**PHARMACEUTICAL AEROSOLS**

**HISTORY**

* In1941 the aerosol spray can was first put to good use by Americans Lyle Goodhue and William Sullivan, who are credited as the inventors of the modern spray can.
* Pressurized aerosol form was developed in early 1950 and was introduced as Medihaler Epi by Ricker Laboratories.

**DEFINITION**

‘A system that depends on the power of a compressed or liquefied gas to expel the contents from the container.’

‘Pressurized dosage forms containing one or more active ingredients which upon actuation emit a fine dispersion of liquid and/or solid materials in a gaseous medium.’

**ADVANTAGES**

* Removal of dose without contamination.
* Directly delivered to the affected area in a desired form.
* Minimized manual contact with drug.
* Rapid response.
* Convenient, easy.
* Controlled and uniform dosage by metered valves.
* No manual contact with patient.

**DISADVANTAGES**

* Costly.
* Difficulty in disposal.
* Difficulty in formulation.
* Q.C testing is complicated.
* Cannot be subjected to heat.

**COMPONENTS**

Aerosols consist of

* + - Propellant
    - Container
    - Valve and Actuator
    - Product concentrate

Product concentrate consists of API, Additives like suspending agent, antioxidants, aqueous and non aqueous solvents, co solvent, emulsifying agents etc

**PROPELLANT**

* Develops pressure within the container.
* Expels the product, when the valve is opened.
* Aids in foam production.
* Vapor pressure differs.

Mainly three types:

1. Liquefied gas system
2. a) Fluorinated hydrocarbon(FHC)

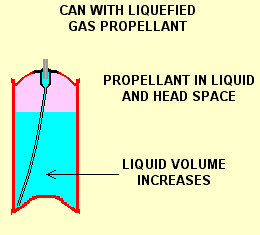
b) Chlorofluorocarbon (CFC)

c) Hydrocarbons (HC)

3. Compressed gas system

**LIQUIFIED GAS SYSTEM**

* Gases at room temperature and atmospheric pressure.
* Liquefied easily by lowering the temperature.
* Boiling point below 700F and vapour pressure 14 - 85 psig.
* When placed into container, immediately separates into a liquid & a vapour phase.



**FLUORINATED HYDROCARBONS**

It is used for oral and inhalation aerosol preparation

**Chemical Name Numerical Designation**

Trichloromonoflouromethane Propellant 11

Dichlorodifluromethane Propellant 12

Dichlorotetrafluromethane Propellant 114

Chloropentaflouroethane Propellant 115

**CHLORO FLURO CARBON (CFC)**

**Advantages**

1. Low inhalation toxicity
2. High chemical stability
3. High purity
4. CFC-11 is a good solvent

**Disadvantages**

1. Destructive to atmospheric Ozone
2. Contributes to “greenhouse effect”
3. High cost

eg.1. Hydrochlorocarbon

2. Hydroflurocarbon

**HYDROCARBONS**

**Chemical Name** **Numerical Designation**

Butane A-17

Isobutane A-31

Propane A-108

It is mainly used for the preparation of topical preparation

1. Chemically stable
2. No hydrolysis
3. Inflammable
4. Low toxicity
5. Lighter than water

**COMPRESSED GAS SYSTEM**

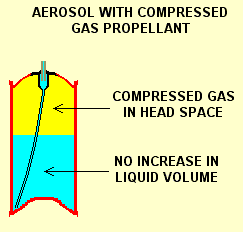
Eg.CO2, NO2

**Advantages**

1. Low inhalation toxicity
2. High chemical stability
3. High purity
4. Inexpensive

**Disadvantages**

1. Require use of a nonvolatile co-solvent
2. Produce coarse droplet sprays
3. Pressure falls during use



**Physicochemical properties of propellants**

* Vapor pressure, Boiling point & Liquid density
* Vapor pressure of mixture of propellants, calculated by Dalton’s law : ‘total pressure in any system is the sum of the individual partial pressures of various components.’
* Raoult’s law regards lowering of the vapor pressure of a liquid by the addition of another substance, States that the depression of the vapor pressure of solvent upon the addition of solute is proportional to the mole fraction of solute molecules in solution.

**CONTAINERS**

Withstand a pressure as high as 140 to 180 psig (pounds per sq. inch gauge) at 1300 F

A. Metals

1. Tin plated steel

(a) Side-seam (three pieces)

(b) Two-piece or drawn

(c) Tin free steel

2. Aluminum

(a) Two-piece

(b) One-piece (extruded or drawn)

3. Stainless steel

B. Glass

1. Uncoated glass

2. Plastic coated glass

**1.Tin plated containers**

* Tin containers, electroplated with sheets of steel plate on both sides.

**2. Aluminum containers**

* Greater resistance to corrosion
* Light weight, not fragile
* Good for light sensitive drugs

**3. Stainless steel container**

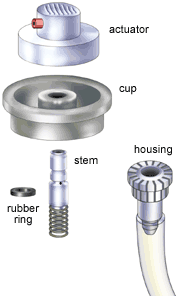
* Limited for smaller size
* Extremely strong and resistant to corrosion
* Withstand pressure

**4. Glass containers**

* Available with plastic or without plastic coating
* Compatible with many additives
* No corrosion problems
* Can have various shape because of molding
* Fragile
* Not for light sensitive drugs

**VALVE**

* + 1. Actuator
    2. Ferrule or mount cap
    3. Valve body or housing
    4. Stem
    5. Gasket
    6. Spring
    7. Dip tube



**ACTUATOR**

* Specially designed button placed on the valve system, helps in easy opening and closing of the valve.
* Directs the spray to the desired area.
* Types of actuaters-

-Spray Actuators

-Foam Actuators

-Solid Stream Actuators

-Special Actuators

**Ferrule/ mounting cup**

* Attach the valve in proper position in container.
* Coated with epoxy resin.

**Valve body / housing**

* Made of nylon/ delrin
* Connect dip tube, stem & actuator
* Determines rate of delivery

**Stem**

* It is made of nylon /delrin /s.steel
* One or more orifice (0.013 to 0.030 inch)

**Gasket**

* It is made of Buna –N, Neoprene rubber

**Spring**

* Hold the gasket in its place
* Made of stainless steel

**Dip tube**

* Made of poly propylene material / poly ethylene
* Inner diameter 0.120 –0.125 inch for less viscous
* Viscous product - 0.195 inch.

**TYPES OF AEROSOL SYSTEM**

Four types :

* + - 1. Solution system / Two phase system
      2. Water based system / Three phase system
      3. Suspension or Dispersion system
      4. Foam system

Aqueous stable foam

Non-Aqueous stable foam

Quick Breaking Foam

Thermal foam

**Two phase system**

* Contains both vapor & liquid.
* Drug soluble in propellant – no co-solvent.
* Propellant 12 – single or mixture.
* In mixture – propellant with vapor pressure less than propellant 12 , vapor pressure reduction, bigger sized aerosol particles.
* E.g. propellant 12/11(30:70), propellant 12/114(45:55).

**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)

**Suspension system**

* Using suspending agent.
* Oral inhalation aerosols.
* Active ingredients dispersed in propellant or mixture
* Physical stability increaseby-
  + Control of moisture content
  + Active ingredients with minimum solubility.
  + Initial particle size < 5 microns
  + Propellant density
  + Suspending agents

**Foam system**

* Consists of aq. or non aq. vehicles, propellant & surfactants.
* Four types-
  + - * Aqueous stable foams
      * Non aqueous stable forms
      * Quick breaking forms
      * Thermal forms
    - **Aqueous stable foams**
      * + Propellant 3-4%
        + Dry spray is produced
        + Propellant – internal phase
        + Steroidal antibiotics
    - **Non aqueous stable foams**
      * + Emulsifying agent - glycol
    - **Quick breaking foams**
      * + Propellant – external phase
        + Topical application
        + Cationic, anionic, non ionic surfactants
    - **Thermal foams**
      * + Delivered as foam on application of heat
        + Shaving creams

**MANUFACTURING OF PHARMACEUTICAL AEROSOLS**

**Apparatus**

1. Cold filling apparatus

2. Pressure filling apparatus

3. Compressed gas filling apparatus

**COLD FILLING APPARATUS**

Insulated box fitted with copper tubings

**Methods**

**Method A**

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

**Method B**

* Product concentrate and propellant chilled to -30 to -40o 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.

**Advantage**: Easy process

**Disadvantage**

* Aqueous products, emulsions cannot be filled.
* For non aqueous systems, moisture appears in final product.

**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.

**Advantages**

* Preferred for solutions, emulsions & suspensions.
* Less contamination.
* Less propellant is lost.
* No refrigeration.

**COMPRESSED GAS FILLING APPARATUS**

* 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

**QUALITY CONTROL TESTS**

It includes the testing of:

» Propellants

» Valves, Actuator, Dip Tubes

» Containers

» Weight Checking

» Leak Testing

» Spray Testing

**Propellants**

Vapor pressure is determined & compared to Specifications.

|  |  |
| --- | --- |
| Parameter | Tested By |
| * Identification * Purity | Gas Chromatography  Moisture, Halogen, Non-Volatile Residue Determinations |

**Valves, Actuators & Dip tubes**

* + - * Take 25 valves & placed on containers,
      * Filled with specific test solution
      * Actuator with 0.020 inch orifice is attached.( containers placed at temp. 25±10 C)
      * Valve is actuated to fullest extent for 2 sec.
      * Repeat for total of 2 individual delivery from each 25 test units.

Individual delivery wt in mg.

Valve delivery per actuation in µL =

Specific gravity of test solution

*Valve Acceptance:* Deliveries Limits

54µL or less ± 15%

55 to 200 µL ± 10%

**Of 50 deliveries**

* If 4 or more are outside limits : valves are rejected
* If 3 individual deliveries are outside limits : another 25 valves are tested

Lot is rejected if more than 1 delivery is outside specification

* If 2 deliveries from 1 valve are beyond limits : another 25 valves are tested

Lot is rejected if more than 1 delivery is outside specification

**Containers**

* Containers are examined for defects in lining.
* Q.C aspects includes degree of conductivity of electric current as measure of exposed metals.
* Glass containers examined for Flaws.

**Weight Checking**

* Add tared empty aerosol container to filling lines which after filling with concentrate are removed & weighed.
* Same procedure is used for checking weight of Propellants.

**Leak Test**

* Done by measuring the Crimp’s dimension & comparing.
* Final testing of valve closure is done by passing filled containers through water bath.

**Spray Testing**

* It is done

-To clear dip tube of pure propellant & concentrate,

-To check for defects in valves & spray pattern.

**EVALUATION TESTS**

**A. Flammability & combustibility:**

1.Flash point

2.Flame Projection

**B. Physicochemical characteristics:**

1.Vapour 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

**E. Extractable Substances**

**A. Flammability & combustibility:**

* **Flash point:**

Apparatus : **Open Cup Tag Apparatus**

Test liquids temp. is allowed to increase slowly & temp. at which vapors ignite is called as Flash Point .

* **Flame Projection:**

Product is sprayed for 4 sec onto flame & exact length is measured with ruler.

**B. Physicochemical characteristics:**

|  |  |
| --- | --- |
| Property | Method |
| 1. Vapor Pressure | » Can Puncturing Device. |
| 2. Density | » Hydrometer,  » Pycnometer. |
| 3. Moisture | » Karl Fisher Method,  » Gas Chromatography. |
| 4. Identification | » Gas Chromatography,  » IR Spectroscopy. |

**C. Performance:**

**1. Aerosol valve discharge rate :**

* Aerosol product of known weight is discharged for specific time.
* By reweighing the container, the change in the wt. per time dispensed is the discharge rate (g/sec).

**2. Spray pattern :**

* The method is based on the impingement of spray on piece of paper that has treated with Dye-Talc mixture.

**3. Dosage with metered valves:**

* Reproducibility of dosage determined by:

-Assay

-Accurate weighing of filled container followed by dispensing several dosage.

* Containers again reweighed & diff. in wt. divided by no. of dosage dispensed gives average dose.

**4. Net Contents :**

* Tared cans placed on filling lines are reweighed & then difference in wt. is equal to net content.
* In Destructive method: opening the container & removing as much of product possible.

**5. Foam stability:**

Methods:

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

**6. Partical Size Determination :**

Methods : » Cascade Impactor,

» Light Scattering Decay.

**a). Cascade Impactor :**

**Principle**:

Stream of particle projected through a series of nozzle & glass slides at high velocity, larger particle impacted on low velocity stage & smaller on higher velocity stage.

**b). Light Scattering Decay:**

**Principle :**

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

**D. Biological testing:**

**1.Therapeutic Activity :**

* For Inhalation Aerosols : Depends on the particle size.
* For Topical Aerosols : Is applied to test areas & absorption of therapeutic ingredient is determined.

**2.Toxicity :**

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

**E. 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.

**LABELING**

Medicinal aerosols should contain at least the following:

* 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 1200 F.
* Use only as directed.