



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Quality control and testing evaluation of pharmaceutical aerosols

*Ruwaida W. Abdo, Najlaa Saadi, Nour I. Hijazi
and Yara A. Suleiman*

Faculty of Pharmacy, Philadelphia University, Amman, Jordan

O U T L I N E

12.1 Introduction	580	12.6 Universal tests and standards for pharmaceutical aerosols	603
12.2 The respiratory tract: a therapeutic perspective	581	12.6.1 Identification	603
12.3 Aerosols dosage forms: fundamental aspects	583	12.6.2 Assay	603
12.3.1 Transport and deposition to lung	586	12.6.3 Relevant impurities	604
12.4 Quality control and formulation characterization: traditional approaches	593	12.6.4 Description	604
12.4.1 In-process quality control and finished product quality control for pharmaceutical aerosols	594	12.7 Evaluation of packaging components of aerosols	604
12.5 Aerosols evaluation parameters	598	12.7.1 Protection	605
12.5.1 Flammability and combustibility	598	12.7.2 Compatibility	605
12.5.2 Therapeutic activity	599	12.7.3 Safety	605
12.5.3 Physicochemical characteristics	599	12.8 Stability testing of aerosol products: International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use guideline	606
12.5.4 Performance	600	12.9 Pharmacokinetic assessment and biological fate of aerosol delivered drugs	607
		12.10 Bioavailability and bioequivalence studies of aerosol: Food and Drug Administration perspective	608

12.11 Futuristic aerosol products: market trend	609	Acknowledgment	611
12.12 Conclusion	610	References	611
Abbreviations	610	Further reading	614

12.1 Introduction

The respiratory system is considered among the most important systems in the human body. The respiratory system is divided into three completely different regions, each with different anatomical units. The primary region is referred to as the head airway region, the second as the lung airway, and the third region as the alveolar one. The inhaled particles that enter the respiratory system during the inhalation process will deposit in one of these regions, where several microorganisms and viruses additionally deposit, initiating different types of respiratory diseases (Tu et al., 2013).

Unfortunately, throughout the years, several critical lethal diseases and complications are developed that would have an effect on this important system inflicting important health issues that reciprocally reduces the quality of life and work productivity and increases the morbidity and mortality burden. Respiratory disorder causes an immense worldwide health burden. It is estimated that 235 million people suffer from asthma (Goetz and Singh, 2016).

Studies address that not less than 200 million people suffer from chronic obstructive pulmonary disease (COPD), out of which a huge number of 65 million experience moderate-to-severe COPD, while 100 million of the adult population endure sleep-disordered breathing, more than 50 million fight with occupational lung diseases, millions of adult population live with pulmonary hypertension, and 8.7 million people develop tuberculosis annually, which total the number to more than 1 billion people suffering from chronic respiratory conditions. On the other hand, at least 2 billion people are exposed to the toxic effects of biomass fuel consumption, 1 billion exposed to outdoor air pollution, and 1 billion exposed to tobacco smoke. The official reports of health societies show that each year, 4 million people die prematurely from chronic respiratory disease (European Respiratory Society Publications Office, 2006; WHO, 2012a).

Clinical studies have demonstrated the precious advantage of inhalation aerosols over systemic therapy for the therapeutic treatment of lung disorders (Borghardt et al., 2018). The inhaled route of administration is chosen to be effective for delivering different types of preventer and reliever drugs to patients with airway obstructions owning the unique advantage of delivering relatively small doses of drug directly to the respiratory tract airways for achieving a high local concentration and diminishing systemic adverse effects; besides they may provide considerable cost savings because of the lower dosage regimens, especially with expensive therapeutic agents. Consequently, this results in a high therapeutic ratio as compared with other systemic drug delivery either through oral or parenteral route of administration (Borghardt et al., 2018). Numerous and countless studies

have shown that the lungs provide substantially superior bioavailability (BA) for macromolecules than any other route of drug delivery to the systemic circulation (Paranjpe and Müller-Goymann, 2014; Javadzadeh and Yaqoubi, 2017).

However, understanding the mechanisms of the inhaled particles deposit within the respiratory system opened the technique ahead to deliver the drug particles directly into the system to deposit there and exerts their anticipated action. This was achieved by developing a pharmaceutical dosage form known as the aerosols that was able to do that. Aerosols dosage forms are designed to be sprayed into the mouth which causes their contents to expel from the container directly into the lungs so as to deposit there and employ their anticipated action. Aerosols contain the active pharmaceutical ingredients (APIs) in combination with additional excipients in the form of fine mist. To form the final dosage, the ingredients are packaged with the aid of pressure to form a pressurized dispenser called the aerosol container. The excipients and therefore the components of the aerosol container along with plenty of other factors are accountable for the aerosols dosage form to indicate optimum function. Thus various quality control tests are performed to these dosage forms to guarantee that the ultimate product is at its optimum performance with the highest safety and that they fulfill product specifications which are going to be discussed in details throughout this chapter (Sahab et al., 2016).

As a conclusion and compared with other routes of administration, inhaled drugs are the backbone of treatment in the care of pulmonary diseases offering significant benefits including target drug delivery with reduced systemic side effects, and rapid onset of action that combined with high and long-term pulmonary BA. To achieve these benefits, several considerations should bear in mind regarding the physiochemical properties of inhaled drugs, and the formulation and device characteristics. A comprehensive understanding of the lung anatomy and pathology along with its associated kinetic processes, such as lung dose, and mechanisms of respiratory particles deposition are necessary to achieve the efficacy of inhaled drugs.

12.2 The respiratory tract: a therapeutic perspective

Respiratory tract diseases will vary from being acute and self-limiting to chronic and life-threatening. In 2012 more than 671,900 people died within the European Union from respiratory system diseases. Chronic lower respiratory diseases such as bronchitis and pneumonia along with lung cancer were most prominent compared to other respiratory system diseases (European Respiratory Society Publications Office 2006; WHO (World Health Organization), 2012a). In the meantime at the United States, respiratory system diseases were responsible for 6.7% of all deaths in 2015 that graded as the fifth major cause of death and the eighth leading cause of health burden worldwide (Dwyer-Lindgren et al., 2017).

The respiratory tract can be divided anatomically into two main portions: upper and lower. The nose, sinuses, pharynx, and upper larynx are components of the upper portion, whereas the lower larynx, trachea, bronchi, and lungs belong to the lower. Accordingly, anatomical classification rhinitis, sinusitis, bronchitis, tonsillitis, nasopharyngitis,

pharyngitis, epiglottitis, and the common cold are considered as upper respiratory tract diseases caused by bacterial or viral pathogens. Examples of such pathogenic microorganisms are stained Gram-positive bacteria such as *Staphylococcus aureus*, *Streptococcus pyogenes*, and *Streptococcus pneumoniae*. On the other hand, *Haemophilus influenzae*, *Klebsiella pneumoniae*, and *Moraxella catarrhalis* are Gram-negative bacteria (Mhlanga et al., 2018). Respiratory viral pathogens that cause illness such as Parainfluenza virus, Coxsackie, influenza virus, coronavirus, rhinovirus, adenovirus, and respiratory syncytial virus are considered of being harmless, nevertheless in third world countries, they are a cause of death (Laut et al., 2015). The policy of resolving upper respiratory tract infections involves relieving pain, reduce congestion, surprising cough, and inhibiting the growth of pathogens or eradicating them. Pharmacological treatment includes several categories of medications such as anticholinergics, antitussives, the first generation of antihistamine, decongestants, corticosteroids, nonsteroidal antiinflammatory drugs, and antivirals. Antibiotics such as amoxicillin, clindamycin, benzathine benzylpenicillin, phenoxymethylpenicillin, and erythromycin are mutual bacterial infections treatments. One of the foremost mistakes in the treatment plan is prescribing antibiotics for the viral pathogenic cause of infections due to a misdiagnosis that consequently elevates the possibility of microbial resistance (Mhlanga et al., 2018).

Pneumonia, TB, acute respiratory distress syndrome, pulmonary edema, pneumoconiosis, and lung cancer are diseases that affect the respiratory alveoli. Meanwhile, asthma, COPD, cystic fibrosis, emphysema, and chronic bronchitis are lung diseases affecting the airways and the tracheal branches. Some diseases distress pleura such as pleural effusion and mesothelioma (Webmd, 2016).

Asthma is a chronic disease of the respiratory tract airways that frequently demonstrates with irritating dry repetitive cough, wheezing, and breathlessness (McGann and Long, 2018). The treatment of choice for patients with persistent asthma is inhaled corticosteroids as well as many formulations and devices such as dry powder inhalers, breath-actuated inhalers, and pressurized metered dose inhalers (MDIs). One example for inhalation aerosol formulated as a pressurized MDI is Beclomethasone dipropionate hydrofluoroalkane inhaled corticosteroids. This medication was approved in the United States for 5-year-old patients or older and is formulated as a solution inhalation aerosol that delivers and distributes the drug to the peripheral airways (Ostrom et al., 2018).

Pneumonia is an acute infection mainly affecting the lung parenchyma. This respiratory disease caused by microscopic pathogens is similar to those bacteria and virus that cause upper respiratory tract infections in addition to fungal causes such as *Paracoccidioides brasiliensis*, *Aspergillus fumigatus*, and *Cryptococcus neoformans*. Immunocompromised patients more frequently experience fungi-caused pneumonia than other patients. In general, pneumonia classified into hospital-acquired and community-acquired pneumonia, where hospital-acquired pneumonia is more dangerous due to multidrug resistant microorganisms that cause this class of diseases. Therapy of pneumonia depends on its category and cause (Sangeetha et al., 2018).

Finally, respiratory diseases are an enormous challenge to life and health and cause an immense worldwide health burden. Emphasizing the diseases of greatest and immediate concern we conclude that asthma is the most common chronic disease, and COPD is the fourth leading cause of death worldwide with growing numbers.

In recent decades, modern medicine has advanced concerning respiratory disorders treatments, and one of the most efficient drug-delivery techniques for those treatments is inhalation therapy using aerosols dosage forms that allow effective delivery of a therapeutically active medicament to the respiratory tract. Understanding the fundamental aspects of the aerosols dosage forms provides the backbone for developing this technique.

12.3 Aerosols dosage forms: fundamental aspects

Pharmaceutical aerosols are products that contain therapeutically active ingredients which are packed under pressure and are previously released upon activation of an appropriate actuator and valve system. The term “aerosols” was originally accustomed to describe a liquid or solid fine mists particles with a specific size range. The term “aerosols” now refers to pressurized packed products that contain the active ingredient(s) and excipients that are dispersed in a liquefied or compressed gas known as the propellant. It is by the power of this propellant that the contents of the aerosols are expelled from their container (USP-NF, 2015). Aerosols dosage forms can be topically, orally, nasally, and systemically inhaled. By incorporating many different APIs into them, aerosols can be used for the treatment of a wide range of diseases, from acne to asthma and lung infections (Ashurst et al., 2000). For example, salbutamol and metaproterenol sulfate are administered by the means of inhalation aerosols for relieving asthma symptoms (Labiris and Dolovich, 2003). Fig. 12.1 shows a salbutamol inhaler dispenser which is used for asthma treatment.

The use of aerosol dosage forms was widely and speedily accepted by patients and their physicians because of the numerous advantages they possess over the other dosage forms, which are as follows (Apiou-Sbirlea et al., 2013):

1. Release accurate doses with eradicated contamination of remaining material.
2. Expand the stability for the contents that are adversely affected by oxidation and moisture.
3. Direct delivery for the medication to the affected area at the desired rate and form such as spray, stream, and foam.
4. Eliminate irritation produced by topical application of topical medication.

Aerosols package consists of propellant, product concentrate, container, valve, and an actuator, as shown in Fig. 12.2. Propellants are accountable for generating proper expelling pressure within the container. Basically, product concentrate of an aerosol in which the active drug combined with suitable excipients can be delivered in three forms of liquid form a solution, suspension, an emulsion or in a form similar to semisolid. There are containers in which the product concentrate is filled. The valve is a part of the package through which the product concentrate is expelled in the desired form and rate. The actuator is an integral part of every aerosol package that allow easy opening and closing of the valve, which is usually designed in an appropriate way to give the desired form of discharge (fine mist, liquid stream spray, coarse spray, etc.) (Apiou-Sbirlea et al., 2013; Newman, 2005).



FIGURE 12.1 Salbutamol inhaler.

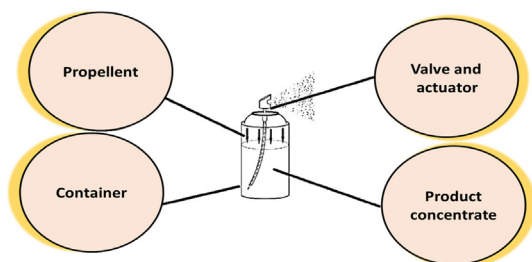


FIGURE 12.2 Components of pressurized aerosol package.

The liquefied gases are very useful as they stay in the form of gases at ambient atmospheric pressure and temperature, then by elevating the pressure or lowering the temperature below their boiling point, they are liquefied. Once these liquefied gases are packed into the sealed containers, they change into liquid and vapor phase. The pressure inside the pressurized aerosol container gradually increases throughout the formation of the vapor phase until establishing equilibrium between the liquefied propellant phase and vapor phase. The liquid contents of the aerosol are pushed against the valve by the action of this pressure, and upon releasing of the valve, the liquid will expel and come in contact with room temperature and atmospheric pressure, thus causing the liquefied propellant to reappear back to the vapor state, leaving the other components to deposit on the surface they are supposed to function upon. Examples of liquefied propellants are fluorocarbons that include dichlorodifluoromethane and dichlorotetrafluoroethane that are usually utilized in oral aerosols, whereas when

compressed gas is used as the propellant gases such as nitrogen or carbon dioxide that are chemically considered inert gas, which is then compressed in the aerosol container, it is due to the expansion of this gas that the power to push the contents out from the container is established. A single or a mixture of propellants can be used in aerosol dosage forms (Lachman and Lieberman, 2011; Peter Floyd et al., 2014).

Aerosol containers can be manufactured from variable materials such as coated metals, glass, and, infrequently, plastic. Containers are engineered to deliver with good stability and efficacy against different product formulations and product performance prospects. The characteristics of the product formulation, type and amount of propellant used, pressure of the aerosol contents, and even the components of the aerosol are all manipulated to alter the characteristics of the dispenser to yield the performance claimed in labeling (Lachman and Lieberman, 2011; Remington and Allen, 2015).

The aerosol valve is a very important part of an aerosol container; it is a vital part responsible for expelling and dispensing the desired dose of the aerosol contents in the desired controlled rate. Valves account for delivering the product concentrate in the preferred form and controlling the flow rate of contents from the container. One of the important points that should be considered during the manufacturing process is that the valve should be resistible for corrosion and withstand the internal pressure encountered due to by-product concentrate and the container. Aerosols valve is also responsible to provide the appropriate amount of medication which is important especially for the delivery of potent therapies, where for this proper dispersion purpose, a valve usually spray about 50–150 mg \pm 10% of liquid materials at one time use of the same valve (John Chadwick, 2007; Lachman and Lieberman, 2011; Remington and Allen, 2015).

The delivery of the aerosols contents depends on the integral function provided by the valve assembly, propellant, product concentrate, container, and actuator. An aerosol valve is a unique feature of this dosage which is a vital part for effective expelling and dispensing the desired dose of the aerosol contents in the controlled rate. Various types of aerosol valves are used depending on the physical form dispensed and how the aerosol to be used.

The types of the valves are variable; mainly two types are applicable—either a continuous spray valve or a metering valve.

1. *Continuous spray valves*: To deliver the product contents constantly in the form of a spray or solid foam stream with or without amount determination. These kinds of valves are the main type used for all categories of pharmaceutical aerosols.
2. *Metering valves*: To deliver the contents for potent medication, they are dispensing the exact amount of medicament upon each time of activation during application.

The basic parts of a valve assembly are given in Fig. 12.3 and can be described as follows (Lashkar, 2012):

- Actuator: It is the push knob which the user presses to activate or deactivate the assembly of the valve system. The physical form of the emitted product concentrate is determined by the combination of the type and amount of propellant used along with the proper actuator design and dimensions.
- Stem: Provides necessary support for the actuator and delivers the contents in the desired form to the chamber of the actuator.

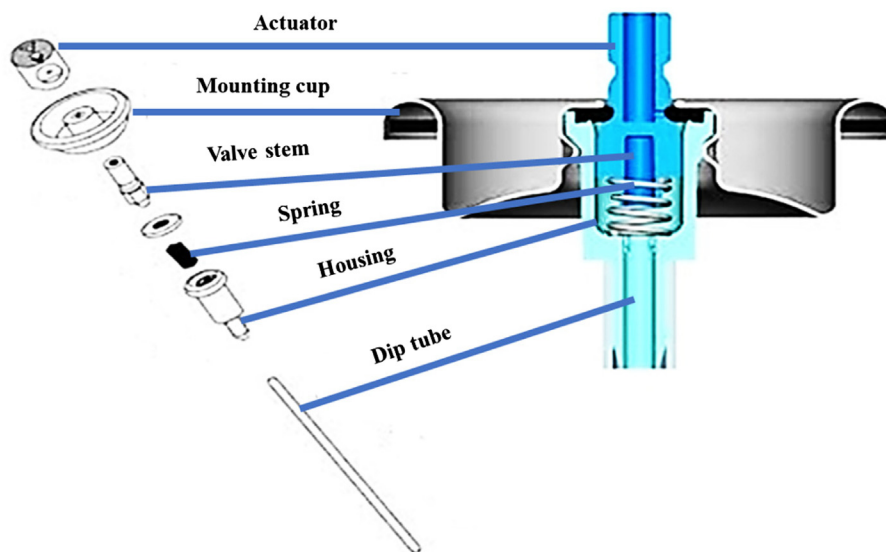


FIGURE 12.3 Valve assembly and its components.

- Gasket:** Serves to prevent leakage of the product concentrate when the valve is in the deactivated position, placed tightly with the stem.
- Spring:** It is that part of the device that allows the actuator draw backup on releasing pressure, returning the valve assembly to the closed position in this way. Besides that, it seals the gasket in place to prevent the outflow of the formulation.
- Mounting cup:** It is normally mounted at the top of the aerosol container serves to hold the valve in place and feature a crimped closure at the opening of the container. The undersigned side of the mounting cup is exposed to the formulation, which imposes the same consideration as the inner part of the container with respect to meeting the criteria of compatibility. If necessary, it may be coated to prevent an undesired interaction.
- Housing:** Positioned directly below the mounting cup and provides the association between the dip tube part and the valve stem along with the actuator. With the stem collaboration, housing orifice helps to control the delivery rate and determine the form in which the content of the product is emitted.
- Dip tube:** It is the part of the valve assembly that extends downstream into the product concentrate aids to transport the contents from the container to the valve. The inner integral dimensions of the dip tube and housing for a particular product are determined according to the viscosity of the product and its intended delivery rate. Fig. 12.3 shows the basic components of the valve assembly and its contents (Lashkar, 2012).

12.3.1 Transport and deposition to lung

Aerosol particles which are directed to the respiratory tract through oral or nasal routes of administration will end up in the respiratory tract, but not all of the inhaled particles entirely will reach the lungs, for example, one administered pump of the MDI includes

million numerous inhaled particles, but only part of these particles will deposit at their intended target site in the respiratory tract; besides that, some of the inhaled particles will be exhaled (Akira et al., 2013). Consequently, this will be a formulating challenging issue in order to accomplish an adequate therapeutic response by delivering the correct desired amount of the drug to reach the lungs (Usmani et al., 2005). In order to design a convenient, effective, and safe aerosol device, it is necessary to consider many factors that have a considerable role in determining the quantity of drug that gets transported and deposited within the lungs; the factors include (1) aerosol properties as the shape, density, and size of inhaled particles; (2) mode of inhalation along with the inhalation pattern (volume inhaled and the flow rate) along with breath-holding time; (3) characteristics of the inhaled carrier gas; and (4) other factors as patient-related factors, pathophysiology factors along with type, and severity of lung diseases (Chantal and Kim Prisk, 2004).

Starting with the means of operation, the distribution of the medication particles within the lungs will be more superficial with greater inhaled volume. In the meanwhile, as the inhalation flow rate is increased, the deposition of the drug in the oropharynx and large central airways by impaction will be greater. Lastly, to achieve adequate drug particles' deposition by the mechanism of gravitational particles sedimentation in the more peripheral parts of the lung, the breath-holding time is a critical factor. The prediction of aerosols properties, especially the aerodynamic diameters, is of significant importance when it comes to deposition of drug particles to the lungs itself. It is more reliable for the particles of $2\ \mu\text{m}$ and larger in diameter to get deposited in the oropharynx and large conducting airways. The particle sizes of a pharmaceutical aerosol formulation are heterodisperse, meaning that they composed of various sizes, 50% of the aerosol elements by mass are smaller than the mass median aerodynamic diameter (MMAD) and the other 50% the particles is larger than the MMAD. The ideal size of the pharmaceutical aerosol particles is not yet well-defined, but, generally, it is known that in order for the inhaled particles to pass into the bronchial tree, the MMAD should not exceed $5\ \mu\text{m}$. The particle size of aerosols could be determined using measurement-related devices as cascade impactor or laser light scattering (Yakubu et al., 2013).

During inhalation the incoming air should undergo a series of direction changes because it flows from the nose or mouth down through the branching airway system of the lung structure. Good understanding for the mechanism of inhaled particles deposition in the respiratory tract is of great worth to assist the toxicology risk of inhalation and to improve efficiency in drug delivery manner when discussing inhalation therapies (Carvalho et al., 2011). Generally, the deposition of particles within the respiratory tract depends on five multiple mechanisms: (1) inertial particles impaction, (2) gravitational sedimentation, (3) electrostatic precipitation, (4) interception, (5) brownian particles diffusion (shown in Fig. 12.4) (Tu et al., 2013).

Inertial impaction is the mechanism of deposition that occurs when airflow changes direction and the particle, which happens to be close to the airway wall, follows its original direction instead of adjusting to the airflow. Particles that are bigger in size than $5\ \mu\text{m}$ are influenced by this deposition mechanism. The inertia of these large aerosol particles led to increasing resistance to change their direction when the flow of air into the respiratory tract changes its path suddenly, this will cause them to deviate away from streamline of air, causing them to impact and deposit on the walls of the airway. The energy of

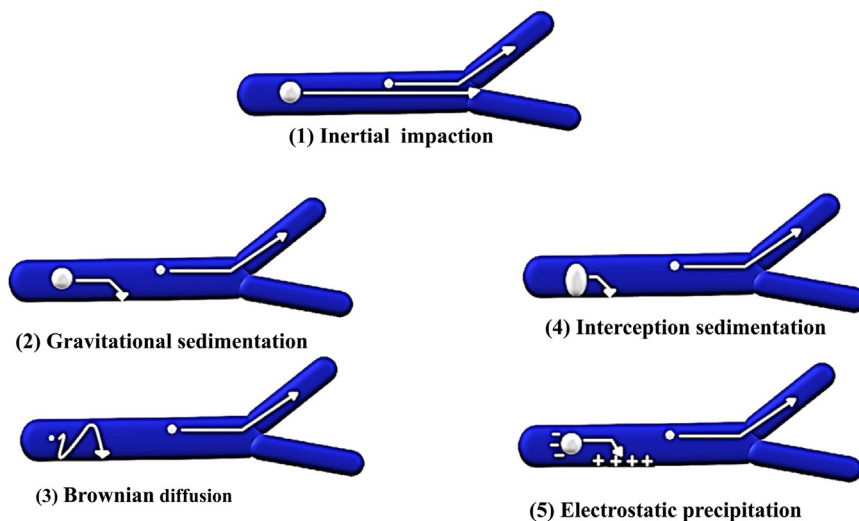


FIGURE 12.4 Five mechanisms of aerosol particle deposition.

particles tends to keep them on their preestablished paths each time the air changes direction through the airways, which can lead to a high propensity to impact on airway surfaces. As a result, some of the particles near the airway surfaces will undergo deposition; this is termed inertial impaction. The possibility of deposition by impaction is subject to the ratio of particle arresting distance to dimensions of respiratory airways at an air-stream's predicted velocity (Fernández Tena and Casan Clarà, 2012). This type deposition mechanism of particles is also reliant on the location of the particles within the airways. The highest prospect of deposition by impaction is in the trachea–bronchial respiratory zone, this means impaction is of foremost concern in the large respiratory airways. For example, in a bifurcation of the human bronchial tree, deposition possibility on inhalation is much higher for an element moving along the middle line of the parent tube than for elements moving nearer to the track walls, and the most likely deposition locations are at or near the carina of the bifurcation (edge of cartilage in the trachea occurs between two main bronchi divisions). The highest degree of deposition by impaction occurs at the throat, and to a lesser extent at other bifurcations (Koullapis et al., 2015).

The higher the particle mass and its mobility, the more difficult it is for the particle to adjust for a curving air stream. Large particles tend to stick to their original path because they have a higher relaxation time compared to small particles.

Using Stokes (Stk) number as a parameter for the characterization of the particles move, the deviation and deposition of the particles will increase with increasing the flow rate along with the growths of particle mass as shown in Eq. (12.1) (Fernández Tena and Casan Clarà, 2012)

$$\text{Stk} = \frac{\rho_p d_p^2 u C_c}{9\mu d} \quad (12.1)$$

where ρ_p is the particle density, d_p is the particle diameter, u is the flow velocity, C_c is the slip correction factor, μ is the dynamic viscosity of carrier gas, and d is the airway's diameter.

The Stk number shows that the probability of a particle to deposit due to impaction is directly proportional to flow velocity, particle density, and diameter, whereas it is inversely proportional to the airway diameter (distance to the surface). Thus deposition by means of inertial impaction is most significant for larger particles moving at a high rate close to the surface. When the diameter of the particle approaches the same magnitude as the mean free path of air molecules, particles experience "slip" at their surface. This error becomes significant for elements that are less than 1 μm . The slip correction factor is inserted in the deposition equations to correct for this error. The greater the Stk, the greater the probability that the inhaled particles will get impacted and not follow their streamline of air and will get deposited on the airway walls by the inertial impaction mechanism (Nicolaou and Zaki, 2016).

In gravitational sedimentation the aerosol particles that fall in the size range of 1–8 μm when entering the respiratory system will settle principally in the alveolar cavities and the small airways by the effect of gravity. Settling or sedimentation is gravity, which makes particles to leave their original air stream. The particle sedimentation or settling distance is equal to its terminal settling velocity (V_{ts}) times the residence time in each airway section.

In order to express the V_{ts} , Eq. (12.2) can be used.

$$V_{ts} = \frac{g\rho_p d_p^2 C_c}{18\mu} \quad (12.2)$$

where g is the acceleration of gravity; ρ_p is the particle density, d_p is the diameter of the particle, C_c is the slip correction factor, and μ is the viscosity of air.

According to the probability of a particle to deposit due to gravitational settling is directly proportional to its density and particle size beside the residence time of the particles. In contrast to inertia, it is inversely proportional to the air stream velocity because the residence time decreases at increasing velocity. This particle deposition mechanism is, therefore, most substantial in the smaller airways and in the gas exchange region where air velocity is low and has its maximum removal outcome when airway surfaces come close to horizontal configurations, which is the case in the alveolar region (Fernández Tena and Casan Clarà, 2012).

Gravitational sedimentation is the most significant mechanism of particles deposition for micron-sized particles in the small airways, which are able to pass through the nasopharynx and the large conducting respiratory airways (Akira et al., 2013).

Brownian diffusion is the manner of deposition for particles smaller than 0.5 μm in diameter. This deposition results when the aerosol particles strike with the air molecules which results in the random motion of the aerosol particles inflicting their deposition within the areas of the airway wherever the velocity of air is low, such as the acinar region. Unlike the inertial impaction and the gravitational sediment-deposition mechanisms, increasing the particle size will reduce the deposition of particles by the Brownian diffusion; thus, in order to enhance the deposition of particles by this mechanism, the

particle size should be reduced. The manner of deposition can be explained by the diffusion coefficient (D) of an aerosol particle which is given in the Stokes–Einstein equation (Eq. 12.3) (Fernández Tena and Casan Clarà, 2012).

Diffusion is a considerable mechanism for the deposition of submicron particles in the pulmonary acinus and the small airways; in contrast to settling and impacting deposition approaches, diffusion is inversely proportional to the particle diameter and is controlled by geometric size rather than aerodynamic size (Akira et al., 2013).

$$D = \frac{k_B T C_c}{3\pi\mu d_p} \quad (12.3)$$

where k_B is the Boltzmann's constant, T is the temperature, d_p is the particle diameter, C_c is the slip correction factor, and μ is the air viscosity.

Interception is the result of the contact of the physical particle with the surface of the airway surfaces because of its physical diameter, such a case is observed when a particle moves into an airway narrower in width than the particle diameter. It is a result of physical contact of a particle with the airway surface because of geometrical features. The probability of deposition by interception depends on the closeness of the air streamline to the airway surface and on the ratio of particle diameter to airway width, which is usually small even in the smallest airways. Interception, generally, is less significant than the other deposition mechanisms and is usually important mostly for fibrous particles (Fernández Tena and Casan Clarà, 2012; Akira et al., 2013).

Particles deposition by the electrostatic precipitation mechanism accounts for less than 10% of the entire deposition through the respiratory tract. This mechanism is important for electrically charged particles that can be deposited when large numbers of shared charged particles drive them toward the airway wall. In absence of the collective repulsion force a charged particle can also be attracted to a neutral surface by image forces and then precipitate. An image force is created by the electrically charged particles itself and is equal but opposite of its own charge. The charges of the opposite image on to the respiratory tract airway surfaces frequently conduct electricity once they are not charged, but the electrically charged particles will be attracted toward the airway walls electrostatically, leading to higher deposition rates compared to neutral particles (Fernández Tena and Casan Clarà, 2012).

12.3.1.1 Total lung deposition

The mutual deposition concerning inhaled molecules throughout the regions of the respiratory system can be identified and measured experimentally by measuring both the concentrations of the inhaled and exhaled monodisperses regarding the aerosols test under controlled conditions, and after certain calculations will produce the output of what is recognized to be the total deposition fraction (DF) that indicate the total fraction of the aerosol particles inhaled and deposited among different respiratory regions. This is considered the simplest and extensively applied measure of mutual deposition of inhaled particles (Löndahl et al., 2014).

If the total DF is identified, the respiratory tract deposited particle dose rate, stated as the total amount of inhaled elements (number, mass, etc.) deposited in the airways during a period of time (e.g., lg/min), can be inferred from the dose-rate calculation:

$$\text{Dose rate} = \text{DF} \times C_{\text{inhaled}} \times \text{MV} \quad (12.4)$$

where C_{inhaled} (e.g., $\mu\text{g}/\text{m}^3$) is the particle concentration of the inhaled air (exposure level: the amount of particle per volume air) and MV is minute ventilation (m^3/min). Of these parameters, DF is the least available factor, because it depends on numerous parameters as the respiratory parameters (rate, route, and volume) and subject-specific morphology of the lungs, as well as on particle size, shape, density, and chemical composition. Oversight of DF from the dose-rate calculation, as is often done, results in a considerable uncertainty of up to a factor of 10, as DF may vary from less than 0.1 to almost 1, mainly depending on particle size (ICRP, 2007).

If the aerodynamic diameter of an aerosol element is larger than $0.5 \mu\text{m}$, the fractional deposition will increase with lowering the breathing frequency which in turn provides enough extra time to permit increasing gravity settling. For the particles that have an aerodynamic diameter larger than $1 \mu\text{m}$, their deposition will increase once the average airflow rate rises up, and because of such type of particles, the inertial impaction deposition mechanism is affected that depends on velocity (Tu et al., 2013).

Inhaled particles sizing in range ($0.4\text{--}0.7 \mu\text{m}$) exhibit minimum mobility, so the diffusion, impaction, and sedimentation mechanisms are not effective in the carrying and deposition of these particles.

Physiological factors influencing respiratory particles' deposition include the frequency of breathing and breathing-approach patterns, the pathway of breathing whether oral or nasal, features of ventilation airflow dynamics, tidal lung volume (displaced air volume between normal inhalation and exhalation), and functional residual capacity (residual amount of gas left in the lungs after normal exhalation). Increasing air flow rates raise the outcome effectiveness effect for the velocity-reliant particles deposition impaction mechanism while decreasing the effectiveness effect for time-reliant particles deposition diffusion and sedimentation mechanisms. Increasing tidal lung volumes permit particles to reach and distribute more in distal respiratory aeries, where the likely main particles deposition are governed by sedimentation and diffusion; therefore, the total input to overall deposition compared to deposition by impaction is increased. During exercise, both tidal volumes and breathing flow rates are increased, resulting in an increased deposition by sedimentation and diffusion in the small respiratory airways and alveoli; on the other hand, those conditions increase particles impaction in the large airways. Finally, mouth breathers will result in more particle deposition in respiratory tract than nose breathers because of the nasal efficient particles filtering compared to that of an oral route (Sankhal et al., 2013).

Anatomical factors also play a significant role in particle deposition, those factors such as respiratory airway length and diameter, alveolar size, and bronchioles branching angles. There is a great number of variations in total respiratory particles deposition among normal healthy subjects breathing in the same pattern because of inters subject variability. Even within the same individual, age and pathological processes along with the

changes in dimensions and features of the tracheobronchial tree of the respiratory system with lung volume. Gender differences in anatomical respiratory system structure and modulators of lung function also cause variations in deposition between men and women. For example, deposition in the lung tracheobronchial tree is higher in women compared to that in men as the average female thorax dimension is smaller than that in men and lower conducting airways volume which is only around 75% that in men. So far, when these anatomical gender volume variances are shared with lesser resting minute ventilation volume (volume of gas inhaled or volume exhaled) and breathing flow rates pragmatic in women, total respiratory particles deposition is lesser in women than in men mainly for the reason that a smaller dispersion of the aerosol occurs in the alveolar distal region of the female lung. Respiratory airway breathing conditions and geometry develop from birth to maturity. These changes affect respiratory elements' deposition in childhood. According to studies on particle deposition among children, the respiratory particles deposition in children tend to be higher compared to that in adults by an average factor of 1.5, and because of their minor lung surface area than that of adults, the quantity of particles deposited per surface area is higher by a factor of 4 or 5 in children (Sankhal et al., 2013).

Finally, environmental factors such as relative humidity, temperature, and gravity are having a prospective impact on particle deposition. Studies of respiratory function done in the absence of gravity during parabolic flights have shown disproportionately reduced deposition for particles in the size range 0.5–3 mm compared to deposition in normal gravity. But on the other hand, these studies also suggested that while particle deposition reduced in absence of gravity, particle peripheral deposition in the lung is enhanced compared to that with normal gravity, and ambient relative humidity can significantly affect hygroscopic particles growth and therefore enhance their deposition efficiency (Sankhal et al., 2013).

12.3.1.2 Regional lung deposition

In order to achieve the desired therapeutic action for a pharmaceutical aerosol, its particles should be deposited at definite regions in the respiratory tract where certainly targeted receptors are present in which they will bind to exert their therapeutic consequence (Cheng, 2014).

While most investigational studies have measured ultimately total deposition only, regional deposition within the lung is significant for evaluating the potential hazard of inhaled elements by assessing the effective dose at the critical site within the lung. The value of deposition in any respiratory region depends on the effectiveness of deposition for the region along with deposition in preceding regions, for example, deposition in respiratory regions such as the head airways or the tracheobronchial region is of essential importance since it provides protection for vital sections such as the alveolar region from harmful and irritating particles. Several aspects that govern the deposition of particles in the head airway region are (1) breathing path whether through the mouth or the nose, (2) breathing flow rate, and (3) inhaled particle size.

As inhaled air passes through the nasal cavities it is humidified, warmed, and filtered, where the principal particles are filtered by impaction and by settling down on nasal hairs and at curvatures in the path of the airflow. For mouth breathing at an inspiratory of 30 L/min flow rate, nearly 90% of aerodynamic diameter particles in the proportion range

of 5–10 μm are deposited formerly once the inhaled air reaches the larynx. For inhaled air inhaled through both mouth and nose, deposition in the head airways increases as average inspiratory flow rate rises. In the meanwhile, airborne micro ultrafine particles, less than 0.01 μm have a substantial deposition on surfaces of the head airways due to their great diffusion coefficients (Cheng, 2014).

Usually, alveolar deposition is determined by measuring the proportion of the inspired particles pass through the head airways region that ultimately deposits in the alveolar region. Such proportion of deposition in the alveolar region is influenced by breathing rate, tidal volume, and particle size which is considered to be a mutual cause of size discriminatory particle deposition in the tracheobronchial region, where declined numbers of particles in the 2–10 μm size range reach the alveolar region, while particles larger than 10 μm failed to reach the alveolar region (Tu et al., 2013).

Understanding the physical and chemical particle properties, such as particle size, that influence the regional particle deposition in the respiratory tract is the key issue to achieve the desired effect for a pharmaceutical aerosol.

In order to confirm the functionality, reproducibility, stability of these aerosols pharmaceutical formulations, the functional performance of the formed systems in a predetermined way with the aid of necessary analytical techniques is needed.

12.4 Quality control and formulation characterization: traditional approaches

In terms of the mutual relationship between pharmaceutical development and manufacture, the regulatory entities are continually developing their requirements to meet the challenges of ensuring the efficacy, quality, and safety of new technologies in the global marketplace. The ultimate responsibility for the quality of therapies and medical devices lies with several national and international regulatory bodies elected to safeguard public health (Copley Scientific, 2015).

Quality is the key issue within the pharmaceutical industry and is the part of good manufacturing practice which ensures that the essential and appropriate tests are actually carried out and that products are not released for sale or supply and consequently for human use until their quality has been arbitrated to be satisfactory according to specifications. Quality control issues are concerned with representative sampling, provisions, specification, testing along with the organization, certification, and release procedures (EudraLex, 2014; Uddin et al., 2016).

Guidelines and procedures of standard quality control tests for pharmaceutical aerosols are described in different pharmacopeias and regulatory affairs. Comparing the standard operating and testing procedure of aerosols between different references and pharmacopeias show minor changes between them with differences in test and their limits. These guidelines vary from country to country. A harmonized standard and specification is possible if there is a universal definition and approval for procedures and measures acceptance criteria to all regions (Teja et al., 2011).

In addition to these pharmacopeias and regulatory bodies, European pharmaceutical aerosol group (EPAG), International Pharmaceutical Aerosol Consortium on Regulation and Science are scientifically investigating the standard and regulations of

operating and testing the procedure of aerosols products, including clinical aspects as appropriate, figure consensus and contributes toward operative regulations and standards through sharing the consequences of its research via technical journals, scientific pharmaceutical conferences, and discussions and negotiations with regulatory bodies. The aim is to create a coordinated scientifically based good practice to provide consensus reference to industry and governmental agencies in order to improve safety and quality standards and to recommend harmonized standards and methodology (Uddin et al., 2016).

12.4.1 In-process quality control and finished product quality control for pharmaceutical aerosols

Among the drug products, for example pharmaceutical aerosols, its in-process quality control (IPQC) and finished product quality control (FPQC) must be maintained under demanding quality control tests to ensure proper active ingredients and pressurized package performance along with safety during use and storage, and that could be ensured through tests mentioned in pharmacopeias for the pharmaceutical aerosols that must strictly be performed to ensure the proper quality. Therefore human health safety can be certified with pharmaceutical aerosols (Indian Pharmacopoeia, 2007; British Pharmacopoeia Commission, 2014; US Pharmacopeia, 2015).

The total quality of the product is assured by the IPQC and FPQC tests. This total quality assurance—dealing process (IPQC and FPQC tests) represents rigorous tests to allow products being completely indefectible before they are launched into the market (Uddin et al., 2015). Many concerns need to be measured in order to obtain a product with appropriate quality depending on the requirements of the national authorities and legislation, and the manufacturers' internal policies for production process (safety, marketing, etc.). For pharmaceutical aerosols, quality evaluation depends on several tests performed throughout the formulation development, in the process and finished product inspection phases (Zhu et al., 2015).

Quality-control tests and standard guiding principles for pharmaceutical aerosols are obtained from pharmacopeias and regulative associations such as British Pharmacopoeia, United States Pharmacopoeia, National Formulary (USP-NF), International Pharmacopoeia, the international pharmaceutical aerosol consortium on regulation and science association, and the EPAG (Uddin et al., 2015). IPQC tests are carried out at regular intervals before the process of product manufacturing is completed. The purpose of IPQC is the monitoring and assessment of the quality of pharmaceutical products' evaluation and carry on necessary production adaptation for the manufacturing process to comply with pharmacopeias. FPQC tests are performed after the completion of the manufacturing process with the purpose of evaluating qualitative and quantitative features of the finished product as well as asses test procedures and their acceptance parameters, that should obey by the finished pharmaceutical product throughout its valid shelf life (Teja et al., 2011).

According to these references and regulatory gridlines, the following evaluating tests must be performed.

12.4.1.1 Spray testing

The driving purpose of this test is to eliminate any pure propellant from the dip tube as well as any concentrate, in addition, to inspect for defects in valves and spray pattern (Kadam et al., 2014). This test method encompasses the impingement of test sprays on the surface of a treated piece of paper with a dye-talc mixture. This is shown in Fig. 12.5 (Uddin et al., 2016).

The nature of the aerosol determines whether a water-soluble or oil-soluble dye is applied. The sprayed particles that strike on the surface of the substrate testing paper cause the dye to be converted into solution and to be absorbed onto the paper. The outcome of this test gives a highlighted record that the spray design latterly can be used for comparative assessment to eventually give a spray pattern record. Most pharmaceuticals carry on a 100% batch inspection which means entirely whole aerosols within a batch are spray tested and concluding records are used to compare different batches. For metered dose aerosols, the spray pattern of an aerosol can have a great effect on the dose of the medication that reaches the patient's lungs [Gardenhire et al., 2013; FDA (U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research) (CDER), 2018].

12.4.1.2 Leak testing

Leak test is done by checking the crimping of the aerosol dispenser valve that must be available to avoid defective containers. This is accomplished by determining the crimp's measurements and ensuring that their dimensions meet specifications. This evaluating test involves allowing the filled containers passing through a water bath and final testing of valve closure is done. Bestowing to this test, leakage is defined as the weight change of the same container before and after being stored in a vertical position at $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$ for a minimum of 3 days. According to the USP-NF, 12 pressurized containers selected at random, aerosol dispensers are selected and weighed in mg, and this is considered as the weight before the positioning (W_1). Allow the filled tested container to stand in an upright correct position at room temperature for at least 3 days, and weigh of each container should be determined again, finding the weight in mg of each container as (W_2). The time during which the containers were under test (T) is determined in hours.

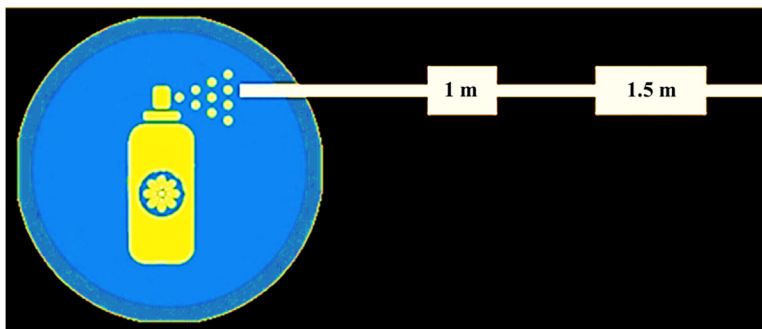


FIGURE 12.5 Aerosols spray test.

Ultimately, the leakage rate of each container is calculated in mg/year as follows (Uddin et al., 2016):

$$\text{Leakage rate} = 365 \times 24/T \times W1 - W2 \quad (12.5)$$

To meet with the standard requirements the average leakage rate of the 12 sample containers is less than 3.5% of the net filled weight per year, and it is necessary for all of the tested containers that none of them leaks more than 5% of the net filled weight per year. If one of the 12 containers leaks more than 5% per year, but none of the containers leaks more than 7% per year, then it is necessary to determine the leakage rate for additional 24 containers. Ultimately, according to requirements, not more than 2 out of the 36 containers should leak more than 7% of the net fill weight per year (Lachman and Lieberman, 2013; USP-NF, 2014).

12.4.1.3 Weight checking

This assessment procedure will check the accuracy of the filling procedure and assurance of uniformity of the final total weight of the product. Tared empty containers are added to concentrate filling lines. Subsequently, they are removed later from the patch and weighed in order to investigate their fitting with the required measures (USP-NF, 2014).

Weight checking is done by periodical addition of empty aerosol container to filling lines which is removed later after being filled with the product concentrate and weighed. The same technique is usually used for checking the weight of the propellants. As a further assessment, the finished product filled container is weighed to check the accuracy of the filling operation. The unit of this test is expressed in pounds and ounces (Pokar et al., 2012).

12.4.1.4 Valve acceptance

This test is a mean of ensuring that valves are procured from technically acceptable sources. Valves are the foundation for operating units and must perform as required because valve problems cause lost production. The previous study performed in 2003 revealed that 43% of valve failures were caused by inadequate design and deficient materials attributable to valve design, operating difficulties, excessive seat leakage, and external leakage, so valve type acceptance testing is needed, through testing of a valve to its design limits of temperature and pressure. The valve acceptance test procedure applies to two categories of metered aerosol valves having the following limits:

Deliveries 54 μL or less (limit's $\pm 15\%$), deliveries 55–200 μL (limit's $\pm 10\%$)

Deliveries of 50 individuals:

If four or more aerosol valves are outside the limits for the specified valve delivery, the valves are rejected. If three individual dispensaries are outside limits, the test is repeated using another 25 new sampled valves. The patch is accepted if not more than one valve delivery is outside the specification; otherwise, the lot is rejected and another 25 valves should be tested (Lachman and Lieberman, 2013).

12.4.1.5 Containers

Various materials are used for containers, tin-plate, aluminum, stainless steel, and certain types of glass. One of the important criteria for the selection of an aerosol container is withstood internal created pressure as high as 140–180 psi at 130°F (Remington and Allen, 2015). Both the coated and uncoated containers are evaluated for defects in the inner lining. Quite a lot of quality control aspects and assessment parameters are applied according to the type of container used. For metal, quality-control aspects include specifications for the extent of electrical current conductivity as a quantitative measure of the exposed metal. Glass containers are inspected for cracks and defects weakness. Other containers common parameters are evaluated such as their parts measurements and weight to guarantee they fulfill with the specifications obligatory (Uddin et al., 2016). The dimensions of the containers neckline and other constructive parts must be checked to determine conformity to specifications (Apiou-Sbirlea et al., 2013).

12.4.1.6 Valves, actuators, and dip tubes

Numerous physical and chemical inquiries should be applied to these aerosols' receptacle fragments, through several steps supported with documentation review. The objective of these tests is to measure the average magnitude of valve delivery and degree of uniformity between discrete valves. Twenty-five valve samples from each batch are chosen using sampling plans indexed by acceptable quality level such as military standard–105D sampling method. These receptacles are full of with standard test solutions each with defined specific gravity proposed to assesses variation in valve delivery. These solutions are alcohol USP-NF, isopropyl myristate (0.1%), dichlorodifluoromethane (49.95%), trichloromonofluoromethane at 25°C. Subsequently, a 0.02-in. actuator is mounted on each valve and then the filled containers are located in 25°C ± 1°C airspace so that they will change to that temperature. These filled receptacles are actuated to the fullest extent for at least 2 seconds and weighed. Difference between determined weights represents delivery in mg. This test is repeated at least twice for each unit from the 25 sample units. Finally, the rate of valve delivery per actuation is calculated in microliters (Apiou-Sbirlea et al., 2013; Uddin et al., 2016).

The valve rate of delivery rate per actuation = individual delivery weights (mg)/specific gravity of the test solution

12.4.1.7 Propellants

The purpose of this test is to identify and to work out the composition of the mixture existing when a blend of the propellants is applied, and see whether or not it matches the label. This test is carried out by performing IR spectrophotometry or gas chromatography. It is inspected for the vapor pressure to determine its moisture content, density, nonvolatile residue, and halogen determination as signs of purity and satisfactoriness of the propellant (Apiou-Sbirlea et al., 2013; USP-NF, 2014).

A pharmaceutical aerosol must satisfy certain standards to claim it to be a quality therapeutic perform drug, so it is mandatory to maintain their quality by variegated numbers evaluation, based on the series of tests carried out during the formulation development and finished product testing stages based on pharmacopeias standards and specifications. The presence of

propellants is the unique feature of this dosage, whose properties, such as flash point, are subject to the quality control evaluations to ensure the proper aerosol performance and safety.

12.5 Aerosols evaluation parameters

Pharmaceutical aerosols should be tested and evaluated in order to ensure that they have satisfactory performance and appropriate safety while being packaged, stored, and used. Thus certain biological, physical, and chemical parameters should be tested and evaluated on aerosols—these tests will be discussed in further details in this section.

12.5.1 Flammability and combustibility

Based on the type and amount of the ingredients, certain pharmaceutical aerosols comprise flammable propellants such as hydrocarbon propellants. Typically, in order to guarantee the safety of such products prior to patient use, storage and transportation flammability and combustibility of aerosols should be evaluated. There are numerous test protocols to quantify the degree of flammability and combustibility based international standards. Flammability and combustibility can be determined through the upcoming procedures (Remington and Allen, 2015).

12.5.1.1 Flash point

The flash point is a temperature that measures the propensity of the test concentrate sample to form a flammable blend with air under controlled defined laboratory conditions. The significances of flash point determination is useful in determining correct conditions for storage, shipping, and to state safety regulations for flammable and combustible materials. In order to determine the flash point of an aerosol, two basic apparatus types are available which are an open cup and closed cup as shown in Fig. 12.6. Closed cup tests purpose to simulate the situation of a fluid spill in a closed environmental condition. For any liquid of the test sample if it is at, or above, its flash point, a fire or explosion is a possibility once exposed to a possible ignition source. In closed cup tests to determine the flash point the investigated sample is placed inside a sealed test cup and introduced to a potential ignition source, determining the temperature at which the sample flashes. Open cup apparatus is used for the standard label (Lashkar, 2012).



Open-cup flash point tester



Closed-cup flash point tester

FIGURE 12.6 Flash point apparatus types.

Flash point test protocol is done by cooling the temperature of the aerosol product to almost 25°F, then the aerosol is captive to the testing apparatus. Gradually start to increase the temperature of the test liquid; the lowest temperature at which the vapor will ignite is recorded and this temperature is the flash point of the tested liquid. The obtained flash point is typically referring to the most flammable component's flash point (Parmar and Patel, 2017). One of the points that should be known is that an open cup apparatus will constantly give a higher flash point than a closed cup one as the open cup permits loss of internal vapors to the atmosphere above the apparatus. Consequently, closed cup assessments are usually specified owing to improved precision (Felton, 2012).

12.5.1.2 Flash extension and flashback

This type of evaluation test is also acknowledged as the flame projection test. The investigated aerosol product is sprayed through an open candle flame for about 4 seconds at a fixed distance of 6 in. (15 cm), by means of a suitable ruler the flame's extension is measured in (cm) and recording the length of the flame projection. An aerosol product is judged flammable if its flame extends 18 in. (46 cm) or more through an open flame, or if the flame flashes back to the actuator. The extension of the flame is reliant on the ingredient's nature of the aerosol's preparation (Lashkar, 2012; UNECE Part III).

12.5.2 Therapeutic activity

Testing the therapeutic activity of aerosols include similar tests to that of evaluating the therapeutic activity of nonaerosols pharmaceutical dosage forms, but in the case of aerosols, it also related to is associated with the particle size spreading. As a primary step, the dosage of the inhaled aerosol must be determined surely prior to testing the therapeutic activity of inhaled aerosol. For topical aerosols, therapeutic activity is determined by topically applying the therapeutically active ingredients directly to the test areas and evaluating the amount of therapeutically active substances absorbed (Lashkar, 2012; Remington and Allen, 2015).

12.5.3 Physicochemical characteristics

Chemical and physical characteristics of aerosols determine their atmospheric removal by gravitational settling, diffusional growth, and extent of water absorption, which leads to size growth and subsequent elimination by both wet and dry deposition. The significance of aerosol size growth and constituent chemical compositions in determining their atmospheric lifetimes is stressed. The basic chemical and physical properties of aerosols include the following.

12.5.3.1 Vapor pressure

Measuring and evaluating the total vapor pressure of an aerosol container could be achieved using special equipment such as a pressure gauge, water bath, test gauge. Determining pressure variation between different patch containers of essential importance because if this variation is extreme will indicate that air is present within the dispenser

headspace which could affect the stability of the product. To measure vapor pressure accurately a “can” puncturing device can be used (Parmar and Patel, 2017).

12.5.3.2 Density

Using different instruments such as a hydrometer or a pycnometer, the relative density of aerosol liquids can be determined. Initially a choke valve, a glass pressure tube, and a metal flanges are fitted all together permitting liquids under pressure to be introduced, then the hydrometer is positioned within the glass pressure tube, then the sample is introduced by the valve. This will cause the rising of the hydrometer halfway the tube’s length, and directly the density can be read. The density is generally expressed as g/ml (Parmar and Patel, 2017).

12.5.3.3 Moisture content

Chromatography and Karl Fischer methods are two of the many methods that have been demonstrated to be useful in evaluating the moisture content of aerosol containers. Usually, moisture content is expressed as a percentage (%). Karl Fischer methods is a precise technique for determining the moisture specifically for water content using Karl Fischer reagent, that interacts selectively and quantitatively with water, to find the moisture content. Karl Fischer reagent consists of a basic solution of sulfur dioxide, iodine, and a solvent, such as alcohol (Remington and Allen, 2015; Lachman and Lieberman, 2011). Based on results seen in stability studies, the limit for moisture content should be established [EMA (European Medicines Agency Inspections), 2006].

12.5.3.4 Identification of propellant

As discussed previously, the two main devices that have been used to evaluate propellants are infrared (IR) spectrophotometry and gas chromatography. These methods are correspondingly used as an indication of each component’s proportion (The theory and practice of industrial pharmacy) (Lachman and Lieberman, 2011).

12.5.3.5 Concentrate propellant ratio

Label fill volumes are based on “liquefied” propellant and concentrate volumes. To determine concentrate volume, propellant volume, and headspace volume (the empty volume in the upper portion of the dispenser at a specified temperature), usually density of concentrate and propellant is used (Tu et al., 2013).

12.5.4 Performance

For evaluating an aerosol, two main considerations should be measured. First is functionality that improves patient-required compliance, minimizes lost, and improves ease of use. Several tests are included for evaluating and predicting aerosol respirable good performance; these evaluating tests will be discussed in further details in this section. The second consideration is the capability of the container system to deliver an accurate amount at the required rate (FDA, 2002; Albert, 2004).

12.5.4.1 Aerosol valve discharge rate

The discharge ratio of an aerosol valve is fined by measuring the quantity of expelled material through the dispenser valve in a given time interval for an identified weight with a standard apparatus being used. After the time interval has passed the aerosol container is reweighted for the discharge ratio to be defined in grams per second. Normally discharging duration is 10 seconds, and the test is conducted under controlled temperature to achieve good reproducibility. Usually, the test is repeated three times to give three determinations (Parmar and Patel, 2017).

12.5.4.2 Leakage

Considering good packaging system functionality and minimizing waste after filling of the aerosol container, each container is to be tested for leakage by means of a suitable advanced detector that is used for halogenated compounds; this detector can automatically and instantaneously detect and reject a leaking container, which grantee optimized operation. Official compendial specifications such as USP XXI-NF (1985) are usually applied in order to gravimetrically determine if the leakage rate from a certain group of containers follow the official norm (Aulton and Taylor, 2013).

12.5.4.3 Particle size determination

There are many types of advanced methods that have been used to find the aerosol's particle size. The cascade impactor and the light scatter decay approaches have been the most widely used methods among another measurement of the mass median diameter of solid aerosol particles. Cascade impaction devices classify particles and droplets present in a sample of aerosol based on those particles' aerodynamic diameters. Though a series of glass slides and nozzles projects a high-velocity stream of particles, an impactor can classify particles into known size ranges. The powerful air jets from these device nozzles impact on flat sampling surfaces, and each phase collects finer sized particles than its predecessor. The large particles are impacted and collected first on the plane stages of lower velocity, and the small particles will pass and get collected at the stages of higher velocity. Particles having adequate inertia will impact on related particular stage collection plate, whilst finer particles will stay entrained in the air stream and move to the next stage where the process is repeated (Lashkar, 2012). Fig. 12.7 illustrates a cascade impactor.

Light scattering decay is based on the principle that as aerosols settle in turbulent condition, at this stage, the particle size is determined by changes in the Tindall beam light intensity. The unit of particle size is expressed as micrometer (Mitchell and Nagel, 2004).

12.5.4.4 Foam stability

According to the formulation, some foam have a lifetime of a limited few seconds and those known as "quick breaking" foam, while other foams can persist up to hours. Different methods can be applied in order to evaluate the stability of foam that is released from an aerosol container. These include using rotational viscometers, visual evaluation of the foam, time determination for a specified mass to penetrate the foam, also time for a given rod to fall that is placed into the foam could use (Lachman and Lieberman, 2011).

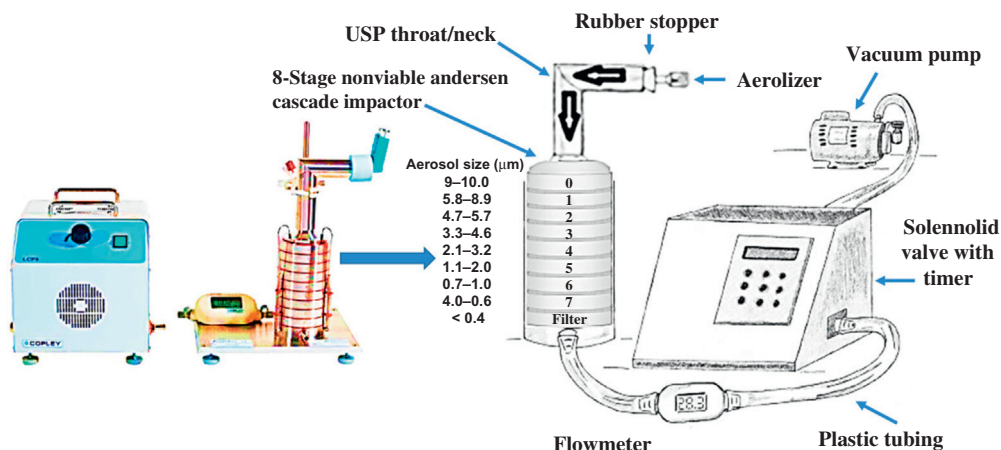


FIGURE 12.7 Andersen cascade impactor.

12.5.4.5 Net content

The net contents (net weight) statement specifies how much available product is in the container that indicates whether an aerosol container has been filled sufficiently that could be estimated using several methods. One such method is that the empty aerosol container is weighted prior to filling, then the container is reweighted after the process of filling and sealing is conducted, the difference between these weights is considered to be the net content (Parmar and Patel, 2017).

12.5.4.6 Spray pattern

This evaluation procedure is important in order to compare different valve and material spray patterns. This assessment relies on spraying the content of the container on a rotating paper impregnated with a dye solution, colored spots are produced and homogeneity of the color indicates a homogeneous spray pattern. The aim behind rotation is controlling the amount of material that comes in contact with the paper depending on the formulation's nature; the type of dye used on the piece of a revolving paper could be a dye-talc mixture and can be a water-soluble dye or an oil-soluble dye. After spraying the content the spray is allowed to collide with the piece of paper where the particles that come in contact with the dye will change into a solution that will get absorbed onto the rotating paper. These give the record for the spray patterns, which can then be used for comparison of different patterns among containers (Lachman and Lieberman, 2011).

12.5.4.7 Dosage with meter valve

Multiple points must be taken into consideration when evaluating the dose delivered through the valve. First consideration is that the dosage emitted each time depressing the valve should be reproducible which can be tested by one of two methods, either by dispensing one or two doses through the valve of the pressurized MDI down into a container with a recovery solution or solvents that will absorb the active ingredient in the formula.

By assaying these materials the amount of the active ingredient can be found. The other method used to evaluate the dosage emitted through a valve is by accurately weighting filled container. Several doses are then dispensed followed by reweighting the container each time, the average dose emitted through the valve can be found by dividing the difference in weight by the number of dispensed doses. The second important confederation is how much of the medication the patient has actually received, this is quite difficult to be evaluated in vitro, but success in this matter is achieved by using an artificially human-like respiratory system (Newman, 2005).

Several tests are included for evaluating and predicting various factors related to aerosol good performance, such as actuator tube design, moisture content, the vapor pressure of propellants, spray pattern, the efficiency of valve crimping and measurement of particle size aerosols. A variety of techniques are employed that are universal to all branches of aerosol performance testing.

12.6 Universal tests and standards for pharmaceutical aerosols

12.6.1 Identification

This qualitative confirmation assessment is also known as the identity test it is applied to verify the type of the pharmaceutically active ingredient(s) claimed to be found in the pharmaceutical aerosol. On the other hand, this test can be also used to differentiate between the components that have similar or closely related structures that might be existing in the formula. Identification tests should be specific for the drug substance, e.g., IR spectroscopy, high-performance liquid chromatography/ultraviolet spectrophotometer (HPLC/UV), HPLC/mass spectrometry (HPLC/MS), or gas chromatography/mass spectrometry (GC/MS) is generally acceptable (Jr Allen, 2013; Uddin et al., 2015, 2016).

12.6.2 Assay

This quantitative active ingredient identity test is also known as the content test. It is used in the determination of the strength or content of the pharmaceutically active ingredient(s) in the aerosol. Using ultraviolet spectrophotometer, absorbance is determined for 1 mL of spray solution taken after adequate dilution. Concentration is determined from the standard plot, and the drug content is calculated as a percentage of the theoretical value (Parmar and Patel, 2017).

$$\text{Drug content} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$$

The amount of drug substance should be determined per weight unit or per volume unit for multidose products, where the usual assay limits for medicinal products apply [EMA (European Medicines Agency Inspections), 2006].

12.6.3 Relevant impurities

Characterization of potential impurities and degradation products that may result from the degradation of the active ingredient in manufacturing or storage or as a result of the new drug synthesis is an important requirement for aerosols safety evaluation (Jr Allen, 2013; Uddin et al., 2015, 2016).

Several methods are applicable in this issue, such as HPLC and gas chromatography, and one of the innovative detectors is charged aerosol detection technology that delivers a good performance to measure analyte charge that is in direct proportion to the amount of the analyte present (Zhang et al., 2013).

12.6.4 Description

It is the specification appearances, it describes pharmaceutical aerosol drug product qualitatively (Uddin et al., 2015). For aerosols a specified description for both the formulation including active ingredient and excipients and along with the complete delivery device characters (e.g., for the description on the specification might read: a red cap or a blue body, linear actuator) should be specified. For nebulization products the instantaneous packaging should be defined (e.g., translucent or opaque low-density polyethylene nebula) [EMA (European Medicines Agency Inspections), 2006].

12.7 Evaluation of packaging components of aerosols

Successful preparing and packaging of pharmaceutical aerosol required certain knowledge, skills, and equipment as with other pharmaceutical products; these processes must be carried out under strict supervision and observance to rigid quality-control requirements. Food and Drug Administration (FDA) guidance document requires the assessment of the main four attributes to establish suitability: protection, drug-delivery performance, safety, and compatibility. All four attributes must be evaluated and proved to have desired concern to the aerosol product performance or the drug product. After signifying container closure system appropriateness, it is essential to define quality control measures that will be used to ensure physical and chemical composition consistency in the packaging components. The quality of components and eventually the container closure system can be monitored using a few simple tests.

Physical considerations such as evaluating seal integrity through determining water vapor transmission, monitoring melting point, and glass transitions of plastics using differential scanning calorimetry thermal analysis, and IR scanning to verify identity should be a part of an ongoing monitoring quality-control program. Dimensional criteria should be defined and monitored such as volume, shape, the thickness of barrier, and design tolerances. Evaluation of chemical composition should also be considered via simple and informative USP-NF physicochemical tests using water, drug product vehicle, and alcohol extractions of plastic components. Satisfying these standards will minimize risk and grant effective product release in an appropriate desired rate (FDA, 2002; Albert, 2004).

Specific modifications for the quality-control system must be carried since part of the manufacturing operations (addition of propellant to concentrate) is carried out during the packaging operation. Specialized equipment capable of handling and packing formulas under high pressure or at relatively low temperatures (about 40°F) must be available in addition to the equipment used for the compounding of liquids, suspensions, emulsions, creams, and ointments. This equipment is usually limited to aerosol or pressurized packaging and, in most instances, cannot be used for other pharmaceutical operations (Lachman and Lieberman, 2011; Aulton and Taylor, 2013).

12.7.1 Protection

A light-resistant container that proposed to offer protection from light was evaluated by performing the USP-NF (661) Light transmission test. This evaluation procedure necessitates the use of a precise and sensitive spectrophotometer, altered for determining the quantity of light transmitted by the container material, especially plastic containers.

Also, by performing and carrying out the USP-NF (661) Water Vapor Permeation test, the capability of a container closure system to protect against transmission of moisture could be evaluated. The USP-NF sets limits to the amount of moisture that can migrate through the packaging systems based upon size and composition of the packaging materials especially for plastic containers (USP-NF, 2015).

12.7.2 Compatibility

A container component compatible with a dosage form must be ascertained to ensure the quality of the drug or the component. Evaluation of nature and/or amount of any chemical permeate from the packaging material to the drug product is realized by a leachability study designed for that purpose. Several sensitive analytical procedures and methods are applicable for that determination, such as liquid chromatography/mass spectrometry, GC/MS, IR scan to evaluate nonvolatile organics and quantitate inorganic elements and provide proof of identity. The leachability study should assess materials that migrate into the vehicle for the length of product shelf life claim at regular time intervals, such as at 1, 3, or 6 months or at 1 or 2 years until the extent of the shelf life claim has been met.

Other changes which may cause degradation of drug product such as pH shifts, precipitates, and discoloration should be evaluated along with assisting the physical stability of the container by evaluating changes in characteristics such as brittleness, using thermal detectors analysis method and hardness testing (Norwood et al., 2008).

12.7.3 Safety

Defining the safety of a packaging component is not a simple process, and a standardized technique has not been recognized. However, all packaging components should be made of constituents that will not leach toxic or disagreeable quantities of constituents during patient drug treatment. The chief consideration is an extraction and isolation study

that is accomplished through incubation of a container sample in different solvents at definite and well-controlled temperatures and times intervals.

The containers used to pack medications are classified with a high degree of concern, such as inhalation aerosols, knowing of degradation products that may be released into the drug product is significant; so prior to performing any of the evaluating chemical tests discussed here, it is important to have accurate descriptive information on the synthesis procedures that have been applied and the solvents used in that procedures, besides knowing the different additives that have been added during product manufacturing.

The USP-NF includes physicochemical tests for evaluating containers material which is applicable, sensitive, quick, and cheap. They help in setting up container material safety. These official tests stated in USP-NF based on water extracts, alcohol, and in nonpolar solvents under precise temperature and time limits. Generally, these tests are mainly valued in determining the materials as high or low in extractable chemicals, besides classifying material extracts in comprehensive terms, such as total extractable nonvolatile deposit, heavy-metals content, residue on ignition, turbidity and buffering capacity (Albert, 2004; USP-NF, 2015).

The estimation of safety will also involve analytical methods and instrumentation to recognize the quality and quantity of the extracted chemicals and to collect sufficient information to allow the identification of potential toxic hazards resulting from the chemical components of the packaging materials. HPLC and gas/liquid (HPLC and GLC, respectively) are influential analytical apparatuses that can identify, separate, and estimate the quantity of volatile and nonvolatile chemicals. The mass spectrum is an important analytical method as it can provide a fragmentation pattern for each molecule, which makes it an excellent and adequate tool for recognizing degradation products or unknown impurities.

Biological reactivity is another part of the containers safety testing and is designed to test the toxicological properties of extractable chemicals. The USP-NF biological reactivity tests can measure and give limits for the safe level of exposure and provide a good evaluation for the toxicological properties, by means of the label specified route of administration (Albert, 2004).

Considering and evaluating the main attributes of preparing and packaging of pharmaceutical aerosol along with evaluating the results of stability tests have large concern for successful aerosol product performance and its shelf life total quality.

12.8 Stability testing of aerosol products: International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use guideline

The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline is a worldwide nonprofit organization underneath Swiss law, mission to achieve better universal harmonization to guarantee effective, high-quality, and safe therapeutic drugs. This organization gathers the pharmaceutical manufacturers and regulatory authorities to investigate and discuss scientific and technical aspects of drugs registration.

One of the important aspects of medicines is stability testing. These tests inspect the environmental influence on drug constituents or finished products with a consideration of time. Ultimately, evaluating the results of stability tests and assess its relation to total quality will be translated as appropriate recommended storage conditions and shelf life for the product. In this guideline, stability test conditions are chosen reliant on an understanding of the impact of climatic conditions in the regions of European countries, the United States, and Japan. In order to condense the amount of stability testing required, the world can be divided into four climatic zones for the purpose of worldwide stability testing, as follows: Zone I: temperate; Zone II: subtropical, with likely high humidity; Zone III: hot/dry; and Zone IV: hot/humid ([ICH Harmonised Tripartite Guideline, 2003](#)).

There are two types of stability evaluation protocols: Electrochemical testing and long-term static testing. The electrochemical testing protocol provides an effective screening tool but is limited to concerning the amount of stability data obtained. Long-term static testing is generally performed at a temperature of 120°F, over a period of 3 months to a year. This type of stability tests provides the most important stability data such as weight loss, physical and chemical changes, concentrate/propellant saturation fluctuations (vapor pressure measurement), maintaining original spray characteristic, and corrosion and concentrate stability ([Parmar and Patel, 2017](#)).

There are four categories for the ICH topic coded assigned for efficacy, safety, quality, and multidisciplinary guidelines. Each guideline focused on a certain field of tests and legislation. Efficacy guidelines specify studies to evaluate the relationship between doses, systematically levels along with therapeutic response for the development of a new drug. Safety guidelines related to in vitro and in vivo preclinical studies as carcinogenicity and genotoxicity tests.

Stability guidelines for finished pharmaceutical products as aerosols are described in several arrangements and titles to ensure standard practice for storage of aerosols. Stability evaluation of new drug substances and finished products define recommendations on stability testing protocols for climatic Zone I and II including temperature, relative humidity, and trial duration considering the requirements for stability testing in climatic zones III and IV to minimize the different storage conditions for submission of a global registration ([ICH Harmonised Tripartite Guideline, 2003](#)).

Quality guidelines are accountable for conducting stability studies, defining relevant impurities testing, and other different approaches related to ensure pharmaceutical quality based on management of risks toward good manufacturing practice. Also, guidelines provide recommendations to applicants who are planning product quality studies to measure pharmacokinetics (PKs), BA, and/or establish bioequivalence (BE).

12.9 Pharmacokinetic assessment and biological fate of aerosol delivered drugs

Estimating the PKs of inhaled drugs is of essential importance to define drug concentration-time profiles in respiratory lung tissue at the site of intended action to predict and describe the efficacy in humans for inhaled drugs. Also, it provides information that is valuable for determining the BA and estimating the lung disposition kinetic parameters of inhaled therapies which in return will help in enhancing the lung delivery of these drugs.

Simultaneously, PK studies can be used as a means of explaining the systemic adverse effects that occur systemically, while the aerosols are inhaled through the mouth (Borghardt et al., 2018).

Physiologically based PK compartmental or noncompartmental methods are used to find PK parameters after inhalation of a drug. On the other hand, by incorporating the physiologically based PK a mathematical model that relating the disposition and response of a given inhaled drug can be obtained (Jessy and Shaikh, 2016).

The widespread availability of sensitive assay methods, such as high-performance liquid chromatography, allows the estimation of plasma and urinary drug levels required for PK evaluation that allows precise and reproducible quantification of drug delivery by determining plasma levels to reflect the effectiveness of lung absorption (Borghardt et al., 2018).

12.10 Bioavailability and bioequivalence studies of aerosol: Food and Drug Administration perspective

In order to guarantee a predictive clinical outcome (i.e., efficacy and safety) of the medicated therapies dosage forms in clinical trials of drugs certain data and information should be followed such as the BA and BE studies. BA studies are related to estimating the rate and extent to which the API is absorbed systemically from a dosage form of a drug product and becomes available to exert its intended therapeutic effect at the targeted site of action. For certain drug dosage forms that are not proposed to be absorbed systemically, BA may be measured based on selected PK measurements to reflect the rate and extent to which API becomes available to employ its desired therapeutic effect at the intended site of action. For lung-delivered therapies, PK parameters assessment have a conventional title role in the quantification of drug delivery to the lungs and provides significant data about the respiratory-medicated aerosols BA, which is complementary to other supplementary techniques such as radiolabeled deposition (Borghardt et al., 2018). BE product-quality studies compare the characteristics of different pharmaceutical alternatives and is defined as “the absence of a significant variance in the identity, potency, quality, rate and extent to which API reaches the site of drug action when administered at the equivalent molar dose under similar controlled conditions compared to pharmaceutical alternatives in a properly designed study.” BE studies are important in developing and approval of generic and new drugs which compared as against clinical trial material to official reference listed drug. To establish BA and BE, *in vitro* and *in vivo* studies can be used, using *in vivo* [PK, pharmacodynamic (PD), or clinical], but in some cases, *in vitro* studies can be used alone (Chen et al., 2001).

BA and BE assessments for some types of aerosols such as locally acting nasal aerosols and sprays are complicated because the drug delivery to the target sites of action does not occur principally after systemic absorption. Although the drug is administered nasally for local action, it has the potential to yield systemic activity, even though plasma levels do not, in general, reflect the amount of drug reaching nasal sites of action. For these reasons, BA and BE studies generally would consider both local delivery and systemic exposure or systemic absorption (FDA, 2003).

The complication of areoles features as a dosage forms and renders them difficult to mimic and climb challengeable questions regarding similarity and type of properties that is essential to be controlled in order to guarantee both the efficacy and the quality of the product. Different aspects have been shown to have predictive or correlative relevance to considerations of BE as radiolabeled imaging of deposited aerosols, deposition imaging expanded to 3D, in vitro performance of the products, the influence of breathing patterns on deposition, and predictive modeling of deposition (Apiou-Sbirlea et al., 2013).

The concept of in vitro BE implies biological consideration of similarity in performance of two or more products using concerns exerting sufficient control on key properties, known to correlate with therapeutic effect, to achieve BE such as breathing patterns and lung deposition. Two inhaler products will show pulmonary BE if the similar dose is delivered and deposited in the lung where the drug enters targeted pulmonary cells with the same rate. The products should also deliver the drug to the same intended central or peripheral parts of the lung (Azarmi et al., 2008).

The US Department of Human and Health Services FDA has no formal guidance on all inhaled products. However, the FDA did publish an outline requirement for clinical documentation of orally inhaled drug products. A foundational element of this approach is qualitative and quantitative formulation and device sameness. This relates to physico-chemical composition and properties of the formulation and components and operation of the device. Similarity at this level underpins the in vitro and in vivo performance (Lee et al., 2009).

12.11 Futuristic aerosol products: market trend

Various advancements in the pharmaceutical aerosol drug delivery systems have been witnessed, that is, in the technology, devices, formulation, and application of pulmonary drug delivery systems, the inhalation pulmonary approach of therapeutic drug delivery is increasingly attracting attention to be explored for medicines that target systemic diseases—it is no longer the preserve of respiratory drugs (Simon Moore, 2016). The size of the market for respiratory inhaler devices continues to expand, with estimates suggesting it will reach \$43 billion by the end 2025—a compound annual growth of 4.3 (Simon Moore, 2016).

Nanotechnology needs special mention when discussing the future of unique developed pharmaceutical products. Nanotechnology and development of innovative inhaled particles engineering techniques are enabling full potential control for the physical particle chrematistics as size, shape, surface-related properties, agglomeration state, along with chemistry of those inhaled particles, enhancing formulations of the unique dosage form and improving drug delivery into the pulmonary system. The market for nanotechnology usage in medicine and drug delivery systems have emerged with innovative and promising applications in prevention, diagnosis, and treatment. It is predicted that by 2021, the total global amount spend on Nanotech Enabled Drug Delivery Therapeutics Market will be around \$136 billion, which would represent 15% of nanomedicines globally (Moghimi et al., 2005).

12.12 Conclusion

The advancements in the pharmaceutical and healthcare industry contributed to drug development in order to meet the demand for effective ways to fight different diseases, have led to the development of countless effective therapeutic drug delivery methods—pharmaceutical inhalation aerosols being one of them. Successful preparing and packaging of pharmaceutical aerosol required certain knowledge, skills, and equipment as with other pharmaceutical products, these processes must be carried out under strict supervision and observance to rigid quality-control requirements. Quality of pharmaceutical aerosols is the key issue within the pharmaceutical industry of pressurized dosage form, IPQC and FPQC must be maintained under rigorous quality control tests to ensure appropriate performance of the package, active ingredients and guarantee safety during storage and use as per specifications of the respective pharmacopeias, and the regulatory requirements of the particular countries. Different studies are clearly revealed through various pharmacopeias suggesting different types of IPQC and FPQC tests for pharmaceutical aerosols with different specifications and standards, the main function of all pharmacopeias is to assure the maximum quality of pharmaceuticals for human health. Establishing harmonized standards, methodology, and regulations of operating and testing procedure of aerosols products are recommended in addition to these pharmacopeias and regulatory bodies.

Considering and evaluating the main four attributes of preparing and packaging of pharmaceutical aerosol (protection, drug delivery performance, safety, and compatibility), along with evaluating the results of stability tests, have large concern for successful aerosol product performance with high total quality and used to estimate appropriate recommended storage conditions and shelf life for the product.

To find PK parameters after inhalation of a drug, physiologically based PK compartmental or noncompartmental methods are used. In order to guarantee a predictive clinical outcome (i.e., efficacy and safety) of the medicated therapies dosage forms in clinical trials of drugs, certain data and information should be followed such as the BA and BE studies using *in vivo* (PK, PD, or clinical), but in some cases, *in vitro* studies can be used alone.

The complication of areoles features makes the assessments of BA and BE for some types of aerosols such as locally acting nasal aerosols and sprays difficult. Different aspects have been shown to have predictive or correlative relevance to considerations of BE, such as radiolabeled imaging of deposited aerosols, deposition imaging expanded to 3D, *in vitro* performance of the products, the influence of breathing patterns on deposition, and predictive modeling of deposition.

Abbreviations

BA	bioavailability
BE	bioequivalence
COPD	chronic obstructive pulmonary disease
Cc	correction factor
DF	deposition fraction
EPAG	European pharmaceutical aerosol group
FPQC	finished product quality control

FDA	Food and Drug Administration
GC/MS	gas chromatography/mass spectrometry
HPLC/UV	high performance liquid chromatography/ultraviolet spectrophotometer
HPLC/MS	high performance liquid chromatography/mass spectrometry
MMAD	mass median aerodynamic diameter
MDI	metered-dose inhaler
PKs	pharmacokinetics
IPQC	in-process quality control
IR	infrared
Stk	Stokes
V_{ts}	terminal settling velocity
API	active pharmaceutical ingredients
ICH	The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
USP-NF	United States Pharmacopoeia National Formulary

Acknowledgment

We would like to thank Dr. Pran Kishore Deb, Assistant Professor at Philadelphia University for his useful and constructive recommendations on this manuscript.

References

- Akira, T., Henry, F.S., Butler, J.P., 2013. Particle transport and deposition: basic physics of particle kinetics. *Compr. Physiol.* 3 (4), 1437–1471.
- Apiou-Sbirlea, G., Newman, S., Fleming, J., Siekmeier, R., Ehrmann, S., Scheuch, G., et al., 2013. Bioequivalence of inhaled drugs: fundamentals, challenges and perspectives. *Ther. Deliv.* 4 (3), 343–367.
- Ashurst, I., Malton, A., Prime, D., Sumby, B., 2000. Latest advances in the development of dry powder inhalers. *Pharm. Sci. Technol. Today* 3 (7), 246–256.
- Aulton, M., Taylor, K., 2013. *The Design and Manufacture of Medicines*, fourth ed. Churchill Livingstone, ISBN: 9780702053931, eBook.
- Azarmi, S., Lobenberg, R., Roa, W.H., Tai, S., Finlay, W.H., 2008. Formulation and in vivo evaluation of effervescent inhalable carrier particles for pulmonary delivery of nanoparticles. *Drug Dev. Ind. Pharm.* 34 (9), 943–947.
- Borghardt, J.M., Kloft, C., Sharma, A., 2018. Inhaled therapy in respiratory disease: the complex interplay of pulmonary kinetic processes. *Can. Respir. J.* 2018, . Available from: <https://doi.org/10.1155/2018/2732017> Article ID 2732017, 11 pages.
- British Pharmacopoeia Commission, 2014. *British Pharmacopoeia*, eighth ed. Stationery Office, Great Britain.
- Carvalho, T., Peters, J., Williams, R., 2011. Influence of Particle Size on Regional Lung Deposition-What Evidence is There? *Int. J. Pharm.* v.406 (no.1-2), 1–10 (ISSN: 0378-5173).
- Chantal, D., Kim Prisk, G., 2004. Aerosol deposition in the human respiratory tract breathing air and 80:20 Heliox. *J. Aerosol Med.* 17 (3), 278–285. 2004.
- Chen, M.-L., Shah, V., Patnaik, R., Adams, W., Hussain, A., Conner, D., et al., 2001. Bioavailability and bioequivalence: an FDA regulatory overview. *Pharm. Res.* 18 (12), 1645–1650.
- Cheng, Y.S., 2014. Mechanisms of pharmaceutical aerosol deposition in the respiratory tract. *AAPS Pharm. SciTech* 5 (3), 630–640.
- Copley Scientific, 2015. *Quality Solutions for Inhaler Testing*. Available from <<http://www.mspscorp.com/images/products/copley-inhaler-testingcatalog2015.pdf>>.
- D.E. Albert, 2004. *Evaluating Pharmaceutical Container Closure Systems*. NAMSA Medical Research Organization. Available from <<https://www.namsa.com/wp-content/uploads/2015/10/Evaluating-Pharmaceutical-Container-Closure-Systems.pdf>>.

- Dwyer-Lindgren, L., Bertozzi-Villa, A., Stubbs, R.W., Morozoff, C., Shirude, S., Naghavi, M., et al., 2017. Trends and patterns of differences in chronic respiratory disease mortality among US counties, 1980-2014. *JAMA* 318 (12), 1136–1149.
- EMA (European Medicines Agency Inspections), 2006. Guideline on The Pharmaceutical Quality of Inhalation and Nasal Products. Available from <<http://www.emea.eu.int>> .
- EudraLex, 2014. The Rules Governing Medicinal Products in the European Union. Available from <http://ec.europa.eu/health/files/eudralex/vol-4/201403_gmp_chapter_6.pdf>.
- European Respiratory Society Publications Office, 2006. Respiratory Diseases in the World Realities of Today – Opportunities for Tomorrow. Print ISBN: 978-1-84984-056-9; e-ISBN: 978-1-84984-057-6.
- FDA, 2002. Guidance for Industry, Container Closure Systems for Packaging Human Drugs and Biologics, (Internet) <<http://www.fda.gov/cber/guidelines.htm>>.
- FDA, 2003. Guidance for Industry, Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action. Available at <<http://www.fda.gov/cder/guidance/index.htm>>.
- FDA (U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research) (CDER), 2018. Metered Dose Inhaler and Dry Powder Inhaler (DPI) Products – Quality Considerations Guidance for Industry, (Internet) Available from <<https://www.fda.gov>> .
- Felton, A.L., 2012. Aerosols. *Remington Essential of Pharmaceutics*. Pharmaceutical Press, pp. 633–650.
- Fernández Tena, A., Casan Clarà, P., 2012. Deposition of inhaled particles in the lungs. *Arch. Bronconeumol.* 48 (7), 240–246.
- Gardenhire, D.S., Ari, A., Hess, D., Myers, T.R., et al., 2013. *A Guide to Aerosol Delivery Devices for Respiratory Therapists*, third ed. American Association for Respiratory Care.
- Goetz, D.M., Singh, S., 2016. Respiratory system disease. *Pediatr. Clin.* 63 (4), 637–659.
- ICH Harmonised Tripartite Guideline, 2003. Stability Testing of New Drug Substances and Products Q1A(R2), (Internet) Available from <<http://www.emea.eu.int>> .
- ICRP, 2007. Human respiratory tract model for radiological protection. In: ICRP Publication 66. Ann Indian Pharmacopoeia Commission. Indian Pharmacopoeia. Indian Pharmacopoeia Commission, Ghaziabad.
- Indian Pharmacopoeia Commission. Indian Pharmacopoeia. Ghaziabad: Indian Pharmacopoeia Commission; 2007.
- Jessy, S., Shaikh, M., 2016. Current development in the evaluation methods of pulmonary drug delivery system. *Indian J. Pharm. Sci.* 78 (3), 294–306.
- Javadzadeh, Y., Yaqoubi, S., 2017. Therapeutic nanostructures for pulmonary drug delivery.. *Nanostructures for Drug Delivery Micro and Nano Technologies*. pp. 619–638.
- Chadwick J., 2007. Aerosol Technical Solutions, Aerosol Anatomy-The Aerosol Laboratory Part2. Accessed <<http://www.spraynow.com/PDFs/SPRAYFeb07.pdf>>.
- Allen, Jr. L.V., 2013. first ed. *Remington: An Introduction to Pharmacy*, 146. Pharmaceutical Press, UK.
- Kadam, P., Kanekar, H., Khale, A., 2014. Pulmonary drug delivery system: current practices and applications. *World J. Pharm. Res.* 3 (6), 204–229.
- Koullapis, P.G., Kassinos, S.C., Bivolarova, M.P., Melikov, A.K., 2015. Particle deposition in a realistic geometry of the human conducting airways: effects of inlet velocity profile, inhalation flowrate and electrostatic charge. *J. Biomech.* Available from: <https://doi.org/10.1016/j.jbiomech.2015.11.029i>.
- Labiris, N.R., Dolovich, M.B., 2003. Pulmonary drug delivery Part I: Physiological factors affecting therapeutic effectiveness of aerosolized medications. *Br. J. Clin. Pharmacol.* 56 (6), 588–599.
- Lachman L., Lieberman, A.H., 2011. Pharmaceutical aerosol. In: *The Theory & Practice of Industrial Pharmacy*, third ed. CBS Publishers & Distributors Pvt. Ltd., pp. 589–618.
- Lachman, L., Lieberman, A.H., 2013. Pharmaceutical aerosol, *The Theory & Practice of Industrial Pharmacy*, 4th edition CBS Publishers & Distributors Pvt. Ltd.
- Lashkar, S., 2012. An overview on: pharmaceutical aerosols. *IRJP* 3 (9), 68–75.
- Laut, A.L., Nuñez, O.M., Maratas, L.L., 2015. Clinical and etiological profile of the pediatric population with upper respiratory tract infection in Ubaldo Laya evacuation center, Iligan city, Philippines. *Int. J. Biosci.* 6 (5), 186–201.
- Lee, S.L., Adams, W.P., Li, B.V., Conner, D.P., Chowdhury, B.A., Yu, L.X., 2009. In vitro considerations to support bioequivalence of locally acting drugs in dry powder inhalers for lung diseases. *AAPS J.* 11 (3), 414–423.
- Löndahl, J., Möller, W., Pagels, J.H., Kreyling, W.G., Swietlicki, E., Schmid, O., 2014. Measurement techniques for respiratory tract deposition of airborne nanoparticles: a critical review. *J. Aerosol. Med. Pulm. Drug Deliv.* 27 (4), 229–254.

- K.A. McGann, S.S. Long, 2018. Respiratory Tract Symptom Complexes.
- Mhlanga, S.C., Duga, A.L., Makunde, A.T., Zwane, S., Menon, S., 2018. Susceptibility pattern of empirical therapy for upper respiratory infections at Pigg's Peak Government Hospital. *Eur. J. Biomed. Pharm. Sci.* 5 (1), 106–111.
- Mitchell, J.P., Nagel, M.W., KONA, 2004. Particle size analysis of aerosols from medicinal inhalers. *Powder Part.* 22, 32–65.
- Moghimi, S.M., Hunter, A.C., Murray, J.C., 2005. Nanomedicine: current status and future prospects. *FASEB J.* 19 (3), 311–330.
- Newman, S.P., 2005. Principles of metered-dose inhaler design, obstructive pulmonary disease, spacer, aerosol, drug delivery. *Respir. Care* 50 (9), 1177–1190. 2005.
- Nicolaou, L., Zaki, T.A., 2016. Characterization of aerosol Stokes number in canonical geometry and idealized extrathoracic airways. *J. Aerosol Sci.* Available from: <https://doi.org/10.1016/j.jaerosci.2016.09.003>.
- Norwood, D.L., Paskiet, D., Ruberto, M., Feinberg, T., Schroeder, A., Poochikian, G., et al., 2008. Best practices for extractables and leachables in orally inhaled and nasal drug products: an overview of the PQRI recommendations. *Pharm. Res.* 25 (4), 727–739.
- N.K. Ostrom, G. Raphael, J. Tillinghast, et al., 2018. Randomized Trial to Assess the Efficacy and Safety of Beclomethasone Dipropionate Breath-Actuated Inhaler in Patients With Asthma. *Allergy & Asthma. Proceedings*, Ocean Side Publications, Inc, Volume 39, Number 2, pp. 117–126(10) Available from: <https://doi.org/10.2500/aap.2018.39.4115>.
- Paranjpe, M., Müller-Goymann, C.C., 2014. Nanoparticle-mediated pulmonary drug delivery: a review. *Int. J. Mol. Sci.* 15 (4), 5852–5873.
- Parmar, K., Patel, M.B., 2017. A review on sublingual spray: novel drug delivery system. *Int. J. Pharm. Sci. Res.* 8 (11), 4533–4539.
- Peter Floyd, R.P.A. Byron Georgalas, R.P.A. Scott Marshall, R.P.A. Chloe Elding, R.P.A., 2014. Impact Assessment Study on the Adaptation to Technical Progress of the Aerosol Dispensers Directive, DG Enterprise and Industry Final Report.
- Pokar, H.G., Patel, K.R., Patel, N.M., 2012. Review on: pharmaceutical aerosol. *Inter Pharm. Sci.* 2, 63–64. Available online <<http://www.ipharmsciencia.com>>.
- Remington, J.P., Allen, L.V., 2015. *The Science & Practice of Pharmacy*, 22nd Ed., Vol. 1. Lippincott Williams & Wilkins, Philadelphia, PA, pp. 1000–1017.
- Sahab Uddin, Md., Hossain, M., Mamun, A., Zaman, S., Asaduzzaman, Md., Rashid, M., 2016. Pharmacopoeial standards and specifications for pharmaceutical aerosols: In-Process and Finished Products Quality Control Tests. *Advances in Research* 6, 1–12. 2016, Article no.AIR.22442, ISSN: 2348-0394, NLM ID: 101666096.
- Sangeetha, K.T., Sreeja, S., Thomas, R., 2018. A prospective study estimating the mupirocin resistance in health care providers with MRSA nasal carriage in a tertiary care hospital in rural South India. *Int. J. Curr. Microbiol. Appl. Sci.* 7 (01), 659–663. ISSN: 2319-7706.
- Sankhal, S., Singh, H.S.S.K., Lalwani, G., 2013. Factors that affect the lung deposition. *Int. J. Mod. Phys.: Conf. Ser.* 22 (2013), 729–732.
- Moore, S., 2016. The future of inhaled medications and inhalation technology: formulations, devices and strategy through non-clinical development. *Development in Life Sciences*. Available online <<http://landing.engage.com/inhalation-white-paper>>.
- Teja, C.H., Balamuralidhara, V., Vinay, S., Sudeendra, B.R., Kumar, T.M.P., 2011. Comparative study of in-process and finished products quality control tests of Indian pharmacopoeia, British pharmacopoeia and United States pharmacopoeia for capsules and liquid orals. *Int. Res. J. Pharm.* 2 (9), 65–66.
- Tu J., Inthavong K., Ahmadi G., 2013. The human respiratory system. In: *Computational Fluid and Particle Dynamics in the Human Respiratory System, Biological and Medical Physics*, Biomedical Engineering, DOI 10.1007/978-94-007-4488-2_2, © Springer Science + Business Media Dordrecht, pp. 19–44.
- Uddin, M.S., Mamun, A.A., Tasnu, T., Asaduzzaman, M., 2015. In-process and finished products quality control tests for pharmaceutical tablets according to pharmacopoeias. *J. Chem. Pharm. Res.* 7 (7), 180–181.
- Uddin, M.S., Mamun, A.A., Rashid, M., Asaduzzaman, M., 2016. In-process and finished products quality control tests for pharmaceutical capsules according to Pharmacopoeias. *Br. J. Pharm. Res.* 9, 1–9.
- UNECE Part III Classification Procedures, Test Methods and Criteria Relating to flammable aerosols of Class 2, Class 3, Class 4, Division 5.1, Class 8, and Class 9, Section 31.6. Available from <https://www.unece.org/fileadmin/DAM/trans/danger/publi/manual/Rev5/English/03en_part3.pdf>.

- US Pharmacopeia, 2015. Aerosols, Nasal Spray, Metered-Dose Inhalers and Dry Power Inhalers. Available: <http://www.pharmacopeia.cn/v29240/usp29nf24s0_c601_viewall>.
- USP-NF (United States Pharmacopeia - National Formulary) 2015.
- USP-NF (United States Pharmacopeia-National Formulary) 2014. Available online <<https://www.uspnf.com>>.
- Usmani, O.S., Biddiscombe, M.F., Barnes, P.J., 2005. Regional lung deposition and bronchodilator response as a function of B2-agonist particle size. *Am. J. Respir. Crit. Care Med.* 172, 1497–1504.
- WebMD Health Corp. Annual report, 2016, <http://www.edgar-online.com> © Copyright 2017, EDGAR Online, Inc.
- WHO (World Health Organization) (2012a). Chronic Respiratory Disease, Asthma. <www.who.int/respiratory/asthma/en/>.
- Yakubu, S.I., Assi, K., Chrystyn, H., 2013. Aerodynamic dose emission characteristics of dry powder inhalers using an Andersen Cascade Impactor with a mixing inlet: The influence of flow and volume, influence of flow and volume. *Int. J. Pharm.* 455, 1–2.
- Zhang, K., Li, Y., Tsang, M., Chetwyn, N.P., 2013. Analysis of pharmaceutical impurities using multi-heartcutting 2D LC coupled with UV-charged aerosol MS detection. *J. Sep. Sci.* 36 (18), 2986–2992.
- Zhu, B., Xu, N., Traini, D., Lewis, D., Young, P.M., 2015. The formation of aerosol particles from solution based pressurized metered dose inhalers and implications of incomplete droplet drying: theoretical and experimental comparison. *Aerosol Sci. Technol.*, pp. 0278–6826 (Online) Journal homepage: <<http://www.tandfonline.com/loi/uast20>>.

Further reading

- Anonymous, 2015. In-Process Revision. Available: <http://www.usp.org/sites/default/files/usp_pdf/EN/USPNF/pharmaceuticalDosageForms.pdf> (accessed 28.09.15.).
- Lipworth, B.J., 1996. Pharmacokinetics of inhaled drugs. *Br. J. Clin. Pharmacol.* 42 (6), 697–705.
- M. Copley, 2007. Cascade Impactors Enter a New Decade. *Manufacturing Chemist*. <www.manufacturing-chemist.info>.
- Principles and Practice of Pediatric Infectious Diseases, fifth ed. Available from: <https://doi.org/10.1016/C2013-0-19020-4>.
- USP XXVII, chap. 661, Containers. <https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/revisions/661_rb_notice.pdf>.
- WHO, 2019. Chronic Respiratory Diseases, Burden of COPD. <www.who.int/respiratory/copd/burden/en/index.html>.
- WHO, 2017. Chronic Respiratory Diseases. <www.who.int/gard/publications/chronic_respiratory_diseases.pdf>.
- WHO (2012b). Global Tuberculosis Report 2012. <www.who.int/tb/publications/global_report/en/>.
- Welankiwar, A., Meshram, G., Tope, S., Wable, H., Barabde, A., Saudagar, S., 2013. Different aspects and strategies on quality control and quality assurance of aerosol dosage form in the pharmaceutical industry. *Int. J. Pharm. Biol. Sci. Arch.* 1 (1), 82–862013. Available from: www.ijpba.in.
- Yakubu, S.I., Assi, K.H., Chrystyn, H., 2013. Aerodynamic dose emission characteristics of dry powder inhalers using an Andersen Cascade Impactor with a mixing inlet: The influence of flow and volume, influence of flow and volume. *Int. J. Pharm.* 455 (1–2), 213–218.