INTRODUCTION

The aerosol container is referred to as a pressurized package in which the therapeutically active drug is dissolved or suspended in compressed or liquefied gas. The delivery of therapeutically active drug in the form of spray or foam or solid stream is dependent on the ability of the liquefied or compressed gas. The advantages of aerosols are as follows:

- The drug sensitivity to the effect of oxygen or moisture is protected and stability is enhanced.
- The drug can be directly applied to the affected areas.
- Administration of drug by aerosol is a rapid process.
- It protects the drug from gastrointestinal tract degradation.
- Hepatic first pass metabolism is avoided.
- Aerosols are used for both systemic and local application.
- Easy to apply.

A sterile dose of drug is dispensed and also the contamination of drug is prevented.

The delivery of contents of aerosol depends on its valve assembly, containers, and actuators as well as on the propellant. The two components of aerosol are product concentrate and propellant. The product concentrate contains the therapeutically active ingredients. The propellant having vapour pressure greater than atmospheric pressure at 40°C (105°F) is responsible for the development of proper pressure in the container to expel the product concentrate in the desired form like spray, mist, solid, foam, stream etc. Propellant can also act as the solvent or vehicle for the product concentrate. Thus aerosol components are classified as shown in Figure 1 and Figure 2.

PROPELLANT

The development of pressure within the container by the propellant causes the opening of valve which expels the product by atomisation or foam formation.

Types of propellant

Depending on the route of administration and use, the propellant can be classified as given in Table 1.

Chlorofluorocarbon (CFC) propellants

The basic characteristics of propellants are chemical inertness, lack of toxicity, lack offlammability and explosiveness. Due to the presence of these characteristics, the chlorofluorocarbon (CFC) propellants P-11, P-12, and P-114 were used in aerosol products for several years. Now a day their uses have been declined as they cause the depletion of ozone layer. But due to their relatively low toxicity and inflammability, they are still use in low amount in the treatment of asthma and chronic obstructive pulmonary disease (COPD). P-134a and P-227 are now been developed and are being incorporated in aerosol formulations in place of P-12.

Principle of releasing out of product concentrates from container

Liquefied propellant or propellant mixture exists in equilibrium with the product concentrate in a sealed aerosol container. The liquefied propellant vapourises and occupies the upper portion of the aerosol container. As the liquefied propellant exists in equilibrium with the propellant in the vapour phase in an aerosol container, so a constant pressure is maintained within the aerosol container. Hence, it is called as a pressurised aerosol container. The pressure exerted by the propellant is called as vapour pressure, measured in psig; is the characteristic of specific propellant. Upon the actuation of the valve, the pressure exerted by the propellant is distributed equally in all direction in the aerosol container, forcing the product concentrate up the dip tube and out of the aerosol container. As the vapour pressure of the propellant in air is lower than inside the aerosol container, so the propellant evaporates on reaching the air and product concentrates dries up as dry particles.

Hydrocarbons Propellants

The environmental acceptance, low toxicity and nonreactivity are the characteristics of hydrocarbons propellants allowing them to be used as the propellant. Hydrocarbons are used in the preparation of water based aerosols as they are not susceptible to hydrolysis due to the absence of chlorine. Since they are immiscible with water, so they remain on the top of water. They provide the force to push the contents out of the container. The disadvantage of Hydrocarbon propellant is flammability, explosiveness. It is being reduced by using a blend of propellant. Also the use of vapour tap valve reduces flammability.

Compressed gas propellants

The use of compressed gas like Nitrogen, Nitrogen dioxide and Carbon dioxide as propellant dispenses products in the form of fine mists, foams or semisolids. It produces fairly wet sprays and the foams are not as stable as produced by the liquefied gas propellant. Unlike the aerosol prepared with liquefied gas propellant, there is no propellant reservoir. The compressed gas propellant is contained in the headspace of the aerosol container which forces the product concentrate...
out of the container. So, higher gas pressure is required in this aerosol. This aerosol finds its application to dispense food products, dental creams, hair preparation and ointments.

CONTAINERS

Aerosol containers are generally made of glass, metals (e.g., tin plated steel, aluminium, and stainless steel), and plastics. The materials of aerosol container to be selected should be able to withstand high pressure. Thus the aerosol containers must withstand pressure as high as 140 to 180 psig (pounds per sq. inch gauge) at 130 °F. Also, the cost, compatibility of the material with the formulation is to be considered. The pressure limitation of aerosol container is as given in Table 2.

Glass

One of the materials is glass whose brittleness limits its use in aerosol containers. Thus glass containers are used in lower pressure and when low amount of propellant are in use such as if the pressure is less than 25psig and propellant content is less than 15%. In order to protect the glass containers against breakage due to high pressure, it is to be coated with plastic coating in two layers. Epoxy and vinyl resins can be used as linings. Vinyl resins are not resistant to high temperature of the steam about 200 °F. But epoxy resins are resistant to steam. These coatings are suitable for low pH water based products.

Metals

Tinplated steel: It provides light and inexpensive aerosol container. The both sides of the tin container are electroplated with sheets of steel plates so as to protect the inside of the container from corrosion and also to prevent the interaction between the tin and the formulation. Oleoresin, phenolic, vinyl, or epoxy coatings are used as the coating materials. The tin plated steel containers are used in topical aerosols.

Aluminium: The aluminium containers are light weight and are less prone to corrosion than other metals. Aluminium is used in most metered dose inhalers (MDIs) and many topical aerosols. Epoxy, vinyl, or phenolic resins coatings are done on aluminium containers to reduce the interaction between the aluminium and the formulation. The seamless aerosol containers manufactured by an impact extrusion process have greater safety against leakage, incompatibility, and corrosion. The container themselves available in sizes ranging from 10 ml to over 1,000 ml.

Stainless steel: As it is strong and resistant to corrosion; no coating is required. Also it can withstand high pressure. The drawback is expensiveness which restricts its sizes to small sized containers.

Plastic

As plastics are highly permeable to vapours and air like oxygen, so interaction with the formulation may occur and also may lead to oxidative degradation of the formulation. Polyethylene tetra phthalate (PET) container as used for some non pharmaceutical products.

VALVES

A valve delivers the drug in desired form and regulates the flow of product concentrate from the container. The valve should be able to withstand the pressure encountered by product concentrate and the container, should be corrosion resistant. The two types of valves available are continuous spray valve and metering valve. The classifications of aerosol valve components are given in Figure 3.

Actuator: It is the button which the users press to activate the valve assembly and controls the easy opening and closing of valve; also directs the spray to the desired area. The actuator contains orifices of varying size and shapes as well as the expansion chamber which determines the type and quantity of propellant used, actuator design and the physical characteristics of the emitted product concentrate in the form of spray or foam, especially in the case of inhalation aerosols where it is necessary to control the proper particle size of the product concentrate. The types of actuator are given in Figure 4.

Stem: The actuator is supported by the stem and the formulation is delivered in the proper form to the chamber of the actuator by the stem. It is made up of Nylor, Delrin, Brass and Stainless steel.

Gasket: The stem and valve are placed tightly in their place by the gasket and the leakage of the formulation is prevented by gasket. It is made up of Buna N and Neoprene rubber.

Spring: The gasket is held in its place by the spring and also helps to keep the valve in closed position when the pressure is released upon actuation of the formulation.

Mounting Cup or Ferrule: The Mounting cup or Ferrule is generally made up of aluminium which serves to place the valve in its position, and attached to the aerosol container. As the underside of the mounting cup Ferrule is exposed to the contents of the container, so it is to be compatible with the contents so as to prevent any interaction. It may be coated with an inert material such as vinyl coating as it prevents any interaction with the contents also corrosion of aluminium is prevented.

Housing or Valve body: The Housing or Valve body located directly below the Mounting cup or Ferrule is made up of Nylor or Delrin work to connect the dip tube and the stem and actuator. The rate of delivery of product and the desired form in which the product is to be emitted is determined by its orifice.

Dip Tube: The dip tube is made up of polyethylene or polypropylene extends from the housing body or valve body down into the product concentrate works to bring the formulation from the container to the valve. The inner diameter of the dip tube depends on the viscosity and the desired rate of delivery of the product. The inner diameter of the dip tube increases with an increase in the viscosity of the formulation. For less viscous solutions, the inner diameter ranges from 0.12 inch to 0.125 inch. While for viscous solution, inner diameter is as large as 0.195 inch.

TYPES OF INHALERS

Depending on the physical state of the dispersed phase and continuous medium, inhaled drug delivery system is classified into three principle categories

1. Pressurised metered dose inhalers (pMDIs)
2. Dry powder inhalers (DPIs)

Metered dose inhaler (pMDIs)

The pressurised metered dose inhalers (pMDIs) as shown in Figure 5; are composed of a canister, and actuator, and sometimes a spacer. The canister is composed of a metering dose valve with an actuating stem. The formulation (containing the active ingredient i.e. drug, a liquefied gas propellant, and a stabilizer) is present in the canister. The drug may be suspended or dissolved in the liquefied gas propellant. Upon actuation, the metering dose valve is opened which releases a single metered dose of medication alongwith the liquefied gas propellant to spray out of a carnister. This process is called cavitation. The liquefied gas propellant is volatile in nature; breaks down into liquid droplets which evaporates rapidly, and the dried micronized drug are inhaled to the lung. But the pressurised metered dose delivery suffers from various drawbacks as follows:-
a. Till 1990s, various chlorofluorocarbons (CFC) were used as the propellant; it caused depletion of ozone layer; so later it was replaced with hydrofluorocarbons. Hydrofluorocarbons suffer from the drawback of greenhouse effect.

b. As pMDIs is pressurised, it emits the dose at high velocity and gets deposited in the oropharynx.

c. The propellant and the cosolvent may extract some of the organic compounds from the device components and leads to chemical degradation.

d. A careful coordination of actuation and inhalation are required.

e. High chances of pharyngeal depositions.

Later on, the formulation related short comings are reduced by Dry powder inhalers (DPIs).

i) **Dry powder inhalers (DPIs)**

The DPIs are advantageous than pMDIs due to the following reasons:

a) DPIs require little or no coordination of actuation and inhalation as they are activated by patient’s inspiratory airflow.

b) DPIs don’t extract organic compounds from the device components in contrast to the pMDIs; and the chances of chemical degradation are lesser than pMDIs.

c) The rate of drug delivery is better than pMDIs.

d) DPIs are efficient, more stable than pMDIs and easier to use than pMDIs.

DPIs are composed of micronized powdered drug particles. The micronized powdered drug particles (of sizes < 5 μm) are mixed with much larger sugar particles (of size < 30 μm) eg. Lactose monohydrate. The smaller drug particles forms loose aggregate with lactose monohydrate. The micronized powdered drug particles have high cohesive force, so they have a tendency of adhering to each other. The addition of large particle sized lactose monohydrate reduces the cohesive force of the micronized drug particles and form loose agglomerate with the micronized drug particles. It helps in an easy deggregation of the agglomerates, upon inhalation, the agglomerates get broken down into its constituent particles, with the help of mechanical devices such as screens, on which the particles agglomerates impact. It releases the smaller sized powdered drug particles into the air to be inhaled to the lung. The larger sized lactose monohydrates particles are left behind in the device and in the mouse throat. The DPIs are classified into two types

- ✔ Unit dose devices
- ✔ Multi dose devices

**Unit-dose devices**: Unit dose devices are being developed as re-useable or disposable single-dose dry powder inhalers. They are designed to be easy to use and inexpensive to manufacture and may be suitable for a wide range of conditions that require a rapid onset of effect or that are for occasional use. One such unit dose device is the filled capsule placed in the device. The capsule shell is opened in the device and the powder is inhaled by the user. The capsule shell remaining in the device is to be discarded after use, so that the device can be reused with a new filled capsule. It cannot provide large dose as in the case of Asthma attack (Disadvantage). A wide range of unit dose dry powder inhalers are in use such as-

- **The Innova™** (Inhale Therapeutic Systems, San Carlos, California, U.S.A.) is a long term used unit dose dry powder inhaler placed in a transparent holding chamber consisting of a stored bolus of compressed air which generate aerosol independent of patient’s inspiratory effort. The transparent holding chamber enables patients to view the aerosol to assure proper dosing. Further, the device is capable to fluidize and extract up to 90% of the dose from the reservoir, thus minimizing waste and enhancing the accuracy and precision of the dosage.

- **The Solo™** device is a short term used patient-driven unit dose dry powder inhaler. It has a built-in flow control to maximize the reproducibility of dose to patient.

- **Multi dose Devices: Turbuhaler** was the first developed multi dose DPIs by A.B. Draco (now a division of Astra Zeneca) capable of delivering carrier-free particles at moderate flow rates. However, one of the drawbacks of the Turbuhaler is that it has a variable rate of delivery due to different flow rate. To work out with the drawback and for multiple dosing and consistent performances, Turbuhaler was replaced by Diskhaler developed by Glaxosmith.

- **Diskhaler** was used to deliver a range of drugs, including salbutamol and beclomethasone. This device uses a circular disk containing of either four or eight powder doses that are maintained in separate aluminium blister reservoirs. On priming the device, the aluminium blister is pierced, and the contents of the pouch are dropped into the dosing chamber. This product had limited commercial success and was superseded in the late 90’s by the Diskuse.

- **Diskuse** is a true multi dose device, having 60 doses in a foil – foil aluminium strip that is opened only at the point just prior to patient inspiration. Consistent performance and broad patient acceptance has allowed the Diskuse to become the gold standard of multi dose powder delivery devices. Others like the GyroHaler® and OmniHaler® are cost-effective, multi-unit dose dry powder inhaler designed to deliver locally acting drugs to the lungs.

- **Clickhaler®** is a multi-dose, reservoir dry powder inhaler. It is approved for use to deliver a number of drugs used to treat patients with asthma and COPD (salbutamol, beclometasone, formoterol, budesonide and procaterol) in Europe and Japan.

- **Clickhaler®** is an automated inexpensive multi - unit dose DPI device.

- **Duohaler®** is a fixed dual-therapy, passive, multi-dose dry powder inhaler where two individual drug formulations are placed in two separate drug reservoirs that feed to two separate metering chambers from which the drugs are delivered to the user in the same breath.

- **PowderHale®** is Vectura’s patented dry powder inhaler formulation technology, designed to allow aerosolised drug particles to achieve high lung penetration with low dose variability. This is achieved by the incorporation of an additional pharmacologically inactive excipient, known as a Force Control Agent (FCA) to the drug formulation.

Although DPIs are advantageous yet it suffers from major drawbacks as under:

a. The dispensing / generalisation of aerosol depend on patient’s inspiratory airflow.

b. DPIs suffer from dose uniformity problems.

c. Complex/expensive development and manufacturing process.

d. It may lead to pharyngeal deposition of the drug.

ii) **Nebulisers**

Nebulizer is a device used to administer aerosolised medication in the form of a mist inhaled into the lungs. Nebulizers use oxygen, compressed air or ultrasonic power to break up medical solutions and suspensions into small aerosol droplets called mists that can be directly inhaled from the mouthpiece of the device. Nebuliser produce a mist of drug containing water droplets for inhalation. The drug is...
present either in solution form or suspension form in the nebulizer. It is usually of two types: Electronic nebulizer and Jet or ultrasonic nebulizer. Jet or ultrasonic nebulizer uses a source of pressurised air to blast a stream of air through a drug containing water reservoir, producing water droplets. In contrast, electronic nebulizers develop mechanical vibration to produce water droplets. The nebulizers are generally used for the treatment of acute conditions (e.g. acute asthma, respiratory infection) or in those patients who have difficulties using other respiratory dosage forms.

Some of the marketed products of nebulizers are as follow:  
**Omron MicroAir Nebulizer:** The features of Omron MicroAir Nebulizer are as under:  
- a) A dense therapeutic aerosol is produced by electronic vibrating mesh technology.  
- b) It allows complete delivery of medication.  
- c) It consists of universal adapters.  
- d) As its lightweight weighs only 6 ounces (170 g) with batteries, so easily portable.  
- e) Ideal for pediatric asthma treatment.  
- f) It saves energy due to low power consumption: 4 hours of continuous operation on 2 alkaline batteries (batteries sold separately) 8 hours when used about 30 minutes a day.  
- g) Smallest size of any electronic nebulizer.  
- h) Detachable nebulizer head for easy cleaning.  
- i) It is an alternative to Metered Dose Inhalers (MDI).  
**DeVilbiss DeVilbiss PulmoMate Compressor / Nebulizer** provides an incomparable combination of quality and value. Its design has been made in such a way that it fits easily into luggage, backpacks for easy transport. The DeVilbiss PulmoMate features an updated compressor/motor for long-term durability and performance.  
**Pari Trek S** is the best compressor nebulizer machine for travelling. This nebulizer include a DC car adapter and good looking portable case which help those who travel a lot by making nebulization treatments in the car possible. The wide use of nebulizer refers to the advantages of nebulizers as follows:  
- A. Patient coordination not required.  
- B. Effective with tidal breathing.  
- C. High dose possible.  
- D. No chlorofluorocarbon (CFC) is released.  
- E. It can be used with supplemental oxygen.  
- F. It can deliver combination therapy if compatible.  
- G. The ultrasonic nebulizer is quiet, has faster delivery; are smaller and more portable.  

The disadvantages of nebulizer are as follows:  
- They are expensive.  
- More electrical power sources are required.  
- Jet nebulizer requires pressurised form of gas.  
- The frequent cleaning of the device is needed.  
- There is a chance of contamination.  
- The suspension of dosage cannot be aerosolized properly.  
- The jet nebulizer produces large and variable sized particles.  
- The ultrasonic stimulation and the rise in temperature cause drug degradation.  

**TYPES OF AEROSOL SYSTEMS**

The aerosol systems are classified as shown in Figure 6  
**Solution system or two phase system**  
It is also called two-phase system as it contains both the vapour and the liquid. Based on the desired spray, the propellant can be used single or a mixture of propellants can be used. Propellant 12 is added alone or in mixture. If propellants having vapour pressure lower than propellant 12 is added to propellant 12, a reduction of vapour pressure is achieved but bigger sized aerosol particles are obtained. Also bigger sized aerosol particles are obtained on addition of cosolvents like ethyl acetate, propylene glycol, ethyl alcohol, glycerine and acetone. No other solvent is required if the drug is soluble in the propellant. The solution system is administered in topical application. Some of the commonly used propellant combinations in solution systems are propellant 12/11 (30:70), propellant 12/114 (45:55), propellant (12/114) (55:45).  
**Water based system or three phase system**  
In the water based or three phase system, large quantity of water is present to solubilise the contents. The water is immiscible with the propellant. Generally water based system is a three phase system consisting of a water phase, vapour phase and the propellant. So, the solubility of propellant in water can be increased by adding a cosolvent such as ethanol and also by adding surfactants at a range of composition 0.5% to 2.0%. The propellant composition ranges from 25 to 60%. The nonpolar surfactants such as esters of Oleic acid, palmitic acid, stearic acids are more preferred than the polar surfactants. The surfactants act by reducing the interfacial tension existing between the water phase and the propellant, and thus produce a uniform dispersion by increasing the solubility of the propellant in the water. The drawback associated with water based system is that the addition of ethanol, not only increases the solubility of propellant in water, but also increases its flammability. The presence of large quantities of water delivers content in liquefied form. The recent advancement is the vapour tap valve and the aquasol valve. In aquasol system, water or the mixture of water and alcohol are used to dissolve the drug. The addition of alcohol increases the solubility of propellant in water. Aquasol system is advantageous than water based system as a vapourised propellant is delivered rather than the liquefied propellant. The vapourised propellant delivers small sized, fine particles and dried contents in the form of fine mist or spray to the site of action. Moreover, the vapourised propellant is non-flammable in nature.  
**Suspension or dispersion systems**  
Suspension or dispersion system is the dispersion of the active ingredients in the propellant or the mixture of propellant by adding surfactants or the suspending agents.  
**Foam system**  
The liquefied propellant is emulsified. Aqueous or nonaqueous vehicles, propellant and the surfactants are its ingredients. Foam system is further classified as aqueous stable, nonaqueous stable and the quick breaking foam.  
**Aqueous stable foams:** The aqueous stable foam consists of propellant in the range of 3.0 to 4.0%. A dry spray is produced by the propellant. As the concentration of propellant goes on increasing, more and more contents are delivered in dried form. As the propellant is present in the internal phase, so the concentration of propellant is less. It finds its application in steroid antibiotics.  
**Non aqueous stable foams:** The nonaqueous stable foam contains glycol as the emulsion base and is used as the emulsifying agent.  
**Quick breaking foams:** Here the external phase is propellant. The product will come out as foam which soon merges to form liquid. This type of system can be applied to small area or larger surface. These are used for topical.
application. Cationic or anionic or non-ionic surfactants are used in the formulation.

**Thermal foams:** The aerosol which is delivered in the form of foam upon the application of heat is called thermal foam. They are used in shaving creams.

**MANUFACTURING OF PHARMACEUTICAL AEROSOLS\(^1,2\)**

The manufacturing of aerosol consists of three types of apparatus

- **Cold filling apparatus:** It consists of an insulated box fitted with copper tubings. The insulated tubings are filled with dry ice or acetone. The copper tubings increase the surface area and cause faster cooling. The hydrocarbon propellant is not to be stored in the copper tubings as it might cause explosion.
- **Pressure filling apparatus:** Pressure filling apparatus consists of a metering burette capable of measuring the amount of propellant to be filled to the aerosol container. The propellant is added through the inlet valve present to the bottom of the valve under its own vapour pressure. A cylinder of nitrogen or compressed gas is attached to the top of the valve and the pressure of nitrogen causes the propellant to flow to the container through the metering burette. The propellant flows to the container stops when the pressure of the flowing propellant becomes equal to the pressure of the container.
- **Compressed gas filling apparatus:** A compressed gas propellant is used. As the compressed gas is under high pressure, so the pressure is reduced by pressure reducing valve. A pressure of 150 pounds per square inch gauge is required to fill the compressed gas propellant in the aerosol container. The product concentrate is placed in the pressure gauge and the valve is crimped in its place. The air is evacuated. The filling head is inserted into the valve opening. Upon the depression of the valve, the compressed gas propellant is allowed to flow into the container. The compressed gas stops flowing when the pressure of the compressed gas flowing to the container from the burette becomes equal to the pressure within the container. In case of increasing the solubility of the gas in the product concentrate and also when an increased amount of compressed gas is required, carbon dioxide and Nitrous dioxide is used. The container is needed to be shaken during and after the filling operation to enhance the solubility of the gas in the product concentrate.

The filling of aerosol product into the container is by two methods:

- **Cold filling method**: Two methods are involved:
  - In the first method, the product concentrates are chilled to a temperature of \(-30 \text{ to } -40^\circ\) F. The chilled product concentrates are added to the chilled aerosol container. The chilled propellant is added through an inlet valve present under side of the valve of the aerosol container.
  - In the second method, both the product concentrate and the propellant are chilled to \(-30 \text{ to } -40^\circ\) F. Then the mixture is added to the chilled container.

In both the above methods, after the aerosol containers are filled, the valves are set in its place and the filled aerosol containers are passed through a water bath in which the contents of the containers are heated to 130 °F to test for leaks and strength. Then the containers are air dried, capped and labelled. Cold filling method is advantageous for the filling of metering valve containing aerosol container. The pressure filling method is more prominent than cold filling method as most of the formulations cannot be cooled to very low temperatures.

- **Pressure filling method**: The product concentrate is filled to the aerosol container through the metering pressure filling burette at room temperature. The propellant is added through the inlet valve located at the base of the valve or under the valve after the crimping of valve. The flow of propellant to the aerosol container continues till the pressure of the filling propellant becomes equal to the pressure within the container. The aerosol container are capped and labelled. The pressure filling methods have the following advantages over the cold filling method:
  - The emulsion, suspensions are unstable at very low temperature. So the pressure filling method is the preferred method then that of cold filling method.
  - The absence of moisture reduces the chance of contamination.
  - The rate of production is high.
  - The chance of loss of propellant is low.

Concentrate filler, Valve placer, Purger and vacuum crimpler, Pressure filler, Leak test tank equipments are used for large scale of production.

**QUALITY CONTROL OF PHARMACEUTICAL AEROSOLS\(^1,2\)**

Quality control of pharmaceutical aerosol includes the testing of propellant, valves, actuator and dip tubes, containers, weight checking, leak testing and spray testing.

**PROPELLANT**

All quality control tests of propellents are accompanied by specification sheets:

- A sample is taken out and vapour pressure is determined which then is compared to specifications. The density is also checked when necessary. Other tests include –
  - Identification of two or more blends of propellant by Gas chromatography.
  - Purity of the propellant is checked by moisture, halogen, and non-volatile residue determinations.

**VALVES, ACTUATORS, AND DIP TUBES**

Both physical and chemical examinations are done. They are sampled according to the standard procedures as found in “Military Standard Mil – STD-105D”. A test method was developed for metered dose pharmaceutical aerosol by Aerosol specifications committee, Industrial Pharmaceutical Technology section, Academy of Pharmaceutical Sciences with an objective of determining the magnitude of valve delivery and degree of uniformity between individual valves. The composition of the test solution is given in Table 3:

**Testing procedure**

- Take 25 valves and placed on suitable containers.
- The containers are filled with specific test solutions.
- A button actuator with 0.02 inch orifice is attached to the valves.
- The filled containers are placed in a suitable atmosphere at a temperature of 25 ± 1°C
- When the products have attained the temperature of 25 ± 1°C, the filled containers are actuated to fullest extent for 2 seconds.
- This procedure is repeated for a total of 2 deliveries from each 25 test units.

The valve delivery per actuation in \(\mu l\) = \(\frac{\text{Individual delivery weight in mg}}{\text{Specific gravity of test solution}}\)

The limits for acceptance as given in Table 4 Out of 50 deliveries:

- If 4 or more deliveries are outside limits, then valves are rejected.
If 3 or more 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 linings. Quality control aspects include degree of conductivity of electric current as measure of exposed metals. Glass containers examined for flaws.

WEIGHT CHECKING
It is done by periodically adding empty tared containers to filling lines which after filling with product concentrate are removed and reweighed. Same procedure is used for checking weight of the propellant.

LEAK TEST
It is done by measuring the crimp’s valve dimension and comparing. Final testing of valve enclosure is done by passing filled containers through the water bath.

SPRAY TESTING
It is done to clear up dip tube of pure propellant and concentrate and to check any defects in the valve and the spray pattern.

EVALUATION TESTS OF PHARMACEUTICAL AEROSOLS

FLAMMABILITY AND COMBUSTIBILITY
It includes Flame projection and Flame extension.

Flame projection: The aerosol product is sprayed to an open flame for about 4 seconds and the extension of the flame is measured with the help of a ruler.

Flash point: Tag Open Cup apparatus is the standard test apparatus. The aerosol product is chilled to a temperature of about – 25 ° F and transferred to the test apparatus. The temperature of the test liquid is increased slowly and the temperature at which the vapours ignite is taken as the flash point. Physicochemical characteristics are given in Table 5.

PERFORMANCE TEST
It includes the following tests

Aerosol Valve Discharge Rate: An aerosol product of known weight is taken and its contents are discharged using standard apparatus for a given period of time. The container is reweighed. Then the change in weight per time dispensed is the discharge rate. The discharge rate can also be expressed as grams per second.

Spray patterns: The method involves the impingement of sprays on a piece of paper that has been treated with dye – talc mixture. It gives a record of the spray pattern.

Dosage with metered valves: The doses are dispensed into the solvents or onto a material that absorbs the active ingredients. The assay of the solution gives the amount of active ingredients present. Another method involves accurate weighing of the filled container followed by dispensing of several doses. The container is then reweighed, and the difference in weight divided by the number of doses dispensed gives the average dose. This process is repeated and the results are compared.

Net contents: The tared cans are placed onto the filling line are weighed, the difference in weight is equal to the net contents. The other method is a Destructive method and consists of weighing a full container and then dispensing the contents. The contents are then weighed. The difference in weight gives the amount of contents present in the container.

Foam stability: The life of a foam ranges from a few seconds (for quick breaking foam) to one hour or more depending on the formulation. The methods which are used to determine the foam stability includes visual evaluation, time for a given mass to penetrate the foam, time for a given rod that is inserted into the foam to fall and rotational viscometer.

Particle size determination: Cascade impactor and light scattering decay methods are used for particle size determination. It is based on the principle that for a stream of particles projected through a series of nozzles and glass slides, the larger particles are impacted first on the lower velocity stage and the smaller particles are impacted on the higher velocity stage.

BIOLGIC TESTING
Therapeutic activity and Toxicity are considered in Biologic testing.

Therapeutic Activity:
For Inhalation Aerosols: The determination of therapeutic activity is dependent on the particle size.
For Topical Aerosols: Therapeutic activity of aerosol products are determined by applying the therapeutically active ingredients topically to the test areas and the amount of therapeutically active substances absorbed is determined.

Toxicity study:
For Topical Aerosols: The topically administered aerosols are checked for chilling effect or irritation in the skin. When aerosol are topically applied, thermistor probe attached to the recording thermometer are used to determine the change in skin temperature for a given period of time.
For Inhalation Aerosols: Inhalation toxicity study is done by exposing test animals to vapours sprayed from the aerosol container.

EXTRACTABLE SUBSTANCES
The composition and the quality of materials used in the manufacturing of elastomeric and plastic components of valve (eg. Stem, gaskets, housing etc) are to selected and checked properly because as organic solvents are the major constituents of the propellant and also used as a vehicle, so it may increase the chance of leaching of constituents from the elastomeric and plastic components of valve into the formulation. This may lead to distortion of the components of valve, changes in the delivery rate of medication, increase in the leak rate and also lead to contamination. So the selected elastomeric and plastic components of valve should be compatible with the formulation. Thus the established profile of each of the elastomeric and plastic components of valve should be correlated to the extractable profile of the aged drug products or placebo, to ensure reproducible quality and purity of the drug product. Specifications and limits for individual and total extractable from different valve components may require the use of different analytical methods.

LABELLING
Medicinal aerosols should contain at least the following warning information on the label as in accordance with appropriate regulations according to USP:

Warning—Avoid inhaling. Avoid spraying into eyes or onto other mucous membranes.

Note—The statement “Avoid inhaling” is not necessary for preparations specifically designed for use by inhalation. The phrase “or other mucous membranes” is not necessary for preparations specifically designed for use on mucous membranes.
**Warning**— Contents under pressure. Do not puncture or incinerate container. Do not expose to heat or store at temperatures above 120 °F (49 °C). Keep out of reach of children.

In addition to the aforementioned warnings, the label of a drug packaged in an aerosol container in which the propellant consists in whole or in part of a halocarbon or hydrocarbon shall, where required under regulations of the FDA, bear either of the following warnings:

**Warning**— Do not inhale directly; deliberate inhalation of contents can cause death.

**Warning**— Use only as directed; intentional misuse by deliberately concentrating and inhaling the contents can be harmful or fatal.
FIGURE 3: Types of actuator

FIGURE 4: Aerosol valve components

FIGURE 5: Pressurised metered dose inhalers (pMDIs)

FIGURE 6: Types of aerosol system

CONCLUSION
Pharmaceutical aerosol is a noninvasive pulmonary drug delivery system which is considered to be one of the best methods as compared to other routes of administration. Its advantages over the other route of administration enhance its wide range of application in the treatment of illness including asthma, chronic obstructive pulmonary diseases (COPD) etc. Some of its advantages include the possibility of directly targeting the drug to the site of action, avoidance of first pass metabolism, rapid action and also reduction of systemic side effects etc. Hence pulmonary route of administration can be successful in the research field in near future.

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