Why and why not?

- Advantages:
  - Less systemic toxicity
  - More rapid onset of medication
  - Delivery to target of action
  - Higher concentrations available in the lung
- Disadvantages:
  - Time and effort consuming
  - Limitation of delivery device

What are the Inhalant drugs?

- **Antiallergic agents**
  - Budesonide
  - Cromolyn sodium
- **Bronchodilators**
  - Ventolin nebules (βagonist)
  - Bricanyl solution (βagonist)
  - Atrovert nebulizer solution (anti-cholinergic)

Inhalant drugs

- **Mucolytic agents**
  - Acetein (Acetylcysteine)
  - Mistabron (Mesna)
- **Antimicrobials**
  - Tobramycin
  - Pentamidine
  - Ribavirin
  - Amphotericin

Inhalant drugs

- **Immune modulators**
  - Cyclosporine
  - Interferon α
  - Interferon γ
- **Vaso-active**
  - Prostacyclin
  - Nitric oxide

Inhalant drugs

- **Anesthetics**

  Opioids

- **Other**

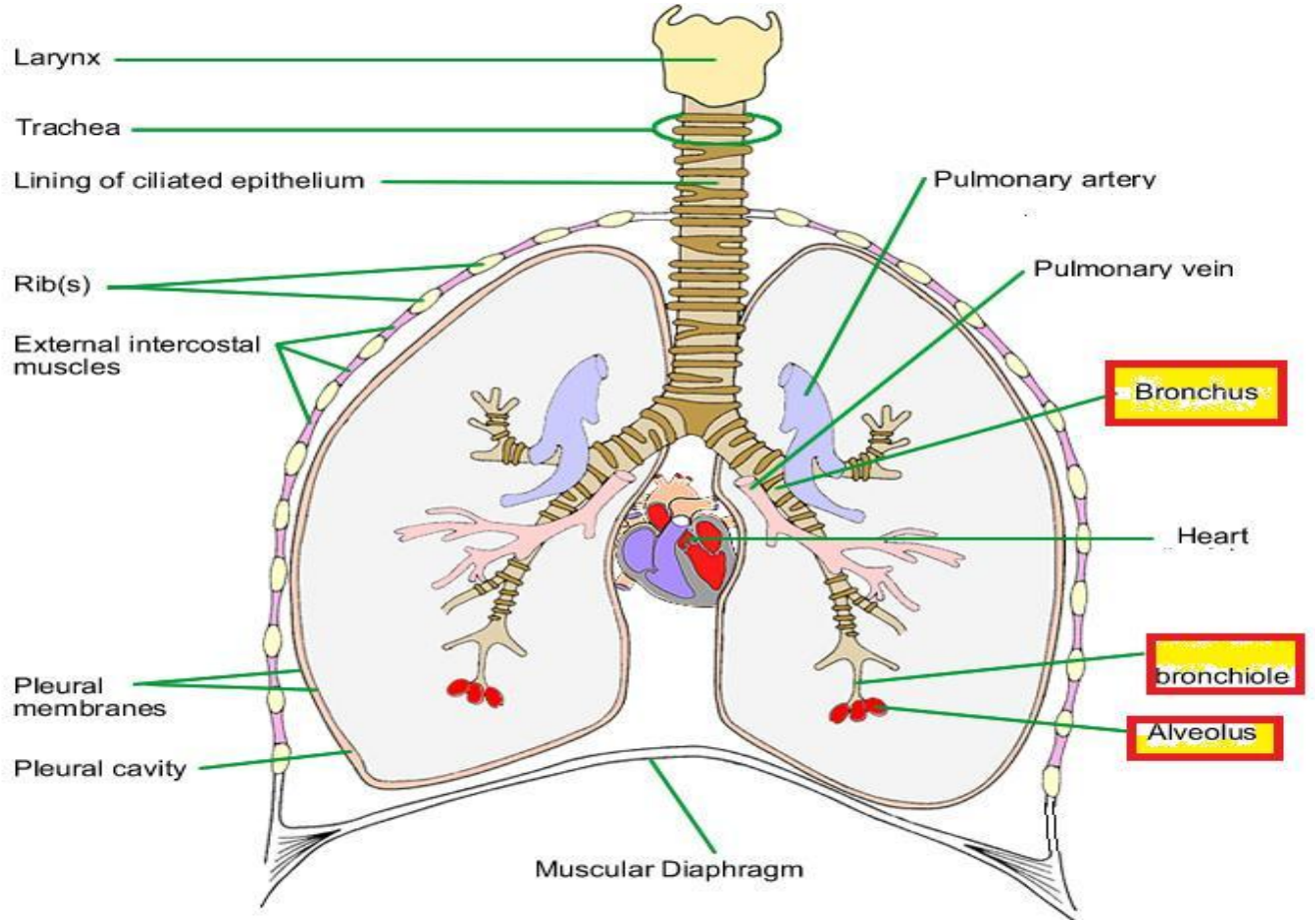
  Granulocyte-Macrophage Colony-Stimulating Factor

  Surfactant

  Interleukin II

  Gene therapy vectors

Regions of Drug absorption in the Pulomonary Epithelium



Respiratory tract characteristics

- Large surface area, good vascularization, immense capacity for solute exchange, ultra-thinness of the pulmonary epithelium
- Conducting region :

  Nasal cavity, nasopharynx, bronchi, bronchioles
- Respiratory region :

  respiratory bronchioles, alveolar ducts and sacs

Particle Size

- MMAD: mass median aerodynamic diameter

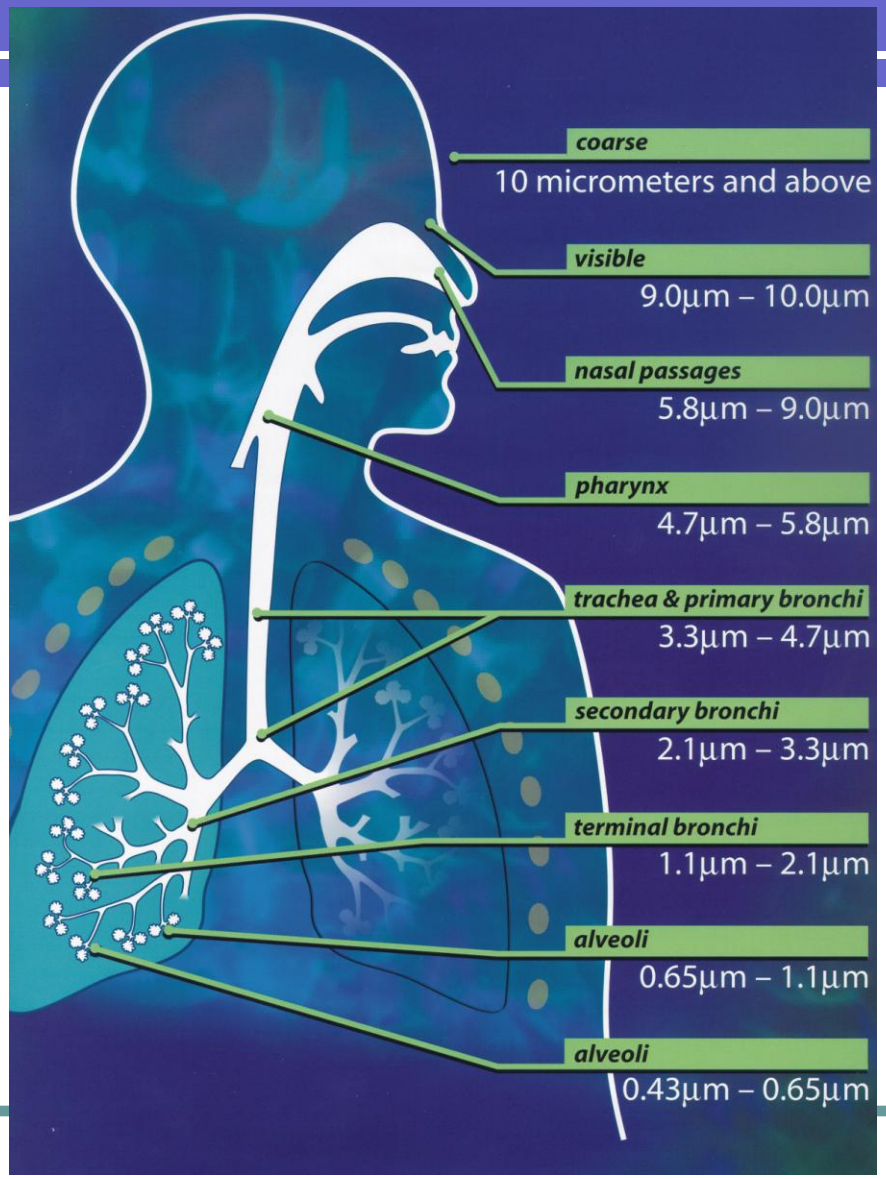
  MMAD <1μm: exhaled

  MMAD 1~5μm: target

  MMAD >5μm: oropharynx

- Strict control of MMAD of the particles ensures the reproducibility of aerosol deposition and retention.

Ideal Particle Size



Particle Size

Table 2. Inhalational Particle Targeting

Anatomic Site of Respiratory Tract	Particle Size for Best Deposition Efficiency (μm)	Breathing Pattern Optimal for Targeting
Orolaryngeal	6-8	Rapid, shallow breathing
Tracheobronchial	4-6	Slow, deep breathing
Alveolar	2-4	Slow, deep breathing

NOTE. Data from Schulz.[67]

Device for Inhalation Therapy

- Selections of device include：
  - 1.Nebulizer: small volume,
    large volume, ultrasonic, pneumatic…
  - 2.Metered dose inhaler, MDI
  - 3.Dry powder inhaler, DPI

Metered-dose inhalers

- A liquid propellant
- A metering valve that dispenses a constant volume of a solution or suspension of the drug in the propellant.
- Inhalation technique is critical for optimal drug delivery – Actuating a MDI out of synchrony may cause negligible lower airway delivery
- Mainly oropharyngeal deposition
- Protein denaturation

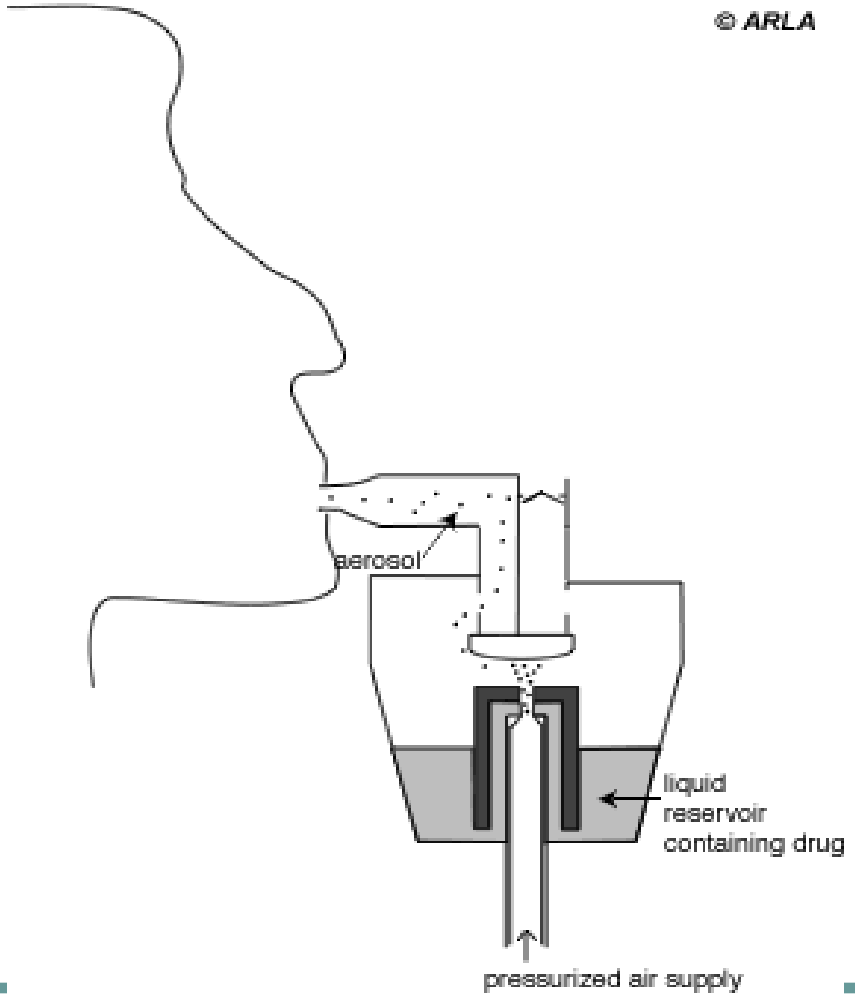
Dry powder inhalers

- No propellant
- Breath-activated, and patient coordination is not as important an issue.
- The drug is formulated in a filler and contained in a capsule that is placed in the device and punctured to release the powder.
- Proteins and macromolecules are more stable in dry powder form, this approach has been preferred for delivery of these compounds by the inhalational route

Nebulizers

- Patient cooperation and coordination is not as critical
- Commercially available nebulizers deliver 12% to 20% of the nebulized dose into the bronchial tree.
- Heterogeneous drops
- Protein denaturation

Nebulizers



Schematic of a vented, valved jet nebulizer.

AEROSOLS

- Are pressured dosage forms containing one or more active ingredients which upon actuation emit a fine dispersion of liquid and/or solid materials in gaseous medium

- 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.

Aerosol

Similarity with other dosage form:

Formulation

Product stability

Therapeutic efficacy

However they differ from most other dosage form:

Dependence upon the function of the container

Valve assembly

Propellant , the added component

Pressurized package

Pressure is applied to the aerosol system through the use of one or more propellants. Upon activation of the valve assembly of the aerosol, it is the pressure exerted by the propellant which forces the contents of the package out through the opening of the valve.

The physical form of the emitted is dependent upon the formulation of the product and and the type of valve employed

AEROSOLS

Aerosol packaging refers to products packaged in a pressurized container having a valve that permits controlled product release as required.

- Depending on the formulation, the valve system and the means of pressurizing, aerosols can be designed to release product in forms ranging from fine mists to heavy pastes.
- **Usages:** Personal care products(perfumes, shaving creams, deodorants, and hair sprays), household products (polishes, cleaners, and room fresheners), smaller market portions(paints, automotive products, and insect sprays), food(limited).
- The **advantage of aerosols**:

·their ability to disperse product into much finer particles that stayed suspended in the air for a much longer time than was available from other systems.

AEROSOLS

Aerosol Propellants.

-A typical aerosol product has a liquid phase and a vapor phase

The liquid phase: contains the product to be expelled.

The vapor phase: at an increased pressure and will force the product up the dip tube and expel it through the nozzle whenever the valve is opened.

- The product typically occupies about 75%, but never more than 92.5%, of the available space.
- Well-designed aerosol containers will deliver 95% or better of the contained product.

AEROSOLS

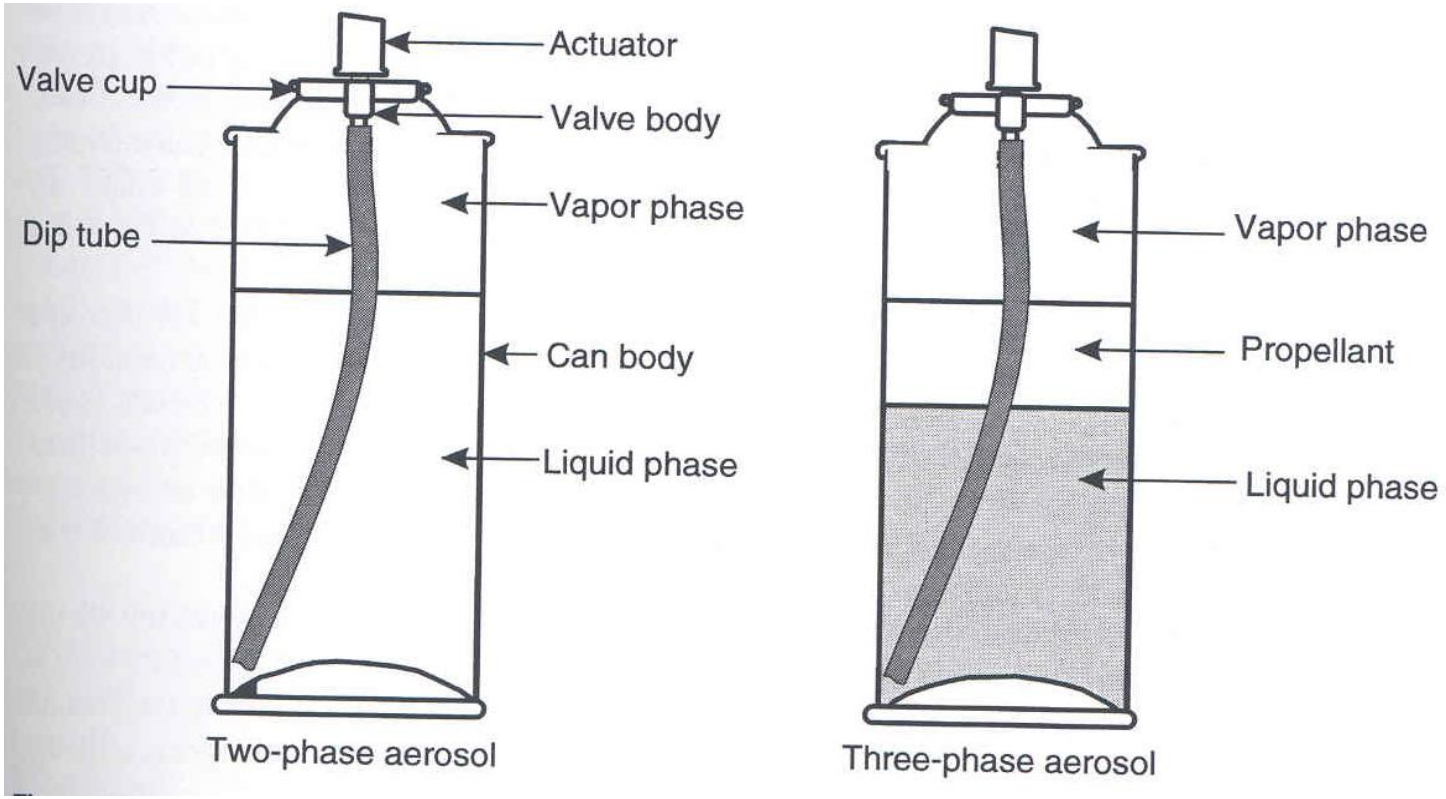
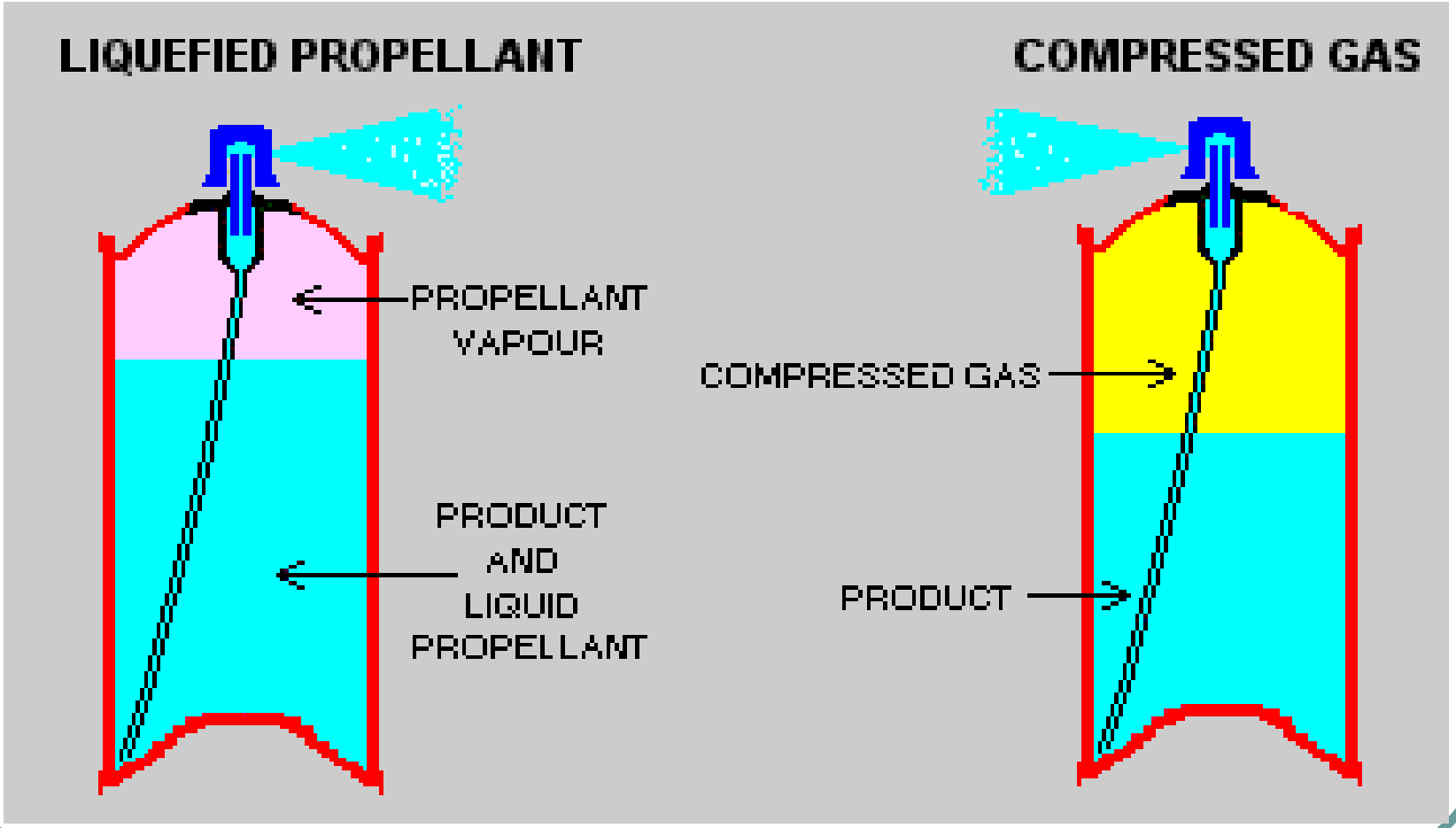


Figure 5.14 In a two-phase aerosol, the propellant is dissolved in the product. In a three-phase system, the propellant forms a separate layer


LIQUEFIED PROPELLANT
COMPRESSED GAS
PROPELLANT VAPOUR
PRODUCT AND LIQUID PROPELLANT
COMPRESSED GAS
PRODUCT

Aerosol

Aerosol product may be design to expel their content as a –

Fine mist

Coarse wet or dry spray

Steady stream or

Stable or fast breaking foams.

The physical form for a given aerosol is based on the intended use of the product.

Eg.for inhalation therapy (treatment of asthma)the particles shall be an the form of fine liquid mist or finely divided small particles.

Aerosol

Particles less than 6 μm will reach respiratory bronchioles and less than 2 μm will reach alveolar ducts and alveoli.

Particle size for dermatological spray would be more coarse.

AEROSOLS

- Aerosols used to provide an airborne mist are termed ***space sprays***. ***Examples****:* room disinfectants, room deodorizers, and space insecticides.

- Aerosols intended to carry the active ingredient to a surface are termed ***Surface sprays or surface coatings***.

- ***Examples:*** dermatologic aerosols, pharmaceutical aerosols, as personal deodorant sprays, cosmetic hair lacquers and sprays, perfumes and cologne sprays, shaving lathers, toothpaste, surface pesticide sprays, paint sprays and others.

Advantages of the Aerosol Dosage Forms

1. A portion of medication may be easily withdrawn from the package without contamination or exposure to the remaining material.
2. Hermetic character, the aerosol container protects medicinal agents from atmospheric oxygen, moisture and even from light.
3. Topical medication may be applied in a uniform, thin layer to the skin, without touching the affected area thus, reducing irritation.
4. By proper formulation and valve control, the physical form and the particles size of the emitted product may be controlled which may contribute to the efficacy of a drug. Example: the fine controlled mist of an inhalant aerosol. Through the use of **metered valves, dosage may be controlled.**
5. Aerosol application is **"clean" process**, requiring little or no **"wash-up"** by the user.

The Aerosol Principle

As aerosol formulation consists of 2 components:

1. **The product concentrate**

   is the active ingredient of the aerosol combined with the required adjuncts, such as antioxidants, surface-active agents, and solvents, to prepare a stable and efficacious product.

2. **The propellant**

   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.

In some aerosols non liquefied compressed gases such as carbon dioxide, nitrogen and nitrous oxide are used as propellants

Aerosol components

- Propellants:

1. Halogenated derivative of hydrocarbons

   Trichloromonofluoromethane; Dichlorodifluoromethane; Dichlorotetrafluoroethane; Chloropentafluoroethane; Monochlorodifluoroethane; Octafluorocyclobutane

2. Low molecular weight hydrocarbons: butane, pentane

3. Compressed gas

   Carbon dioxide, Nitrogen, Nitrous oxide

Test for propellants

Vapour pressure

Density

Gas chromatography test for purity

Moisture, halogen, non-volatile residue

Aerosol Container and Valve Assembly

- **The effectiveness of the aerosol depends on:**
  1. proper combination of formulation,
  2. container
  3. valve assembly.
- The formulation must not chemically interact with the container or valve components to avoid unstability of the formulation.
- The container and the valve must be capable of withstanding the pressure required by the product
- It must be corrosive resistant
- Valve must contribute to the form of the product to be emitted.

AEROSOL SYSTEMS

SPACE AEROSOLS usually operate at pressures between 30 to 40 psig (pounds per square inch gauge) at 70^0F and may contain as much as 85% propellant

SURFACE AEROLSOLS commonly contain 30 to 70% propellant with pressures between 25 to 55 psig at 70^0F

FOAM AEROSOLS usually operate between 35 and 55 psig at 70^0F and may contain only 6 to 10% propellant

AEROSOL SYSTEMS

TWO PHASE SYSTEM = comprised (1) the liquid phase – propellant and product concentrate (2) the vapor phase

THREE PHASE SYSTEM = comprised (1) layer of water immiscible liquid propellant, (2) layer of highly aqueous product concentrate, and (3) vapor pressure

COMPRESSED GAS SYSTEM = compressed rather liquefied, gases may be used to pressure aerosols. The pressure of the compressed gas contained in the headspace of the aerosol container forces the product concentrate up the dip tube and out of the valve

Examples: Nitrogen; carbon dioxide; nitrous oxide

Containers

1. Glass, uncoated or plastic coated
2. Metal, including tinplated steel, aluminum, and stainless steel
3. Plastics

The selection of containers for an aerosol product is based on

1. Its adaptability to production methods
2. Compatibility with formulation components
3. Ability to sustain the pressure intended for the product
4. The interest in design and aesthetic appeal on the part of the manufacturer, and
5. Cost

VALVE ASSEMBLY

- The function of the valve assembly is to permit the expulsion of the contents of the can in the desired form, at the desired rate, and, in the case of metered valve, in the proper amount or dose.
- The materials used in the manufacture of valves must be inert and approved.
- Among the materials used in making valve parts are plastic, rubber, aluminum, and stainless steel.

Actuators

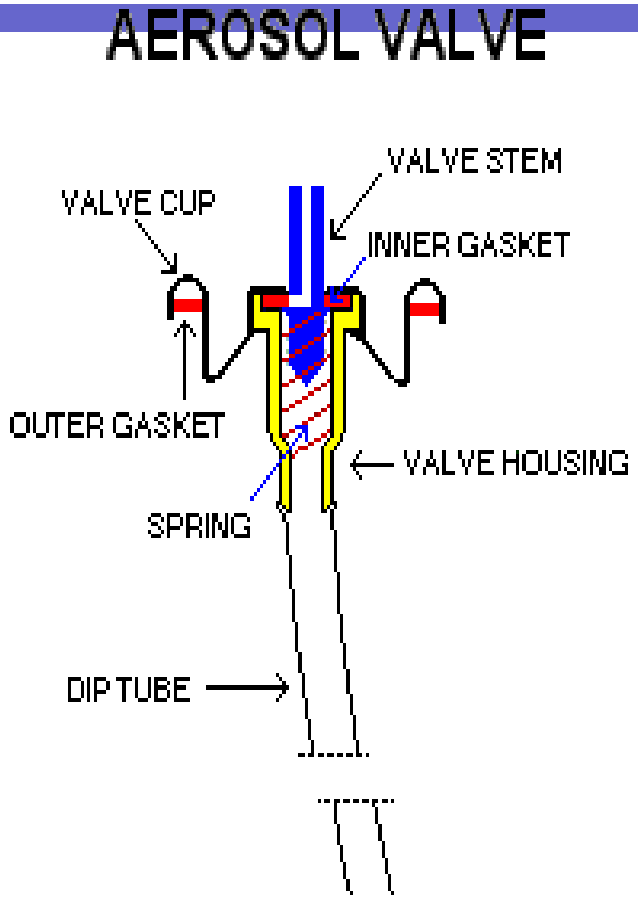
- Actuators: is the fitting attached to an aerosol valve stem, which when depressed or moved, open the valve, and directs the spray containing the drug preparation to the desired area.

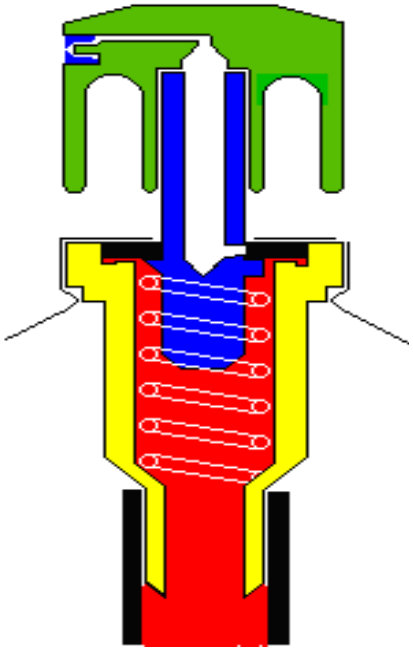
Parts of Aerosol Valve

Actuator	The actuator is the button which the user presses to activate the valve assembly for the emission of the product.
Stem	The stem supports the actuator and delivers the formulation in the proper form to the chamber of the actuat
Gasket	The gasket, placed snugly with the stem, serves to prevent leakage of the formulation when the valve is in closed position
Spring	The spring holds the gasket in place and also is the mechanism by which the actuator retracts when pressure is released, thereby returning the valve to the closed position
Mounting cup	The mounting cup, which is attached to the aerosol can or container, serves to hold the valve in place.
Housing	The housing, located directly below the mounting cup, serves as the link between 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	The dip tube, which extends from the housing down into the product, serves to bring the formulation from the container to the valve.

- Valve Cup :- typically constructed from tinplated steel, or aluminium.
- Outer Gasket :- this is the seal between the valve cup and the aerosol can.
- Valve Housing :- contains the valve stem, spring and inner gasket.
- Valve Stem :- in effect, the tap through which the product flows.
- Inner Gasket :- covers the hole in the valve stem.
- Valve Spring :- usually stainless steel.
- Dip Tube :- allows the liquid to enter the valve.
- Actuator (not shown) :- fits onto the valve stem.

Aerosol valve





Metered Dose Inhalers (MDIs)

Example: Allupent. Each metered dose is delivered through the mouthpiece upon actuation of the aerosol unit's valve

Nitrolingual spray - permits a patient to spray droplets onto or under the tongue for acute relief of an attack, or prophylaxis, of angina pectoris due to coronary artery disease. The product contains 200 doses of nitroglycerin in a propellant mixture of dichlorofluoromethane and dichlorotetrafluoroethane

Filling Operations

Fluorinated hydrocarbon gases may be liquefied by cooling below their boiling points or by compressing the gas at room temperature. These 2 features are utilized in the filling of aerosol containers with propellant.

Cold Filling

Both the product concentrate and the propellant must be cooled to temperatures of -30^0 to $-40\ ^0F$. This temperature is necessary to liquefy the propellant gas. The cooling system may be a mixture of dry ice and acetone.

Pressure Filling

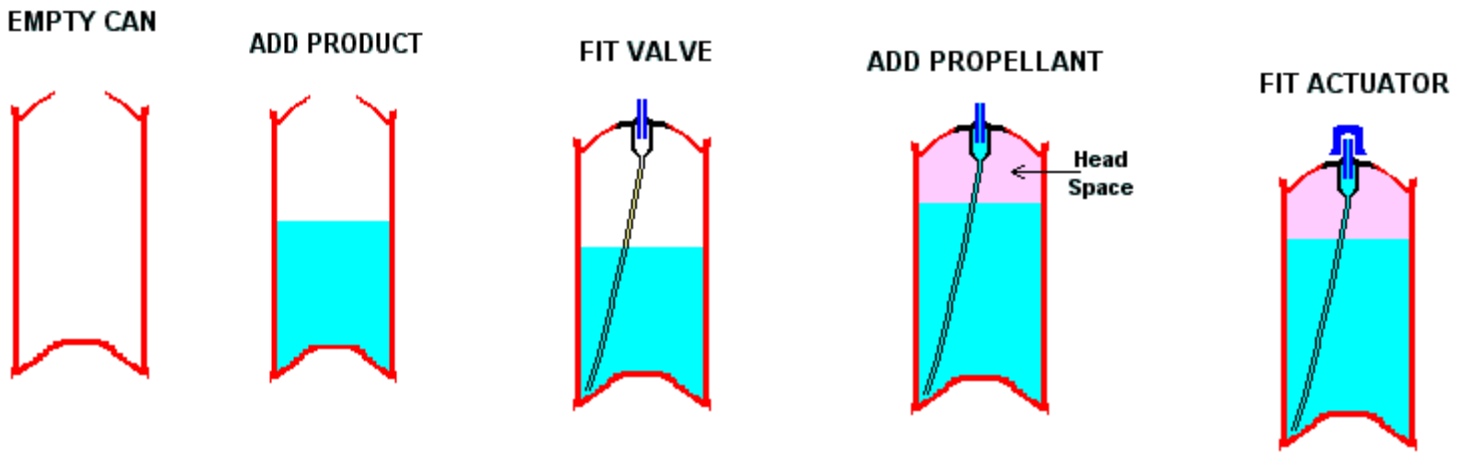
The product concentrate is quantitatively placed in the aerosol container, the valve assembly is inserted and crimped into place, and liquefied gas, under pressure, is metered into the valve stem from a pressure burette.

- **HOW AEROSOLS ARE FILLED**
- These all have to be assembled, and this is achieved using automatic filling machinery which can operate at speeds in excess of 400 cans per minute. For conventional aerosols the key steps in the filling process are:-
- 1. Start with an empty aerosol container. This will be made of tinplate or aluminium, or perhaps glass.

  The capacity of the container will be greater than that which is declared on the pack.
- 2. The product, usually in the form of a liquid, is now added.

  This contains all the active ingredients, except for the propellant.

  The volume of liquid is very carefully controlled to ensure that it conforms with Weights & Measures legislation.
- 3. The Aerosol valve is now fitted (crimped) to the can. This is a very critical operation and the crimping machinery has to be carefully set up to ensure that the can / valve seal does not leak.


EMPTY CAN
ADD PRODUCT
FIT VALVE
ADD PROPELLANT
Head
Space
FIT ACTUATOR

- Where a 'small' actuator is to be used, this will be fitted on to the valve before it is crimped onto the can.
- The propellant is now injected under pressure, through the valve. The propellant may be in the form of a liquified gas, or a compressed gas.
  If a liquified gas is used it will exist as both a liquid, and vapour in the aerosol can head space. The volume of liquid in the can will increase.
  If a compressed gas is used, it will usually only be in the head space, above the liquid in the can, and there will be little or no increase in liquid volume.
  Again, the volume of liquid is very carefully controlled to ensure that it conforms with Weights & Measures legislation.The aerosol is now in a pressurised state due to the addition of the propellant. The cans are now immersed in a water bath at 50°C to check for any leaks. Any cans that leak are rejected.
- If a large, or special, actuator is required it is fitted now. Where necessary, a dust cap is also fitted.

  Finally the can will be date / batch coded, and shrink wrapped or boxed as required.

Testing the Filled Containers

Container is tested under various environmental conditions

1. Leaks
2. Weakness in the valve assembly or container
3. Proper function s of the valve
4. The valve discharge rate - determine by discharging a portion of the contents of a previously weighed aerosol during a given period of time, and calculating, by the difference in weight, the grams of contents discharged per unit of time.
5. Particle size distribution of the spray
6. For accuracy and reproducibility of dosage when using metered valves

Sample Products

SALBUTAMOL

LIBRENTIN INHALER

Aerosol characteristics:

Particle size distribution

Uniformity of dose for metered valve

Delivery rate

Wetness and temperature of the spray

Spray pattern

Velocity of spray

Foam density

Fluid viscosity

Extractable substances

- Leaching of extractable from plastic components into the formulation is a potential serious problem.
- Extractable include: antioxidants, plasticizers, monomers, nitrosamine, vulcanization accelerators, etc., should be identified and minimized.
- The composition and the quality of materials used in the manufacturing of the *valve* components must be carefully selected and controlled. Their compatibility with formulation components should be well established to minimize change in the medication delivery, leak rate, impurity profile of the drug product over time.

Containers:

Made of glass, plastic or metal as stainless steel, aluminum, tin.

Extractable or leachable and particulates on the internal surfaces of containers should be controlled.

Manufacturing process controls usually include:

monitoring of proper formulation and propellant fill weight and pressure testing, leak testing, and valve function testing of the finished aerosol.

Aerosols

Topical Aerosols

- Aerosols packages for topical use on the skin which include:

  Antiinfectives: Povidone - iodine, Tolnaftate

  Adrenocortical steroids: Betamethasone and Triamcinolone Acetonide

  Local anesthetic: Dibucaine hydrochloride

Vaginal and Rectal Aerosols

- Aerosols foams are commercially available containing estrogenic substances and contraceptives agents.

Example:

ProctoFoam - contains pramoxine hydrochloride

- use to relieve inflammatory anorectal disorder

Topical Aerosols

Delivery rate and delivered amount

Only perform these tests on containers fitted with continuous valves.

Procedure:

Select not less than 4 aerosol containers, weigh, actuate each valve for 5 seconds, weigh each container again.

Calculate the average delivery rate in g per second, for each container.

Calculate the total weight loss from the container. This is the delivered amount.

Pressure test

- Only perform this test on topical aerosols fitted with continuous valves.
- Select 4 aerosol containers, determine the pressure in each container by placing a calibrated pressure gauge on the valve stem.

Leakage Test

Only perform on topical aerosols fitted with continuous valves.

Select 12 aerosol containers, weigh each container, mg W_1, allow to stand in upright position at temp. 25°C for not less than 3 days,

weigh again each container, record the weight, mg as W_2, calculate the leakage rate mg/year.

365x(24/t) (W1-w2)

- Flame extension test
- The product is sprayed for 4 seconds into a flame, the extension of the flame is measured by a ruler.

- Spray pattern test
- By spraying the content of the container on a rotating paper impregnated with a dye solution, coloured spots are produced Homogeneity of the colour indicates a homogenous spray pattern.

- Uniformity of dosage units
- The test is required for aerosols fitted with dose-metered valves, metered dose inhaler and dry powder inhalers.
- The drug content of at last 9 of the 10 doses collected from *one inhaler*, are between 75% and 125% of label claim, and none is outside the range of 65% to 135% of the label claim.
- If the contents of not more than 3 doses are outside the range of 75% to 125%, but within the range of 65% to 135% of label claim, *select 2 additional* inhalers and follow the procedure for analyzing 10 doses from each.
- The requirements are met if not more than 3 results, out of *the 30 values*, lie outside the range of 75% to 125% of label claim and none is outside the range of 65%to 135% of label claim.

Particle size

- The particle or droplet size distribution in the spray discharged from metered-dose inhalers or from dry powder inhalers are important characteristics used in judging inhaler performance.

Inhaler aerosol

INHALANTS

- Are drugs or combinations of drugs that by virtue of their high vapor pressure can be carried by an air current into the nasal passage where they exert their effect.

- The device in which they are administered is termed an ***inhaler.***

- **Examples:**
  1. Amyl Nitrite Inhalant - treatment of anginal pain
  2. Propylhexedrine Inhalant - nasal decongestant

INHALATIONS

Inhalations are drugs or solutions of drugs administered by the nasal or oral respiratory route.

- A widely used instrument capable of producing fine particles for inhalation therapy is the **NEBULIZERS.**
- When volatile medication is added to the water in the chamber, the medication is volatilizes and also inhaled by the patient, **HUMIDIFIERS** will be used.

Common Inhaled Steroids

Table 7-7 Comparative Adult Inhaled Daily Corticosteroid Doses

Drug	*Low Dose*	*Medium Dose*	*High Dose*
beclomethasone dipropionate CFC (Beclovent®)	168–504 mcg	504–840 mcg	>840 mcg
beclomethasone	80–240 mcg twice daily	240–280 mcg twice daily	>480 mcg
diproprionate HFA (Qvar®); budesonide DPI (Pulmicort®)	200–600 mcg	600–1,200 mcg	>1,200 mcg
flunisolide (Aerobid®)	500–1,000 mcg	1,000–2,000 mcg	>2,000 mcg
fluticasone (MDI)	88–264 mcg	264–660 mcg	>660 mcg
(Flovent®) (DPI)	100–300 mcg	300–600 mcg	>600 mcg
mometasone furoate (Asmanex®)	220 mcg	220 mcg b.i.d.	440 mcg b.i.d.
triamcinolone acetonide (Azmacort®)	400–1,000 mcg	1,000–2,000 mcg	>2,000 mcg