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Abstract
Nebulizers are widely used for the inhalation of drug solutions in a variety of respiratory diseases. The efficacy of nebulizer therapy is influenced by a great number of factors, including the design of the device and the characteristics of the drug solution. Incorrect cleaning, maintenance and disinfection procedures may change the nebulizer performance in time, whereas patient factors can influence the lung deposition of the generated aerosol. In this review the technical aspects of nebulization of drug solutions will be discussed. Two main parameters are generally used to evaluate the performance of nebulizers: the droplet size distribution of the aerosol and the drug output rate. The droplet size distribution and the drug output rate are basically determined by the design and user conditions of the nebulizer. A higher gas flow of the compressor in a jet nebulizer or a higher vibration frequency of the piezo electric crystal in an ultrasonic nebulizer, decreases the droplet size. The choice of the type of nebulizer for nebulization of a certain drug solution may initially be based on laboratory evaluation. The major part of the mass or volume distribution should preferably correspond with aerodynamic particle diameters in the range of 1 to 5 micrometer. The intended drug output must be realized within a reasonable nebulization time (less than 30 min). From the drug output only a minor fraction will be deposited in the lung. The relation between in vitro and in vivo deposition is only partly understood and to date it has not been possible to predict drug delivery only from in vitro studies on nebulizers. Therefore, studies in patients should be performed before a drug solution for nebulization can be recommended for clinical practice.
The mechanical properties of nebulizers are likely to change during use. An average utilization time of nebulizers is not available. Therefore, the performance of nebulizers should be checked periodically.
Patient compliance in nebulizer therapy is relatively low. This is partly due to the fact that, at present, drug solutions for nebulizers cannot be administered efficiently within a short period of time. More efficient systems should be developed. If possible, nebulizers should be substituted to more efficient systems, e.g. dry powder inhalers or metered dose inhalers.

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Introduction

Inhalation is a common technique of drug administration to patients with a variety of lung diseases [1 2]. Several classes of drugs are available for inhalation, e.g. ß$_2$-agonist drugs, corticosteroids and anticholinergic drugs. Next to these anti-asthma drugs, inhalation of antibiotics is frequently applied for patients with Cystic Fibrosis (CF) [3 4]. Whereas pentamidine has been used for the prophylaxis of Pneumocystis pneumonia in patients infected with HIV virus [5 6] ing extent for the administration of drugs with systemic action that can either not be absorbed by the gastro-intestinal tract or suffer from a first pass effect.

In inhalation therapy the drugs are administered directly to the site of action. As a result, the lag time of the action onset of the drug is short, less drug substance is needed and systemic side effects are reduced.

Three types of devices are commonly used for the administration of drugs to the respiratory tract: nebulizers, pressurized metered dose inhalers (pMDI) and dry powder inhalers (DPI). An adequate understanding of the advantages and disadvantages of the different systems is required to make a proper choice between the systems [7 8].

For a long time the MDI has been considered as a convenient device most commonly used in inhalation therapy [9 10]. MDIs contain the drug in suspension, emulsion or solution to which a propellant has been added. When the device is activated, a metered dose is released at high velocity, which requires a simultaneous inhalation by the patient. Therefore, a precise coordination of both actions (activation and inhalation) by the patient is mandatory. Obviously the device as such is unsuitable for young children who lack the required coordination [11]. The high velocity of the aerosol constitutes an inherent disadvantage of the system because it leads to a significant oropharyngeal deposition. To facilitate the coordination, breath actuated MDIs have been introduced. In these devices the inspiratory flow triggers dose release. A disadvantage of MDIs is the so called "cold freon effect" caused by rapid evaporation of the propellant. The cooled aerosol can cause bronchoconstriction. The use of a spacer can partly overcome these disadvantages. Until recently chlorofluorocarbons (CFC) were used as propellant. Because of the environmental burden caused by the CFC most devices are being reformulated with HFA227 or 134A or exchanged by alternative devices.

A dry powder inhalation system consists of a dry powder formulation, a dosing principle and an inhaler device [7]. In most systems the micronized drug is formulated with an inert excipient, like crystalline alpha lactose monohydrate, but excipient free DPIs have also been developed (e.g. the Pulmicort Turbuhaler). Dry powder inhalers use the inspiratory flow of the patient for dose entrainment and disintegration of the powder formulation. The dose is delivered from a multiple dose reservoir or from a single dose unit (capsule or blister) during inhalation. The first inhaler on the market was the Spinhaler, a single dose DPI based on encapsulated powder. Some DPIs require a relatively high inspiratory flow rate in order to deliver an acceptable mass fraction of the dose as fine particles. For other types of dry powder inhalers, the flow increase rate is rather the relevant flow parameter [12]. The required inspiratory flow curve can not always be attained, especially not by patients with severe bronchoobstruction or young children

are typically used in situations when severe obstruction of the airways or insufficient coordination by the patient does not allow the use of other systems. They are for example recommended for young patients who cannot manage other devices. Furthermore, nebulizers are used for drugs that cannot or have not yet been formulated as DPI or MDI, such as antibiotics, enzymes or mucolytic drugs. Finally, nebulization of $ß_2$-agonists and anticholinergic drugs is common practice in acute asthma.

A drawback of inhalation therapy with nebulizers is the low deposition efficiency of the drug in the target area. On average, only 10% of the dose released from the nebulizer will reach the site of action, which is low compared to dry powder inhalers for which lung deposition between 20 and 30% of the dose have been reported [13]. The variability of the inhaler performance is high and the deposition in the lung can range from 0 to 30% of the released dose [14]. For potent drugs, like $ß_2$-agonists and corticosteroids, which are dosed in quantities below 1 milligram, the desired clinical effect will still be obtained with nebulizers in spite of low efficiency of the drug delivery. However, for the delivery of antibiotics which are dosed in milligrams, efficient systems are paramount in order to reduce the time needed for inhalation of the total required dose and to attain sufficient therapeutic efficacy. Furthermore, pulmonary delivery of new drug substances like proteins and peptides and complex formulations of liposomes or genetic material containing viral vectors require improved efficiency [15].

An appropriate device and an appropriate formulation allows nebulization of many drugs in a wide range of doses [16]. However, a proper understanding of the working principle and the factors influencing the performance of nebulizers is essential for an effective use [1 17]. Knowledge of the basics of nebulization is required in order to be able to prescribe the proper dose and to understand the difference between the prescribed nominal dose and the amount thereof delivered to the lung [18]. In this paper we will discuss the technical aspects of the nebulization of drug solutions.

Types of nebulizers

There are two basic types of nebulizers, the jet and the ultrasonic nebulizer. The jet nebulizer uses compressed air to aerosolize the drug solutions, whereas the ultrasonic nebulizer uses energy from high frequency sound waves.

Jet nebulizers have evolved from the conventional type to the open vent and finally to the breath assisted type. In jet nebulizers, the droplet generator is a two-fluid atomizer. Different designs of the same basic principle are used. For a typical jet nebulizer, compressed air passes through a narrow hole and entrains the drug solution from one or more capillaries mainly by momentum transfer. The complex liquid break-up process is largely depending on the nozzle design and usually a combination of turbulent rupture of the instable liquid column and secondary droplet break-up. In its simplest form, the air impinges directly on a solid jet of liquid (e.g figure 1, showing the Hudson T Updraft® Tefa, Nieuwegein. The

to the required range for inhalation. Only smaller droplets with less inertia can follow the streamlines of the air and pass the baffle.

A different nebulizer design with an open vent is shown in figure 2 (Sidestream® Medic-Aid, Romedic,

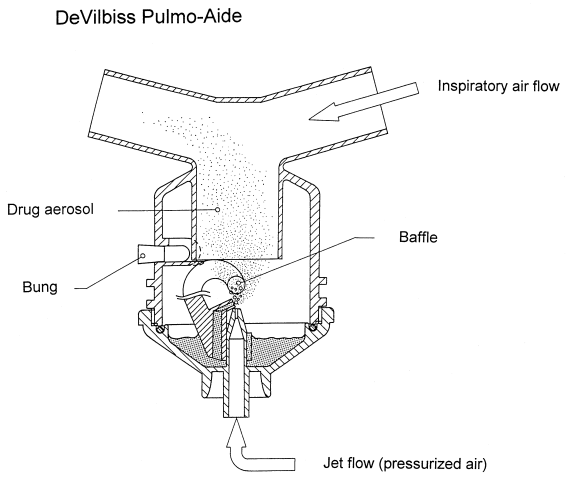


Figure 1

In this figure the working principle of the jet nebulizer is explained using a schematic presentation of the Hudson T Updraft nebulizer. The gas flow from the compressor (DeVilbiss Pulmo-Aide) passes through a narrow hole, impinges on the entrained drug solution and droplets are formed. Larger droplets are trapped by the baffle. Small particles pass the baffle and are available for inhalation by the inspiratory flow.

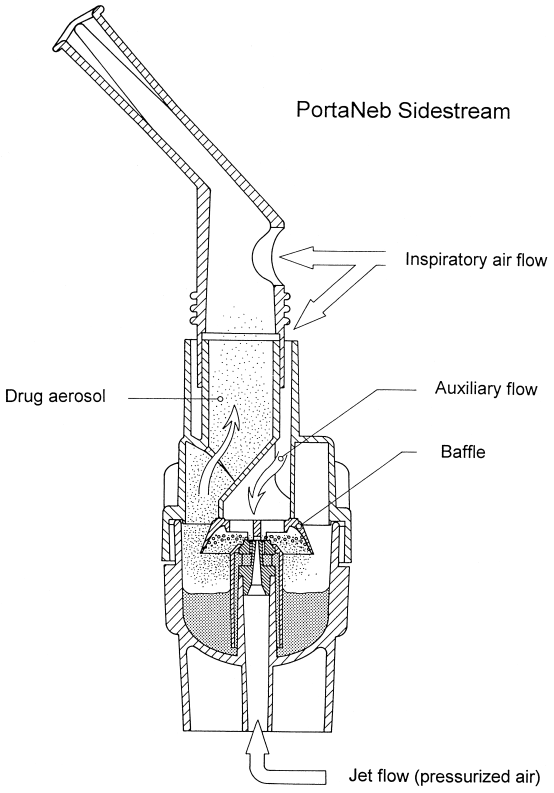
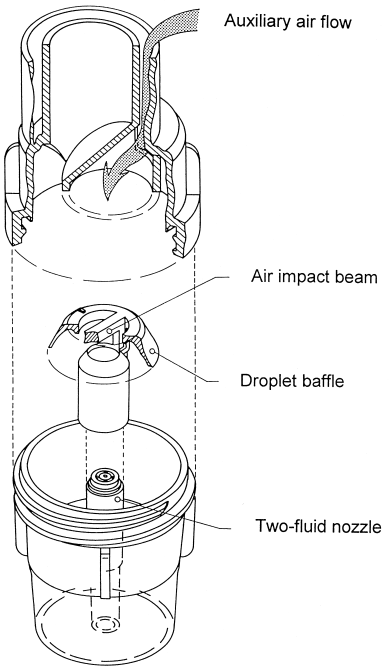


Figure 2

A schematic presentation of the Sidestream open vent nebulizer. Part of the inspiratory air (auxiliary flow) is leaded through the nebulization chamber. This improves droplet entrainment from the nozzle area. The nebulizer

the inspiratory air flow to pass through the nebulization chamber. The auxiliary air flow improves droplet entrainment from the nozzle area, thereby reducing the droplet concentration inside this chamber. This results in less coalescence of droplets and less collision between droplets and the inner wall of the nebulization chamber. Consequences are a reduced droplet size and an increased drug output rate. The latter may lead to shorter nebulization times. A further reduction of the droplet size is possible (although not proven yet) from faster solvent evaporation. It is sometimes claimed that the auxiliary air flow can reduce the jet flow for the same respirable output. This is a misconception which may let to reduced lung deposition. The higher drug output rate to the patient with auxiliary flow through the open vent is solely a consequence of the better entrainment. The rate of droplet generation is entirely determined by the jet flow rate (for a given nozzle design in combination with a given drug solution). The jet flow rate also influences the droplet size distribution. Reducing the jet flow results in increasing median droplet size. Therefore, only the recommended jet flow rate should be used, unless the droplet size distribution at deviating flow rates has been checked previously.

The nozzle design of the Sidestream® is depicted more in detail in figure 3. The two-fluid nozzle consists of a central air jet, surrounded by four liquid capillaries. The air flow impacts on a beam and is forced to skim the capillary tube orifices, thereby entraining the drug solution. Disintegration of the liquid column results in droplets with various sizes. As for the Hudson T Updraft® (figure 1), only smaller droplets are entrained past the baffle. Larger droplets are collected and returned to the reservoir. The vent of this type of nebulizer has no valve. With a continuously working compressor (continuous droplet generation),



PortaNeb Sidestream

Figure 3

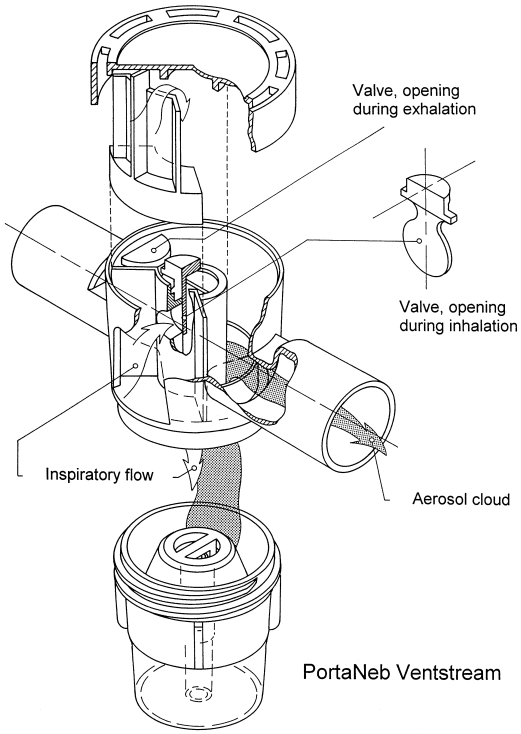
A detailed presentation of the nozzle design of the

ronment through this vent when the patient stops or interrupts inhalation or does not inhale fast enough. The dimensions of the nozzle and the baffle exhibit the inevitable spread of molded products. Because the droplet size distribution is directly related to these dimensions, a certain inter-device variation may be expected.

Reduction of the waste by at least 50% of the nebulized dose may be achieved by so-called breath assisted open vent nebulizers. Figure 4 shows the Ventstream®, which has exactly the same nebulization chamber as the Sidestream® but a different vent for the inspiratory air. This vent has a flexible membrane (valve) which opens only during inhalation. Meanwhile, a similar membrane in the outlet tube closes the route for exhalation. Also in contrast with the Sidestream®, nearly the complete inspiratory flow is directed through the nebulization chamber. During exhalation, the inlet vent closes and the valve in the exhaust tube opens in order to discharge the used air. When the patient does not inhale, both valves are closed in order to prevent waste of the produced drug aerosol to the environment.

In practice, there exists a wide variation in the performance of different types of nebulizers [9 19 20]. Droplet size distribution and output rate are also influenced by the physical properties of the drug solution (suspension) and air flow rate from the compressor. These variables make a careful selection critical for an optimal therapy with this type of inhalation system.

In an ultrasonic nebulizer, droplets are produced by a rapidly vibrating piezoelectric crystal. The frequency of the vibrating crystal determines the droplet size for a given solution. In most ultrasonic nebulizers the



PortaNeb Ventstream

Figure 4

A schematic presentation of the Ventstream nebulizer. In this breath assisted nebulizer an extra vent opens during inhalation only. The extra vent is closed during exhalation, resulting in a reduction of aerosol wasted to the

drug solution in a drug reservoir. Ultrasonic nebulizers are more quiet and generally smaller than jet nebulizers. Therefore, they are easier to handle and preferred by many patients [16]. The performance in the clinical practice of both types of nebulizers is influenced by several factors which will be discussed in more detail in the next paragraphs.

Performance of nebulizers

There are two main parameters which determine the performance of nebulizers: the droplet size distribution of the aerosol and the drug output rate. However, it should be taken into account that the performance of the nebulizer is also influenced by patient related factors [21].

Droplet size distribution

The droplet size distribution is important for the actual deposition in the lung. The fraction of droplets with an aerodynamic diameter between 1 and 5 micrometer is preferable for central and deep lung penetration at moderate flow rates of 60 l/min [14 22]. Smaller droplets will be exhaled to great extent while the larger ones will impact in the oropharynx and the upper airways. It is difficult to compare particle sizing results from different studies. The set up of the equipment, the measuring equipment and its software, the characteristics of the drug solution and, in case of jet nebulizers, the compressor used, are all factors that affect the final result. Therefore, only the basic aspects will be discussed in this paper.

The droplet size distribution of an aerosol can be described statistically. Aerosols from a nebulizer are heterodisperse and, in most cases, conform to a log normal distribution [16]. The particle size distribution of an aerosol can be determined by laser diffraction analysis [20 23]. Other suitable techniques are cascade impactor analysis and aerosol electrical mobility [20 24 25]. Laser diffraction analysis is based on the principle of light scattering by particles. The diffraction pattern of a particle is related to the particle diameter and particle shape. Different light scattering theories may be used to transform the complex diffraction pattern into a size distribution. Diffraction patterns of irregular particles are too complex, and therefore the calculations are based on the assumption that the particles are spherical.

A simple characterization of the aerosol cloud from a nebulizer is by the median diameter of the droplets in the cloud. With laser diffraction analysis, a volume median diameter (VMD) is obtained. VMD corresponds with the particle diameter that divides the volume distribution curve in two equal parts. Assuming that the particles density is independent of particle diameter, the VMD equals the mass median diameter (MMD). Diameters measured with laser diffraction technique are based upon geometric particle dimensions. For the spherical droplets in the aerosol cloud from nebulizers, the equivalent volume diameter (D_e) equals the measured (mass) median geometric diameter. This simplifies calculation of the measured (mass) median geometric diameter into a (mass) median aerodynamic size with the equation [26]:

shape factor and D_a is the aerodynamic particle diameter, which is the diameter of a unit density sphere that has the same terminal settling velocity in still air as the considered particle. For spherical droplets from aqueous drug solutions (in low concentrations), also the dynamic shape factor and droplet density have unity and so, the aerodynamic diameter equals the measured geometric diameter. No corrections are necessary and the volume distribution curve from laser diffraction analysis (calculated on the basis of spherical particles too) yields a correct mass median aerodynamic diameter (MMAD). Only for drug solutions in high concentrations, a correction for the true droplet density may be desirable.

Drug output rate

The drug output rate is another important factor to compare nebulizers. For delivery of a high dose to the lungs, nebulizers with a high output rate are preferred in order to confine the nebulization time. The output of nebulizers can be described by the aerosolized volume or the aerosolized mass of drug [8]. The output rate is defined as the mass of drug converted to aerosol per unit time. The nebulized volume can be determined simply by weighing the nebulizer before and after use. Results may be misleading because they do not take into account the increase in drug concentration within the nebulizer caused by evaporation of the solvent. Therefore drug output rate in mg/min is a better parameter for the nebulizer output [20 27].

Physical factors of the drug solution

Droplet size distribution

The droplet size distribution and the drug output rate are basically determined by the design and user conditions of the nebulizer. The physical characteristics of the drug solution will also influence the droplet size. A higher gas flow of the compressor in a jet or a higher vibration frequency of the piezo electric crystal in an ultrasonic nebulizer, decrease the droplet size.

The primary droplet size from specific nozzle designs has been expressed in mathematical formulas, containing the relevant variables, such as the nozzle diameter, the mass flow rates of the air and drug solution and physical constants of the air and the drug solution [e.g. 24 28]

A higher gas flow and a smaller diameter of the nozzle, theoretically decrease the primary droplet size. Practically, smaller droplets at a higher gas flow from the compressor have indeed been found for several jet nebulizers [23 29]. It is not possible to use these formulas to calculate the size of the droplets leaving the mouthpiece of the nebulizer. The primary droplet size distribution is modified by the classifying effect of the baffle(s). Only relatively small droplets can pass these baffle(s). Furthermore, droplet size changes during its way to the mouthpiece, due to evaporation of the liquid, droplet aggregation, condensation and deposition on the inner walls of the nebulization chamber and tubing.

In an ultrasonic nebulizer the vibrations of the piezoelectric crystal are transmitted to the surface of the drug solution in a reservoir. If the transmitted energy

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