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Scope and limitations on aerosol drug delivery for the treatment of infectious respiratory diseases

Hana Douafer, PhD¹, Véronique Andrieu, PhD² and Jean Michel Brunel, PhD^{1*}

Corresponding Author:

Jean-Michel Brunel, PhD

¹ Aix Marseille Univ, INSERM, SSA, MCT, 13385 Marseille, France. E-mail : bruneljm@yahoo.fr.
Phone : (+33) 689271645

²Aix Marseille Univ, IRD, APHM, MEPHI, IHU Méditerranée Infection, Faculté de Médecine et de Pharmacie, 13385 Marseille, France.

Abstract:

The rise of antimicrobial resistance has created an urgent need for the development of new methods for antibiotics delivery to patients with pulmonary infections in order to mainly increase the effectiveness of the drugs administration, to minimize the risk of emergence of resistant strains, and to prevent patients reinfection. Since bacterial resistance is often related to antibiotic concentration, their pulmonary administration could eradicate strains resistant to the same drug at the concentration achieved through the systemic circulation. Pulmonary administration offers several advantages; it directly targets the site of the infection which allows the inhaled dose of the drug to be reduced compared to that administered orally or parenterally while keeping the same local effect. The review article is made with an objective to compile information about various existing modern technologies developed to provide greater patient compliance and reduce the undesirable side effect of the drugs. In conclusion, aerosol antibiotic delivery appears as one of the best technologies for the treatment of pulmonary infectious diseases and able to limit the systemic adverse effects related to the high drug dose and to make life easier for the patients.

Keywords: bacterial infections – aerosol drug delivery – antibiotics – infectious respiratory diseases

1. Introduction:

Different modes of administration have been developed for the delivery of drugs and nano-drugs to treat or diagnose lung diseases such as lung cancer, tuberculosis and cystic fibrosis [1]. In this context, the rise of antimicrobial resistance has created an urgent need for the development of new methods for antibiotics delivery to patients with pulmonary infections in order to mainly increase

the effectiveness of the drugs administration, to minimize the risk of emergence of resistant strains, and to prevent patients reinfection [2]. Thus, the pulmonary tract has experienced a real renewed interest in the administration of inhaled antibiotics as a precious tool in the management of lung diseases such as cystic fibrosis (CF), tuberculosis (TB), non-Cystic Fibrosis Bronchiectasis (non-CFB) and pneumonia [2-6]. The most common lung disease Cystic fibrosis is a genetic disease characterized by an autosomal recessive disorder due to a mutation in the transmembrane conductance regulator gene (CFTR) which lead to thickening of secretions from several organs [7, 8]. Although this abnormality is the source of numerous complications, the most troublesome clinical feature is chronic *Pseudomonas aeruginosa* infection, which is associated with acute exacerbations and progressive lung damage requiring rapid management of patients with antibiotic therapy [7] [9]. In this context the administration of antipseudomonal antibiotics by inhalation has allowed the delivery of high concentrations directly to the lungs with minimal systemic absorption and toxicity [10, 11]. The most commonly used antibiotics in aerosol form for the long-term management of *P. aeruginosa* infection in CF patients are tobramycin and colistimethate sodium [9, 10].

In this review we will focus our attention on the scope and limitation of aerosol drug delivery for the treatment of infectious diseases.

2. Anatomy:

In humans, the respiratory system represents a complex system with a close structure-activity relationship and divided mainly into two vital regions: the conductive airways and the respiratory region. The conductive region consists of: the nasal cavity, the sinuses, the nasopharynx, the oropharynx, the larynx, the trachea, the bronchi and the bronchioles, and it accomplished the role of filtration, humidification and warming of the air, while the respiratory region is composed of respiratory bronchioles, alveolar ducts and alveolar sacs[12, 13].

Throughout the respiratory epithelium, the transepithelial transport of drugs differs quantitatively between these two regions. Due to the reduced surface and the low regional blood flow the drug transport is more limited in the upper respiratory tract mainly because of the large filtering capacity of this region which allows the elimination of 90% of inhaled particles. However, the lower respiratory tract and the alveolar spaces representing 95% of the pulmonary surface, are directly related to systemic circulation through pulmonary circulation. It is also noteworthy that the

morphology of epithelial cells, the pulmonary blood/gas barrier, pore size, and the depth of the narrow junctions of alveolar and endothelial cells allow for better transepithelial drugs transport [12, 14].

From top to bottom we can distinguish:

- The oral cavity: which ensures the communication between the breathing apparatus and the external environment in case of obliteration of the nostrils.
- Pharynx: a muscular duct that represents a common pathway between the respiratory and digestive system.
- Larynx: which is a phonation organ and a narrowed part of the respiratory system.
- The trachea: a long duct of 10 to 15 cm, which follows the larynx, consisting of a succession of superimposed cartilaginous rings, its mucosa is lined with a ciliate epithelium.
- The lung, a viscera in the form of a half-cone, of soft and elastic consistency, comparable to a sponge soaked in air and blood.

Both lungs are located in the thorax, on either side of the heart, wrapped in pleura, and divided into lobes by splits (deep slits), the right lung comprises three lobes (superior, middle and inferior), while the left one is split into just two lobes (superior and inferior). Each lobe contains bronchi, all attached to the trachea, and ramify into narrower bronchioles, which end in a sudden dilation that forms the alveolar sac. The wall of the latter, very thin, constitutes the site of the respiratory exchanges [15, 16].

The main functions of the lungs are to ensure gas exchange between the blood and the outside environment, as well as the maintenance of homeostatic systemic pH [16].

When inhaled, oxygen charged air reaches the bloodstream after passing through the trachea, bronchi, bronchioles, alveoli and then crosses the alveolar wall, while the air charged with carbon dioxide follows the reverse path [15, 16]. Both upper and lower pulmonary veins convey oxygen-rich blood from both lungs to the left atrium, while the pulmonary artery brings back the oxygen-poor blood saturated with carbon dioxide to the lungs. It is noted that in humans, there is no contact at no level of the small circulation, between the oxygenated blood and the oxygen-poor blood.

3. Drug delivery targeting approach to the lung

The development of a targeted drug delivery system is currently experiencing an increasing attention due to limitations associated with conventional treatment of chronic diseases [12]. The efficacy of a drug is conditioned by numerous factors including the method of administration, which influences the concentration of the drug at the targeted site since a concentration above or below the optimal concentration range responsible for the maximum activity may increase the drug toxicity or its inefficiency.

Targeted administration of a drug improves its therapeutic index by increasing its specificity. This is due to the targeting of drug molecules to a particular tissue, intracellular compartment or cell, by controlling the release kinetics and protecting the therapeutic agents [17, 18]. Thus, the development of colloidal delivery systems (such as liposomes, micelles and nanoparticles) has opened up a new frontier for improved treatment delivery. However, this targeted delivery to special organs or sites represents one of the most challenging areas of research in pharmaceutical science [19]. There are two modes of therapeutic targeting, a passive and an active one [20]. Passive targeting takes advantage of the microenvironmental difference between normal and disease cells by using the advantages of the pathophysiological conditions of the cells including increased vascularization, overexpression of surface receptors, increased porosity and varied morphology [21, 22]. On the other hand, active targeting is a well-controlled process improving drug retention at the targeted site of action [20]. Thus, it facilitates the delivery of biomolecules such as DNA and RNA by overcoming rejection by the physiological barrier. This mode aims at improving target specificity by using a surface receptor-oriented method for which the designed ligands have a high affinity [20, 23]. Over the years, colloidal drug delivery systems, especially nanoparticles, have received a great deal of attention. Nanoparticles presented numerous advantages over other drug delivery systems due to their intrinsic characteristics (such as their small size, large surface area and their ability to modify their surface properties leading them to be delivered by various routes including parenteral, oral, intraocular, transdermal or pulmonary route [19].

- 1) Pulmonary targeted nanoparticles delivery via intravenous injection:** different types of nanoparticles were used to assess the distribution of nanoparticles in the body after intravenous injection. Nevertheless, their accumulation mainly takes place in organs of the reticuloendothelial system such as the liver, spleen and lungs [24, 25]. However, the passive targeting of nanoparticles to the lungs requires the use of particles larger than 7 μm to ensure their retention in alveolar capillaries. This can lead to nanoparticles agglomeration due to

the breakdown of repulsive forces between the particles [26]. Therefore, the accumulation of nanoparticles in the lungs after injection appears to be difficult to reach [19].

- 2) **Conjugation of nanoparticles to antibodies for lung targeting:** Monoclonal antibodies [27] can be exploited for active targeting and improved drug delivery by attaching them to molecules or drug delivery systems [28, 29]. This approach has been used to target lung tumors using antibody-modified nanoparticles [30]. However, the results showed that particle size was more important than the affinity of the monoclonal antibodies for the targeted tumor cells [19].
- 3) **Lung targeting using oral nanoparticles:** Traditionally, the oral route of administration has been recommended for the delivery of drug therapy in conventional dosage forms. Thus, its use for targeting the lungs via nanoparticle administration has not yielded promising results [19].

In this context, aerosol therapy has become a popular method for the administration of therapeutic or diagnostic compounds, either locally or systematically [31] [1]. Targeted delivery of nanoparticles to the lungs is a new area of interest as it reduces the dose required and the side effects encountered by decreasing systemic exposure [19, 32]. In addition, the properties of the vector can be modified to target specific cell types [32].

4. Pulmonary administration

Currently, many drug delivery systems are used and aim for an optimal drug administration by minimizing drug degradation, decreasing its side effects and increasing its bioavailability. In this context, the pulmonary route has become an attractive pathway of a considerable scientific and biomedical interest, mainly because it allows a targeted administration directly within the respiratory system as well as a local deposition and systemic absorption. Therefore, many devices and techniques for pulmonary drug delivery have been widely developed in recent years [13].

This non-invasive route of administration has a large absorption surface (about 70140 m²) and a good permeability due to its extremely fine and richly vascularized membrane. In terms of local administration, this mode of drug topical application helps to reduce the side effects caused by the high systemic concentrations observed with conventional administration methods, which also reduces the cost of treatment since the doses used are lower [16]. In comparison with the oral

route, systemic drug administration by pulmonary route allows rapid absorption, low degradation due to the comparatively lower enzymatic activity at the pulmonary level, and to the ability to avoid the effect of the first hepatic passage, which results in a better bioavailability, especially for peptide drugs [12, 16].

Nowadays, numerous respiratory and systemic pathologies are treated with pulmonary-administered medications, we can mention asthma, local infectious diseases, and chronic obstructive pulmonary disease COPD [33, 34]. Also, many companies have benefited from the pulmonary pathway advantages to develop inhaled forms allowing the systemic administration of insulin, human growth hormones and oxytocin [13, 16].

4.1 Aerosol therapy

Aerosol therapy, a practice that has been used since antiquity, is now enjoying a real revival of interest. It consists of "administering drugs in aerosol form into the lungs through the airways". The word "aerosol" is used to define a particle system which diameter is small enough to remain suspended in the air. These particles can be liquid (droplets) or solid (powder), of different shapes and sizes [35]. The main purpose of aerosol therapy is usually the local delivery of the drug, when the lung is the organ targeted by the treatment administered, but it can also be used in certain cases for a systemic administration allowing the drug to reach the general circulation and thus reach its desired site of action [36]. This mode of administration increases the speed and the efficiency of the treatment, and limits the side effects due to the local deposition of drug particles, however, the effectiveness of the treatment is conditioned by several factors, in particular the aerosol deposition site in the respiratory tract, which is influenced by the physical properties of the aerosol, the inhalation conditions and the anatomy of the respiratory airways [35].

The aerodynamic properties of aerosols determine their deposition site, these properties are influenced by the size and density of the particles that constitute the aerosol, and since the latter is an heterogeneous polydisperse system of particles of different sizes and shapes, the equivalent aerodynamic diameter (D_{ae}) is defined to characterize the particle sizes whatever their weight, their shape and their density [35]. The site of deposition of an inhaled particle in the lungs is mainly conditioned by its aerodynamic diameter (D_{ae}) and the breathing pattern of the patient [37]. Thus, aerodynamic particle size distribution and particle velocity are considered to be the two main

physical factors affecting the total and regional deposition of inhaled substances in the human respiratory tract [38]. The aerodynamic diameter is the geometric diameter related to the speed in flight of a particle, if it is assumed to be spherical and to have a density of 1 g/cm³; in other words, the geometric diameter of a spherical particle with a unit density (1 g/cm³) is equivalent to its aerodynamic diameter [39]. Since many natural particles have mass densities close to 1 g/cm³, and considering that sphericity is a natural tendency based on surface energy considerations, such a "base" particle was shown to be useful in discussing the sites and extent of aerosol particle deposition in the lungs as a function of particle size [39].

The static interpretation of the mass distribution of the aerosol particles is based on the mass median aerodynamic diameter (MMAD), which shares the mass of the aerosol particles in two half, 50% of particles having an aerodynamic diameter lower than MMAD and 50% having an aerodynamic diameter greater than MMAD (Figure 1) [35]. In addition, some importance is also given to the fine particle component of aerosols. The fine particle fraction (FPF) is defined as the percentage of particles that have an aerodynamic diameter less than 5 μm, the optimal particle size for lung deposition [33, 40]. The FPF is calculated as the ratio of the FPD to DD [41], where Delivered Dose (DD) represents the total mass of drug administered into the device (NGI) from the mouthpiece of the inhaler excluding the amount deposited on the nebulizer.

$$\text{FPF (\%)} = \frac{\text{Fine Particles Dose (diameter <5 } \mu\text{m)}}{\text{Delivered Dose}} * 100$$

In addition, Fine Particle Dose (FPD) correspond to the mass of particles with an aerodynamic diameter less than 5 μm. [42] The emitted dose (ED) represents the total mass of drug emitted from the inhaler device [41].

Aerosol therapy is indicated primarily as an emergency treatment for the management of asthma, bronchitis, laryngitis, and decompensation for chronic obstructive pulmonary disease (COPD) and primary pulmonary arterial hypertension (PAH). It is also recommended for the chronic treatment of Broncho pneumopathies, pneumocystosis and cystic fibrosis [43].

In addition, the use of the pulmonary route is not limited to therapeutic purposes but also can be used for diagnostic, especially to determine the nature and severity of pulmonary diseases, for example in asthmatic patients, the bronchial provocation test with histamine, methacholine or hypertonic saline solution is used to determine the degree of hyperactivity of respiratory tracts.

4.2 Inhalation biopharmaceutics

A biopharmaceutical product is defined according to the European Union regulations as «A biological medicinal product' such as 'a pharmaceutical substance based on proteins or nucleic acids used for therapeutic or diagnostic purposes in vivo and produced by means other than direct extraction from a native biological source (unmodified) ». (Commission Directive 2003/63/EC) [44, 45]. In other words, biopharmaceuticals are complex molecules often prepared from living systems and endowed with a certain specificity, novelty and promising ability to treat chronic diseases for which there is not yet any effective treatment [45].

Currently several biopharmaceutical products (most of them protein-based) are approved in the United States and Europe for the treatment of various diseases [46, 47]. Although these products are delivered by injection, their administration by other routes has been studied [48]. Injection administration causes many problems that limit patient adherence to treatment, including the need for a health care professional with some expertise [49]. In addition, oral administration of biopharmaceuticals remains quite difficult due to their low bioavailability due to first-pass metabolism and their potent susceptibility to gastrointestinal enzymes [50]. In this context, the administration of inhaled biopharmaceuticals is currently attracting considerable attention mainly because of the efficiency of absorption of some of these molecules by the lungs [51]. Inhalation delivery of biopharmaceuticals has proven to be interesting due to the large surface area of the lungs and the proximity of the alveolar and vascular systems, which maximizes the potential for medical delivery to the lung and/or systemic circulation [51].

However, although a large number of biopharmaceuticals are currently being studied for delivery by inhalation [52], only one product is currently approved by the FDA and marketed in its inhaled form, the Pulmozyme (recombinant human deoxyribonuclease, DNase), used to reduce the viscosity of mucus in the lungs of cystic fibrosis patients [51]. In addition, the formulation of insulin (one of the most studied proteins for inhalation administration), proposed by Pfizer (Exubera), for pulmonary administration received marketing approval in 2006 from the FDA and the European Medicines Agency [51].

Due to the practical, non-invasive self-administration that promotes patient comfort, offered by the pulmonary route, the demand for the development of biopharmaceuticals in inhaled dosage forms

is increasing for the long-term management of chronic diseases [51]. However, the formulation of inhalation biopharmaceuticals presents many challenges for scientists. Depending on the objectives of administration, inhaled particles must have a specific size distribution for effective delivery to the desired site of action [49]. Biopharmaceuticals often have a complex three-dimensional structure, so the formulation and aerosol generation processes must be carried out in such a way as to ensure the non-denaturation or modification of the molecules, since the slightest change in structure or surface properties could affect its efficacy, toxicity and/or immunogenicity [51]. Incorporation of excipients is often necessary to achieve a particle size in the respirable particle range and a maximum shelf life. For protein therapies, the most commonly used excipients include mannitol, sucrose, sodium chloride and trehalose [53]. In addition, biopharmaceuticals are relatively large molecules, requiring the addition of an absorption enhancer to be absorbed at the alveolar level [54]. This could potentially increase the particle size as a result of their entrapment or encapsulation within the absorption activators [55]. Not only the aerodynamic size of the particles produced but also the properties of their surface must be controlled because micronization increases the particles charge, thus favoring their aggregation [49].

Another challenge is the rapid elimination of proteins from the lungs, which requires repeated administration of these biopharmaceuticals (once or twice a day), limiting patient compliance [50, 51, 56]. In this context, PEGylation appears to be a promising approach to ensure the therapeutic efficacy of proteins, since conjugation with polyethylene glycol (PEG) improves the stability of the protein and prolongs its retention in intact form in the body [49]. It consists of the covalent attachment of one or more chains of PEG (a polymer composed of repeating units of ethylene glycol) to a molecule [57]. This reduces the frequency of pulmonary administration and thus improves patient compliance, especially in the case of chronic treatments [49].

4.3 Mechanism of aerosol particle clearance after inhalation

Inside the respiratory tract, inhaled particles are either eliminated to the outside, or absorbed into the blood or lymphatic circulation, or degraded [58]. The human lung possesses numerous mechanisms in different regions of the airways to prevent aerosol particles from entering the deep lung [59, 60]. Although these mechanisms protect the respiratory tract from disastrous exposure to foreign materials, they constitute real barriers to the administration of drugs by inhalation [37]. Therefore, in order for a drug particle to reach deep into the lungs, it must be able to overcome the following barriers [60].

- 1) **Mucociliary clearance (MCC):** primarily, the oropharyngeal region and the bronchial tree are excellent filters for removing insoluble inhaled particles and pathogens deposited on the ciliated epithelium [60]. This escalating mucociliary transport system, which acts as a potential physical barrier to drug penetration, is composed of un-hairy secretory cells and hairy cells [61, 62]. Thus, in healthy subjects, the majority of particles deposited in the tracheobronchial region of the respiratory tract will be removed within 24 hours [59].
- 2) **Mechanical clearance:** Another innate line of defense is represented by mechanical clearance, which includes coughing, sneezing or ingestion of inhaled particles deposited in the upper respiratory tract. This mechanism concerns particles presenting a size $\geq 10 \mu\text{m}$ and occurs instantaneously after their deposition in the large airways due to the high airflow in this region [59]. Thus, cough becomes the main release mechanism in many respiratory diseases (such as bronchitis, asthma or pneumonia) where MCC is altered, which requires maintaining the particle size above $\leq 10 \mu\text{m}$ to achieve the optimal effect of the drug [63, 64]. In addition, even smaller particles that can escape and be deposited in the alveolar region of the lung undergo a number of mechanisms that inhibit their absorption [61, 65]. These absorption barriers act to varying degrees by inhibiting the permeation of drugs into the circulation : the mucus layer, the fluid layer of the alveolar mucosa, the alveolar epithelium, macrophages and other cells [60].
- 3) **Alveolar Macrophages (AM):** macrophages residing in the alveolar space are considered essential cells for the maintenance of homeostatic tissue processes, repair and immunity [66] [61]. They perform a central maintenance function in the innate immune response, killing pathogens and removing poorly soluble inhaled particles remaining in the alveolar space for a sufficient amount of time [61]. This greatly reduces the amount of drug needed to observe a therapeutic effect [59, 67]. However, they are ineffective in removing particles smaller than 200 nm [37]. In addition, they participate in the mechanism of activation of adaptive immune responses through cytokine secretion and signal transduction [61, 66]. On the other hand, alveolar macrophages represent the main obstacle to the controlled release of drugs into the alveoli [59]. The majority of the materials used to enhance the release of a drug present all the physico-chemical characteristics rendering them as an ideal target for elimination [63, 64].

4) Enzymatic degradation: Another impediment to the development of controlled-release forms of drugs via the pulmonary route is clearance by metabolic degradation [68]. Although the level of degradation enzymes and the pulmonary capacity for metabolism are lower than those of the hepatic system, expression of families of cytochromes P450 (CYP) in the lungs is observed [68]. Some of them such as CYP2S and CYP2F have been identified as specific to the lungs [69]. In addition, other Phase II metabolic enzymes (such as esterases and peptidases) are also expressed in the lung even if their concentrations differ considerably between the different types of cells lining the different regions of the lungs [70].

4.4 Mechanism and factors influencing particles deposition

The pulmonary delivery of drugs in aerosol form is mainly based on two modes of administration: nasal inhalation and oral inhalation. However, several anatomical features (narrower airway light) restrict nasal administration and make oral administration more favourable [71]. In this area, many studies have demonstrated that oral administration is better for particles with a diameter of 5 μm , with a loss percentage of only 20% compared to 85% in the case of nasal administration [64, 72].

The efficacy of inhaled treatments depends not only on the active substance but it is also balanced by the drug proportion deposited in the lungs [73, 74] as well as its site of deposition in the airways. For some substances this proportion is retained in the peripheral areas of the respiratory tract [75]. Thus, the respiratory tract has been the subject of numerous studies over the past 50 years, mainly to assess the dosimetry of inhalants mostly those resulting from exposure at occupational levels [76, 77]. In this context, the results of these studies allowed a better understanding of the mechanisms of deposition and transport of aerosols [33].

Many factors determine and influence the site of deposition of inhaled particles, we can distinguish:

1) Factors related to the physical properties of the aerosol: such as the size of the particles generated by the inhalation device, their shape, density, electrical charge and hygroscopicity. Three main parameters determine these physical parameters: the chemical formulation of the medicinal product including the active substance, the aerosol-generating apparatus and the vector gas. Thus, two different nebulizers can generate from the same drug two aerosols with different MMADs whereas two different drugs nebulized with the same device can give two aerosols with different physical parameters.

- 2) Factors related to the inhalation conditions including parameters related to the respiratory rhythm such as inspiratory flow, volume of inspiration, breathing break at the end of inspiration and hand-blowing coordination.
- 3) Respiratory tract factors, such as faster mucociliary clearance at the proximal airway and airway geometry that depends primarily on age, sex, nature and severity of obstructive bronchial disease [33, 73, 78, 79].

Numerous studies have been carried out extensively using *in vivo*, *in vitro* and mathematical models to study aerosol deposition in the lungs [80]. Thus, the amount of drug reaching the respiratory tract has been shown to be directly proportional to its clinical efficacy [81].

Recently, new studies on the oro-pharyngeal deposition of drugs have identified other factors controlling the transport and the oro-pharyngeal deposition, including particle velocity, the mouthpiece diameter and the electrostatic effects related to the delivery device [33, 82-85].

Primarily, the size of the inhaled particles and their inhalation rate constitute determinant factors for their deposit in the different parts of the respiratory tract [86, 87]. This deposit is the interaction of different fundamental physical mechanisms [88]. However, impaction, sedimentation, and diffusion constitute the main deposition mechanisms and are discussed below [89].

1) **Inertial impaction:** it depends on the flow rate conditioned by the particles aerodynamic diameter. This mechanism concerns large particles or droplets ($\geq 5 \mu\text{m}$) since inhaled particles tend to move in a straight line [87, 89]. At high speed, large particles cannot follow the path of the airflow in an area implying an important change of direction [60, 89]. As a result, particles of large size and high mass (density) strike (colloid) and settle in areas where the airway of the upper respiratory tract branches off [80]. The probability of impact increases with increasing air speed, breathing frequency and particle size [60]. Thus, impaction represents the main deposition mechanism observed in the upper respiratory tract and the oro-pharyngeal and tracheo-bronchial regions where air velocity is high and airflow is turbulent [71, 90, 91]. It is also noteworthy that it can be partially influenced by hyperventilation (

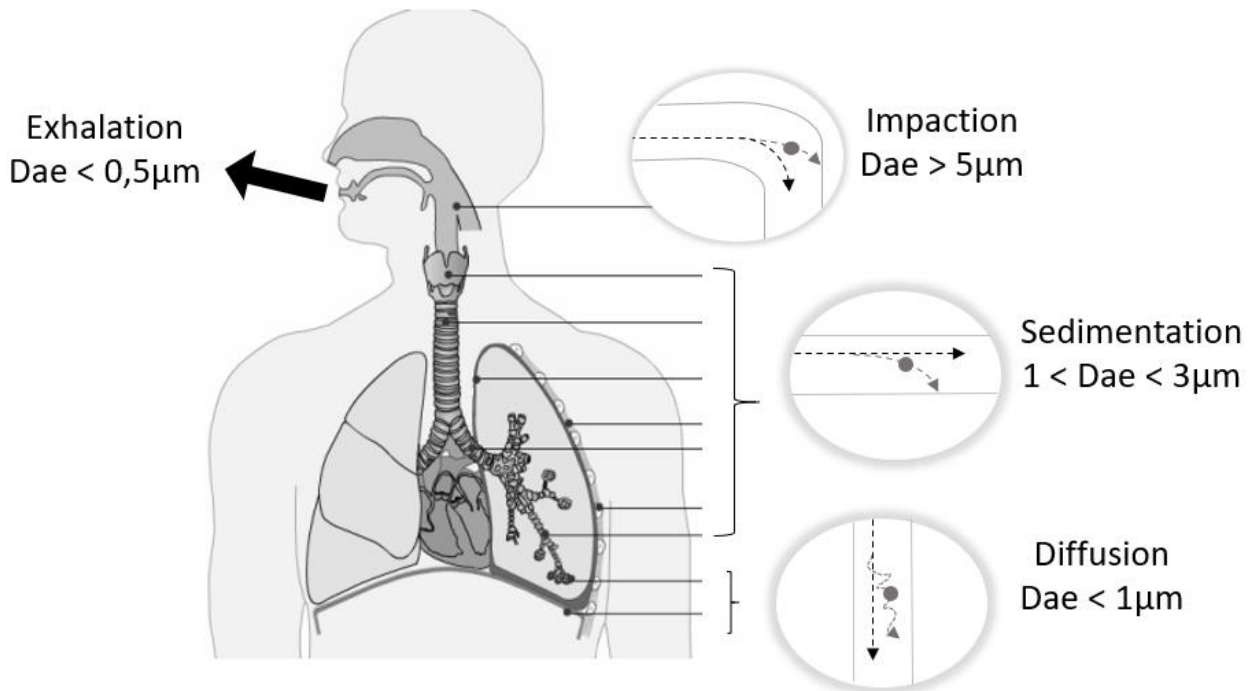


Figure 2-a) [71].

- 2) **Sedimentation:** it is the mechanism by which particles are deposited in areas of slower airflow (the lower respiratory tract of the bronchi and in the alveolar region) [89]. Particles with an aerodynamic diameter between 0.5 and $5\mu\text{m}$ can avoid impaction in the upper airways and thus reach the lower tracheobronchial and alveolar regions where they are deposited by sedimentation [89]. This latter occurs when the gravitational force acting on a particle exceeds the total force of air resistance [60]. Thus, particles in the dispersed phase settle and fall out of the air stream at a constant rate due to gravity or a centrifugal force imposed in these lung regions [60, 80]. This mechanism is observed mainly for particles larger than $0.5\mu\text{m}$ [64, 87, 91, 92]. The probability of particle deposition by sedimentation is proportional to the residence time in the airways and increases with the particle size whereas it decreases by increasing the respiratory rate [60]. On the other hand, it can be influenced by the breathing pause at the end of inspiration which allows time for gravity to take place (

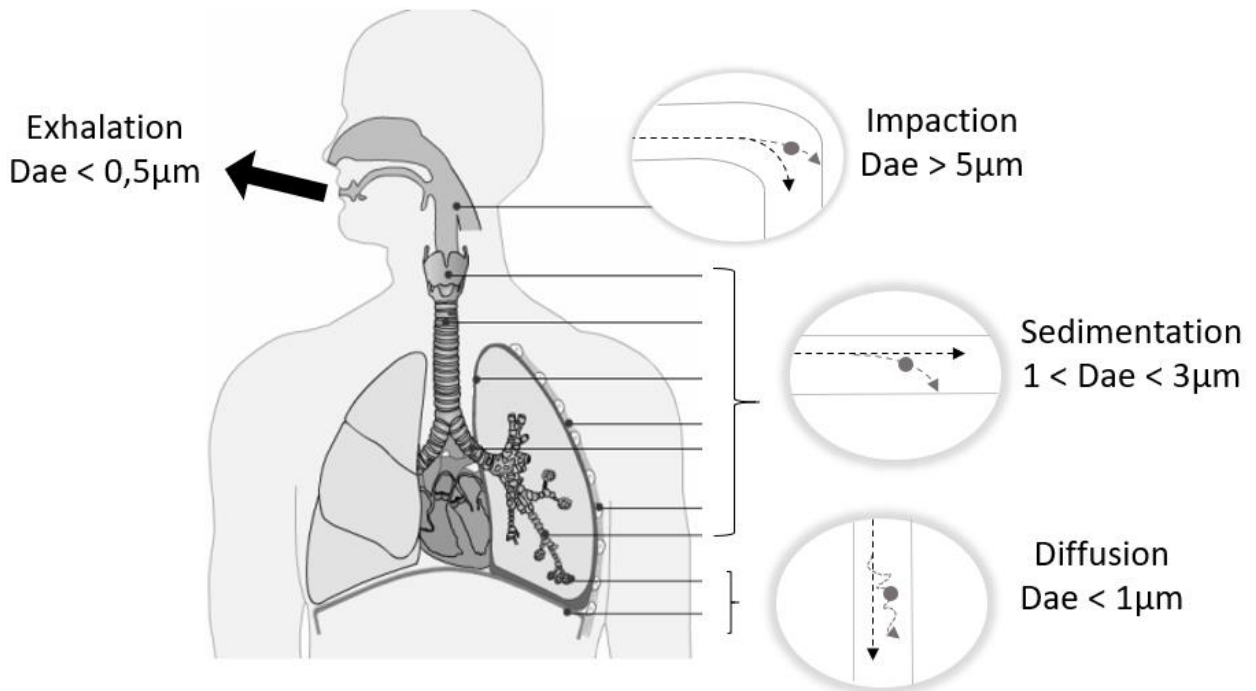


Figure 2-b) [93].

- 3) Diffusion:** it is the main deposition mechanism for particles smaller than $0.5\ \mu\text{m}$, caused by Brownian motions [89]. The collision of gas molecules with small aerosol particles exerts discrete and non-uniform pressures on the particles surface, resulting in a random Brownian motion [60]. This latter leads to the deposition of the drug and its diffusion into the alveoli [80]. Diffusion is governed by geometric rather than aerodynamic particle size [94-96]. The Brownian motion is more important with the decrease in particle size and airflow, and becomes the main mechanism for particles deposition in the bronchioles, alveoli and at the bifurcations of the bronchial airways [60, 89]. The probability of diffusion deposition in the alveolar region increases as the airway is narrowed and residence time increased (

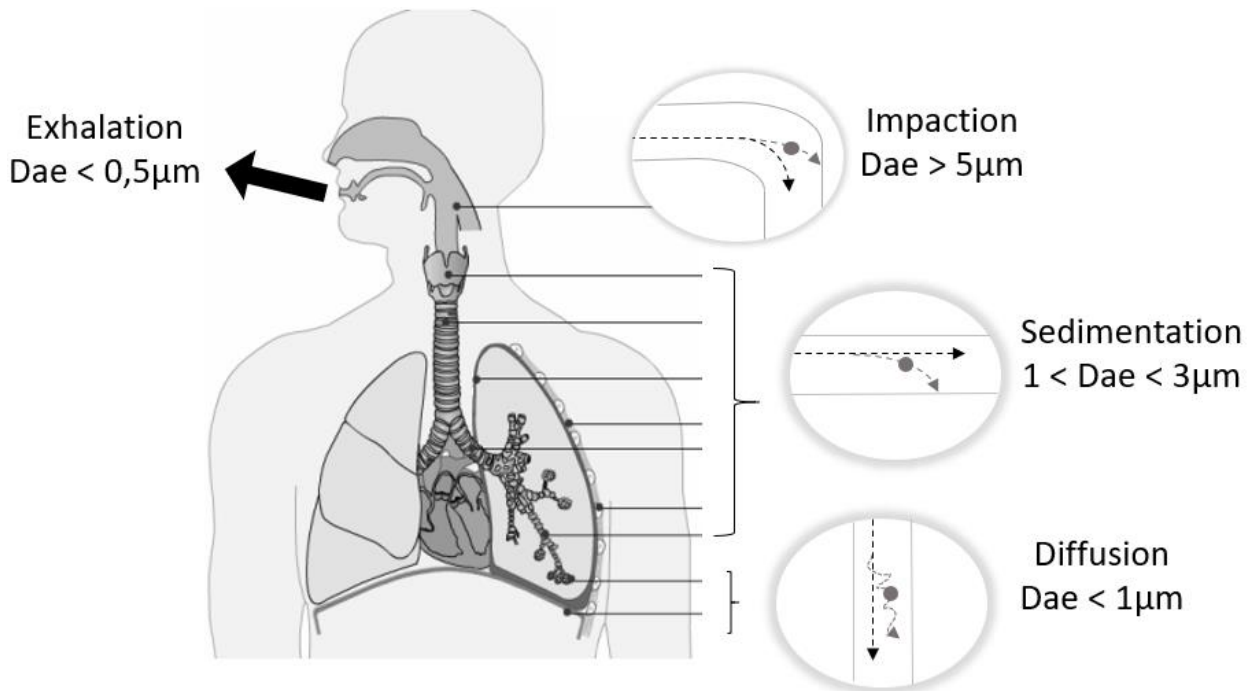


Figure 2-c) [97].

Particles suspended in the air, will be inhaled, and enter the airways via nasal or oral routes. The particle's inhalability is defined by its ability to enter the main airways; it depends on the aerodynamic diameter of the inhaled particles and represents the fraction of air that enters the airways. Once inside the respiratory tract, inhaled particles can settle in different regions [33, 73, 78].

The airflow undergoes changes in speed and direction as it enters deeper into the respiratory system. At the trachea level, the airflow is of a maximum speed, which decreases when the air passes in the lungs. Then, in the upper respiratory tract, the elasticity of the lungs gives rise to a change in geometry, favoring the impaction of large particles ($> 5 \mu\text{m}$) since they can not follow the air flow. The carinii bifurcation represents the main impact site of inhaled particles. Generally, a significant portion of the dose emitted by MDI and DPI is deposited by impaction at the oropharyngeal level. Particles with a diameter between ($2\text{-}5 \mu\text{m}$) undergo a reduction in the influence of inertial effects. They deposit by gravitational sedimentation at the small airways level and the alveolar region. While, the finest particles ($< 2 \mu\text{m}$) are subjected to Brownian motions and deposit by diffusion randomly on the walls and the periphery of the lungs (**Figure 3**) [33, 73, 78].

5. Inhalation devices:

Inhalation forms are one of the most difficult pharmaceutical forms to develop [86]. The complexity of this form stems from the fact that its efficacy depends not only on the pharmacologically active molecule, but also on its formulation and above all on the delivery system [86]. Consequently, a successful development of inhalation therapies requires good optimization of the entire system (drug, formulation and device) [86]. Thus, the design of the inhalation device is of paramount importance to achieve better delivery of the drug in aerosol form with an optimal particle size distribution to ensure deposition in the desired region of the lung [86, 98, 99].

The delivery of medicines in form of aerosol to the pulmonary system is assured mainly by three inhalation devices : nebulizers (air-jet, ultrasonic and vibrating mesh nebulizers), Metered Dose Inhalers (MDI), and dry powder inhalers (DPI) [100] [101, 102]. In addition, a new class has recently been introduced, the class of Soft Mist Inhalers (SMIs). This classification takes into account the physical state of the dispersed phase and that of the continuous medium [40].

5.1 Nebulizers:

Nebulizers are devices for converting drug solutions into aerosol for inhalation [103, 104]. The drug substance is dissolved or suspended in a liquid (usually water) [40]. They use two main mechanisms for the generation of aerosols: mechanical or electrical mechanisms. Thus, there are two main types of nebulizers:

- 1) **Air jet nebulizers** that use a source of compressed air or oxygen for the creation of the aerosol droplets from a solution or suspension for nebulization (such as Medix® and Pari LC Plus®) (**Figure 4**)
- 2) **Ultrasonic nebulizers** whose aerosol creation is based on the vibrations of a piezoelectric crystal that generate high frequency sound waves (such as the AeroSonic® and Sonix 2000 systems®) (

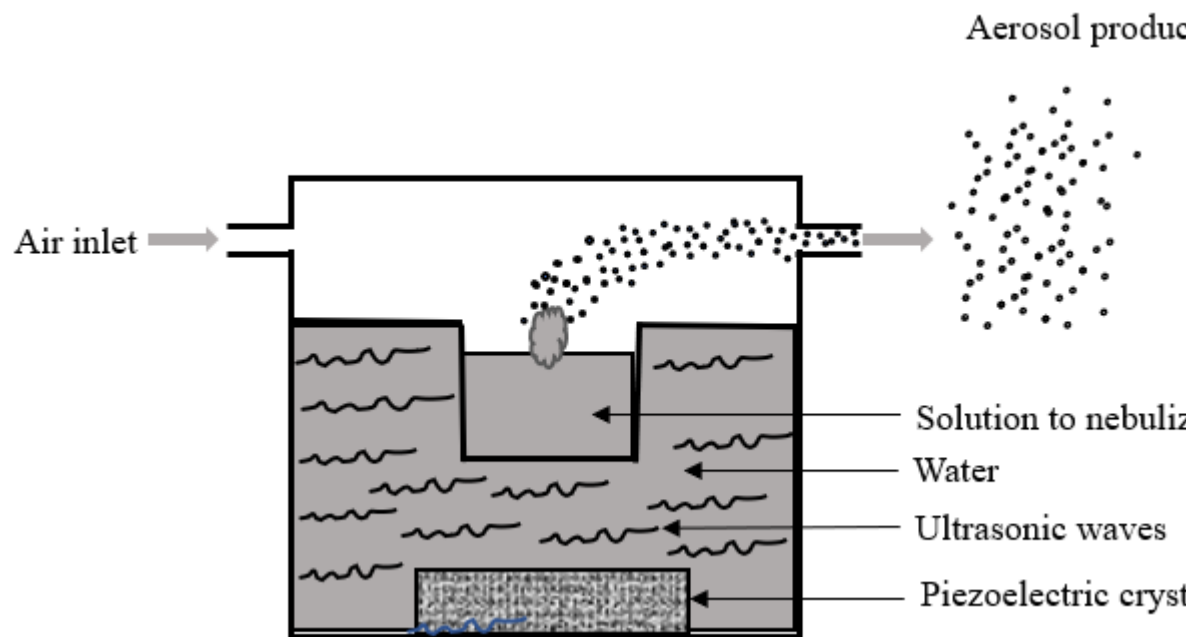


Figure 5) [103].

- 3) **Vibrating mesh nebulizers** are defined as micropump systems because of their aerosol-generating mechanism involving energy forcing the medical liquid to flow through small openings in a plate or a membrane (**Figure 6**) [105].

With the progress of nebulisation technology, numerous new methods have been developed, in particular those using ultrasound and electrohydrodynamic atomization [106-108], allowing more rigorous control of the atomisation process to provide monodisperse or reduced-dispersion aerosols with the possibility of droplet size adjustment [109], by changing the operating frequency of the ultrasonic vibration through the design of the electrode [110-112]. Thus, surface acoustic wave atomization (SAW) is a simple and fast technique that can be performed on a chip-scale microdevice for the generation of aerosol droplets in the micron and submicron range [110, 113]. Compared to standard ultrasonic atomization techniques [114], it offers much higher operating frequencies and therefore allows the generation of smaller droplet sizes constituting monodisperse aerosols [110], Thus, it has been considered as a promising alternative to ultrasonic nebulization and represents a revolution in microfluidic technology in the formation of nanoparticles for targeted drug delivery and many other applications [115]. In addition, due to the higher working frequency, the propensity of the sprayed drug to denaturation is greatly reduced [116, 117].

New nebulizers based on emerging technologies such as microfluidic atomization by surface acoustic waves have demonstrated a high delivery efficiency (FPF ranging from 70 to 80%). It is also noteworthy that some of them are equipped with digital software control and performance feedback of the nebulizer [118]. Their use has been shown to be effective in the generation of appropriate aerosols containing salbutamol, used for the treatment of asthma. The droplets of the produced aerosol had an optimal MMAD size of 2.84 μm , suitable for deposition in the region targeted by the treatment, with approximately 70-80% of the drug supplied to the atomizer deposited in the lung [109].

Nebulizers are polyvalent devices that have been used for the nebulization of a wide range of therapeutic ingredients, allowing passive administration to patients [40, 103]. However, they are bulky, require an external power source, a long time of administration and a good training of the patient or a professional supervision [88]. Otherwise, their limited portability and relatively high costs have limited their use to hospital and ambulatory care [40, 119, 120].

5.2 Metered dose inhalers MDIs:

Metered Dose Inhalers (MDIs) are another system of drug conversion into aerosol, known for its reliability and low cost [100]. MDIs are used to deliver dissolved or suspended active ingredient in a nonpolar volatile propellant or in a combination of propellants with solvents [40].

They allow the delivery of a metered volume of propellant containing a predetermined amount of the active ingredient. The device consists of three main parts: the reservoir intended to contain the drug (dissolved or suspended in the propellant), the metering valve and the spray actuator, responsible for creating the aerosol cloud (**Figure 7**) [103].

The first MDI was approved in 1956, then because of their ease of use they represented the most popular inhalation delivery system. They are known as the pillar of asthma inhalation therapy [101, 121, 122]. They represent about 80% of the world market mainly because it is a portable device, discreet, and relatively easy to use especially in critical situations such as acute asthma attack. In addition, their high sealability prevents microbial contamination and gives them a long life expectancy, this makes the MDI an attractive device for the pharmaceutical industry [40, 123].

Chlorofluorocarbon (CFC) was the first propellant used in MDIs [32]. However, because of their deleterious effect on the ozone layer, their use have been banned by the United Nations in

accordance with the Montreal Protocol [86, 124]. After numerous trials, hydrofluoroalkanes (HFA), in particular HFA-134a and HFA-227 were chosen to replace CFCs propellants because of their properties adapted to this pharmaceutical dosage form [38, 86]. HFAs are chlorine-free and therefore have no ozone-depleting potential. Thus, beclomethasone and albuterol, two main drugs used in the treatment of asthma, have been formulated in HFA-134a and are currently approved in several countries [38, 125]. However, HFAs possess different physical and chemical properties than CFCs [86]. CFC-based MDIs require the use of surfactants to improve the physical stability of the suspensions, to prevent drug particles aggregation and to lubricate the dosing valve. In the case of HFA-based MDIs, their limited surfactant solubilizing power lead to the use of ethanol to dissolve surfactants. Thus, some ethanol-soluble steroids (such as beclomethasone dipropionate) form a solution in the HFA-based formulation, rather than a suspension obtained in the CFC. These solutions may result in aerosols with a higher Fine Particles Fraction allowing greater drug deposition into the periphery of the lung [86, 125].

In addition to solubilization problems and compatibility between active ingredient and propellant encountered during the formulation of MDIs (especially in the case of certain peptide-based drugs), several disadvantages such as the clogging of the valve, the growth of particle size during storage and the high initial velocity of the spray resulting in a high oropharyngeal deposition and substantial loss of the drug have been encountered [103]. Furthermore, pressure devices have high percentages of drug loss: systematically greater than 70% and may exceed 90% [122]. Thus, their use is limited to the treatment of superficial lesions due to the low drug deposition in the lungs [100].

Recently, MDIs with a MMAD close to 1 μm have been developed and marketed since they present interesting properties relative to lung deposition, but to date no application with antibiotics was reported.

5.3 Dry powder inhalers (DPIs)

A third pulmonary delivery system was developed to address coordination issues and to avoid the use of chlorofluorocarbon (CFC) propellants: Dry Powder Inhalers (DPI) [100].

The use of these dry pulmonary delivery devices has become very attractive since they offer several advantages including the chemical stability of the powder compared to aqueous solutions administered by nebulization [126]. They are suitable for the delivery of poorly water-soluble

drugs, peptides and protein-based drugs fragile to shear stresses produced during inhalation [127]. Otherwise, no storage problems (i.e. respect of the cold chain or those related to the powders reconstitution into nebulization solutions) are encountered which is particularly interesting in the case of antibiotics and vaccines in developing countries where cold storage and transport can be problematic [128].

In addition, DPIs are easy to use, much more practical than conventional jet nebulizers because they are small, portable and reduce significantly the time required for dose administration [129-131], which allows a greater patient compliance [132].

In comparison with the MDIs, most DPIs are actuated by the patient's breath which allows automatic coordination between the initiation of the inhaler and the inhalation of the patient [133, 134], therefore they do not require coordination between actuation and inhalation for the drug release. They have the advantage of not using any propellant, in particular CFCs [100, 133, 135, 136]. In addition, they allow a better pulmonary delivery of drugs unlike MDIs that work under pressure and emit the drug dose at high speed, resulting in premature deposition in the oropharynx [40, 137, 138].

Dry powder inhalers deliver drug formulations as a respirable powder alone or mixed with a non-respirable carrier [139-141]. They are classified into two classes:

- 1) **Passive DPIs** that depend entirely on the patient's inspiratory capacity. They use the inspiratory flow to provide the energy needed to disperse the powder [119]. The major disadvantage of this class is the dependence of their performance on the inhalation rate, which results in a high intra and interindividual variability, particularly in patients with respiratory diseases [142]. This first generation of DPIs is known for its low efficiency in terms of fine particle fraction FPF (the fraction of emitted particles that are less than 5 μm) (10 to 15%) and the inconsistency in the emitted dose (ED) [143-145].
- 2) **Active DPIs** “the New Generation DPIs” have been designed to overcome this issue and to ensure a dosing accuracy and a reproducible aerosolization. They bring an external energy to disperse the powder and do not depend on the patient's inspiration flow [119, 142]. Thus, a higher dispersion efficiency is encountered with respect to that obtained with passive DPIs. On the other hand, it is noteworthy that this energy comes either from a compressed gas or

from vibrating piezoelectric crystals [146, 147].

The DPIs are primarily useful for pulmonary or systemic delivery under conditions where the patient's inspiratory power can not be invoked [148, 149]. Depending on the powder administration method, they are classified into three types:

Single-dose DPIs that deliver a single dose contained in a capsule (gelatin or hydroxypropyl methylcellulose HPMC) that will be perforated by DPI actuation to release the powder. Multi-dose devices that contain several pre-filled doses in capsules or blisters and multi-dose DPIs composed of powder-filled reservoir. In this latter case, the doses are sampled by a measuring system at each actuation by patient (**Figure 8**) [119, 150].

The first generation of dry powders for inhalation has been based on the preparation of simple powders (obtained by a simple mixture of micronized drugs) and simple inhalers (passive capsule DPIs). The second generation consists of the same first-generation simple powders associated with more technically sophisticated devices [98]. Traditionally, Most DPI formulations have been composed of a mixture of micronized drug particles mixed with lactose as a carrier, or sometimes aggregates of pure drug particles. For these formulations, the manufacturers have focused on optimizing the performance of the inhalation devices, for example by improving the design of the mouthpiece, they have been able to achieve low air turbulence and therefore more effective disintegration and a higher dose of fine particles [144]. These devices included passive multidose inhalers and active dry powder inhalers [98].

The third generation of inhalable powders is characterized by sophisticated powders (size, granulometry...) and the use of very simple inhalation devices [98]. It should be noted that optimization of inhaled treatment delivery can be achieved not only through improved devices, but also through a more sophisticated formulation that disperses easily in the inhaler air-stream and can thus be delivered using simple inhalation devices [151]. Thus, sophisticated powders are characterized by improved fluidization and reduced inter-particle cohesion. Advances in particle engineering have led to better control of particles properties, including particle size and distribution, morphology, porosity, density, and surface energy. Control of these properties has in turn led to optimal control of attributes such as powder fluidization, dispersibility, chemical stability and pharmacokinetic/pharmacodynamic properties, allowing for optimal delivery by inhalation most often by simple devices [98].

The powder dispersion from a DPI involves two consecutive mechanisms, the process called "fluidification" which allows the delivery of a precise drug dose in the air inhaled by the patient in a single breath, then particle agglomerates are broken down to create a breathable cloud of fine particles that will be transported to the lungs with the inspired air [81, 142, 152, 153].

Deagglomeration is favored by increasing turbulence of the air flow [154, 155]. Thus, a greater inspiratory effort of the patient allows a better dispersion of the agglomerates and the creation of an aerosol with finer particles compared to a lower flow rate in patients suffering from respiratory problems (severe obstruction of the respiratory tract). However, a very rapid inhalation can lead to significant pharyngeal deposition by impaction [103].

Two main problems are encountered when formulating DPIs; the relatively low percentage of fine particles (FPF) and emitted dose (ED), this is generally attributed to the inter-particle forces and their tendency to form agglomerates rendering their dispersion very difficult and preventing their optimal deposition at the pulmonary level [119, 156].

Conventionally, powder for inhalation is formulated from micronized medicinal particles with a diameter ranging from 1 to 5 μm mixed with large carrier particles (excipient) to improve their flow, reduce their aggregation and facilitate their dispersion [152, 153, 157]. By DPI actuation, the mixture of drug and excipient particles is dispersed by shearing or by the mechanical forces generated by the inspiration. The large particles of the excipients are deposited on the oropharynx and will then be swallowed in the gastrointestinal tract while the small particles of the drug continue on their way to the lungs [119]. Thus, in dry formulations for inhalation the support must be carefully selected on the basis of their physico-chemical properties such as size and morphology, which profoundly affect the performance of the formulation [40]. The most used excipient is lactose because of its benefits and especially its approval by the FDA for use in DPI [119]. However, allergy problems, lactose intolerance in some patients as well as reduction property and lactose reactions with some drugs have led to the search for other carriers, some even are approved outside the US such as non-reducing sugars (e.g., trehalose), mannitol, glucose, sodium chloride, sorbitol, raffinose and dextrose [158, 159]. The use of polymers such as polyvinylpyrrolidone (PVP) and polylactic-co-glycolic acid (PLGA) has been also investigated as potent excipients for inhalation [160] whereas cyclic oligosaccharides such as cyclodextrins have been proposed to improve the solubility of hydrophobic compounds, stabilize the active ingredients against degradation and improve the aerodynamic performance of dry powders [40, 161-164].

On the other hand, the combination of the active ingredients with carrier excipients causes variations of the particles properties that result from interactions between the drug, the excipient and the inhaler [165]. Consequently, the aerodynamic behavior, the deposition site and the emitted dose vary considerably [166]. Moreover, the particle size distribution of the active substance is modified by the addition of excipients which greatly influences the DPI effectiveness [40]. Their function as carrier particles aims to reduce inter-particle cohesion by occupying the high-energy sites of the drug particles, thereby improving drug handling, distribution, and dosage. They are critical determinants of overall DPI performance since they can account for more than 99% of the product weight. Furthermore, adhesive forces must be carefully taken into account since inadequate separation of the drug from the carrier change the active substance particle size distribution and constitute the main cause of deposition problems [40].

In addition, the excipients approved by the US Food and Drug Administration (FDA) for pulmonary administration are very limited in number (**Table 1**) [167, 168] and their potent use is limited to biocompatible or endogenous compounds in the lungs that can be metabolized or eliminated easily [120].

Effective delivery of the powder requires that the adhesion forces between the active ingredient and the carrier are not too strong to allow easy detachment of the carrier during inhalation. Thus, a balance between the adhesion and cohesion forces must be adjusted to ensure enough adhesion which in turn ensures the stability of the formulation (homogeneous mixing and uniformity of the dose) and also to allow an easy detachment between drug particles and carrier ones. Thus, it has been reported that the effectiveness of a powder formulation is strongly influenced by the lactose quality, its source, size and particle size distribution [169, 170]. Although, the more sophisticated inhaler design using active dispersion of powders and the electronic synchronization allowed the resolution of the formulation problems, these inhalers are complex and expensive and their reliability and practicality were doubted [143]. Given the limited number of excipients allowed for inhalation [88] and in order to solve the formulation problems related to lactose or other carriers, several studies have targeted the design of systems without support. These formulations are obtained by particle engineering techniques. They prevent the problems of mixing uniformity and particles aerosolization. In addition, these carrier free formulations are particularly beneficial in the case of high dose drugs such as antibiotics, the absence or limited amount of excipient makes their pulmonary administration possible and limits the inhaled weight for other drugs. At the same time,

many inhalers have been developed to ensure the efficient delivery and dispersion of this type of formulation [169].

Table 1. Approved or excipients of interest used for inhalation formulations

	Nature [Ref]	Excipients	Functions
Excipients used for nebulization	Salts [88]	- Sodium chloride (NaCl)	- Adjust solutions osmolarity to approximately 300 mosmol/l
	Acids / Bases [88]	- Hydrochloric acid (HCl) - Sodium hydroxide (NaOH) - Citric acid - Phosphates - Trometamol	- Adjust the formulation pH to neutrality.
	Surfactants [88]	- Polysorbates - Sorbitanes	- Facilitate the dispersion or dissolution of drugs
	Cosolvents[88]	- Ethanol	- Solubilizing the active substances, - Used in small amounts to avoid lung irritation.
	Preservatives [88]	- Methylparaben - Propylparaben	- Ensuring the long-term conservation of products
Excipients used in MDIs	Propellants [88]	- Hydrofluoroalkanes HFA - HFA 134a (1,1,1,2-tetrafluoroethane) - HFA 227 (heptafluoropropane)	- Drugs are either suspended or dissolved in a propellant
	Cosolvents[88]	- Ethanol	- Overcoming problems of drug particles instability in HFA propellants
	Surfactants [88]	- Sorbitan trioleate (SPAN 85) - Oleic acid - Soya lecithin	- Facilitating the dispersion of suspended drug particles or the dissolution of a partially soluble drugs
	Preservatives [88]	- Antioxidants (ascorbic acid) - Chelating agents (EDTA)	- Improving chemical stability
Excipients	Sugars [171, 172]	- Lactose - Glucose - Mannitol	- Improving the particles aerosolization properties in DPIs

		- Trehalose	
	Amino acids [171-173]	- L-leucine - Trileucine	- Improving the powder dispersion by reducing the cohesive forces of the particles and - Protecting powder from humidity (coating agent for the drug particles)
	Hydrophobic additives [88]	- Mg stearate	- Protection for drug moisture
	Lipids [88]	- Dipalmitoylphosphatidylcholine DPPC - Cholesterol	- Used in liposomes, matrix, coating
	Surfactants [88]	- Poloxamer	- Particle engineering of light and porous particles

5.3.1 Particle engineering for inhalation:

The recent progress and the increasing sophistication of inhalation therapy has generated a considerable interest for the development of new technologies to formulate inhalable particles made to measure allowing optimal pulmonary delivery [143]. Particle engineering is a practical tool allowing a controlled production of particles with desired characteristics at a lower cost. A wide variety of techniques has emerged over the past decades to produce particles with desirable respirable properties such as: narrow particle size distribution, improved dispersion and optimized bioavailability for simple use. Some are even with extended release and/or precise targeting [88, 143, 174], which has led to the appearance of new classes of therapeutic products intended for pulmonary administration [98]. Otherwise, the geometric size of these particles between (100 nm and 100 μ m) gives them a diversity of physicochemical and biological properties. For example, ultrafine particles can bypass clearance by macrophages and pass easily through the pulmonary epithelium. Although this property is particularly interesting for systemic administration, it is also related to an apparent increase in toxicity. [175-178].

Several epidemiological studies reported the link between increased exposure to high concentrations of fine or ultrafine particles and adverse health effects [175, 179]. Mainly, the observation of cardiovascular effects triggered the discussion on the improved passage of these particles through the respiratory epithelium to the circulation and subsequently to other target

organs (such as the heart, liver and brain) with harmful consequences on heart function, blood coagulation and central nervous system functions [175, 180]. In addition, due to their high specific surface area, these ultrafine particles are considered to have a specific toxicity, which could lead to the induction of oxygen radicals and the catalysis of chemical reactions [175, 181-183].

5.4 Soft Mist Inhalers SMIs

In order to improve drug delivery to the lungs and especially to overcome the difficulties encountered by patients with the use of MDIs and DPIs (reducing patient coordination requirements, allowing easy use without inspiratory effort), a new inhalation system has been designed: the Soft Mist Inhalers SMIs [184]. Thus, SMIs are spray devices like MDIs, which atomize the drug solution allowing it to be delivered as a finer mist and in a slower manner compared to other spray devices. The longer spray duration is intended to facilitate or reduce patient coordination between actuation and inhalation required for MDIs [102, 185].

Currently, only one product belonging to this class is available on the market: Respimat® Soft Mist™ Inhaler (Boehringer Ingelheim, Ingelheim am Rhein, Germany) [102], developed with the

	Inhalation device	Class	Active pharmaceutical ingredient	Indications
Nebulizer	PARI LC® PLUS	Air-jet nebulizer	Tobramycin solution for inhalation (TSI)	<i>Pseudomonas aeruginosa</i> infection in cystic fibrosis patients
	Pari eFlow®	Active vibrating meshes nebulizer	Tobramycin	<i>Pseudomonas aeruginosa</i> infection in cystic fibrosis patients
SMI	SPIRIVA®	Respimat® Soft Mist™ inhaler	Tiotropium	Treatment of chronic obstructive pulmonary disease
MDI	Alvesco® HFA	HFA Metred Dose Inhaler	Ciclesonide	Management of asthma
DPI	TOBI Podhaler	Dry Powder Inhaler	Tobramycin inhalation powder (TIP)	<i>Pseudomonas aeruginosa</i> infection in cystic fibrosis patients

characteristics of an ideal inhaler that works independently of the patient's inhalation effort [184].

For spraying a precise dose of the drug solution into fine inhalable particles, the Respimat® inhaler uses an extremely fine nozzle system, the Uniblock, without the use of propellant. The resulting aerosol is characterized by a high Fine Particle Fraction FPF and a favorable lung deposition profile compared to DPIs and MDIs (lung deposition of the drug substance is maximized while its

oropharyngeal deposition is minimized). Due to its greater drug delivery efficiency, the Respimat® inhaler allows the administration of lower doses while providing better symptom control and a high therapeutic ratio [184, 186]. Clinical equivalence between Respimat® and HandiHaler® has been demonstrated in the administration of tiotropium for the treatment of chronic obstructive pulmonary disease. However, comparative studies have shown that patients preferred Respimat® because of its ease of use [184]. The first units of the Respimat® "disposable" inhaler were working with a single cartridge, from which the aerosol was generated. Once the specified number of doses reached the inhaler locked and could no longer be used. Consequently, it has been updated to optimize the number of doses available and make it reusable up to six cartridges. This update aims to improve the usability and environmental impact of the Respimat® inhaler, while maintaining its pharmaceutical performance [186].

Table 2. Examples of marketed inhalation devices

6. Inhaled antibiotics:

Aerosolized antibiotics are increasingly used for the management of *Pseudomonas aeruginosa* lung infections associated with cystic fibrosis (CF) that are generally associated with a rapid loss of lung function and a significant decrease in survival [187-189]. Repeated administration of inhaled antibiotics to these patients has been increasingly practiced over the past two decades, [190] circumventing the problems of poor penetration of the antibiotics into the parenchymal lung tissue and bronchial secretions as well as their systemic toxicity due to prolonged exposure encountered with intravenous administration [191]. In addition, inhaled antibiotics have improved the lung function and decreased the rate of hospitalization (Table 1) [192].

Until 2011, the only antibiotics approved for pulmonary administration were tobramycin [Tobramycin Inhalation Solution (**TIS** ; **TOBI**®, 300 mg/5 mL)], sodium colistimethate [Colistine for nebulization (**Colimycine** ®, 1 MUI/ 3 mL)], and more recently, aztreonam [Aztreonam Inhalation Solution (**AZLI** ; **Cayston**®, 75 mg)] [193]. In 2018, formulation of amikacin for inhalation [Amikacin Liposome Inhalation Suspension (**ALIS** ; **Arikayce**®, 70mg/mL)] was approved by the United States Food and Drug Administration (FDA)[194].

In this context, tobramycin was marketed as a solution called TOBI® (300 mg / 5 mL) administrated using a reusable jet nebulizer PARI LC PLUS™ combined with an appropriate

compressor ensuring a flow rate of 4 to 6 L/min, and also under the name Bramitob® (300 mg/4 mL) in combination with the reusable jet nebulizer PARI LC PLUS™ and the PARI TURBO BOY™ compressor [191]. Thus, a dose of 300 mg of tobramycin administered twice daily intermittently (28 days of treatment / 28 days of rest) significantly improves lung function and reduces the density of *P. aeruginosa* in sputum [191, 195, 196]. It is also noteworthy that several studies reported a potent reduction of the airway inflammation as well as a total eradication of *P. aeruginosa* for up to three months after ending the treatment [196-198].

Colistin is another typical example of drugs that have benefited from the advantages of an inhaled administration. Thus, in 1985, a preliminary study showed that local administration of inhaled colistin was clinically effective for the treatment of cystic fibrosis patients [199] and another found that colistin inhalation reduces the deterioration of lung function as well as the inflammatory response that typically occurs after the completion of intravenous anti-pseudomonal therapy course [200].

However, the commercially available antibiotics in solutions for nebulization have several drawbacks, since their administration requires a compressor and a nebulizer and takes about 20 min per dose without considering the time required for cleaning and disinfecting the equipment. These disadvantages can be a significant treatment burden and lead to poor adherence to treatment, especially for cystic fibrosis patients who often receive multiple chronic therapies [192, 201, 202]. On the other hand, the favorable characteristics of dry powder inhalers (DPIs) (reduced administration time, elimination of the need for the administration equipment cleaning and drug refrigeration and improvement of portability) have attracted the attention of researchers to DPIs as an alternative to nebulizers in order to solve the problems of antibiotics delivery by inhalation. However, most DPIs deliver only small amounts in the microgram range. Therefore, the approach tends to overcome this problem by designing a dry powder antibiotic formulation that could deliver therapeutic pulmonary doses while maintaining desirable aerosol characteristics [192, 193]. Thus, in 2007 [192] a formulation of tobramycin in the form of hollow, porous particles creating an easily dispersible powder and usable with a simple dry powder inhaler (DPI) was reported constituting an important advance in aerosol drug delivery. The administration of a single dose of tobramycin of 4 capsules of 28 mg (112 mg) in a powder form (TIP) demonstrated a superior and faster efficacy than the 300 mg dose of tobramycin solution used for nebulization (TSI). The delivery of tobramycin powder to the lungs was almost three times more effective than tobramycin inhalable

solution and well tolerated by most of the treated patients [192]. This latter protocol was the subject of two phase 3 studies demonstrating its safety to provide a clinical benefit by improving the lung function and decreasing the microbial load of *P. aeruginosa* in sputum with a more convenient delivery system for patient quality of life and clinical outcomes [192, 193, 203]. Unfortunately, such a treatment with tobramycin has revealed several drawbacks including the potential safety risks associated with long-term treatment with aminoglycosides, the possibility of developing resistance to tobramycin by *P. aeruginosa*, and the problem of antagonism between tobramycin and the constituents of sputum [204-207]. This antagonism has been attributed to several factors, such as the acidity and high ionic strength of sputum as well as the inhibition of tobramycin activity by its potential binding to sputum components (such as mucin glycoproteins and DNA) [207]. Additionally, concerning the cystic fibrosis patients, the glycoprotein content in the sputum is greatly increased, up to 2.5 times higher than the overall average [208]. Thus, in this latter case the dose of antibiotic required to maximize deposition and absorption in the lungs should be increased. Therefore, the development of new inhaled antibiotics capable of resisting sputum inhibition or aerosolization degradation seems justified. These antibiotics will be more effective in the management of endo-bronchial infections in patients with cystic fibrosis (i.e. providing effective bacterial inhibition at a lower dose delivered to the respiratory tract) [207]. In this context, the formulation of aztreonam in the form of its lysine salt was developed for pulmonary administration. In contrast to the antagonism phenomenon observed with tobramycin, aztreonam lysinate has not shown a decrease in activity in the presence of the sputum components of cystic fibrosis patients [207]. The study of the pharmacokinetics and tolerability of aztreonam lysinate at increasing doses (75, 150 and 225 mg) showed immediately after a single dose for the three levels used a concentration of aztreonam in sputum higher than its MIC known against *P. aeruginosa* (32mg/ml)[207]. In addition, systemic exposure was low, plasma concentrations of aztreonam have been shown to be much lower than those observed with intravenous administration and those associated with systemic toxicity [207]. Based on these results, additional studies have been performed to evaluate the safety, the tolerability and the efficacy of inhaled aztreonam according to different patient criteria and dosing regimens [209-211]. It is noteworthy that short-term use of inhaled aztreonam does not decrease the susceptibility of *P. aeruginosa* to aztreonam and is not associated with the appearance of new pathogens in lungs [209]. Furthermore, inhaled aztreonam has been demonstrated to be an effective adjunctive treatment for chronic *P. aeruginosa* respiratory

tract infections in patients with cystic fibrosis who have already been treated intensively with inhaled tobramycin [210]. Moreover, for patients with moderate to severe pulmonary exacerbation who have not received an antipseudomonal antibiotic or azithromycin, a 28-day treatment with inhaled aztreonam significantly improves respiratory symptoms [211].

On the other hand, the biofilm-like mode of growth considerably slows down the penetration of aminoglycosides and represents a major challenge for antibiotic delivery [212], due to the electrostatic interaction of aminoglycosides with mucus and biofilm matrix and their low activity against bacteria with slow growth phenotype [213]. In such a situation, the approach envisioned consisted in the direct administration of antibiotics to the lungs via inhalation but the very small size of the inhaled particles lead to their rapid elimination in the lungs [214, 215], limiting the time the antibiotic remains at a concentration above its Minimum Inhibitory Concentration (MIC) in the local vicinity of the bacteria. Thus, this short residence time in the lungs requires repeated administration of at least twice a day [212]. In 2008, an effective delivery ensuring enough quantities of the antibiotic in and around the targeted infection sites over a prolonged period that could significantly improve aminoglycoside treatment of cystic fibrosis lung infections was realized by using inhaled liposomes [212]. In this context, intratracheal delivery of an inhaled liposome formulation of tobramycin significantly increased drug retention time in the lungs and improved the expected antibacterial activity [216-218].

The study of the mechanism of action of an amikacin-based nanoscale liposome designed specifically for pulmonary nebulization demonstrated an easy penetration into the biofilms and infected mucus with slow and continuous release of liposomal amikacin into the lungs of rats, considerably more effective than those obtained with inhaled free amikacin and could represent an interesting alternative for the treatment of chronic lung infections [212].

In September 2018, Amikacin Liposome Inhalation Suspension (ALIS; ARIKAYCE®) was approved by the FDA as the first drug usable for the management of the nontuberculous mycobacterial (NTM) lung disease caused by *Mycobacterium avium* complex (MAC) [219].

It is noteworthy that Non-Tuberculous Mycobacteria Lung Disease (NTM-LD) are particularly difficult to treat since it requires the use of large amounts of antibiotics in the lungs while maintaining low systemic concentrations to avoid toxicity [220]. Thus, the formulation of amikacin as a suspension of inhalable liposomes was demonstrated to facilitate the penetration of amikacin into the mucus of Non-Tuberculous Mycobacteria (NTM), enhances its uptake into macrophages,

both in vitro and in vivo, and allow its retention in the respiratory tract and lung tissue. [219]. Additionally, once inhaled, ALIS disperses in the lungs and passes through mucus to reach infected areas. Administration of ALIS in healthy animals resulted in a good distribution of amikacin in the lungs (presence of amikacin in all lobes of both lungs) [221]. Although mucus represents an additional obstacle to the distribution of inhaled particles, the administration of amikacin in the form of liposomes facilitates its diffusion through 500–1000 mm thick human mucus in only 30 min [222]. However, many respiratory adverse events have been reported during the first month of treatment mainly affecting both upper airway (dysphonia, cough, oropharyngeal pain) and lower airway (dyspnea, wheezing, bronchospasm) [223, 224].

A recent study reported that these adverse events can be managed using a variety of over-the-counter techniques and approaches that allow patients to continue using this treatment. Taking the example of dysphonia (the most reported adverse event), which was significantly resolved by ingesting soothing fluids, gargling with warm water or glycerin, and rinsing the mouth after nebulization [219]. It should be noticed that patient education before and during treatment with ALIS is essential to maximize the potential for successful therapy. Thus, well-informed patients are more aware of treatment-related adverse events and symptom management strategies without the need for provider intervention or discontinuation of treatment, which significantly improves both tolerance and compliance [219].

7. Conclusion

The administration of antibiotic treatments in their inhaled form via the pulmonary route has demonstrated its effectiveness in the management of pulmonary infectious diseases. Although, inhaled forms are considered as complex dosage form and difficult to develop due to the necessity to a strict control of aerosol particle size distribution as well as their aerodynamic behavior and their surface properties to ensure optimal deposition at the target infection site. This route of administration has been shown to maximize the pulmonary concentration of antibiotics while minimizing side effects due to low systemic exposure. In addition, most studies have confirmed the acceptable safety profile of inhaled antibiotics. Unlike systemic administration of antibiotics, which is the main driver of bacterial resistance to antimicrobials, local pulmonary administration of antibiotics is not associated with increased resistance or systemic toxicity.

Thus, through this review of different novel techniques that are being made available for the treatment of infectious respiratory diseases via inhalation, we can firmly conclude that the development of such drug delivery techniques will constitute the future for infectious diseases treatment and will significantly improve the quality of life of the patients.

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List of abbreviations

CF = Cystic fibrosis

TB = Tuberculosis

non-CFB= non-Cystic Fibrosis Bronchiectasis

CFTR = Transmembrane Conductance Regulator gene

pH = potential for Hydrogen

DNA = Deoxyribonucleic acid

RNA = Ribonucleic acid

Dae = Aerodynamic Diameter

MMAD = Median Mass Aerodynamic Diameter

FPF = Fine Particle Fraction

COPD = Chronic Obstructive Pulmonary Disease

PAH = Primary Pulmonary Arterial Hypertension
MCC = Mucociliary clearance
AM = Alveolar Macrophage
MDI = Metered Dose Inhaler
DPI = Dry Powder Inhaler
SMI = Soft Mist Inhaler
SAW = surface acoustic wave
CFC = Chlorofluorocarbon
HFA = Hydrofluoroalkanes
NaCl = Sodium chloride
HCl = Hydrochloric acid
NaOH = Sodium hydroxide
EDTA = Ethylenediaminetetraacetic acid
DPPC = Dipalmitoylphosphatidylcholine
ED = Emitted Dose
HPMC = Hydroxypropyl Methylcellulose
FDA = Food and Drug Administration
US = United States
PVP = Polyvinylpyrrolidone
PLGA = Polylactic-Co-Glycolic Acid
TIP = Tobramycin Inhalation Powder
TSI = Tobramycin Solution for Inhalation
DNA = Deoxyribonucleic Acid
MIC = Minimum Inhibitory Concentration

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SEND REPRINTS TO:

Jean-Michel Brunel, PhD

¹ Aix Marseille Univ, INSERM, SSA, MCT, 13385 Marseille, France. E-mail : bruneljm@yahoo.fr.
Phone : (+33) 689271645

Drug [Ref]	Form	Resolved problems	Advantages	Limitations
Tobramycin [191]	Solution for nebulization: – TOBI® (300 mg/5mL) – Bramitob® (300 mg/4mL)	– Poor penetration of antibiotics into parenchymal lung tissue and bronchial secretions – Systemic toxicity of antibiotics administered by IV due to prolonged exposure	– Lung levels higher than those obtained by enteral or parenteral administration – Improvement of the lung function decrease in the rate of hospitalization – Reduction of <i>P. aeruginosa</i> density in sputum	
Colistin [200]	Solutions for nebulization – Colimycine® (1 MUI/ 3 mL)	– The development of resistance to tobramycin by <i>P.aeruginosa</i> – Low diffusibility of colistin by systemic administration	– Inhalable colistin does not induce resistance of <i>P. aeruginosa</i> or secondary infection with other colistin-resistant microorganisms – Local administration of inhaled colistin reduces the deterioration of lung function and the inflammatory response	– The administration requires a compressor and a nebulizer – Nebulization takes about 20 min per dose – Long time to clean and disinfect the equipment
Aztreonam [207]	Solution for nebulization – Cayston® (75 mg)	– The potential safety risks associated with long-term treatment with aminoglycosides – The problem of antagonism between tobramycin and the constituents of sputum	– Aztreonam lysinate has not shown a decrease in activity in the presence of the sputum components of patients with cystic fibrosis – Aztreonam plasma are much lower than those observed with intravenous administration – The short-term use of inhaled aztreonam does not decrease the susceptibility of <i>P. aeruginosa</i> to aztreonam and is not associated with the appearance of new pathogens in lungs	
Tobramycin [192]	Powder for inhalation	– Antibiotics solutions for nebulization drawbacks which lead to poor adherence to treatment	– Administration of a single dose of tobramycin 112 mg in powder form (TIP) demonstrated superior and faster efficacy than a 300 mg dose of tobramycin solution for nebulization (TSI) – It took less than 1/3 of the time to administer	– Most DPIs deliver only small amounts in the microgram range (µg).
Amikacin [212, 219]	Liposomes formulation for nebulization – Arikayce® (70 mg/mL)	– The biofilm-like mode of growth considerably slows down the penetration of aminoglycosides. – The very small size of the inhaled particles results in their rapid elimination in the lungs. – Drug not approved for the management of NTM Lung Disease	– The direct administration of antibiotics to the lungs via inhalation in the form of inhaled liposomes deliver antibiotics in a sustained manner – Easy penetration into biofilms and infected mucus – Slow and continuous release of liposomal amikacin into the lungs – More effective than inhaled free amikacin – Significantly increases drug retention in the lungs and thus improve antibacterial activity	– Many respiratory adverse events affecting both the upper airway (dysphonia, cough, oropharyngeal pain) and the lower airway (dyspnea, wheezing, bronchospasm).

Table 3. Advantages and limitations of different marketed potent aerosolized antibiotics

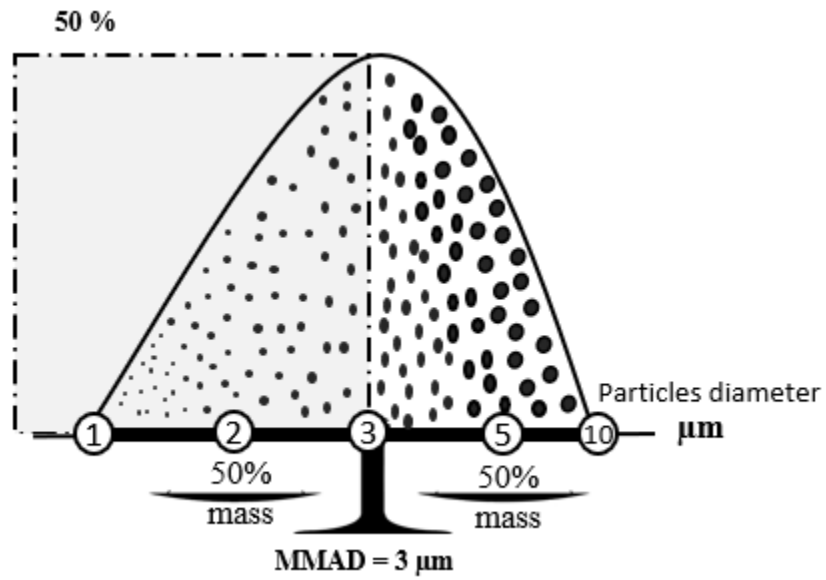


Figure 1. Aerosol mass distribution curve

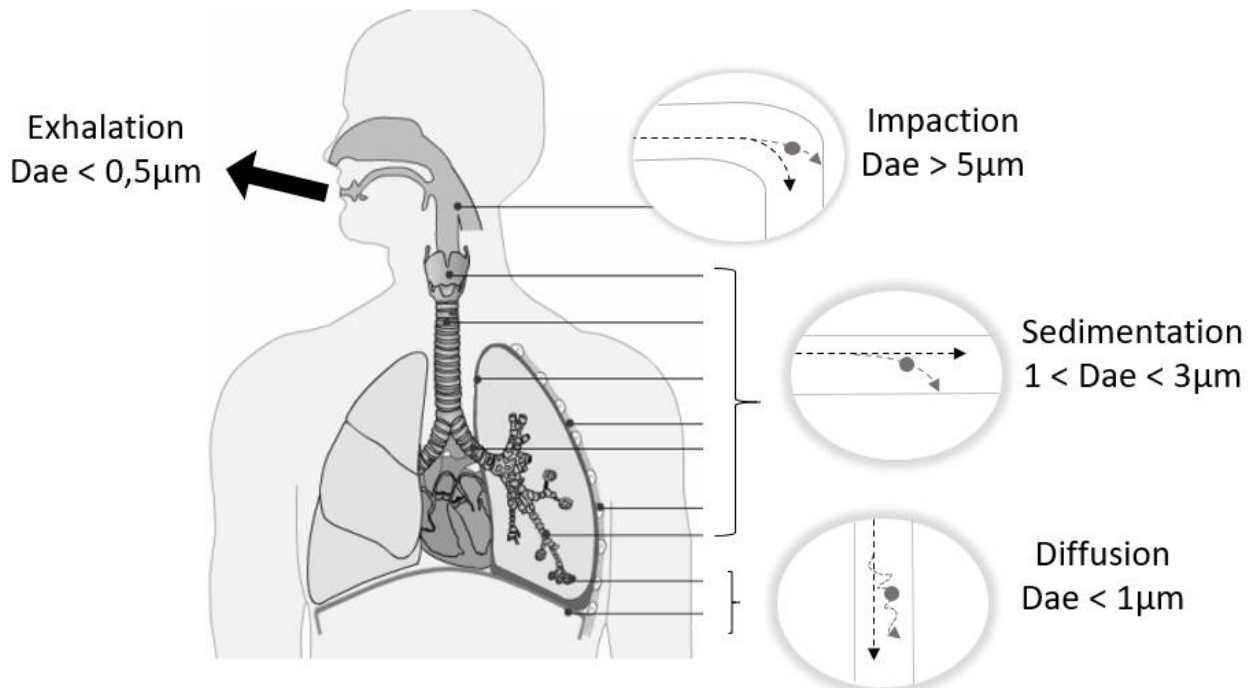


Figure 2. Schematic diagram of the main modes of aerosol particles deposition in the respiratory tract.

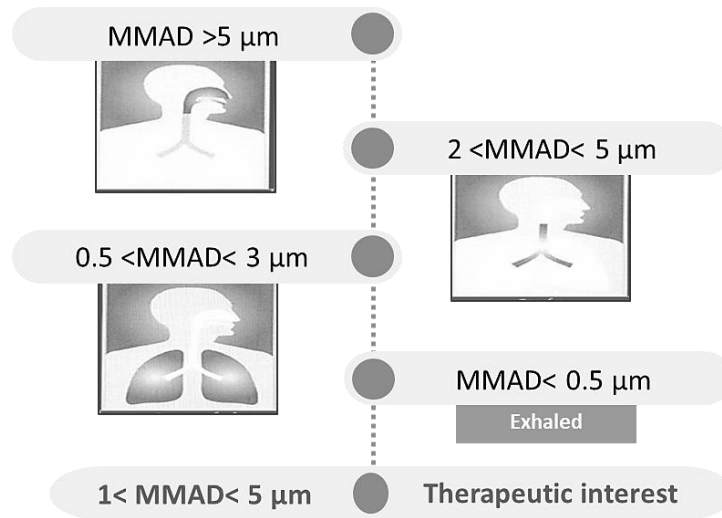


Figure 3. Particles deposition in the respiratory tract according to their size

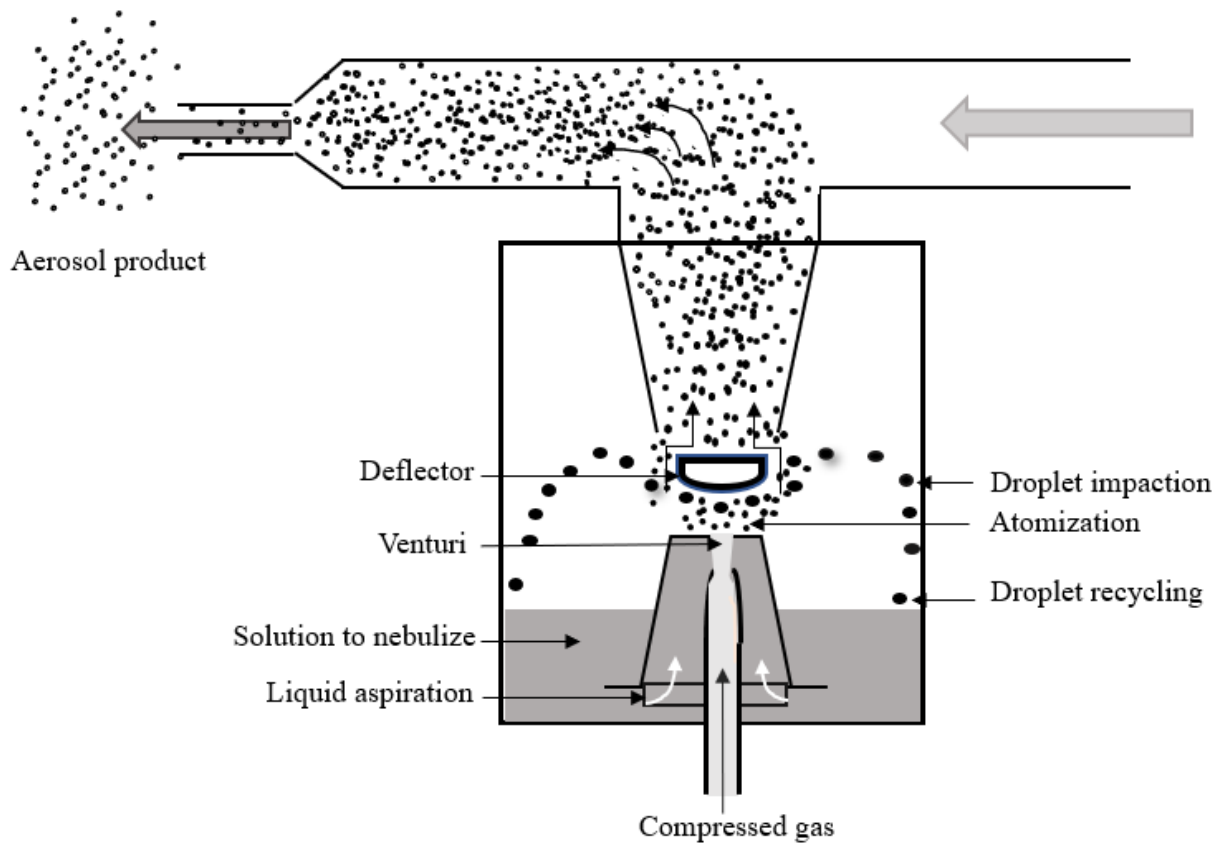


Figure 4. Schematic diagram of an air jet nebulizer

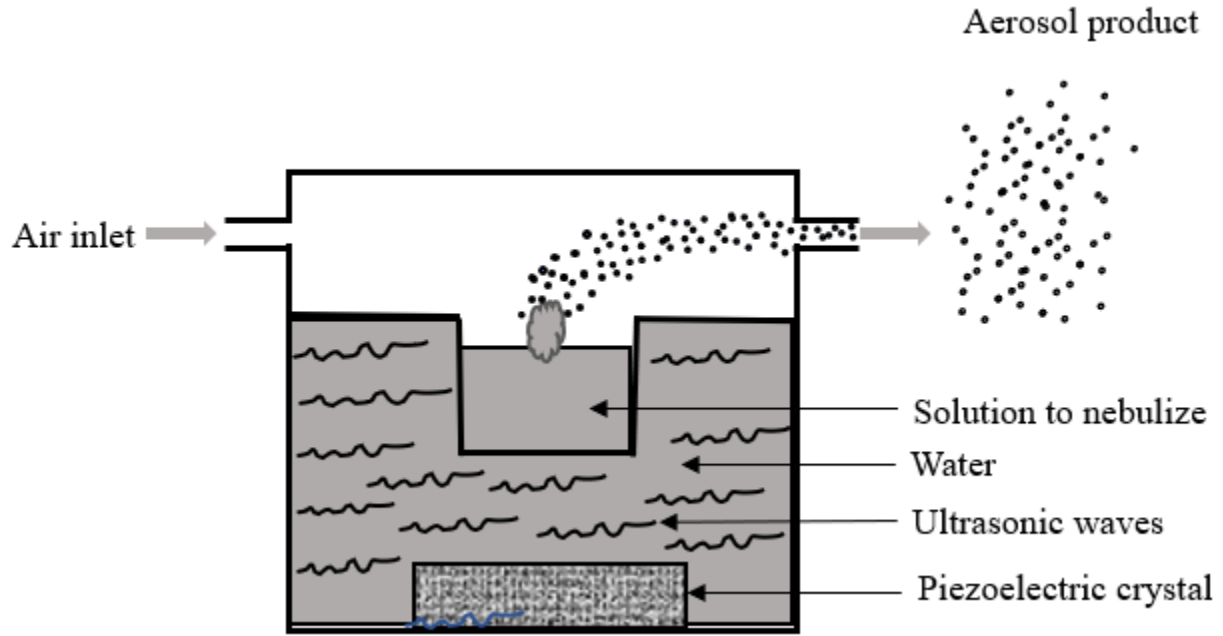


Figure 5. Schematic diagram of an ultrasonic nebulizers

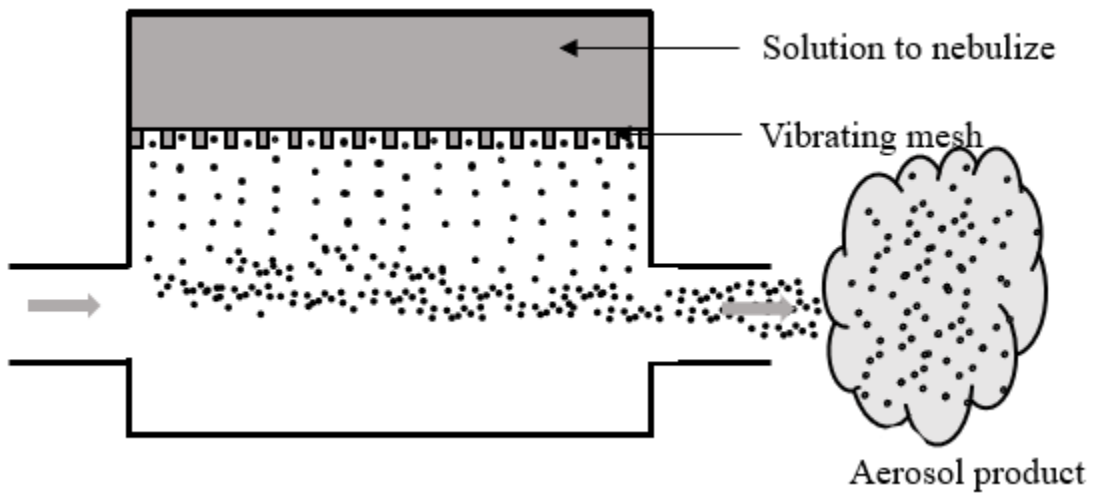


Figure 6. Diagrammatic representation of a vibrating mesh nebulizer

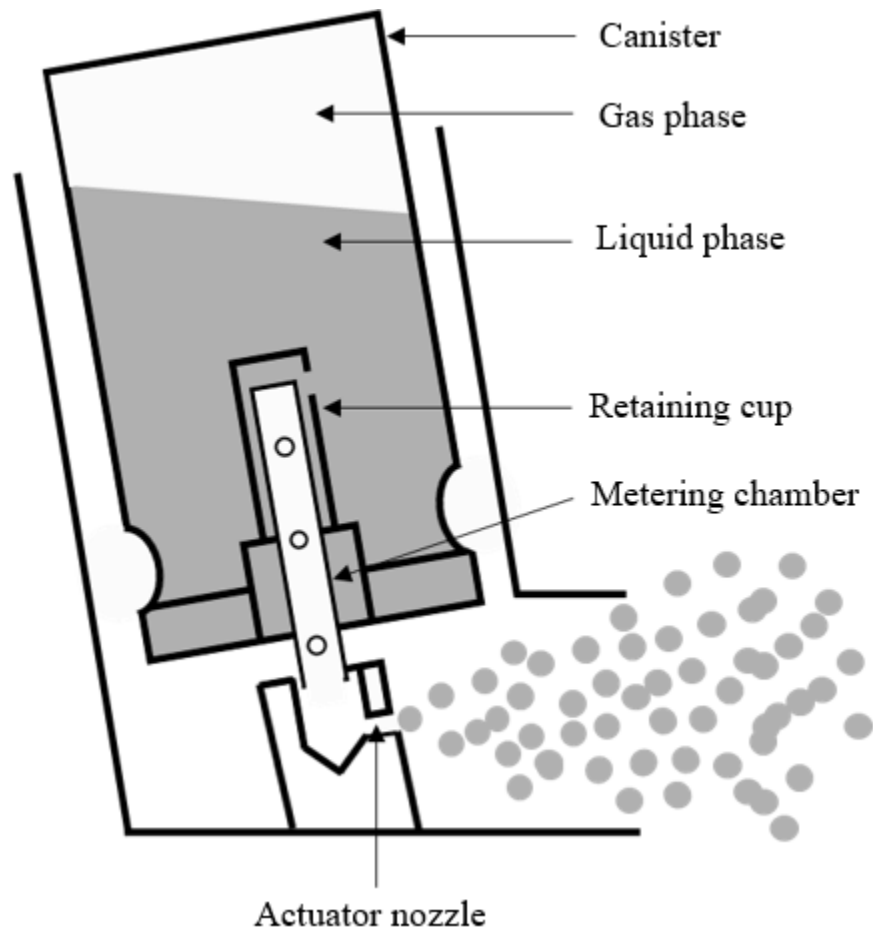


Figure 7. Schematic diagram of pressurized Metered-Dose Inhalers MDI

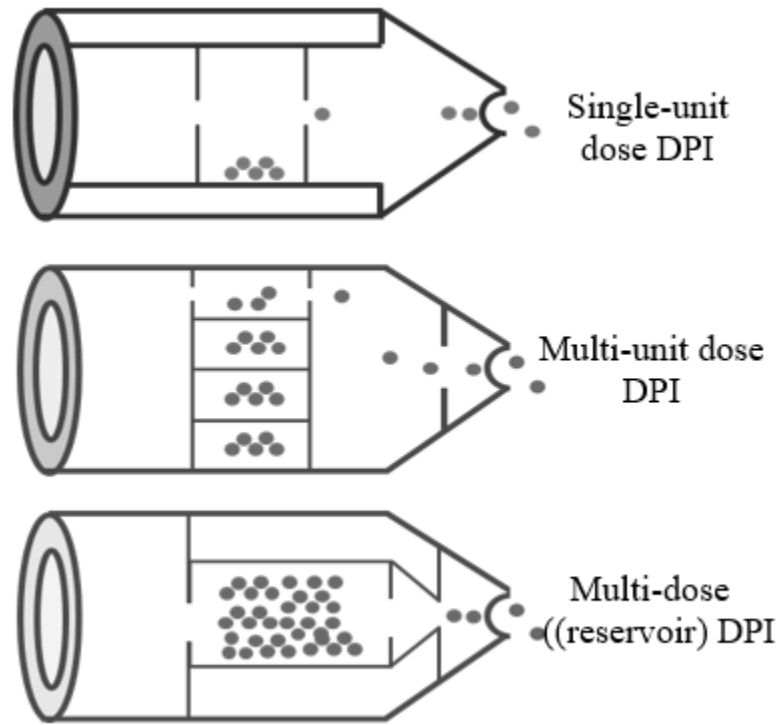


Figure 8. Diagrammatic representation of dry powder inhaler types