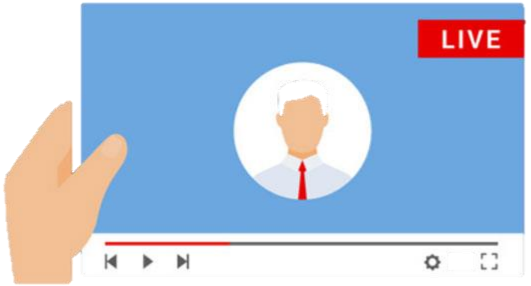
Prepared by RAJAT GOEL



Welcome to GPAT "Live online class"

Lecture: Pharmaceutics Aerosols

AIC. LMCP Foundation L.M College of Pharmacy Navarangpura, Ahmedabad - 380009

Introduction

- Aerosol is a **pressurized dosage forms** containing **one or more therapeutic active ingredients** which upon actuation **emit a fine dispersion** of liquid and/or solid materials **in a gaseous medium**

- Aerosol products intended for local activity in the respiratory tract appeared in 1955 , when **Epinephrine** was made available in a pressurized package

Advantages and Disadvantages

Advantages

- Easily withdrawal of drug
- Easy and convenient to apply
- Faster Onset of action → Avoid the first pass metabolism
- No manual/ direct contact with the medicament
- A specific amount of dose or drug can be removed
- No microorganism can enter
- Protect the photosensitive medicaments and oxygen sensitive material
- Irritation can be reduced

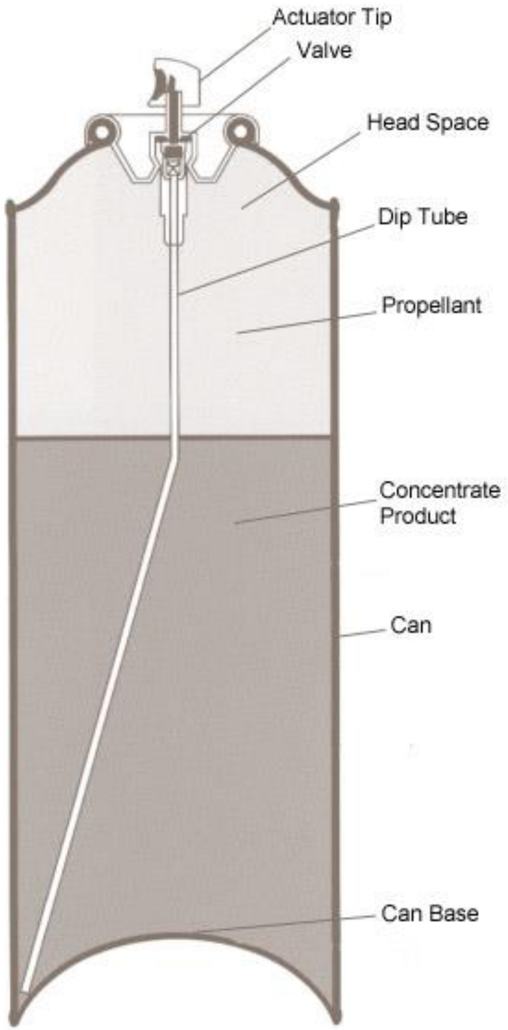
Disadvantages

- Costly
- Difficult disposal of empty aerosol containers.
- Allergic in some cases
- Explosive
- Some formulation is difficult
- Sometimes propellants may cause toxic reactions

Components of Aerosols

An aerosol product consist of following component parts :

1. Propellant
2. Container
3. Valve and actuator
4. Product concentrate



Components: Propellant

- They are called as **heart of the aerosols.** (5-95%)
- It expels the product from container.
- The **propellant** is responsible for **developing the proper pressure** within the container.
- **Aids in the atomization** or foam production of the product
- They must **readily evaporate with high pressure at low amount.**
- They are mainly of two types either ***liquefied gas or compressed gas***.
- The **liquefied gas** includes chlorofluorohydrocarbons (CFC), hydrocarbons, hydro-fluorocarbons, hydrocarbons ether, etc.
- The **compressed gas** can be water immiscible (like argon, nitrogen) or can be water miscible (like CO_2 , NO_2).

Components: Propellant

- Depending on the route of administration and use,

I) Type-I Propellant A- Liquefied Gas

1) For oral and inhalation (Fluorinated hydrocarbons)

Tri-chloro-mono-flouro methane (propellant 11)

Di-chloro di-fluro methane (propellant 12)

2) Topical Pharmaceutical aerosols (Hydrocarbons)

Propane

Butane

II) Type-II Propellant B - Compressed Gas Propellants

1) Compound gases

Nitrogen

Carbon dioxide

Components: Propellant

CHLORO FLUORO CARBONS

- Propellant of choice for oral and inhalation

Advantages

- Chemical inertness
- Lack of toxicity
- Non flammability.
- Lack of explosiveness

Disadvantages

- High cost
- It depletes the ozone layer

Examples:

Trichloromonofluoromethane - Propellant 11

Dichlorodifluoromethane - Propellant 12

Dichlorotetrafluoroethane - Propellant 114

Blends of various fluorocarbon propellants are generally used for pharmaceutical aerosols. Blending is done on the basis of desired final pressure

Components: Propellant

Nomenclature of CHLORO FLUORO CARBONS

- Naming consists of 3 digits which is read from right to left. If starting digit is zero then naming is in 2 digits.
    1. First digits shows no. of fluorine atoms
    2. Second digit show no. of hydrogen atoms + 1 or one more hydrogen then the actual no. of hydrogens
    3. Third digit shows carbon atom – 1 or one carbon atom less than the actual no. of carbons
    4. The remaining valency of carbon is filled with chlorine.
- e.g.:-- 011 (have one fluorine, no hydrogen and one carbon)

Components: Propellant

HYDROCARBONS

- Propellant of choice for tropical

Advantages

- Inexpensive
- Excellent solvents
- It does not cause ozone depletion

Disadvantages

- Inflammable
- Unknown toxicity produced

Examples:

Propane - Propellant A-108

Isobutane - Propellant A-31

Butane - Propellant A-17

GPAT QUESTION

Propellant 114 is known as

A. Tri-chloro-mono-flouro methane

B. Di-chloro di-fluoro methane

C. Di-chloro-tetra-fluoro ethane

D. None

Components: Propellant

Raoult's Law

- The vapor pressure of a mixture consisting of two individual propellants is equal to the sum of the mole fraction of each component present multiplied by the vapor pressure of each pure propellant at the desired temperature

$$p_a = \frac{n_a}{n_a + n_b} p_A^0 = N_A p_A^0$$

$$p_b = \frac{n_b}{n_b + n_a} p_B^0 = N_B p_B^0$$

$$P = p_a + p_b$$

p_a = Partial vapor pressure of propellant A

p_A^o = Vapor pressure of pure propellant A

n_a = Moles of propellant A

n_b = Moles of propellant B

N_A = Mole fraction of component A

N_B = Mole fraction of component B

GPAT QUESTION

What is the vapor pressure (in psig) of a mixture of propellants 11 and 12 in a 70:30 ratio?

P-11: molecular weight - 137.38; Vapor Pressure = 13.4 psia

P-12: molecular weight - 120.93; Vapor Pressure = 84.9 psia

Solution

Question: What is the vapor pressure of a mixture of propellants 11 and 12 in a 70:30 ratio?

P-11: molecular weight - 137.38; Vapor Pressure = 13.4 psia

P-12: molecular weight - 120.93; Vapor Pressure = 84.9 psia

$$n_{11} = \frac{weight\ of\ P-11}{mol.\ weight\ of\ P-11} = \frac{70\ g}{137.38\ g/mole} = 0.5095\ mole$$

$$n_{12} = \frac{weight\ of\ P-12}{mol.\ weight\ of\ P-12} = \frac{30\ g}{120.93\ g/mole} = 0.2481\ mole$$

$$p_{11} = \frac{n_{11}}{n_{11}+n_{12}}\ X\ P_{11}^{0} = \frac{0.5095\ mole}{0.5095\ mole + 0.2481\ mole}\ X\ 13.4\ psia = 9.01\ psia$$

$$p_{12} = \frac{n_{12}}{n_{11}+n_{12}}\ X\ P_{12}^{0} = \frac{0.2481\ mole}{0.5095\ mole + 0.2481\ mole}\ X\ 84.9\ psia = 27.8\ psia$$

$$P_{total} = p_{11} + p_{12} = 9.01 + 27.8 = \mathbf{36.81\ psia = 22.11\ psig}$$

Components: Containers

- They must be able to withstand pressures as high as 140 to 180 psig (pounds per sq. inch gauge) at 130 F

AEROSOL CONTAINERS

Metals

Tinplated steel

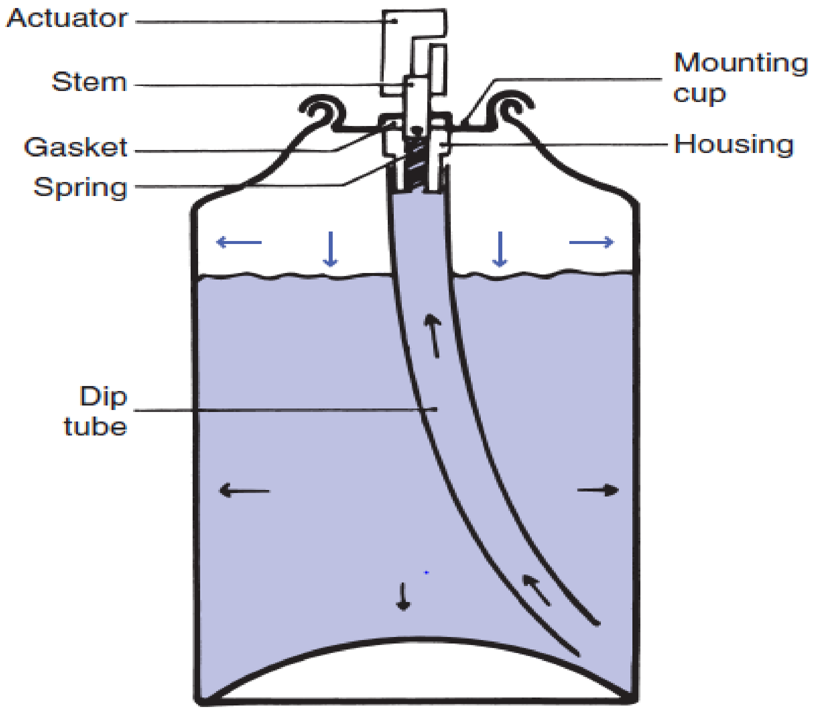
Aluminum

Stainless steel

Glass

Uncoated glass

Plastic coated glass



Components: Containers

(A) **Metals:--**

1. **Tin Plated Steel:**

- Tin-plated steel containers are the most widely used metal containers for aerosols.
- Because the starting material is in sheets, the completed aerosol cylinders are seamed and soldered to provide a sealed unit.
- It can be coated to prevent corrosion.
- **It may be (a) Side seam (three piece) (b) Two Piece (c) Tin-free steel**

Components: Containers

(A) Metals:--

2. **Aluminum:**

- Aluminum containers are manufactured by extrusion or by other methods that make them seamless.
- They have the advantage over the seam type of container of greater safety against leakage, incompatibility, and corrosion*(ethanol + propellant 11).

3. **Stainless steel:**

- Stainless steel is employed to produce containers for certain small-volume aerosols in which a great deal of chemical resistance is required.
- The main limitation of stainless steel containers is their high cost.

Components: Containers

(B) Glass containers

- These containers are preferred because of its Aesthetic value and absence of incompatibilities.
- These containers are limited to the products having a lower pressure (33 psig) and lower percentage of the propellant.
- Used for topical and MDI aerosols.

Two types of glass aerosol containers

i) Uncoated glass container:

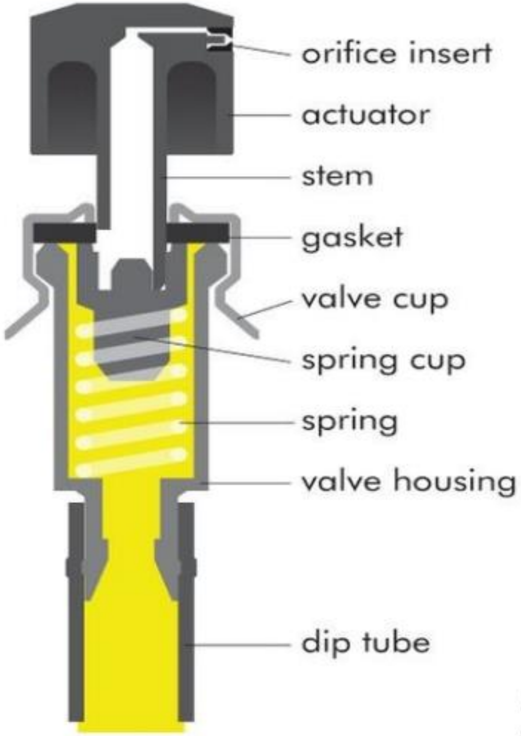
Less cost and high clarity and contents can be viewed at all times.

ii) Plastic coated glass containers:

These are protected by plastic coating that prevents the glass from shattering in the event of breakage.

Components: Valve

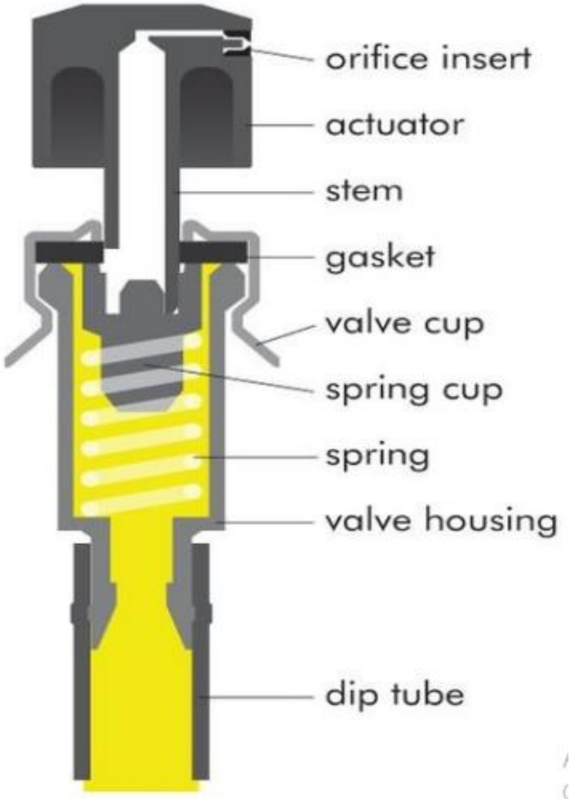
- The function of the valve assembly is to permit expulsion of the contents of the can in the desired form, at the desired rate, and in the case of metered valves, in the proper amount or dose.
- The materials used in the manufacture of valves must be inert to the formulations
- Among the materials used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



Components: Valve

- The usual aerosol valve assembly is composed of the following parts:

1. Actuator
2. Stem
3. Gasket
4. Spring
5. Mounting cup (ferrule)
6. Housing
7. Dip tube



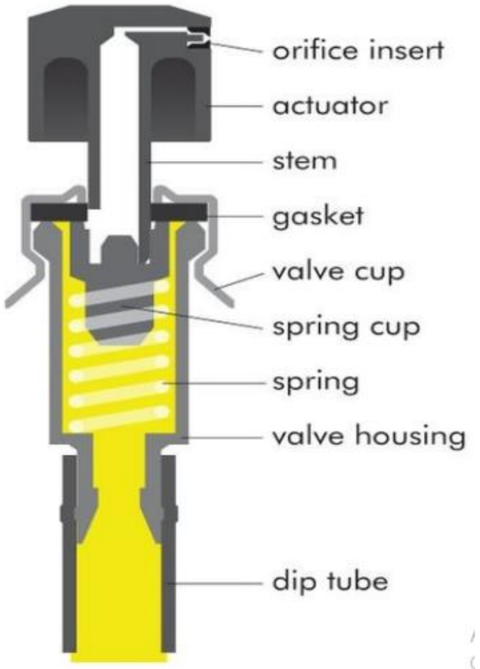
Components: Valve

Actuator

- Button the user presses to activate the valve assembly for emission of the product.
- Permits easy opening and closing of the valve.
- From orifice in the actuator that the product is discharged.
- Decides the physical form (mist, coarse spray, solid stream, or foam) of final product

Different types actuators are

1. **Spray**
2. **Foam**
3. **Solid stream**
4. **Special applications**



Components: Valve

Actuator – Spray actuator

- Capable of dispersing the stream of product concentrate and propellant into relatively small particles
- The combination of propellant vaporization and actuator orifice and internal channels can deliver the spray in the desired particle size range

Foam actuators

- Consist of relatively large orifices
- The orifices allow for passage of the product into a relativ... where it can expand and dispensed

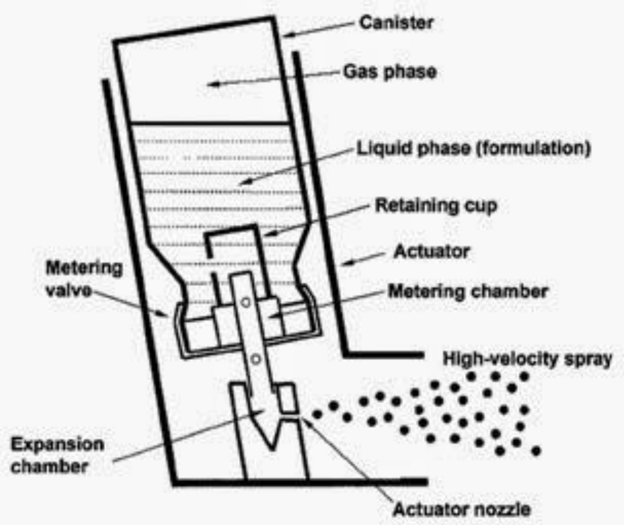
Components: Valve

Solid stream actuator

- These are for dispensing of semisolid products as ointments
- Large openings allow for passage of the product through the valve stem and into the actuator

Special actuators

- Used for pharmaceutical and medical aerosol require a specially designed actuator
- **Metered dose inhalers (MDIs):** To increased interest in modifying MDIs to minimize the number of administration error and to improve the drug delivery of aerosols particles into the drug delivery system of the nasal passage ways and respiratory tract. The PSD required is <10 micrometers
- **Dry powder inhalers (DPI):** consist of a powdered drug formulation and device in which aerosolization of the powder is driven by patient inspiration through the device



Components: Valve

Stem

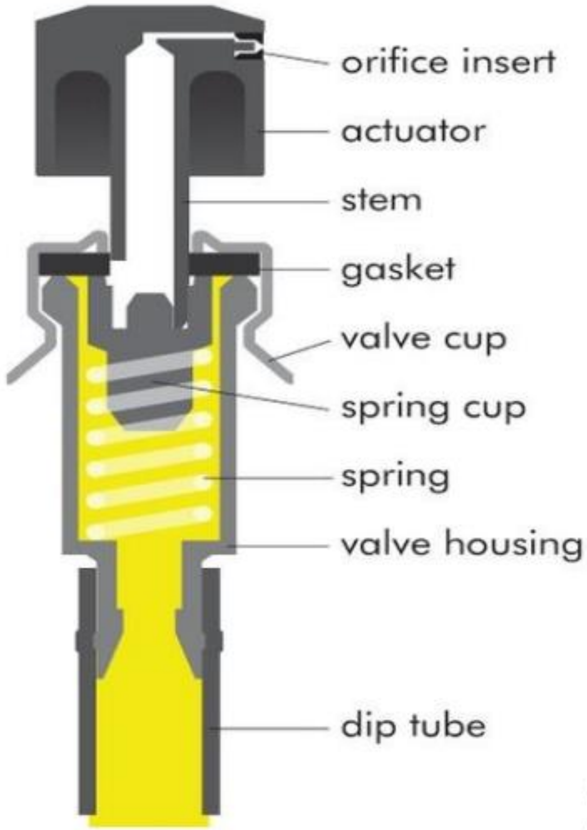
- **Supports the actuator** and delivers the formulation in the proper form to the chamber of the actuator.
- **Made of Nylon and Derrin**

Gasket

- Placed with the stem and prevents leakage of the formulation
- **Made of Buna-N or Neoprene rubber**

Spring

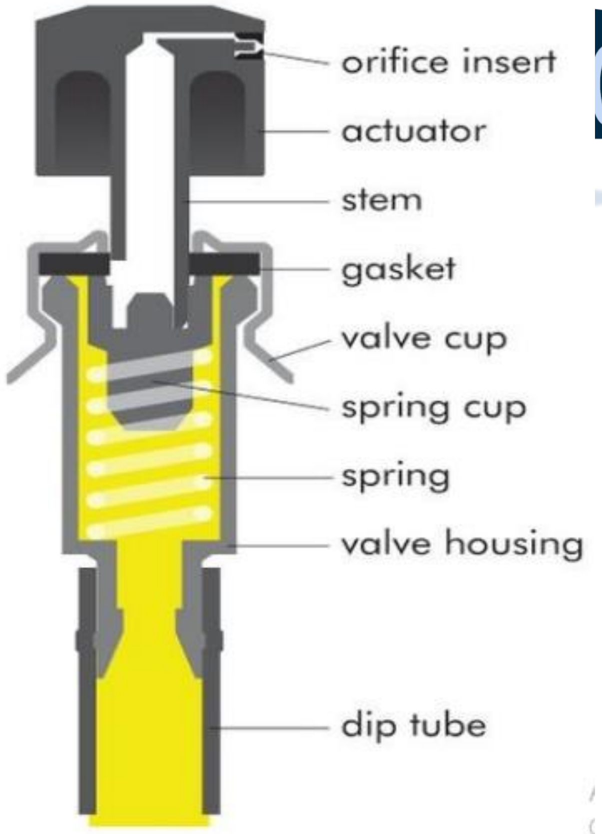
- Holds the gasket in place and is the mechanism by which the actuator retracts when pressure is released, returning the valve to the closed position
- **Stainless steel is used**



Components: Valve

Mounting cup (Valve cap; ferrule)

- Used to attach valve to container.
- **Made from Tin plated steel, Al , Brass .**
- Under side of the valve cup is coated with single or double epoxy or vinyl resins



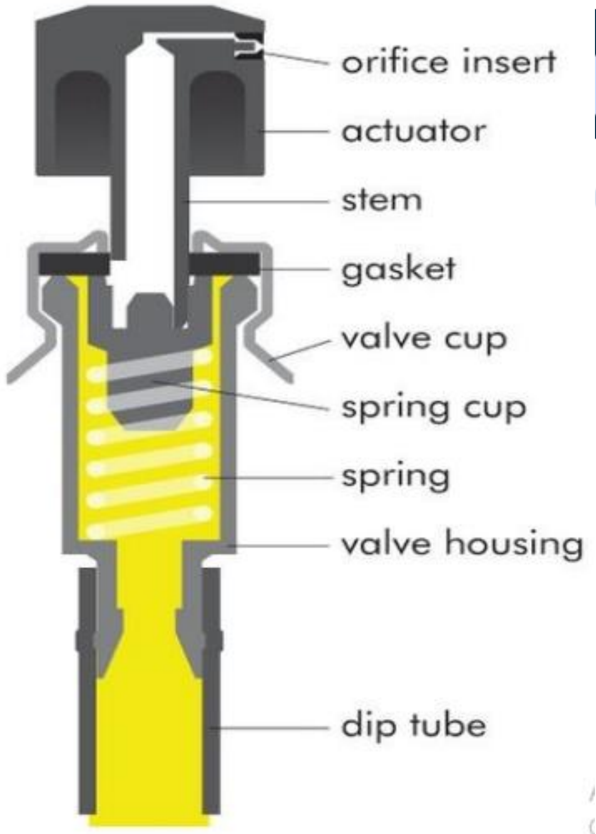
Valve body or housing

- Directly below the mounting cup, the housing links the dip tube and the stem and actuator
- Made up of Nylon or Derlin
- Opening at the point of the attachment of the dip tube range from **0.013 inch to 0.080 inch**

Components: Valve

Dip tube:

- Extends from the housing down into the product; brings the formulation from the container to the valve
- **Made from Poly ethylene or poly propylene**
- **Commonly used Dip tube is about 0.120 inch to 0.125 inch**



GPAT QUESTION

Gasket is made up of

A. Buna-N
B. Neoprene rubber
C. Both A and B
D. None

Formulation of Aerosols

- Contains two essential components
    - Product concentrate
    - Propellant

- **Product concentrate** contains ingredients or mixture of active ingredients and other such as solvents, antioxidants and surfactants
- **Propellant:** May be single or blend of various propellants. Blends of propellant used in a pharmaceutical formulation to achieve desired solubility characteristics

Types of aerosol systems

- Solution system
- Suspension or Dispersion systems
- Foam systems
  - Aqueous stable foams
  - Non aqueous stable foams
  - Quick-breaking foams
  - Thermal foams
- Intranasal aerosol

Types of aerosol systems

Solution system

Two phase system

- Contains both vapor & liquid phase
- Drug soluble in propellant – no other solvent is required

Three phase system

- Contains water phase, vapor phase and the propellant
- Water immiscible with propellant – solubility increased by adding,
    - Co – solvent (ethanol)
    - Surfactants (0.5% - 2.0%) – non polar (esters of oleic acid, palmitic acid, stearic acid)

Types of aerosol systems

Foam systems

- Consists of aq. or non aq. vehicles, propellant & surfactants

Aqueous stable foams:

- Propellant content usually is about 8 to 10% v/v
- As amount of propellant increases a stiffer and dryer foam is produced
- Lower concentration yield wetter foams
- Steroidal antibiotics

Non aqueous stable foams

- Formulated through the various glycols such as polyethylene glycol

    - Quick-breaking foams
    - Thermal foams

- Intranasal aerosol

Types of aerosol systems

Foam systems

- Consists of aq. or non aq. vehicles, propellant & surfactants

Quick-breaking foams

- Topical application
- Cationic, anionic, non ionic surfactant

Thermal foams

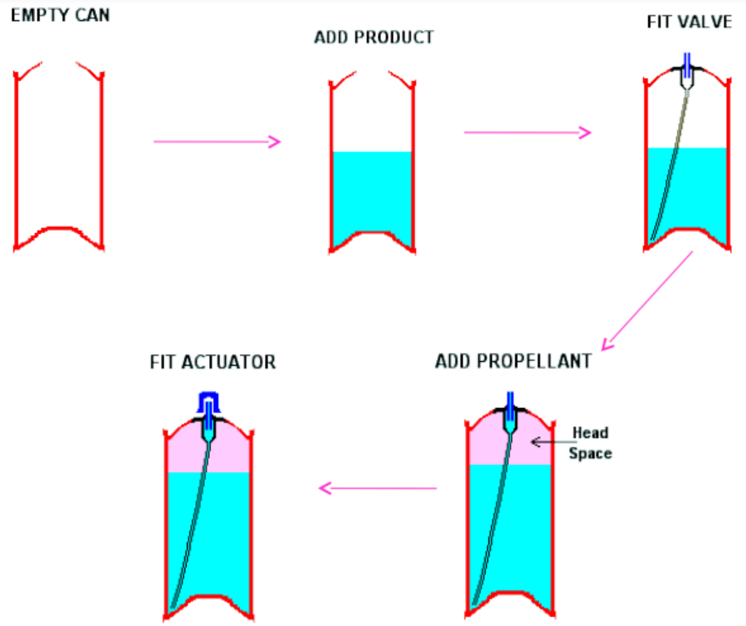
- Used to produce warm foam for shaving

Intranasal aerosol

- Intended for the deposition of medication into the nasal passage ways
- Drugs intended to produce local or systemic effect can be used

Manufacture of pharmaceutical aerosols

- Pressure filling apparatus
- Cold filling apparatus
- Compressed gas filling apparatus



Pressure filling apparatus

- Consists of metering burette – measures the amount of propellant to be filled

Method

- Product concentrate is filled through the burette at room temperature
- Propellant is added through the inlet valve.
- Flow of propellant stops when pressure of filling propellant become equal to the pressure within the container

Pressure filling apparatus

ADVANTAGES OF PRESSURE FILLING:

- Solutions, emulsions, suspensions can be filled by this method as chilling does not occur
- Less Contamination due to moisture
- High production speed can be achieved
- Loss of propellant is less
- No refrigeration

DISADVANTAGES OF PRESSURE FILLING:

- Certain types of metering valves can be handled only by the cold filling process or through use of an under the cap filler and valve crimper
- **Process is slower than Cold filling method**

Cold filling apparatus

- It consist of an insulated box fitted with copper tubings and the tubings are coiled to increase the area exposed to cooling

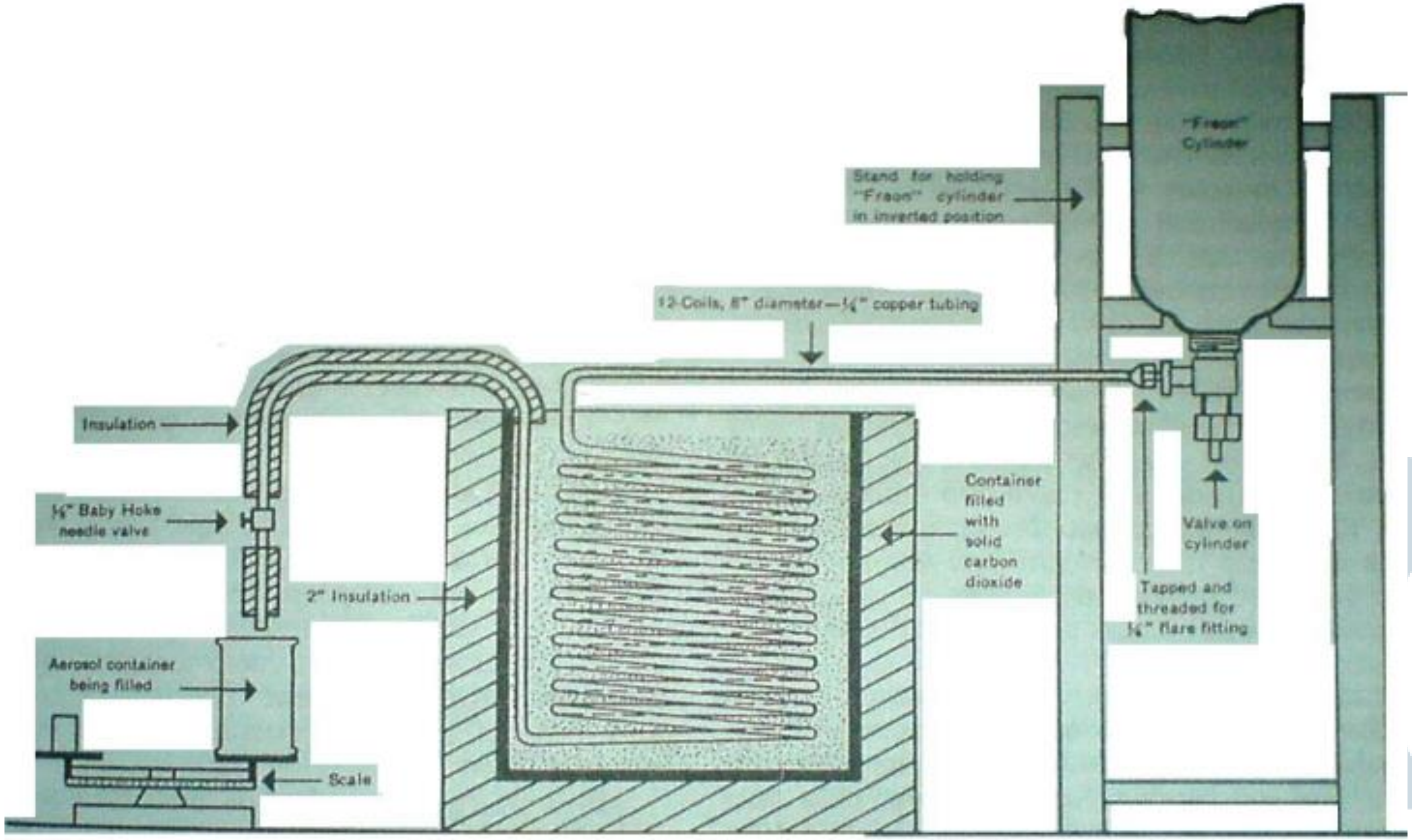
Method A

- Product concentrate chilled to -30 to -40 F
- Chilled product added to chilled container
- Chilled propellant added through inlet valve

Method B

- Product concentrate and propellant chilled to -30 to -40 F
- Mixture added to chilled container
- *The valves are set in place*
- *Filled containers passed through water bath (contents heated to 130o F)*
- *Containers dried, capped and labeled*

Cold filling apparatus



Cold filling apparatus

Advantage

- Easy process

Disadvantages

- Aqueous products, emulsions and those products adversely affected by cold temperature cannot be filled by this method

Compressed gas filling apparatus

APOMIND

- Propellant – compressed gas
- Pressure reduced by pressure reducing valve
- Pressure used – 150 psig

Method

- Product concentrate placed in container
- Valve crimped in its place
- Air evacuated by vacuum pump
- Filling head inserted into valve opening, valve depressed & gas allowed to flow into container
- Container shaken during and after filling by mechanical shakers

GPAT QUESTION

Gas filling involves chilling of all the components at

A. -30 to -40 F

B. -30 to -40 C

C. -30 to -40 K

D. -30 to -40 R

Evaluation tests

A. Flammability and combustibility :

1. Flash point
2. Flame Projection

B. Physicochemical characteristics :

1. Vapor pressure
2. Density
3. Moisture content
4. Identification of Propellants
5. Concentrate – propellant ratio

Evaluation tests

C. Performance:

1. Aerosol valve discharge rate
2. Spray pattern
3. Net contents
5. Foam stability
6. Particle size determination
7. Leakage

D. Biological testing :

1. Therapeutic activity
2. Toxicity studies

A. Flammability and combustibility

Flash point:

Apparatus : **Tag Open Cup Apparatus**

- Product is chilled to – 25°F
- Test liquid temperature is allowed to increase slowly and the temperature at which vapors ignite is called as Flash Point

Flame Projection:

- Product is sprayed for 4 sec into a flame and the flame is extended ,exact length is measured with a ruler

B. Physicochemical characteristics

1. **Vapor Pressure**
   » Pressure gauge
   » Can Puncturing Device.
2. **Density**
   » Hydrometer,
   » Pycnometer.
3. **Moisture**
   » Karl Fisher Method,
   » Gas Chromatography.
4. **Identification of propellants**
   » Gas Chromatography,
   » IR Spectroscopy.

C. Performance

Aerosol valve discharge rate

- Contents of the aerosol product of known weight is discharged for specific period of time
- By reweighing the container after the time limit, the change in the weight per time dispensed gives the discharge rate (g/sec)

C. Performance

Spray pattern

- The method is based on the impingement of spray on piece of paper that has been treated with Dye-Talc mixture
- The particles that strike the paper cause the dye to go into solution and to be adsorbed onto paper giving a record of spray for comparison purpose

C. Performance

Net Contents :

- Tared cans that have been placed onto the filling lines are reweighed and the difference in weight is equal to the net contents
- **In Destructive method:** weighing a full container and then dispensing as much of the content as possible
- The contents are then weighed . This gives the net content

C. Performance

Foam stability

- Visual Evaluation
- Time for given mass to penetrate the foam
- Time for given rod that is inserted into the foam to fall
- Rotational Viscometer

Particle Size Determination :

- Cascade Impactor
- Light Scattering Decay

D. Biological testing

Therapeutic Activity

- **For Inhalation Aerosols:** Depends on the particle size distribution
- **For Topical Aerosols:** Is applied to test areas and absorption of therapeutic ingredients can be determined

Toxicity

- **For Inhalation Aerosols:** Exposing test animals to vapor sprayed from aerosol container
- **For Topical Aerosols:** Irritation & chilling effects are determined

Labelling

- Avoid inhaling. Avoid spraying into eyes or onto other mucous membranes
- Contents under pressure . Do not puncture or incinerate container
- Do not expose to heat or store at temperature above 120 F
- Use only as directed

GPAT QUESTION

The nature of propellant is determined by

A. RF method

B. GC

C. UV

D. NMR

e of

THANK YOU