A review of the technical aspects of drug nebulization

• P.P.H. Le Brun, A.H. de Boer, H.G.M. Heijerman and H.W. Frijlink

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P.P.H. Le Brun (correspondence)**:** Central Hospital Pharmacy The Hague, P.O. Box 43100, 2504 AC Den Haag, The Netherlands, e-mail: AHZ@wxs.nl
A.H. de Boer and **H.W. Frijlink:** Department of Pharmaceutical Technology and Biopharmacy, University of Groningen, Groningen, The Netherlands
H.G.M. Heijerman: Adult Cystic Fibrosis Center, Department of Pulmonology, Leyenburg Hospital, Den Haag, The Netherlands

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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]. Recently, the pulmonary route is proposed to increasing 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.

Nebulizers are used to aerosolize drug solutions

and sometimes drug suspensions for inhalation. They 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 Netherlands). Large droplets impact on one or more baffles, in order to refine the droplet size distribution 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,

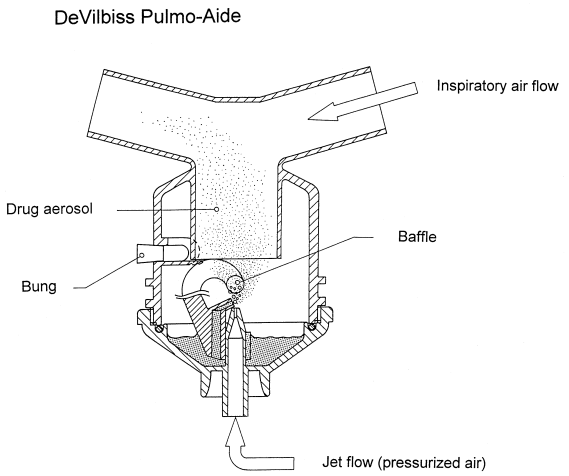


Figure 1

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.

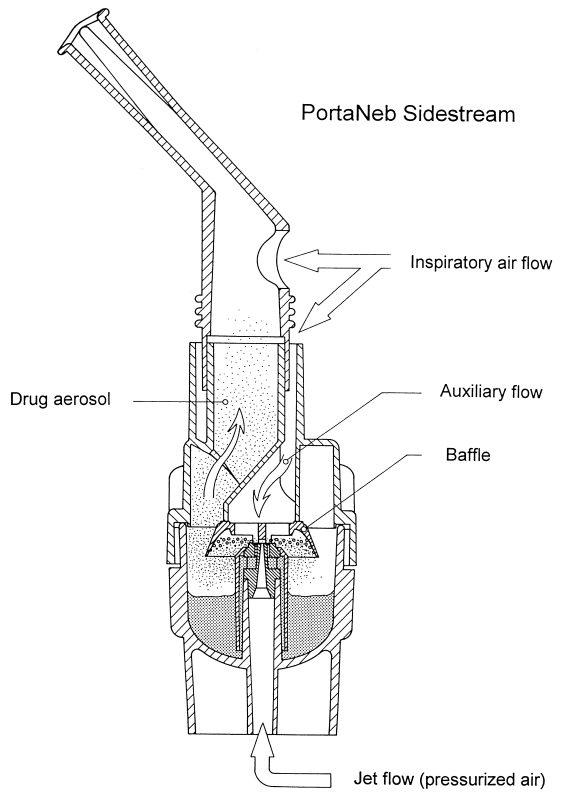


Figure 2

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 is combined to a PortaNeb compressor.

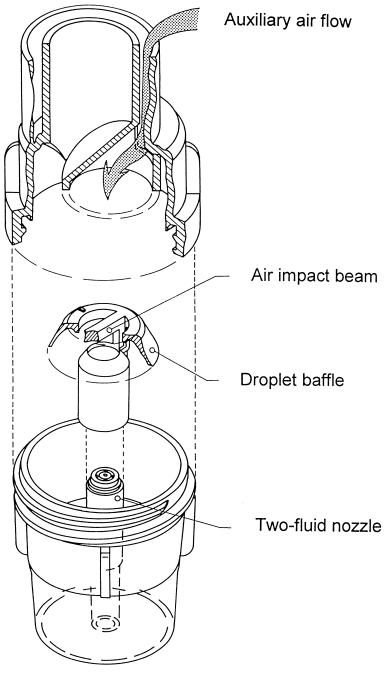
Meersen, The Netherlands). The vent allows part of the inspiratory air flow to pass through the nebulization chamber. The auxiliary air flow improves droplet entrainment from the nozzle area, thereby reducing the droplet concentration inside this chamber. This results in less coalescence of droplets 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), part of the aerosol cloud may be wasted to the environment 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.

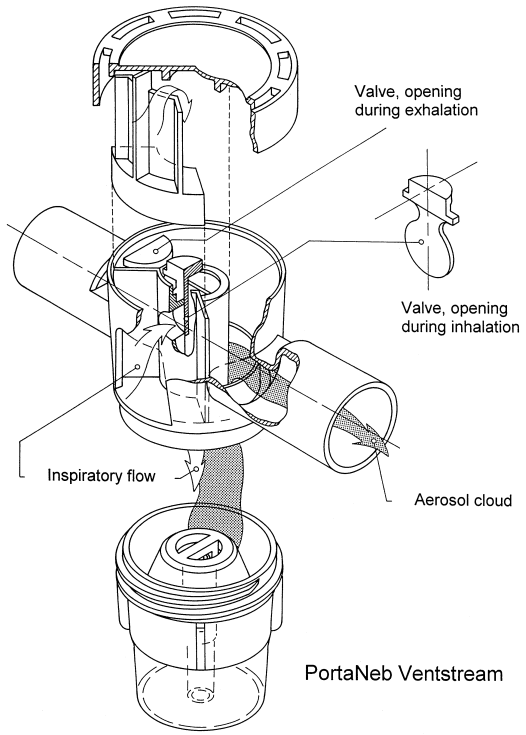
In an ultrasonic nebulizer, droplets are produced by a rapidly vibrating piezoelectric crystal. The frequency of the vibrating crystal determines the droplet size for a given solution. In most ultrasonic nebulizers the



PortaNeb Sidestream

Figure 3

A detailed presentation of the nozzle design of the Sidestream and the Ventstream nebulizer



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 surrounding.

vibrations are transferred directly to the surface of 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]:

$$D_a = D_e(r_p/i)^{0.5}$$

where r_p is the particle true density, i the dynamic 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 is sufficient, standing capillary waves are formed on

the surface of the solution. Droplets are disrupted from the crests of the capillary waves [8]. According to Mercer [24] the threshold amplitude for the generation of capillary waves is given by

$$A = 4n/fl$$

where
A = threshold amplitude
n = viscosity of liquid
f = frequency of acoustic signal
l = capillary wavelength

Droplets are formed from the crests of the waves when the amplitude exceeds the threshold amplitude by a factor of about four. The mean diameter of droplets is proportional to the capillary wavelength (l). The proportionality constant is independent of the acoustic frequency, the nature of the liquid and the mode of atomization [24]. The capillary wavelength is given by the formula:

$$l = (8pg/rf^2)^{1/3}$$

where
g = surface tension of the solution
r = density of the solution
f = frequency of acoustic signal

A common value for the proportionality constant when related to the number median droplet diameter (D_{nm}) was found by Lang [30]:

$$D_{nm} = 0.34l$$

It is apparent from these formulas that the droplet size is inversely proportional to the 2/3 power of the acoustic frequency. The gas flow in a jet nebulizer or the frequency of the crystal in an ultrasonic nebulizer are elements of their basic designs.

As can be derived from the above mentioned formulas, the physical properties of the drug solution, such as viscosity, surface tension, and related factors like temperature and concentration, affect the droplet size. However, it is difficult to find confirmation of these effects in practice. Furthermore, the prediction of the effect of the solution characteristics is difficult. The formulas are developed in order to estimate the primary droplet size, whereas the emitted aerosol is affected by the baffle design and the geometry of the nebulizer too. Consequently, over 99% of the droplets are recycled back into the drug reservoir.
Theoretically, the viscosity of the drug solution must influence the mass flow rate of the liquid through the nozzles of jet nebulizers. According to derived empirical formulas for the droplet size [e.g. 24], this must affect the average primary droplet size too. Practically however, conflicting experimental results have been found.

Newman et al. reported that several jet nebulizers tend to produce smaller droplets as the viscosity of the solution increases [31]. These results are in agreement with those of McCallion et al. [32] for glycerol-water and propylene glycol-water mixtures, whereas for silicon fluids an increase in droplet size was found for higher viscosities. Le Brun et al. investigated the droplet size distribution of tobramycin solutions (0-30% w/v) [27]. Initially a decrease was found in the range from 0 to 10%; from 10 to 30% no further decrease in droplet size distribution was found whereas the viscosity increased from 2.6 to 6.7 mPa/s. Hinds et al. also found small changes in droplet size for several solutions with different viscosities [33].

For ultrasonic nebulizers the relation between viscosity and droplet size distributions seems more obvious. In the above mentioned study by McCallion et al. [32] two ultrasonic nebulizers were compared too. The droplet size was proportional to the viscosity. This can be explained from the formula for the threshold amplitude. Since the threshold is higher for increased viscosities many viscous solutions can not be nebulized at all by this type of nebulizers. Boucher et al., reported that solutions with a viscosity above 10 cp are difficult to aerosolize with ultrasonic nebulizers [34]. Temperature and concentration of the drug solution influence the viscosity of the solution and thereby the performance of the ultrasonic nebulizers.

According to proposed formulas for droplet size from jet nebulizers [24] the surface tension of the solution is expected to be directly related to the diameter of the primary droplets. McCallion et al. [32] summarized several studies and concluded that the expected relation is not clearly reflected in experimental results.

The equations given for droplet formation by ultrasonic nebulizers suggest that the median droplet diameter increases with increasing surface tension of the drug solution. McCallion et al. indeed found a trend suggesting this proportionality [35], however no clear relationship was established. An increased surface tension can cause the formation of a foam, which might limit the formation of an aerosol.

The different results in above mentioned studies might be explained from the use of different solutions. Viscosity and surface tension both influence the primary droplet size. In combination with other factors, these parameters, with different effects upon droplet formation, complicate interpretation of possible correlations. Furthermore, as mentioned above, only the primary droplet size can be estimated from the physical properties of the solution. The final droplet size distribution leaving the mouthpiece will always be limited by the mechanical construction of the nebulizer. Therefore, the size distribution of the aerosol cloud leaving the nebulizer should be established experimentally for each solution to nebulized.

Drug output and drug output rate

As explained above for the several types of jet nebulizers, the output rate of the breath assisted, open vent type is larger than the output rate of the open vent nebulizer, which consequently has a higher output rate when compared to the conventional nebulizer [20 36 37 38]. Above mentioned factors for the droplet size distribution are also applicable to the drug output rate. Gas flow in jet nebulizers and vibration frequency in ultrasonic are proportionally related to drug output rate [25 39].

Also the drug concentration is directly related to the output rate, although the improvement that can be obtained by increasing the concentration is limited. Higher concentrations may also result in higher viscosities which, as reported, can cause an opposite effect. In a range of tobramycin concentrations Le

Brun et al. found an optimum at a concentration of 20% w/v tobramycin (as sulfate) in water for both ultrasonic and jet nebulizers [27]

The volume of the drug solution is a factor that affects the total drug output. There is a residual volume for every nebulizer that can not be aerosolized. For reasons of efficiency it is preferred that the residual volume is only a small fraction of the total volume fill [29]. A nebulizer with a residual volume of 1 ml filled with a drug solution of 2 ml will release only 50% of the drug solution. This percentage will be 75% if the nebulizer can and will be filled with 4 ml. However, a disadvantage of a larger volume can be a longer nebulization time required to aerosolize the solution. In clinical practice a nebulization time of 15 to 30 minutes is acceptable. Longer periods will jeopardize the patient compliance. Consequently it can be concluded that there is an optimum with respect to fill volume and concentration.

Patient factors

Laboratory evaluation of nebulizers with a specific drug solution provide information on the droplet size distribution, drug output rate and thus the expected performance of the tested combination of nebulizer and drug solution. Laboratory evaluation is mandatory before the combination can be used by the patient. However, patient factors complicate the prediction of the final in vivo performance and are a further factor to be considered in the evaluation of the therapy. In an in vitro study Le Brun et al. found differences in the performance with regard to droplet size distribution for jet and ultrasonic nebulizers both loaded with solutions of tobramycin [20 27]. The in vitro observed differences were not reflected in two separate patient studies with these nebulizers. The pharmacokinetics after inhalation, used as an indirect measure for evaluation of drug deposition, were comparable in both studies with six patients [40 41].

It is a known fact that patient compliance is poor in inhalation therapy. A few evaluating studies are known referring to compliance. In a study on children with respiratory diseases a compliance of 47.6% with the prescribed inhalation therapy was found [42]. Whereas Cochrane found a mean compliance of only 56.8% in a study with 93 patients on inhalation therapy [43]. The low compliance is understandable because it usually takes a lot of time and energy to inhale the prescribed medication on a daily basis. Another aspect of the daily routine is the maintenance of the nebulizer. Cleaning and disinfection is necessary in order to prevent contamination of the nebulizer and subsequently possible infections [44]. Cleaning and disinfection procedures might influence the performance of nebulizers. Therefore, the performance of nebulizers should be checked periodically.

Furthermore, the breathing pattern through the nebulizer influences the actual inhaled dose. It influences the sites of deposition. However, the deposition in the lung is complicated by the physiology of the lung and its clinical situation which determines the geometry of the inspiratory system. Gamma scintigraphy studies with CF patients by Laube in 1998 indicated that a high inspiratory flow rate resulted in a more central airway deposition, whereas lower inspiratory flow rates resulted in a more peripheral deposition [45]. Studies with radio isotopes are useful to determine the deposition patterns in patients. As expected, it could be shown that lung deposition varies with age and particle size distribution of the inhaled aerosol [46 47]. Eventually, only clinical efficacy studies can proof the relevance of nebulizer therapy.

Developments

A new type of nebulizer with the so called adaptive aerosol delivery (AAD) technology seems promising. A nebulizer with AAD adapts to the individual breathing pattern of the patient and delivers the aerosol only during inhalation. In an AAD nebulizer the breathing pattern of the patient is analyzed to determine the shape of the inspiratory and expiratory flow pattern. The system then pulses aerosol during inhalation only and each pulse is matched to the previously determined inspiration time. The breathing pattern is monitored continuously and the AAD responds to changes in the pattern. Furthermore, the system is programmed to deliver a preset metered dose. Because there is no loss during exhalation, the AAD nebulizer is more efficient than the conventional nebulizer and, in case of expensive drugs, more cost effective. An example of the AAD nebulizer is the Halolite® from Medic Aid.

As stated before, patient compliance in nebulizer therapy is low and an average lung deposition for nebulizer therapy of only 10% is rather poor. These factors limit the clinical efficacy of nebulization therapy.

The performance of a new generation of DPIs offers an opportunity to replace traditional nebulizers. The reasons that some nebulizer drugs are not reformulated into dry powder formulations are both technical and commercial [48]. In case of the nebulization of tobramycin with a general accepted dosing schedule of 300 mg two times daily, an average amount of only 30 mg will reach the target area. With a more efficient device, for example a DPI with an efficiency of 30%, an average dose of only 90 mg might be sufficient. Assuming a dose of 20 mg per inhalation, only 4 to 5 inhalations would be required to administer the desired dose. Although this can be performed in minutes, the number of doses is still rather high. Therefore, a DPI might be especially an alternative for low dose antibiotics, for example colistin which is used in the nebulizer in doses of 80 - 160 mg twice daily.

An example of a commercial limitation is rhDNase (dornase) [48]. The dose is 2.5 mg in 2.5 ml solution. Assuming an efficiency of 10% from the nebulizer only approximately 0.25 mg will be deposited in the lung. A nominal dose of 0.25 mg can be administered with a DPI. However, large investments are necessary to develop and register a new dosage form which will be used only by the limited number of patients with cystic fibrosis. The small population of patients makes a positive return of investments highly unlikely and therefore such a development is not attractive for the pharmaceutical industry.

Conclusions and recommendation

The choice for a nebulizer to aerosolize a certain drug solution should be based on laboratory evaluation

regarding the particle size distribution and the drug output. The major part of the droplet size distribution should preferably be within the range of 1 to 5 micrometer. The intended drug output must be realized within a reasonable nebulization time (e.g.15 to 30 min).
It should be emphasized that only a minor fraction of the released drug solution will be deposited in the lung.

The in vitro in vivo relation is only partly understood and to date it is not possible to predict drug delivery from in vitro studies on nebulizers only. Patient factors have to be taken into account and should be evaluated in pilot studies before aerosolization of a particular drug solution with a particular nebulizer 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 and, 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.

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