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Pharmaceutical Aerosol

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ABSTRACT: The packaging of therapeutically active ingredients in a pressurized system is not new to the pharmaceutical industry. According to present day usage, an aerosol is defined as a pressurized dosage form that depends on the power of a compressed or liquefied gas (propellant) to expel the contents from the container. This technology was applied for the development of pharmaceutical aerosols in the early 1950s. These aerosol products are intended for topical administration for the treatment of burns, minor cuts and bruises, infections, and various other dermatologic conditions. They also found applications for local activity in the respiratory tract and in 1955 epinephrine was made available as a pressurized package. Based on their acceptability to both physician and patient, and their widespread use, pharmaceutical aerosols represent a significant dosage form and should be considered along with other dosage forms, such as tablets, capsules, solutions, etc. Topical preparations are also well suited for presentation in the form of aerosols or sprays.

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INTRODUCTION:

Aerosols are colloidal dispersions of liquids or solids in gases. In general, mists and fogs possess liquid dispersed phases, while smokes, fumes and dusts are dispersions of solid particles in gases. In common with other colloidal dispersions aerosols may be prepared by either dispersion or condensation methods. The latter type involves the initial production of supersaturated vapour of the material that is to be dispersed. This may be achieved by super-cooling the vapour. The supersaturation eventually leads to the formulation of nuclei, which grow into particles of colloidal dimensions. The preparation of aerosols by dispersion methods is of great interest in pharmacy and may be achieved by the use of pressurized containers. For example, the pressure inside these

containers may be produced by a liquefied gas, which is known as the propellant. If a solution or a suspension of active ingredients is contained in the liquid propellant or in a mixture of this liquid and an additional solvent, then when a valve on the container is opened the vapour pressure of the propellant forces the mixture out of the container. The large expansion of the propellant at room temperature and atmospheric pressure produces a dispersion of the active ingredients in air [1].

Some of the objectives of aerosols include the medical treatment of respiratory diseases in man and animals, delivery of deodorants and sprays as well as few agricultural applications.

AEROSOL:

Pharmaceutical aerosols are the pressurized dosage forms that contain one or more active ingredients, which upon activation release a fine dispersion of liquid or solid materials in a gaseous medium. The gas used for this purpose is known as propellant. The particle size of the liquid or solid particles is less than 50 µm in diameter. Medicated aerosols are intended for administration into respiratory or nasal passage [2].

An aerosol product consists of the following components.

- Propellant.
- Container.
- Valve and actuator.
- Drugs.

Advantages [3]:

- Convenience and ease of application.
- Eliminate contamination of products with foreign materials.
- Absence of manual contact with medication.
- Due to lack of oxygen in the container, oxidation is prevented.
- Direct local application.
- Controlled and uniform dosage.
- High concentration of drugs over a limited area.
- Reduced danger of decomposition of the medications.
- Better penetration.
- Clean process.
- Economic and no wastage of drugs.
- Shelf-life and stability of aerosol is more.
- Aerosol package remains completely sealed and free from atmospheric contaminants.
- Drying of product due to evaporation is nil.
- Sterility of the product is maintained.
- Onset of action is fast.
- No help from a nurse or doctor is required.
- Aerosol container protects the photo-sensitive drugs.

Disadvantages [3, 4]:

- Costlier.
- Filling and sealing is not easy.
- Disposal of empty cans is difficult.
- They must be stored in a cool place.
- Propellant may cause toxic reactions.
- Refrigerant effect of propellant causes discomfort.
- Catalytic oxidation of some drugs like Vitamin C, Epinephrine, etc may occur.

APPLICATIONS OF AEROSOL [4]:

Systemic action - Bronchodilator (Example: Epinephrine hydrochloride).

Topical preparations:

Local anaesthetics (Example: Benzocaine, Xylocaine), Local analgesics (Example: Ethyl chloride), Antiseptics (Example: Chlorhexidine), Burn aid, Fungicidal agents Athelete's foot, Anti-parasitic agents (Example: Agents for scabies), Anti-inflammatory agents (Example: Hydrocortisone), and Antibiotics (Example: Neomycin).

Cosmetic preparations:

Example: Hair sprays, perfumes, shaving foam, body deodorants, anti-perspirant, etc.

Administration to body cavity:

Ear (Treatment of Otitis media), Nose (Decongestant), and Throat (Sore throat).

FORMULATIONS AND MANUFACTURING OF AEROSOL [3,5]:

- Propellant.
- Container.
- Valve assembly.
- Actuator.
- Dip tube.
- Product concentrate.

Propellants:

The propellant is responsible for developing the proper pressure within the container and it expels the product when the valve is opened and aids in the atomization or foam production of the product [6].

Ideal qualities of propellants:

- Vapour pressure: Propellant should possess vapour pressure of 15 to 100 psig (per square inch gauge) at 70º F.

- Cost: Cost of the propellant has to be low so that the ultimate price of the aerosol product is low.
- Flammability: It should be non-flammable.
- Inertness: It should be chemically inert and non-reactive.
- Colour and odor: It should be free from odor and colour.
- Solvent power: Good solvent action on number of therapeutically active ingredients.
- Toxicity: It should be non-toxic.
- Irritability: It should be free from the irritation effect.
- Stability: It must be stable.
- Purity: It must be pure.

Types of Propellants:

A. Fluorocarbons:

(a) Methane series-

Propellant – 11, Propellant – 12 and Propellant – 22

(b) Ethane series-

Propellant – 113, Propellant – 114, Propellant – 142 and Propellant – 152

(c) Butane series- Propellant – 318

B. Hydrocarbons: Propane, Iso-butane and N-butane

C. Compressed gases:

(a) Soluble- N_2O (Nitrous oxide) and CO_2 (Carbon dioxide)

(b) Insoluble- N_2 (Nitrogen)

Some blends of fluorocarbon propellants for pharmaceutical aerosols are:

- Trichloro monofluoro methane (11).
- Trichloro monofluoro ethane (12).
- Dichloro tetrafluoro ethane (114).

Selection of propellant is based on its boiling point, vapour pressure and density [7]. The vapour pressure of a mixture of propellants can be calculated according to Dalton's law, which states that: The total pressure in any system is equal to the sum of the individual or partial pressure of various components.

Raoult's law [8]:

The lowering of vapour pressure of liquid by addition of another substance states that the depression of the vapour pressure of a solvent upon the addition of a solute is proportional to the mole fraction of solute molecules in the solution.

Given the ideal behavior, the vapour 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 vapour pressure of each pure propellant at the desired temperature.

For propellant – A

$P_a = X\ P_A^o$ …….(1)

$P_a = N_A\ P_A^o$ …….(2)

Where, P_a = partial vapour pressure of propellant A, P_A^o = vapour pressure of pure propellant a, na = moles of propellant A, nb = moles of propellant B and N_A = mole fraction of component A.

For propellant – B

$P_b = X\ P_B^o$ …….(3)

$P_b = N_B\ P_B^o$ …….(4)

Where, P_b = partial vapour pressure of propellant B, P_B^o = vapour pressure of pure propellant B, na = moles of propellant A, nb = moles of propellant B and N_B = mole fraction of component A.

The total vapour pressure of system will be-

$P = P_a + P_b$ …….(5)

Containers [9]:

Aerosol containers are made up of the following materials and are designed to withstand pressures as high as 140 to 180 p.s.i.g. at 54 ºC.

- Metals such as aluminium, stainless steel and tin plated steel.
- Glass - uncoated or plastic coated.
- Plastics –

Metallic container:

The merits of the Tin plated steel are light in weight and inexpensive, requires additional steel, Coating is usually organic in nature (oleoresin, Phenolic and vinyl), and liner (single or double coat) is added to container prior to fabrication.

The advantages of the Aluminium are corrosion resistant, incidence of incompatibilities in aluminium aerosol containers is less, and added resistance can be obtained by coating.

The Stainless steel is costly, no organic coating is required, and mainly used for inhalations.

The glass is non-corrosive and has a greater degree of freedom in design. Two types of glass containers are available that are uncoated (low cost and high clarity) and coated (plastic coated glass container).

Valve Assembly [10]:

The valve in the aerosol facilitates the dispensing of the product. Ideal pharmaceutical valves should be easily opened and closed, capable of delivering the content in the desired form, and deliver a given amount of

medication. Constructed of material approved by the Food and Drug Administration.

There are two types of aerosol valves [11] that are Continuous spray valves and Metered valves.

An aerosol valve has different components [11, 12] that are Actuator, Stem, Gasket, Spring, Housing (valve body), Mounting cup or ferrule, and Dip tube.

- *Actuator:* It activates the valve assembly and permits the easy opening and closing of the valve. It is through the orifice in the actuator that the product is discharged.
- *Stem:* It supports the actuator and delivers the formulation in the proper form to the chamber of actuator. One or more orifices are set into the stem. They may be made up of nylon or brass or stainless steel.
- *Gasket:* It serves to prevent the leakage of the formulation when the valve is in the closed position. It is made up of Buna – N or neoprene rubber.
- *Spring:* The spring serves to hold gaskets in place. It returns the valves to its closed position when the actuator is depressed and released. It is made up of stainless steel.
- *Mounting cup or ferrule:* It is used to attach the valve proper to the container. It is made up of steel or aluminium.
- *Housing or valve body:* This is located directly below the mounting cup. It serves as a link between the dip tube, stem and actuator. It may be made up of nylon or delrin.
- *Dip tube:* The dip tube extends from housing down into the product. It serves to bring the formulation from the container to the valve. The selection of the dip tube depends upon the viscosity of the product and desired delivery rate.

Product concentrate:

The product concentrate consists of active ingredients or a mixture of active ingredients and other necessary agents such as solvents, anti-oxidants and surfactants.

METERED VALVE AEROSOLS [13,14]:

The metered valve aerosols permit only a specified quantity of the product to come out at any single go. Such valves actually consist of two valve chambers, both of which are connected to the actuator button.

Working:

When the actuator button is in closed position, the lower chamber valve is in open position and the upper chamber valve in the closed position. The product fills itself upto the upper chamber valve in the stationary position. As soon as the actuator button is pressed, the lower chamber valve gets closed preventing any further flow of product from the container. At the same time, the upper chamber valve opens allowing the product present between the upper and the lower chamber valves to flow out. On release of the actuator button, the positions of the upper and lower chamber valve gets reversed. Such valves are very handy for pharmaceutical products where measured doses have to be delivered.

Packaging of aerosols [15]:

The aerosol products can be filled in two ways: Cold fill process and Pressure fill process.

Cold fill process:

This process is used to fill metered aerosol products containing fluorocarbon propellants. By lowering the temperature of a propellant below its boiling point, the propellant becomes liquid at atmospheric pressure.

The active ingredients or concentrate and propellant are cooled to a low temperature of about -30 to -40 ºF. The chilled concentrate is poured into the chilled container and propellant is added. Sufficient time is given for the propellant to partially vaporize in order to expel the air present in the container. The valve is fitted on to the container, which is placed into a water bath so that the contents are heated to 130 ºF (54 ºC) in order to check any leakage and strength of the container.

Pressure fill process:

This process is used for filling aerosols containing hydrocarbon propellant. The product concentrate is placed into the container and the valve is sealed. The propellant is forced through the valve under pressure. After this, the container is immersed in a water bath at 130ºF (54ºC) in order to check any leakage and strength of the container. The air present in the container must be expelled before filling the contents into the aerosol container [16].

Types of aerosol systems:

Aerosol systems may be of two types:

Two phase system:

Here the product is a solid insoluble in the propellant or it is solid or liquid which dissolves in it.

Three phase system:

Here the product is immiscible with the propellant. The medicaments are dissolved in a liquid which does not mix with the liquefied propellant [17].

EVALUATION OF AEROSOLS [18,19]:

- Flammability and combustibility.
  - Flash point.
  - Flame extension.
- Physico-chemical characteristics.
  - Vapour pressure.
  - Density.
  - Moisture.
  - Identification of propellant.
  - Concentrate – propellant ratio.
- Performance.
  - Aerosol – valve discharge rate.
  - Spray pattern.
  - Dosage with metered valves.
  - Net contents
  - Foam stability
  - Particle size determination
  - Leakage
- Biological characteristics
  - Biologic testing.
  - Therapeutic activity.

Flash Point:

This is determined by use of the Standard Tag Open Cup Apparatus. The test liquid is allowed to increase slowly in temperature and the temperature at which the vapors ignite is taken as a flash point.

Flame extension:

The product is sprayed for about 4 seconds into a flame. Depending on the nature of formulation, the flame is extended; the exact length being measured with a ruler.

Vapour Pressure:

It is important that the pressure variation from container to container be determined, since excessive variation indicates the presence of air in the headspace. It can be determined by using a Pressure Gauge.

Density:

The density of an aerosol system may be accurately determined through the use of a Hydrometer or Pycnometer.

Moisture:

The *Karl Fischer method* has been accepted to a great extent. Gas Chromatography has also been used.

Identification of propellant:

Gas Chromatography and IR (Infra-red) Spectrometry have been used to identify the propellants and also to indicate the proportion of each component in the blend.

Concentrate-propellant ratio:

Gas Chromatography and IR (Infra-red) Spectrometry have been used to identify the concentrate-propellant ratio.

Aerosol valve discharge rate:

This is determined by taking an aerosol product of known weight and discharging the contents for a given period of time using standard apparatus. By re-weighing the container, after the time limit has expired, the change in weight per time dispensed is the discharge rate, which can then be expressed as grams per second.

Spray pattern:

This method is based on the impingement of the spray on a piece of paper that has been treated with a dye-talc mixture. Depending on the nature of the aerosol, an oil-soluble or water-soluble dye is used.

Dosage with metered valves:

This is used to determine the reproducibility of dosage each time the valve is depressed and the amount of medication actually received by the patient.

Net contents:

Several methods can be used to determine whether sufficient product has been placed into each container.

Foam stability:

The life of foam can range from a few seconds to one hour or more depending on the formulation. This can be determined by Visual evaluation and Rotational viscometer.

Particle size determination:

The particle size of the aerosol product can be determined by using two methods that are Cascade impactor and Light scatter decay.

The Cascade Impactor operates on the principle that in a stream of particles projected through a series of nozzles and glass slides at high velocity, the larger particles become impacted first on the lower velocity stages, and the smaller particles pass on and are collected at higher velocity stages.

Leakage:

After filling and sealing, the container is immersed in a water bath at 130ºF (54ºC) in order to check any leakage.

Biologic testing:

Biologic testing of aerosol products should have a consideration of therapeutic efficacy and toxicity.

Therapeutic activity:

The dosage of the product has to be determined for inhalation aerosols. Topical preparations are applied to

the test areas in the usual manner and adsorption of therapeutic ingredients can be determined [19, 20].

CONCLUSION:

Pharmaceutical aerosols are non-invasive pulmonary drug delivery systems, which are considered to be one of the best methods as compared to other routes of drug administration. Their advantages over other routes of administration enhance their wide range of applications in the treatment of illnesses including asthma, chronic obstructive pulmonary diseases (COPD), etc. Some of the advantages include the possibility of direct targeting the drug to its site of action, avoidance of first pass effect, rapid action and also reduction of systemic side effects. Therefore, pulmonary route of administration in the form of aerosols can be successful in the research field in the near future.

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