AEROSOLS

Mr. Abhijeet A. Aher
Assistant Professor,
MES's College of Pharmacy, Sonai
Tal- Newasa, Dist- Ahmednagar
Email- abhijeet.aher9@gmail.com
Mobile- 9890609283

INTRODUCTION

- Aerosol or Pressurized package is defined as "A system that depends on the power of a compressed gas or liquefied gas to expel the contents from the container."
- Pharmaceutical Aerosol is defined as aerosol product containing active ingredients dissolved ,suspended or emulsified in a propellant or a mixture of solvent and propellant.These intended for oral or topical administration or for administration into the eye, nose ,ear, rectum and vagina.

ADVANTAGES OF AEROSOLS

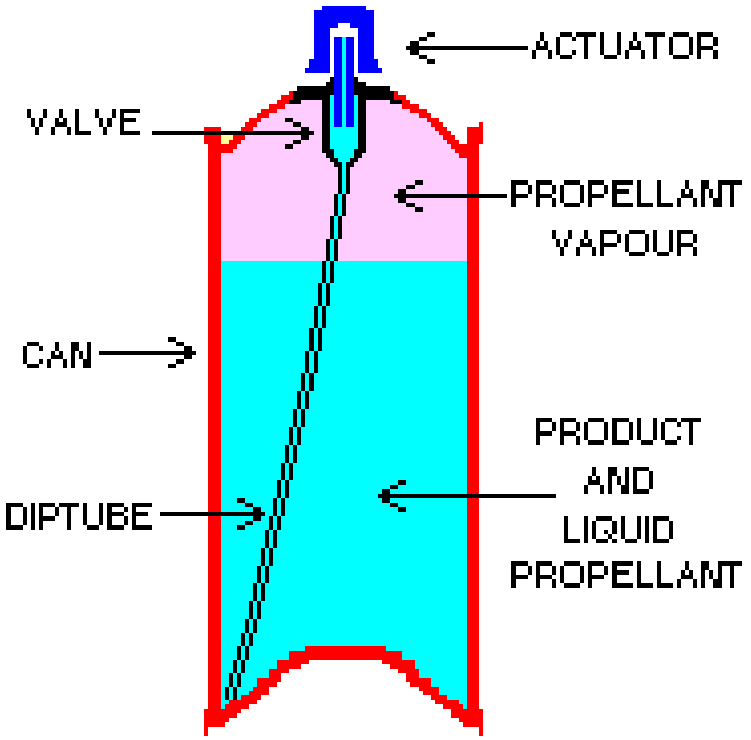
- A dose can be removed with out contamination of materials.
- Stability is enhanced.
- Sterility can be maintained.
- The medication can be delivered directly to the affected area. (localized action)
- Ease and convenience of application.
- Application of medication in thin layer .
- Rapid response to the medicament .
- Bypasses First pass effect.

DISADVANTAGES OF AEROSOLS

- Expensive.
- Chlorofluorocarbon propellants cause Ozone layer depletion.
- Inflammability
- Toxicity
- Explosive

COMPONENTS OF AEROSOLS

- Propellant
- Container
- Valve and actuator
- Product concentrate



PROPELLANTS

- Responsible for developing proper pressure within the container.
- Provide driving force to expel the product from the container.

TYPES OF PROPELLANTS

(a) Liquefied gases Propellants

(b) Compressed gases Propellants

LIQUEFIED GAS PROPELLANTS

- Liquefied propellants are gases that exist as liquids under pressure.
- Because the propellant exists mainly as a liquid, but it will also be in the head space as a gas.
- The product is used up as the valve is opened, some of the liquid propellant turns to gas and keeps the head space full of gas.
- In this way the pressure can remains essentially constant and the spray performance is maintained throughout the life of the aerosol.

CHLORO FLUORO CARBONS

- Propellant of choice for oral inhalation and sprays .

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

HYDROCARBONS

- Can be used for water based aerosols and topical use.

Advantages

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

Disadvantages

- Inflammable
- Unknown toxicity produced

Ex: Propane - Propellant A-108

Isobutane - Propellant A-31

Butane - Propellant A-17

HYDROFLUORO CARBONS AND HYDRO CHLORO FLUORO CARBONS

•These compounds break down in the atmosphere at faster rate than CFCs.

• Lower ozone destroying effect.

Advantages

- Low inhalation toxicity
- High chemical stability
- High purity
- Not ozone depleting

Disadvantages

- Poor solvent
- High cost

Examples: Heptafluoro propane (HFA-227)

Tetrafluoroethane (HFA-134a)

Difluoroethane - Propellant 152a

Chlorodifluoromethane - Propellant 22

Chlorodifluoroethane - Propellant 142 b

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

A . Metals

1. Tinplated steel
2. Aluminum
3. Stainless steel

B. Glass

1. Uncoated glass
2. Plastic coated glass

TIN PLATED STEEL CONTAINERS

- It consist of a sheet of steel plate, this sheet is coated with tin by electrolytic process .
- The coated sheet is cut into three pieces (top , bottom and body) .
- The top, bottom are attached to body by soldering .
- When required it is coated with organic material usually oleoresin, phenolic , vinyl or epoxy coating .
- Welding eliminates soldering process, Saves considerable manufacturing time and decreases the product/container interaction.
- Recent developments in welding include Soudronic system and Conoweld system.

ALUMINIUM CONTAINERS

- Used for inhalation and topical aerosols .
- Manufactured by impact extrusion process.
- Light in weight, less fragile, Less incompatibility due to its seamless nature.
- Greater resistance to corrosion .
- Pure water and pure ethanol cause corrosion to Al containers.
- Added resistance can be obtained by coating inside of the container with organic coating like phenolic , vinyl or epoxy and polyamide resins.

STAINLESS STEEL CONTAINERS

- Used for inhalation aerosols

Advantage :

- Extremely Strong.
- Resistant to many materials.
- No need for internal coating.

Disadvantage :

- Costly

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.

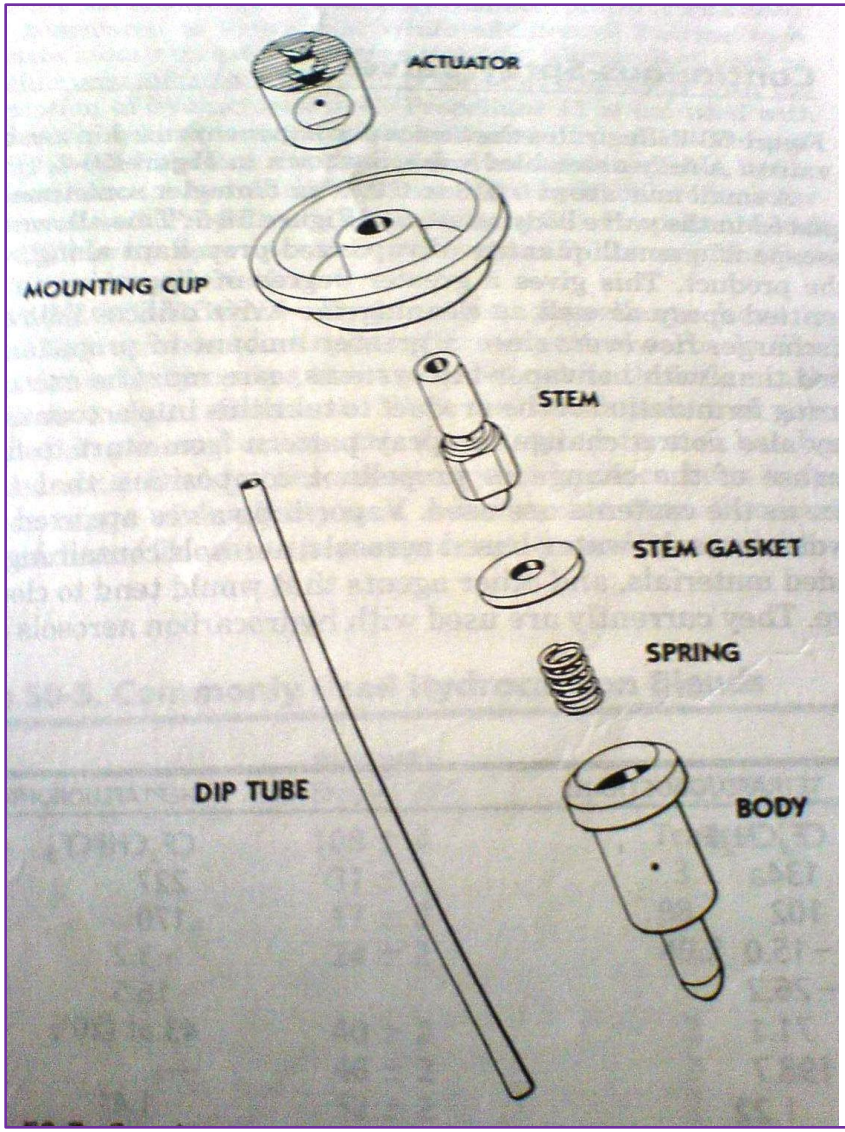
VALVES

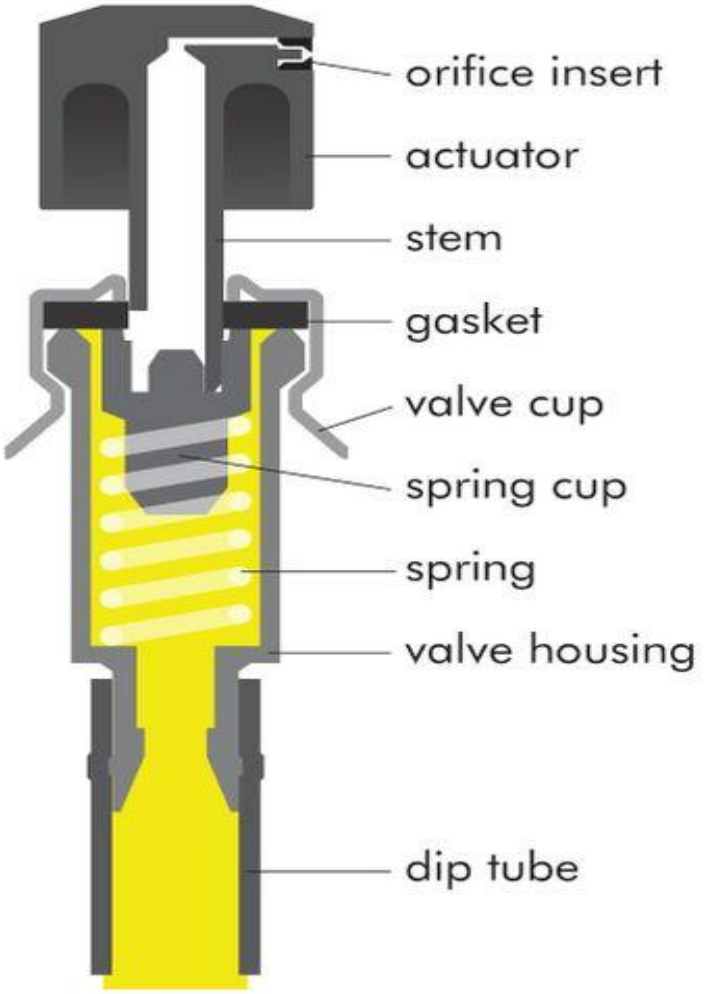
- Easy to open and close .
- Capable of delivering the content in the desired form such as spray, foam, solid stream etc.
- It can deliver a given amount of medicament .

TYPES OF VALVES :

1. Continuous spray valve
2. Metering valves

VALVE ASSEMBLY



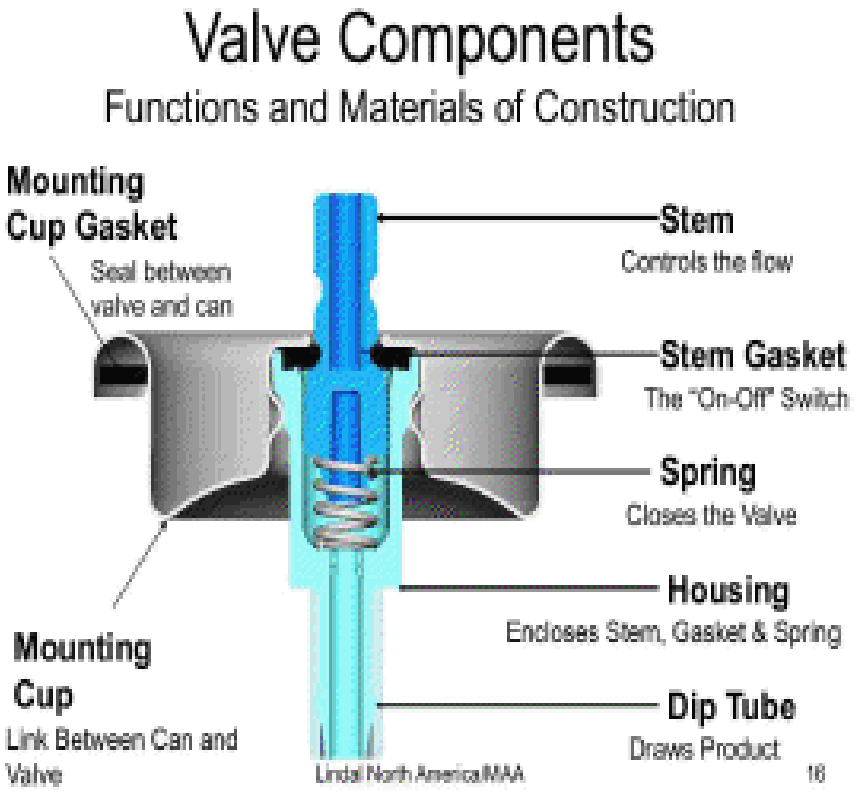


CONTINUOUS SPRAY VALVE

- Used for topical aerosols .

Valves assembly consists :

- Ferrule or mounting cup
- Valve body or housing
- Stem
- Dip tube
- Gasket
- Spring



FERRULE OR MOUNTING CUP :

- 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 :

- Made up of Nylon or Derlin and contains a opening at the point of attachment of dip tube. (0.013 to 0.080 inch)

STEM :

- Made from Nylon or Derlin , brass and stainless steel can also be used.

GASKET :

- Made from Buna-N and neoprene rubber.

SPRING :

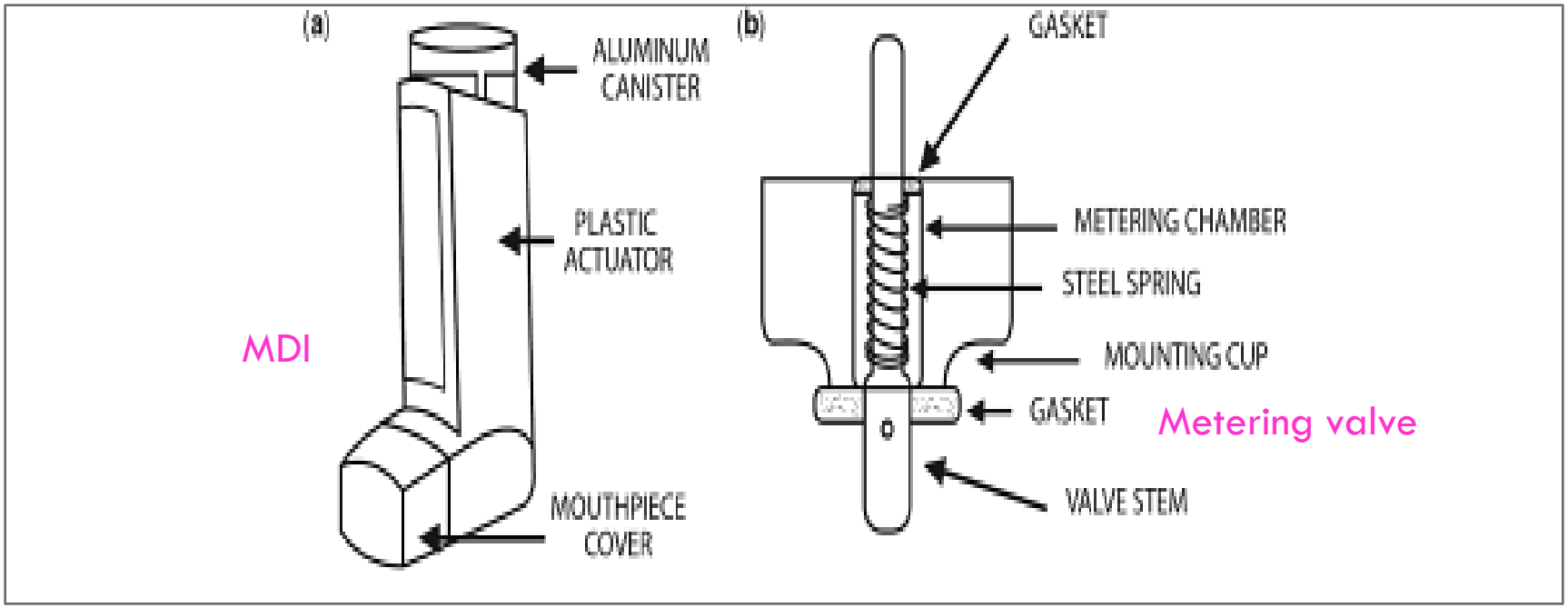
- Made from Stainless steel .
- Used to hold gasket in place.

DIP TUBE :

- Made from Poly ethylene or poly propylene.
- Inner diameter 0.120 – 0.125 inch.
- However for Capillary dip tube inner diameter is 0.050 inch and for highly viscous products it is 0.195 inch.

METERING VALVES

- Used for dispensing of potent medication.
- Operates on the principle of a chamber whose size determines the amount of medication dispensed.
- Approximately 50 to 150 ml ±10 % of liquid materials can be dispensed at one time with the use of such valve.



ACTUATORS

• These are specially designed buttons which helps in delivering the drug in desired form i.e., spray, wet stream, foam or solid stream .

TYPES OF ACTUATORS :

• Spray actuators

• Foam actuators

• Solid steam actuators

• Special actuators

SPRAY ACTUATORS:

• It can be used for topical preparation, such as antiseptics, local anesthetics and spray on bandages etc.

• It allows the stream of product concentrate and propellant to pass through various openings and dispense as spray.

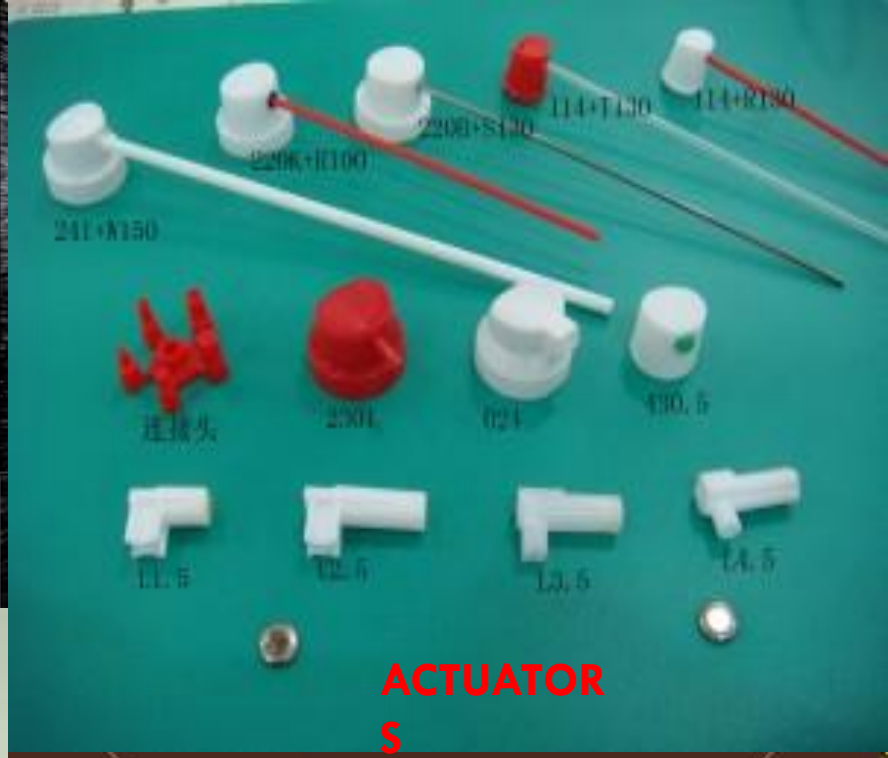
FOAM ACTUATORS :

• It consist of large orifice which ranges from 0.070—0.125 inch .

SOLID STREAM ACTUATORS :

• These actuators are required for dispensing semi solid products such as ointments .


SPRAY


ACTUATOR
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ACTUATORS


FOAM

METERED DOSE INHALERS

- Used to minimize the number of administration errors.
- To improve the drug delivery of aerosolized particles into the nasal passageways and respiratory tract.

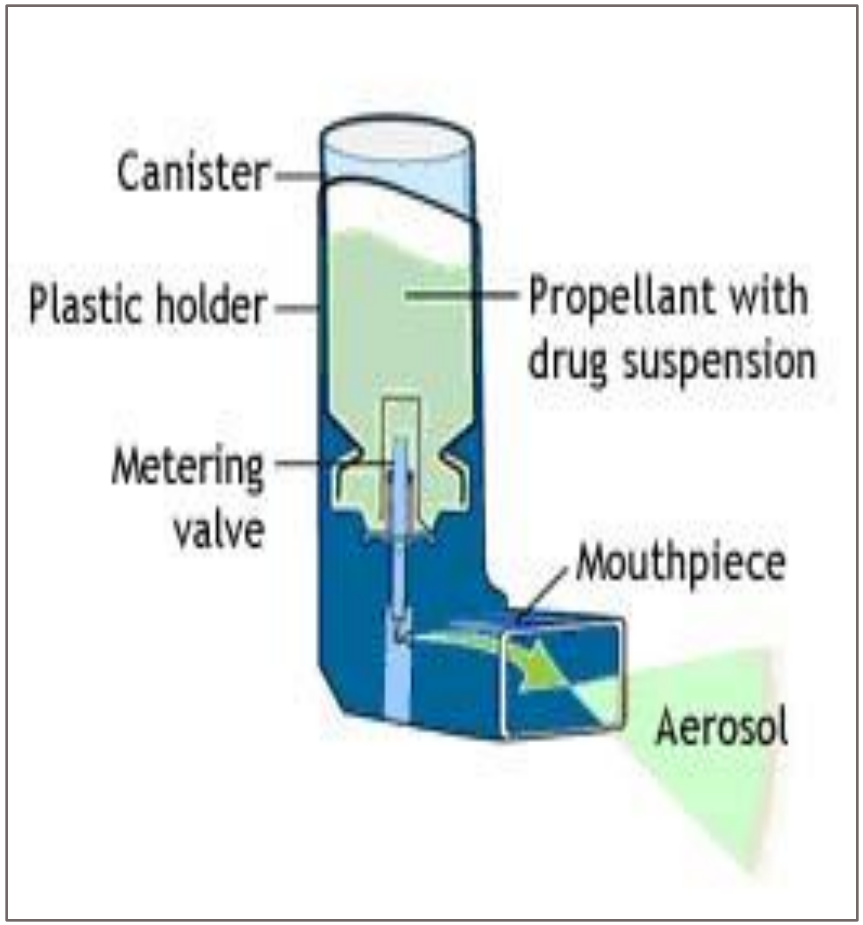
Advantages of MDI:

- It delivers specified amount of dose .
- Portable and compact.
- Quick to use , no contamination of product.
- Dose-dose reproducibility is high.

Disadvantages of MDI :

- Low lung deposition ; high pharyngeal deposition .
- Coordination of MDI actuation and patient inhalation is needed.

Metered Dose Inhalers (MDIs)



MARKETED PHARMACEUTICAL AEROSOL PRODUCTS

Metered Dose inhalers :

BRAND NAME	DRUG	USE
Flovent Diskus	Fluticasone	Asthma
Advair	Fluticasone and Salmeterol	Asthma
Aerobid	Flunisolide	Asthma
Qvar	Beclomethasone	Asthma
Proventil	Albuterol	Bronchospasm

FORMULATION OF AEROSOLS

- It consist of two essential components :

1. Product concentrate and
2. Propellant

Product concentrate :

Active ingredient or mixture of active ingredients and other necessary agents such as solvents, anti oxidants and surfactants.

Propellant :

- Single or blend of various propellants is used.
- Blend with solvents is used to achieve desired solubility characteristics.

TYPES OF SYSTEMS

TYPES OF AEROSOL SYSTEMS :

- Solution system
- Water based system
- Suspension or Dispersion systems
- Foam systems
    1. Aqueous stable foams
    2. Non aqueous stable foams
    3. Quick-breaking foams
    4. Thermal foams
- Intranasal aerosols

SOLUTION SYSTEM

- This system is also referred to as Two phase system consists of vapor and liquid phase.
- If active ingredient is soluble in propellant ,no other solvent is required.
- The vapor pressure of system is reduced by the addition of less volatile solvents such as ethanol, acetone , propylene glycol, glycerin, ethyl acetate. This results in production of larger particles upon spraying.
- Amount of Propellant may vary from 5% (for foams) to 95% (for inhalations).

General formula	**weight %**
Active drug	- to 10-15
Propellant 12/11 (50:50)	- to 100

- Depending on water content the final product may be solution or three phase system.

- Solution aerosols produce a fine to coarse spray.

- Hydrocarbon propellant A-70 produces drier particles while propellants A-17 and A-31 tend to produce a wetter spray.

- These are useful for topical preparations.

- Packaged in Plastic coated glass containers.

WATER BASED SYSTEM

- Large amounts of water can be used to replace all or part of the non aqueous solvents used in aerosols.
- Produce spray or foam.
- To produce spray, formulation must consist of dispersion of active ingredients and other solvents in emulsion system in which the propellant is in the external phase.
- Since propellant and water are not miscible, a three phase aerosol forms (propellant, water and vapor phases).
- Ethanol can be used as cosolvent to solubilize propellant in water. It also reduces surface tension aiding in the production of smaller particles .
- 0.5 to 2% of surfactant is used to produce a homogenous dispersion.

SUSPENSION SYSTEM

- It involves dispersion of active ingredient in the propellant or mixture of propellants.
- To decrease the rate of settling of dispersed particles, surfactants or suspending agents can be added.
- Primarily used for inhalation aerosols.

Example:

Formulation	Weight%
Epinephrine bitartrate (1-5 Microns)	0.50
Sorbitan trioleate	0.50
Propellant -114	49.50
Propellant -12	49.50

Epinephrine bitartrate has minimum solubility in propellant system but soluble in fluids in the lungs.

Physical stability of aerosol dispersion can be increased by:

1. Reduction of initial particle size to less than 5 µm.
2. Adjustment of density of propellant and suspensoid so that they are equalized.
3. Use of dispersing agents.
4. Use of derivatives of active ingredients with minimum solubility in propellant system.

FOAM SYSTEMS

• Emulsion and foam aerosols consist of active ingredients, aqueous or non aqueous vehicle, surfactant, Propellant and are dispensed as a stable or quick breaking foam depending on the nature of the ingredients and the formulation.

AQUEOUS STABLE FOAM :

Formulation	%w/w
Active ingredient	
Oil waxes	
o/w surfactant	95-96.5
Water	
Hydrocarbon Propellant (3 -5%)	3.5-5

- Total propellant content is usually (3 or 5% w/w).
- As the amount of propellant increases a stiffer and dryer foam is produced.
- Lower propellant concentrations yield wetter foams.
- Hydrocarbon and compressed gas propellants are used.

NON-AQUEOUS STABLE FOAM :

Formulation	%w/w
Glycol	91-92.5
Emulsifying agent	4
Hydrocarbon propellant	3.5-5

- Glycols such as poly ethylene glycols are used.
- Emulsifying agent is propylene glycol monostearate.

QUICK BREAKING FOAM :

- Propellant is in the external phase .
- When dispensed the product is emitted as a foam, which then collapses into a liquid.
- Especially applicable to topical medications .

Formulation	%w/w
Ethyl alcohol	46-66
Surfactant	0.5-5
Water	28-42
Hydrocarbon Propellant	3-15

- Surfactant should be soluble in both alcohol and water and can be of non ionic or cationic or anionic type.

THERMAL FOAM :

- Used to produce warm foam for shaving .
- Used to dispense hair colors and dyes but were unsuccessful due to the corrosion problems and are expensive , inconvenient to use and lack of effectiveness.

INTRANASAL AEROSOLS :

- Intended to deposit medication into nasal passages for local or systemic effect.

ADVANTAGES

- Deliver measured dose of drug.
- Require lower doses compared to other systemic products.
- Excellent depth of penetration into the nasal passage way.
- Decreased mucosal irritability .
- Maintenance of sterility from dose to dose.
- Greater flexibility in the product formulation.

MANUFACTURE OF PHARMACEUTICAL AEROSOLS

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

PRESSURE FILLING APPARATUS

- It consists of a pressure burette capable of metering small volumes of liquefied gas into the aerosol container under pressure.
- Propellant is added through an inlet valve located at the bottom or top of the pressure burette.
- The propellant is allowed to flow with its own vapor pressure in the container through aerosol valve.
- The trapped air escapes out from the upper valve.

- The propellant stops flowing when the pressure of burette and container becomes equal.
- If further propellant is to be added, a hose (rubber pipe) leading to a cylinder of nitrogen is attached to the upper valve, the pressure exerted by nitrogen helps in the flow of the propellant into the container.
- Another pressure filling device makes use of piston arrangement and is capable of maintaining positive pressure .
- This type of device cannot be used for filling inhalation aerosols which have metered valves.

PROCEDURE:

•This method involves filling of the concentrate into the container at the room temperature.

• Then the valve is placed in the container and crimped.

• Through the opening of the valve the propellant are added.

• Since the opening of the valve are smaller in size ranging from 0.018-0.030 inches, it limits the production and the process becomes slow.

• But with the use of rotary filling machines and newer filling heads where the propellants are filled through valve stem, the production rate is increased.

• The trapped air in the container and air present in head space is removed before filling the propellant to protect the products from getting adversely affected.

• Various units used in pressure filling line are arranged in the following order :

Unscrambler , Air cleaner , Concentrate filler , Valve placer , Purger ,Valve crimper , Propellant filler ,Water bath , Labeler , Coder and Packing table .

• Purger ,vacuum crimper and pressure filler are replaced with a single unit if filling is carried by ‘under the cap’ method.

ADVANTAGES OF PRESSURE FILLING:

- Solutions, emulsions, suspensions can be filled by this method.
- Contamination due to moisture is less.
- High production speed can be achieved.
- Loss of propellant is less.

DISADVANTAGES :

- Certain types of metering valves can not be handled.
- Process is slower than Cold filling method.

Pressure burette

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.
- The insulated box should be filled with dry ice or acetone prior to use.
- The apparatus can be operated with or without metered valves.
- Hydrocarbon propellant cannot be filled into aerosol containers using this apparatus because large amount of propellant escapes out and vaporizes.
- This may lead to formation of an explosive mixture .
- Fluorocarbon vapors do not form any explosive or flammable mixture though their vapors are heavier than air.

PROCEDURE:

- Non aqueous products which can withstand low temperatures of - 40°F are used in this method.
- The product concentrate is chilled to a temperature of - 40°F and filled into already chilled container.
- Then the chilled propellant is added completely in 1 or 2 stages, depending on the amount.
- Another method is to chill both the product concentrate and propellant in a separate pressure vessel to - 40 °F and then filling them into the container.
- The valve is placed and crimped on to the container.
- Then test for leakage and strength of container is carried out by passing container into a heated water bath, where the contents of the container are heated to 130°F. After this, the containers are air dried , capped and labeled.

• Various units used in cold filling methods are :
Unscrambler, Air cleaner ,Concentrate filler ,Propellant filler ,Valve placer ,Valve crimper ,Water bath ,Labeler, Coder and Packing table .

• The cold filling method is no longer being used, as it has been replaced by pressure filling method.

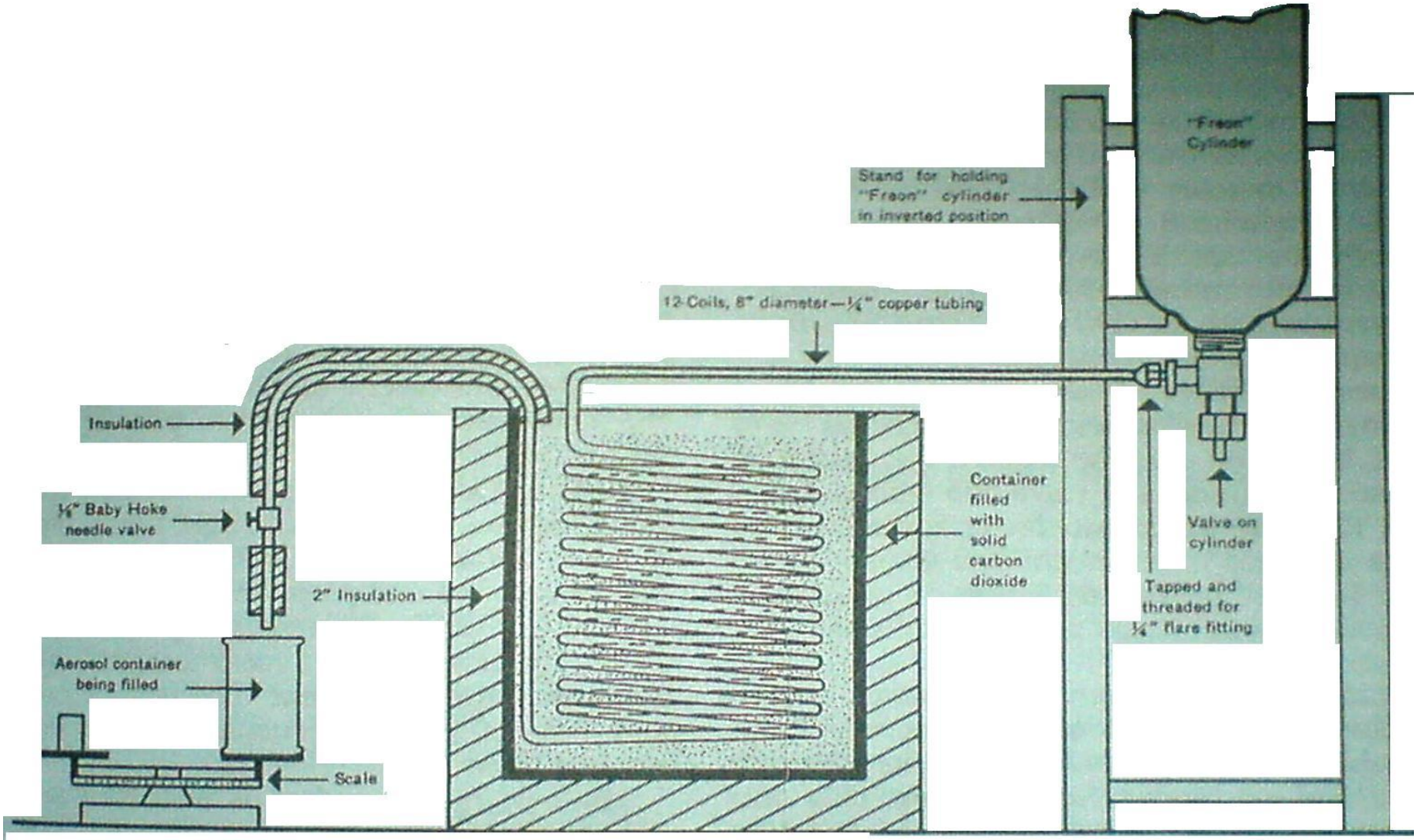
Advantage:

• Easy process .

Disadvantages :

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

COLD FILLING APPARATUS



COMPRESSED GAS FILLING APPARATUS

- Compressed gases have high pressure hence a pressure reducing valve is required.
- The apparatus consists of delivery gauge.
- A flexible hose pipe which can withstand 150 pounds per square inch gauge pressure is attached to the delivery gauge along with the filling head.
- A flow indicator is also present in specialized equipments.

PROCEDURE :

- The product concentrate is filled into the container.
- Valve is placed and crimped on the container.
- With the help of vacuum pump the air is removed from the container.
- Filling head is put in the opening of the valve and the valve is depressed and the gas is allowed to flow in to container.
- The gas stops flowing if the delivery pressure and the pressure within the container become equal.
- Carbon dioxide and nitrous oxide is used if more amount of gas is required.
- High solubility of the gas in the product can be achieved by shaking the container manually or with the help of mechanical shakers.

QUALITY CONTROL TESTS

It includes the testing of

1. Propellants
2. Valves, Actuators and Dip Tubes
3. Containers
4. Weight Checking
5. Leak Testing
6. Spray Testing

1. PROPELLANTS :

- Vapor pressure and density of the propellant are determined and compared with specification sheet.

Parameter	Tested By
Identification	Gas Chromatography IR Spectroscopy
Purity and acceptability	Moisture, Halogen, Non-Volatile Residue determinations

2. VALVES , ACTUATORS AND DIP TUBES :

- Sampling is done according to standard procedures as found in Military Standards “MIL-STD-105D”.
- For metered dose aerosol valves ,test methods were developed by
  - → ‘Aerosol Specifications Committee’
  - → ‘Industrial Pharmaceutical Technology Section
  - → ‘Academy Of Pharmaceutical Sciences.
- The objective of this test is to determine magnitude of valve delivery & degree of uniformity between individual valves.
- Standard test solutions were proposed to rule out variation in valve delivery.

TEST SOLUTIONS

Ingredients % w/w	Test Solutions 'A'	Test Solutions 'B'	Test Solutions 'C'
Iso Propyl Myristate	0.10%	0.10%	0.10%
Dichloro Difluoro methane	49.95%	25.0%	50.25%
Dichloro tetrafluoro ethane	49.95%	25.0%	24.75%
Trichloro monofluoro methane	-	-	24.9%
Alcohol USP	-	49.9%	-
Specific Gravity @ 25°c	1.384	1.092	1.388

Testing Procedure:

- Take 25 valves and placed on containers filled with specific test solution.
- Actuator with 0.020 inch orifice is attached.
- Temperature -25±1°C.
- Valve is actuated to fullest extent for 2 sec and weighed.
- Again the valve is actuated for 2 sec and weighed.
- Difference between them represents delivery in mg.
- Repeat this for a total of 2 individual deliveries from each of 25 test units.

$$\text{Valve delivery per actuation in } \mu L = \frac{\text{Individual delivery wt in mg.}}{\text{Specific gravity of test solution}}$$

Valve Acceptance:

Deliveries	Limit's
54µL or less	± 15%
55 to 200 µL	± 10%

Of the 50 individual deliveries,

- If 4 or more are outside the limits : valves are rejected
- If 3 deliveries are outside limits : another 25 valves are tested.

  Lot is rejected if more than 1 delivery is outside the specifications.
- If 2 deliveries from 1 valve are beyond limits : another 25 valves are tested.

  Lot is rejected if more than1 delivery is outside specification.

3. CONTAINERS :

- Containers are examined for defects in lining.
- Quality control aspects includes degree of conductivity of electric current as measure of exposed metals.
- Glass containers examined for Flaws.

4. WEIGHT CHECKING :

- Is done by periodically adding to the filling line tared empty aerosol containers, which after filling with concentrate are removed & weighed.
- Same procedure is used for checking weight of Propellants being added.

5. LEAK TESTING :

- It is a means of checking crimping of the valve and detect the defective containers due to leakage.
- Is done by measuring the Crimp's dimension & comparing.
- Final testing of valve closure is done by passing the filled containers through water bath.

6. SPRAY TESTING :

- Most pharmaceutical aerosols are 100% spray tested.
- This serves to clear the dip tube of pure propellant and pure concentrate.
- To check for defects in valves and spray pattern.

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

C. Performance:

1. Aerosol valve discharge rate
2. Spray pattern
3. Dosage with metered valves
4. Net contents
5. Foam stability
6. Particle size determination

D. Biological testing :

1. Therapeutic activity
2. Toxicity studies

A. Flammability and combustibility

1. Flash point:

Apparatus : Tag Open Cup Apparatus

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

2. 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:

Property	Method
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.

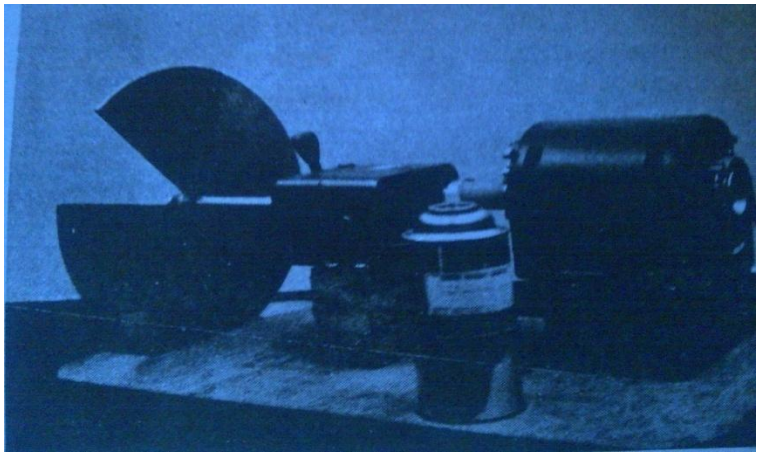
C. Performance:

1. 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).

2. 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.



3. Dosage with metered valves :

- Reproducibility of dosage can be determined by:

»Assay techniques

»Accurate weighing of filled container followed by dispensing of several doses . Containers are then reweighed and difference in weight divided by number of doses dispensed gives average dose.

4. 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.

5. Foam stability :

Methods : » Visual Evaluation,

» Time for given mass to penetrate the foam,

» Time for given rod that is inserted into the foam to fall ,

» Rotational Viscometer.

6. Particle Size Determination :

Methods : » Cascade Impactor,

» Light Scattering Decay.

a). Cascade Impactor :

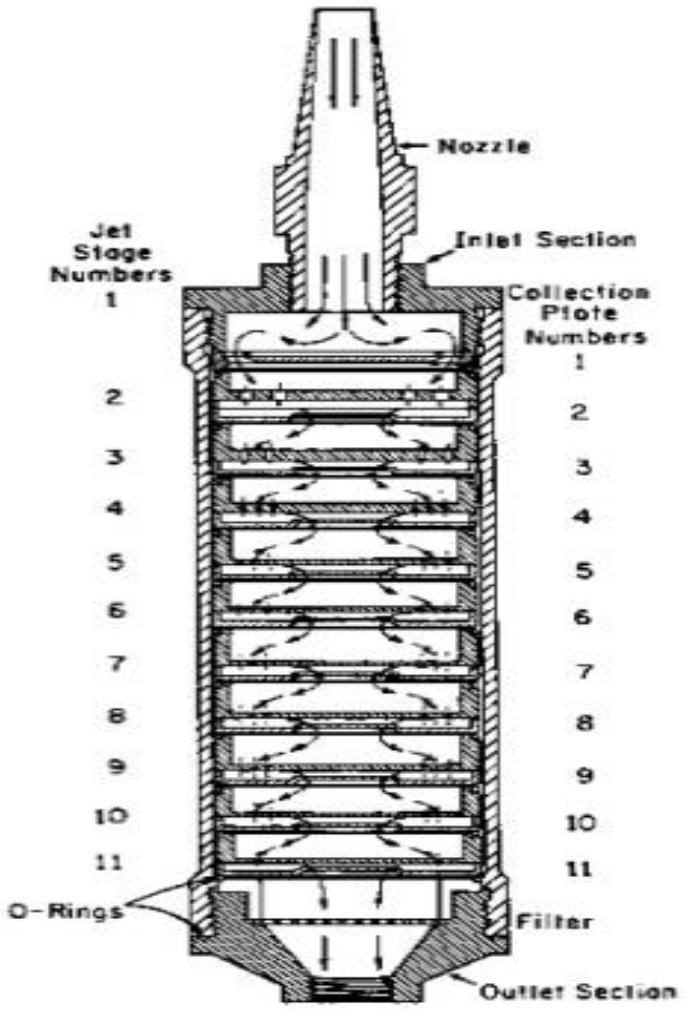
Principle :

Stream of particles projected through a series of nozzles and glass slides at high velocity, larger particle are impacted first on lower velocity stage and smaller particles are collected at higher velocity stage.

b). Light Scattering Decay :

Principle :

As aerosol settles under turbulent conditions, the change in the light intensity of a Tyndall beam is measured.



D. Biological testing:

1.Therapeutic Activity :

» For Inhalation Aerosols : dosage of the product is determined and is related to the particle size distribution.

» For Topical Aerosols : is applied to test areas and adsorption of therapeutic ingredient is determined.

2.Toxicity :

» For Inhalation Aerosols : exposing test animals to vapors sprayed from aerosol container.

» For Topical Aerosols : Irritation and Chilling effects are determined.

Thank you……