Expert Opinion

New advances in aerosolised drug delivery: vibrating membrane nebuliser technology

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Innovative nebuliser systems bear the potential to greatly improve and expand the administration of therapeutic aerosols for the treatment of respiratory diseases. Exploiting the technology of a microperforated vibrating membrane offers a close control of the droplet size that is being generated and targeted to reach the lower airways, with little oropharyngeal deposition, thereby reducing undesired side effects. The greatly improved efficiency of such devices, as exemplified by the eFlow® nebuliser (PARI), provides further advantages for the patient. A high respirable fraction due to the precisely defined perforations, low residual losses and the high liquid output rate combine to produce a highly efficient and fast administration of inhaled medications. Portability, ease of handling and noiseless operation have a positive effect on patient compliance, control of the therapy by the physician and the therapy costs.

Keywords: aerosol, droplet size targeting, microperforated membrane, nebulisation time, nozzle, respirable dose, vibrating membrane nebuliser

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1. Introduction

Nebulisers are ideal for the delivery of high doses of medication to the respiratory tract and have major applications today in the treatment of asthma, chronic obstructive pulmonary disease and cystic fibrosis (CF). The treatment is taken over several minutes of breathing, requiring only minimal coordination and effort in comparison with pressurised metered dose inhalers or dry powder inhalers [1]. Conventional jet nebulisers require a mains-operated compressor or a large battery power source and are therefore relatively bulky. Due to a high residue in the nebuliser reservoir and aerosol losses they deliver only ~ 30% of the filled drug to the patient. In comparison, novel nebulisers that use microperforated membranes offer higher efficiencies, better portability and ease of handling. Among these, the authors of this paper chose to look closely at nebulisers with an actively vibrating microperforated membrane. This review also compares these with nebulisers in which the membrane is passive.

This paper shows that the requirements of future nebulisation therapies using highly specialised drugs, and the expectations of patients and physicians regarding safety and efficacy of the treatment, can be better fulfilled using vibrating membrane nebuliser technology.

1.1 Overview of the market

In recent years, new and innovative inhalation devices have been developed that introduce unique aerosol-generating principles, such as the microperforated vibrating membrane. Some of these are already on the market and provide for improved drug therapy with aerosolised liquid formulations. These are particularly successful in filling the important niche in the treatment of severe sufferers and special age groups (asthma, chronic obstructive pulmonary disease) who are not able to use pressurised metered dose inhalers, or dry powder inhalers, or where

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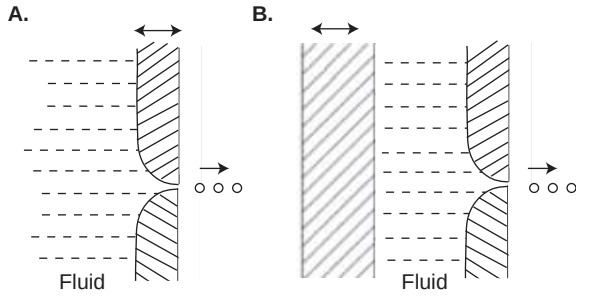

Figure 1. Schematic comparing active and passive nozzle membranes. A. The active nozzle membrane generates the acoustic pressure by its own vibration. **B.** In contrast, the passive nozzle membrane requires a separate transducer, which must also be in contact with the liquid.

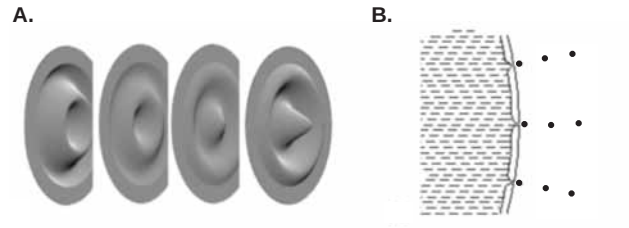

Figure 2. Schematic of a resonant system. A. A model of a bending mode of the active membrane at four points in time of a single cycle (depiction of the amplitude of the vibration is strongly exaggerated). The nozzles are placed at the centre of the membrane where the amplitude is greatest. **B.** Pressure built up by the vibration causes droplets to be ejected through the nozzles, on average one droplet per cycle.

liquid drug formulations are the only choice for taking their inhaled medications (CF).

Commercial devices include the eFlow® rapid (PARI), the AeroNeb® Go and AeroNeb Pro (Nektar Therapeutics) nebulisers: the latter for use in ventilator applications.

2. How vibrating membrane nebulisers work

It has been known for many years that ultrasonically vibrating a membrane of tapered nozzles against a bulk liquid will generate a plume of droplets without the need for compressed gas [2]. However, it was not until relatively recently that medical application of this principle has been made possible on the basis of TouchSpray® Technology (The Technology Partnership) and OnQ® Technology (Nektar Therapeutics)

The underlying physical principle of the microperforated membrane nebulisers, of both active and passive type, is in many instances similar to that of ink-jet printers: the fluid is in contact with a membrane, the opposite side of which is open to the air. The membrane is perforated by a large number of nozzle orifices. Alternating pressure in the fluid is built up in the vicinity of the membrane, causing the fluid to be ejected through the nozzles as uniformly sized droplets, creating an aerosol. A sizeable acoustic pressure is then applied as the driving force, typically generated by a piezoelectric transducer. The transfer of energy follows the pattern of 'piezoelectric to mechanical to acoustic to droplet'. The advantage of any particular implementation of this principle lies in the efficiency with which these energy transfers are technically resolved.

It is specific to the vibrating membrane technology that is described in this paper that the acoustic pressure at the membrane is generated by the high-frequency vibration of the nozzle membrane itself. This is a more efficient process than in the case of a passive nozzle membrane, where the pressure is created by a piezoelectric transducer that is adjacent to the nozzle entrances, forming a liquid-filled gap between the actuator and the membrane (Figure 1).

For vibrating membrane nebulisers, the uniformity and consistency of the particle size is defined by the nozzles, thereby allowing the aerosol to be tailored for a particular therapy. In contrast to jet or ultrasonic nebulisers, where an extremely broad spectrum of droplets is generated (requiring baffles for separation of the large recirculating droplets from the smaller respirable ones), a first-pass generation of respirable droplets can be achieved. This primary aerosol has a narrow size distribution and almost eliminates the medication losses that are associated with liquid adhesion to the impaction surfaces in jet or ultrasonic nebulisers. Aerosolisation occurs without exposure of the liquid to high repeated shear stresses or heat, making it suitable for the pulmonary and nasal administration of fragile drug molecules such as proteins and peptides. Delivery of the low-velocity primary aerosol leaving the nozzles is carefully provided through the device to maximise lung deposition.

2.1 Efficiency features of the TouchSpray Technology

The TouchSpray Technology addresses the demand for high efficiency by designing a resonant system. In particular, the membrane is driven at a frequency for which the amplitude of the vibrational movement at the centre of the membrane is particularly large. The resulting acoustic pressure is thereby focused into the vicinity of the nozzle (Figure 2). Typical frequencies are ~ 100 kHz.

A further important consideration is the unwanted transfer of vibrational energy to the mechanical surroundings of the atomising head. To keep this energy loss to a minimum, a flexible mounting, similar to that of an engine in the structure of an automobile, has been achieved using thin spokes between the substrate of the actuator and the head mount (Figure 3A).

The TouchSpray Technology enables an efficient transfer of electrical energy into the formation of the aerosol in a precisely controllable, miniaturised piezoelectric device. The embodiment of this advanced technology in the eFlow nebuliser has made it available to the patient community.

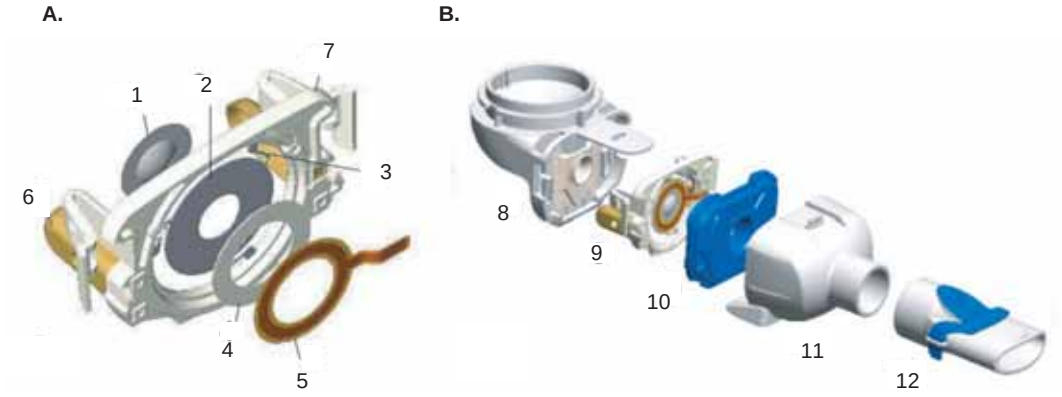

Figure 3. Design of atomising head (A) and nebuliser handset (B). A. Exploded view of the atomising head (1: membrane, 2: substrate, 3: spokes, 4: piezo element, 5: flexible electrical contact, 6: electrical contact pins, 7: head mount). **B.** Exploded view of the nebuliser handset (8: reservoir, 9: atomising head, 10: inhalation valve, 11: mixing chamber, 12: mouthpiece with exhalation valve).

2.2 Efficiency features of the eFlow device

For the overall drug delivery efficiency, there are aspects beyond the actual aerolisation of the drug by the atomising head. The continuous operation of the atomising head produces a stream of concentrated aerosol into the mixing chamber (Figure 3B), from where it will be drawn into the respiratory tract by inhalation. To reduce droplet deposition by impact on the surfaces of the mixing chamber, it is essential that the mixing chamber be fully flushed during the inspiratory phase and that it will not be submitted to unnecessary turbulence during the exhalation phase. This has been achieved by a suitable configuration of the atomising head, inhalation valve, mixing chamber and exhalation valve [101]. The vertically oriented atomising head sprays in the direction of intake flow, reaching the patient's mouth without deflection. The resulting flow minimises aerosol deposition within the mixing chamber and adjacent mouthpiece. The exhalation valve is arranged to allow for effective collection of the aerosol in the mixing chamber, while minimising losses during exhalation. Thereby, a larger portion of the filled drug will be delivered to the patient's mouth in a shorter period of time.

The combined effects of the efficiency features, the high aerosol output rate of the atomising head and the low residue and aerosol losses, along with enhanced delivery rate of the device lead to a significantly reduced treatment time and improved use of valuable drug compounds (refer to Section 6).

3. eFlow® design and manufacturing

A medical device, as a marketable product, must offer a convincing solution for the everyday needs of the patient. These include ease of handling, cleaning and disinfection in everyday use. The design of a medical device must also take many other aspects into account, not least the requirements of viable production. Finally, safety requirements must be satisfied, as demanded by regulatory agencies.

The main components of the eFlow device are the control unit and the nebuliser handset (Figure 4). In order to ease the handling and cleaning procedures for the patient, minimising the overall number of nebuliser parts must always be a major objective of the design process. These parts are produced using state-of-the-art manufacturing technologies, such as multi-component injection moulding or overmoulding of metal parts.

In choosing the materials for the vibrating system of the atomising head, technical requirements first consider elastic properties and formability. However, equally important, regulatory and hygienic considerations require that the nebuliser components be made of biocompatible materials and be constructed in such a way as to offer a minimum of narrow gaps and crevices that could not be readily cleaned and dried. In addition, the materials must be highly corrosion resistant, due to the saline basis of typical aqueous inhalation formulations. Medical grade stainless steel offers the necessary properties, is widely available in a thickness suitable for the vibrating membrane and can be formed by numerous methods.

Most important for the development of TouchSpray Technology was a suitable process for manufacturing the large number of nozzles in the thin membrane. Laser drilling allows for the necessary accuracy and, with suitable refinements, lends itself to automated production. The drilling procedure defines the number and position of the nozzles, their tapered shape and exit orifice. By appropriate adjustment of the parameters for the drilling process, the membrane can be optimised for the production of droplets of a certain size. There are other aspects to be considered for the resulting droplet size, such as the viscosity and surface tension of the liquid formulation, which necessitate the customisation of the

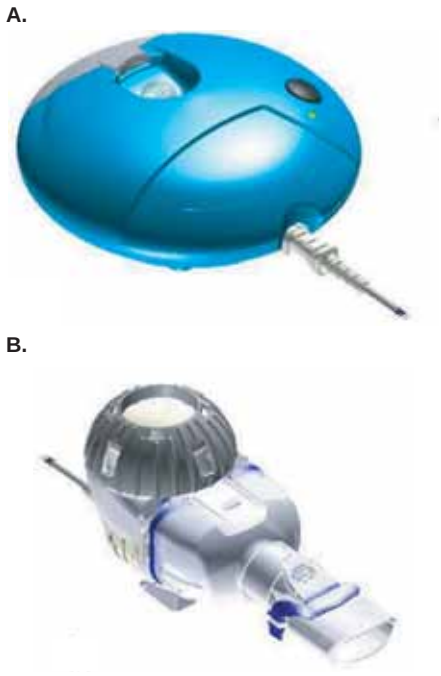

Figure 4. Example of the eFlow® nebuliser. A. Control unit. **B.** Handset.

membrane to the physical properties of the particular drug or class of drugs (refer to Section 4).

After the laser drilling process, residuals of molten material are removed by electro-polishing, whereby the surfaces of the membrane and the tapered nozzles are clean and produce low resistance to the fluid flow (Figure 5).

To ensure consistent inhalation therapy, the stability with which hundreds of thousands of nozzles are reproducibly drilled every day is guaranteed on the basis of continuous in-process quality control [3]. One of the methods is a camera recording online the amount of light passing through each single nozzle (Figure 6A).

The membranes are then ready to be assembled with other components to an atomising head (Figure 3A). The basic bonding process is gluing in a clean-room environment using a medical-grade adhesive. The transfer of acoustic energy from the piezoelectric actuator to the membrane requires strong bonds that will not deteriorate due to the high-temperature stressing during thermal disinfection or sterilisation in an autoclave, or due to the ultrasonic stressing during operation. Exhaustive testing in the development stage showed that the choice of the adhesive and bonding procedure is of utmost importance. Continuous sampling from production batches for endurance tests ensures the meeting of the specified lifetime of the atomising head.

The optimisation of the resonant system dictates the accuracy with which parts must be assembled and specified. An inline quality control measurement has been devised that makes use of the resonant character of the vibrational

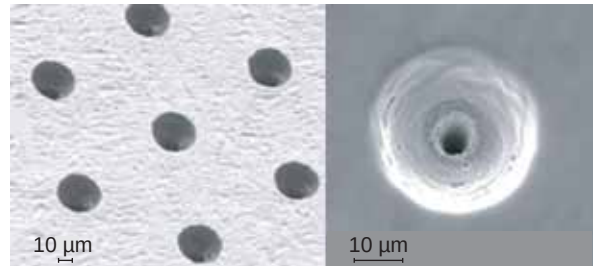

Figure 5. Scanning electron microscopy images of nozzles viewed from the fluid side of the vibrating membrane. The holes are laser drilled and cleaned by electro-polishing.

response of the system to detect deviations from the internal standard (Figure 6B). Conforming to the constraints of narrow tolerances allows a high liquid-output rate with low power consumption and the resulting reduction of treatment time for the patient.

The most relevant quantities to ensure consistent quality of the final product are the droplet size distribution characteristics (mass median diameter [MMD] and geometric standard deviation [GSD]) and the total aerosol output rate, for which internal standards have been set. In the final testing of the atomising heads, using laser diffraction and gravimetric measurements (Figure 6C), the heads must conform to these standards before they can be released.

The control unit of the device provides the power drive for the hand-held nebuliser and also makes use of the 'intelligent' piezoelectric system. To enhance the ease of handling, the electronic driving circuit has been devised to use the same piezoelectric element that drives the vibrating membrane to also act as a fluid detection sensor that will switch the device off when the resevoir is empty. The vibrating membrane doubles as a beeper to give the patient audible feedback signals indicating the status of the treatment.

4. Device regulatory approval

In order to market a medical device for human use, it must be first submitted for evaluation and approval with the regulatory agencies. In the US, nebulisers can generally be cleared for commercial distribution by the 510(k) premarket notification procedure. This aims to demonstrate that the device is as safe and effective as (i.e., substantially equivalent to) a legally marketed device. The data in the 510(k) submission for the eFlow included test results from aerosol characterisation studies in comparison with the predicate devices. Using cascade impactor studies for the drug products albuterol sulfate, cromolyn sodium and ipratropium bromide, the eFlow, LC STAR® (PARI) and AeroNeb Go devices were compared [4].

In addition, a simulated user test was performed to show that the device meets the specifications regarding particle size distribution, output rate and nebulisation time during the

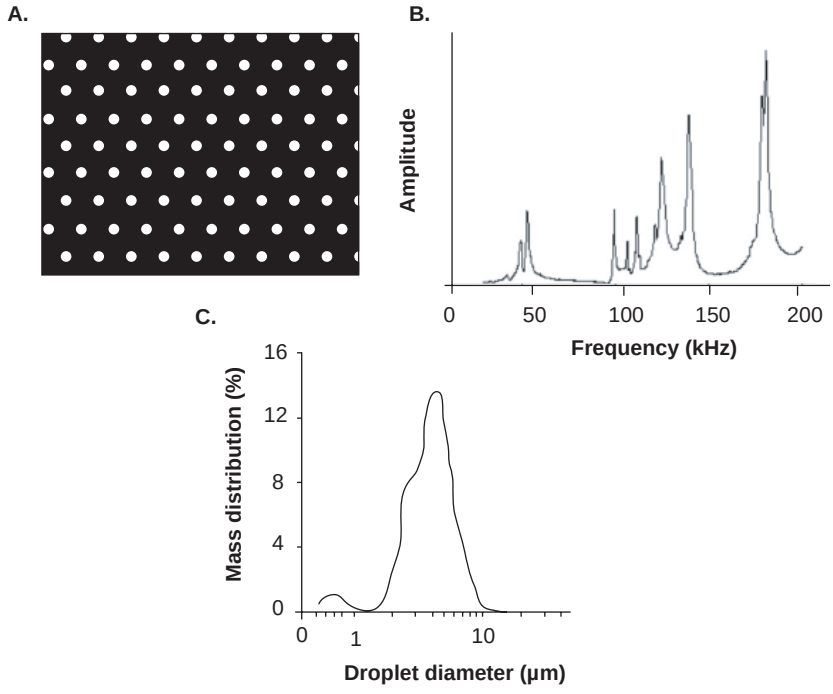

Figure 6. Inline quality assurance measurements include specific performance related fingerprints. A. Camera recording of light throughput of micro-perforated membrane to secure reproducible nozzle orifice sizes. **B.** Vibrometer spectrum to monitor overall accuracy of the assembly process (relative amplitude). **C.** Droplet size distribution as determined by laser diffraction to determine key aerosol characteristics (mass median diameter, geometric standard deviation).

lifetime of the nebuliser, as stated in the Instruction for Use. 510(k) clearance to market the first eFlow nebuliser product was obtained in 2004.

In addition to the same data set, an extensive investigation on safety requirements was presented for the European Certificate of Conformity required for CE marking, in which the biocompatibility and toxicity tests, risk and technical failure analysis according to the international guideline ISO/IEC 14971 were evaluated. The European market launch of the first model (eFlow rapid), adapted for use with approved drugs for inhalation in CF, was in May 2005.

5. Diversification of the device platform

The growing range of devices within the eFlow product family is built up using individually interchangeable modular components, including different control units, medication reservoirs, valve systems and mixing chambers. Two models are available for use with currently approved and marketed drug formulations, primarily for CF (eFlow rapid in the EU) and paediatric asthma therapies (eMotion™ in Japan); for example, with tobramycin or cromolyn sodium. Compared with compressor-driven jet nebulisers, the eFlow product family offers the advantage of shorter nebulisation times, silent operation and more mobility for the user [5,6].

Development efforts are devoted to models with further improved drug delivery efficiency, for the treatment of small children and for use in ventilator care settings. These, together with other models of the device platform, are intended for use with new drug formulations in clinical trials and for subsequent licensing and commercialisation by pharmaceutical partners.

In order to tap the full potential of the technology, optimisation of the device and the medication must be performed side by side by adjusting the physical properties (e.g., viscosity and surface tension) of the drug formulation to the device characteristics, and *vice versa*.

Customisation of the device performance is primarily achieved by choosing suitable parameters for the atomising head. By changing the dimensions of the nozzles, the droplet size and output characteristics may be tailored for specific drug formulations, therapeutic indications or patient groups. Further optimisation is achieved by a proper choice of the other nebuliser components, such as the medication reservoir or mixing chamber.

The goal of a customisation is to bring the eFlow-inherent advantages in its performance (efficiency in use of the drug and of the patients' time as described in Section 6) to apply in full to the new drug and application.

For a new device configuration, the correct usage will be defined and, in such a case, the possible need for a new 510(k) approval must be specifically considered.

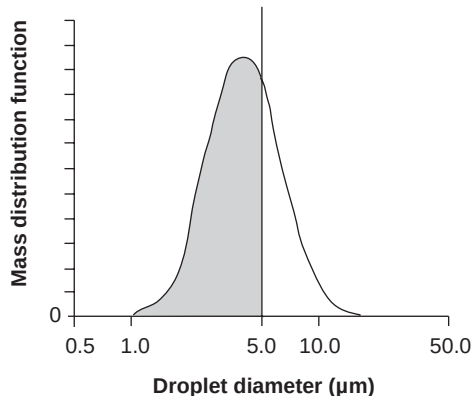

Figure 7. Log-normal mass distribution of droplets with mass median diameter equal to 4 µm and a geometric standard deviation of 1.5. The respirable fraction is equal to 71%.

6. Performance profile

The function of the nozzles is to cause the acoustic pressure on the liquid side of the membrane to produce regularly sized droplets downstream of the nozzle exit. The nozzle shape has been optimised for the creation of individual droplets, whereby the size is mainly defined by the size of the exit orifice. Roughly speaking, every nozzle will produce one droplet on average per swing of the membrane, with a remarkably uniform size. This will be shown to be an essential advantage for the performance of the nebuliser.

In this section, the authors will characterise the performance of a nebuliser device with a particular drug with the help of three quantities. The respirable fraction (RF), respirable dose (RD) and the respirable drug delivery rate (RDDR) give technical dimensions to the concept of a more efficient use of the drug and of the patient's time.

The distribution of particle sizes in an aerosol is frequently described in terms of the mass of fluid contained in droplets with a particular diameter. This particle mass distribution is typically of log-normal shape and can be described by its MMD and GSD. Figure 7 shows the theoretical form of a distribution function with an MMD of 4 µm and a GSD of 1.5, as an example for a vibrating membrane nebuliser. For such a distribution, 68% of the total mass is contained in droplets with sizes of 2.6 – 6.0 µm. Within the medical community, a generally accepted characteristic of the droplet size distribution is the RF, representing the percentage of the drug mass contained in droplets with diameters < 5 µm, which are considered able to penetrate the lower respiratory tract. For the above-mentioned distribution, the RF is 71%. An actual distribution curve as determined by laser-diffraction methods for one particular eFlow atomising head is shown in Figure 6C.

A high value of the RF is a prerequisite for efficient drug delivery to the lungs; however, it is by no means the only consideration. Only a certain portion of the volume of liquid filled into the nebuliser will actually be delivered to the patient, the rest is either lost due to residues or deposition within the nebuliser, or is lost in aerosol form during exhalation. The delivered dose of the drug will have to be tested under simulated breathing conditions for each distinct drug product using a standardised bench setup. By multiplying the delivered dose by the RF, the RD can be obtained. This is quoted either in micrograms of drug or as a percentage of the filled drug, and is an expression of the delivered mass of drug contained within droplets that are fine enough to be able to penetrate the lungs of a patient.

A further important aspect of drug delivery performance is the speed with which the drug is nebulised and administered to the patient's lungs. Again, the proportion considered as respirable (< 5 µm) is what is more relevant. The RDDR in micrograms per minute is a meaningful measure for the respirable amount of drug delivered per unit time. Practically, it will be determined by dividing the RD (in micrograms) by the inhalation time (in minutes).

The performance profile of the eFlow nebuliser shows high values in all three measures. To begin with, as the result of the controlled generation of droplets through a large number of closely identical nozzles in the vibrating membrane, the distribution of droplet sizes will be exceptionally narrow.

Standard atomising heads can be specified as required to produce droplet sizes in the range of 2.5 – 4.5 µm MMD, and with GSD values typically of 1.4 – 1.6. Correspondingly, RF lies between 60 and 98% [7].

Furthermore, the droplets leave the orifice of the nozzle at a moderate speed so that few will be lost by impact on the walls of the nebuliser. Considerable reduction of aerosol losses has been achieved by using a mixing chamber with valves, as discussed in Section 2.2.

A comparison of losses has been made between eFlow and a state-of-the-art jet nebuliser (LC STAR) using *in-vitro* measurements. With glutathione sodium, a highly viscous drug formulation (2 mPas), the eFlow achieves a MMD of 3.3 µm and a GSD of 1.5, and the LC STAR has a distribution with a MMD of 2.9 µm and a GSD of 2.4, whereby both have equal RFs of 82% [8]. Despite the equivalent value of RF, the RD is a factor of 2.5 higher for eFlow. This result highlights the importance of the controlled air flow within the mixing chamber and reduced residue in the resevoir.

A high RD measured during breath simulation is indicative of the efficiency with which the medicine is being used. In other words, for liquid formulations presently on the market, a smaller volume of drug will be needed with the eFlow nebuliser to deliver an equivalent RD than has been the case with traditional nebulisers. Therefore, for existing therapies in CF, the eFlow rapid has been developed on the basis of delivering an equivalent RD to that achieved with proven traditional systems, such as the LC PLUS® jet nebuliser [109]. For novel medications and therapies with the eFlow nebuliser, the required filled volume and drug concentration for a particular desired RD may be determined using standardised aerosol characterisation

methods. Any conclusions on drug/device characteristics and specifications drawn from *in-vitro* testing must be verified *in vivo* by controlled clinical studies with the advice and guidance from the relevant regulatory agencies.

The ability of the vibrating membrane technology to nebulise at a high-output rate is of immediate interest to the patient. When comparing nebulisation times, this must be referring to the time in which equivalent RDs will be inhaled. It has been shown that, compared with the LC PLUS nebuliser, the eFlow was a factor of 2.4 – 3.0 faster in delivering equivalent doses of three major drugs (albuterol sulfate, cromolyn sodium, colistimethate sodium) [10], and eFlow rapid was 2.6-times faster with tobramycin [9].

A special aspect of nebulisation therapy is the use of drugs in suspension formulations. It has been shown that eFlow brings the same advantage as jet nebulisers in performance over ultrasonic nebulisers with a suspension-based formulation [11].

Combined efficiency features of the TouchSpray Technology incorporated in the eFlow device (refer to Section 2.1) enable satisfactory delivery, even with highly viscous drugs [4,12].

7. Clinical and postmarketing experience

eFlow is available as the platform device for use in preclinical and clinical studies to evaluate technical feasibility and clinical benefit with different drug formulations. As the device received the CE marking in Europe and 510(k) clearance by the FDA in 2004, its use in clinical studies is facilitated by compliance with the relevant medical device regulations.

The device was planned for use in a number of clinical programs. Under the first of such programmes, the eFlow electronic nebuliser has been licensed by Corus Pharma, for the clinical development of inhaled aztreonam lysinate, a monobactam antibiotic being studied for the treatment of *Pseudomonas aeruginosa* infections in CF. The properties of the drug formulation and the device have been optimised to provide for a treatment of only ~ 2-min duration, compared with 15 min with established first-line inhaled antibiotic treatment. Phase II trials of inhaled aztreonam lysinate have been completed, and Phase III trials are under way.

eFlow rapid, the first European model, has performed convincingly since entering the market in 2005. The first postmarketing analysis shows a very positive response from the CF community. Apart from increased mobility and silent operation, it is, above all, the significant reduction in therapy time that is considered as an improvement in quality of life [13]. Patients have reported a reduction from 2 h/day spent with their overall nebuliser therapy to only 30 min/day. More detailed data regarding eFlow and patient compliance will be published in the future. As stated in the Instructions for Use, the average operating life of the atomising head is 6 months, based on daily multiple uses and regular cleaning and disinfection cycles.

The potential of the vibrating membrane technology is demonstrated by the eFlow nebuliser platform, which encompasses the marketed versions of eFlow rapid (EU), eFlow SCF (US), eMotion (Japan) and, for use in clinical trials, customised versions of the eFlow platform [14].

8. Alternative technologies

Three vibrating membrane nebuliser systems are commercially available. Apart from eFlow, the vibrating membrane principle is also applied in the AeroNeb Go and AeroNeb Pro products. In both cases the vibrating membrane is made of a nickel-palladium alloy by electroforming. The AeroNeb Pro is used for ventilator applications in an intensive care environment. Unlike the AeroNeb Pro, the AeroNeb Go cannot be sterilised by an autoclave process and is intended for single-patient home care.

As an example of a passive mesh nebuliser, the MicroAir® (Omron Corporation), in which the pressure wave is produced by a piezoelectric transducer horn within the fluid, has a particularly compact design. The material of the nozzle membrane is also an electroformed alloy. According to the Instructions for Use, the membrane can be disinfected in boiling water.

There are further nebulisers in development, based on the principle of a microperforated membrane, which are expected to reach a marketable stage in the early future. One example is a system using a passive nozzle plate etched in silicon. Pfeiffer has licensed the chip-based technology from Microflow Engineering and has a small-sized nebuliser in the development pipeline. The small liquid chamber between the nozzle membrane and the piezo-activated transducer surface is refilled by a pump.

A further example is the disposable drug cartridge with an integrated disposable mesh that is under development by AerovectRx Corporation. The system is based on a fluid reservoir that is enclosed between a nozzle membrane and a flexible metal membrane. This cartridge is placed so that the flexible metal membrane is in contact with an external piezoelectric transducer. The nozzle membrane is produced by an electroplating process. The technology is licensed from the US Centers for Disease Control and Prevention.

Based on the same technology as MicroAir, i-Neb™ has been described in connection with the AAD® System by Respironics Inc., which features a breath-controlled delivery algorithm [15].

Electroforming the nickel–palladium membrane or etching a silicon membrane in batch processes, which are predestined for high-volume production, introduce materials that are not as straightforward in the subsequent production processes as stainless steel. The laser-drilling applied in the TouchSpray Technology is more easily adapted to the requirements of the final product.

8.1 Comparative studies

In an internal *in vitro* study of RDDR, three vibrating membrane systems on the market have been compared (i.e., with an active membrane for the eFlow rapid and the AeroNeb Go, and with a passive membrane the U22 MicroAir nebuliser).

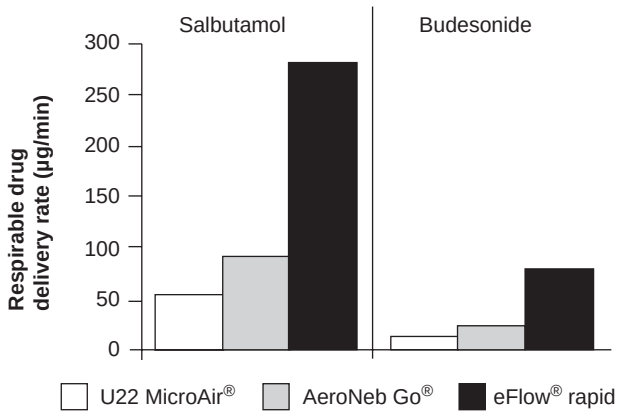

Figure 8. Respirable drug delivery rate (i.e., the rate at which drug in respirable droplets [< 5 µm]) is inhaled by the patient) for salbutamol (1200 µg/ml) and budesonide (500 µg/ml), as tested for three nebulisers.

Two drug formulations were used for the comparison: salbutamol 1200µg/ml as a representative of an aqueous solution (viscosity: 1.03 mPas; surface tension: 71 mN/m) and budesonide 500µg/ml as a representative of a suspension (viscosity: 1.10 mPas; surface tension: 32 mN/m).

The delivered dose was determined using analytical methods allowing breath simulation measurements, and the RFs were established using laser diffraction measurements of particle size distributions. All of the measurements were randomised and performed in duplicate. Relative humidity (50%) and temperature (23°C) of the intake air were accurately controlled; and the peak airflow was 20 l/min. All of the three systems had similar particle size distributions with a MMD of 4.5 – 5.0 µm and a GSD of 1.6 to 1.8. The results are shown in Figure 8.

A comparison of the three systems confirms that the technology is beneficial to nebulisers that are light, silent, mobile and with relatively narrow particle size distributions. The differences in performance result from the drug and treatment-time related efficiencies. In particular, the treatment time for equivalent doses using eFlow rapid is shorter by more than a factor of 2.5, compared with AeroNeb Go, and a factor of 4 compared with MicroAir.

This advantage is derived from the efficient energy conversion of the TouchSpray Technology and the low drug losses inherent to the eFlow mixing chamber and valve system (refer to Section 2).

Similar results have been reported independently [16], using a novel antibiotic.

9. Conclusion

Inhalation is becoming increasingly recognised as the preferred route of administration of pharmaceutical compounds to the lungs when treating various respiratory diseases. The technology of vibrating membrane nebulisers permits a close control of the droplet size and thereby direct targeting to the site of action in the lower airways, reducing undesired side effects. The highly improved efficiency of the technology adds up to further advantages for the patient. The high RF due to the narrow distribution of droplet sizes, the high RD as a result of low residual volume and aerosol losses and the high output rate altogether lead to a dramatic shortening of the required treatment time for a desired dose and improvement of delivery efficiency (i.e., the use of drug loaded into the nebuliser reservoir). This, in turn, together with further improvements of the device handling, has a positive effect on patient compliance and better control of the therapy by the physician, potentially resulting in an overall reduction of treatment costs. It is to be expected that the general acceptance of inhalation therapy will benefit from this development. This may help encouraging activities and willingness to invest in the clinical assessment and regulatory approval of novel inhaled medications.

10. Expert opinion

Use of the vibrating membrane technology in nebulisers such as the eFlow has the potential of expanding the market of pulmonary and nasal treatments into a number of specialty pharmaceutical segments in the near future. These may include:

- Optimised treatments for childhood asthma using low-dose steroidal or NSAIDs;
- Delivery of aerosolised surfactants in premature babies or to improve other conditions in lung diseases;
- Treatment of ventilator-associated or hospital-acquired pulmonary infections;
- New inhaled antibacterial, antifungal and antiviral products to treat both chronic and acute respiratory conditions;
- Delivery of anti-inflammatory, antibacterial, antifungal and antiviral agents to the nasal and sinus cavities using an oscillating aerosol [17-19];
- Immunosuppressant therapy for the prevention and treatment of lung transplant rejection;
- Pulmonary administration of protease inhibitors for the treatment of α-1-antitrypsin deficiency and related conditions;
- Inhaled applications in oncology;
- Non-invasive application of compounds via the lungs for systemic delivery;
- Delivery of recombinant DNA/RNA for the treatment of genetic disorders;
- Delivery of immunoglobulin for the therapy of immune disorders.

Further development on the basis of this technology platform will address the needs of reduced development costs (liquid-based inhaler products versus pressurised or dry powder systems); reduced regulatory burden (drug and device combination product versus the device as an integral part of

the drug product, such as with metered dose inhalers/dry powder inhalers); as well as increasingly complex safety aspects, more efficient use, advanced targeting of medication and facilitating individual disease management capabilities. The long-term future for drug delivery by TouchSpray Technology is extensive, enabling new and exciting products in the broader medical fields, such as:

- Bolus delivery inhalers extending the field of liquid-based drug formulations and novel compounds (proteins, peptides) into metered dose inhalers and dry powder inhalers-type pulmonary applications;
- Nasal spray delivery devices;
- Ophthalmic delivery devices;
- Delivery of drug compounds to the skin.

Developments are under way at PARI and The Technology Partnership to enable high-volume production of the TouchSpray aerosol generator, creating a wide range of opportunities for future TouchSpray-enabled products. From the patient's point of view, such products will address current unmet needs to assist with compliance, convenience and ease of use. Technically, these products will provide increased delivery efficiency, improved targeting and deliver a broader spectrum of drugs, including new chemical entities (e.g., proteins, peptides, high molecular weight compounds).

In an environment where the regulatory requirements on new delivery devices are becoming increasingly demanding, TouchSpray Technology has the potential to meet these requirements and, in doing so, revolutionise the drug delivery device market.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. KNOCH M, KELLER M: The customised electronic nebuliser: a new category of liquid aerosol drug delivery system. *Expert Opin. Drug Deliv.* (2005) 2(2):370-390.
   - A thorough review of the drug fomulation aspects.
2. MAEHARA N, UEHA S, MORI E: Influence of the vibrating system of a multipinhole-plate ultrasonic nebuliser on its performance. *Rev. Sci. Instrum.* (1986) 57:2870-2876.
3. STANGL R: Quality control of inhalers for clinical studies. *Proceedings of the Drug Delivery to the Lungs XIV*, London, UK (2003):168-171.
4. SEEMANN S, WEINSTEIN L: Satisfying CDRH and FDA´s 510(k) demands for device reliability with a complex electromechanical device: eFlow®. *Respiratory Drug Delivery X*, Boca Raton, FL, USA (2006):279-286.
5. ADACHI YS, ITAZAWA T, NAKABAYASHI M *et al.*: Safety and usefulness of a novel eMotion™ electric mesh nebuliser in children with asthma. *Allergol. Intern.* (2006) 55:167-171.
6. KELLER M, BUCHOLSKI A, SEEMANN S, SCHMITT A, KNOCH M: Reduction in nebulisation time of aqueous drug solutions by the eFlow® rapid in comparison to a jet nebuliser to improve patient convenience and compliance. *Eur. Respir. J.* (2005) 26:338s.
7. STANGL R: Development of a nebuliser product platform. *Proceedings of Drug Delivery to the Lungs XVI*, Edinburgh, UK (2005):242-245.
   - A detailed abstract of the product concept.
8. KELLER M, BUCHOLSKI A, BALCKE A, REUL K, KNOCH M: Assessment of nebulisation efficiency of a reduced glutathione-sodium solution (GSH) by a PARI LC STAR® and the eFlow® electronic nebuliser. *J. Cystic Fibr.* (2005) 4:30.
9. SEEMANN S, SCHMITT A, WALDNER R, HUG M, KNOCH M: Improving aerosol drug delivery in CF therapy. *J. Cystic Fibr.* (2005) 4:31.
10. SEEMANN S, WALDNER R, TSERVISTAS M, KNOCH M: A new electronic inhaler (eFlow®) to improve delivery of inhaled medications in CF patients. *Am. J. Resp. Crit. Care Med.* (2004) 169:A392.
11. KELLER M, JAUERNIG J, LINTZ FC, KNOCH M: Nebuliser nanosuspensions: important device and formulation interactions. *Respiratory Drug Delivery VIII*, Tucson, AZ, USA (2002):197-206.
    - An extensive discussion of nebulisation of suspensions.
12. SCHUSCHNIG U, KELLER M, LINTZ FC *et al.*: Customisation of the eFlow™ electronic inhaler to target pulmonary delivery of aztreonam formulations for the treatment of lung infections. *Proceedings of Drug Delivery to the Lungs XIII*, London, UK (2002):252-256.
13. RATJEN F, RIETSCHEL E, KASEL D *et al.* : Pharmacokinetics of inhaled colestin in patients with cystic fibrosis. *J. Antimicrob. Chemother.* (2006) 57:306-311
14. STANGL R, SEEMANN S, KNOCH M: Customizing an electronic nebuliser. *J. Aerosol. Med.* (2005)18:106.
15. DENYER J, NIKANDER K, SMITH NJ: Adaptive Aerosol Delivery (AAD®) technology. *Expert Opin. Drug Deliv.* (2004) 1(1):165-176
16. GELLER DE, KESSER KC: Aerosol device analysis for delivery of a novel inhaled antibiotic. *J. Aerosol Med.* (2005) 18:105.
17. SCHUSCHNIG U, KELLER M, KNOCH M, BODEN N, KULLMANN KH: Deposition of Pulmozyme® into the sinus cavities of a human nasal cast model using PARI SINUS™. *Respiratory Drug Delivery X*, Boca Raton, FL, USA (2006):737-740.
18. SCHUSCHNIG U, URBISCHEK M, LUBER M *et al.*: Comparison of delivery efficiency in a nasal cast model of fluticasone propionate suspensions and a novel solution aerosolized via the PARI VibrENT. *Respiratory Drug Delivery X*, Boca Raton, FL, USA (2006):741-744.
19. BOEHM A, LUBER M, MENTZEL H, KNOCH M: Investigating drug delivery to the sinuses – an *in vitro* deposition study using a nasal cast model. *Respiratory Drug Delivery X*, Boca Raton, FL, USA (2006):601-604.

Patent

101. PARI GMBH: US6962151 (2005).

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