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2. Aerosols

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2.1 Aerosols

Definition: An **aerosol** is suspension of fine solid particle or liquid droplets in air or another gas. Aerosols can be natural or anthropogenic. The term *aerosol* commonly refers to the particulate/air mixture, as opposed to the particulate matter alone.

The technology of pharmaceutical aerosols has rapidly developed in the recent few years. Inhalational therapeutics have offered various advantages over other conventional drugs with other routes of administration.

However, health concerns as well as ecological limitations have been reported and hence encouraged the researchers in the field of pharmaceutical industry to search for other enhanced alternatives. Aerosols are the pressurized systems, which act by releasing either continuous or metered dose of fine mist spray after a proper activation of its valve system. The anatomical features of the respiratory system have made it an attractive target site for some pharmaceutical preparations having limited delivery by other routes of administration. About 70 years from now, various devices will have started to be used for the delivery of inhaled drugs to treat different respiratory conditions. The development of new charging technologies has started to take place for a better drug deposition of these preparations. Inhalational therapeutics can be found in various forms in which each of them offers distinctive characteristics.

The deposition of the aerosolized particles is an issue of significant impact as it influences the efficiency of the prescribed therapeutics. Inhalational therapeutics can deposit in the airways via five different mechanisms where one or more of them are usually followed.

Propellants play an essential role in all of the manufactured aerosols. Different classes of propellants are used to formulate such dosage forms. In addition, different technologies are available to manufacture pharmaceutical aerosols. Nevertheless,

Testing of pharmaceutical aerosols and their deposition efficiency is an important process, which can be done by various deposition models developed for such purposes. Numerous numbers of reports have been provided to continuously update the new advancement in the pharmaceutical aerosol technology, allowing for additional studies to be conducted.

The packaging of therapeutically active ingredients in a pressurized system is not new to the pharmaceutical industry. According to present day usage, an aerosol or pressurized package is defined as "a system that depends on the power of a compressed or liquefied gas to expel the contents from the container." It is in light of this definition that the terms aerosol, pressure pack- age, pressurized package, and other similar terms are used in this chapter.

A. Respiratory Track:

From an engineering point of view the geometry of the respiratory tract is not well known.

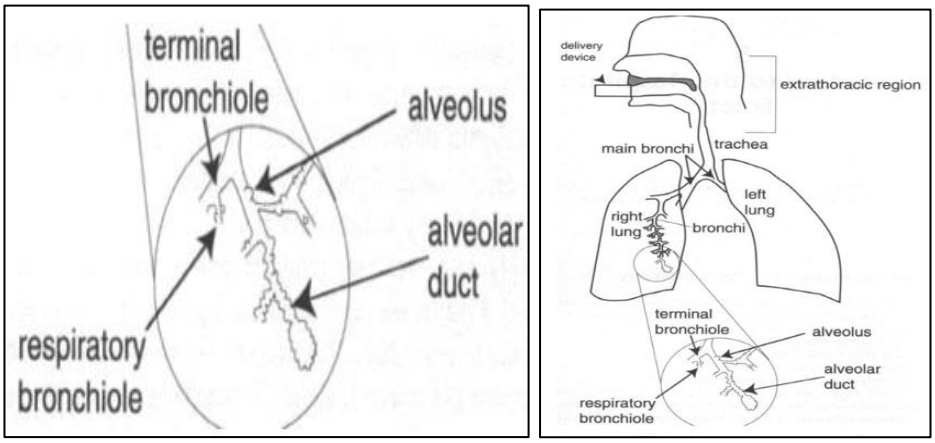

Figure 2.1: Respiratory Track

- Geometry contains fine detail.
- Geometry is time dependent.
- Geometry varies between individuals.
- Topologically the lungs simply consist of a series of bifurcating pipes.
- Three basic regions
- Extra thoracic region ("upper air ways")
- Tracheo-bronchial region
- Alveolar región

B. Extra thoracic region:

Extra thoracic region ("upper air ways")

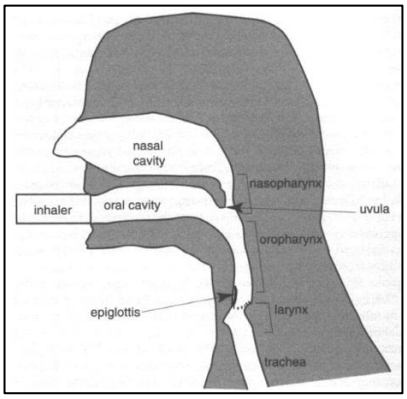

Figure 2.2: Extra Thoracic Region

- Oral cavity ("mouth") transient with variation in position of tongue and jaw
- Nasal cavity
- Larynx (constricted entrance to trachea containing vocal cords and 'trap door')
- Pharynx (throat region of between larynx and mouth 'oropharynx' and between larynx and nose 'nasopharynx')

Alveolar Region:

- Contains all parts of the lung with alveoli.
- All the daughter generations from a single terminal bronchiole is called acinus

Respirator Bronchioles

- first generation daughter branching after the terminal bronchioles
- Relatively few alveoli

Subsequent generations will have an increasing number of alveoli.

- Alveoli ducts
- Entirely covered by alveoli
- Several generations
- Alveoli sacs

2.2 Pharmaceutical Aerosol Applications:

Pharmaceutical aerosols including metered-dose inhalers (MDIs) and dry powder inhalers (DPIs) are devices that deliver a specific quantity of drug to the lungs. The particle size distribution and shape of the delivered dose is more critical for inhalation aerosols than for most other conventional drug products because these factors greatly influence the deposition profile in the lungs of the patient. The optimum aerodynamic particle size distribution for most inhalation aerosols has generally been recognized as being in the range of 1-5 µm.

Although the compendial tests for pharmaceutical aerosols are based on cascade impactors, microscopic analysis can provide valuable information on particle size and shape distribution of the drug particles such as:

- The presence of large particles
- Changes in morphology of the drug substance particle
- Extent of agglomeration
- Crystal growth
- Presence of foreign particulate matter

Although pressurized packages existed during the early 1900s, it was not until 1942, when the first aerosol insecticide was developed by Good- hue and Sullivan of the United States Department of Agriculture, that the aerosol industry was begun.

The principles of aerosol technology were applied to the development of pharmaceutical aerosols in the early 1950s. These aerosol products were intended for topical administration for the treatment of burns, minor cuts and bruises, infections, and various dermatologic. conditions.

Aerosol products intended for local activity in the respiratory tract appeared in 1955, when epinephrine was made available in a pressurized package. Based on their acceptability to both patient and physician, and their wide- spread use, pharmaceutical aerosols represent a significant dosage form and should be considered along with other dosage forms, such as tab- lets, capsules, solutions, etc.

An examination of the aerosol dosage form reveals the following specific advantages over other dosage forms:

a. A dose can be removed without contamination of remaining material. Stability is enhanced for those substances adversely affected by oxygen and/or moisture. When sterility is an important factor, it can be maintained while a dose is being dispensed.
b. The medication can be delivered directly to the affected area in a desired form, such as spray, stream, quick-breaking foam, or stable foam.
c. Irritation produced by the mechanical application of topical medication is reduced or eliminated. Other advantages are ease and convenience of application and application of medication in a thin layer.

Components of Aerosol Package:

An aerosol product consists of the following component parts:

A. propellant
B. Container
C. valve and actuator
D. product concentrate

A. 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. Various types of propellants are utilized.

While the fluorinated hydrocarbons such as trichloromonofluoromethane (propellant 11), dichlorodifluoromethane (propellant 12), and dichlorotetrafluoroethane (propellant 114) find widespread use in most aerosols for oral and in- halation use, topical pharmaceutical aerosols utilize hydrocarbons (propane, butane, and iso- butane) and compressed gases such as nitrogen, carbon dioxide, and nitrous oxide. The physicochemical properties of the propellants have been reviewed in other publications Listed in Table 20-1 are the commonly used propellants together with several of their physicochemical properties. Those properties of particular interest to the industrial pharmacist have been included. Blends of various fluorocarbon propellants are generally used for pharmaceutical.

B. Container:

Aerosol container, any package, usually a metal can or plastic bottle, designed to dispense its liquid contents as a mist or foam. This type of container was developed in 1941 by the American chemist Lyle D. Goodhue and others for dispensing insecticides. Since that time a wide variety of products ranging from disinfectants to whipping cream have been packaged in aerosol containers. The most common type of aerosol container consists of a shell, a valve, a "dip tube" that extends from the valve to the liquid product, and a liquefied-gas propellant under pressure. The liquid product is generally mixed with the propellant. When the valve is opened, this solution moves up the dip tube and out the valve. The propellant vaporizes as it is released into the atmosphere, dispersing the product in the form of fine particles. In foam packs, such as shaving cream, the propellant and product are present together as an emulsion. On release, the liquid vaporizes, whipping the whole into a foam.

C. Valve and actuator:

Aerosol **valves** are devices that release products in spray mode from containers under pressure. The most common applications are in the packaging of personal deodorants, hair sprays, insecticides, household and food products, decoration and technical products. Most of the aerosol valves are continuous spray mode.

The **actuator** controls the fineness of the product spray, as well as the amount of product that is dispensed. When you press down on it, the valve is opened. When the valve opens, the pressure is released from the top of the aerosol can and the pressurized propellant tries to escape from the can.

D. Product concentrate:

An aerosol formulation consists of two components: the product concentrate and the propellant. The product concentrate is the active drug combined with additional ingredients or co-solvents required to make a stable and efficacious product. The concentrate can be a solution, suspension, emulsion, semisolid, or powder.

2.3 Mechanisms of Pharmaceutical Aerosol Deposition in The Respiratory Tract:

Aerosol delivery is noninvasive and is effective in much lower doses than required for oral administration. Currently, there are several types of therapeutic aerosol delivery systems, including the pressurized metered-dose inhaler, the dry powder inhaler, the medical nebulizer, the solution mist inhaler, and the nasal sprays. Both oral and nasal inhalation routes are used for the delivery of therapeutic aerosols. Following inhalation therapy, only a fraction of the dose reaches the expected target area. Knowledge of the amount of drug actually deposited is essential in designing the delivery system or devices to optimize the delivery efficiency to the targeted region of the respiratory tract. Aerosol deposition mechanisms in the human respiratory tract have been well studied. Prediction of pharmaceutical aerosol deposition using established lung deposition models has limited

success primarily because they underestimated oropharyngeal deposition. Recent studies of oropharyngeal deposition of several drug delivery systems identify other factors associated with the delivery system that dominates the transport and deposition of the oropharyngeal region. Computational fluid dynamic simulation of the aerosol transport and deposition in the respiratory tract has provided important insight into these processes. Investigation of nasal spray deposition mechanisms is also discussed.

Delivery of a therapeutic agent by inhalation has seen increasing applications for many respiratory diseases, including asthma, COPD, allergies, and influenza. Aerosol delivery has advantages: it delivers medication directly to where it is needed, and it avoids the first-pass effect with minimum reduction of bioavailability. In addition, the inhalation route has been extensively researched as an alternative for systematic administration of proteins and peptides because of the large surface area in the pulmonary region and rapid absorption of the delivered drug from the alveolar region to the blood. Aerosol delivery is noninvasive and is effective in much lower doses than required for oral administration. Currently, there are several types of therapeutic aerosol delivery systems, including the pressurized metered-dose inhaler (pMDI), the dry powder inhaler (DPI), the medical nebulizer, the solution mist inhaler, and nasal sprays.

It is responsible for developing the power pressure within the container and also expel the product when the valve is opened and, in the atomization, or foam production of the product.

- **For oral and inhalation:**
  a. Eg: Fluorinated hydrocarbons
  b. Dichlorodiflurome thane (propellant 12)
  c. Dichlorotetraflurome thane (propellant 114)

- **Topical preparation:**
  a. Propane
  b. Butane
  c. Isobutane

- **Compound gases:**
  a. Nitrogen
  b. Carbon di oxide
  c. Nitrous oxide
- **Containers:** They mustgauge) atat pressure as high as 140 to 180 psig (pounds per sq. inch gauge) at 1300 F.

A. Metals:

a. Tinplated steel:

- Side-seam (three pieces)
- Two-piece or drawn.
- Tin free steel

b. Aluminium:

- Two-piece
- One-piece (extruded or drawn)

c. Stainless steel:

B. Glass:

a. Uncoated glass
b. Plastic coated glass

2.3.1 Physiochemical Properties of Propellants:

a. Vapor pressure
b. Boiling points
c. Liquid density

A. Valves:

- To deliver the drug in desired form.
- To give proper amount of medication.
- Not differ from valve to valve of medication in pharmaceutical preparation.

B. Types:

- Continuous spray valve
- High speed production technique.
- Metering valves
- Dispersing of potent medication at proper dispersion/ spray approximately 50 to 150 mg ±10 % of liquid materials at one time use of same valve.

2.4 Manufacturing of Pharmaceutical Aerosols:

Apparatus:

A. Pressure Filling Apparatus:

A pressure filling system for filling aerosol cans with liquid includes an enclosure including a top wall, a Bottom wall, and side walls which form a filling chamber. An air operated pump is positioned within the filling chamber. A liquid supply tube extends into the chamber and into the pump. Such formulations can be filled into individual aerosol canisters by one of two conventional methods: pressure filling or cold filling. Cold filling generally involves the preparation of a mixture of the nonvolatile components at room temperature and ambient pressure to form a concentrate.

B. 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 pressure filling system for filling aerosol cans with liquid includes an enclosure including a top wall, a bottom wall, and side wall which form a filling chamber.

An air operated pump is positioned within the filling chamber. A liquid supply tube extends into the chamber and into the pump.

C. Quality Control for Pharmaceutical Aerosols:

- Propellants
- Valves, actuator and dip tubes
- Testing procedure
- Valve acceptance
- Containers
- Weight checking
- Leak testing
- Spray testing

D. Evaluation Parameters of Pharmaceutical Aerosols

a. Flammability and combustibility:

- Flash point
- Flame extension, including flashback.

b. Physiochemical characteristics:

- Density
- Moisture content
- Identification of propellant(s)
- Concentrate-propellant ratio
- Vapor pressure

c. Performance:

- Spray pattern
- Aerosol valve discharge rate
- Dosage with metered valves
- Net contents
- Foam stability

- Particle size determination
- Leakage

d. Biologic characteristics:

e. Therapeutic activity:

Flame Projection:

This test indicates the effect of an Aerosol formulation on the extension of an open flame. Product is sprayed for 4 second into flame. Depending on the nature of formulation, the flame is extended, and exact length was measured with ruer.

Flash point:

Determined by using STD Tag open cap apparatus.

Steps - Aerosol product is chilled to temperature of 25-degree F and transferred to the test

- apparatus.
- Temperature of test liquid increased slowly, and the temperature at which the vapor
- ignites is taken as flash.
- Calculated for flammable component, which in cash of topical hydrocarbon.

Foam Stability:

Visual evaluation.

- Time for given mass to penetrate the foam.
- Times for given rod that is inserted into the foam to fall.
- The use of rotational viscometers.

Net contents:

- Weight method
- Filled full container and dispensing the contents.

2.5 Metered Dose Inhalers:

A metered-dose inhaler consists of three major components; the canister which is produced in aluminium or stainless steel by means of deep drawing, where the formulation resides; the metering valve, which allows a metered quantity of the formulation to be dispensed with each actuation; and an actuator (or mouthpiece) which allows the patient to operate the device and directs the aerosol into the patient's lungs. The formulation itself is made up of the drug, a liquefied gas propellant and, in many cases, stabilising excipients.

The actuator contains the mating discharge nozzle and generally includes a dust cap to prevent contamination. Metered-dose inhalers are only one type of inhaler, but they are the most commonly used type. The replacement of chlorofluorocarbons propellants with hydrofluoroalkanes (HFA) resulted in the redesign of metered-dose inhalers in the 1990s. For one variety of beclomethasone inhaler, this redesign resulted in considerably smaller aerosol particles being produced and led to an increase of potency.

The MDI device consists of a canister, and actuator, and sometimes a spacer. The canister itself consists of a metering dose valve with an actuating stem. The formulation resides within the canister and is made up of the drug, a liquefied gas propellant, and often stabilizing excipients. Actuation of the device releases a single metered dose of liquid propellant that contains the medication. The volatile propellant breaks up into droplets which then evaporate, creating an aerosol containing micronized drug that is inhaled into the lungs.

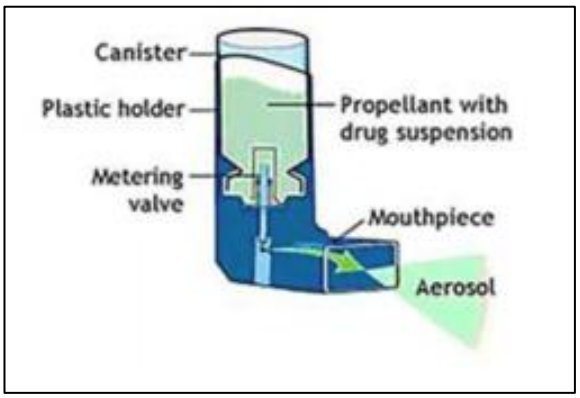

Figure 2.3: Metered Dose Inhalers

The dose delivered by an MDI can be analyzed using a microscope, or preferable an automated image analyzer. A brochodiator MDI was examined using the PSA300 image analysis system. The particle size and shape distribution is shown below:

Table 2.1: The Particle Size and Shape Distribution

	Size	Roundness	Aspect Ratio
D10:	2.3	0.43	1.19
D50:	3.9	0.6	1.51
D90:	6.4	0.78	2.05
Minimum:	0.6	0.27	1.07
Maximum:	8	0.93	3.27
Mean:	4.21	0.61	1.58

A. Dry Powder Inhalers :

Dry powder inhalers (DPIs) have been available commercially since approximately 1970, although the earliest prototypes were described several decades earlier. DPIs contain a powder formulation, which most frequently consists of an ordered mixture of micronized drug (<5 μm in diameter) and larger carrier lactose particles that are required to improve powder flow properties.

The patient's inhalation through the device is used to disperse the powder and to ensure that some of the dose is carried into the lungs (Figure 2.3). An alternative type of formulation used in some DPIs consists either of micronized drug particles alone loosely aggregated into small spherules or of cospheronized drug and lactose.

Table 2.2: Dry Powder Inhalers

	Size	Roundness	Aspect Ratio
D10:	2.4	0.48	1.15
D50:	4.8	0.68	1.37
D90:	8.6	0.83	1.86
Minimum:	0.6	0.24	1.05
Maximum:	15.7	0.93	3.68
Mean:	5.49	0.667	1.46

B. Ideal DPI:

- Effective dosing
- Uniform dose
- Targeted delivery
- Operable at low inhalation flow rates
- Efficient device
- Easy to use.

C. Formulation:

DPI formulations are generally engineered composites, containing a drug material of micron size formulated with or without a large carrier material.

The formulation is formulated around a device that when actuated by patient is capable of producing a respirable aerosol cloud that penetrates the respiratory tract and reaches the site of action.

D. DPI Design Issues:

Inhaler design, especially the geometry of the mouthpiece, is critical for patients to produce an air flow sufficient to lift the drug from the dose chamber, break up the agglomerates in the turbulent air stream and deliver the drug dose to the lungs as therapeutically effective fine particles.

When the patient actuates the DPI and inhales, airflow though the device creates shear and turbulence; air is introduced in to the powder bed and the static powder blend is fluidized and enters the patient airways. There the drug particles separate from the carrier particles and are carried deep into the lungs to exert the effects.

E. Evolution:

- Appearance
- Identity
- Microbial limits
- Water content
- Extractives
- Drug related impurities

F. Nebulizer:

A nebulizer changes medication from a liquid to a mist so you can inhale it into your lungs. Nebulizers come in home (tabletop) and portable models. Home nebulizers are larger, and you have to plug them into an electrical outlet. Portable nebulizers run on batteries, or you can plug them into a car outlet. Some are only a bit bigger than a deck of cards, so you can carry them in a bag or briefcase.You may need a doctor's prescription for a nebulizer, or you can get one at your pediatrician's office. Many people also get breathing treatments at their doctor's office.

Home nebulizers cost about $50 and up, plus the cost of accessories. Portable nebulizers usually cost a little more.Health insurance policies usually cover nebulizers under their durable medical equipment portion. But most insurance companies want you to work with a certain supplier. Check with your insurance provider before buying or renting a nebulizer. Your health care team should be able to help you.

Types of Nebulizers:

a. Jet. This uses compressed gas to make an aerosol (tiny particles of medication in the air).

b. Ultrasonic. This makes an aerosol through high-frequency vibrations. The particles are larger than with a jet nebulizer.

c. Mesh. Liquid passes through a very fine mesh to form the aerosol. This kind of nebulizer puts out the smallest particles. It's also the most expensive.

2.6 Drug Delivery:

A. Pulmonary Delivery of Peptide and Proteins:

Pulmonary delivery offers direct drug targeting for local diseases such as asthma, chronic obstructive pulmonary disease (COPD), and cystic fibrosis. Inhalation therapy may also be applied to treating systemic diseases, as it has some advantages over other routes of administration. The lungs provide a large surface area and high blood supply for drug absorption into the systemic circulation. It also avoids the first pass hepatic metabolism that orally delivered drugs undergo. Furthermore, inhalation is less invasive than injection, which is the conventional delivery method for many proteins. Thus, interest in developing inhaled proteins and peptides for systemic treatments has been increasing in recent decades. The respiratory route has favorable properties for the absorption of proteins and peptides. On the other hand, the lungs also have pulmonary clearance and metabolic pathways to guard against foreign macromolecules.

These natural defense mechanisms can inadvertently oppose therapeutic protein delivery and need to be overcome if absorption is to increase. Active research is being carried out in pulmonary delivery of proteins, but so far very few respirable proteins have been marketed and practically no absorption enhancers have been approved. Most of the in vivo efficacy and toxicity studies have been conducted on animals, and not yet on humans. As proteins and peptides are complex and fragile molecules, there are formulation challenges that need to be overcome. Knowledge in this field is continually progressing and inhalation will become a convenient administration method for proteins and peptides, particularly for local delivery, in the future.

B. Sterile dosage forms loaded nanosystems for parenteral, nasal, pulmonary and ocular administration:

Currently, many pharmacologically active compounds are formulated as sterile dosage forms. These include parenteral, nasal, pulmonary, and ocular preparations. Different nanosystems have been successfully formulated and loaded into these dosage forms. Delivery of these nanosystems via invasive and noninvasive routes offers many advantages. Despite being invasive, parenteral administration of nanosystems remains the route of choice, owing to the overcoming absorption barriers and rapidity of action, while noninvasive routes such as pulmonary, ocular and nasal are widely investigated due to the advantages of localizing drug action and minimizing adverse events. In this chapter, the composition, characteristic and different types of these sterile dosage forms were outlined. In-process and release specifications of these preparations were also generally mentioned. Delivery of nanoformulation and their applications via invasive and noninvasive routes were discussed.

C. Quality and Performance test - Aerodynamic Particle Size Distribution:

The APSD of pharmaceutical aerosols describes the mass of drug in a range of particle sizes produced by the inhaler. It is important in two respects. First, aerodynamic diameter has been correlated with lung deposition through a variety of mechanisms. The aerodynamic

diameter is defined as the diameter of a unit density sphere with the same terminal settling velocity as the observed particle. It differs from the geometric diameter according to Stokes' Law, which equates particle behavior in terms of terminal settling velocity (V) and accounts for both shape and density.

2.7 Pharmaceutical Aerosols - Uses and Advantages:

2.7.1 Types of Pharmaceutical Aerosols:

Generally, pharmaceutical aerosols are stored in two types of inhalers viz., Metered-Dose Inhalers (MDIs) and Dry Powder Inhalers (DPIs). MDIs and DPIs deliver a specific quantity of drug to the lungs through pulmonary tracks on external surface of body parts. Both types of products are used to treat lung diseases characterized by obstruction of airflow and shortness of breath, including asthma and chronic obstructive pulmonary disease (COPD), as well as respiratory infections and cystic fibrosis. The inhalation route offers further potential for systemic drug delivery.

A. Applications:

Administration of drugs from an aerosol is very easy and they can be applied directly on the affected parts or abraded skin introduced into body cavity and passages. When sprayed on skin, some of propellants (e.g., ethyl chloride) cool the tissue due to sudden expansion of propellant. For these reasons, pharmaceutical aerosols have a wide range of applications in the treatment of a patient due to its beneficial effect over the other dosage form. It is used very effective treatment of illness of asthma and chronic obstructive pulmonary disease (COPD). In a recent study, it has been observed that inline dry powder inhalers offer a potentially effective option to deliver high dose inhaled medications simultaneously with mechanical ventilation. Inline DPI which are actuated using a low volume of air (LV-DPI) are available for efficiently deliver pharmaceutical aerosols during low flow nasal cannula (LFNC) therapy. Pharmaceutical aerosols are also very effective in the treatment of diseases like diabetes, angina pectoris and many others.

B. Advantages:

Pharmaceutical aerosols are gaining popularity due to certain advantage.

- Pharmaceutical aerosols are easy to apply.
- Aerosol administration gives very efficient and quick relief.
- The stability of drug is enhanced by storing in MDIs and DPIs since the drug is not comes in contact atmospheric oxygen and moisture.
- 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 can be avoided.
- Aerosols can be used for both systemic and local applications.
- A sterile dose of drug is dispensed and also the contamination of drug is prevented.

C. Working:

A spring holds the valve tightly in place. The valve is operated through a push button type actuator (item no. 4) which is normally remain in its up position. The function of the actuator is to open the valve and produce required types of discharge. The drug (item no. 5. either fiquid or solid powder) is kept in suspense or in solution of a propellant (item no. 6) whose vapor occupies the empty space of the container, and its vapor creates pressure inside the container. The function of the propellant is to develop pressure within the container and to expel the product. Different types of propetants are used: Tri-chloro-fluoro-methane, di-chloro-di-fluoro-methane are most commonly used. When the actuator button is pressed towards bottom, the spring is compressed, and it allows to open the valve. The pressurized drug and propellant escape through an opening at the top of the valve as aerosol or mist jet. Again, when the actuator button released, the spring expands and close the valve.

Drug delivery to the lungs is an attractive route for local treatment of pulmonary disease such as asthma, and chronic obstructive pulmonary disorder (COPD), and also delivering drugs systemically. In particular, significant research and development efforts have been put into dry powder aerosols which require no propellant, have superior chemical stability compared with solution, and are easy for patients to use. There are two types of dry powder inhalers, passive or breath actuated devices, and active devices. With passive devices, the energy for dispersion is generated by the patient's inspiratory effort. In contrast, active devices minimize inspiratory effort by using an independent means (motor or compressed gas) to fluidize the powder. In the literature, the active devices have also been referred to the third generation DPI.

Clinical efficacy of inhaled therapeutics is governed by lung deposition, which depends on the aerosol properties. For DPIs, the aerosol properties are related to the dispersion of the powder, governed by the complex interaction between patient inspiratory flow rate, the device, and the formulation. The effect of these variables on deposition in the lungs can be examined by in vivo lung deposition studies. Inline DPIs are pharmaceutical aerosol produced using a gas stream supplied from a positive pressure source, such as an air-filled syringe or manual ventilation bag. Advantages of these devices compared with conventional inhalation driven DPIs include high quality aerosol generation, use in subjects that cannot generate sufficient inspiratory flow, reproducible aerosol delivery, assistance with deep inspiration and breath hold. As aerosol generation is not dependent on patient inspiratory effort and following inspiration instructions, inline devices may be useful for administering aerosols to infants and young children. Based on operation with a positive pressure gas source, these devices can also be used to administer aerosols during Invasive and non-invasive ventilation.

A vast majority of studies considering aerosol delivery during mechanical ventilation have implemented nebulizers and metered dose inhaters. in contrast, few studies have considered DPI delivery during mechanical ventilation. This limited use may be because of the perception that humidity in the ventilation system will degrade the powder quality and aerosolization performance. However, successful inline DPI devices for use with humidified systems have separated the humidified ventilation and DPI actuation gas streams.

The product concentrate in the container is in equilibrium between liquid & gaseous state. When actuator is pressed the valve opens. Since the product is under pressure, the vapour above the liquid concentrate pushes the products down. Then the product gets expelled through dip-tube from the container.

2.8 Production of Aerosol:

Pressure filing method. In this method, the products concentrate is placed in the container and closed with the valve. The product is maintained below entical temperature/slightly below boiling point (critical temperature is defined as the temperature above which the liquid can no longer exist as liquid or in easy term, temperature above which liquid show properties which are intermediate between gas & liquid). The propellant gets liquefied in the container.

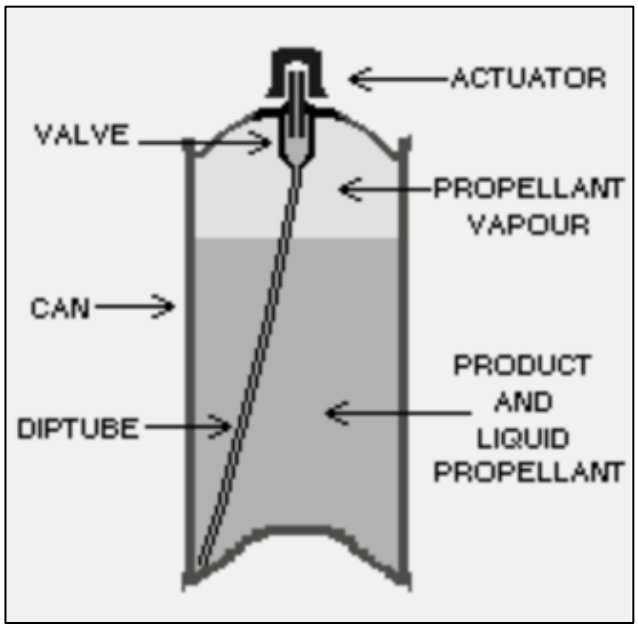

Figure 2.4: Production of Aerosol

Conclusion: The field of inhaled pharmaceutical aerosols is growing rapidly due to the inhaled medications for treatment of systemic illness gain. populanty. With the explosive growth of inhaled pharmaceutical aerosols comes the need for engineers and scientists to perform the research, development and manufacturing of these products. However, this field is interdisciplinary, require knowledge in a diverse range of subjects besides pharmaceutical which includes mechanics, fluid mechanics, transport phenomena, interfacial science, physical chemistry, respiratory physiology. anatomy as well as pulmonology as a result, it is difficult to newcomers as well as experienced practitioners to acquire knowledge necessary implement their products based on pharmaceutical aerosols. Aerodynamic particle size distributions of pharmaceutical aerosols are important for determining the inhaled dose from medical inhalers and nebulizers as well as the drug's spatial distribution within the lungs upon deposition.

Pharmaceutical aerosols (MDIs and DPIs) are subject to the current good manufacturing practice (cGMP) requirements for drugs and devices. Current good manufacturing practice requirements for combination products, including an explanation of a streamlined approach for demonstrating compliance with both drug and device cGMP requirements. In particular, design controls (21 CFR 820.30) apply to any combination product that includes a device constituent part that is subject to them, including all MDIs and DPIs. Essentially, design control activities confirm that there are no negative interactions between constituent parts, and assure that their combined use results in a combination product that is safe and effective and performs as expected. Guidance for industry on pharmaceutical development addresses product design and development procedures, reflecting quality by design principles.

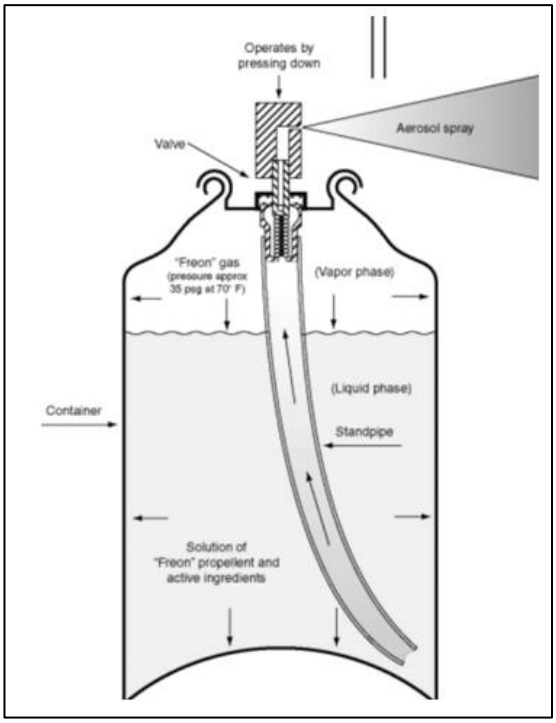

Figure 2.5: Pharmaceutical Aerosols

Thus, a good knowledge of cGMP is necessary besides other multidisciplinary subjects mentioned above to maintain good quality and efficient use of pharmaceutical aerosols.

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