip tube.
- The use of water with another solvent (ex. ethanol) gives a system which , when shaken forms a dispersion of the active ingredient plus solvent in the propellant

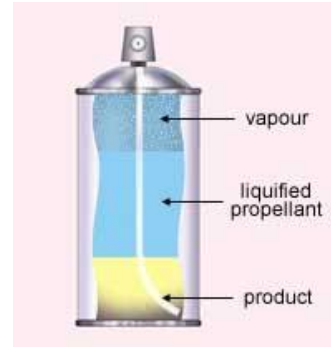
33

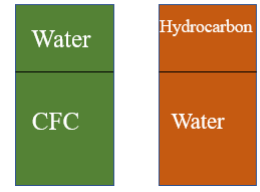
33

# Aerosols systems and formulation

**Two layer systems:**

- If CFC propellant is used (more dense than water) the propellant layer lies beneath the aqueous layer.
- hydrocarbon propellants in contrast are less dense than water.
- To avoid expulsion of the reservoir of liquefied propellant, the dip tube must extend only within the aqueous phase (product concentrate) and not down into the layer of liquefied propellant.




34

34

# Aerosols systems and formulation

***Suspension systems***

- The finely-divided active ingredient is suspended in the liquefied propellant.
- Aggregation (agglomeration) must be controlled since it may cause valve blockage and hence inaccuracy of dose.
- The physical stability can be increased (aggregation can be reduced) by:
  - Controlling moisture content of the system below 300 ppm (0.03%)
  - Using a derivative of active drug that is poorly soluble in propellant
  - Having a propellant with similar density to suspended drug so that settling rate is reduced.
  - Using particles in the range of 1 –5 microns.
  - The inclusion of surfactant or dispersing agent (lubricants for particles passing through the valve orifice).

$$u = \frac{d^2 g (\rho_s - \rho_f)}{18 \eta}$$



35

# Aerosols systems and formulation

***Emulsion systems (Foam systems)***

- In an emulsion system, the propellant is incorporated into the emulsion and the product is dispensed as a stable or quick breaking foam, depending on the formulation.

1) Aqueous stable foam

- The liquefied propellant constitutes the internal phase and water the external phase of the emulsion (O/W)
- The total amount of propellant is typically 3 - 5 % w/w.
- As the amount of propellant increases, a stiffer and dryer foam is produced.



36

# Aerosols systems and formulation

***Emulsion systems (Foam systems)***

2) Non aqueous stable foams

- These may be formulated through the use of various glycols such as PEGs as external phase instead of water.(O/PEG)
- The most effective emulsifying agent in such systems was found to be the class of glycol esters (ex. Propylene glycol monostearate).

3) Quick breaking foams

- In this system the propellant is the external phase.(W/O)
- When dispensed the product is emitted as a foam which then collapses into a liquid.
- The surfactant may be of the nonionic, anionic, or cationic type.



37

# Aerosols systems and formulation

**3) Compressed Gas Systems**

- These systems can be used to dispense a product such as a semisolid, a wet spray, or a foam.
- Nitrogen is insoluble and immiscible with product concentrate, while carbon dioxide and nitrous oxide are slightly miscible.
- The use of gases that are insoluble in the product concentrate, as is nitrogen, will result in emission of a product in essentially **the same form as it was** placed in the container (ex. Semisolid).
- The gases that are slightly soluble in the concentrate can cause **some change in product** on emission from container and are used in dispensing foams.

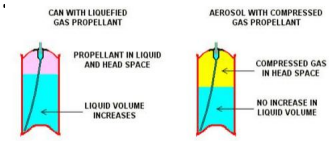


38

# Aerosols systems and formulation

**3) Compressed Gas Systems**

- Advantages of nitrogen as a propellant:
  - inert behavior toward other formulative components
  - protective influence on products subject to oxidation.
  - odorless and tasteless gas and thus does not contribute adversely to the smell or taste of a product.
- Unlike aerosols prepared with liquefied gas propellants, compressed gas—filled aerosols have no reservoir of propellant.
- Thus higher gas pressures are required in these systems, and the pressure in these aerosols diminishes as the product is used.




39

39

## Aerosol Container and Valve Assembly

- The effectiveness of a pharmaceutical aerosol depends on achieving the proper combination of formulation, container, and valve assembly.
- The formulation must not chemically interact with the container or valve components so as to interfere with the stability of the formulation or with the integrity and operation of the container and valve assembly.
- The container and valve must be capable of withstanding the pressure required by the product, it must resist corrosion, and the valve must contribute to the form of the product to be emitted.

40

40

# Choice of container material

Container choice is dependent on different factors such as:

- the pressure of the system
  - Metal containers are generally used at higher pressures than glass
- compatibility with formulation components such as:

•Solvent used inside the container

•Metal containers for aqueous preparations must be internally coated (except stainless steel)

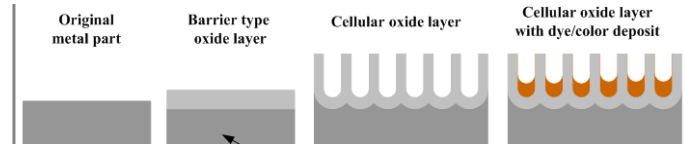
•Absolute ethanol attacks aluminum, however this attack can be inhibited by adding 2-3% water or by anodizing the container.(decorative, durable, corrosion-resistant, anodic oxide finish)

•pH of the product

•Epoxy and vinyl lining are suitable for low pH preparations

•the interest in aesthetic appeal

•the cost




41



# Containers

**Tinplate containers**

The tinplate (Sn) container consists of a sheet of steel plate that has been electroplated on both sides with tin.

Advantages: light, cheap, durable

**Aluminum containers**

- Greater resistance to corrosion than tinplate
- Less danger of incompatibility
- However. it is corroded by pure water and pure ethanol.

❑For tinplate and aluminum containers, added resistance can be obtained by coating the inside of the container with organic materials such as epoxy, vinyl or phenolic resins.

42

## Containers

**Stainless steel containers**

- They have been used for inhalation aerosols
- They are extremely strong and resistant to corrosion
- They do not require coating generally
- High cost

**Plastic containers**

- They have not been used extensively for aerosol containers.
- Polyethylene-terephthalate have been used commercially for a non-pharmaceutical presentation

43

43

## Containers

**Glass containers**

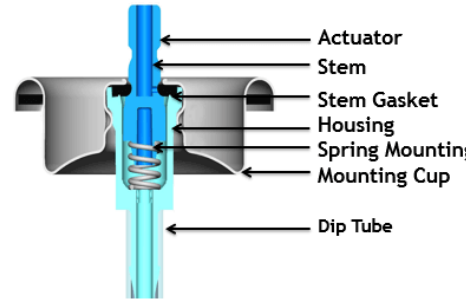
- They are available with or without plastic outer coatings (to increase their impact resistance).
- The use of glass is limited to those products having lower pressure and lower percentage of propellant
- When the total pressure of an aerosol system is below 25 psig and no more than 50% propellant is used, glass containers are considered quite safe.
- It is used in perfumes, colognes, cosmetics and pharmaceuticals.


44

44

# Valve assembly

- Pharmaceutical aerosols may be dispensed as spray, foam, solid stream. They may or may not need dosage control.
- The function of valves is:
  - To deliver the content in the desired form and rate
  - To deliver a proper amount of a medication (in the case of metered dose valves)




45

45

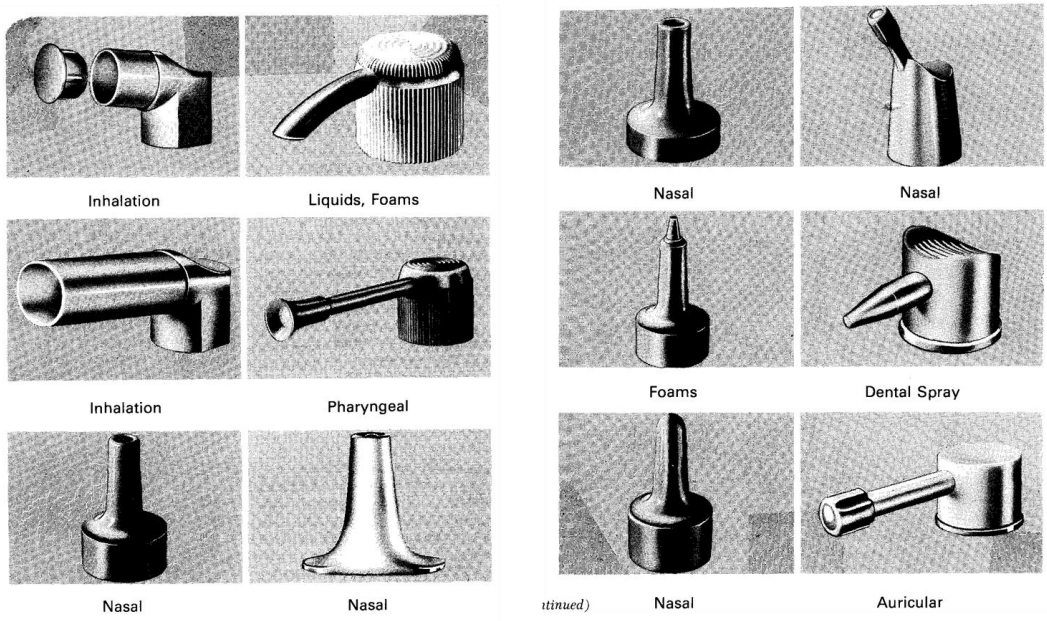
# Valve parts

**Actuator**

- It is the button the user presses to activate the valve assembly for emission of the product.
- The design of the inner chamber and size of the emission orifice of the actuator contribute to the physical form (mist, coarse spray, solid stream, or foam) in which the product is discharged.
- The type and quantity of propellant used and the actuator design and dimensions control the particle size of the emitted product.
- Larger orifices (and less propellant) are used for products to be emitted as foams and solid streams than for those intended to be sprays or mists.

46

46


Inhalation
Liquids, Foams
Nasal
Nasal
Inhalation
Pharyngeal
Foams
Dental Spray
Nasal
Nasal
Nasal
Auricular

47

47

48

48

# Valve parts

**Stem**

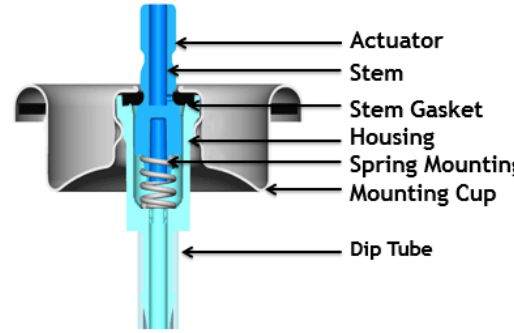
- Supports the actuator and delivers the formulation in the proper form to the chamber of the actuator.

**Gasket**

- Placed tightly with the stem, pre vents leakage of the formulation when the valve is closed.

**Spring**

- Holds the gasket in place and is the mechanism by which the actuator retracts when pressure is released, returning the valve to the closed position.






49

# Valve parts

**Mounting cup**

- Attached to the aerosol can or container, holds the valve in place. The underside of the mounting cup is exposed to the formulation (compatibility criteria similar to the inner part of the container).

**Housing**

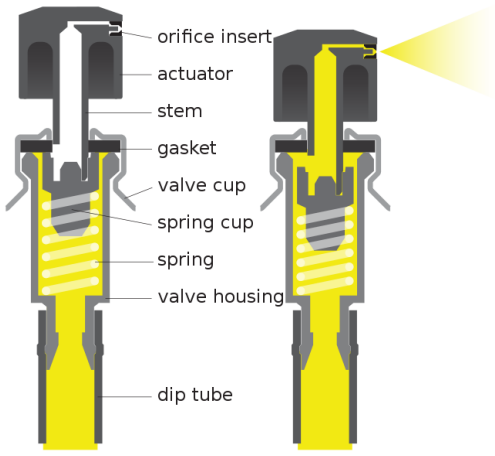
- Directly below the mounting cup, the housing links the dip tube and the stem and actuator. With the stem, its orifice helps to determine the delivery rate and the form in which the product is emitted.

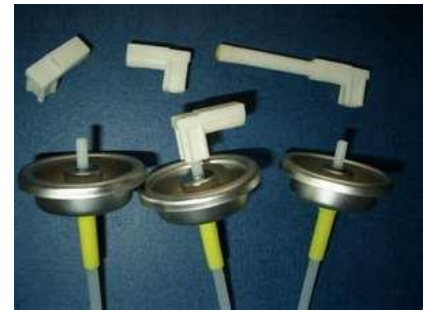
**Dip tube**

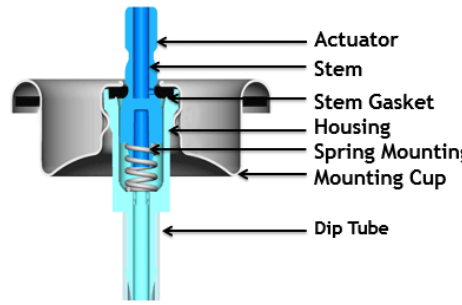
- Extends from the housing down into the product; brings the formulation from the container to the valve. The viscosity of the product and its intended delivery rate dictate to a large extent the inner dimensions of the dip tube and housing for a particular product.



50







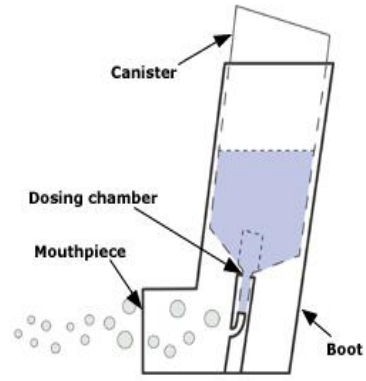

51

## Metered Dose Inhalers

- Metering valves are employed when the formulation is a potent medication, as in inhalation therapy.
- In these metered valve systems, the amount of material discharged is regulated by an auxiliary valve chamber by virtue of its capacity or dimensions.
- A single depression of the actuator causes evacuation of this chamber and delivery of its contents.
- The integrity of the chamber is controlled by a dual valve mechanism.
- When the actuator valve is closed, the chamber is opened to the content and vice versa.



52


53

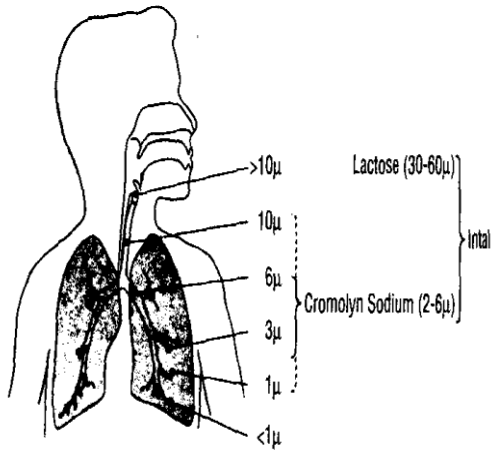
53

## Metered Dose Inhalers

- The USP contains a test to determine quantitatively the amount of medication from a metered valve.
- The effectiveness of delivering medication to the lower reaches of the lungs for local or systemic effects depends in part on the particle size of the inhaled drug.
- Breathing patterns and the depth of respiration also play important roles in the deposition of inhaled aerosols to the lungs.
- Analysis of dose uniformity, particle size distribution patterns, and the respirable fractions of aerosol-delivered particles are areas of research in developing aerosol products for optimal oral therapy.

54

54



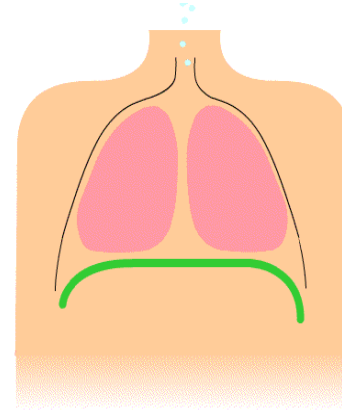



**FIGURE 14.11** Relationship of INTAL (cromolyn sodium, Fisons) particle size to airway penetration. (Courtesy of Fisons Corporation.)

55

55

## Metered Dose Aerosols

- A unique translingual aeroso1 formulation of nitroglycerin (Nitrolingual Spray, Rhone Polenc Rorer) Permits a patient to spray droplets of nitroglycerin onto or under the tongue for acute relief of an attack or for prophylaxis of angina pectoris due to coronary artery disease.
- The product is not to be inhaled.
- At the onset of an attack, two metered spray emissions, each containing 0.4 mg of nitroglycerin, are administered.


56

56

# Filling Operations

**Cold Filling**

- In the cold method, both the product concentrate and the propellant must be cooled to -34.5°C to -40°C to liquefy the propellant gas.
- After the chilled product concentrate has been quantitatively metered into an equally cold aerosol container, the liquefied gas is added.
- Alternatively, the concentrate and the propellant are chilled together and the mixture added to the container.
- The heavy vapors of the cold liquid propellant generally displace the air in the container.

57

57

# Filling Operations

**Cold Filling**

- The temperature of component must be carefully controlled to prevent loss due to evaporation.
- When sufficient propellant has been added, the valve assembly is inserted and crimped into place.
- Because of the low temperatures required, aqueous systems cannot be filled by this process, since the water turns to ice.
- For nonaqueous systems, some moisture usually appears in the final product due to the condensation of atmospheric **moisture** within the cold containers.

58

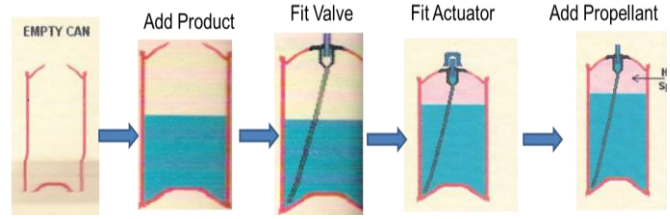
58

# Filling Operations -Pressure Filling

By the pressure method, the product concentrate is quantitatively placed in the aerosol container, the valve assembly is inserted and crimped into place, and the liquefied gas, under pressure, is metered into the valve stem from a pressure burette.

The desired amount of propellant is allowed to enter the container under its own vapor pressure. When the pressure in the container equals that in the burette, the propellant stops flowing.

Additional propellant may be added by increasing the pressure in the filling apparatus through the use of compressed air or nitrogen gas.



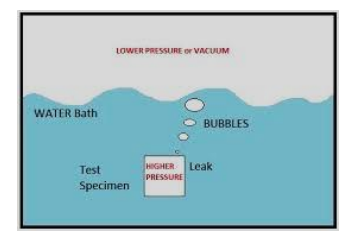

59

59

# Filling Operations

## Pressure Filling

- The trapped air in the package may be ignored if it does not interfere with the quality or stability of the product, or it may be evacuated with a special apparatus.
- After the container is filled, the valve actuator is tested for proper function.
- Pressure filling is used for most pharmaceutical aerosols. It has two advantages over cold filling:
  - less danger of moisture contamination of the product,
  - less propellant is lost in the process.



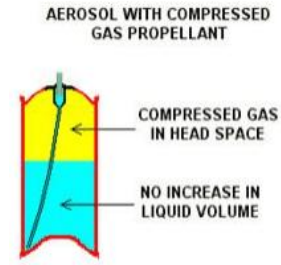

60

60

# Filling Operations

## Pressure Filling

- When compressed gases are employed as the propellant the procedure is similar but:
  - The compressed gas is then passed into the container through a **pressure-reducing valve** attached to the gas cylinder;
  - For gases like carbon dioxide and nitrous oxide, which are slightly soluble in the product concentrate, the container is manually or mechanically shaken during the filling operation to achieve the desired pressure in the head space of the aerosol container.




$$V \propto \frac{1}{P}$$

61

61

# Bag on Valve (BOV) Aerosols

- In BOV aerosols, the product is placed inside a laminated aluminum bag while the propellant is filled in the space between bag and can.
- The product is dispensed by the propellant simply squeezing the bag when the spray button is pressed.
- Because of the separation between product and propellant, BOV can be used with compressed air or nitrogen.


62

62

# Bag on Valve (BOV) Aerosols

Advantages of BOV aerosols:

- Used with eco-friendly air or nitrogen
- Avoid use of liquefied propellants:
  - ✓ avoid product concentrate-propellant interaction
  - ✓ avoid toxicity and flammability concerns
  - ✓ reduce cost
- Up to 100% product emptying
- Longer shelf life


63

63

# Testing the Filled Aerosol Containers

After filling by either method, the aerosol container is tested for :

- leaks or weakness in the valve assembly or container (under various environmental conditions)
- The valve discharge rate

This is determined by discharging a **portion** of the contents of a previously weighed aerosol during a period, and calculating, by the **difference in weight**, the grams of contents discharged per unit of time.


- spray patterns (intermittent or continuous)
- particle size distribution of the spray,
- accuracy and reproducibility of dosage when using metered valves.

64

64

## Packaging, Labeling, and Storage

- The pharmaceutical aerosols is actually packaged as part of the manufacturing process.
- Most aerosol products have a protective cap or cover that fits snugly(tightly) over the valve and mounting cup:
  1. for protecting the valve against contamination with dust and dirt.
  2. to prevent accidental activation of the valve assembly
  3. serves a decorative function.
- Most aerosols have the manufacturer's label printed directly on the container or on firmly affixed paper.

65

65

## Packaging, Labeling, and Storage

- Aerosols have usual and special labeling requirements for use and storage:
  - Labels must warn users not to puncture pressurized containers, not to use or store them near heat or an open flame, and not to incinerate them. (Exposure to temperatures > 49°C may burst an aerosol container).
  - Storage between 15°C and 30°C (Most medications in aerosol containers are intended for use at ambient room temperatures.
  - When the canisters are cold, less than the usual spray may result.
  - This may be particularly important to users of metered-dose inhalation sprays.)
  - Pharmaceutical aerosols special labels: shaking before use, holding at the proper angle and/or distance from the target; and special detailed instructions for inhaler devices.


66

66

# Topical Aerosols

- Aerosol packages for use on the skin include:
  - the anti-infective agents: povidone iodine, tolnaftate, and thimerosal;
  - the adrenocortical steroids: betamethasone dipropionate and valerate, dexamethasone, and triamcinolone acetonide;
  - the local anesthetic dibucaine hydrochloride.
- The topical aerosols allows the preparation to be applied to the desired surface area without the use of the fingertips.
- Disadvantages to the use of topical aerosols:
  - the difficulty in applying the medication to a small area
  - the greater expense associated with the aerosol package.

67

67

# Vaginal and Rectal Aerosols

- Aerosol foams containing estrogenic substances and contraceptive agents are commercially available.
- The foams are used intravaginally in the same manner as for creams. The aerosol package contains an inserter that is filled with foam and the contents placed in the vagina through activation of the plunger.
- The foams are generally o/w emulsions resembling light creams.
- Some commercial rectal foams use inserters. One such product, ProctoFoam (Reed & Cam- rick), contains pramoxine hydrochloride to relieve inflammatory anorectal disorders.



68

68

# Dry powder inhalers

- In dry powder inhaler (DPI) systems, drug is inhaled as a cloud of fine particles.
- The drug may be:
  - preloaded in an inhalation device
  - filled into hard gelatin capsules or foil blister discs which are loaded into a device prior to use.


69

69

# Dry powder inhalers

**Advantages**

- DPIs are propellant-free and usually do not contain any excipient, other than a carrier, which is usually lactose.
- They are breath actuated, avoiding the problems of inhalation/actuation coordination encountered with pressurized metered-dose inhalers (pMDI).
- DPIs can deliver larger drug doses than pMDIs, which are limited by the volume of the metering valve and the maximum suspension concentration that can be employed without causing valve clogging.

70

70

# Dry powder inhalers

**Disdvantages**

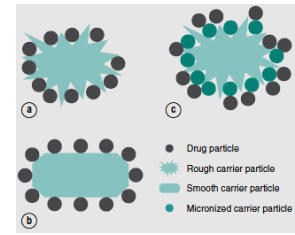
- Liberation of powders from the device and the deaggregation of particles are limited by the patient's ability to inhale, which in the case of respiratory disease may be impaired.
- DPIs are exposed to ambient atmospheric conditions, which may reduce formulation stability. For instance, elevated humidity may cause powders to aggregate.
- DPIs are generally less efficient at drug delivery than pMDIs, such that twice the dose is often required for delivery from a DPI compared to the equivalent pMDI.



71

# Formulation of dry powder inhalers

- Drug particles of a suitable size (preferably less than 5 µm), for use in inhalation systems are produced by:
  - micronization
  - spray drying
  - spray freeze drying
  - Supercritical fluid technology



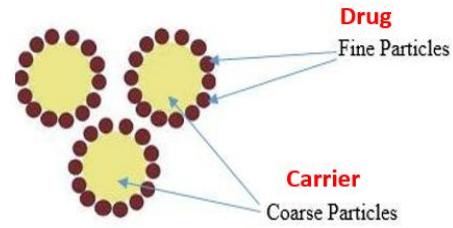

- The small particles have poor flow properties because of their static, cohesive and adhesive nature.
- The flowability of a powder is affected by physical properties, including particle size and shape, density, surface roughness, hardness, moisture content and bulk density.



72

# Formulation of dry powder inhalers

- To improve their flow properties, poorly flowing drug particles are generally mixed with larger 'carrier' particles (median size usually 30–150 µm) of an inert excipient, usually lactose (α-lactose monohydrate).
- Drug and carrier particles are mixed to produce an ordered mix in which the small drug particles attach to the surface of the larger carrier particles.
- This not only improves liberation of the drug from the inhalation device by improving powder flow, but also improves the uniformity of capsule or device filling.




73

73

# Formulation of dry powder inhalers

- Once liberated from the device, the turbulent air flow generated within the inhalation device should be sufficient for the deaggregation of the drug/ carrier aggregates.
- The larger carrier particles impact in the throat, whereas smaller drug particles are carried in the inhaled air deeper into the respiratory tract.
- The success of DPI formulations depends on the adhesion of drug and carrier during mixing and filling of devices or hard gelatin capsules, followed by the ability of the drug to detach from the carrier during inhalation, such that free drug is available to penetrate to the peripheral airways.

74

74

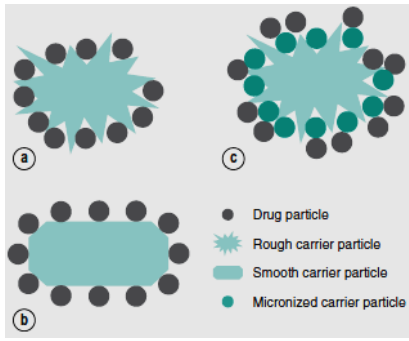
# Formulation of dry powder inhalers

- **Adhesion and detachment** will depend on:
  - the morphology of the particle surfaces
  - surface energies

  which may be influenced by the chemical nature of the materials involved and the nature of powder processing.
- A ternary mix may be employed to control adhesion. Thus, fine particle size lactose can be added to conventional carrier lactose, to occupy the high energy sites on the larger carrier particles.
- Only low energy sites remain for drug-carrier interaction, enhancing the detachment of drug particles during inhalation of the formulation.
- Likewise, materials such as leucine and magnesium stearate may be included in formulations to modify the adhesion properties between drug and carrier particles.

75

75



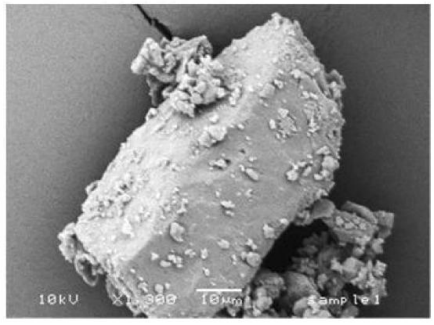





**Figure 4**
Types d'inhalateurs de poudre sèche disponibles en Suisse

76

76