Expert Opinion

The customised electronic nebuliser: a new category of liquid aerosol drug delivery systems

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Inhalation of aerosols is the preferred route of administration of pharmaceutical compounds to the lungs when treating various respiratory diseases. Inhaled antibiotics, hormones, peptides and proteins are potential candidates for direct targeting to the site of action, thus minimising systemic absorption, dilution and undesired side effects, as much lower doses (as low as a fiftieth) are sufficient to achieve a similar therapeutic effect, compared with oral administration. A quick relief from the symptoms and a good tolerance are the main advantages of aerosol therapy. A new class of electronic delivery device is now starting to enter the market. The eFlow® electronic nebuliser (PARI GmbH, Germany) provides improved portability and, in some instances, cuts treatment time to only a fraction of what has been experienced with current nebulised therapy. Drug formulations and the device can be mutually adapted and matched for optimal characteristics to meet the desired therapeutic target. Reformulation of known and proven compounds in a liquid format are commercially attractive as they present a relatively low development risk for potential drug candidates and, thus, have become a preferred pathway for the development of new inhalation products.

Keywords: aerosol, electronic nebuliser, inhalation, liquid formulation, patient compliance

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1. The market for aerosolised medications

The deposition of aerosolised drug in the lungs is determined by different factors, that is, patient- and drug/device-related factors. The individual lung anatomy and the breathing manoeuvre of the patient have a major impact on drug deposition. On the other hand, the design, function and quality of the device, as well as the interaction of drug formulation and device, play an important role. Crucial parameters are the delivery efficiency and consistency, particle size and aerosol plume velocity [1].

An inhalation system has to produce a particle size distribution suitable for delivery to the lungs. For inhaled delivery of medications, the fraction of respirable particles or droplets (percentage of particle mass in the range of 1 – 5 µm in diameter) should be maximised [1]. Particles in this size range will be deposited primarily by sedimentation in the peripheral lung regions, the bronchioles and alveoli. Sedimentation is the major mechanism of deposition in the therapeutic use of aerosols. Although 3 – 5 µm particles are ideal for topical applications, particles of 1 – 3 µm are needed for systemic administration of drugs via the lungs, such as insulin, hormones and opioids [1]. Inertial impaction associated with larger particles (diameter > 5 µm) should be minimised to avoid undesired oropharyngeal deposition.

Three systems for administration of aerosolised medications are widely used and are described in this section.

1.1 Pressurised metered-dose inhalers

In pressurised metered-dose inhalers (pMDI) the drug is either suspended or dissolved in a propellant and filled under pressure into a canister. Releasing a metered volume of the fluid causes the propellant to expand and evaporate rapidly, leaving the drug in the form of dry aerosol particles suitable for inhalation [2]. For more than five decades pMDIs have represented the largest part of the respiratory market, namely for the treatment of asthma and chronic obstructive pulmonary disease (COPD). In the last decade of the twentieth century extensive investments have been made by the pharmaceutical industry to convert propellant systems from chlorofluorocarbon (CFC) to more environmentally friendly hydrofluroalkane (HFA) formulations. In this context a trend has been followed towards solution-type pMDIs (Qvar™ [3M Pharmaceuticals], Modulite® [Chiesi Farmaceutici] platform technology) [3,4] as a replacement for drugs in suspension in order to overcome formulation challenges, such as particle growth and sedimentation requiring shaking before use to maintain dose-to-dose consistency [5]. Such efforts typically led to investments in the several hundred million US dollars range and regulatory constraints severely limit the scope for further product improvements and modifications following approval.

Although the therapeutic result was highly dependent on the hand–lung coordination ability of the patient in the past, today there are a number of systems available, which use add-on spacers or holding chambers (e.g., Nebuchamber® [AstraZeneca], Aerochamber® [Trudell Medical International], Babyhaler® [GlaxoSmithKline]) [6-8] or incorporate a breath actuator (Autohaler™ [3M Pharmaceuticals], Easybreathe® [IVAX, London, UK]) [3] to overcome this potential reason for huge dosage inaccuracy. Breath actuators also improve metering accuracy, being dependent on the force and speed of the actuation [5,9]. With the new systems, reduced plume velocity helps release the aerosol over a larger portion of the inhalation cycle, thus reducing intra- and interpatient dosing variability. To adequately treat poorly coordinating patients and small children, the pMDI has to be used in combination with a spacer or a holding chamber device, which holds the aerosol for a limited period of time until it is inhaled by the patient. However, add-on features, such as spacers, breath actuators and dose counters increase the costs for pMDIs significantly and, thus, reduce its price advantage compared with DPIs and novel aqueous droplet inhalers.

One imminent restriction of the pMDI technology is its limitation on the drug dose that can be administered. The typical dosing range for a pMDI and current metering valve systems is in the range of 50 – 500 µg/actuation (personal experience of author). Smaller doses may cause problems regarding dose uniformity, whereas doses > 500 µg cannot be delivered with an acceptable percentage of respirable particles. This drawback is especially apparent with hygroscopic drug compounds, such as disodium cromoglycate (DSCG). Thus, the fine particle fraction (particles < 5 µm) of a CFC pMDI may fall from ~ 40% for a salbutamol pMDI delivering 100 µg/puff to ~ 15% for DSCG delivering a nominal dose of 1000 µg/puff [5].

1.2 Dry powder inhalers

Dry powder inhalers (DPIs) can be classified [1,9] in single dose systems, utilising premetered powders in capsules (e.g., Spinhaler® [Fisons/Rhone Poulenc Rorer], Aerolizer™ [Novartis Pharmaceuticals], Handihaler® [Boehringer Ingelheim]), premetered multidose systems utilising either capsules (e.g., Boehringer Ingelheim Inhalator), blisters (Diskhaler® [GlaxoSmithKline], Diskus® [GlaxoSmithKline]) or an *in situ* metering system loaded with a bulk powder reservoir (Turbuhaler® [AstraZeneca], Easyhaler® [Orion Pharma], Clickhaler® [Celltech Group], Twisthaler® [Schering-Plough], Novolizer® [Viatris], Certihaler® [Skye-Pharma/Novartis] and so on), or a compressed powder (MAG-haler® [Mundipharma GmbH], Ultrahaler® [Fisons/Rhone Poulenc Rorer]). Alternatively, DPIs can be characterised as passive (powder deagglomeration by patients breathing force) or active DPIs making use of a breath-independent powder deagglomeration mechanism, such as an impeller or razor blade (MAG-haler, Ultrahaler). Four major formulation technologies are used in current DPI systems:

- powder agglomerates in the form of spheronised drug or soft pellets (Turbuhaler)
- free flowing lactose powder blends in bulk reservoirs (e.g., Easyhaler, Clickhaler, Novolizer, Certihaler)
- low-density, porous powders (Pulmospheres®, AIR® [Alliance Pharmaceutical Corp.])
- compressed powder granulates or isostatic ring tablets (Ultrahaler, MAG-haler)

In general, shear forces generated by the patient's inhalation flow are used to deagglomerate the soft pellets or ordered powder mixtures to scrape off drug particles, which are commonly adhered to carrier particles such as glucose or lactose [1]. Contrary to pMDIs, most DPIs vary significantly in design and performance with respect to pressure drop, inter- and intradevice dose uniformity, effect of inspiratory flow rates on the emitted dose and so on [1,9]. New DPI developments have been directed towards improved dispersion characteristics and dosing reproducibility; for example, by the addition of magnesium stearate to the lactose carrier [10]. Porous low-density powders have shown advantages regarding a high drug load and reduced flow dependency of the inhaled dose, even with simple DPI devices [11,12].

DPI systems have been designed for both single, as well as multiple dosages, and several new products have been approved as combination therapies, for example, a long-acting bronchodilator as well as a corticosteroid in one single dose (Symbicort® [AstraZeneca], Advair® [GlaxoSmithKline]). As with pMDIs, performance requirements meeting with regulatory guidelines and demands are significant constraints making the development of multi-dose systems an expensive task.

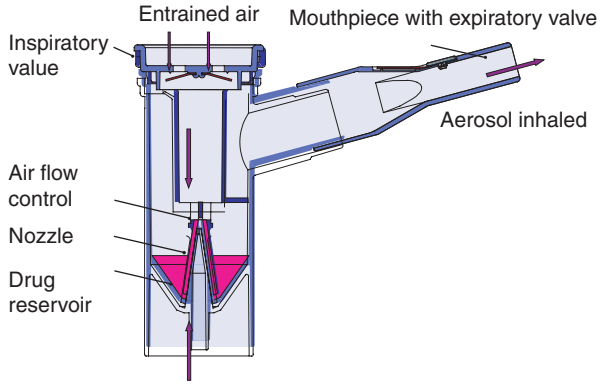

Figure 1. Breath-enhanced nebuliser system.

The environmentally friendly and easy-to-use image of DPIs has made them very popular and a competitive alternative to pMDIs in the asthma and COPD market.

1.3 Nebulisers

There are two widely known classes of medical nebulisers: the jet nebuliser, which is powered by compressed air, and the ultrasonic nebuliser, which derives the energy required to aerosolise drugs from high frequency sound waves. Nebulisers are ideal for the delivery of high doses of medication to the respiratory tract with major applications in the treatment of asthma, COPD and cystic fibrosis. They fill an important niche in the treatment of young children and the elderly, especially in exacerbations and emergency situations. The treatment requires only minimal coordination and effort in comparison with pMDIs or DPIs. Although nebulised drugs receive marketing authorisation from the Food and Drug Administration (FDA) or European Medicines Evaluation Agency (EMEA) via a separate new drug approval (NDA), nebulisers receive clearance to market via a 510k premarket notification in the US (CDRH Guideline 784), and via CE Marking in the EU. Similarly, as with propellant and powder technologies, product innovations on both the drug and device will help to transform and strengthen the future position of nebulisers in the respiratory field.

2. Current nebuliser technology

2.1 Jet nebulisers

Jet nebulisers are driven either by a portable compressor or from a central air supply. Essentially, a high-speed air flow through a narrow nozzle orifice entrains and disperses the liquid into droplets (primary generation) via a viscosity-induced instability [13]. Droplet dispersion is improved by impaction on a baffle structure adjacent to the nozzle orifice transferring kinetic energy further into increased droplet surface area (secondary generation). The resulting droplet size distribution still contains only a small fraction of respirable aerosol (droplets < 5 – 6 µm in size) and the large droplets are recirculated within the nebuliser by means of secondary impaction structures. This process is associated with evaporation effects that cause the gas phase to be nearly saturated with vapour, as well as a temperature decrease within the nebuliser. A considerable part of the vapour arises from the larger recirculating droplets, thus increasing drug concentration in the remaining liquid.

As assessment of nebuliser systems cannot be done with a simple gravimetric measurement alone [14], proper *in vitro* testing of nebulised aerosols requires quantification of the drug content delivered under simulated breathing conditions. Cascade impactors allow for measurement of the aerodynamic droplet size distribution with respect to drug mass; however, care must be taken to avoid evaporation of droplets, which may be caused by the set up itself [15]. The European Standard for nebulisers [16] describes a simplified type-testing method for the head-to-head comparison of nebuliser systems using an aqueous sodium fluoride (NaF) surrogate solution. However, as physicochemical properties of solutions and suspensions can deviate substantially from NaF solution, the results do not reflect the specific drug/device interaction [17-20].

For nebulisation of suspensions, small droplets cannot carry larger suspension particles and, thus, droplets with no or preferential containment of suspension particles in larger droplets can occur [21]. Therefore, chemical assay is necessary for proper particle sizing of nebulised suspensions. For liposomal formulations, disruption of liposomes can occur due to mechanical stresses during nebulisation, possibly during primary generation [22] and/or secondary generation, although such disruption is device-specific and is most pronounced for large liposomes [23].

There are three common types of jet nebulisers: constant output (unvented), breath-enhanced (vented) and breath-activated. Constant output nebulisers produce aerosol at a constant rate and the aerosol is diluted during inspiration by air entrainment via a T-piece or mask. Typically, ≥ 50% of the aerosol is wasted to the environment during exhalation. The breath-enhanced nebuliser (**Figure 1**) entrains inhalation air in the droplet production region and produces aerosol at a higher rate during inspiration, but at a lower rate during expiration using a valve system. This allows ~ 70% of the aerosol to be delivered to the patient during continuous nebulisation, compared with only ~ 50% using a constant output system [24]. Examples of breath-enhanced nebulisers are the PARI LC PLUS® and LC STAR® (PARI GmbH, Stamberg, Germany) and the Ventstream® (Profile Respiratory Systems). Breath-actuated nebulisers release mechanically (AeroEclipse®, Trudell Medical, Ontario, Canada) or electronically (ProDose®, Profile Therapeutics, Bognor Regis, UK) controlled doses of aerosol only during inspiration, or a portion thereof, and theoretically may improve delivery to 100% of the generated aerosol. However, beyond dose control and reduced contamination of room air, the benefits of such systems are currently relatively low due to long treatment times

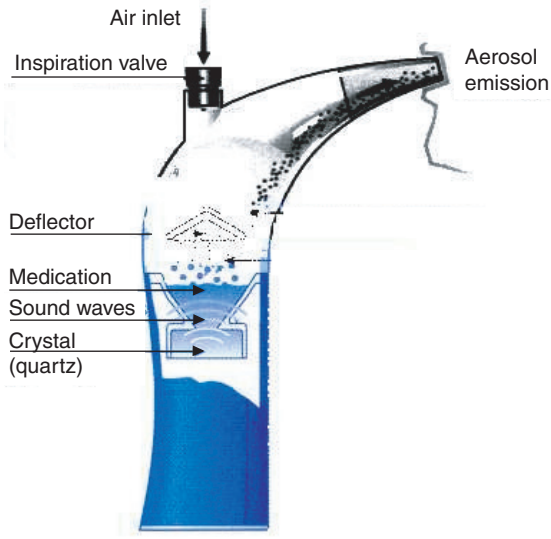

Figure 2. Ultrasonic nebuliser system.

and the high residual drug losses inherent with jet nebulisers in general.

With jet nebulisers all commonly available inhalation solutions and suspensions can be administered. Mechanical damage, which may cause denaturation of sensitive drug compounds (e.g., proteins and peptides), is minimised.

2.2 Ultrasonic nebulisers

Ultrasonic nebulisers use a piezoelectric transducer in order to create droplets from an open liquid reservoir. Pressure waves emitted from the piezovibrator at the bottom of the reservoir progress towards the surface forming a fountain within the wave focus. Droplets are formed by highly energetic surface instabilities in the lower part of the fountain [25]. This process does not effectively aerosolise drug in suspension, as the majority of the suspension particles are retained in the reservoir [26]. As the energy is transferred through the liquid container it becomes evident that physicochemical properties of drug formulations (e.g., dynamic viscosity and surface tension) have a strong effect on aerosol particle size and output rate, and failure may occur with high viscosity liquids [25,27]. In most ultrasonic nebulisers the heat produced by the piezoelement can result in denaturation of proteins and other thermally sensitive compounds [28,29]. In some devices, the drug formulation is in direct contact with the piezovibrator, causing concerns regarding cleaning and microbial contamination. Newer devices avoid this problem by using decalcified or distilled water as a transfer medium in which a separate, easy-to-clean or disposable drug container is inserted (**Figure 2**). The high density of the generated aerosol makes ultrasonic nebulisers ideal for airway humidification; however, the above mentioned constraints and high costs have limited their therapeutic use.

3. Novel nebulisation technology

In recent years new and innovative inhalation devices have occurred, which cannot be classified in the known schemes. Innovative in this context is not defined as an evolutionary improvement of existing devices, such as dose counters, spacers, holding chambers or breath activation mechanisms. Rather, innovative inhalation devices introduce new and unique aerosol-generating principles. They often use sensors with sophisticated electronics and software in order to support and optimise the functionality of the device. Thus, medications can be delivered in predictable and consistent quantities to the deep lungs and new drug formulation technologies allow for further optimising therapy.

The drug/device combination needs to be optimised with respect to three major requirements: the aerosolisation process must be stable and predictable over the lifetime of the device, the delivered dose must be consistent over a wide range of ambient conditions and breathing patterns and the particle size distribution and mode of delivery (continuous versus breath activated versus discrete bolus delivery) must be optimised for the target area in the lungs. The patient's ability and motivation to use an inhalation device is another important factor for successful therapy, and novel technology can be utilised to improve patient compliance and adherence. One of the most important demands is that treatment time should be as short as possible.

Physicians and therapists often overlook the dilemma of poor and variable device performance, which, in combination with the uncertainty of patient compliance, may lead to a lack of confidence in nebuliser therapy. A profound technical knowledge is required in order to provide the best therapy, which should be tailored to the individual [30], and the level of feedback the physician receives is a critical success factor. Improving the device–formulation interaction and the patient–device interface helps physicians to gain better therapy control.

3.1 Vibrating membrane electronic nebuliser technology

With this technology, a thin perforated membrane is actuated by an annular piezoelement to vibrate in a resonant bending mode (TouchSpray™ Technology, The Technology Partnership plc, Melbourn, UK). The holes have a tapered shape with larger cross-section on the liquid supply side and narrower cross-section on the opposite side from where the droplets emerge. During the vibrational motion, sound pressure is built up in the vicinity of the membrane, thus ejecting the fluid through the holes as uniformly sized droplets and creating the aerosol [31]. Depending on the therapeutic application, the hole sizes can be adjusted from 2 µm upwards, with several hundred to several thousand holes in each membrane. **Figure 3** illustrates the dispersion principle and set up, which is currently in development for a number of new aerosol delivery devices. These may cover a wide range of requirements, from low-dose

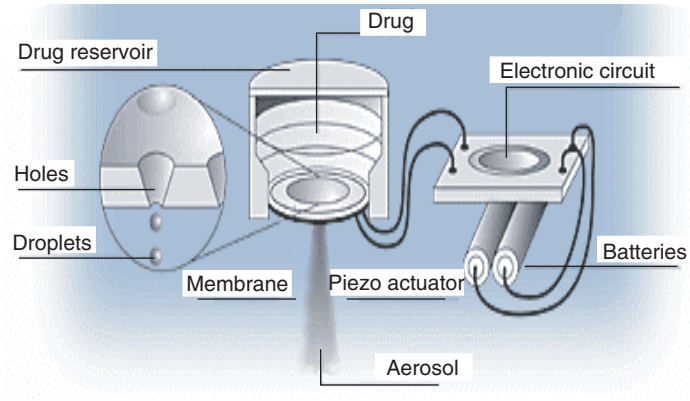

Figure 3. Vibrating membrane liquid dispersion principle.

Figure 4. eFlow® electronic nebuliser (PARI GmbH).

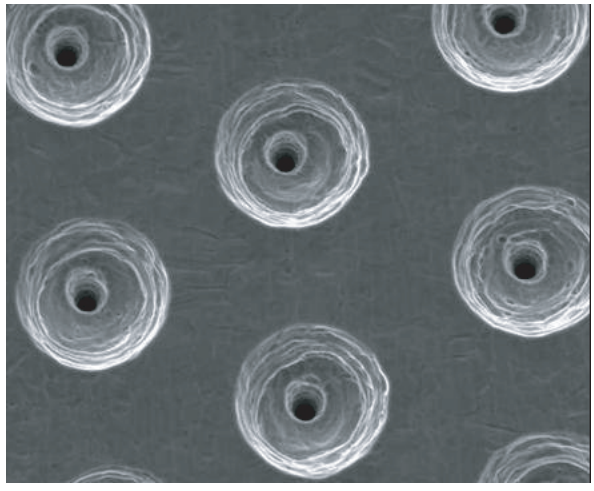

Figure 5. Electron microscopic view of the laser-drilled membrane used in eFlow® (PARI GmbH).

single-breath applications, to treatments over several minutes for the delivery of large volumes and high doses of drug solutions or suspensions. The force behind the development of this new technology is to improve the delivery efficiency dramatically, compared with jet and traditional ultrasonic nebulisers [17,19,33]. This should allow for much smaller liquid volumes at higher drug concentrations to be administered during each treatment, which in turn will result in shorter treatment times and better acceptability of nebuliser therapy [32].

Treatment costs are of major concern to the caregivers and new device technology may help to reduce medication costs, due to a more efficient utilisation of expensive drug compounds. Costs for devices are typically small compared with the medication in indications such as cystic fibrosis (CF) (e.g., 1 – 2% of an annual inhaled antibiotic treatment) and increased costs for novel devices must be justified by an improved patient compliance and outcome. Only long-term can the enormously high development costs for new technologies be recovered, and time will tell whether prices can be adapted to current reimbursement schemes, as novel devices will successfully penetrate the mass markets in asthma and COPD.

4. Electronic nebuliser device platform

The eFlow® electronic nebuliser (PARI GmbH, **Figure 4**) is the first device out of a suite of products, which are planned to emerge from the TouchSpray vibrating membrane technology in the forthcoming years. The eFlow is able to deliver a wide range of drug volumes (0.5 – 5 ml) and dosages (0.01 – 1000 mg), thus allowing the patient to take his/her treatment during consecutive spontaneous breathing. Other products under development are foreseen to cover a broad range of applications and, thus, will present a variety of functional and performance characteristics. These include a breath trigger mechanism to further improve efficiency and consistency of dosing, as well as to reduce exhaust of aerosol from the system during exhalation. Optional indicators for guided breathing may help to reduce inter- and intraindividual variability in lung deposition. Delivery of discrete boluses of aerosolised medications could extend the range towards lower doses for new biological compounds, such as proteins and peptides, or present a convenient and less deterrent alternative to injections in systemic therapies.

The core component of the system, the aerosol head, contains the perforated membrane and ring-shaped piezoelectric actuator, which is driven by an electronic circuit to vibrate the membrane. The membrane is made of stainless steel with the

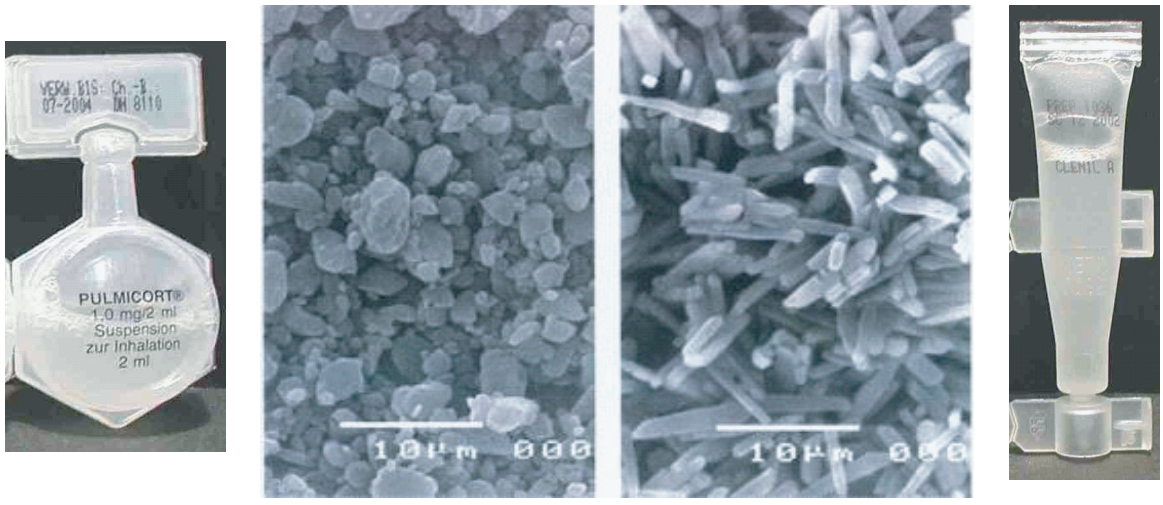

Figure 6. Pharmaceutical products and crystal structures of two nebuliser suspensions. Left: budesonide (Pulmicort® Respules, AstraZeneca), right: beclomethasone-dipropionate (Clenil®, Chiesi). Pictures taken from the poster *in vitro* comparison of Pulmicort Respules with Clenil per aerosol in combination with three nebulisers. Published by VAGHI A, BERG E, LIJEDAHL S, SVENSSON JO at the *Annual Congress of the European Respiratory Society*, Stockholm, Sweden, 2002.

Figure 7. Test set-up to measure the aerosol distribution pattern using a baby cast. Used with permission from KELLER M, JAUERNIG J, SCHUEEPP K *et al*.: Using infant deposition models to improve inhaler system design. *Proceedings of the Respiratory Drug Delivery IX*, Palm Desert, California, USA (2004):221-231.

holes precisely shaped by a laser drilling process (**Figure 5**). Physical properties of the optimised drug formulations, together with a specific hole size and shape, form a unique combination of parameters determining the resulting droplet-size distribution. Therefore, such variables need to be matched in order to optimise the drug/device system and meet the desired performance characteristics. The 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. Since the device received the CE Marking in Europe and 510k clearance by the FDA in summer 2004, its use in clinical studies is facilitated by compliance with the relevant medical device regulations.

As a first step, in each instance, *in vitro* results are generated and customisation is then progressed towards an optimal drug/device combination for use in final Phase III clinical trials. Such trials are needed to support NDA with the specific device by the FDA or EU regulatory agencies. One example is an optimised formulation of tobramycin for the treatment of pseudomonas infection in CF patients for administration by the eFlow device. The drug concentration and physicochemical characteristics have been adjusted for tobramycin 100 mg/ml in a physiologically acceptable solution. Using a dose of 150 mg in 1.5 ml, under standardised *in vitro* conditions, the new device delivers an equivalent respirable dose within ~ 3 min compared with ~ 12 min with the established treatment regimen (300 mg/5 ml in a jet nebuliser) [32].

Another example is an improved administration of budesonide, a corticosteroid for the anti-inflammatory treatment of asthma in very young children. Until now, beclomethasone-dipropionate (Clenil®, Chiesi, Italy) and budesonide (Pulmicort® Respules, AstraZeneca, Switzerland) are commercially available as microsuspensions for nebulised therapy only. However, as the micronised drug particles are quite large and variable in size (**Figure 6**), these suspensions are not ideally suited to be nebulised in the small droplets required

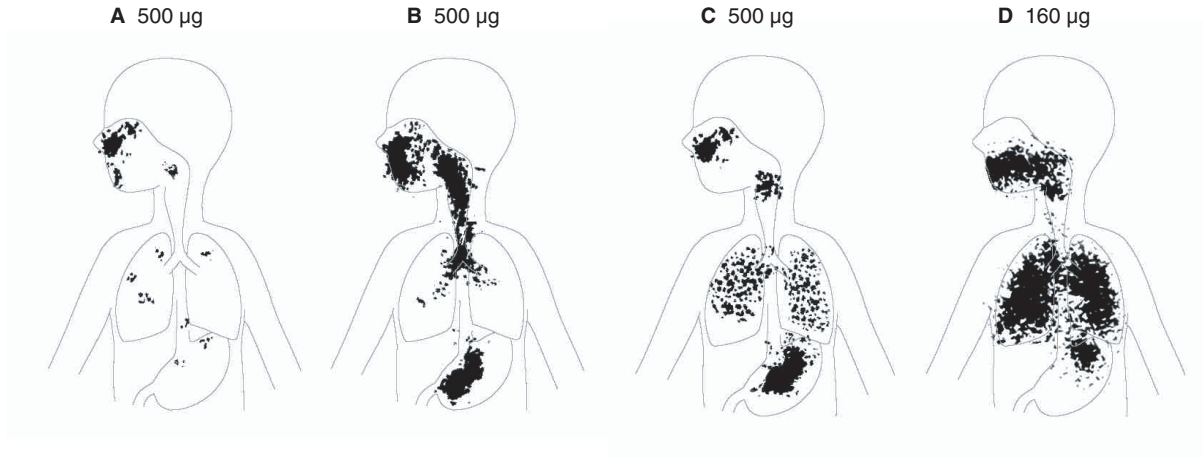

Figure 8. *In vivo* γ-scintigraphy images of four children on inhalation using different nebuliser/drug configurations. Used with permission from KELLER M, JAUERNIG J, SCHUEEPP K *et al*.: Using infant deposition models to improve inhaler system design. *Proceedings of the Respiratory Drug Delivery IX*, Palm Desert, California, USA (2004):221-231. **A.** LC PLUS®/Pulmicort® 0.25mg/ 2 ml, poorly fitting mask (32 months, 0.1% to lung). **B.** LC PLUS®/Pulmicort® 0.25mg/ 2 ml, crying during inhalation (36 months, 1% to lung). **C.** LC PLUS®/Pulmicort® 0.25mg/ 2 ml, tightly fitting mask (34 months, 8% to lung). **D.** eFlow® Baby/BUDeFlow™ 0.16mg/ 0.8 ml, tightly fitting mask (38 months, 36% to lung).

Table 1. Effect of device and formulation on *in vitro* lung dose and cast deposition on nebulisation of a novel micellar budesonide solution or Pulmicort® suspension by eFlow® Baby prototypes or PARI LC PLUS® nebulisers operated by a PARI BOY® N compressor (PRONEB® Ultra in the USA).

Device/drug combination	Nominal dose µg/ml	Lung dose (%)	Lung dose (µg)	Cast deposition (%)	Cast deposition (µg)	Nebulisation time (min)
eFlow® Baby/ BUDeFlow™ (n = 8)	100/0.5	28.9 ± 2.4	28.9 ± 2.4	20.2 ± 1.9	20.2 ± 1.9	3.91 ± 0.59
eFlow® Baby/ Pulmicort® (n = 6)	500/2	12 ± 1.3	59.8 ± 6.5	13.1 ± 1.9	66.7 ± 9.6	9.84 ± 1.64
LC PLUS®/ BUDeFlow™ (n = 6)	400/2	5.6 ± 0.1	22.6 ± 0.6	9 ± 0.9	36.1 ± 3.7	6.04 ± 0.26
LC PLUS®/ Pulmicort® (n = 6)	400/2	2 ± 0.2	29.8 ± 0.9	6.8 ± 0.4	33.8 ± 2.1	5.67 ± 0.52

From KELLER M, JAUERNIG J, SCHUEEPP K *et al*.: Using infant deposition models to improve inhaler system design. *Proceedings of the Respiratory Drug Delivery IX,* Palm Desert, California, USA (2004):221-231.

for inhalation therapy in young children. Therefore, alternative formulation techniques, such as submicron suspensions [19] and a micellar solution [33], have been investigated and nebulisation by a customised eFlow device has demonstrated clear advantages over the commercial micro suspension. The optimised drug/device combination with a droplet mass median diameter of 2.8 µm showed a several-fold higher drug delivery efficiency compared with the standard treatment (Pulmicort with jet nebuliser) [33]. A Sophia Anatomic Infant Nose Throat (SAINT) cast [34] was used to investigate the *in vitro* deposition pattern of an eFlow Baby nebuliser prototype under simulated breathing conditions (**Figure** 7). The effect of device and formulation on the *in vitro* lung dose and cast deposition is summarised in **Table 1**. In addition, γ-scintigraphy studies in young children were conducted using radiolabelled budesonide to collect information on actual drug deposition in the lungs. Lung deposition was 36 and 38% of the loaded dose in two young children (38 and 31 months) when inhaling quietly, with a tightly fitting face mask from eFlow Baby prototypes using 0.8 ml of the novel budesonide solution. In comparison, lung deposition was only 5 and 8% in two other children (34 and 33 months) inhaling quietly from a jet nebuliser using Pulmicort (2 ml). For the same system, even less favourable lung deposition was found in a child with a poorly fitting face mask (0.1%) and a crying child (1%). Examples of γ-scintigraphy images are shown in **Figure 8** [33]. As a result of the increased delivery efficiency and improved droplet-size distribution provided by the optimised drug/device system, the drug (budesonide) may be formulated with a much smaller nominal dose and volume

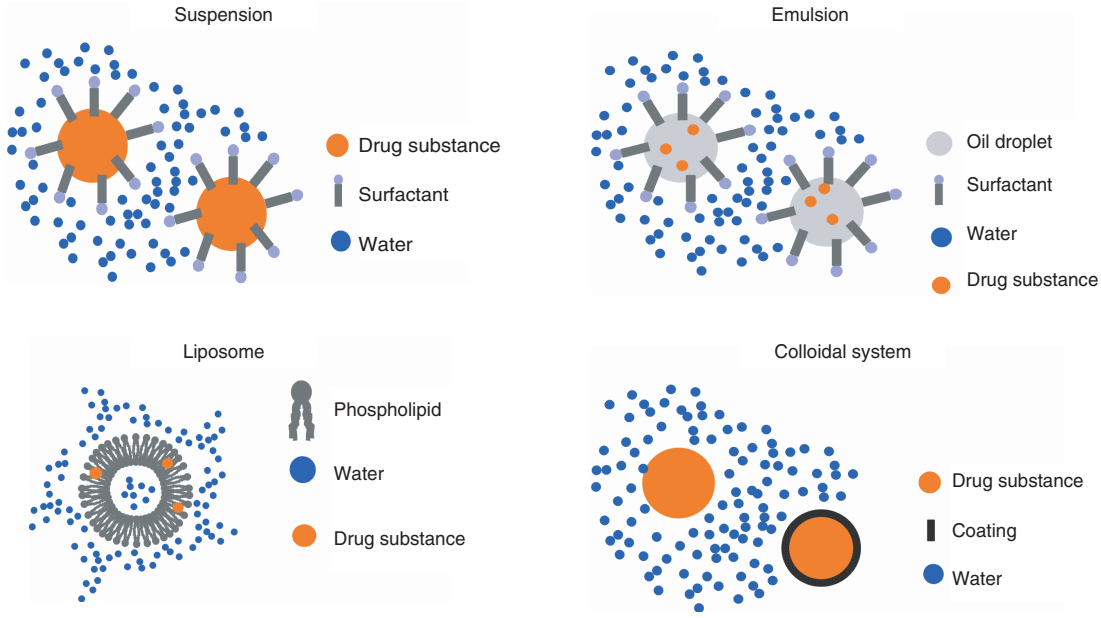

Figure 9. Examples of dispersed aqueous systems suitable for nebulisation.

compared with the commercial product. Due to reduced oropharyngeal deposition (see cast deposition in **Table 1**) the eFlow Baby/BUDeFlow combination also has the potential to minimise side effects while maintaining an equivalent dose to the lungs in childhood corticosteroid therapy.

Clinical programmes will be ongoing for a number of years before novel drug formulations can be approved with the device. However, in order for the technology to provide early benefit for the patient, the first product version of eFlow will be designed to be compatible with currently approved medications used with nebuliser systems. The initial target population are CF patients who may receive an immediate advantage by a significant shortage of treatment time using their major antibiotic (TOBI®, Chiron, CA, USA) and mucolytic (Pulmozyme®, Roche, Switzerland) treatment.

5. Current drug formulations for nebulisation

One advantage of nebulisers over pMDIs and DPIs is their capability of delivering drug in a wide dose and volume range. In the past, pharmaceutical companies focused primarily on aqueous inhalation drug products, which could be developed and manufactured in a simple, fast and straightforward way. Most drug formulations for nebulisers represent simple aqueous solutions containing water soluble drug salts, such as salbutamol sulfate, ipratropium bromide and disodium cromoglycate, and water soluble peptides, such as dornase alpha (Pulmozyme).

However, many drugs suitable for the treatment of lung diseases, such as asthma, COPD or CF are poorly water soluble. As an example, corticosteroids (beclomethasone, budesonide, fluticasone) require a more sophisticated formulation approach; in effect, all drug compounds for the topical treatment of lung diseases may be beneficial when provided in a liquid format suitable for delivery via a nebuliser system. However, the use of organic solvents, such as ethanol or propylene glycol, as solubilisation enhancers for lipophilic drugs, such as cyclosporin [35], is questionable, as most organic solvents are irritant on inhalation according to their material data safety sheets.

This stimulated the development of aqueous suspension drug products (e.g., Pulmicort Respules, Clenil, **Figure 6**), which have become very popular for nebuliser administration. However, suspensions containing micronised drugs are by far more complex to develop, manufacture and sterilise than solutions. A major issue of suspensions is particle growth and/or agglomeration when stored, due to Ostwald ripening [36,37]. As sterile filtration is not applicable if the particle size range is > 200 nm, other methods must be used to avoid contamination and growth of microorganisms on storage.

The pH of solutions and suspensions can be adjusted either by the addition of an acid (e.g., hydrochloric or sulfuric acid) or a base (sodium hydroxide). In case of insufficient stability of the formulation, aqueous buffered systems (citrate, phosphate) may be added to keep the pH within a physiological range. Isotonicity is usually adjusted by the addition of sodium chloride or mannitol.

6. Novel optimised formulations for nebulisation

If a drug is molecularly dissolved it can be classified as a real solution, whereas colloidal solutions consist of homogeneously dispersed drug particles in a colloidal size range (< 100 nm). **Figure 9** schematically illustrates the

difference of four dispersed systems applicable as inhalation formulations. These systems require excipients, such as surfactants, lecithin, phospholipids or polymers, to facilitate the solubilisation process. Phospholipids, which are contained in lecithin of plant or animal origin, are very popular due to their occurrence in cell membranes.

As an example, a novel micellar solution of budesonide has been developed (PARI GmbH, Germany) consisting of micelles in a size range of ~ 10 – 25 nm, confirmed by photon correlation spectroscopy [33]. Solubilisation was achieved by an amphiphilic surfactant with a high hydrophile-lipophile balance value, lecithin and/or phospholipids mixture blended in a distinct ratio. As similar excipients have been used as contained in a commercially available artificial lung surfactant (Exosurf®, GlaxoSmithKline), toxicological safety can be expected [38]. Exosurf has been used for the treatment of both adult and childhood respiratory distress syndrome. Lipophilic water insoluble drugs, such as cyclosporin and fluticasone–propionate can also be solubilised by this novel formulation technology.

The progress in drug delivery, with respect to other dosage forms (oral, parenteral), has stimulated the development of new aqueous inhalation drug products utilising more sophisticated pharmaceutical technologies [36,39]. Process technologies used for the manufacture of particulate systems in the nanosize range (< 200 nm) are of particular interest for nebuliser applications, which can be classified as follows [37]:

- Nanocrystals and nanosuspensions [36,39] may be obtained by wet milling or high-pressure homogenisation processes. In many cases they contain a polymer or surfactant to coat the drug particles, thus improving stability.
- Nanocapsules [36,39] are solidified micellar systems, microemulsions or coated colloidal solid-drug systems, in which the drug is embodied in a polymer, such as ethylcellulose. They can be produced by spray drying a drug polymer solution, nanosuspension and water-in-oil emulsion, or by polymerisation methods.
- Liposomes can be classified into small unilamellar vesicles, which have a size range of 20 – 50 nm, and large unilamellar or multilamellar vesicles, which have a size range of ≤ 1 μm. Liposomes are concentric vesicles and their shell is formed by one or several water insoluble phospholipid bilayers. The lipophilic parts of the phospholipids are facing each other, whereas the hydrophilic parts face towards the aqueous outer phase and nucleus. Hydrophilic drugs are encapsulated in the aqueous nucleus and interstitium, whereas lipophilic drugs are incorporated in the lipid layer of the phospholipid membranes. Liposomes are widely used in dermatological preparations and cosmetics, but are less popular as pharmaceutical dosage forms due to their limited drug encapsulation capacity and poor shelf-life properties [37,39,40]. One product example being used off label for inhalation is a liposomal formulation of the antifungal drug amphotericin B (Ambisome®, Fujisawa, IL, USA). Of the lipophilic drug, 50 mg are incorporated in the lipophilic phospholipid bilayer. Liposomes are suitable drug carriers as they can solubilise drug molecules, reduce the toxicity of a drug substance and improve cell permeation to target specific cells [39,40]. Examples are the reduced nephrotoxicity of amphotericin B [39,41,42], or cardiotoxicity of the cytostatic doxorubicin (Doxil®, Ortho Biotech, NJ, USA) [39,43] on intravenous administration when liposomal formulations are used.

Cyclodextrins offer an interesting and promising approach for solubilisation, which are ring-forming oligosaccharides consisting of six, seven or eight glucose molecules and which have a sweet taste on inhalation [44,45]. The α-, β- and γ- cyclodextrins differ with respect to their molecular weight (927.9 – 1297) and size of the cavity defined by the inner (0.57 – 95 nm) and outer (1.37 – 1.69 nm) diameter. The fate of β-cyclodextrin and some of its derivatives has been studied following pulmonary administration in order to evaluate the feasibility of using β-cyclodextrins for sustaining pulmonary drug action or for controlling systemic drug levels [46]. A water insoluble drug can be solubilised by molecular inclusion in the cavity with the potential to yield the following benefits:

- simple straightforward manufacturing and sterilisation process
- stabilisation of drugs that are instable in a dissolved state
- taste masking of unpleasant tasting and locally irritating drugs
- improvement of bioavailability

In case the previously mentioned pharmaceutical technologies are inappropriate to obtain a physicochemical stable drug product, powders or lyophilisates offer alternatives. Such formulations are in general more stable than liquid formulations and an aqueous solution can be prepared prior to use by dissolving the powder with suitable diluents. For example, an aztreonam lysinate salt has been developed (PARI, GmbH, Germany), which is manufactured by a distinct freeze-drying process. The sterile lyophilisate offers the benefit that it can be rapidly dissolved by 0.17% saline. The physicochemical properties of the resulting solution have been matched to generate an aerosol of specific characteristics using a customised eFlow device [47]. A further convenience for the user could be introduced by an integral dual chamber system containing both the powder and the diluent in separate compartments for dissolution by a simple manipulation step.

The controlled (slow release) delivery of drugs to the lungs may reduce the frequency of inhalation treatments [48] and in the future may offer a more convenient treatment by inhaled drug products. Dispersed systems having particle sizes < 200 nm will offer new perspectives for poorly water soluble drugs, as long as regulatory requirements to prove their safety will be kept at an acceptable level [49]. A primary objective for the development of novel pulmonary drug delivery systems is the use of

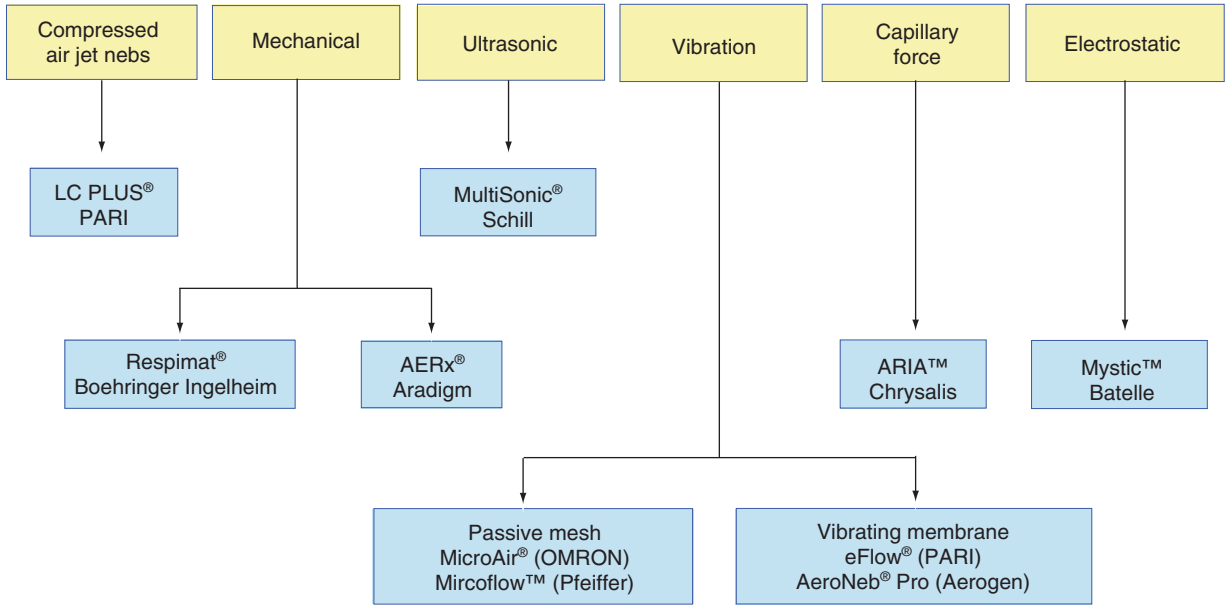

Figure 10. Overview of proven and novel liquid aerosolisation technologies.

excipients regarded as safe for inhalation, and the applicability of a cost effective manufacturing and sterile filtration process or, if possible, other established sterilisation processes.

7. Current clinical studies

The eFlow electronic nebuliser has been licensed for two clinical development programmes by Corus Pharma Inc. (WA, USA). The first, Cayston™ (aztreonam lysinate for inhalation) is a monobactam antibiotic being studied for the treatment of *Pseudomonas aeruginosa* infections in CF. Phase II trials for Cayston have been completed, and Phase III trials are expected to start early 2005. The second is lidocaine solution for inhalation, which is currently under study in Phase II trials for management of asthma symptoms [50].

8. Potential applications

The improved tobramycin (100 mg/ml) and micellar budesonide solutions mentioned in Section 6 are two examples of how established therapies can be modified to the patients' benefit using a novel delivery system. Primary targets are the reduction of side effects and the burden of time-consuming treatments. In such instances, apart from miniaturisation and noiseless operation, the technological innovation is perceived by a more acceptable therapy compared with current inhalation practice.

A European orphan drug designation has been granted (PARI GmbH, Germany) for inhaled cyclosporin A (CSA), which is currently in development as a novel aqueous formulation for the prevention and treatment of lung transplant rejection. As the drug is delivered directly to the target organ, inhaled CSA may substantially reduce side effects compared with oral treatment and, in combination with the eFlow device, will provide a convenient, rapid way of administration.

In general, novel electronic nebulisers, such as eFlow, in combination with improved and customised formulations, may provide significant advantages compared with current oral and intravenous therapies in the treatment of respiratory tract diseases (e.g., asthma, COPD, bronchiectasis, CF, lung emphysema, pulmonary infections by bacteria, fungi, viruses, sarcosidosis, idiopathic pulmonary fibrosis, pulmonary arterial hypertension, lung cancer). In addition, such devices are suitable for systemic delivery of drugs, which cannot be given orally, such as peptides, proteins or drugs with a poor bioavailability, and when injection is regarded as inappropriate.

9. Alternative technologies

Figure 10 shows an overview of the different liquid aerosol generation principles and technologies with typical representatives of the devices under development. Some of the novel nebulisers will be launched to market within the next couple of years and provide improved nebulised drug therapy.

Jet and ultrasonic nebulisers fall under established technology and are described in detail in Section 2. The category of mechanical systems uses pressurised liquid to eject droplets suitable for inhalation from microholes in a wafer substrate or blister package. Pressure of ~ 300 bar is built up via a piston, driven by either a loaded spring [51] or a cam 3[52]. A multidose (Respimat®, Boehringer Ingelheim, Germany) as well as a unitdose system (AERx®, Aradigm, CA, USA) have been realised.

Passive mesh nebulisers (e.g., MicroAir®, OMRON, Japan) create droplets using a piezoelectric actuator; however, other than with the vibrating membrane type devices, a horn transducer adjacent to the mesh is vibrated to create the pressure fluctuations for droplet ejection rather than the mesh itself. Thus, output rates produced with small droplet sizes are limited using this technology, and proper cleaning of the mesh is more critical due to potential clogging of the microholes.

Vibrating membrane technology has been presented not only as a unitdose nebuliser system, but in a multidose design (AeroDose®, AeroGen, CA, USA) [53] as well. This, however, has not yet successfully advanced to a commercial scale. Commercial devices are the eFlow (PARI, Germany), the AeroNeb® Go and, AeroNeb Pro nebulisers (AeroGen, CA, USA), the latter being used in ventilator applications.

A capillary force aerosol generator uses the principle of controlled particle growth by condensation of a vaporised liquid formulation (ARIA™, Chrysalis, VA, USA). The liquid is fed through a heated capillary to completely evaporate the drug on passage. Expansion of the vapour causes it to cool down and form regularly sized droplets [54].

Atomisation, by means of electrostatic charge, is an old principle, which has been discussed for use in respiratory therapy [55]. Two electrodes are charged with a high voltage of ~ 30 kV, one of which contains a central capillary tube for liquid supply. By electrostatic forces a liquid cone forms at the tip of the electrode dispersing a fine mist of droplets [56]. This principle has been realised in a prototype drug delivery system (Mystic™, Batelle, OH, USA) [57].

All of these principles have demonstrated technical feasibility to generate aerosols suitable for inhalation. However, each requires special drug formulations with distinct physical properties to obtain optimal performance in combination with the respective device technology, the most important ones being dynamic viscosity and surface tension of the liquid. In particular, heating can only be applied to thermally stable drug compounds. For electrostatic dispersion, liquids with certain conductivities and low surface tension, such as ethanol, are preferred [55].

10. Conclusion

Within the last couple of years it has been recognised that inhalation using novel nebulisers offers new perspectives in drug administration, for both local and systemic drug delivery. The progress in device developments shows that ne-bulised drug therapy is in the midst of a renaissance, especially for the delivery of new drugs, such as antagonists, peptides and proteins. Contrary to pMDIs and DPIs, nebulisers allow for administration of an aqueous drug formulation being physiologically more compatible with the humidified environment of the lungs than pMDIS and DPIs. Furthermore, there is more flexibility to deliver drugs in a wide dose range and by spontaneous breathing. Breath-actuated electronic nebulisers, equipped with feedback and monitoring systems will help to further optimise drug delivery. Those device developments focussing on patients' demands for shorter treatment times will have the greatest impact on improving efficacy and patient compliance.

It is becoming more evident that drug delivery is the result of a complex interaction of device and drug formulation. Hence, the nebuliser currently used as a general purpose system in the market may no longer present a useful concept. Differences in performance characteristics (up to 10-fold variability in the delivered respirable dose [58]) do not fulfil the demands of a modern evidence-based drug therapy approach. Therefore, distinct specifications for both the device and drug formulation need to be set and thorough *in vitro* and *in vivo* assessment of the drug delivery system will be necessary to demonstrate safety and efficacy, as well as patient benefit. This includes *in vitro* aerosol characterisation supported by γ-scintigraphy studies, as well as assessment of pharmacokinetic (e.g., blood plasma drug levels) and pharmacodynamic (e.g., lung function tests) parameters. Different patient groups (e.g., pediatric, severe sufferers) and diseases (e.g., asthma, CF) may require specific approaches for clinical testing. This difficult task calls for an integral interdisciplinary development approach involving scientists from many disciplines (engineering, physics, electronics, chemistry, pharmacology, pharmaceutical packaging, regulatory and clinical affairs) and with in-depth knowledge and competences in the inhalation field. In this context, however, care must be taken to keep total development expenses under control to avoid inhalation therapy becoming unaffordable for the public healthcare providers. Evidently, regulatory requirements are becoming more restrictive and, thus, counterproductive for the approval of innovative drug products. Although incentives are offered by the approval agencies in the form of extended (e.g., in case clinical trials include the paediatric patient population) or facilitated marketing protection (e.g., for rare indications and fatal diseases via orphan drug designation), an overly bureaucratic and formalistic regulation will still be detrimental and discourage research organisations and the pharmaceutical industry to develop and commercialise new inhalation products.

11. Expert opinion

Many drugs that are approved and have been proven for certain indications have the potential to be effective in other indications as well, and thus provide an opportunity for extending their life cycle. Examples are acetysalecylic acid (Aspirin® [Bayer HealthCare]) for the treatment of headache, which may be used as an inhibitor of thrombocyte aggregation, or sildenafil citrate (Viagra® [Pfizer]) originally intended for the treatment of erectile dysfunction and also being effective in treating pulmonary hypertension. The variety of pharmacological effects are mostly classified as undesired side effects, yet may include some unexploited and valuable treatment options. Potentially, a number of drugs may be useful for new indications if an approved formulation for inhalation was available (e.g., amiloride, heparin etc.). In addition, some drug products showing either serious side effects (e.g.,

cyclosporin) or insufficient efficacy (amphotericin B) when administered orally may provide enhanced therapeutic safety and efficacy via the inhaled route.

Novel pharmaceutical technologies, in combination with more efficient nebulisers, could revolutionise the pulmonary delivery of such drugs if the expenses on animal safety studies can be kept reasonable. Contrary to oral drug delivery products, there are more restrictions on sophisticated pulmonary drug delivery systems, as the generation of animal safety data is a costly and time-consuming task. Only a few excipients are regarded as safe for inhalation so far, as they have been used for decades irrespective of the limited basis of safety data. However, new regulatory demands on safety data are in many cases exaggerated and questionable when taking into account that the lungs are the organ in most intimate contact with our environment, where dust particles and countless airborne toxins are a permanent burden. With the right balance of regulatory precautions, clinical benefit and serving important unmet needs, novel electronic nebulisers, such as the eFlow, will stimulate growth in new specialised respiratory markets.

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