Chapter 9
Oral Inhalers

Elena Haettig and Marc Schneider

Abstract This chapter focuses on the pulmonary application of drugs, which is of great importance for the local treatment of lung-related diseases like asthma and COPD but has also been put more into the focus for systemic treatment of a multitude of diseases lately. An important aspect for inhalation is the geometry and anatomy of the respiratory tract. The system of airways, best imagined as branches, is the root of the aerodynamic properties that are used to apply drugs through inhalation and explain the various ways particles are deposited in the lungs. In order to maximize the drug delivery efficiency, the properties of the aerosol need to be optimized in order to profit off this innate aerodynamic setup. Systems to qualify aerosols related to their aerodynamic properties have been implemented but come with their downfalls, especially when it comes to transferring the results onto the human respiratory system. This needs to be taken into account when developing new inhalation devices. As the number of inhalation devices grows, it is important to understand the basic mechanism and the advantages of each system in order to optimize treatment for patients.

Keywords Aerodynamic properties · Shape factor · Aerosol generation · Pulmonal deposition · Airway geometry · Particle engineering

9.1 Introduction

Inhalation therapy dates back at least 4000 years to India where powdered Durata plants were smoked through a pipe to take advantage of their bronchodilating contents [4]. Since then, a lot of advances have been made with 1956 being described as the beginning of the modern era of inhalation therapy due to the introduction of

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S. A. Khan (ed.), *Essentials of Industrial Pharmacy*, AAPS Advances in the Pharmaceutical Sciences Series 46, https://doi.org/10.1007/978-3-030-84977-1_9

the first metered dose inhaler [78]. Right now, inhalation therapy mainly focuses on local therapy for diseases concerning the lungs like asthma, COPD, or infections, and small molecules as well as macromolecules like proteins (Pulmozyme®) are used. But there is a lot of effort done in current research to use pulmonary application as a less invasive alternative to parenteral application in medication that acts systemically. So far, for systemic effect, inhalable formulations containing insulin (Afrezza® and Excurba®), loxapine as an antipsychotic (Adasuve®), or cannabis and its natural or synthetic constituents have been approved.

There are a lot of advantages of inhalation therapy in comparison to oral or parenteral application mostly due to the higher local drug concentration and reduced systemic absorption through the lung which leads to lower systemic side effects. This is of great importance for locally acting drugs like corticoids or adrenergic drugs. Since there is a fraction of the inhaled drug that will be swallowed and make its way through the intestines, using drugs with low oral bioavailability will further decrease systemic side effects. There is also lower drug metabolism [11, 16] compared to other administration routes. This is especially interesting for macromolecules like peptides and proteins which show a rapid degradation in the intestinal tract due to the high number of peptidases and proteinases. In contrast to orally administered drugs, it also bypasses the liver and with that its first pass effect. The enzymatic makeup in the lungs seems to be similar compared to that of the liver, though lower in number [10], which in return can be used as catalyzers for the activation of prodrugs [17]. Its large surface area makes it an interesting target for systemic applications. A big problem for inhalation therapy for local and systemic administration of drugs is physical barriers like clearance through mucus and macrophages or successful penetration of the surfactant and the strong dependence on patients' inhalation maneuvers.

9.2 Respiratory Tract

9.2.1 Macrostructure

The respiratory tract as a generational model was first described by Weibel and is now accepted by most scientists and can be imagined in the form of a tree starting at the trachea which forms the main airway and generation 0. In each generation the airways divide into two smaller airways. This runs from the trachea (generation 0) to the bronchi (gen. 1) and all the way to the bronchioles with the alveoli attached [87]. The alveoli are air sacs or cuplike structures where the gas exchange happens. In order for this to take place, the distance between the wall of the alveolus and the capillary, the blood-air barrier, has to be extremely close. It is because of the large number of alveoli that the surface area of the lungs is so extensive, which increases the amount of gas that can diffuse between the capillaries and the lung. It is similar to the effect of the villi in the intestines. The alveoli start to form at the 17th

generation, and with every generation more and more alveoli emerge. The total number of alveoli differs from source to source, and a lot of textbooks claim a number of 200–300 million [30, 40], while newer calculations put the number at around 500 million, depending on the method used to count the alveoli [68]. The generational model, and with that the airways, is completed at generation 23 with the last alveoli.

The characteristics of each of the generations also have an impact on how we administer pharmaceuticals via inhalation. Velocity of the air is an important aspect to consider in understanding how the particles are carried through the airways influencing deposition. The velocity increases through the first four generations due to decreasing overall diameter in accordance with Bernoulli's principle. Bernoulli's principle suggests that velocity of a fluid in a tube is inversely proportional to its diameter. This is also valid for air as flowing gases are also considered fluids. The maximum velocity is reached in the third generation [30], where the area of the total cross section is the lowest [87]. Afterward the cross-sectional area increases with each generation and in return the air velocity decreases. In the alveolar duct and sacs, the air is nearly not moving anymore [27], changing the dominant deposition mechanism for particles.

The airways can be sectioned into a conducting and a respiratory region. The conducting region is made up of generation 0–16 and is not participating in the gas exchange. The main function of this region is connecting the external environment to the respiratory zone. While doing so, it also conditions the air to optimize gas exchange by increasing the humidity and temperature of the incoming air [45]. Due to the higher velocity and its bifurcations, it also filters bigger particles and ejects them with the help of mucus that is mostly found in this region of the lung. The respiratory region begins with the first appearance of alveoli. It consists of respiratory bronchioles, alveolar ducts, and alveoli. This is the region where the gas exchange happens.

The exact area of the lung surface is subject to big discussion. The estimates vary widely depending on the method used for calculation. Weibel, known for his description of the lung branches as generations, estimated the lung surface to be 130 m^2 with the help of stereological histology and electron microscopy [88], while other estimates say that 1 m^2/kg of lung surface seems to be found in most mammals [52], which matches the estimates of other working groups. Another problem to consider is that the surface area of the lungs changes throughout the phases of ventilation. During inhalation the surface area increases while it decreases during exhalation. But either way, the surface area that can work as an absorption area is probably in a similar order of magnitude or even larger than that of the intestines, which has been recently estimated to be around 35 m^2 [41], explaining the interest of research in using the lungs as a possible target area for systemic drug delivery. Summarizing this, the overall area of the lung varies depending on the publication from 70 to 140 m^2. In contrast, the conducting airways only sum up to an area of ~2 m^2 [36].

9.2.2 Microstructure

The main purpose of the epithelium is to separate the external from the internal environment of our body. This important task protects the systemic bloodstream from substances that are toxic to our organs. This is possible due to the tight junctions found in between epithelial cells. But next to protecting the body from toxic substances, the main function of the lung epithelium is to remove carbon dioxide from the bloodstream and saturating it with oxygen which is then carried everywhere in the body and makes the function of all organs possible.

The epithelium in the airways consists of a variety of different types of cells. The composition of epithelium is characteristic for the specific region in the respiratory tract. Ciliated cells are found in the conducting region that move mucus upward through coordinated movement of their cilia, which can be imagined as hairlike structures on the luminal surface of the cells [90]. Other cells in the epithelium of the conducting region include club and goblet cells. Goblet cells secret the mucus [74] and therefore provide an important defense mechanism of the lungs.

The two cell types compromising the epithelium of alveoli are alveolar type I cells that make up around 97% of cells in the alveolar epithelium [39] and alveolar type II cells. Type I cells are found on the luminal surface of the alveoli and are responsible for the gas exchange between the respiratory tract and the bloodstream. The diffusion of O_2 and CO_2 is possible due to a partial pressure gradient across the tissue. O_2 goes from 100 mmHg in the alveoli to 40 mmHg in the pulmonary capillaries, while CO_2 goes from 40 mmHg to 45 mmHg the other way round [30]. To provide little resistance to the diffusion of oxygen and carbon dioxide, the type I cells are extremely thin (~100 nm) facilitating and guaranteeing the main function of the lung: to supply the body with oxygen.

Alveolar type II cells secret surfactant. Surfactant is a lipoprotein complex made up of different phospholipids, neutral lipids, and proteins [21] that reduce the surface tension on the alveoli walls which lowers the work of breathing and prevents the collapse of alveoli at the end of expiration. Surfactant also serves as an additional barrier to the systemic circulation and is therefore an additional obstacle when administering drugs that are supposed to act systemically. Surfactant may lead to aggregation of proteins [17] and peptides which would hinder the systemic uptake and make them more prone to endocytosis by macrophages. Alveolar type II cells are also responsible for the regeneration of the epithelium by serving as progenitor cells and differentiating into type I cells if those have been damaged [6, 26].

Smooth muscle cells line part of the airways from trachea to the terminal bronchioles [1] and are separated from the epithelium by a connective tissue called the lamina propria. Their task in healthy individuals is not fully understood yet, but they are thought to be responsible for the bronchoconstriction in chronic obstructive diseases like asthma and COPD [2, 49]. And they are usually targeted by bronchodilating agents given in inhalation therapy.

As mentioned above, mucus is secreted from the goblet cells and mainly consists of mucins and proteoglycans [55]. It is tasked with the hydration of the epithelium

to make sure it does not dry out. On top of that it also humidifies the air to close to 100% humidity [45] until it reaches the alveoli. Mucus also serves as a defense mechanism in two ways. It contains lysozyme and other defense proteins and peptides as an active way to protect the body from infections [47, 77]. Passively, the mucociliary clearance is responsible to remove foreign materials which are trapped in mucus and transported toward the trachea through the coordinated movements of cilia of ciliated cells and get either swallowed or ejected. Mucus also plays a part in different diseases, most noteworthy being cystic fibrosis wherein the composition of mucus is pathologically viscous leading to infections and an inability of the lungs to function properly [32].

Next to mucociliary clearance there are other defense mechanisms within the respiratory tract. One being the macrophages in the alveoli. There is no mucociliary clearance in the alveoli because mucus would hinder the gas exchange, so alveolar macrophages are the primary way of defense for the body. As in every other part of the body, they phagocytose pathogens and deposited particles, release antimicrobial substances, and control inflammation processes through the release of cytokines. Thus they also play a role in diseases like asthma and COPD and may play a minor part in the remodeling processes seen as sequelae of these diseases [46, 83].

9.3 Mechanism of Particle Deposition

Generally, the inhaled particles are carried by the inhaled stream of air through the airways. Due to different forces acting upon the particles and especially the inert mass, their direction can differ from the air path. To get an understanding of how particles behave, the forces present in the respiratory system need to be considered.

The first force is the drag force; it acts opposite to the relative motion of the particle [27]. As with every other fluid, the Stokes law also applies to the stream of inhaled air, which leads to the following definition of the drag force F_D:

$$F_D = 3\pi\eta d * \left(\overrightarrow{v_p} - \overrightarrow{v_f}\right)$$

(η, viscosity of air; d, particle diameter; $\overrightarrow{v_p}$, velocity of particles; $\overrightarrow{v_f}$, velocity of fluid/air)

The Stokes law only applies if the relative velocity of the air on the particle surface is zero. This is not the case if the observed particles are smaller than 10 μm [18]. In that case the drag force is divided by the Cunningham slip correction factor (C_s) which leads to the following equation: F_D/C_s

The other two forces acting upon a particle are the gravitational force F_G which is determined by the particle's mass

$$F_G = m_p * g$$

and a stochastic force F_t [81], which represents the collisions leading to the Brownian motion. These are collisions of the surrounding fluid with the observed particle. The collisions and therefore the Brownian motion are temperature dependent and correlate positively, meaning it increases with increasing temperature.

The sum of these three forces is the motion of a particle in the airstream that travels through the lung and is brought together in the Langevin equation [13]:

$$m_p * \frac{dv_p}{dt} = -F_D + F_G + F_t$$

Depending on the part of the respiratory tract and the size of the particles, the importance of the respective forces shifts, and this leads to different ways the particles are deposited.

The main deposition mechanisms for inhalation therapy are impaction, sedimentation, and diffusion.

9.3.1 Impaction

Based on Newton's laws of motion, an object is going to stay in its current movement unless a force from outside is going to act on it. This is called inertia and means that the particles are going to stay on their existing trajectories rather than following the airstream. If the deviation from the airstream gets too strong, the particles will collide with the airway wall [22] get deposited. This way of deposition is called *impaction* [27]. This is described by the first term, the drag force, of the Langevin equation. This often occurs at or near bifurcations due to the fast changes in the air streamline direction and mostly happens in the first few generations as a result of the higher velocity and the higher possibility of turbulences compared to the following generations [69, 81]. Impaction is dependent on a particle's Stokes number (Stk). The Stk suggests that two particles with different properties might still have the same airborne behavior:

$$Stk = \frac{\rho d^2 v}{18 \eta L}.$$

(ρ, particle density; d, particle diameter; *v*, speed of the air; η, viscosity of air; L, characteristics of passage, e.g., diameter)

Rather than looking at the actual diameter, the Stk number indicates that a combination of size and density is more conclusive about the airborne motion of a particle than size or mass. This relationship can be expressed by the aerodynamic diameter ($d_{æ}$), which is derived from the Stk number [33]:

$$d_{\text{ae}} = \left(\frac{\rho}{\rho_{Ref}} \right)^{0,5} * d.$$

(ρ, particle density; ρ_{ref}, density of a reference material (commonly 1000 kg/m^3); d, particle diameter)

If the Stk number is small, the particles are expected to follow the airstream more closely because the necessary force to overcome the inertia is smaller. The larger the aerodynamic diameter, the more likely it is for particles to get deposited by impaction. This mostly concerns particles with an aerodynamic diameter larger than 5 μm.

9.3.2 Sedimentation

Sedimentation is the most effective deposition mechanism for inhaled pharmaceuticals in the respiratory region [81]. Since most particles larger than 5 μm have been deposited by impaction in the upper parts of the airways, this mode of deposition mostly concerns particles in the range of 1–8 μm [27]. The range of particle sizes differs throughout publications, which illustrates that the exact deposition mechanism is influenced by a variety of circumstances regarding the patient (size, gender, anatomy, the breathing patterns), and the properties of the particles (size distribution, shape, surface structure, and more) and size ranges will only give estimates of the most likely way a particle is deposited. Further toward the end of the respiratory tract, drag force still comes into play, but the gravitational force gains importance due to the decreasing air velocity in the smaller airways. With lower velocities, the momentum and Stk number decrease and with that does the chance of impaction. Rather, the particles deposit from nearly not moving air due to gravitational forces. Since gravitational deposition is a time-dependent process, its importance also decreases with higher breathing rates. It is obvious from this consideration that the breathing maneuver, the strength of inhalation, breath holding, and strength of exhalation will impact on the deposition.

9.3.3 Diffusion

As mentioned above, Brownian motion is described as the motion of particles or molecules due to collisions with surrounding particles and molecules. Next to the temperature dependency, an aspect to consider is the mobility of the particles within the surrounding. This mobility is determined by the viscosity and the radii of the particles. This was described by multiple scientists [31, 80, 84] independently from each other and is now known as the Einstein relation. This leads to a diffusion coefficient representing this phenomenon:

$$D = \frac{C_S * k_B * T}{6\pi * \eta * r}$$

(D, diffusion coefficient; k_B = Boltzmann's constant; T, temperature; η, dynamic viscosity of the fluid; r, radius of the particle; $C_{s,}$ Cunningham slip factor) [81]

As seen already for the drag force, the Cunningham slip factor has to be added into the equation. *Diffusion* in the context of particle deposition means that particles move through Brownian motion in the air and make random contact with the airway wall. It is a purely statistical deposition mechanism. Diffusion is important for very small particles of 1 μm and smaller. For particles this small, the gravitational force can be neglected [81]. It only happens in the alveoli when the air practically does not move, because only then the motion initiated by the collisions between the particles is not superimposed by convective motion. As with sedimentation the number of particles deposited increases with decreasing breathing rates [44] because the air is stationary for a longer period, providing the particles with more time to come in contact with the alveolar walls.

On top of that there are other mechanisms like interception which concerns particles with an elongated shape like asbestos fibers; in that case the particles do not leave the airstream, but due to their size they still get close enough to interact with the airway wall and get deposited. Furthermore, electrostatic interactions that only concern particles with a surface charge can also play a role. And these mechanisms can become important points to consider dependent on the properties of the administered particles.

9.4 Particle Engineering

When engineering particles for inhalation therapy, there are different factors to contemplate when it comes to particle properties.

Size is the largest factor to a successful delivery to the lungs. As discussed in the previous chapter, size often determines which part of the respiratory tract is reached by a particle. But it has to be recognized that different drugs that act locally might not have the same ideal deposition area in the respiratory tract. Rather, the ideal deposition area is dictated by the drug target. If targeting specific areas that have a higher density of the specific receptors would be pursued, it could lead to a far more efficient pharmaceutical therapy. Unfortunately, even for historically long targeted receptors like b-adrenoreceptors, there has not been much research into the regional distribution within the lungs [17]. Generally, 1–5 μm is regarded as best for delivery in the lungs. Here the aerodynamic diameter is always in focus and not the geometric size of the particles as described above. With decreasing size of particles, there is higher surface energy and that comes with an increased risk of agglomeration changing pulmonary deposition.

When talking about stability of size, another factor to consider is hygroscopicity of the microparticle material. In DPI there typically is a prolonged storage in powder form which could lead to an uptake of water and in return to higher agglomeration. On top of that, the humidity increases within the respiratory system which may increase the size and change the density of the particles [44, 81] leading to different flight properties and as a result to a less ideal deposition mechanism and area. While the storage stability mostly concerns DPI, the growth of particles during their travel through the respiratory system is of importance for pMDI as well.

But the aerodynamic diameter is not only comprised of size, as shown above density is also a factor. A great example from nature is pollen. These rather large particles are actually able to travel quite deep into the lungs. This is explained by their low density [18, 27]. A particle with twice the diameter but ¼ of density has the same aerodynamic size and would behave the same way in a fluid, in this case air, according to Stokes. Due to the larger size and increased surface area, the tendency of the particles to agglomerate will decrease [27], solving a recurring problem of particle engineering for inhalation therapy.

While talking about particles for inhalation therapy, the focus is usually on spherical particles. There are lots of advantages that can explain that circumstance; spheres do not have a lot of contact area which reduces the tendency to aggregate and yield good flow properties. They are also rather easy to produce in industry-scale quantities through milling or spray drying. But there are other shapes that have properties of interest for pulmonary application. Elongated, fiber-like particles align according to their shape with the airflow. Thus, the relevant parameter for the aerodynamic behavior is the diameter rather than the length of the particles. Furthermore, fiber-like particles have shape factors >1 reducing the aerodynamic diameter in comparison to spheric particles. In consequence, they often travel deeper into the lung. A good example of that behavior are asbestos fibers. The toxic mechanism behind asbestos is attributed to their shape in combination with their bio-resistance and the consequent retention time of those fibers in the lung. There is research done to use these properties in order to optimize the release profiles in pulmonary application [61].

9.5 Analysis of Aerodynamic Particle Properties

As discussed before, the aerodynamic diameter is an important factor in predicting how a particle is going to be deposited in the airway. In order to assess the aerodynamic particle size distribution (APSD), a multitude of apparatuses and techniques have been developed and tested. The US and EU Pharmacopeias primarily focus on an impact-based measurement by a so-called cascade impactor [58].

A cascade impactor (illustrated in Fig. 9.1) can be imagined as a tower of multiple stages build upon each other representing generations, though it has less than 24 stages. The inhalation device is fixed onto a tube at the top. At the bottom a vacuum pump draws the air in a consistent velocity through the different stages.

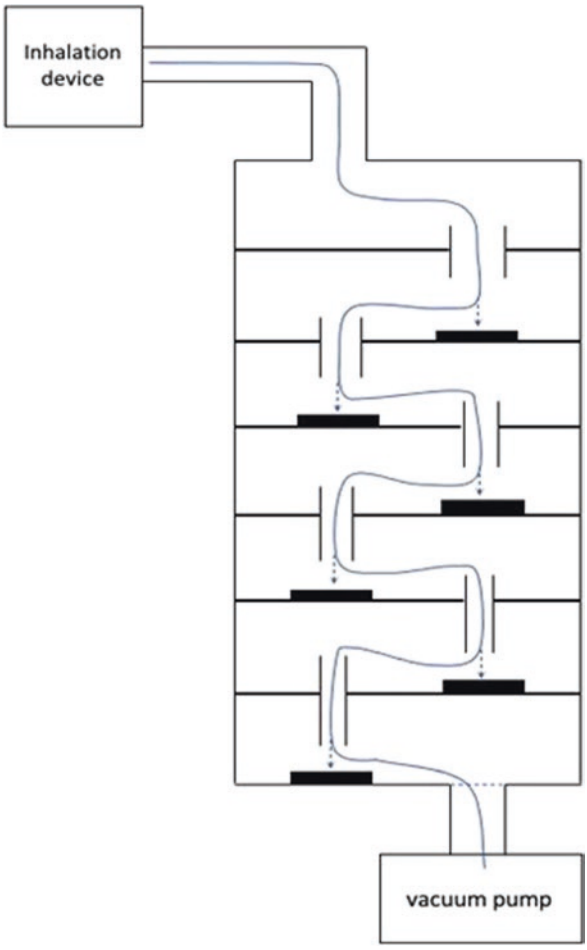

Fig. 9.1 Sketch of the principal setup of a cascade impactor. The blue line indicates the airstream initiated by the vacuum pump on the bottom of the system. The air flows through the connecting tubes from plate to plate with increasing velocity

Each stage is connected to the following with a straight tube that gets narrower by each stage. This increases the velocity of the air traveling through the tubes. The placement of this tube changes on each stage. Underneath the exit of each tube is an impaction plate for the particles that are not able to follow the airstream, thus impacting on the plate. As the air carrying the particles streams through the different stages with increasing velocity due to the decreasing diameter of the tubes, it gets harder for the particles to follow the air path. This holds true especially for larger masses. Additionally, a pre-separator can be mounted before the first stage in order to remove big particles [73], like lactose carrier particles so the results in the following stages are not distorted. Each stage has a specific cutoff which is defined by the diameter of spherical particles with a specific density (commonly 1 kg/L) that will deposit with a 50% probability. This is also depicted in Fig. 9.2.

From the deposition pattern on the different stages, the resulting mass distribution is connected to the size of the particles by the mass median aerodynamic

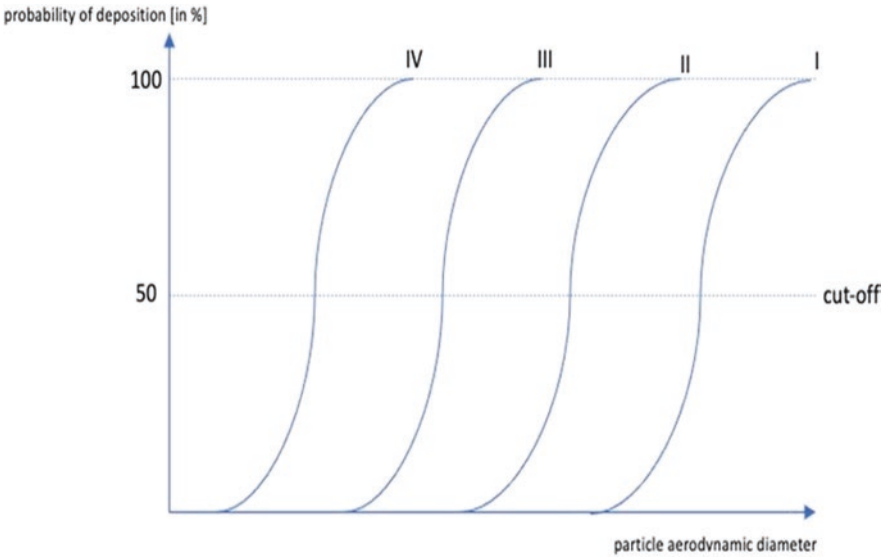

Fig. 9.2 Deposition probability of particles with a certain aerodynamic diameter in cascade stage I–IV

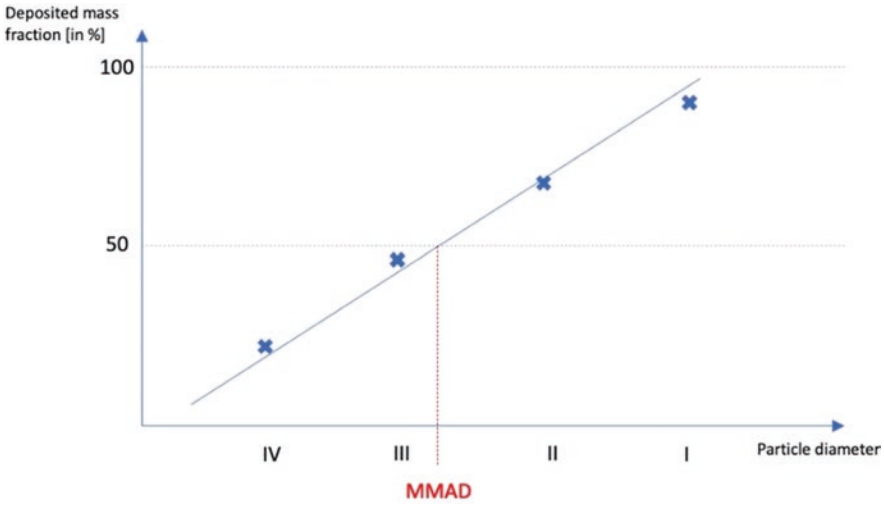

Fig. 9.3 Graphic evaluation of MMAD with the cutoff of stages I–IV of a cascade impactor

diameter (MMAD) splitting the deposited particles in two parts of equal weight. A graphical evaluation is illustrated in Fig. 9.3.

The next-generation impactor [56] (NGI) generally works the same way. But rather than having air travel vertically downward, it travels in a zigzag motion up and down horizontally facilitating handling such as sample collection and cleaning.

The impact plates might be small pools of liquid rather than solid plates. This is mostly used to determine the concentration of drug that gets deposited in each stage. The ability to further analyze the concentration of active pharmaceutical ingredients is a major advantage that cascade impactors/impingers have over other techniques [59].

Generally, particles for inhalation are not monodisperse, so rather than getting one aerodynamic diameter, the particles are going to be distributed over several stages leading to an aerodynamic particle size distribution. As mentioned already, this size distribution can be described by a common parameter, the mass median aerodynamic diameter. The MMAD is the aerodynamic diameter at which 50% of the mass is made up of particles with a lower aerodynamic diameter.

The tested inhalation device determines which impactor is to be used, how many stages, and whether a pre-separator is required by the pharmacopeias.

Though appreciated for its simplicity as a quality control apparatus, its simplicity might also be the downfall for cascade impactors as a research tool to determine the aerodynamic behavior of inhalation formulations in the clinical context. The main points of critique are the vast difference of structure to the anatomy of human airways, especially interindividual variety and the consistent airflow which is not represented in the inhalation process of humans. This holds especially true for the glottis/throat which shows huge variety and also is vastly changing during childhood. Therefore, the Alberta Idealized Throat was established trying to address this part [76].

Other techniques to measure APSD that are not mentioned or favored by pharmacopeias are measurement through the time-of-flight method or laser diffraction. The latter is especially suitable for aqueous preparations as is the case in nebulization [58].

9.6 Devices

The market of pulmonary drug devices is steadily growing, from $19.6B in 2010 [7] to $38.1B in 2017 [8]. This makes it an interesting field for pharmaceutical companies to invest into further research and bring forth new innovations. There are different devices to inhale pharmaceuticals. Each designed for different purposes and different target patients.

9.6.1 Pressurized Metered Dose Inhalers

The pressurized metered dose inhaler (pMDI) was first developed in 1956 (Medihaler®; Riker Laboratories, Inc) [37] and changed the world of aerosol inhalation. It still has a big role in inhalation therapy though innovations are now mostly found in other areas.

9.6.1.1 Device Structure

pMDI consists of a canister that is, in most cases, made out of aluminum [65] and often coated internally to reduce interactions between formulation and the canister wall [19], a metering valve, and an actuator. For protection and better handling, it is usually placed in a plastic case.

The metering valve is the most important part of the pMDI. It is responsible to keep the doses of the released aerosol consistent. To ensure this, a metering chamber with a specific volume is part of the metering valve. This chamber stores the next dose until needed. Once the patient activates the release, the metering valve opens toward the exterior and releases the dose and afterward refills the chamber again to be ready for the next dose. This is possible because once the dose is released and the valve stem closes the path to the outside again, a pressure gradient forms in which there is close to atmospheric pressure within the metering chamber and significantly higher pressure in the canister [19]. Therefore, the formulation is drawn into the metering chamber and stays there until the next release is activated.

Before the propellants were changed from chlorofluorocarbons (CFCs) to hydrofluorocarbons (HFCs) (reasons below), patients were able to check how empty their pMDI was by putting it in a bowl of water. If it was floating on the surface, it was empty. This floating test or counting the already administered doses and subtracting it from the total available doses were the only ways to determine remaining doses. After the introduction of HFCs, the float test was not possible anymore which led to complaints by MDI users and ultimately resulted in the introduction of dose counters [50]. These dose counters might show a specific number or indicate a color pattern whether a new inhaler should be acquired.

As with every other instance of drug packaging, all components of the device have to be inert to the formulation and be able to withstand the high pressure.

9.6.1.2 Formulation

The pMDI formulation consists of a propellant, an active drug, and excipients like co-solvents and surfactants [19]. The propellants are vapors with a boiling point below room temperature. Due to the pressure inside of the canister, there is an equilibrium of the vapor and its liquid phase. Consequently, a consistent pressure in the canister is ensured, which in return guarantees a consistent aerosol generation and a consistent repeated released dose (first dose is equal to last dose ejected). If the gas could not be liquified by increasing pressure but one would simply compress the gas, an aerosol would still be formed at activation, but with each dose that is administered, the pressure in the canister would decrease [62]. And due to the dose optimally aerosolized being dependent on the pressure currently present in the canister, the deposited doses would decrease over time. In the case of an equilibrium of vapor and liquid phase being present, once a dose is administered, part of the liquid phase evaporates and the pressure is automatically adjusted to the previous pressure (Fig. 9.4).

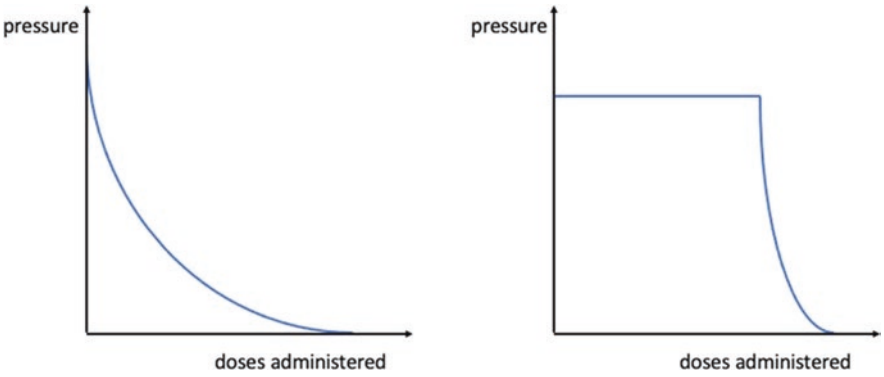

Fig. 9.4 Pressure in canister filled with compressed gas (left) and liquified compressed gas (right)

The active ingredient is dissolved or suspended in the propellant. When the release is activated, the high pressure created by pushing the fluid through the nozzle leads to the formation of small droplets. Due to the low boiling point of the propellant, the propellant evaporates once it leaves the canister which reduces the size of the droplet.

The main propellants in inhalers used to be chlorofluorocarbons (CFCs), but due to their ozone-depleting nature, their use has been banned in the Montreal Protocol of 1989. That brought forth the use of hydrofluorocarbons (HFC), also called hydrofluoroalkanes (HFA). Today HFC-134a (1,1,1,2-tetrafluoroethane) and HFC-227 (1,1,1,2,3,3,3-heptafluoropropane) are the most commonly used propellants for pMDIs. In comparison to CFCs, HFCs do not contain chlorine and do not add to the depletion of ozone in the atmosphere. But they are still very potent greenhouse gases. This causes the future of HFCs in inhalation therapy to be questionable.

A big disadvantage of HFCs compared to CFCs is that a lot of drugs are not soluble in the propellant, so co-solvents are necessary making the formulation more complex [19]. With both CFCs and HFCs, a so-called Freon effect (named after the trade name of several halocarbons) is observed, in which the patient stops inhaling once the propellant reaches the mouth and airway because of a cold sensation on the mucosa [9].

9.6.1.3 Actuation

Pressurized metered dose inhalers can be divided into coordination and breath-actuated devices. For the coordination devices the patient is required to breathe in at the exact time as they activate the release of the aerosol to ensure a sufficient number of particles reach the lungs. A lot of patients, especially those of very young and old age, have difficulties coordinating the actuation, possibly leading to insufficient drug application. The breath-actuated devices like the Autohaler® were developed to solve these difficulties [9, 67]. These devices get activated once the patient breathes

in and a vacuum is formed at the mouthpiece, a click sound signaling the release of a dose.

9.6.1.4 Spacers

In a lot of cases, the use of a spacer is recommended to overcome or at least reduce those problems with pMDIs. A spacer is a wide tube that is mounted onto the MDI device. A lot of spacer devices also offer the option to add a mask on the mouthpiece of the spacer. If a spacer is used, the particles are inhaled from standing air rather than a fast stream of air. That means that there is no coordination required; the dose is ejected into the spacer and can be inhaled through multiple breaths. In addition, large particles are already deposited in the spacer which reduces the undesired deposition in oropharyngeal region [28, 29] and consequently possible side effects in the upper airways. Because of this, the use of a spacer is always indicated when glucocorticoids are administered. Once a problem with spacers that has since been addressed by newer devices was electrostatic precipitation on the spacer walls [5], but due to modern devices made with materials without electrostatic potential, this problem could be reduced [12, 79]. For young children and in some cases also adults and elderly patients, a face mask increases the inhalation efficiency if they are unable to produce a tight seal around the mouthpiece [43, 60].

9.6.2 Dry Powder Inhalers

Dry powder inhalers (DPI) originally gained traction as an alternative for the pMDIs after CFCs were banned in 1989 [23]. Previous DPIs were unattractive due to poor drug delivery efficiency [25]. Only when alternatives were desperately needed, advances in design would make DPIs a viable option next to MDIs and nebulizers. Besides circumventing the use of CFCs or HFCs, an additional advantage of DPIs is that there is no coordination from the patient needed between actuation and inhalation. All inhalers are breath-actuated, decreasing the chance of improper inhalation due to coordination difficulties.

The success of DPIs is based on three aspects: the design of the device, the formulation, and the patient's inhalation effort [35].

9.6.2.1 Design of DPI Devices

In comparison to pMDIs, there is a vast variety of different devices with different dosing mechanisms with new ones being patented and marketed constantly. The general categorization is into single-dose and multidose devices. Single-dose devices are fed capsules filled with one dose each. In order to release the powder, the capsules get perforated, usually by piercing the capsule through pressing buttons

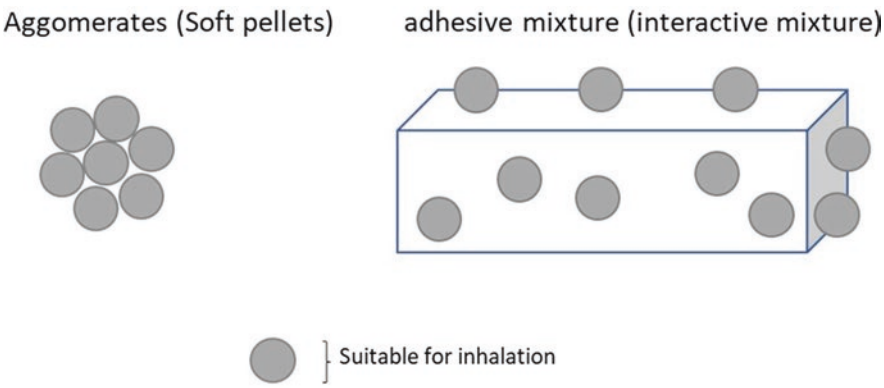

Fig. 9.5 Sketch of a soft pellet from particles suited for inhalation (left) and of an adhesive mixture having the micronized drug adsorbed on a carrier system (often lactose crystals)

on the outside of the device that are connected to small needles on the inside. Multidose inhalers, on the other hand, have a reservoir of multiple doses already present in the inhaler, either as a blister (e.g., in Diskus®, GSK) or a powder reservoir (e.g., in the Turbuhaler®, AstraZeneca). In inhalers with a powder reservoir, the continued flowability of the powder has to be guaranteed, especially with respect to humidity.

The particles in the powder are either present as agglomerates or adhesive mixtures. Both systems are designed to release the individual particles until they reach the airways (Fig. 9.5)

Therefore, the biggest problem to be addressed when designing an inhaler is the sufficient dispersion of particles by the airstream. Inhalers are designed to increase the dispersion force in different ways depending on the individual model. There are different strategies like a circulation chamber that makes sure that only smaller particles can leave the nozzle as seen in the NEXThaler® or a narrow spiral-shaped channel like the Turbuhaler® has [19, 89], in which the bigger particles get deposited on the inner wall of the channel due to impaction and many more. In single-dose inhalers, the dispersion of the particles is facilitated by the movement of the pierced capsule during inhalation.

The design of each device reflects on the airflow resistance and varies widely between the different devices [48]. Responsible for this is the need for local pressure drop or high air velocities that ensure that the full dose is carried by the air and sufficient deagglomeration has taken place [35]. De Boer [24] was able to show that a higher airflow resistance did not actually relate to higher work of breathing as one would expect. Which airflow resistance is most comfortable for patients is disputed [3, 14, 24].

Regardless of dispersion technology, a big influence on the drug delivery efficiency with DPIs that cannot be influenced by the design is the inhalation effort by the patient. This is a big disadvantage of DPIs over MDIs (though it is important to note that a minimum inspiratory flow rate is required during pMDI use as well,

estimated at 20 L/min [38]). The dependency on a patient's ability to inhale becomes a problem once their breathing is temporarily or permanently obstructed, so either in an acute asthma attack or patients with severe asthma/COPD. Contrary to what one would expect, devices with higher airflow resistance require lower inspiratory flow rates to reach ideal drug release [15]. The reason for this lies in the mechanism of powder deagglomeration. Higher-resistance devices rely on the airflow resistance within the device to deagglomerate the drug powder. In low-resistance devices, the lack of resistance-induced turbulences leads to the inhalation airflow rate being the main cause of redispersion. Subsequently, a higher inspiratory flow rate is needed for devices with lower intrinsic resistance [20]. Pulmicort Turbuhaler® being the exception due to having a high resistance and a high inspiratory flow rate [54]. The lowest required flow rate which often depends on the patient's lung condition and which can be of great importance for the success of inhalation therapy, varies greatly in between devices. There is no data bank filled with the exact flow rate for each device, but Haidl et al. put together a list with already available data of previous publications. Often the values differ between publications. The results are shown in Fig. 9.6 [38]. If possible, the flow rate necessary to be achieved by the patient for a specific device was distinguished into insufficient, acceptable but room for improvement and optimum flow rate.

The variety of devices does not only present in their physical mechanism to redisperse agglomerates or their air flow resistance, but it also leads to very different modes of operation. This poses a problem if devices are switched and can lead to mishandling unless an adequate training for the patient has taken place [70].

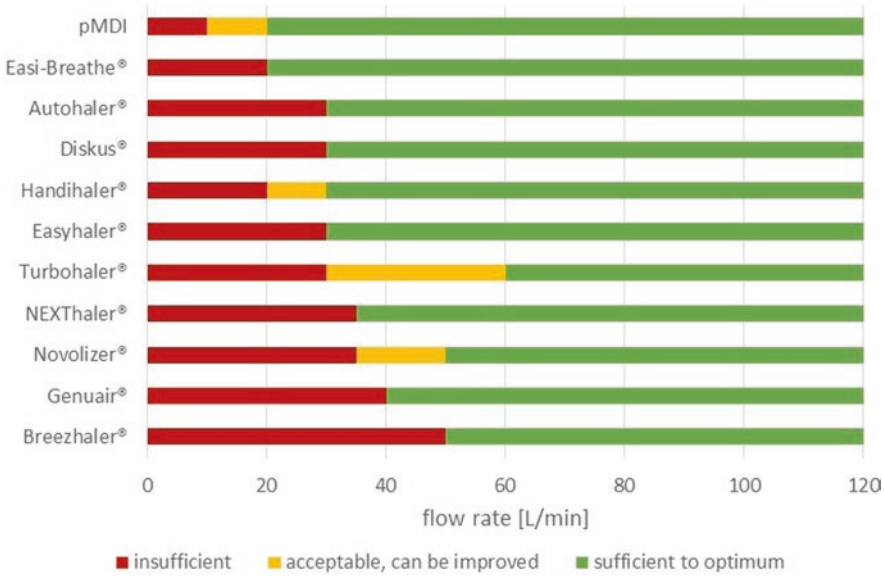

Fig. 9.6 Lowest required inspiratory flow rate with different devices to achieve insufficient, acceptable, or sufficient drug delivery to the lungs. (Adapted from Haidl et al. [38] (permission obtained))

9.6.2.2 Formulation

In order for the drug to reach the desired lung region, the drug particles should be in the range of 1–3 μm. This can be achieved by micronizing larger particles or growing them to the desired size by spray drying, for example. Due to their small size, inhalation drug particles tend to agglomerate due to their high surface energy. As a result, deagglomeration is an important process to consider, and designing the device, as investigated above, accordingly has a big influence on its success. The other option of ensuring small particle size even after longer storage is mixing coarse carrier particles with the small drug particles which are prone to aggregation (so-called interactive mixture). In most cases, α-lactose is used as the carrier particles to which the smaller particles adhere to, mostly due to Van der Waals forces. During the inhalation process, the coarse particles separate and the small drug particles are released without any further chance to aggregate. The lactose, depositing in the oropharynx, can irritate the throat leading to coughing. At the same time, the sweet taste often indicates to the patient that the dose has been released. With the absence of the Freon effect, this is reassuring to many patients.

If a biodegradable polymer were to be used as carriers of drug particles, controlled release in the airways could be possible.

A way to bypass the problem of aggregation is the "storage" of the particles as a monolithic tablet. Before use, a dose will be created by scraping off a controlled amount of drug. This system was first introduced by the MAGhaler®, also known as Jethaler® [25]. Due to the short time between the preparation of the particles and the application, aggregation is less prevalent, but breathing into the inhaler still needs to be avoided as for all other DPIs.

9.6.3 Soft Mist Inhaler (SMI)

The newest innovation in inhalation therapy is the soft mist inhaler (sometimes also called liquid spray inhalers). It is a propellant-free, multidose reusable inhaler. First developed by Boehringer Ingelheim and marketed under the name "Respimat", the heart of the SMI is the uniblock nozzle that produces two fine jets of drug solution angled toward each other. This causes droplets under controlled conditions. As a result of the lower velocity of the aerosol and the longer dispensing time, inhalation is not as dependent on simultaneous actuation and inhalation as is the case with the pMDI. But the amount of drug released from the SMI is also consistent and not determined by the lung capacity as it is for DPIs [86]. It is powered by a spring that is wound up mechanically by the patient before use.

The disadvantage of the SMI is the small range of possible fluids that can be used due to the proneness of the nozzle to get blocked. This limits the possible fluids to low viscous drug solutions but not dispersions.

Next to Respimat®, two other systems, the AERx system and Medspray nozzle, are in clinical trials. Both are based on the principle of Rayleigh breakup for the generation of droplets [51].

9.6.4 Nebulizers

As with SMIs, nebulizers form small droplets of the drug solution or suspension in order to reach the deeper lung areas, but in contrast to SMI, a nebulizer dose is usually administered in multiple breaths. The big advantage of nebulizers compared to other inhalation devices is that even high doses of drugs can be aerosolized [69] and can also be used for off-label use of other drug solutions.

There are different types of nebulizers that are characterized by their mechanism to form these small droplets.

9.6.4.1 Jet Nebulizers

The first and oldest one is the jet nebulizer which uses a compressor in order to compress gas or air that streams through a narrow pipe (Fig. 9.7). At the orifice of the pipe, as a result of the high velocity and the sudden change of gas pressure leading to high shear stress, the gas breaks up the fluid brought there by a feeding tube into a polydisperse mix of aerosolized droplets. Due to the high velocity, the bigger droplets collide with a baffle that is placed some distance from the orifice and fall back down in the drug solution reservoir [71].

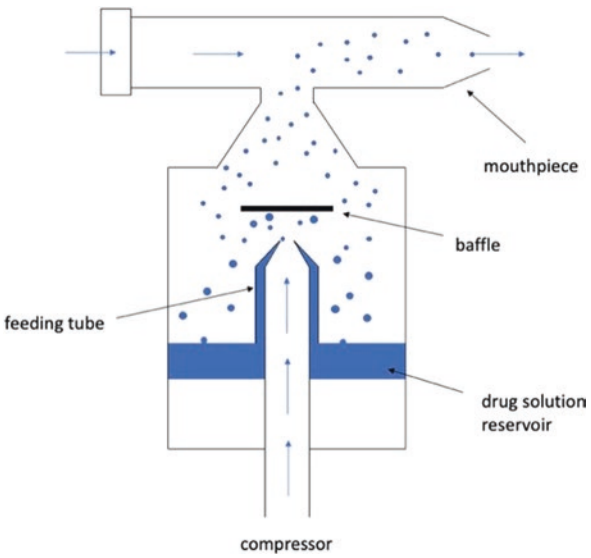

Fig. 9.7 Schematic of a jet nebulizer

This can pose a problem because part of the solvent will evaporate while the droplets are suspended in the air, leading to an increasing concentration of the drug solution [57]. The smaller particles, as discussed before, are more likely to follow the air stream around the baffle and exit the nebulizer through the mouthpiece. Jet nebulizers have a multitude of disadvantages like the need for a compressor, the orifice that is suspectable to wear off due to the pressure of the compressed air or the cleaning procedures [64]. Additionally, the high shear stress caused by the air velocity might lead to degradation of the drug, especially for stress-susceptible drugs like proteins [42] or nucleic acids [53].

9.6.4.2 Ultrasonic Nebulizers

The preferred nebulizers use ultrasonic vibrations caused by a piezoelectric transducer to aerosolize the liquid which removes the need for compressed air/gas. The first of its kind, appropriately called the "ultrasonic nebulizer," uses the vibrations to form droplets on the surface of a drug solution reservoir. The exact mechanism of droplet generation is disputed [71, 91]. This leads to polydisperse droplets as well, the larger ones recover back to the reservoir due to gravity and baffles installed within the device, while the smaller ones get carried by the stream of air through the mouthpiece into the airways of the patient. The piezoelectric transducer is either in direct contact with the liquid containing the drug or is separated from it by a liquid interface. The liquid interface prevents the drug solution from overheating [34].

9.6.4.3 Mesh Nebulizers

The second kind of nebulizer using a piezoelectric transducer is the mesh nebulizer. The drug solution or suspension does not have an open surface but rather is directly covered by a mesh. There are two different setups used in these mesh nebulizers. One being the passive way (Fig. 9.8), in which a thin layer of the drug solution or suspension is placed in between the piezoelectric transducer and a stationary mesh. The vibrations of the transducer are conducted through the fluid containing the drug leading to fluctuating surface levels at the mesh. Every time the fluid presses against

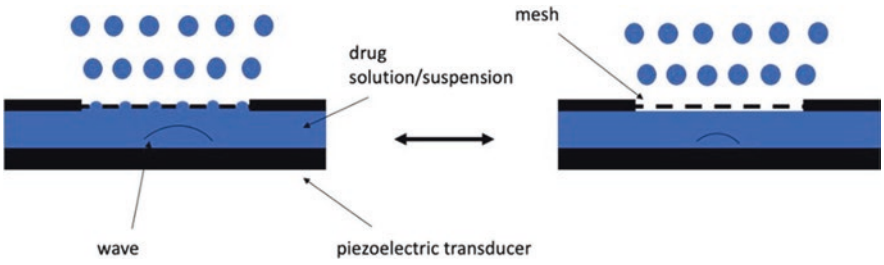

Fig. 9.8 Passive setup; at different phases of oscillation

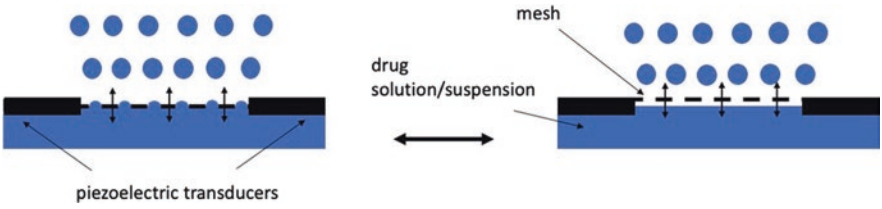

Fig. 9.9 Active setup; at different phases of oscillation

the mesh, small droplets exit through the holes [71]. According to Rayleigh's theory, the droplets released are approximately twice the size of the holes in the mesh [72].

The active setup (Fig. 9.9) has the transducer mounted onto the mesh, which means the vibrations are not carried by the fluid but by the mesh itself. The vibrations lead to a periodically changing height of the mesh relative to the fluid surface and the mesh basically pushing the fluid through its holes releasing the droplets [66].

In both cases, the droplet size is directly connected to the hole sizes of the mesh. If the holes in the mesh are comparable in size, it can be expected that the droplets are as well.

There are several situations where nebulizers present as the best option for inhalation therapy, especially if high drug doses have to be delivered or for very young and old patients since there is no specific inhalation technique required. They are also often used by patients with cystic fibrosis or pulmonary hypertension [71]. But nebulizers have the big disadvantages to not be as portable as their counterparts even after the introduction of portable nebulizers like PARI eFlow® and having a strict cleaning regimen that often puts them in the shadow of the other inhalers.

9.7 Choice of Inhaler

In order to choose the best inhaler for a specific patient, the health and ability of the patient as well as the properties of each inhaler device has to be taken into account. The pros and cons of the different inhalation device systems [9, 75, 82] are described in Table 9.1.

There are a plethora of flow charts and questionnaires developed to simplify the decision of which inhaler is the best choice for a specific patient [63, 82, 85]. While they all differ slightly, most of the times the same factors are examined: availability of drug, age of the patient, state of consciousness, ability to inhale spontaneously, coordination skills, and possible inhalation flow rate. An example of such a flowchart is represented in Fig. 9.10.

Table 9.1 Advantages and limitations of inhalation device systems

Device	Advantages	Limitations
pMDI	Portable	Coordination required
	Multidose	Propellant required
	Short treatment time	Large amount of deposition in oropharyngeal region
	Inexpensive	--Same mode of action in most devices
	Less dependent on inhalation effort of patient	
	Consistent dosing	
DPI	Portable	Dependent on inhalation maneuver
	Short treatment time	May not be possible in emergency
	Breath-actuated	Risk of agglomeration
	Dose indicator	Devices cannot be exchanged without training
	No propellant	Cannot be used by young children
Nebulizers	No specific technique required	Not as portable
	For all ages	Some need outside energy source
	Unconscious patients	Long treatment times
	High doses can be aerosolized	Extensive cleaning regimens
		Expensive
SMI	Portable	Only few drugs available
	Multidose	Not breath-actuated
	Less dependent on inhalation effort of patient	
	Less coordination required	
	Dose indicator	
	No propellant	
	No spacer needed	

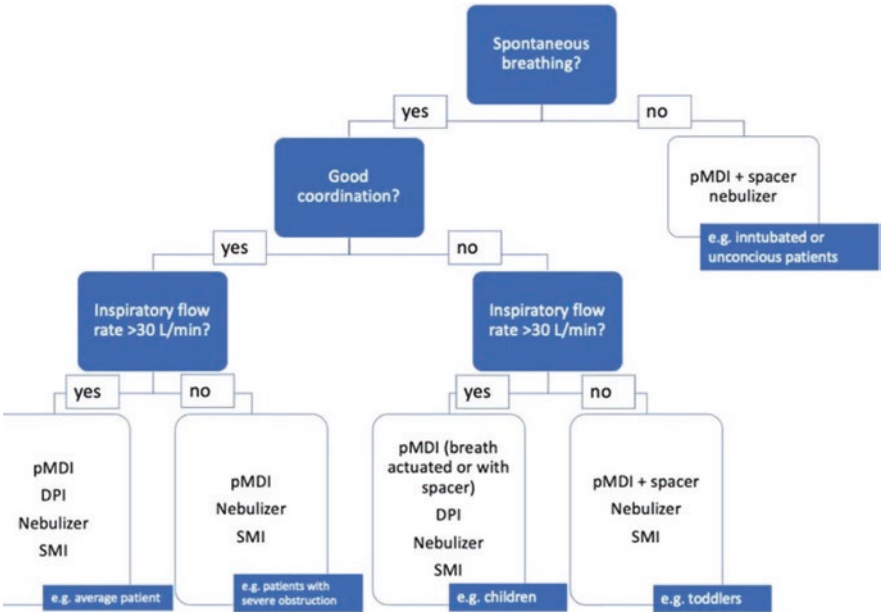

Fig. 9.10 One possible flowchart to determine ideal inhalation device. (Adapted from [85])

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