Principles of nebulizer technology

A review of nebulizers and a look to the future

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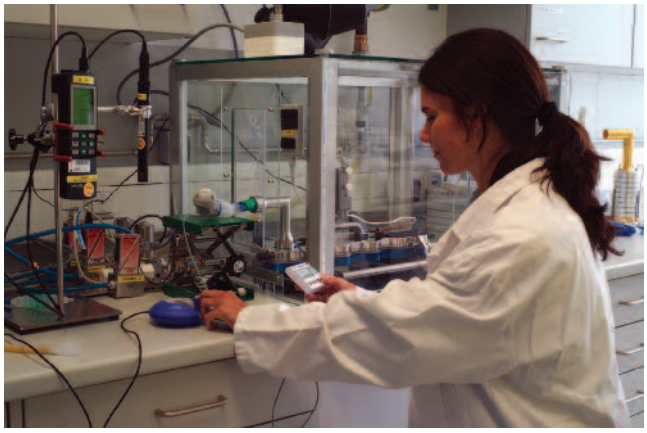
Introduction

Nebulizers are probably one of the oldest types of aerosol delivery devices, dating back more than 100 years, when engineers first began designing spray devices similar to perfume spray pumps to enable them to deliver medication solutions to patients' lungs.[1] This technology has been greatly improved since and many highly sophisticated jet nebulizer devices are available today.[2] During the recent decade, the first of a new generation of electronic nebulizers appeared in which devices make use of a perforated membrane to produce the aerosol. Nowadays, most experts think in the categories of traditional jet nebulizers and modern electronic nebulizers, often termed soft mist inhalers, when discussing nebulizer technology. It will be helpful to keep that classification in mind for the purpose of this article.

Nebulizer technology itself can be divided into two main categories. The first technology addresses the process of aerosol generation. This is a key step since, without producing droplets of a suitable size range at an acceptable generation rate, all subsequent attempts to deliver the medicine to the lungs will be severely hindered.

The second aspect of nebulizer technology is equally important and addresses aerosol application, i.e. the methods by which the aerosol can be delivered to the patient. Aerosol application with nebulizers occurs while the patient breathes normally (tidally) through the device for several minutes, in contrast to dry powder inhalers and pressurized metered dose inhalers, where the patient inhales the drug in one or a few breaths. It becomes clear that, at best, only 50% of the aerosol will be inhaled, unless the aerosol delivery system is designed to prevent aerosol from being wasted to the environment during the exhalation phase of the breathing maneuver. Also, not all of the 50% that is inhaled will be deposited in the lungs, as some droplets will deposit in the oropharynx and others will be exhaled. The exact amount depends upon the aerosol size distribution, breathing pattern, airway geometry and any synchronization of aerosol production with breathing pattern.



Aerosol generation

For jet nebulizers, the aerosol is generated using the Venturi principle (Figure 1). Compressed air, generated by a compressor or taken from the wall gas supply in hospitals, is introduced into the central channel of the nozzle and draws the liquid medication up through the side channels. Meeting at the outlet of the nozzle, the compressed air disperses the liquid and generates a primary aerosol with a very broad droplet size distribution containing many droplets too large to be suitable for lung delivery.[3] Most jet nebulizers, therefore, have an integrated baffle system, where the large droplets are removed by impaction and circulated back into the medication reservoir. It is possible to have baffle systems as flexible inserts. By using different baffle geometries, the cut-off for removing the large droplets, and thus the median droplet size of the aerosol, can be varied.

A new variation of the nebulization principle came with the introduction of ultrasonic nebulizers. These devices use an ultrasonic actuator to introduce vibrational energy of a frequency between 1 to 2.5 MHz into the

Figure 1

A jet nebulizer nozzle and flexible nozzle inserts with baffle system

liquid medication in the reservoir. This creates a standing wave at the surface of the liquid from which large primary and small secondary droplets are emitted. Again, baffle systems are used to filter out and recirculate the large droplets. One disadvantage of some ultrasonic devices is the high energy input into the medication solution, which causes the liquid to heat to a point which may be detrimental to some of the more labile protein-based drug formulations.[4]

More recent advances have been made with the development of devices that use a perforated membrane (also termed "mesh") to generate aerosol droplets. These membranes can be stationary or passive (with a vibrating horn pushing the liquid through the pores) or active (with the membrane itself vibrating and extruding the liquid). Figure 2 illustrates the active vibrating membrane with tapered pores used in Touch Spray technology (The Technology Partnership). In contrast to conventional ultrasonic nebulizers, the piezo element acts on the membrane and not on the medication and requires less energy (120 kHz). This allows nebulization of heat sensitive protein solutions, which can show considerable activity loss in traditional ultrasonic nebulizers, as shown by Figure 3.[5]

Figure 2

Aerosol generation by a vibrating membrane nebulizer system

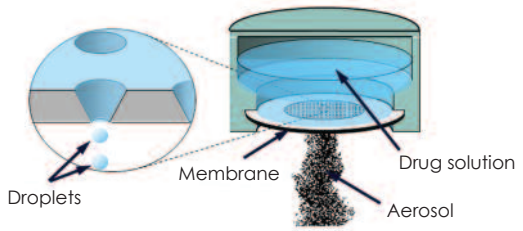
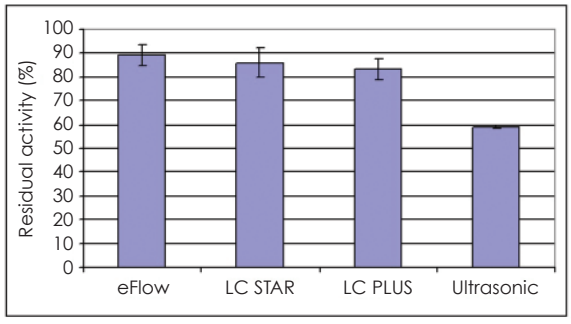


Figure 3

A protein formulation (DNase, Pulmozyme), which is approved in the PARI LC Plus jet nebulizer, remains active when nebulized by a vibrating membrane nebulizer (eFlow, PARI Pharma) but looses activity in an ultrasonic nebulizer.



An additional advantage of membrane nebulizers is generation of only primary droplets yet no secondary droplets that would have to be removed from the aerosol by baffle systems. Avoiding the need for recirculation and initially obtaining the appropriate droplet size makes the aerosol generation process more efficient and helps reduce treatment time, making the application more convenient for the patient.

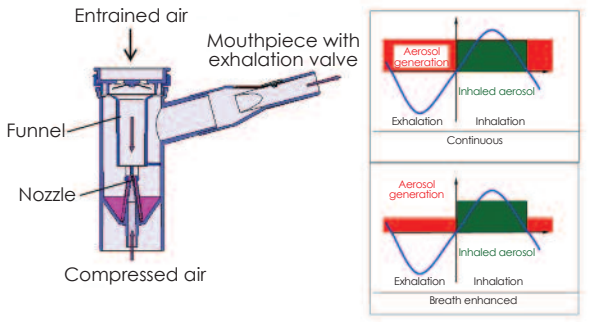
Aerosol application

The second part of nebulizer technology is ensuring as much generated aerosol as possible can be inhaled by the patient. A large development effort is therefore focused on the way in which the delivered dose (the amount of drug taken up by the patient) can be optimized and aerosol losses during the exhalation phase of the breathing maneuver can be minimized.

The early jet nebulizers were continuously operating devices, where the aerosol was produced at the same rate throughout the treatment and 50% of the nebulized medication would be directly lost during exhalation (not counting other drug losses, for example, drug left in the device as not-aerosolized residue). With the introduction of breath enhanced jet nebulizers, it was possible to reduce the aerosol delivery rate during exhalation and increase it during inhalation. This was achieved by a funnel and valve system[6] as shown in Figure 4. The aerosol is continuously generated at the nozzle of the jet nebulizer and presented to the patient at the mouthpiece. During inhalation, additional air is entrained through the funnel and increases the rate at which the aerosol exits the nebulizer. During expiration, the pressure generated by the exhaled air flow closes the valve of the funnel and the aerosol exits the nebulizer at a reduced rate through the exhalation valve. This is indicated by the illustrative sketches included in Figure 4, where the red areas repre-

Figure 4

A breath enhanced jet nebulizer. The graphs illustrate flow rate over time (blue line) and aerosol generated over time (red and green area, arbitrary scale).



sent aerosol lost during exhalation, and the green areas represent aerosol taken up by the patient.

The concept of a breath actuated jet nebulizer has been realized in the AeroEclipse (Trudell Medical). This device contains a mechanism by which the Venturi nozzle that generates the aerosol is blocked completely during exhalation. When the patient inhales, the inspiratory airflow opens the nozzle and allows aerosol production to start. This mechanism is triggered by an airflow of 15 L/min, which most patients can achieve easily during inhalation. The system can also be locked in continuous mode for those patients who have difficulty triggering the actuator.[7] Figure 5 illustrates the way in which the breath actuating mechanism operates.

With the application of adaptive aerosol delivery (AAD), the timing of aerosol generation can be adapted to the patient's breathing pattern.[8] Nebulizers operating with the AAD principle, for example the I-neb (Phillips Respironics), monitor the first three breaths of the patient at the start of the inhalation session. From this data, the electronic device estimates the best sequence of aerosol generation and pulses the aerosol into the subsequent breaths (Figure 6). The aerosol is delivered during the first part of the breath, leaving about one second at the end of the inhalation phase without aerosol production to prevent wastage of drug that only enters the upper airways at the end of inspiration and is then exhaled. The process of monitoring the breaths and calculating the pulses is repeated throughout the inhalation session. In this way, the system can adapt itself to the breathing pattern of the patient, provided changes are not too abrupt over time.

Another approach to minimizing aerosol losses during exhalation is bolus inhalation, where the aerosol is continuously produced but retained within the device during exhalation and released to the patient in the inhalation phase. This can be achieved using a valved aerosol chamber that allows an aerosol bolus to build up during exhalation. Figure 7 shows the way in which this principle has been integrated into devices of the eFlow technology platform (PARI Pharma GmbH).[9] During exhalation, the inspiratory valve is closed and the exhaled air exits the device through the expiratory valve without entering the aerosol chamber where the aerosol is collected. On inhalation, the inspiratory valve opens and the inhaled air entrains the aerosol bolus and delivers it to the patient. In the next exhalation phase, the inspiratory valve closes again and a new aerosol bolus is built up in the aerosol chamber.

Patient monitoring systems

While nebulizers with improved technology for generating and delivering aerosolized medication have been the focus of development in the past years, the task of improving patient adherence has received growing attention recently. It is well known there can be a significant difference between prescribing treatments and treatments actually taken.[10] Non-adherence to a treatment regimen decreases the efficacy of every day therapy, even if a drug is highly effective and the device very efficient. In addition, if the inhalation therapy is correctly applied within clinical trials, non-adherence to a therapy regimen can result in mistaken interpretation of drug efficacy.

Figure 5

A breath actuated jet nebulizer. The graph illustrates flow rate over time (blue line) and aerosol generated over time (green area, arbitrary scale).

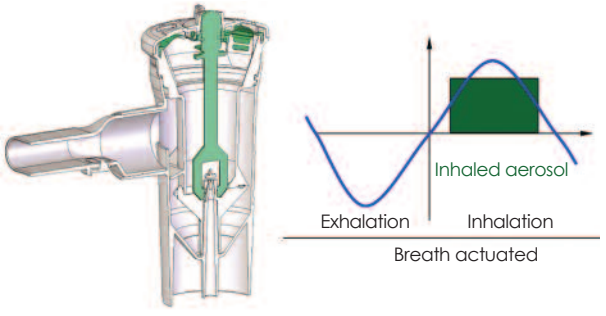


Figure 6

Adaptive aerosol delivery

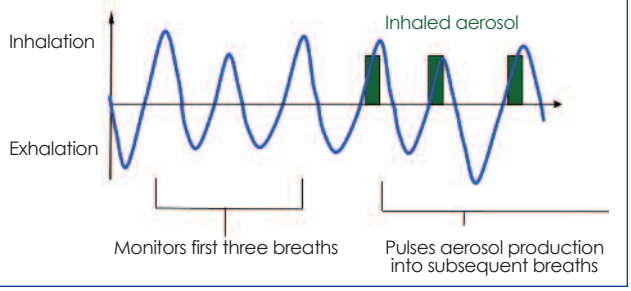
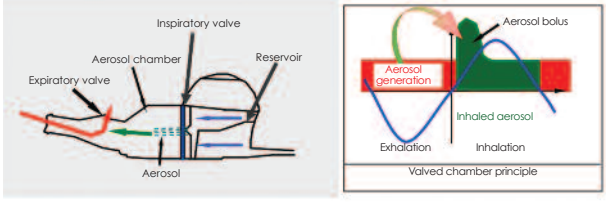


Figure 7

A breath enhanced jet nebulizer. The graphs illustrate flow rate over time (blue line) and aerosol generated over time (red and green area, arbitrary scale).



However, with the arrival of new electronic nebulizers, it is now possible to automatically record the instances when a patient uses a device. Such patient monitoring systems are available for the I-neb, eFlow and Akita (Activaero GmbH) technology platforms[11-13] and provide the option to measure the patient's adherence over time. The possibilities arising from this new technology include allowing patients to monitor their own adherence, allowing doctors to check patients' adherence at regular intervals and having call centers phone patients and remind them to take vital medication. In addition, in a clinical trial where the outcome was somewhat lower than expected, these devices can be very useful tools in determining whether a drug did not work or was not taken.

These patient monitoring systems of course have to adequately address patients' sensitive data and not interfere with personal wishes for privacy, i.e. they must overcome the "Big Brother Effect." It therefore remains to be seen if, or in what form, these systems find their place in commercial products.

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