Pulmonary

6

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Contents

Abstract

The two main determinants for medicine deposition in the respiratory tract are the aerodynamic size distribution of the aerosol and the manoeuvre with which the aerosol is inhaled. They govern the mechanisms that are responsible for particle deposition in the lungs. By varying the inhalation manoeuvre, not only the distribution in the airways for the same aerosol is changed; in many cases also the amount and properties of the delivered fine particle dose are affected. The complex interplay between inhalation manoeuvre, aerosol properties and site of deposition has led to many misconceptions regarding the best inhaler choice for individual patients and the way these inhalers need to be operated to achieve optimal therapy for the patient. In this chapter the medicine deposition mechanisms for inhaled aerosols are explained as functions of the variables involved. In addition, the working principles of different inhaler types are described and it is discussed how their performance depends on many inhalation variables. Finally, some persistent misconceptions in the literature about the most preferable dry powder inhaler properties and performance are unravelled.

Keywords

Deposition mechanisms • Inhalation manoeuvre • Pulmonary administration • Pulmonary drug delivery • Therapeutic aerosol • Biopharmaceutics • Particle size • Dry powder inhaler • Metered-dose inhaler • Nebuliser • Novel liquid inhaler

Based upon the Chap. 28 Luchtwegen by Anne de Boer and Liesbeth Ruijgrok in the 2009 edition of Recepteerkunde.

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Y. Bouwman-Boer et al. (eds.), *Practical Pharmaceutics*,
DOI 10.1007/978-3-319-15814-3_6,

6.1 Orientation

Pulmonary administration of medicines currently has the primary objective to achieve local effects in the respiratory tract of patients with chronic diseases like asthma, chronic obstructive pulmonary disease (COPD) and cystic fibrosis (CF). For half a century, inhalation therapy has been the cornerstone in the management of these diseases and the often life-time therapies aim to suppress inflammatory processes and bacterial infection in order to reduce hospitalisations and to improve the patient's quality of life. They also give relief to the patient in moments of bronchoconstriction. The advantages of pulmonary administration of medicines for local treatment are well known. The active substances are delivered directly to the site of action which leads to a faster response than via the systemic route. It may also result in higher local active substance concentrations and this could reduce the total dose by as much as a factor 10 compared to oral or intravenous administration. This has the advantage that systemic side effects are reduced and in combination with being a non-invasive method of administration, inhalation therapy may lead to better patient compliance.

More recently, it has been recognised that pulmonary administration of medicines may be a good alternative for other therapies too. The respiratory tract is the port of entry for many bacteria and viruses and infectious diseases like influenza, tuberculosis and measles which can be prevented or treated effectively with inhaled vaccines, antibiotics and anti-viral medicines respectively. Lastly, the respiratory tract can be used for delivering systemically acting medicines which are not effectively absorbed by the gastro-intestinal tract or are rapidly metabolised by the first-pass-effect in the liver. Inhalation can potentially replace the more invasive parenteral routes of administration used for these active substances to increase their bioavailability and the adherence to therapy. An example is loxapine for acute treatment of agitation in patients with bipolar disorder or schizophrenia which has only 30 % bioavailability after oral administration, versus 90 % after intramuscular injection. Very recently (2012), approval for an inhaled loxapine formulation has been received which has a very high absorption of $>$ 90 % within seconds (Adasuve®, Alexza Pharmaceuticals). Currently many more devices and formulations for such new applications are in development or being tested and it may be expected that in the very near future several of them will be introduced to the market. Because most inhaled products are registered combinations of an active substance or a combination of substances and a suitable administration device, their manufacturing is not described in this chapter. Instead, their principles of operation are explained in relation to the variables that influence their performance. Basically these variables are the same as those controlling particle deposition in the human respiratory tract and the underlying mechanisms for that will be discussed as well.

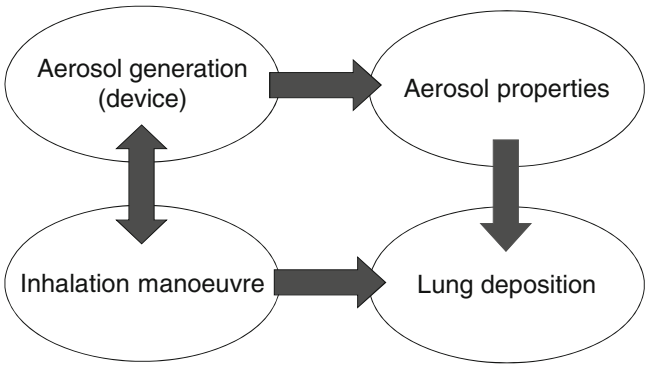

Fig. 6.1 Principle variables and interactions in pulmonary administration of medicines

In contrast with oral administration of tablets or capsules, pulmonary administration is a complex process with many variables involved as well as several interactions between these variables depending upon the type of aerosol generation device used. The most basic scheme of variables and interactions is presented in Fig. 6.1.

For many inhalation devices, the inhalation manoeuvre has an influence on the aerosol generation process. Either the air stream through the aerosolisation device delivers the energy for the aerosolisation process (e.g. for passive dry powder inhalers), or it alters the aerosol properties from the device (e.g. by coalescence or evaporation of droplets from nebulisers and metered-dose inhalers). The aerosol generation device may also influence the inspiratory flow manoeuvre by its resistance to airflow. A high resistance limits the flow rate to be achieved and this influences the deposition pattern in the respiratory tract in a positive way. Generally, a poor understanding exists regarding the precise role of airflow resistance, flow rate and aerosol properties in pulmonary therapies particularly with dry powder inhalers. Therefore, it is the aim of this chapter not only to explain the influence of the inhalation manoeuvre on the working principles of various aerosol generation devices and the mechanisms that govern aerosol deposition in the respiratory tract, but also to unravel some persistent misconceptions.

Administration devices for medicines used to treat asthma and COPD are prescription products, with an exception for some nebulised (medicine) formulations. Medicines such as amphotericin B or antibiotics (colistimethate sodium, tobramycin sulphate or gentamicin) for nebulisation in CF therapy are sometimes still partly prepared by hospital pharmacists, and so are nebulised solutions for bronchial challenge testing. Although product formulation and the method of preparation of formulations for inhalation are not the main subjects of this chapter, recommendations are given in the subparagraphs about nebulisation.

6.2 Definitions and Terms

6.2.1 Definitions in the European Pharmacopoeia: Preparations for Inhalation

The European Pharmacopoeia (Ph. Eur.) describes preparations for inhalation as liquid or solid preparations intended for administration as vapours or aerosols to the lung to obtain a local or systemic effect. These preparations may contain one or more active substances and, depending on the type, also propellants, co-solvents, diluents, antimicrobial preservatives, and solubilising and stabilising agents that do not adversely affect the functions of the mucosa of the respiratory tract or its cilia. The Ph. Eur. refers to three types of administration devices for inhalation preparations: nebulisers, pressured Metered-Dose Inhalers (MDI) and Dry Powder Inhalers (DPI). An appropriate size distribution has to be delivered to the patient so that a significant fraction is deposited in the lung and fine particle characteristics are determined by one of the methods for "Aerodynamic assessment of fine particles" in the Ph. Eur. The Ph. Eur. distinguishes between "Liquid preparations for inhalation" and "Powders for inhalation".

The liquid preparations for inhalation are divided into (A) preparations intended to be converted into vapour, (B) liquid preparations for nebulisation and (C) pressurised metered-dose preparations for inhalation. They are added to hot water to obtain inhalable vapours or converted into aerosols by continuously operating nebulisers or metered-dose nebulisers, and they can be solutions, suspensions or emulsions. They may be prepared by dilution of concentrated preparations or by dissolution of powders. The pH of liquid preparations for use in continuously operating nebulisers has to be within the range between 3 and 8.5. Suspensions or emulsions have to be readily dispersible on shaking and remain sufficiently stable to enable the correct dose to be delivered.

Powders for inhalation are not defined other than that they are presented as single-dose or multidose powders and that the active substances may be combined with a suitable carrier to facilitate their use. If the powder is for a single-dose (pre-metered) inhaler, the device is loaded with powders pre-dispensed in capsules or other suitable pharmaceutical forms. For inhalers using a powder reservoir, individual doses are isolated from the bulk with a metering mechanism within the inhaler.

Important for all different preparations and delivery devices is that they meet the requirements for uniformity of the delivered dose and the number of deliveries per inhaler for multidose inhalers. Also the fine particle dose has to be tested and calculated, but there are no specifications in the Ph. Eur. to meet this most important parameter. Some specific terms and definitions related to pulmonary administration of medicines are given and explained in this paragraph. For various terms different definitions or explanations are given in the literature and specific product information leaflets and it is important to recognise the implications of that.

6.2.2 The Other Definitions

6.2.2.1 Adhesive Mixture

An adhesive mixture is a type of formulation for micronised active substances for inhalation in which the small active substance particles adhere by natural forces (mainly Van der Waals forces) to the surface of much larger carrier (or host) particles.

6.2.2.2 Aerodynamic Diameter (D_A)

The aerodynamic behaviour of aerosol particles depends on their diameter, density and shape. To compare the behaviour of particles that have different properties with each other, the aerodynamic diameter (D_A) has been introduced, which standardises for particle shape and density. By definition the aerodynamic diameter of a particle is the diameter of a sphere with unit density having the same terminal settling velocity as the particle in consideration. Only for aqueous droplets with a spherical shape and unit density the aerodynamic diameter equals the geometric diameter. For non-spherical particles, the aerodynamic diameter can be expressed in terms of equivalent volume diameter (D_E), particle shape factor (χ) and particle density (ρ) (see definitions): $D_A = D_E.(\rho/\chi)^{0.5}$

6.2.2.3 Aerosol

An aerosol is a (colloidal) dispersion of particles in a gas, which for therapeutic aerosols is air. There is no definition for the particle size distribution of an aerosol, but most airborne particles are within the size range between 0.2 and 20 μm.

6.2.2.4 Breathhold Pause

This is the period during which breathing is interrupted after inhalation of an aerosol. By not immediately exhaling after inhalation, particles in the central and peripheral airways are given time to deposit by sedimentation and make contact with the epithelial lining fluid of the airways.

6.2.2.5 Carrier Particle

See adhesive mixture. Carrier particles in marketed formulations are exclusively alpha lactose monohydrate crystals, mainly in size distributions between 20 and

150 μm, but they may contain substantial amounts of fine lactose < 10 μm.

6.2.2.6 Deposition

This is the act of bringing an aerosol particle in contact with the airway wall. Different deposition mechanisms exist and it depends primarily on the particle's aerodynamic diameter (see definition) and velocity in which part of the airways an aerosol particle is most likely to be deposited.

6.2.2.7 Deposition Mechanism

Deposition mechanisms are principles by which particles can be deposited onto airway walls. For inhaled aerosol particles only two major mechanisms are important: inertial deposition and sedimentation (see definitions). In the literature also diffusion, interception and electrostatic precipitation are sometimes mentioned as deposition mechanisms, but these mechanisms, if occurring at all, are of lower relevance.

6.2.2.8 Deposition Modelling

Deposition modelling consists of simulation of the deposition in the lungs on the basis of deposition probability equations for inertial impaction, sedimentation, and diffusion.

6.2.2.9 Dose

The dose is the amount of active substance (to be) delivered from the inhalation device. Different definitions for the dose can be given for MDIs and DPIs. Basically, there is a difference between the label claim (also: nominal dose) and the delivered dose (also: emitted dose). The label claim is the dose as measured into the dose compartment of the device (for single-dose or multiple unit dose dry powder inhalers) or as measured by the device (for MDIs and multidose DPIs which both have a metering chamber). The delivered dose is the amount of active substance leaving the mouthpiece of the inhaler, which is lower than the label claim due to inhaler (mainly in the mouthpiece) retentions (for MDIs and DPIs) and incomplete emptying of the dose compartment (for DPIs only). Some manufacturers of DPIs weigh between 10 % and 20 % more than the label claim into the dose compartments to compensate for the inhaler retention, whereas others use an average delivered dose as label claim. This shades the difference between label claim and delivered dose. Delivered doses vary not only between devices; for DPIs they mostly also depend on the flow rate for the same type of device. A special situation concerns nebulisers where the delivered lung dose may not only depend on the retention in the nebulisation cup, but also on aerosol losses during periods of exhalation. Next to (nominal or delivered) dose, the fine particle dose (or fraction) is important (see FPD and FPF).

6.2.2.10 Drag Force (F_D)

Particles moving relative to the surrounding air are subjected to a resisting force by collision with air molecules. This force is the same whether the particle moves through the air or the airflows past the particle. For small airborne aerosol particles the resisting force, or drag force (F_D), is described by Stokes' law: $F_D = 3.\pi.\eta.U.D$, to which several correction factors may be applied (as for the shape factor: see definition). In this equation η is the dynamic viscosity of the air, U is the particle velocity (relative to the air) and D is the particle diameter.

6.2.2.11 Equivalent Volume Diameter (D_E)

The equivalent volume diameter (D_E) of an irregularly shaped particle is the diameter of a sphere having the same volume as the particle in consideration. The equivalent volume diameter is used to describe the dynamic particle behaviour of non-spherical particles in combination with the shape factor (see definition).

6.2.2.12 Fine Particle Dose (FPD) and Fine Particle Fraction (FPF)

Fine particle dose (FPD) and fine particle fraction (FPF) have to be defined by particle size (distribution). Based on their ability to target the site of action in the lungs, FPDs in the literature are frequently defined as the mass fractions of particles < 5 μm in the delivered aerosol. However, particles < 1 μm are not desired as they are exhaled to large extent, whereas for total and deep lung deposition particles in the narrow size range from 1 to 3 μm may be more appropriate. FPD is given in microgram or milligram active substance. FPF is a relative measure of FPD, expressed as percent of the dose for which both the label claim and the delivered dose can be used (see label claim).

6.2.2.13 Geometric Standard Deviation (GSD)

Geometric standard deviation (GSD) is a measure of the distribution of particle sizes which can be used for log-normal volume (or mass) distributions as function of the diameter:

$$GSD = (D_{84.13}/D_{15.87})^{0.5}$$

$D_{15.87}$ is the diameter corresponding with 15.87 % cumulative volume (or mass) and $D_{84.13}$ is the diameter corresponding with 84.13 % cumulative volume (or mass).

6.2.2.14 Impaction Parameter (IP)

The impaction parameter (IP) of an aerosol particle is the product of the particle density (ρ), the square of the particle's (aerodynamic) diameter (D) and its velocity (U):

$$IP = \rho.D^2.U.$$

The parameter predicts the chance of impaction against an obstruction in the flow direction of the particle and can for instance be used to predict oropharyngeal deposition. Practically, instead of particle velocity sometimes the flow rate (Φ) through an inhaler is used, but this does not enable comparative evaluations between different inhalers when the cross sections for airflow in the mouthpieces are different between the inhalers as this will result in different velocities.

6.2.2.15 Impactor

Multistage impactors or cascade impactors are used for aerosol particle size analysis. By drawing a constant flow rate through an impactor nozzle, airborne particles may or may not be collected on an impaction plate underneath the nozzle depending on their aerodynamic diameter and velocity. The cut-off diameter of an impactor varies with the flow rate through the nozzle, and by placing impactors with decreasing nozzle diameters in serial arrangement a mass distribution as function of the aerodynamic diameter can be obtained. The United States and European Pharmacopoeias show different types of impactors to be used for aerosols of which the nine-stage Andersen impactor is most popular in the USA and the seven-stage Next Generation Impactor (NGI) is most frequently used in Europe.

6.2.2.16 Inertial Impaction

One of the two dominant deposition mechanisms for aerosol particles in the respiratory tract (see definitions) is inertial deposition or impaction. Inertial deposition is based on the particle's inertia or momentum, which is the product of particle mass (m) and velocity (U). Inertial deposition occurs particularly in the upper respiratory tract where air velocity is high and the largest aerosol particles are still airborne.

6.2.2.17 Inspiratory Flow Rate

The volume of air per unit time through an inhaler during inspiration is the inspiratory flow rate, which is expressed in L/min. Generally, the flow rate through an inhaler quite rapidly reaches a maximum value (peak inspiratory flow, PIF) followed by a slower decrease to zero flow. As a general rule, the average flow rate equals approximately 70 % of PIF. From the average flow rate and the total inhalation time the inhaled volume (V) can be computed. The flow rate influences the particle size distribution in the aerosol and the deposition pattern in the respiratory tract.

6.2.2.18 Label Claim

The label claim of DPIs and MDIs is the amount of active substance corresponding with a unit dose. Different label claims are used and there is a tendency in Europe to change from metered dose to delivered dose for the label claim, which is an estimated value for the amount of active substance leaving the mouthpiece. For fine particle fractions (FPFs) it is important to know which type of label claim has been used as reference, or a comparative evaluation between different devices will be impossible.

6.2.2.19 Median Diameter

The median diameter corresponds with the 50 % value of a cumulative number, volume or mass percent distribution as function of the diameter. Fifty percent of the volume (number or mass) of the aerosol is in larger, and 50 % is in smaller particles than the median diameter. For a volume distribution it is the volume median diameter, for a mass distribution the mass median diameter. When the mass percent is expressed as a function of the aerodynamic diameter, reference can be made to the mass median aerodynamic diameter (MMAD).

6.2.2.20 Mass Median Aerodynamic Diameter (MMAD)

The MMAD is a parameter frequently used to characterise therapeutic aerosols. MMAD alone is not very useful however, as it provides no information about the size distribution in the aerosol and the mass fraction of the dose (label claim) processed into a suitable aerosol. Fine particle dose and fraction are more meaningful parameters, particularly for DPIs (see definitions).

6.2.2.21 Monodisperse Aerosol

In a monodisperse aerosol all particles have the same diameter. In practice, monodisperse aerosols are very difficult to obtain and therefore, aerosols are considered monodisperse when their geometric standard deviation (GSD) is smaller than 1.2 (see definition).

6.2.2.22 Plume Velocity

The plume velocity is the velocity with which an aerosol is released from an MDI. Generally, the plume velocity from hydrofluoroalkane (HFA) holding MDIs is much lower than that from chlorofluorocarbon (CFC) holding MDIs, but this may depend on the presence of a co-solvent.

6.2.2.23 Polydisperse Aerosol

In a polydisperse aerosol the particles have different diameters and the size distribution is such that the geometric standard deviation (GSD) has a value larger than 1.2 (see definitions).

6.2.2.24 Resistance (Against Airflow)

Inhalers are flow constrictors which reduce the flow rate (Φ) to be achieved during inhalation. Their behaviour in this respect complies with the general equation for orifice types of airflow resistances ($\Phi = Fu(A).\sqrt{dP}$), where Fu(A) is a

function of the cross section (A) for airflow and dP is the pressure drop across the inhaler (in kPa). Fu(A) may be complex but fairly constant over a wide range of flow rates and contains flow coefficients depending on the precise inhaler design. The reciprocal value of Fu(A) is the inhaler's resistance to airflow (R).

6.2.2.25 Sedimentation

One of the two dominant deposition mechanisms for aerosol particles in the respiratory tract (see definitions) is sedimentation or stationary settling. Sedimentation occurs under influence of the force of gravity and settling (falling) particles reach a terminal (stationary) settling velocity once the force of gravity is in equilibrium with the drag force (see definitions). The terminal settling velocity (U_{TS}) is proportional to the square of the particle diameter (D) and also depends on particle density (ρ) and shape factor (χ: see definitions):

$U_{TS} = (\rho.D^2.g.C_c)/(18\eta.\chi)$ in which g is the acceleration of gravity, C_c is the Cunningham correction factor for slip flow and η is the dynamic viscosity of the air.

6.2.2.26 Shape and Shape Factor (χ)

Only aqueous aerosol droplets and some particles obtained from (spray) drying of droplets are perfectly round. Most solid aerosol particles have other shapes, and also when spherical particles cluster together their shape changes from round into irregular. The shape of a particle affects its drag force (see definition) and in particle dynamics shape is characterised by a (dynamic) shape factor. This factor for a non-spherical particle is defined as the ratio of the actual resistance force to the resistance force of a sphere having the same volume and velocity relative to the air. The factor is applied to make corrections for Stokes' law for the drag force (see drag force) which influences both inertial impaction and sedimentation.

6.2.2.27 Stopping Distance

The stopping distance or inertial range is the distance a particle will travel in still air with all external forces eliminated, except for the drag (resistance) force of the air which decelerates the particle to zero velocity. The stopping distance depends on the particle's momentum, which is the product of particle mass and velocity (m.U).

6.2.2.28 Target Area

The target area is the area in the respiratory tract where the action of the inhaled medicine is most needed. The target area may either be part of the respiratory tract or the whole lung, depending on the medicine.

6.3 Biopharmaceutics

Aerosol particles carrying the active substance have to make contact with the walls of the respiratory tract in the target area and the medicine has to be dissolved before it can become active. In this paragraph, the anatomy of the human respiratory tract is described in view of its function as transport route and target area for inhaled medicines.

6.3.1 The Human Respiratory Tract

For pulmonary administration of medicines the mouth is the port of entry (see Fig. 6.2). Inhaled air carries the aerosol from the inhalation devices past the oral cavity, pharynx and larynx before it enters the tracheobronchial tree. Starting with the trachea (generation 0) most airways branch into two (some in more) smaller airways, which comprise the following generation. The trachea branches (bifurcates) into two main bronchi (generation 1) which bifurcate further into five lobar bronchi (generation 2) and so on, until eventually the alveolar sacs (alveoli) are formed. Estimates for the number of branchings (airway generations) from the trachea to the alveoli in the literature vary between 20 and 28 and the number of airway ducts in each generation is roughly 2 to the power of the generation number; for example, in generation 8 there exist 2^8 (256) airway ducts. The number of alveoli does not comply with this geometric sequence however, and is much higher up to an estimated 300–800 million [1]. The airway system can be subdivided in many different ways. Clinically, large airways (with diameters > 2 mm) are frequently distinguished from small airways (with diameters < 2 mm). In addition, the terms upper and lower airways are frequently used, but with different definitions. From the viewpoint of fluid and particle dynamics dividing the airways into conducting, transitional and peripheral airways seems more practical. Clear definitions for these regions have never been given but on the basis of airflow velocity and functional and anatomical differences the conducting airways are referred to as the generations 0–11, the transitional airways as the generations 12–16 and the peripheral airways as the generations 17–23 in this chapter. In aerosol deposition studies with radiolabeled substances partitioning is often into central, intermediate and regional airways on the basis of two-dimensional γ-camera images. The average angle of bifurcation is 37° which from the fluid dynamics point of view is the angle with the least disturbance of the flow pattern. Lung models used for deposition simulation in the literature mostly give only 23 generations (e.g. the Weibel model) and only few are extended to 26 generations (e.g. the Hansen and Ampaya model) [2].

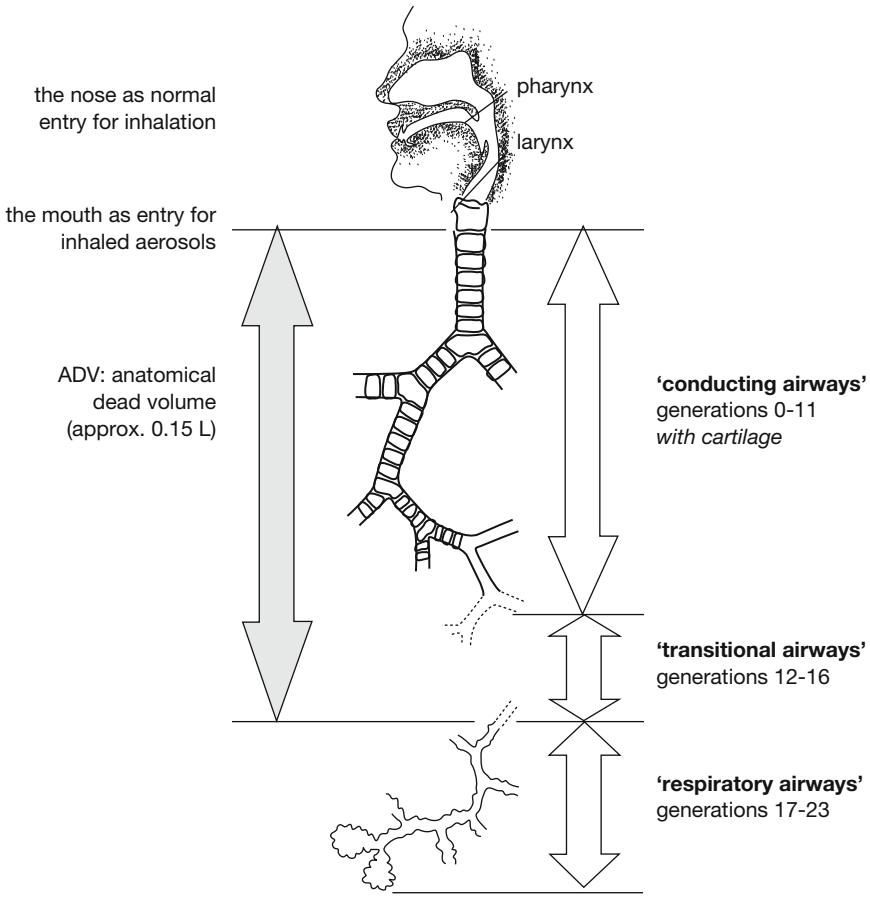

Fig. 6.2 The airways as transport route for aerosols. The anatomical dead volume of 0.15 L is for adults; the total number of airway generations (23), based on the Weibel model, is by approximation. Source: Recepteerkunde 2009, ©KNMP

From the trachea to the small bronchi cartilage is present in the walls of the airways. In the trachea cartilages are C-shaped, in the bronchi they appear as interspersed small plates of elastic tissue. The cartilages in the trachea are joined by smooth muscle which continues into the bronchi and bronchioles where the muscles encircle the airways completely. Further down the respiratory tract, smooth muscle becomes less until it is absent in the alveoli. The airways are covered with epithelium of which the type varies within the tract. There are glands (upper respiratory tract) and mucus producing goblet cells, and most of the epithelial cells (into the bronchi) are ciliated cells. The cilia beat upwards, moving mucus (including all, in the mucus, entrapped foreign inhaled particles) towards the throat where it is swallowed. In the alveoli neither mucus nor ciliated cells are present and mainly alveolar macrophages are responsible for destroying foreign material. The walls of the alveoli contain surfactant secreting cells. Surfactant decreases the surface tension of the alveolar lining fluid preventing collapse and assisting re-inflation of the lung after exhalation.

Different lung models are used to describe the human airways as transport route for inhaled aerosol particles [2]. All these models have in common that they are simplifications of reality presenting the airways as round pipes with defined lengths and diameters. From the trachea with an estimated diameter of 15–18 mm (in adults) the airway diameter decreases towards the alveolar ducts, whereas the number of airways increases. The increase in number (from 1 to approximately 8×10^6, assuming 23 generations) is much higher than the decrease in diameter (from 18 to approximately 0.4 mm). As a consequence, the cross section for airflow, after an initial decrease in the first four generations, increases exponentially towards the alveoli, which corresponds to an exponential decrease of the air velocity. In the terminal bronchioles the air stands practically still and its velocity reaches the same value as the terminal settling velocity of particles in the size range between 5 and 6 μm.

6.3.2 Spirogram and Lung Volumes

The total lung capacity (TLC) of healthy adult subjects varies between approximately 4 L (female) and 6 L (male), but during tidal breathing at rest only a fraction of this volume is refreshed: approximately 0.5 L. During severe exercise, this tidal volume (TV) increases to about 1.5–2.5 L, which means that a considerable part of the TLC is not used. In fact, a residual volume (RV = approximately 25 % of TLC) cannot be exhaled at all to prevent collapse of the lungs. Tidal breathing is not on top of the residual volume, but on top of the functional residual capacity (FRC), which after exhalation leaves a volume of about 2.3 L of air in the lungs for an adult male. The alveolar volume is about 2.1 L and this implies that during tidal breathing air refreshment by convective transport takes place mainly above the alveolar volume. Hence, to reach the alveoli effectively with an inhaled aerosol, a preceding exhalation to residual volume is necessary.

6.3.3 Target Areas for Inhaled Medicines

The precise area to target in the lungs depends on the type of medicine given and the mechanism of action for this medicine. Most of the active substances used for inhalation interact with cell receptors in the respiratory tract [3]. For asthma and COPD these include mainly β_2-adrenoceptor agonists and muscarinic receptor antagonists (anticholinergics). The distribution of receptors over the lung is an important determinant of both the clinical effect of the medicine and the desired site of deposition for the active substance. The primary action of β_2-agonists is to relax airway smooth muscle. β_2-agonists target β_2-receptors that are present in high concentration in lung tissue and localised to several cell types which, next to smooth muscle, are epithelium, vascular smooth muscle and submucosal glands [3]. They also target β_1-receptors localised to submucosal glands. There is a uniform distribution of β-receptors also on the alveolar wall with a ratio of β_1 to β_2 receptors of 2:1. The density of β_2-receptors in airway smooth muscle does not change down the respiratory tract and is the same in small and large airways. Therefore β_2-agonists may dilate all airways and this is relevant to asthma and COPD where small airways are involved. To achieve acute relief of bronchoconstriction, reaching the larger airways, which have the highest resistance to airflow, is mostly sufficient.

Inhaled anticholinergics are the most effective class of bronchodilators in COPD patients. Muscarinic receptors are localised to smooth muscle of all airways, but the density decreases down the respiratory tract. They are also localised to airway epithelium and submucosal glands [3]. Four subtypes of muscarinic receptors exist in the lungs and those mediating bronchoconstriction belong to the M_3-receptor subtype on endothelial cells which release nitric oxide (NO). Muscarinic receptors of the M_3 subtype also mediate mucus secretion and so do receptors of the M_1 subtype, whereas autoreceptors in the human airways belong to the M_2 subtype. Medicines like ipratropium bromide block prejunctional M_2-receptors and postjunctional M_3-receptors in airway smooth muscle with equal efficacy. The presence of M_2-receptors has also been demonstrated in airway smooth muscle and M_1- and M_3-receptors are both present in submucosal glands, whereas M_1-receptors can also be found in the lung parenchyma. Recently, it has been suggested that muscarinic receptors may have a much greater role in the pathophysiology of obstructive airway diseases than previously thought [4]. Active substances like tiotropium may potentially inhibit airway inflammation and remodelling, and it has recently been shown that aclidinium may play an important role in inhibiting fibroblast-myofibroblast transition, which is a key step in peribronchiolar fibrosis formation [5]. Deposition in the whole lung is therefore desirable for anticholinergics in spite of the fact that cholinergic activity in the lung is most pronounced in the large airways [6].

Inhaled corticosteroids (ICSs) are the mainstay of asthma management. Their effects are mediated by glucocorticoid receptors in target cells of the lung. Almost every cell has glucocorticoid receptors, but the number per cell varies with the type of tissue and in the airways the highest density is found in endothelial and epithelial cells [3]. Airway epithelial cells, which express multiple inflammatory proteins dominating the inflammation in asthma, may be the major target for ICSs. Because epithelial cells are present throughout the entire lung, all airways have to be targeted with ICSs.

Many specific mediator receptors are involved in asthma but they are so abundant that specific antagonists for these receptors have little effect, with an exception for cysteinyl leukotriene-1 (cys-LT_1) receptors which are distributed predominantly on airway smooth muscle and (to a lesser extent) on macrophages. Their numbers are small, however, and this may explain why antileukotrienes like montelukast and zafirlukast, which prevent predominantly leukotriene-induced bronchoconstriction, are less effective than β_2-agonists.

6.3.4 Side Effects and Toxicity

Side effects can be the result of unwanted systemic action, toxicity, irritation and hypersensitivity following sensitisation. Both the active substances and excipients can cause side effects and in addition to the chemical nature of the inhaled compounds, also physical properties can be relevant. An example can be given for salbutamol, for which it has been shown that increasing the dose may result

in increased side effects without improving the therapeutic effect [7]. Also specific salts of an active substance may be less favourable, as they can increase the degree of irritation from particle deposition on the mucosa [8]. Irritation may result in severe cough and chest tightness; both may further depend on the precise site of deposition which depends on particle size and/or flow rate. Dry powder formulations for low dose substances in asthma and COPD therapy previously contained only alpha lactose monohydrate as carrier (or diluent) excipient. In some countries, there has been concern about the use of lactose in inhaled medication because of some rare cases of bovine spongiform encephalopathy (BSE), but it is highly unlikely that the prions causing BSE can be found in this excipient. Currently, many formulations are introduced to the market which contain magnesium stearate as force control agent to improve powder dispersion (e.g. Chiesi Foster NEXThaler®, Novartis Seebri Breezhaler® and GSK Breo Ellipta®). Although the use of this practically insoluble excipient has been approved, its long term safety may be questioned. Still uncertain are also the long term effects of various excipients in high dose medicines, such as lung surfactant (dipalmitoylphosphatidylcholine, DPPC) in various particle engineered powders, hydrogenated soya phosphatidylcholine (HSPC) and cholesterol in liposomal formulations, and poly lactic acid (PLA) and poly lactic-co-glycolic acid (PLGA) in insoluble microspheres. The arguments for safety are that the compounds are not foreign to the lungs or that they do not interfere with physiological processes. However, interference for substances like DPPC are likely to depend also on their concentration, and for instance metabolic lactic acid is an important mediator of myofibroblast differentiation via a pH-dependent activation of transforming growth factor-β [9]. MDI formulations contain various excipients too, of which some have been less abundantly used since the replacement of CFC by HFA propellants. Furthermore, most HFA-MDIs have a lower plume velocity and a higher plume temperature than CFC devices which reduces the cold-freon effect and local side effects from substantial throat deposition.

6.4 Mechanisms of Aerosol Deposition and Aerosol Characterisation

6.4.1 Forces Acting on Inhaled Aerosol Particles

Aerosol particles transported in a steady laminar air stream have basically the same velocity and flow direction as the air, but in contrast with the air molecules particles have a much higher inertia. Therefore, they cannot follow rapid changes in velocity or direction of the airflow, which for instance occur in curved airways, at bifurcations or around local obstructions. In such areas or in turbulent air streams particle trajectories and velocities may differ from the stream lines of the air and under these conditions, a drag or resistance force of the air is added to the force of gravity acting on the particle. Whereas the particle's inertia tends to maintain particle motion in the original direction, the drag force tends to change this direction into that of the air stream. The tendency of a particle to maintain its state of motion in still air is expressed by its stopping distance (S) which is related to the particle momentum. For the sake of simplicity and an easier understanding, it can be imagined that a particle following a curvilinear trajectory is subjected to a centrifugal force. This adds a third force acting on particles in a bent airway as depicted in Fig. 6.3.

$$F_C = m.U_{T^2}.R^{-1} \tag{6.1}$$

$$F_D = 3.\pi.\eta.U_{PA}.D \left(\begin{array}{l} \text{for spherical particles} \\ >1\ \mu\text{m with unit density} \end{array} \right) \tag{6.2}$$

$$F_G = m.g \tag{6.3}$$

Where:
m is the particle mass
U_T is the tangential velocity
R is the radius of the bent
η is the dynamic viscosity of the air
U_{PA} is the particle velocity relative to the air velocity
D is the particle diameter
g is the acceleration of gravity

Of these forces, the centrifugal force and force of gravity are a function of the particle mass, which is proportional to the third power of the particle diameter, whereas the drag force is proportional to the first power of the diameter. The

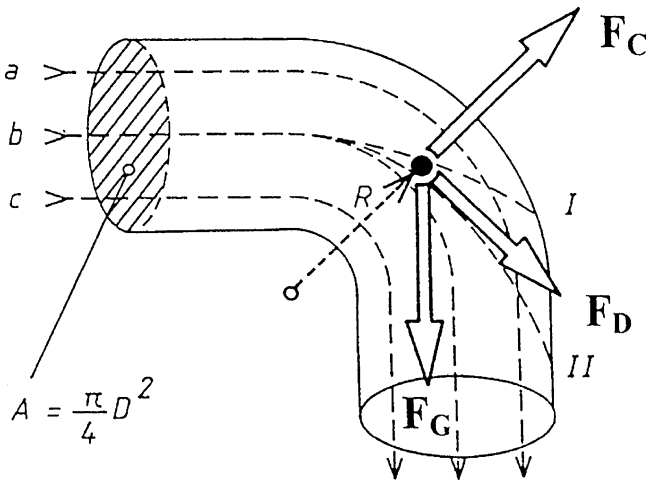

Fig. 6.3 Forces acting on airborne particles in a bent airway. Source: Recepteerkunde 2009, ©KNMP

drag force and the centrifugal force depend on the particle velocity, whereas the force of gravity does not. This has the important implication that the balance between these forces can be influenced by changing the particle diameter, particle velocity, or (as a determinant for particle mass) particle density. Because the particle shape influences the drag force, the shape factor is a fourth determinant for a particle's aerodynamic behaviour.

6.4.2 Deposition Mechanisms in the Respiratory Tract

The balance between the three forces acting on airborne particles results in dominance of either inertial impaction or sedimentation, which are the two main deposition mechanisms in the respiratory tract. Inertial impaction occurs when particles have a high momentum and the air suddenly changes its direction. This situation is met in the human throat and the upper airways where the air velocity is high and the largest particles in the aerosol are still present in the inhaled air stream. For such particles the ratio of centrifugal force to drag force is relatively high, meaning that they have a great chance of colliding with the airway wall based on their high inertia, which event is referred to as inertial impaction. As the largest particles are removed in the upper airways and the air (and thus particle) velocity decreases down the respiratory tract, particle inertia and the drag force decrease and the force of gravity becomes more dominant. This leads to settling (falling) of particles in the central and peripheral airways and when the settling time is long enough it could result in deposition by sedimentation. For a small fraction of the finest particles ($D \ll 1$ μm) Brownian motion may become noticeable. This mechanism of displacement, resulting from particle collision with surrounding air molecules, causes particle movement with a randomly changing direction which could lead to contact with the wall of an airway. However, because the displacement velocity by Brownian motion (or diffusion) is very low, and so is the mass fraction of the dose represented by particles smaller than 1 μm, this mechanism of deposition does not contribute substantially to total deposition. Also electrostatic capturing of particles is mentioned in the literature as a possibility to bring aerosol particles in contact with airway walls but for the relevance of this mechanism there is no experimental evidence. One aspect that is still relatively unexplored and needs further investigation is the possibility that particles change their mass during passage through the respiratory tract, e.g. by moisture sorption [10]. Such particles may be inhaled as small (submicrometer) to avoid high deposition fractions in the oropharynx and larger airways and increase in weight in the high humidity within the airway system to enhance sedimentation deposition in the deep lung.

6.4.3 Sedimentation Takes Time

Particle settling in the respiratory tract occurs under the influence of the force of gravity and the drag force. In the stationary situation these forces counterbalance each other and this enables to calculate the stationary or terminal settling velocity (see terms and definitions) which is proportional to the square of the particle diameter. For spherical particles with unit density in the range of diameters between 0.5 and 5 μm, which covers the range of interest for inhalation, the terminal settling velocities are given in Table 6.1.

Table 6.1 shows that particles of 1 μm, or smaller, are less favourable for inhalation because their settling time is too low. Even for a total residence time of 7.5 s in the smallest airways, the falling distance of a 1 μm particle is no more than 50 % of the diameter of that airway, if the air stands completely still. In practice, the air velocity remains much higher than the particle's settling velocity, even in these most distal airways (e.g. 2.5 mm/s in generation 22 at an inspiratory flow rate of 60 L/min), and this can influence sedimentation in a negative or positive way. Moreover, most distal airways are not horizontal ducts and a falling distance of 50 % of the airway diameter does not provide an average 50 % chance for deposition of particles entering the airway randomly distributed over its cross section. As a consequence of all this, the deposition efficiency of very fine particles is low and exponentially decreases with decreasing diameter. This is reflected in the fraction of small particles exhaled again, which is known for particles in the size range between 1.5 and 6 μm [11]. Figure 6.4 shows the relationship between particle diameter and measured exhaled fraction for monodisperse aerosols, and the extrapolation of this relationship towards particles of 1 μm. The trend computed matches very well the relationship which presents the time needed to fall a distance equal to the diameter of a peripheral airway (0.43 mm).

Table 6.1 Terminal settling velocities in still air of spherical particles with unit density

Particle diameter (μm)	Terminal settling velocity (μm/s)	Average settling time[a] (s)
0.5	7.5	30
1	30	7.5
2	120	1.9
3	271	0.8
4	482	0.5
5	753	0.3

[a]The average settling time is the time needed to fall a distance (H) that equals 50 % of the diameter of a respiratory bronchiole (H = 0.225 mm)

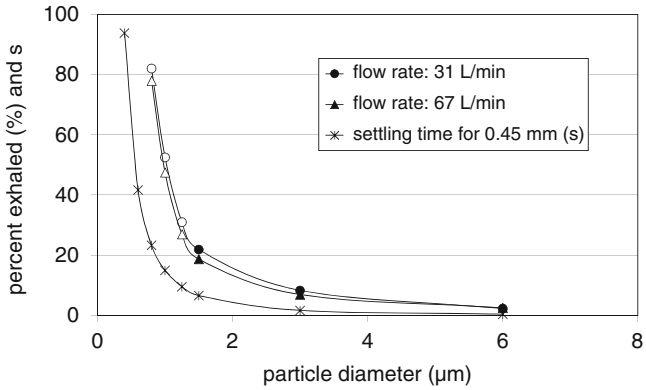

Fig. 6.4 Trends for the percentage particles exhaled and the time needed to fall a distance that equals the diameter of a peripheral airway (0.43 mm), both as function of the aerodynamic particle diameter. The percentage exhaled for 1 µm particles is obtained from extrapolation (using a second order polynomial equation); exhalation data for 1.5; 3 and 6 µm particles derived from Usmani et al. [11] and extrapolation of the correlationships towards particles of 1 µm

6.4.4 The Influence of Particle Shape and Density

The terminal settling velocities and average settling times given in Table 6.1 are for spherical particles with unit density which is the density of water (1 g/cm^3). This may well apply for wet aerosol droplets from aqueous solutions of active substances which take a spherical shape as soon as they have been formed under the influence of the surface tension. Solid aerosol particles from dry powder inhalers have different properties. Such particles may exhibit a variety of different shapes and also have different densities, depending on how they were prepared. Particles obtained from micronisation are mostly crystalline and have density values typically in the range between approximately 1.25–1.55 g/cm^3. Due to the size reduction process (breaking of larger particles) micronised particles have irregular shapes which, however, never deviate extremely from the spherical shape. This is in contrast to particles obtained with anti-solvent precipitation or super critical drying which can have shapes varying from cubic to plate or needle like. An increasing number of high dose medicines for inhalation are currently produced with spray drying techniques, yielding particles with high internal porosity or corrugated surfaces to enhance dispersion during inhalation. Such particles may largely be spherical, but they have low densities, frequently much smaller than 1 g/cm^3. Both the particle density and shape influence the aerodynamic behaviour of aerosol particles and this affects deposition in the human airways. Figure 6.3 shows that the force of gravity and the centrifugal force both depend on the particle density (ρ). All three forces furthermore depend on the particle diameter, but non-spherical particles have different dimensions in different directions and therefore, a unique diameter to characterise such particles cannot simply be given. For this reason, the equivalent volume diameter (D_E) was introduced, which is the diameter of a spherical particle with the same volume as the non-spherical particle. Finally, the drag or resistance force strongly depends on the particle shape. This does not show in the equation given in Fig. 6.3, which is therefore only valid for spherical particles. To standardise for both shape and density, the aerodynamic diameter is used, which by definition is the diameter of a sphere with unit density having the same terminal settling velocity as the irregular particle in consideration.

6.4.5 Polydisperse Aerosols and the MMAD

All currently marketed inhaler devices produce polydisperse aerosols of which the individual particles have different sizes. Therefore, they cannot be characterised by a single diameter. In fact, for most solid aerosols from dry powder inhalers the particles may have different shapes too, which is the reason to characterise them with aerodynamic diameters. To be able to express polydisperse aerosols with a single parameter, the median aerodynamic diameter (MAD) was introduced. When the aerodynamic size range which covers the population of particles in the aerosol is divided into different classes and the volume or mass fraction within each size class is expressed as function of the class mean diameter, a volume or mass distribution as function of the aerodynamic diameter is obtained. This volume or mass frequency distribution can be transferred into a cumulative percent distribution of which the 50 % value corresponds with the volume or mass median aerodynamic diameter (VMAD or MMAD). This is the diameter indicating that 50 % of the total aerosol volume or mass is in larger, and 50 % is in smaller particles. When particles of all sizes in the aerosol have the same density, which is mostly the case, then VMAD equals MMAD.

MMAD is frequently presented as the parameter characterising aerosols from inhalation devices best. This is not true however. To judge the quality of a therapeutic aerosol from a particular type of inhaler, more information is needed. The MMAD does not give any information about the size distribution of the aerosol particles. Substantial mass fractions may be outside the desired size range for adequate deposition of active substance in the target area, even when MMAD looks very favourable. Moreover, MMAD does not give information about the mass fraction of the dose (label claim) that has been delivered within the desired size range. For all types of inhalers, the delivered fine particle dose (FPD) is much lower than the label claim and this may vary from 10 % to 60 % for DPIs and up to 90 % for

MDIs. For these reasons it is best to define first the FPD in terms of desired size range and mass percent (of the label claim, yielding the fine particle fraction, FPF) and next compute the MMAD for this size range. In the literature, mostly FPF < 5 μm is mentioned as the relevant fine particle fraction, but practically FPF 1–5 μm is more meaningful because of the low deposition efficiency of submicron particles (Fig. 6.4).

6.4.6 Deposition Efficiencies and the Most Preferable Size Distribution

The deposition mechanisms mentioned previously have different efficiencies which, in addition to the particle properties, depend on the velocity with which the particles enter the respiratory tract and their residence time in the tract. The velocity is most important for inertial impaction in the oropharynx and larger (mainly conducting and transitional) airways. The likelihood of particles to be deposited in the mouth and throat or larger airways is a function of their momentum, which is the product of particle mass and velocity and can be predicted with the impaction parameter.

An experimental relationship between impaction parameter (based on inhaled flow rate) and oropharyngeal deposition from a study with monodisperse particles is shown in Fig. 6.5. The highest value in this relationship is for 6 μm particles inhaled at a flow rate of 67 L/min; the lowest for 1.5 μm particles inhaled at 31 L/min [6].

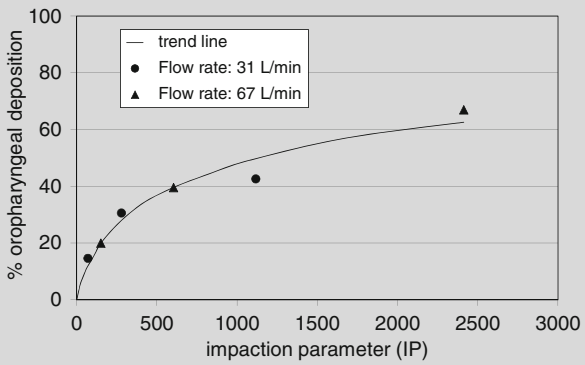

Fig. 6.5 Experimental relationship between percent oropharyngeal deposition and impaction parameter computed as $IP = D^2.\Phi$, where D is the aerodynamic particle diameter (micrometre) and Φ is the flow rate with which the particle is inhaled (L/min). Data derived from Usmani et al. [11]

The figure makes clear that substantial lung doses cannot be obtained with particles larger than 6 μm, unless they are inhaled very slowly which from dry powder inhalers is often not possible. Large particles also deposit effectively in the larger airways where initially the velocity increases (until generation 4) before it slows down. This has the consequence that particles larger than 3 μm from DPIs do not effectively enter the peripheral lung.

The residence time is more relevant to small particles which have to deposit mainly by sedimentation in the central and peripheral airways. In these regions, the flow rate is strongly reduced and large particles are not present in large numbers due to which inertial impaction is less prominent. Sedimentation takes time however, as explained above, and particularly for particles in the size range below 1.0–1.5 μm a residence time of several seconds may be needed to obtain a noteworthy deposition by sedimentation. This practically confines the diameter for most effective total lung deposition to the very narrow aerodynamic size range between 1 and 1.5 and 3 μm. Only for bronchodilators which need to target predominantly the larger airways, particles in the size range between 3 and 6 μm may be more effective [11].

6.4.7 Medicine Distribution over the Entire Respiratory Tract

One of the aspects that is often neglected, but may be of utmost importance for effective therapy, is the active substance concentration achieved in different lung regions. Most *in vivo* deposition studies with radiolabeled substances from dry powder inhalers teach that the deposition fractions in the central, intermediate and peripheral lung are very roughly one third of the total lung dose each [12–14]. This is more or less confirmed by deposition modelling studies with monodisperse particles of 3 μm inhaled at a moderate flow rate of 30 L/min [15], although a good comparison in this respect is not possible as different lung regions are defined differently in these studies. Considering the exponentially increasing internal surface area of the airways from the trachea to the alveoli, which differs roughly by a factor 130 between the generations 0–11 (conducting airways) and 17–23 (peripheral airways) based on the Weibel model, it may be concluded that there must be a dramatic difference in active substance concentration (in $\mu g/cm^2$) between these regions. A difference in definition for the different lung regions, or a considerable deviation from the deposition distribution (approximately one third of the total lung dose in each region) does not really change this conclusion. This may have the consequence that the peripheral lung is underdosed with for instance antibiotics, which need to

reach their minimum inhibitory concentration (MIC) value to become effective. In fact, not reaching the MIC value could result in bacterial resistance development and this is an aspect that will need serious consideration when changing from systemic to pulmonary administration for therapies against pulmonary infections. In this respect, also changing from approved formulation-device combinations to off-label combinations (e.g. in nebulisation) is potentially a risk when the delivered fine particle dose and the inhalation manoeuvre are not exactly the same.

6.4.8 Practical Implications for the Inhalation Manoeuvre

The optimal inspiratory manoeuvre for inhalation of a therapeutic aerosol depends on how it influences the aerosol generation process and the deposition pattern in the respiratory tract (Fig. 6.1). Its effect on the aerosol properties will be discussed in the next paragraphs in which the working principles of different aerosol generation devices are explained. From the deposition point of view particularly the (peak) flow rate, the inhaled volume and a certain breathhold pause are relevant, but good inhalation starts with exhalation to residual volume. As explained above, only with an inhalation from residual volume the alveoli can be reached effectively. Considering the dependence of inertial impaction in the oropharynx and first airway generations on the particle velocity, it may also be clear that a high flow rate during inhalation should be avoided, but the optimum in this respect depends on the performance of the aerosol generation device too. For good (dry powder) inhaler performance, even the acceleration to peak flow (flow increase rate) may be important. Inhalation should be continued until total lung capacity is reached. Premature stopping of the inhalation manoeuvre again has the consequence that the most distal airways are not reached with the aerosol, but it can also mean the total dose is not delivered. Once the smallest aerosol particles have reached the peripheral lung, they must stay there for a certain period of time to give sedimentation a chance and a breathhold pause of several seconds (preferably 5–10) is desired before starting exhalation.

6.5 Aerosol Generation Devices

Basically four different types of commercially available aerosol generation devices exist: dry powder inhalers (DPIs), metered-dose inhalers (MDIs), classic jet and ultrasonic nebulisers and a new class of high-performance liquid inhalers. Each of these categories has many different variations of the same basic design and working principle and they may also have significantly different performances. In the following paragraphs, firstly the conceptual design of the different types will be described and then their working principle will be explained. This has to be known to make the best possible choice for individual patients and to give an appropriate instruction for use. Only examples of specific devices will be discussed in more detail, because the still growing number of devices in each category is too extensive to make a complete survey.

6.5.1 Dry Powder Inhalers (DPIs)

DPIs are relatively new and their designs and working principles may not only be quite complex but also rather diverse between the different types, which easily leads to incorrect or suboptimal use. DPIs contain the active substance in the dry state which is beneficial from the viewpoint of stability. They can deliver much higher doses than MDIs and be disposable which is particularly desired for hygroscopic formulations of active substances, antibiotics against which bacterial resistance development has been reported and single-dose administrations such as vaccinations. Aerosol generation in DPIs is mostly breath activated, which eliminates the need for a good hand-lung coordination but requires the generation of sufficient flow rates and inhaled volumes to release a sufficiently high fine particle dose. DPIs have much higher airflow resistances than MDIs, which limits the attainable flow rate and by that, oropharyngeal deposition. Furthermore, DPIs can deliver higher fine particle fractions and finer aerosols at higher flow rates, which compensates to a certain extent for the increasing losses in the mouth, throat and upper airways when the patient inhales more forcefully, which results in an increased dominance of inertial particle impaction. DPIs exist not only in a large variety of different designs, they also have different performance properties and resistances to airflow. These differences in design and performance may be functional and have been chosen carefully to obtain the most optimal deposition of the active substance at the site of action. However, in many cases they may also be different for the same type (or class) of active substance(s), all having the same target area. These differences may lead to considerable variation in the delivered fine particle dose at this site of action. Differences in ease of handling, the flow manoeuvre needed and airflow resistance may be aspects to consider particularly for special patient groups, such as children and severe COPD patients. In the next paragraphs, the general design with some specific examples of DPIs will be presented and discussed in relation to their performances and the required operational procedures to obtain the best delivery of active substance.

6.5.1.1 Basic Design of DPIs

The primary functional parts of a dry powder inhaler are schematically shown in Fig. 6.6 and include a powder formulation, a dose (measuring) system, a dispersion principle for the powder formulation, a mouthpiece and a housing for all parts. Additionally, the inhaler may have various secondary features, including a dose counter, giving the number of doses left in the device, a compartment with desiccant to keep the powder formulation dry and a signalling to the patient that the inhalation manoeuvre is correct or has been completed. Different choices can be made for each of the functional parts and a good and compatible combination has to be chosen and developed to obtain the maximal result.

6.5.1.2 The Powder Formulation

The powder formulation contains the active substance in the correct aerodynamic size distribution, which for most currently marketed formulations is either obtained by micronisation or by spray drying. Both techniques produce polydisperse particles and their mass median aerodynamic diameter is preferably in the range between 1 and 5 μm, depending on the precise target area. Particles within this size range are extremely cohesive, whereas the powder masses to be measured are miniscule and mostly less than 5–500 micrograms for the active substances used in asthma and COPD treatment. Such small quantities of micronised powders cannot be delivered in a reproducible way without improving their flow properties and increasing their volume. They are formulated into free-flowing powders either by blending with coarse lactose carrier particles into so-called adhesive mixtures or by preparing highly porous soft spherical agglomerates with or without micronised lactose excipient. For high dose medicines in the range from a few to a few 100 mg, frequently special particle engineering techniques are used which produce low density particles or particles with a corrugated surface. Both types of powders, which require the use of special volatile agents or surfactants and often multi-step processes, have improved flowability and can be delivered without further dilution or formulation.

6.5.1.3 Dose (Measuring) Systems for the Powders

Basically two different types of dose principles exist for the inhalation of powders in currently marketed inhalers; preloaded single-dose compartments or multidose reservoirs with a measuring mechanism that has to be operated by the patient. Both principles have pros and cons and which type is most appropriate also depends on the properties of the powder formulation. Preloaded single-dose compartments include mainly capsules and blisters. Capsules are stored separately and inserted individually into the inhaler when needed. They have to be pierced to discharge the powder which in currently used inhalers occurs during high speed spinning (e.g. Breezhaler®) or vibration (e.g. Boehringer HandiHaler®) in

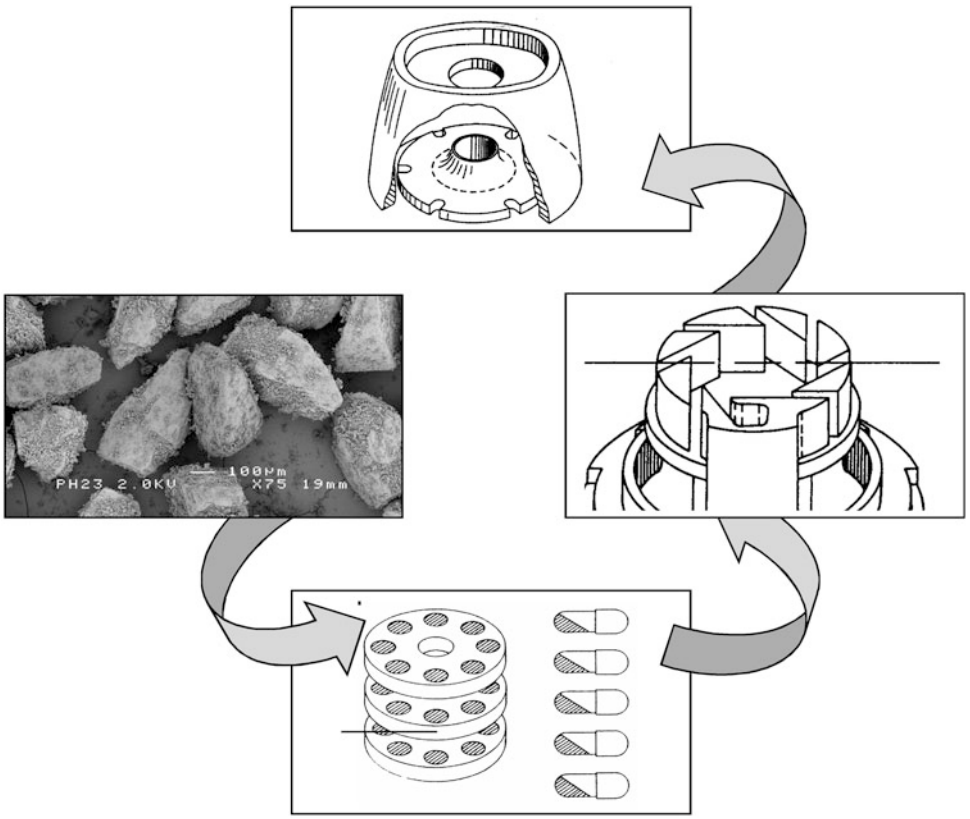

Fig. 6.6 The primary functional parts of a dry powder inhaler including a powder formulation, a dose (measuring) system, a powder dispersion principle and a mouthpiece (with flow control and aerosol directing functions)

swirl chambers or narrow channels during inhalation. Hard gelatine capsules have been the standard for more than 30 years in dry powder inhalation, but many newly developed medicines are now delivered with hydroxypropylmethylcellulose (HPMC) capsules. Particularly for moisture sensitive formulations HPMC capsules are more appropriate as they contain less water. HPMC capsules are also less prone to tribocharge during spinning and vibration and their tendency to fragment or indent at extremely low and high relative humidities of the air is considerably less when being pierced. This reduces the risk of inhalation of capsule fragments and poor capsule emptying. Gelatine capsules on the other hand have a much lower oxygen permeability. Capsules size 3 for inhalation typically contain powder masses between 5 and 45 mg depending on the type of active substance and formulation. Aluminium blisters used for inhalation are mostly smaller and contain less than 10 mg of powder. Blisters can be provided individually (e.g. Elpen, Elpenhaler®), be part of a disk (e.g. GSK Diskhaler®, with four to eight cavities), or be on a long strip for 60 doses which is coiled into a spiral in the inhaler (e.g. GSK Diskus®). Access to the powder is obtained either by piercing the blister foil and cover lid (Diskhaler®) or by separating both parts from each other (Diskus® and Elpenhaler®). For blisters on a disk or a strip, a transport mechanism is needed as part of the inhaler design. When the blister foil and cover lid are pierced, parts of the lidding strip projecting into the powder cup may prevent complete emptying of the dose. Although this is not likely to result in serious underdosing, it causes inhaler pollution which may be a burden to the patient.

In contrast to single-dose compartments, multidose reservoirs require good flow properties for the powder formulation. To isolate single doses from the powder bulk, a slide (e.g. AstraZeneca Genuair®), disk (e.g. AstraZeneca Turbuhaler®) or cylinder (e.g. Orion Easyhaler®) with small cavities is used as measuring principle making contact with the powder container. A transport mechanism displaces the measuring principle and the filling of the cavities is basically by action of the force of gravity. This requires that the inhaler is kept in the prescribed position during dose measuring to assure good powder flow into the measuring cavity. Disks and cylinders have several dose cavities along their circumference and transporting them means that a filled cavity is positioned in line with the powder channel towards the dispersion principle, whereas simultaneously an empty cavity is positioned underneath the powder container which is then filled. Slides have a single cavity which is pushed forward for the inhalation and drawn back for filling. The Turbuhaler® has a more complex dose measuring mechanism as this inhaler makes use of spherical agglomerates which are scraped into tiny dose measuring holes in a series of successive scraper chambers between the bulk container and the discharge channel. Therefore, the position in which the inhaler is held during dose measuring is less critical. On the other hand, the mechanical stability of such pellets is less than that of adhesive mixtures and this makes the inhaler more sensitive to falling or violent motions. All multi-reservoir inhalers are protected against double dosing. When the dose measuring mechanism is operated repeatedly without inhalation in between, the dosing disk or cylinder is rotated with filled cavities into which no additional powder can be measured. The only risk of not inhaling after dose activation is powder waste from the dose cavity which is in line with the discharge channel. This leads to inhaler pollution. The (Meda) Novolizer® and Genuair® have a different protection principle. Their measuring slide is put into position for inhalation with a knob and drawn back to the filling position automatically by an air valve only when sufficient flow rate is generated by the patient to guarantee good emptying and dispersion. Patients that are unable to generate this flow rate cannot use these dry powder inhalers and need to be treated with an MDI. The NEXThaler® has a similar dose measuring slide which is transported (to and fro) by the protective hood of the inhaler whereas an air triggered valve removes a plate which covers the powder cup until sufficient airflow has been generated. For extreme moisture sensitive powders, multidose reservoir inhalers may be less appropriate.

6.5.1.4 Powder Dispersion Mechanisms

As explained above, micronised particles of active substances are formulated (by agglomeration) into freely flowing powders to facilitate reproducible dose measuring. The agglomerates prepared are too large to reach the target area in the lungs and they must be dispersed (de-agglomerated). Particles of active substances blended with coarse carrier particles into so-called adhesive mixtures have to be detached from the lactose carrier particle surface onto which they adhere mainly by Van der Waals forces. In soft spherical agglomerates, cohesion (or adhesion) forces of the same nature between the small active substance (and excipient) particles have to be overcome during inhalation. Different types of de-agglomeration forces can be used and frequently emptying of the capsules and blisters and dispersion of the powder formulation occurs (at least partly) simultaneously. Most effective are inertial forces which are the result of particle collision against inhaler walls or that of high speed particle spinning and circulation. Particles may also impact with each other. Inertial forces as generated in the Novolizer®, Genuair®, (Teva) Spiromax®, (MSD) Twisthaler® and (Chiesi) NEXThaler® are proportional with the third power of the particle diameter. Drag and lift forces occur during emptying of the dose compartment or in turbulent air streams in or around special flow bodies. They are the result of considerable differences between the air and particle velocities and are largely proportional to the first power of the particle diameter. Therefore, they are much lower than inertial forces. They are also less effective when

the carrier particles have a high surface rugosity. The Turbuhaler® makes use of friction forces in addition to inertial forces. The soft agglomerates in this device pass a spiral-shaped channel in which centrifugal forces are responsible for considerable friction with the outer wall of this channel. The interaction between the drag force of the air stream pushing the particles forward and the friction forces with the inhaler wall causes internal shear which leads to disruption into smaller particles.

All dispersion forces in so-called passive (breath operated) inhalers are derived from the kinetic energy of the inhaled air stream. For well-designed inhalers with effective de-agglomeration principles this leads to a better dispersion at a higher flow rate. In addition to that, the particles in the aerosol may become finer. In contrast with what is frequently claimed in the literature [16], this is an advantage as it contributes to a more constant (patient independent) therapy. The finer particles reduce the increased deposition propensity in the oropharynx and upper airways, whereas the higher fine particle dose compensates for higher losses in the same regions. This results in a more constant central and peripheral lung deposition as has been shown for the Novolizer® in a study with radiolabeled budesonide [12]. Dispersion of the formulations is also improved by utilising the available energy within the inhaled air stream more efficiently. In most multi-dose reservoir inhalers, the powder is released from the inhaler mouthpiece within split seconds. Hence, a major part of the kinetic energy remains unused for dispersion. By keeping the particles in circulation for a certain period, a better de-agglomeration can be obtained, providing that the bulk of the aerosol is delivered within the first litre of air inhaled. The classifier types of dispersion principles in the Novolizer® and Genuair® have the longest circulation times followed by the Spiromax® and NEXThaler®, which have different circulation chambers. However for all these devices, the dose emission times remain shorter than those for most capsule inhalers. All these differences in design lead to considerable differences in dispersion efficiency and thus result in a large variation of fine particle doses at the same pressure drop across the inhaler. They also result in considerable differences in how the fine particle dose changes with the flow rate and thus, the degree of compensation for the effective flow rate on lung deposition.

6.5.1.5 The Mouthpiece

The inhaler mouthpiece can have different functions. It has been shown that minor variations of the mouthpiece geometry of an inhaler like the (Novartis) Aerolizer® may have a great effect on the throat deposition [17]. Active substance deposition in the throat is not only relevant because it reduces the lung dose but also because of possible local side effects, particularly from inhaled corticosteroids. Throat deposition is for a large part caused by carrier particles onto which a significant part of the dose remains attached during dispersion. The mouthpiece may also be used to fine-tune the total airflow resistance of the inhaler. This principle has been used in the Novolizer®, Genuair® and Diskus®. The Diskus® has two air holes on either side of the exit channel for the aerosol whereas the Novolizer® and Genuair® have a bypass that creates a clean air sheet around the aerosol to reduce deposition in the oral cavity. Compared to other DPIs, the Novolizer® and Genuair® have a different discharge pattern for the carrier particles as a consequence of which these particles are not deposited in the throat, but in the mouth from which they can easily be rinsed to prevent local side effects.

The Inhaler Resistance

Resistance to airflow is an inhaler property that is a direct consequence of its basic design, but can be fine-tuned with the mouthpiece. Persistent misconceptions exist about the inhaler resistance and hamper an optimal inhaler choice for individual patients and the correct use of DPIs. It is often postulated that operating a high resistance inhaler requires a greater effort and a higher amount of work than using a low resistance device [18]. It has also been described that patients have to inhale deeply and forcefully when using a DPI in order to receive the correct dose and that failure in this way is a common error when patients use their DPI [19]. This has resulted in the belief that patients with reduced vital capacity may have difficulties in operating high resistance inhalers effectively [16, 20]. As a response to this, the ERS/ISAM task force group has classified DPIs according to their flow rate (Φ) corresponding with a 4 kPa pressure drop across the inhaler into low resistance ($\Phi > 90$ L/min), medium resistance (60 L/min $< \Phi <$ 90 L/min), medium/high resistance (50 L/min $< \Phi <$ 60 L/min) and high resistance ($\Phi < 50$ L/min) [19]. They also explained that ‘because the internal energy in a DPI will be the same whether a patient inhales slowly through a DPI with a high resistance, or inhales quickly through a DPI with low resistance, the de-agglomeration of the powder will be the same’.

Reality is rather different, however. The amount of work for inhaling a certain volume of air through inhalers is independent of the inhaler resistance, as can be computed by expressing the energy in terms of flow rate, pressure drop and inhalation time. A lower flow rate at the same pressure drop through a high resistance inhaler is completely compensated by the longer time needed to inhale the same volume. Patients do not necessarily have to inhale deeply and forcefully to receive the correct (lung) dose. On the contrary, some inhalers are more effective when the flow rate is limited and a maximal value is not exceeded, as will be explained below. Therefore, whether patients with reduced vital

(continued)

capacity, e.g. severe COPD patients, have difficulties with operating a DPI correctly does not depend on the inhaler resistance, but on the severity of their disease. In fact all subjects, healthy or not, are able to generate a higher pressure drop across a higher resistance [21], but the value achieved at any resistance decreases with the degree of vital capacity reduction. Whether the pressure drop value achieved is sufficient for good DPI performance or not depends on the fine particle dose delivered at that pressure drop. There is no such thing as an internal energy in a DPI. What does exist is the kinetic energy of the inhaled air stream which is utilised to generate the de-agglomeration forces. Because different de-agglomeration forces are applied in different DPI designs, which may have different dispersion efficiencies, de-agglomeration cannot be expected to be the same on the basis of equal kinetic energy. In fact, fine particle doses vary considerably between inhalers at the same pressure drop and inhaled volume as will be shown and discussed in the next paragraph.

Patients with severely reduced vital capacity are often short-winded and have high breathing frequencies. Despite the fact that they may be capable of achieving sufficient pressure drop across the DPI, they may be unable to inhale sufficiently long to release the total dose from the inhaler or to transport sufficient aerosol to the central and deep lung. And inhaling against a high resistance may feel less comfortable than inhaling against a low resistance because it takes much longer before the same volume of air is inhaled, even if the amount of work is the same. Therefore, the choice of DPI resistance for a particular patient has to be balanced between patient acceptance and the benefits of a high resistance regarding lung deposition. In this respect, it should also be taken into consideration that many DPIs allow for a number of short inhalations to complete the administration of a single dose. Furthermore it has to be acknowledged that the total inhalation time including preceding exhalation and a breathhold pause is much longer than the time needed to inhale a certain volume of air and the DPI resistance has only a minor effect on that.

6.5.1.6 DPI Performance and Its Relevance to the Therapy

The airflow resistances of some currently marketed devices are presented in Table 6.2.

The difference between the highest and lowest flow rates corresponding with 4 kPa is by the factor 2.7. Although a good comparison between different inhalers cannot be made in this respect because different mouthpieces may result in different exit velocities at the same flow rate, the effect of flow rate on oropharyngeal losses for the same DPI may well be estimated from Fig. 6.5. Such a great difference in flow rates as between the extremes in Table 6.2 is likely to influence oropharyngeal losses considerably and the losses become more pronounced when the particle diameter increases. In addition to that, the lung deposition in the entire lung is shifted to larger diameters when the flow rate is increased. Whether this is disadvantageous for lung deposition or not depends on many factors, including the precise target area for the active substance, the size distribution of the aerosol and the range over which the flow rate can be varied. Lung deposition also depends on how the delivered fine particle dose changes with the flow rate. If the target area is in the larger airways the effect of the flow rate on the deposition pattern is less important than when the central or peripheral lung has to be targeted. The relatively high concentration of active substance in the larger airways compared to the peripheral lung is partly responsible for that; for most inhaled medicines the upper airways are relatively overdosed.

Table 6.2 Airflow resistances and flow rates corresponding with 4 kPa pressure drop for a number of currently marketed dry powder inhalers with asthma and COPD medication

Inhaler	Resistance ($kPa^{0.5}.min.L^{-1}$)	Flow rate at 4 kPa (L/min)
Budesonide Cyclohaler	0.019	105
Flixotide Diskus	0.026	78
Seretide Diskus	0.027	75
Budesonide Novolizer	0.028	71
Rolenium Elpenhaler	0.029	68
Budesonide Easyhaler	0.033	61
Symbicort Turbuhaler	0.034	59
Foster NEXThaler	0.034	59
Pulmicort Turbuhaler	0.037	54
Spiriva HandiHaler	0.051	39

Some fine particle doses as percent of the label claim are presented in Fig. 6.7 as function of the pressure drop for ICS from ICS-DPIs or inhalers with a combination of ICS and a β_2-agonist. The differences are rather extreme and roughly two different categories can be distinguished: inhalers with a constant fine particle output (e.g. Elpenhaler® and Diskus®) and inhalers of which the delivered FPF becomes higher when the flow rate is increased. Obviously, a high FPF is desired and most preferable is a high FPF delivered at a low flow rate. From the combination of the data in Table 6.2 and Fig. 6.7, it can be concluded that the Symbicort Turbuhaler® (29.5 %), Flixotide Diskus® (28.1 %) and budesonide Novolizer® (22.9 %) deliver the highest FPFs (<5 μm) at 2 kPa, corresponding with flow rates of 41.5, 54.5 and 50.5 L/min, respectively. The budesonide Cyclohaler® delivers the same FPF at 2 kPa as the Novolizer®, but this is at a much higher flow rate of 74.5 L/min. From Fig. 6.7 it may also be clear that inhalation through the Elpenhaler®, Diskus® and Cyclohaler® should not be forcefully, as recommended in the ERS/ISAM task force report [19], because this will not result in a higher delivered fine particle dose. On the contrary, a lower peripheral and central lung dose will be obtained due to higher oropharyngeal losses and the changes in lung distribution. For the Turbuhalers, Novolizer® and Easyhaler® the effect of inhalation effort is less critical because the losses and shift in deposition are more or less compensated by the increasing FPF, and the compensation is highest between 2 and 4 kPa. But even for the Turbuhalers and Novolizer®, an inhalation effort that will result in pressure drops higher than 4 kPa is not needed. Much more important it is to exhale deeply first before inhaling to total lung capacity, to assure aerosol penetration into the most distal airways, and finally to keep the breath for approximately 5–10 s to give sedimentation a chance.

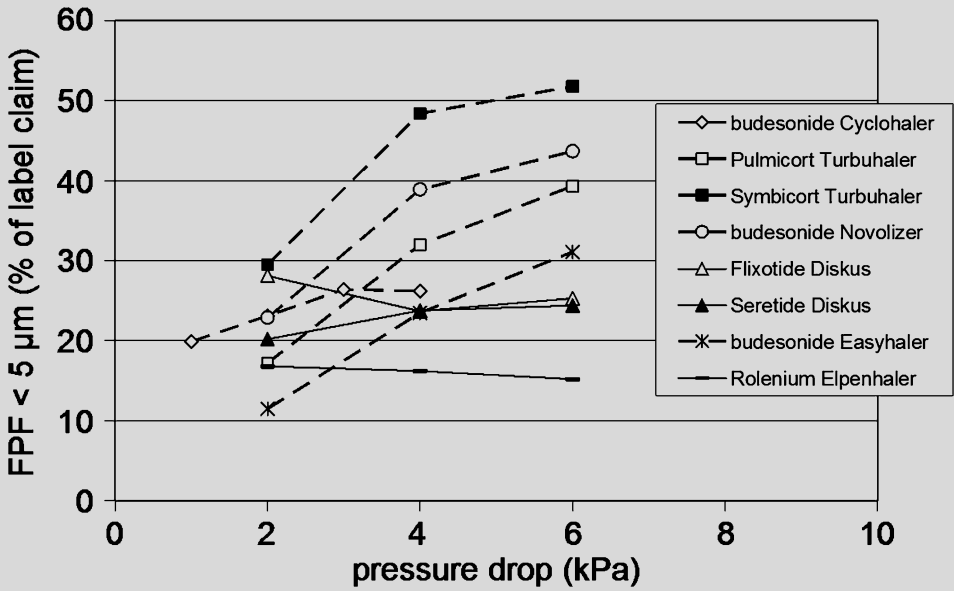

Fig. 6.7 Fine particle fractions < 5 μm (expressed as percent of the label claim) as function of the pressure drop across the inhaler

Aspects needing careful consideration when choosing a DPI for the individual patient are the ease of handling and risk of inhalation errors. Both are relevant to good adherence to the therapy and the efficacy of the treatment. In spite of numerous publications on these aspects good recommendations cannot be given because of the contradicting outcomes of the studies, of which several were reviewed by Lavorini et al. [22]. What does assist in the correct use of a DPI is signalling to the patient, as for instance given by the Novolizer® and Genuair®. Both devices give acoustic and visual signalling when the flow rate for good performance is achieved, after which the patient has to continue inhalation with the same effort for another 1–1.5 s.

6.5.2 Metered Dose Inhalers (MDIs)

In contrast to DPIs the basic design of MDI hardware is well described in the literature [23, 24]. Most MDIs apparently have a simpler design than DPIs and a key advantage of MDI systems is their low cost per dose. They are portable, convenient and have widespread acceptance by patients and clinicians. Basically they all have the same operational principle and furthermore all MDIs deliver a constant fine particle dose (independent of the flow rate). Whereas they have a relatively low resistance to airflow and this all makes the inhalation instruction less dependent on the individual type of MDI. The most relevant differences between types are in the actuator design and medicine formulation (solution or suspension), in which the type of propellant and the presence of co-solvents play an important role because of their influence on the (plume) velocity with which the aerosol is released from the actuator and rate of droplet evaporation.

6.5.2.1 Basic Design of MDIs

The general design of an MDI is shown in Fig. 6.8. The main body of an MDI is a small canister for the medicine formulation which is sized to contain sufficient volume for the labelled number of doses. The formulation contains a propellant (a gas with a high vapour pressure) which is one of the key components of an MDI. On top of the medicine formulation canister a metering valve or chamber is crimped. This has to separate a defined volume of the solution or suspension from the canister containing the amount of medicine for a single dose. The metering chamber is connected to a hollow stem that ends against the actuator orifice. On actuation of the MDI, the stem penetrates the metering chamber which becomes closed to the formulation reservoir and opens to the nozzle block in the actuator. This results in discharge of the formulation from the metering chamber through the stem and atomisation through the actuator orifice by propellant evaporation and gas expansion.

6.5.2.2 The Medicine Formulation

In contrast to DPIs, most MDIs contain a wide variety of different excipients. In the original design of the first MDIs on the market in 1957 (Medihaler-Epi™ and -Iso™, 3M-Riker), the propellant was a relatively low-pressure chlorofluorocarbon (CFC11, 12 and 114, or a mixture of these compounds). Initially, the choice of the type of propellant was rather driven by manufacturing convenience and formulation stability than by performance, and delivery to the lung was frequently as low as 5–10 % of the label claim. The Montreal protocol signed in 1987 and ratified in 1989 put an end to the use of CFCs because of their contribution to the depletion of the ozone-layer, and the CFCs needed to be replaced by hydrofluoroalkanes (HFAs) of which HFA 127 and 134a evolved as most suitable. Both HFAs used have broadly similar thermodynamic properties as CFC

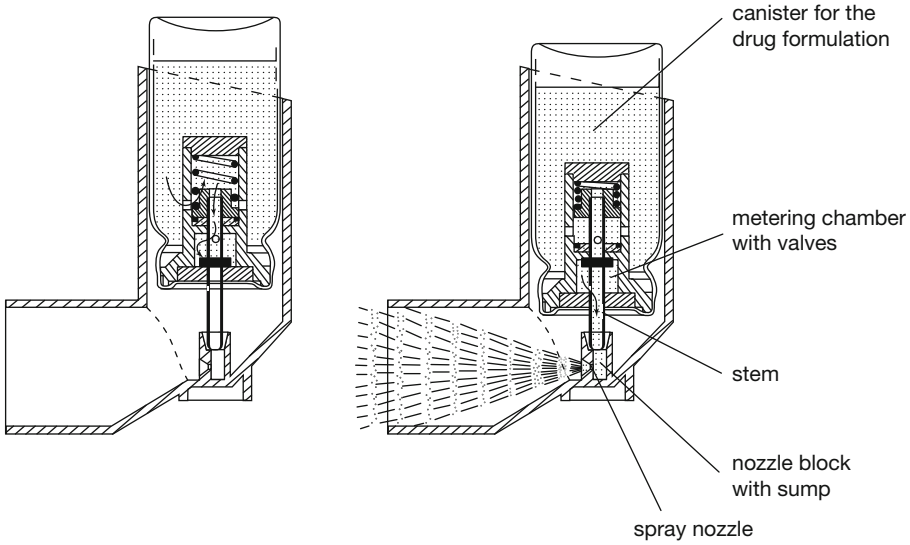

Fig. 6.8 Basic design of an MDI before (*left*) and during activation (*right*). Source: Recepteerkunde 2009, ©KNMP

12, but they are chemically different and this raised problems with certain active substances regarding solubility [25]. The active substance solubility problem is further complicated by the fact that previously used surfactants or other excipients for CFC-MDIs are insoluble in the HFAs too. For that reason co-solvents are currently often added to the formulations. Solution MDIs may have several advantages over suspension aerosols, including a higher physical stability, a more homogeneous formulation and potentially a larger fine particle dose. On the other hand, the primary co-solvent ethanol may change the size distribution of the aerosol and the evaporation rate of these droplets, whereas the excipients used in solution aerosols may also influence the pharmacological effect [25].

Suspension aerosols require that the active substance is added in a suitable size distribution to the formulation. The size distribution is obtained with the same techniques as used for dry powder inhalers, including micronisation in a fluid energy mill, spray drying and super-critical fluid drying. Whether this size distribution is the same as needed for adequate deposition in the target area depends on the concentration of active substance in the suspension. If the concentration is low, individual droplets from the actuator contain single particles of active substance and the size distribution of the suspended particles equals that required for lung deposition. If the concentration is high, droplets may contain multiple particles of active substance which cluster into small agglomerates upon evaporation of the volatile excipients. Such MDIs need finer particles in suspension. A primary concern for suspension MDIs is their physical instability due to phase separation, flocculation, agglomeration and sedimentation. Some of these processes may be irreversible and moisture ingress may negatively influence them. The active substance must also practically be insoluble in the formulation to prevent Ostwald ripening or the suspension must be thermodynamically stable if a certain level of solubility exists. Stability may further depend on the anomeric form or salt used for the active substance. In addition to co-solvents, a wide variety of other excipients may be present in the formulation, including surfactants (e.g. soya lecithin, sorbitan trioleate or oleic acid), suspending aids (e.g. PEG, PVP), bulking agents for low-concentration suspension MDIs (e.g. lactose, maltose, glycine and leucine) and traces of lubricant (silicone oil) for the metering valve.

The change from CFC to HFA propellants had consequences for delivery of the active substance to the respiratory tract. Improved delivery of beclomethasone dipropionate (BDP) from a HFA based MDI was explained by the much finer aerosol (with an average particle size of 1.1 μm) compared to CFC-BDP metered-dose inhalers, which deliver aerosols with average particle diameters of 3.5–4 μm [26]. This led to the conclusion that from a HFA-MDI only half the BDP dose is needed for the same efficacy as from a CFC-MDI [27]. More important for delivery of active substance to the lung may be the difference in plume velocity between CFC and HFA containing MDIs, however. In different studies the spray patterns [28], velocities [29] and impact forces [30] of different MDI types have been measured and the results show that CFC products have forceful plumes whereas most HFA systems produce much softer plumes. The use of HFA does not guarantee a lower plume velocity, however. The difference in velocities between CFC and HFA is for a large part due to the difference in nozzle diameters between both systems and some MDIs which use HFA propellants have a high aerosol velocity too (e.g. GSK Flixotide®).

6.5.2.3 The Metering Chamber (Valve)

The metering chamber is the MDI part with greatest complexity. To deliver a consistent amount of medicine, the valve must release a consistent mass of the bulk formulation with each actuation and the concentration of active substance in the measured mass must each time be the same. In fact the metering chamber has two valves. At rest, one (inner) valve is open to the canister to fill the chamber and this valve closes upon actuation after which a second (outer) valve is opened to release the contents of the chamber through the stem (Fig. 6.9).

The metering chamber, sealed with a ferrule onto the canister, must meet many other criteria amongst which low leakage during storage, low moisture transmission, low actuation forces and low extractables and leachables are the most important. Different designs exist for the metering chamber and many MDIs have a concept with a so-called retaining cup around the actual metering chamber. Without the retaining cup the metering chamber may drain out during storage of the MDI between inhalations or due to ‘shake out’ by the patient through the open valve between the metering chamber and the canister. The retaining cup is filled from the top of the canister when the MDI is in the inverted position (as during inhalation of a dose) and remains thus filled when the MDI is placed with the metering chamber in upright position. Retaining cups prevent not only loss of prime but also increase consistency of delivered dose when the canister approaches the end of labelled contents. Many other special

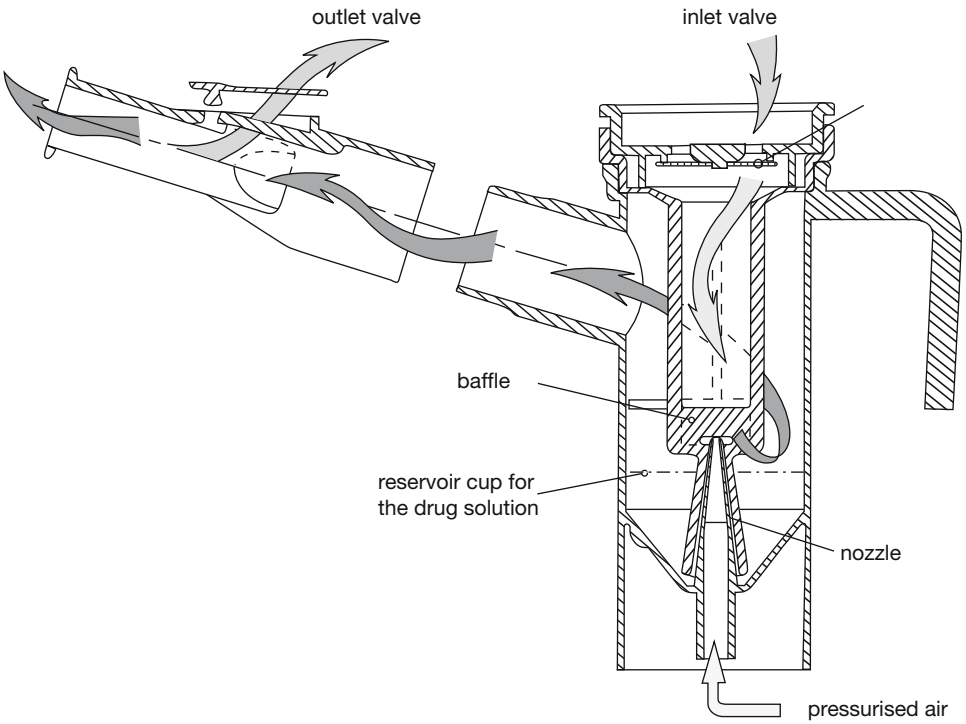

Fig. 6.9 Design of a jet nebuliser. Source: Recepteerkunde 2009, ©KNMP

metering chambers, e.g. with narrow and tortuous inlet channels, or 'fast-fill, fast empty' (FFFE) principles are in use or in development. They have been described or referred to elsewhere and will not be discussed here [31].

6.5.2.4 The Actuator

The actuator is the patient interface of the MDI in which the aerosol is formed. It is the mouthpiece of the MDI where the tip of the hollow stem from the metering chamber is positioned against a ledge in a nozzle block (Fig. 6.8). The nozzle block has a small expansion chamber (sump) which ends in a spray nozzle (also: atomisation or actuator orifice). The atomisation process is complex and starts already in the hollow stem when vapour cavities are formed in the liquid medicine formulation due to rapid expansion after the pressure is reduced compared to that in the confinement of the metering chamber. This process of expansion is continued in the sump, followed by rapid flashing of the propellant after exiting the spray nozzle [24]. Nozzle diameters are typically in the range between 0.3 and 0.6 mm and the precise geometry of the various parts of the actuator control the atomisation time as well as the size distribution of the aerosol and by that, the delivered fine particle dose. Also relevant is the geometry of the mouthpiece of which the length was originally 3–4 times longer than that for currently marketed MDIs. A long mouthpiece collects droplets that would otherwise be deposited mainly in the oropharynx. Shortening has improved portability, but it introduces the need for add-on devices (spacers or valved holding chambers). Also the mouthpiece shape and diameter affect aerosol delivery. Although several improvements have been implemented through the years, in many respects the actuator is still quite similar to its original design [31].

6.5.2.5 MDI Design and its Relevance to the Therapy

As a consequence of its push-and-breath design, MDIs require a good hand-lung coordination. Depending on the actuator design, the discharge time of a dose is typically between 0.1 and 0.5 s [24] and poor coordination may result in high losses in the mouth and throat region (in combination with the high exit velocity of the aerosol) and insufficient penetration of the active substance into the peripheral lung. Due to the extraction of heat from the mouth and throat cavity for evaporation of the propellant, patients may experience a 'cold-freon' effect which could negatively influence the inhalation manoeuvre. This cold freon-effect is particularly noticeable for CFC-MDIs having generally much lower plume temperatures (−20 °C to −30 °C) than HFA systems, although some HFA-MDIs also produce very cold plumes (e.g. Flixotide). To overcome these problems, particularly for small children and elder patients, various add-on devices can be used which either elongate the distance between the nozzle and the throat, or keep the aerosol in storage until it is inhaled. Aerosol storage in so-called valved holding chambers (VHCs) not only reduces the high throat deposition and the cold-freon effect, it also eliminates the hand-lung coordination problem. However VHCs may cause

considerable reduction of the delivered lung dose depending on how they are used, as discussed in the next paragraph. Healthcare workers giving instructions for use, should be informed about the design and properties of the MDIs they prescribe, as well as about the way these MDIs are used by their patients in order to estimate the risk of incorrect medicine delivery. For correct use of a suspension MDI, good shaking of the canister prior to dose activation is necessary in order to homogenise the suspension. Some patients tend to use their MDI upside down which could lead to incorrect refilling of the metering chamber, depending on its design.

6.5.2.6 Valved Holding Chambers (VHCs)

VHCs are storage chambers for the aerosols from MDIs with a valve in the mouthpiece. The one-way valve, which is meant to prevent exhalation through the VHC, should also remain closed during firing of an aerosol into the chamber and open when the patient inhales through the mouthpiece. Different types of VHCs exist with different volumes, made of different construction materials. VHCs reduce the oropharyngeal deposition from MDIs with a high plume velocity, but they also reduce the inhaled dose as the result of losses into the chamber which may be the result of inertial impaction against the end with the valve, electrostatic interactions with the chamber walls and sedimentation. To reduce the losses by electrostatic interactions, it is recommended to wash the spacer before use with a highly diluted solution of household detergent and dry it to the air (dip and dry method). This method is equally effective as priming with doses, which is a loss of medication. Also after coating with detergent or priming, losses in a VHC can be substantial, however, and they increase with decreasing relative air humidity (RH). For corticosteroids the dose from a well prepared VHC at low RH (30 %) may be reduced to 20–40 % of the dose directly from the MDI. At higher RH (75 %) the reduction may still be 40–70 % of the MDI dose, depending on the type of VHC and medicine formulation used. Metal VHCs or antistatic VHCs do not need priming or washing, but losses in antistatic plastic VHCs are influenced by the RH too. Losses due to sedimentation are less extreme and limited to approximately 30 % after 20 s (compared to the delivered dose immediately after firing into the VHC). Special attention should be given to VHCs used in combination with a face mask for very young children. When the mask does not fit closely to the child's face, unmedicated air is inhaled. A small leakage of approximately 0.5 cm^2 may result in near-complete bypassing of the VHC which has the consequence that only a fraction of the dose is delivered to the respiratory tract [32].

Because patients may accidentally exhale through their VHCs depending on the design or performance of the valve system, contamination with micro-organisms is possible. In VHCs used over a period of 4 months by children with asthma and recurrent cough, species of *Bacillus* and *Staphylococcus* could be detected. In a total of 64 VHCs only one was infected with *Pseudomonas aeruginosa* and no other pathogenic organisms could be found. The presence of *Bacillus* and *Staphylococcus* appeared to be independent of the type of VHC used and the cleaning procedure [33].

6.5.3 Nebulisers

Nebulisers are less frequently used than DPIs and MDIs and their application is mainly confined to active substances that are not available in registered inhalation devices (which can for instance be high dose medicines) or to the administration of medication to ventilated patients.

Basically three different types of nebulisers exist:

1. Jet nebulisers, which consist of a two-fluid nozzle connected to a reservoir cup for the medicine solution and a compressor or a compressed air system
2. Ultrasonic nebulisers
3. (Vibrating) membrane inhalers with a high output rate based on different aerosol generation principles, designs and performances

Jet nebulisers in the home situation are increasingly replaced by (vibrating) membrane inhalers which give better control over the medicine delivery to the respiratory tract than the classic jet and ultrasonic nebulisers, and may increase the adherence to the therapy.

In contrast to DPIs and MDIs, nebulisers do not contain a medicine formulation. Nebulisers receive market clearance in the USA via a 510(k) premarket notification (CDRH Guideline 784) and by CE marking in Europe. They can either be developed for the administration of a particular type of a solution or suspension of an active substance, or a medicine may be licensed for the administration with a particular type of nebuliser. An example is tobramycin solution (TOBI®, Novartis) which is licensed in the USA for use with the Pari LC Plus® nebuliser in combination with the DeVilbiss Pulmo-Aide® compressor. In Europe, a 'suitable' compressor is allowed, which for TOBI® for the LC Plus® nebuliser is specified as a compressor with a jet pressure between 110 and 217 kPa or a jet flow between 4 and 6 L/min. In practice, suitable compressors are not always used and the LC Plus® is also frequently exchanged with vibrating mesh devices, like the Pari eFlow rapid®. This is a consequence of the fact that in most countries the purchase of nebulisers is not regulated as tightly as the purchase of medication and patients can get hold of nebuliser equipment without medical advice. This situation has not really changed since the European Respiratory Society (ERS) issued their guidelines on the use of nebulisers in 2001 [34]. In fact, many nebuliser systems are still sold without or with no printed information regarding their use and the

hope of the ERS task force that their guidelines would improve clinical practice in the use of nebulised therapy throughout Europe has not come true.

6.5.3.1 Basic Design of Jet Nebulisers

The basic design of a jet nebuliser is shown in Fig. 6.9. A jet nebuliser has a reservoir cup for the solution (suspension) of the active substance and a nozzle. The nozzle starts at the bottom of the medicine reservoir and consists of two co-axial tubes ending on the same level above the medicine solution. One of the co-axial tubes is connected to a supply system for compressed air, the other tube is open on its lower side to allow medicine solution to enter this tube. For reasons of design, mostly the inner tube is for compressed air, whereas the outer tube is for the medicine solution. The air jet leaving the nozzle exit entrains liquid from the outer tube by momentum transfer. The liquid jet disrupts by shear forces into droplets with a size distribution that is too wide for inhalation. For that reason, a baffle is placed at a short distance above the nozzle. Droplets that are too large to reach the site of action in the lungs impact against this baffle according to the same principle as described for medicine particle deposition in the oropharynx and return to the liquid reservoir. Only the smallest droplets can pass the baffle and mix with the inhaled air stream.

Many different types of jet nebulisers exist and they differ not only in the properties of the delivered aerosol regarding the size distribution and output rate, but also in the efficiency with which the aerosol is delivered to the patient. They can be distinguished in:

- Nebulisers without valves
- Nebulisers with open valves
- Nebulisers with breath assisted valves
- Breath actuated nebulisers (BAN)

Most basic nebulisers (e.g. Hudson T Updraft®) have no valves. They continuously produce the aerosol which is released into a chamber connected with a T-shaped mouthpiece. One of the branches of this mouthpiece delivers the aerosol to the patient's respiratory tract during inhalation. Aerosol losses to the environment are relatively high because the patient also exhales through the same T-shaped mouthpiece and the approximate ratio for exhalation to inhalation time during normal breathing is 2:1. Exhaled air may entrain aerosol from the nebulisation cup too and release it to the environment. For that reason, different valve systems have been developed to increase the aerosol mass delivered to the patient. The most simple example is an open valve (e.g. Respironics Sidestream®) which directs (part of the) inhaled air through the aerosol chamber to flush this chamber, thereby increasing the aerosol output. Open valve systems have further evolved into breath assisted open valve nebulisers (e.g. Repironics Sidestream Plus® and Pari LC Plus®). Such nebulisers have inlet and outlet valves which open and close in an alternating way during the inhalation cycle. Upon inhalation, the inlet valve opens to enable the inhaled air to entrain the aerosol from the aerosol chamber. Meanwhile the outlet valve, which is in an elongated mouthpiece, is closed. During exhalation, the inlet valve closes to prevent aerosol escaping from the nebuliser whereas the outlet valve opens to bypass the exhaled air. In the meanwhile, the aerosol produced accumulates in the aerosol chamber and elongated mouthpiece. The outlet valve may be connected with a filter to collect exhaled aerosol particles. With such a double valve (with filter) system, the aerosol losses to the environment can be minimised. Inlet valves may be complex to reduce the range of attainable flow rates in favour of central and deep lung deposition (e.g. Pari LC Sprint® with PIF control). Such valves have an increased resistance when the flow rate becomes too high and limit the flow rate to approximately 25 L/min. Mechanical breath actuated nebulisers (e.g. Trudell AeroEclipse®) interrupt aerosol production during periods of exhalation. They have a diaphragm which moves down an actuator piston to start the nebulisation process when the flow rate has reached a threshold value of approximately 8–15 L/min [35]. During exhalation, the actuator piston moves up again to stop the aerosol production and to eliminate waste to the environment. Some modern liquid inhalers have an electronic instead of a mechanical breath actuation system, but they will be discussed separately.

6.5.3.2 Jet Nebuliser Use, Performance and Maintenance

The performance of a jet nebuliser depends on many different parameters. The jet pressure, or jet flow rate, is one of the primary determinants for the droplet size distribution of the delivered aerosol [36]. A higher jet flow rate results in smaller particles and because the size distribution of an aerosol affects the site of deposition in the respiratory tract, replacing the compressor by another type may change the efficacy of the therapy if the jet pressures of both compressors are not the same. The jet flow rate furthermore determines the nebulisation time. Additionally, the physical properties of the solution of the active substance may influence the size distribution of the aerosol and the output rate of a nebuliser [37]. These properties, of which the surface tension, viscosity and density are the most relevant, depend not only on the type of active substance in solution, but also on the concentration of the active substance [36–39]. Furthermore, the flow rate may influence the size distribution of the aerosol from a jet nebuliser and the influence increases with decreasing jet flow rate [36]. Finally, good maintenance of a nebuliser is important. Nebuliser cups are used over longer periods, varying from several months to years, and particularly when antibiotics are nebulised, good cleaning

and disinfection on a regular basis are of utmost importance. Disinfection may prevent bacterial resistance development in the medicine administration device and re-infection of the patient by medicine-resistant strains. During cleaning and disinfection, nebulisers are frequently disassembled and patients should take care that re-assembling occurs precisely as prescribed. Small variations in the distance between the nozzle exit and the baffle considerably influence the size distribution of the aerosol and so does a minor change in the diameter of the nozzle exit. Clogged nozzle exits should therefore never be opened with a sharp pin, but by submersion in warm water with some household detergent and using the compressed air from the compressor to remove the plug if it does not completely dissolve.

Major disadvantages of jet nebulisers are their long preparation, cleaning and nebulisation times and their low lung deposition efficiency. Total administration times can cumulate to more than 30 min, whereas estimated mean lung doses in well controlled clinical studies vary between only 9–20 % for breath enhanced and breath-actuated nebulisers [40]. The lung deposition in real life may even be considerably lower as patients are tempted to combine nebulisation with other activities. This may for instance result in keeping the nebulisation cup not in the prescribed position. It has been shown that controlling the inspiratory flow manoeuvre significantly increases the lung dose and reduces the variability in lung deposition from jet nebulisers. Flow and volume regulated inhalation technology with the Akita Jet® (Activaero) has shown that 60 mg nebulised tobramycin with this system and the LC Star® nebuliser can result in the same serum level after 1 h as 240 mg nebulised tobramycin with an LC Plus®/PariBoy® N combination in less than half the administration time [41]. The Akita system is voluminous however and reduces the mobility of the patient. Finally, and in contrast, the delivered lung dose may considerably deteriorate from using long, tortuous and/or corrugated tubings as in the treatment of mechanically ventilated patients. Total lung deposition in such patients from jet nebulisers may be as low as 2.3 % [42]. Successful administration of inhaled medication to mechanically ventilated patients requires special equipment and arrangements which is not further discussed in this chapter.

6.5.3.3 Basic Design of Ultrasonic Nebulisers

Ultrasonic nebulisers make use of piezo technology to create an aerosol from a solution of active substance. In such nebulisers the high frequency mechanical vibration of a piezoelectric element is transmitted to a solution of the medicine which creates standing capillary waves on the surface of that solution. Small droplets break free from the crests of these waves and constitute the aerosol. The mean droplet diameter is a function of the frequency of the acoustic signal, the surface tension, density and viscosity of the medicine solution [43]. Basically two different classes of ultrasonic nebulisers exist: those in which the ultrasonic vibration is directly transmitted to the medicine solution and those in which the oscillation is transmitted indirectly via an outer bath. A third type of ultrasonic nebulisers making use of perforated membranes (vibrating membrane technology) will be discussed in Sect. 6.5.4.

6.5.3.4 Ultrasonic Nebuliser Use and Performance

As for jet nebulisers, a great variety of different designs exists for ultrasonic nebulisers. Which type to select primarily depends on the desired droplet size distribution. The design, in particular the operating frequency, is a major determinant for the aerosol characteristics but also incorrect use may influence the aerosol properties. Particularly the filling degree of the outer bath of jacketed nebulisers proves to be very critical for performance. Ultrasonic devices may also have a baffle to return large droplets to the medicine reservoir and a fan to assist the fine particle output. The size of the droplets is often larger and the aerosol output rate higher compared to jet nebulisers. Evaporation is less extreme in ultrasonic nebulisers however, and therefore the increase in concentration of the active substance with aerosolisation time is lower. Residual volumes in ultrasonic nebulisers are higher. Solutions of high viscosity and suspensions of active substance (e.g. budesonide) cannot efficiently be atomised by ultrasonic nebulisers. In contrast to jet nebulisers, where a drop in temperature can be observed due to evaporation, the temperature of solutions in the reservoir of ultrasonic nebulisers increases during the atomisation process. This may result in partial degradation of heat sensitive substances, such as proteins. Liposomal formulations have successfully been delivered with ultrasonic nebulisers, although some disruption of vesicles has been observed and increasing the vesicle stability by use of substances such as cholesterol is recommended [44]. Ultrasonic nebulisers do not require compressors and are generally much smaller and less heavy than jet nebulisers. In addition, they are almost silent, but these advantages have not made them very popular in most European countries [34]. Therefore, they are not discussed further (see also novel liquid inhalers).

6.5.3.5 The Choice of Device and Instructions for Use

A great variety of jet and ultrasonic nebulisers is available for a wide range of size distributions and different output rates [45]. If an inhaler is approved for the administration of a particular type of medicine formulation, it should be the first choice for that application. If the nebuliser or compressor (for jet nebulisers) is not available, as for instance

(in Europe) the DeVilbiss Pulmo-Aide® compressor for TOBI®with the LC Plus®, an alternative with the same specifications should be selected. For a compressor, this is the jet flow through the nebuliser cup. Also when a jet nebuliser is connected to a compressed air system (as is mostly the case in hospitals and nursing institutes) it should be controlled such that the pressure regulator is set to the correct value for the type of nebuliser cup used. This must be checked when the nebuliser is operated. Only when patient adherence to the therapy is very low, for instance due to very long nebulisation times, a change of device may be considered, as a (slightly) different lung deposition pattern could be less bad for the patient than omitting the medication on a regular basis.

6.5.4 Novel Liquid Inhalers

In addition to classic jet and ultrasonic nebulisers a new class of high-performance novel liquid aerosol delivery devices has become available. They have a high aerosol output rate in common (yielding a dense mist) and most of them have a perforated vibrating membrane (mesh) as aerosol generator. The oscillations are obtained with piezo technology which in combination with the membrane is referred to as vibrating membrane technology (VMT). Basically two slightly different principles can be distinguished: those in which the membrane is oscillated (e.g. Pari eFlow rapid®) and those in which a horn transducer adjacent to the membrane is vibrated (e.g. Philips Respironics I-neb®). The perforated membrane makes contact with the medicine solution and the pressure pulses of the liquid against the membrane force the medicine solution (or suspension) through the tiny holes which determine the size of the droplets. Principles based on Rayleigh break-up of liquid jets forced through the perforated membrane under a constant pressure are still in development (e.g. Aradigm AERx Essence®). Only one alternative principle is currently available on the market: the Respimat® soft mist inhaler (Boehringer Ingelheim). Although the Respimat® has a different design, it will also briefly be explained in this paragraph. A good review of novel liquid nebulisers based on different aerosolisation principles has been given by Knoch and Keller (2005) [46].

Compared to classic jet and ultrasonic nebulisers, most novel liquid inhalers have the advantages of:

- Much shorter nebulisation times
- Delivering narrower size distributions
- Being small and portable
- Being battery operated, which eliminates the need for mains
- Being less noisy
- Having lower fill and residual volumes
- (Optional) Breath controlled or adaptive medicine delivery
- (Optional) Patient monitoring and feedback

Reduction of the nebulisation time and a greater convenience in handling may increase the patient's acceptance and this can reflect positively on the adherence to the therapy. Many novel liquid inhalers are electronic devices. This offers possibilities for patient monitoring and feedback, but also for so-called adaptive aerosol delivery (AAD), a principle of medicine delivery which has been described elsewhere [46]. In brief, a flow sensor in the inhaler measures the patient's breathing pattern and the system's software computes the mean of a few breathing cycles. The average breathing cycle is the basis for pulsed aerosol delivery only during periods of inhalation, thereby avoiding waste during exhalation. It is believed that the narrow size distributions of the aerosols from membrane nebulisers contribute to better targeting, but there is no evidence yet for that from deposition studies.

Different novel liquid inhalers are on the market for different applications and only some representative examples are described in more detail in this section.

6.5.4.1 Respimat®, Boehringer Ingelheim

The working principle of the Respimat® has been described before by Zierenberg [47]. In the Respimat®, a medicine reservoir is connected to a capillary tube with a one-way valve. During preparation of the device, a spring is loaded and medicine solution is drawn through the capillary into a metering chamber. When the patient presses the dose release button, the metered volume of medicine solution is pressed through a so-called uniblock with a nozzle by mechanical power of the preloaded spring. The nozzle releases two converging jets at precisely controlled angles which collide with each other at a short distance from the nozzle exits. This creates a slow-moving fine mist. The inhaler is re-usable but the medicine reservoir is replaceable. When a new cartridge is inserted, the inhaler has to be primed to expel air from its inner parts. The Respimat® is available with tiotropium bromide (Spiriva®) and ipratropium bromide with salbutamol (Combivent®). The inhalation technique is similar to that for an MDI and requires a good hand-lung coordination. The emission time is longer (approximately 1.5 s) and the exit velocity is lower (approximately 0.8 m/s) compared to MDIs, however. The fine particle dose from the Respimat® strongly depends on the inspiratory flow rate, which due to the low resistance can be very high (2 kPa corresponds with 125 L/min). Measured with a cooled Next Generation Impactor to minimise droplet evaporation, FPF 1–5 μm from the Spiriva Respimat® decreases from over 40 down to 28 % when the flow rate is increased from 30 to 90 L/min. The reason is a strong reduction of

particularly the larger particle fractions (from 35 % at 30 L/min to 20 % at 90 L/min for the fraction 3–6 μm). As a consequence, the fraction < 3 μm remains more or less constant (18 % at 30 L/min versus 22 % at 90 L/min), but this is partly the result of a much higher fraction < 1 μm at the higher flow rate (8.0 % versus 1.8 %). Therefore, it should be recommended not to inhale with much greater effort as during tidal breathing through the Respimat®.

6.5.4.2 eFlow (Rapid)®, Pari

The Pari eFlow rapid® is an example of a vibrating mesh nebuliser [48]. The eFlow® platform makes use of the TouchSpray™ (piezoelectric) technology [49] and the rapid®, as one of the members of the eFlow® family, is designed to deliver nebulised medicines used in CF therapy. It reached the European market in 2005 and according to the manufacturer, this device has already reached approximately 75 % market share amongst European CF patients. The eFlow rapid® consists of a controller and a handset. The handset comprises the medication reservoir with an aerosol chamber, the vibrating membrane in contact with the medicine solution and the mouthpiece. The membrane has a large number of tapered holes that narrow towards the aerosol release side. During vibration, sound pressure is build up in the vicinity of the membrane thus ejecting the fluid through the holes. Because all holes have the same size, the droplet size distribution in the aerosol is rather narrow. According to Pari, the hole diameters can be adjusted from 2 μm upwards to meet the requirements for different therapeutic applications. Also according to the manufacturer, the mass median aerodynamic diameter of TOBI® (tobramycin), measured at 28.3 L/min, is 3.95 μm from the eFlow rapid® versus 3.5 μm for the Pari LC Plus® jet nebuliser with PariBoy N® compressor. The difference has to be confirmed in several independent studies and it can increase when a more powerful compressor (with higher jet pressure) is used for the LC Plus®. On the basis of the differences in MMAD and the span of the size distribution, it must be expected that both nebulisation devices result in different distributions of active substance over the lung and therefore, they cannot be considered completely equivalent in this respect. The average nebulisation time with the eFlow rapid® is considerably shorter than with classic jet nebulisers and the reduction can be more than 50 %. CF patients do use their eFlow rapid® also for the administration of other medication, like salbutamol, ipratropium bromide, terbutaline, colistimethate sodium, rhDNase and acetylcysteine. This has the risk of membrane pollution, as patients do not always clean their nebuliser equipment properly after use. It can result in clogging of holes in the perforated membrane, which does not result in a change in particle size, but in a reduced output rate [50]. This leads to longer nebulisation times and may be at the cost of the patient's adherence to the therapy. Pari has developed a function test for the membrane and a cleaning device (easycare), but after a number of cleanings the membrane should be replaced.

6.5.4.3 I-neb®, Philips Respironics

The I-neb® is a membrane (mesh) nebuliser with an AAD system which is approved for the delivery of iloprost in the USA and in Europe as a multipurpose nebuliser for special applications included in the medicine license [51]. The I-neb® consists of a mouthpiece, a medication chamber and a handpiece. The medication chamber comprises a horn with the mesh plate which has 5,000–6,000 holes of 3 μm in diameter. The piezo crystal imposes a high frequency upward and downward movement upon the horn and this pushes the liquid through the holes in the plate. The I-neb® is operated with discs that are programmed for delivery of specific medicine formulations. These discs have microchips that correspond with the I-neb® handpiece about the dose, the dosing frequency, the number of doses and other variables related to the medicine administered. The I-neb® AAD system has two different modes of operation: the tidal breathing mode (TBM) and the target inhalation mode (TIM) which is for slow and deep inhalation. The TBM mode is suitable for most adults and children of 2 years and older; for optimal use of the TIM mode, patients need to have a forced vital capacity > 1.75 L. Breathing with TIM increases lung deposition and reduces total treatment time. It is claimed that the majority of medicine in the aerosol from the I-neb® (60–80 %) is within the size fraction < 5 μm. Due to its higher efficiency compared to classic jet nebulisers, a threefold reduction in medicine volume and up to a fivefold reduction in nominal dose may be possible with the I-neb® with the AAD system [51].

Similar portable mesh nebulisers are available from Omron (MicroAir NE-U22®) and Aerogen (Aeroneb Go®). The Aeroneb Go® is based on the OnQ™ vibrating mesh technology which comprises a dome-shaped aperture plate containing over 1,000 precision-formed tapered holes, surrounded by a vibrational element. The aperture plate is caused to vibrate at over 128,000 times per second. Aerogen also have a multidose vibrating mesh nebuliser (Aerodose®) [52] and two VMT devices for hospital use (Aeroneb Pro® and Aeroneb Solo®). The Aeroneb Pro® is a reusable, multi-patient use nebuliser which is suitable for hospital environments where the appropriate sanitisation facilities are available. This autoclavable nebuliser provides effective dose delivery of physician-prescribed inhalation solutions for infants through

(continued)

adults in both on and off ventilator applications. The Aeroneb Solo® is a single-patient use nebuliser for continuous and/or intermittent nebulisation, ensuring targeted delivery of active substance to the smallest airways in the lungs. The silent operation of the Aeroneb Solo® allows it to be used in paediatric ICUs where noise levels are critical. The Solo® has a low residual volume (<0.1 mL for 3 mL dose). The Omron MicroAir NE-U22® has a vibrating horn within the liquid reservoir that pushes the liquid through the membrane. The frequency of oscillation of this horn is 180 kHz and the particle diameter claimed for the MicroAir is 5 μm. For the MicroAir it is recommended that the vibrating mesh cap is replaced every 6 months to maintain its peak performance.

The novel liquid inhalers have several specific pros and cons. An attractive feature is the potential for a single platform to deliver multiple inhaled medicines in complex treatment regimens, like in CF [51]. However, it has to be recommended that patients and physicians do not decide to change from an approved (medicine-nebuliser) combination to a novel liquid inhaler when the medicine formulation has not yet been tested first in the VMT device. Neither should patients decide to use their inhaler for other medication than the medicine for which their mesh nebuliser was prescribed. Different solutions of active substance may result in aerosols with different size distributions due to differences in physico-chemical properties and this can lead to poor targeting of the site of action (poor efficacy of the therapy) compared to delivery with the approved nebuliser. Another advantage of the new class of nebulisers is the wide range of doses that can be delivered with these devices. Pari claim a range from a few micrograms up to several grams. Also the possibility to store data about the use of the inhaler and to give immediate feedback to the patient about the inhalation performance may be an advantage. Synchronising aerosol delivery with the breathing manoeuvre (as with AAD) may furthermore considerably improve the efficacy of the delivery of active substance to the lungs. Reduced nebulisation time, smaller and mostly battery operated devices and a more silent operation are likely to increase patients' adherence to the therapy compared to classic jet and ultrasonic devices, but whether a better adherence is really achieved has still to be proven. The high price of most novel liquid inhalers is a serious drawback and could become a reason for healh funders to deny reimbursement when improved adherence is not shown. Vibrating meshes are also vulnerable to pollution and the need for good cleaning must be emphasised. Patients should clean their inhaler thoroughly and immediately after use according to the instructions in order to prevent clogging of the apertures in the membrane. In practice, patients are not always compliant with the instructions, however, and it has been shown that off-clinic use may result in a significant change in performance within a period of 6 months [50]. Finally, also the most recently developed systems require at least 2–4 min for the administration of a dose and this excludes the time needed for preparation and cleaning of the equipment. For patients with multiple medicine therapies, this is still burdensome. For a number of applications, dry powder inhalation may be a better alternative, also because dry powders are more stable than medicine solutions. Therefore, they need no cold chain storage.

6.6 Medicine Formulations for Nebulisation

Many marketed medicine formulations for nebulisation are available, but in contrast to preparations for dry powder inhalers and metered-dose inhalers, solutions and suspensions for nebulisation are also prepared in pharmacies. Marketed formulations may furthermore have to be diluted, depending on the type of inhaler used. Many nebulisers have a residual volume between 1 and 2 ml and the fill volume has to compensate for these losses. Compensation is also needed for the amount of medicine in the residual volume. Diluted formulations must be used within 24 h after preparation because of poor stability. Most nebulised medicines fall into two physico-chemical categories: solutions and suspensions [34]. For solutions it is assumed that the medicine is homogeneously distributed throughout all droplets. Suspensions are inherently more complicated as their density may be less homogeneous and individual droplets may contain different amounts of the active substance. This could lead to a droplet size dependent concentration of the active substance or a considerable change in concentration with nebulisation time. Below some of the most relevant aspects regarding the preparation of medicine solutions and suspensions for nebulisation are summarised; additional general recommendations for preparation, labelling, testing and packaging can be found elsewhere in this book.

6.6.1 Medicine Solutions

Medicine solutions for nebulisation may contain several additives such as co-solvents, solubilising and stabilising agents, antimicrobial preservatives, salts and pH-regulators to adjust the acidity and tonicity of the solution. Additives may contribute to the osmotic value. Both high and low osmotic values can produce cough and bronchoconstriction

(or both). If the patient shows signs and symptoms of bronchospasm, baseline spirometry before dose administration is recommended, followed by spirometry at 15 and 30 min post-dose. Active substances such as salbutamol, terbutaline and ipratropium are mostly dissolved in isotonic saline (0.9 % sodium chloride). Sodium chloride strengths between 3 % and 7 % are also used for nebulisation, but they may not be mixed with other medicines. To enhance the solubility of active substance in water or saline, the addition of a co-solvent may be needed and surfactants can be added. Also controlling the acidity may lead to a better solubility and the European Pharmacopoeia allows to vary the pH within the range between 3 and 8. However, it is known that aerosols with a pH below 4.5 can cause cough and bronchoconstriction, particularly in asthmatic patients, and some caution is therefore required. The medicine in solution may also change the pH of the solvent and pH-regulators such as sulphuric acid and sodium hydroxide are frequently added to keep the acidity within the desired range. If the solubility of active substance and stability allow for it, it is best to keep the acidity close to neutral as the pH in healthy lungs ranges between 7 and 8.

6.6.2 Medicine Suspensions

Currently, suspensions prepared from micronised active substances are the only marketed delivery system for nebulisation of poorly water soluble substances such as steroids and cyclosporine [53]. Several problems are inherent in nebulising micro-suspensions and they vary from non-optimised lung deposition for the active substance to heterodispersity of the active substance concentration in the aerosol droplets and poor compatibility with different types of nebulisers, particularly ultrasonic devices. Suspensions may also have poor stability and the two components (solid and liquid) tend to separate with time within the formulation by sedimentation or flocculation, depending on the particle density relative to that of the liquid. Several jet nebulisers can deliver suspensions quite effectively, even independently of the primary particle size [54], but ultrasonic devices may convert primarily the continuous phase into aerosol whereas vibrating mesh inhalers can be blocked by particles being larger than the pore diameter of the membrane.

In addition to solutions and suspensions, liposomal formulations of active substances are used and various nanoemulsion-based formulations and micellar solutions are explored for nebulisation [55]. Currently, no marketed inhaled liposomal products are available [56], but liposomal amphotericin B for injection or infusion is frequently used for nebulisation against invasive fungal pulmonary infections. Compared to amphotericin B, which is relatively instable and therefore commercially available as a complex with sodium desoxycholate, the liposomal formulation has a higher tolerability profile. Most liposomal formulations are currently developed for sustained release however, and two liposomal antibiotics for nebulisation (Arikace®, Insmed, for amikacin and Lipoquin® and Pulmaquin®, Aradigm, for ciprofloxacin) have received orphan drug designation to treat lung infections caused by nontuberculosis mycobacterial (by the European Medicines Agency) and for inhalation in bronchiectasis (by the US Food and Drug Administration (FDA)) respectively. Which type of nebuliser to use best for liposomal formulations may not only depend on the desired particle size distribution of the aerosol and aerosol output rate, but also on relevant physico-chemical properties of the formulation. Both jet and ultrasonic nebulisers damage the liposome structures and the smaller the droplet size, the greater the damage may be. The degree of disruption also depends on the excipients used, and the inclusion of cholesterol or DPPC increases the resistance to disruptive forces [44]. The liposomal ciprofloxacin Pulmaquin® is developed for Aradigm's AERx® pulmonary medicine delivery platform (with perforated mesh).

6.6.3 Stability of Formulations for Nebulisation

Most ready-to-use liquid preparations for nebulisation are supplied in single-dose vials and according to the European Pharmacopoeia, they have to be sterile and preservative-free. When they are supplied in multidose containers, they have to be sterile if they do not contain an antimicrobial preservative or when the preparation does not have adequate antimicrobial properties itself. The multidose containers have to be designed to prevent microbial contamination of their contents during storage and use. A wide variety of preservatives is available but some of them, like phenol, bisulfites, edetate and benzalkonium chloride can cause airway irritation and result in bronchoconstriction or reduce the efficacy of the medicine [57]. Other compounds such as chlorobutanol, methyl- and propyl-parahydroxybenzoate and also benzalkonium chloride are ciliotoxic at

concentrations equal to or lower than those in use for preserving aqueous formulations [58, 59]. Ciliotoxicity, reduced medicine efficacy and airway irritation resulting in cough and chest tightness are the reasons why many bactericidal agents have been removed now from marketed medicine formulations. Some alternatives have been presented as less harmful, like chlorocresol and chlorbutanol [60] but generally it may be safer to supply sterile preservative-free liquid formulations for nebulisation in unit dose vials.

In formulations for nebulisation also the stability of the active substance itself in solution must be taken into consideration. For instance, colistimethate sodium (CMS), increasingly used to treat multi-resistant gram negative infections by nebulisation, spontaneously hydrolyses in aqueous solution to form colistin A (polymyxin E1) and colistin B (polymyxin E2/B). High levels of these decomposition products have been associated with nephrotoxicity and even death and in 2007 the FDA issued an alert after a patient died following the inhalation of a solution of CMS. CMS is supplied as a lyophilised powder and current recommendations state that CMS should be reconstituted no more than 24 h prior to the administration by nebulisation [61]. It is important to note that sterile water is the diluent recommended by the major manufacturers because reconstituted CMS in saline is significantly less stable [62]. Recently, the stability of reconstituted CMS for injection in sterile water was investigated at different storage temperatures and it was found that total colistin A and B formation at room temperature in 24 h is less than 1 % [61].

6.6.4 Mixing of Formulations for Nebulisation

Most product information leaflets for nebulised medicine formulations discourage mixing of marketed formulations but in practice different formulations are frequently mixed to increase patient comfort. Particularly CF patients tend to combine medicines in order to save time as well as to overcome adverse effects (e.g. bronchoconstriction) of one active substance (antibiotic) by another (salbutamol). They also tend to refill their nebuliser with a new medicine without emptying and cleaning the nebuliser between the administrations. Relatively little has been reported in the literature about the compatibility of medicine mixtures, however, and interactions may be expected with respect to chemical and physical stability, droplet size distribution of the aerosol, nebuliser output rate and therapeutic effect. From a survey of studies on chemical stability, it is known that particularly dornase alpha (Pulmozyme®) is incompatible with many other nebulised medicine formulations due to inactivation of the protein [63]. Additives, like stabilisers that work well in some medicine formulations, may be incompatible with other preparations and induce cloudiness or precipitation. For instance, benzalkonium chloride may form an oily, non-crystalline complex with cromolyn, depending upon its concentration [64]. Benzalkonium chloride is also incompatible with colistin, whereas edetate is known to increase the activity of azithromycin [65] and colistimethate sodium [66] by chelating divalent cations such as calcium. The effect of mixing medicine solutions or suspensions on nebulisation performance is studied even less although for a few combinations data can be found in the literature. For instance, it has been shown that inhalation solutions of Pulmozyme® can be mixed with tobramycin (Bramitob® or TOBI®) as one of the few examples of compatibility for dornase alpha without changing the stability of these products and their aerosolisation performance [67]. In contrast, mixing salbutamol with other medicine solutions may change the mass median aerodynamic diameter in either direction, depending on the combination and the type of nebuliser used [68]. The changes in median diameter can be as high as 50 % and also the span of the size distribution and the delivered respirable mass are influenced. This may have a considerable effect on the dose delivered to the site of action and thus the efficacy of the therapy. For these reasons, mixing medicine formulations for nebulisation should preferably be avoided unless they are needed to obtain good adherence to the therapy. In the latter case, desired combinations need not only to be tested on chemical and physical stability, but also on their aerosolisation performance in the nebuliser used for the administration. Furthermore, mixtures should be made from preservative free solutions and suspensions to avoid incompatibilities with these additives.

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