Key points

- Mesh nebulisers can be used to nebulise aqueous drugs and suspensions; however, with suspensions, there can be a reduction in performance in terms of aerosol output rate and inhaled mass.
- Based only on *in vitro* studies, marketed mesh nebulisers for ambulatory patients might reduce the nebulisation time without reducing drug efficiency or overdose risk.
- The effect of disinfection and cleaning on marketed mesh nebulisers' performances remains to be assessed.

The mesh nebuliser:
a recent technical innovation for aerosol delivery

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Educational aims

- To define the differences between the new mesh nebulisers and conventional jet and ultrasonic nebulisers.
- To give recommendations regarding the choice of a mesh nebuliser in order to administer a therapeutic aerosol.

Summary

A nebuliser is a device that converts a liquid into aerosol droplets and must be loaded with the medication before each treatment. There are three types of nebulisers: jet nebulisers, which can nebulise all drugs and can be disposable; ultrasonic nebulisers, which are silent but can only nebulise aqueous solutions and may heat the drug; and mesh nebulisers, which can be used to nebulise aqueous solutions, but can be less efficient in nebulising suspensions. The latter are silent, portable and small. They can reduce the nebulisation time without reducing drug efficiency, but disinfecting and cleaning can be difficult.

An aerosol is the preferred means by which drugs can be administered into the airways, thus increasing drug efficiency and limiting toxic effects. An aerosol is defined as a system of low-velocity fine particles in a gas (*i.e.* a suspension). Particles can be solid or liquid and can be spherical or of other shapes. Aerosol therapy is defined as drug administration in the form of an aerosol into a patient's airways. Its efficiency depends on the drug used and the aerosol's physical and chemical properties, as well as the patient's breathing pattern, lung anatomy and physiology. The aerosol's physical properties are determined by the aerosol generator, and different techniques can be used to produce a medical aerosol. Metered dose inhalers (MDIs) and dry powder inhalers (DPIs) are portable and deliver small aerosol volumes rapidly. In addition, the aerosol generator and the drug are indissociable, since the drug is packaged in the MDI or DPI. Nebulisers can deliver high aerosol volumes and can be used with different drugs. A nebuliser is defined as a device that can convert a liquid into aerosol droplets, which must be loaded with the medication before each treatment [1].

In 2001, the European Respiratory Society (ERS) published detailed guidelines on the use of nebulisers. The aim of this review is not to

repeat the detailed information given in the guidelines, but to give an update about some of the newer devices that were not covered in the 2001 guidelines. Indeed, new nebuliser technology based on the mesh system has been developed and marketed over the last 2 years. However, these new nebulisers have been available on the market without relevant clinical evaluation. Thus, this paper will provide an overview on existing knowledge about the mesh nebuliser, explain the differences between the different commercial mesh nebulisers and define their place among jet and ultrasonic nebulisers.

Nebuliser principles

Current nebulisers

1. Jet nebulisers

Jet nebulisation was the first technical operation developed for aerosol production (figure 1). It uses gas flow either from a compressor or a central air supply. The gas passes through a small aperture in the nebuliser in order to pick up and atomise the liquid drug. The aerosol that is generated by atomisation contains large and small droplets, and is driven to a baffle. Large droplets are impacted by the baffle and forced onto the side of the nebuliser to be recycled in liquid form in a reservoir. More than 90% of the droplets produced by atomisation are selected and recirculated in the nebuliser to be recycled in the liquid-drug reservoir. Small droplets are transported out of the nebuliser by the gas to be inhaled by the patient.

The drug mass loaded in the nebuliser is greater than that delivered as an aerosol to the patient. Part of the drug mass is trapped in the nebuliser as residual mass and another significant part is lost in the form of aerosol particles in the ambient air during exhalation as leakage.

There are three types of jet nebulisers, which are defined by their output during inhalation [2].

- Standard unvented nebulisers are those with a constant output during the patient's inhalation and exhalation phases.
- Breath-enhanced vented nebulisers produce a higher aerosol output during the inhalation phase and lower output during the exhalation phase.
- Dosimetric or breath-actuated nebulisers only produce an aerosol during the inhalation phase or a fraction of it.

Jet nebulisers nebulise all types of liquid (solutions, suspensions, oils, *etc.*). The residual

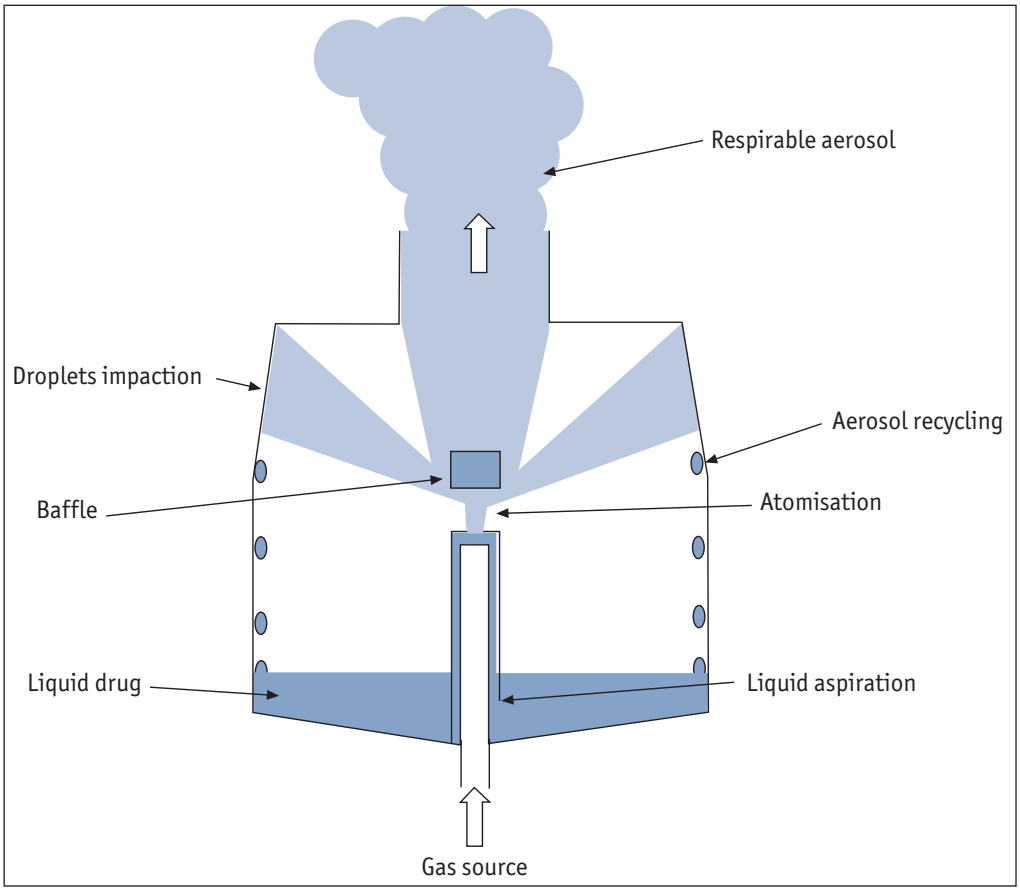

Figure 1
Jet nebuliser principle.

mass is ~50% of the drug mass loaded into the nebuliser and the aerosol is cooled.

Jet nebulisation can partially destroy brittle active drug compounds (*e.g.* liposomes, adenovirus), due to the mechanical stress of atomisation. They are often portable and disposable, but compressors are often noisy and bulky.

2. Ultrasonic nebulisers

Ultrasonic nebulisers use the vibration (1.2–2.4 MHz) of a piezo-electric crystal to generate the aerosol (figure 2). Vibrations are transmitted to a liquid drug, generating a liquid-drug fountain comprising large and small droplets. Large droplets drop into the liquid-drug reservoir or are thrown onto the side of the nebuliser and recycled. Small droplets are stored in the nebulisation chamber to be inhaled by the patient or leave the nebuliser with the airflow produced by a ventilator. Like the jet nebuliser, some residual mass is trapped in the nebuliser, but there is little leakage since there is no gas source to transport the aerosol out of the nebuliser during exhalation.

There are two types of ultrasonic nebulisers.

- Standard nebulisers are those where the drug is directly in contact with the piezo-electric transducer. This contact causes the drug temperature to increase due to heating of the transducer. In addition the piezo-electric transducer is difficult to disinfect.
- Ultrasonic nebulisers with a water interface use a volume of water between the piezo-electric transducer and a separate reservoir for the drug. Water reduces drug heating and the drug is not in contact with the transducer.

Ultrasonic nebulisers do not nebulise suspensions or liquids with high viscosity or a high surface tension [3], the residual mass is often >50% of the drug mass loaded in the nebuliser and the aerosol is heated. Ultrasonic nebulisers are silent, but often bulky.

New nebuliser technology

New nebulisers based on mesh technology have recently been introduced into the market. They can operate with batteries and are small enough to be carried. They are efficient, silent and comply with active drug compounds. Mesh nebulisers can be classified into two types: static mesh and vibrating mesh nebulisers. Table 1 shows the characteristics of several different mesh nebulisers.

1. Static mesh nebulisers

Static mesh nebulisers apply a force on the liquid drug to push it through a static mesh (figure 3). The first mesh nebuliser had a limited introduction in the 1980s by Omron Healthcare (Bannockburn, IL, USA). The Micro air® NE-U22V nebuliser uses an ultrasonic transducer to generate vibration (180 kHz) of the liquid drug and push the droplets through the static mesh [4], which can then be inhaled directly by the patient. Unlike jet and ultrasonic nebulisers, the aerosol is not recycled in the mesh nebuliser. Droplets generated through the mesh have a

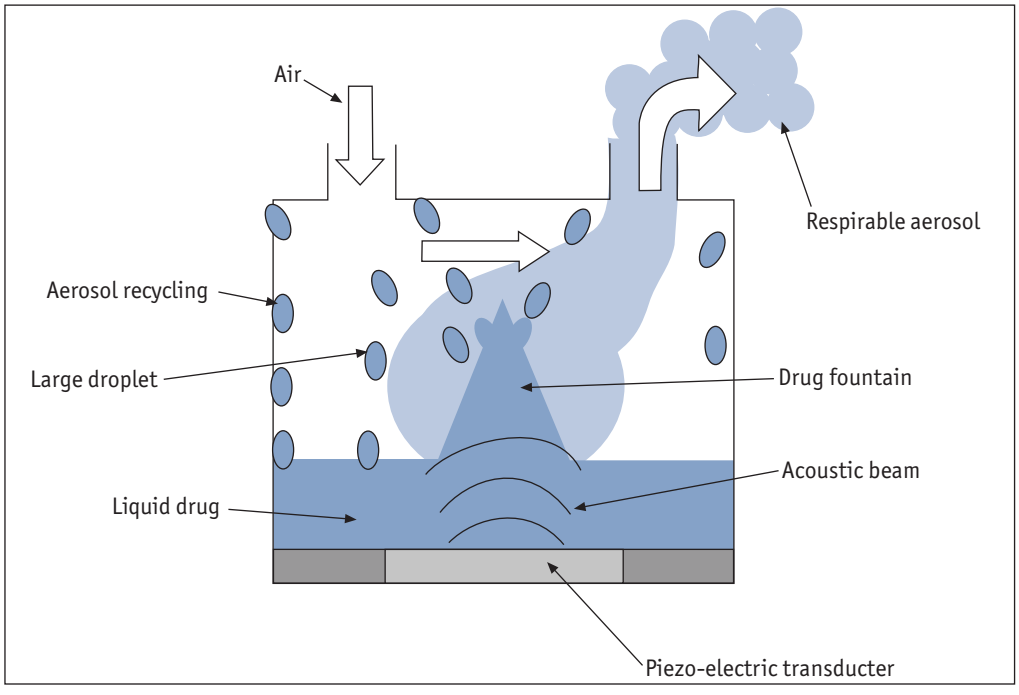

Figure 2
Ultrasonic nebuliser principle.

Table 1 Mesh nebuliser characteristics

Name	Nebuliser type	Disinfection	Life cycle	Patient	Maximum volume load
Microair® NU22V	Static mesh	Benzalkonium solution (1%)	?	Ambulatory	7 mL
Aeroneb® Go	Vibrating mesh	No recommendations	1 year	Ambulatory	6 mL
Aeroneb® Pro	Vibrating mesh	Autoclave	1 year	Mechanical ventilation	10 mL
eFlow® rapid	Vibrating mesh	Autoclave	6 months	Ambulatory	6 mL

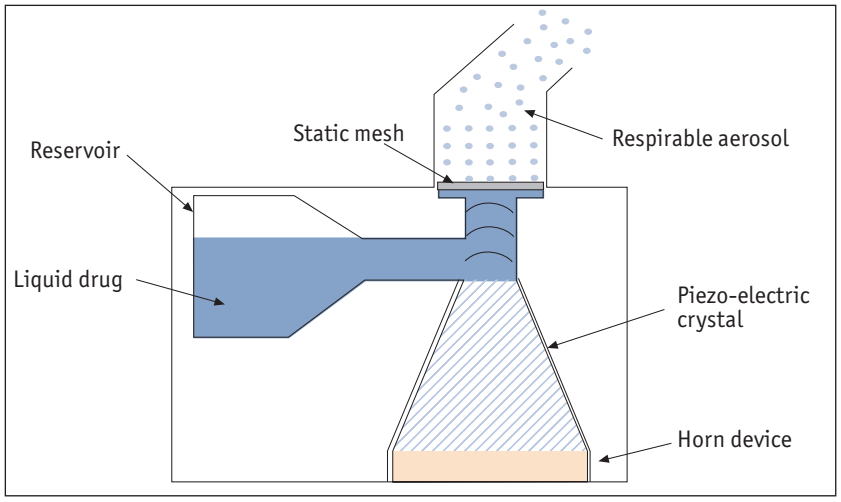

Figure 3
Static mesh nebuliser principle.

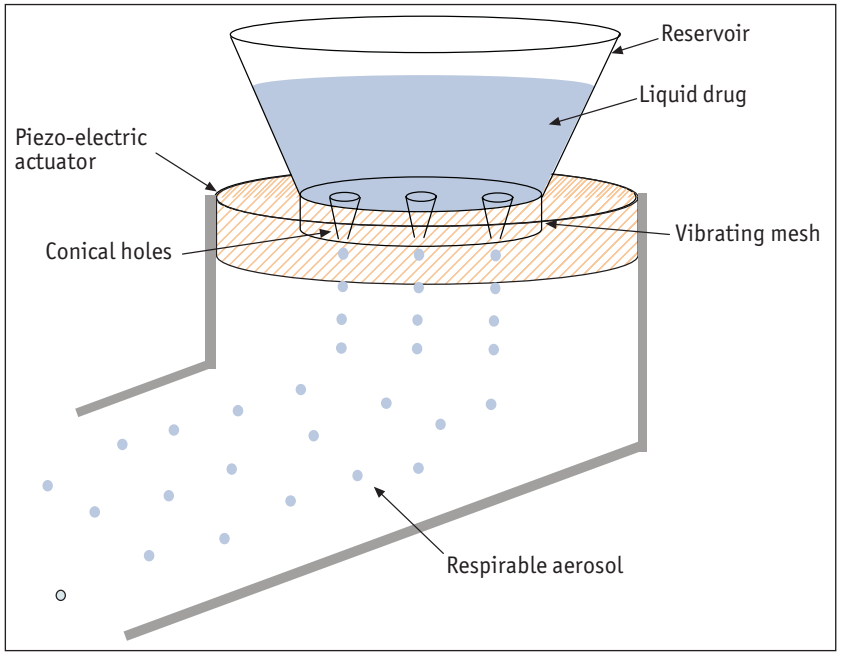

Figure 4
Vibrating mesh nebuliser principle.

similar size to the mesh aperture diameter. The Micro air® NE-U22V mesh is made of a metal alloy. It contains 6,000 holes with a diameter of ~3 µm, which are produced by electroplating. The Micro air® NE-U22V can nebulise aqueous solutions and suspensions [5]. The residual volume in the nebuliser reservoir is ~0.3 mL. The mesh cannot be disinfected by an autoclave process, and, instead, should be submerged in a 0.1% solution of benzalkonium for 10–15 min. Other cleaning agents such as bleach must not be used due to a risk of corrosion. The Omron mesh must be cleaned by generating a distilled-water aerosol. It can be loaded with a maximum volume of 7 mL.

2. Vibrating mesh nebulisers

Vibrating mesh nebulisers use mesh deformation or vibration to push the liquid drug through the mesh (figure 4). An annular piezo element, which is in contact with the mesh, is used to produce vibration around the mesh, and the liquid drug is in direct contact with the mesh. Holes in the mesh have a conical structure, with the largest cross-section of the cone in contact with the liquid drug [6]. The mesh deforms into the liquid side, thus pumping and loading the holes with liquid. This deformation on the other side of the liquid-drug reservoir ejects droplets through the holes, which can be inhaled by the patient.

The Aeroneb® Go is a vibrating mesh nebuliser (Nektar Therapeutics, San Carlos, CA, USA), which utilises a horizontal mesh containing 1,000 holes obtained by electrolysis, and vibrates at 100 kHz (figure 5). It consists of a nebuliser and a separate battery pack or AC power adapter. There is a reservoir above the mesh, and the aerosol is produced towards the bottom of the nebuliser. Droplets ejected from holes at a moderate velocity are selected by impaction on the nebuliser base. Residual drug mass is negligible in the reservoir, but can be appreciable in the nebuliser. The aerosol leaves the nebuliser in standing cloud at low velocity.

During inhalation, ambient air crosses the nebuliser aperture to transport the aerosol to the patient. During exhalation, exhaled air pushes the aerosol produced out of the nebuliser through the same aperture. Thus, there is aerosol leakage in ambient air and appreciable residual drug mass in the nebuliser.

Aeroneb® Go mesh cannot be disinfected by an autoclave process and there are no specific recommendations for disinfecting the Aeroneb® Go nebuliser. It must be cleaned manually with liquid soap and not with detergent or in a dishwasher. Aeroneb® Go must only be used for a single patient and must be replaced every year. It can be loaded with a maximum volume of 6 mL.

Aeroneb® Pro is designed to be used during mechanical ventilation. It can be sterilised by an autoclave process. In order to obtain the best performance, it is recommended to connect the Aeroneb® Pro in the inspiratory circuit, but not necessarily near the Y piece [7]. This nebuliser can be used for different patients and must be changed every year. It can be loaded with a maximum volume of 10 mL. Both Aeroneb® Go and Aeroneb® Pro can nebulise aqueous solutions and suspensions.

eFlow® rapid (Pari, Munich, Germany) is the most recent vibrating mesh nebuliser to be marketed in Europe. Its metallic mesh has been developed by ODEM (Touchspray™ technology; ODEM, Cambridge, UK). It contains 4,000 holes obtained by a high-speed laser drilling process and has a vibration frequency of 116 kHz. eFlow® rapid consists of a valved nebuliser and a separate battery pack or AC power adapter. It uses a vertical mesh with an adjacent reservoir, which contains a 1.2-mL dead volume to limit nebulised aerosol drug mass, thus avoiding drug overdose. The aerosol is produced horizontally at a moderate velocity in a small valved chamber and leaves the nebuliser in standing cloud at a low velocity. When the patient inhales, the expiratory valve placed on the mouthpiece is closed and the valve next to the mesh is open. Ambient air enters the chamber through the aperture close to the mesh, crosses the chamber and transports the aerosol to the patient. During exhalation, the expiratory valve is opened and the inspiratory valve is closed. Exhaled air leaves the nebuliser by the expiratory valve and does not cross the chamber where the aerosol produced is stored. With this nebuliser system, there is little aerosol leakage, but there is a residual volume of ~1.2 mL to avoid drug overdose and, thus, to decrease nebulisation time. eFlow® rapid can nebulise aqueous solutions and suspensions, and can be loaded with a maximum volume of 6 mL. The eFlow® rapid mesh should be sterilised in an autoclave (<121°C) and can be cleaned by submersing in hot water (40°C) for 5 minutes. The mesh must be changed every 6 months.

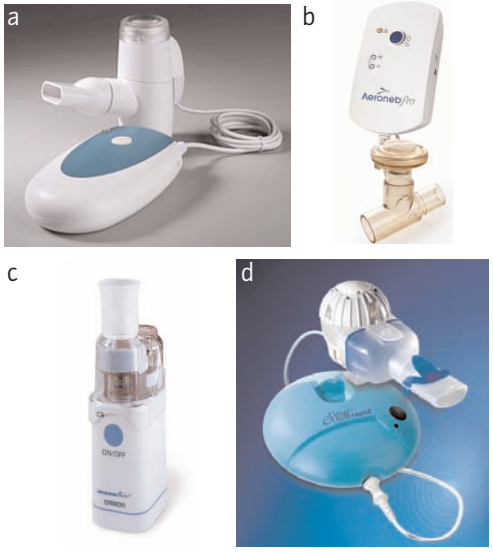

Figure 5
Photographs of commercial mesh nebulisers that are currently available: a) Aeroneb® Go nebuliser (Nektar Therapeutics); b) Aeroneb® Pro nebuliser (Nektar Therapeutics); c) Micro air® NE-U22V (Omron Healthcare); and d) eFlow® rapid (Pari).

Mesh nebuliser performance

In vitro performance

The *in vitro* performance of nebulisers can be defined by two parameters. The inhalable mass is defined as the drug mass, in the form of an aerosol, produced by the nebuliser that reaches the patient's mouth. It predicts the amount of drug penetrating into the patient's airways. The particle-size distribution of the aerosol predicts the region of aerosol deposition in the patient's airways. Particles with an aerodynamic diameter of 1–5 µm have a chance of being deposited in the lungs of adult patients. The optimal particle size for children is throught to be smaller. Mass median aerosol diameter (MMAD) is a statistical parameter that describes the aerosol size. Mesh nebulisers have been evaluated *in vitro* in different studies in accordance with European standards, using a filter method and a pump that models patient inhalation. The MMAD obtained with Micro air® NE-U22V ranged 3.2–4.8 µm with salbutamol [8]. Tests carried out with a reference solution (*i.e.* NaF) gave an MMAD of 5.0 µm for Aeroneb® Go [9] and 4.1 µm for eFlow® rapid. The inhaled fraction, expressed as

a percentage of nebuliser volume loaded in the reservoir, was 35% for Micro air® NE-U22V, 24% for Aeroneb® Go and 25% for eFlow® rapid. The aerosol output rate was 0.13 mL per minute for Micro air® NE-U22V, 0.15 mL per minute with Aeroneb® Go and 0.35 mL per minute with eFlow® rapid. With the exception of eFlow® rapid nebulisers, gold-standard jet nebulisers and mesh nebulisers have similar performance in terms of output rate (table 2). For example, the Pari LC+ jet nebuliser, tested in accordance with European standards, gave an MMAD of 4.4 µm, an inhaled fraction of 23% and an aerosol output rate of 0.17 mL per minute [10]. Micro air® NE-U22V and Aeroneb® Go nebulisers have smaller residual volumes than jet and ultrasonic nebulisers, but their performance is reduced due to aerosol leakage during exhalation. Micro air® NE-U22V and Aeroneb® Go nebulisers produce a constant output during inhalation and exhalation phases.

The physical properties of drug formulations slightly influence the particle size produced [11]. Vibrating mesh nebulisers are adapted to nebulise marketed drugs with a particle size adequate for lung deposition [12]. However, drug formulations can have a major influence on aerosol output rate [12] and on the inhaled fraction [13].

Suspensions with a high surface tension, such as budesonide, can decrease the performance of vibrating mesh nebulisers with regards to output rate and inhaled mass. Moreover, blockage of mesh holes during nebulisation has been reported with drug suspensions [5]. This problem may not arise with all mesh nebulisers; for example, Aeroneb® Go has been shown to be more efficient than the Pari LC+ jet nebuliser in nebulising Pulmicort® (AstraZeneca, UK) [13].

In terms of particle size and inhaled mass, mesh nebulisers (*i.e.* Micro air® NE-U22V, Aeroneb® Go and eFlow® rapid) are comparable to gold-standard jet nebulisers for administering aqueous solutions and *in vitro* data do not support the idea of overdosing. The only performance difference concerns the output rate of eFlow® rapid. Due to the residual volume in its reservoir, the high output of the vibrating mesh and the valve system, it can theoretically administer the same amount of drug into patients as jet nebulisers, but in half the treatment time [14]. In terms of output rate, these *in vitro* data could support the idea of overdosing with regards to the amount of drug deposited per unit time. Aeroneb® Go and Micro air® NE-U22V nebulisers have treatment times that are equivalent to jet nebulisers [8, 15].

In vivo performance

Only a few studies have been published on aerosol deposition with the mesh nebulisers that are available on the market. A modified Micro air® NE-U22V nebuliser (breath activated) has been tested with a radiolabelled solution, and 18% of the drug loaded in the reservoir was deposited in the patient's lung [16]. If the inhalable mass ratio between Micro air® NE-U22V breath-activated nebuliser and the continuous Micro air® NE-U22V nebuliser is considered to be equal to the ratio between the inspiratory time and total time (due to leakage), the amount of aerosol deposited in the lungs should be divided by three. The drug fraction deposited in the lung should be 6% with the commercialised Micro air® NE-U22V. This theoretical result is the same as that obtained with the Pari LC+ jet nebuliser [16].

eFlow® rapid nebuliser has been tested on nine patients with TOBI® (Chiron, Emeryville, CA, USA) [17]. The serum level after Tobi inhalation was in the range of that reported with standard therapy using Pari LC+ jet nebuliser, but the nebulisation time was halved. This pilot study seems to confirm the *in vitro* results in terms of inhalable mass and particle size obtained with

Table 2 *Mesh nebuliser performance compared with a breath-enhanced jet nebuliser*

Name	MMAD µm	Output rate in standing cloud mL per min	Residual volume mL	Nebuliser type
Micro air® NE-U22V	*4–7*	*0.2–0.3*	*0.3*	*Standard*
Aeroneb® Go	*3–5*	*0.3–0.5*	*0.3–0.9*	*Standard*
Aeroneb® Pro	*3–5*	*0.3–0.5*	*<0.3*	*Standard*
eFlow® rapid	*3–5*	*0.3–0.7*	*>1.2*	*Breath enhanced*
Pari LC+	*4–6*	*0.2–0.3*	*>1.2*	*Breath enhanced*

eFlow® rapid nebuliser and Pari LC+ nebuliser to administrate Tobi [14].

The Aeroneb® Pro has been tested with amikacin in mechanical ventilation on patients with purulent excretion [18]. Amikacin was assayed in urinary excretion after 24 hours, since this reflects the dose delivered to the lungs. It was found that the Aeroneb® Pro delivered twice as much drug mass to patients' lungs as the conventional MistyNeb® jet nebuliser (Cardinal Health, Toronto, ON, Canada).

The way forward

Considering the *in vitro* results in terms of inhalable mass and particle size and considering the current *in vivo* results, available mesh nebulisers might be suitable for nebulising aqueous solution. However, they are not always suitable for nebulising suspensions, such as budesonide. To adapt budesonide to Pari eFlow®, the company is developing a new formulation called BUDeFlow®. This drug is a high-concentration, low-volume budesonide solution, especially developed to optimise treatment with the eFlow® nebuliser [19].

The mesh nebulisers presently available are not ideal, but they have been developed for nebulising currently marketed liquid-drug formulations without theoretical risk of overdose. A way of optimising drug delivery by aerosol with mesh nebulisers is to activate the nebulisation only during the inhalation phase. However, this increases the treatment time with current drug volumes. Therefore, mesh nebulisers need to be developed in accordance with different drug formulations (volume, surface tension, *etc.*). The eFlow® BT, a mesh nebuliser developed by Pari and operating only during inhalation, has doubled the inhaled fraction in a comparison with the continuously operating eFlow® (92% *versus* 54%) [15]. Aerodose® (Nektar Therapeutics, San Carlos, CA, USA) and Ineb® (Omron Healthcare and Profile Therapeutics, West Sussex, UK) utilise the mesh system and produce a controlled aerosol drug mass only during the inhalation phase or a fraction of it. Aerodose® is being assessed with insulin for diabetic patients and has been tested with tobramycin solution for cystic fibrosis.

Conclusion

Mesh nebulisers are small, silent, portable and comply with active drug compounds. Disinfection of the mesh is not always possible and mesh systems appear to be less robust than jet nebulisers. Marketed mesh nebulisers, such as Micro air® NE-U22V, Aeroneb® Go and eFlow® rapid, for ambulatory patients, are probably similar in performance to gold-standard jet nebulisers in terms of inhaled drug mass and particle size. However, proper pharmacokinetic studies and bioequivalence studies are needed to support this. The Aeroneb® Pro nebuliser is designed for mechanical ventilation and is more efficient than standard jet nebulisers. Mesh nebulisers can be used to nebulise aqueous drugs, but, for suspensions, there may be a reduction in performance in terms of aerosol output rate and inhaled mass. So far, there are no relevant published studies evaluating the bioequivalence between marketed mesh nebulisers and current jet nebulisers. In the future, marketed mesh nebulisers should be tested *in vivo* to determine bioequivalence and clinical equivalence, and new optimal mesh nebulisers could be developed for a known drug formulation.

Educational questions

1. Which nebuliser types can be used to nebulise Pulmicort®?
   a) A jet nebuliser.
   b) An ultrasonic nebuliser.
   c) A mesh nebuliser.
2. Which nebuliser system is suitable and adequate for patients who experience asthma attacks?
   a) Disposable standard jet nebuliser with a mask.
   b) Breath-enhanced jet nebuliser with a mask.
   c) Ultrasonic nebuliser with a mouthpiece.
   d) Mesh nebuliser with a mask.
3. Which nebulisers must be loaded with the addition of an isotonic solution to nebulise 2 mL of Atrovent®?
   a) Mistyneb® jet nebuliser.
   b) Aeroneb® Go vibrating mesh nebuliser.
   c) Micro air® NU22V static mesh nebuliser.
   d) eFlow® rapid vibrating mesh nebuliser.

Suggested answers

1. a and c, but there is a risk of mesh blockage and lower efficiency
2. a
3. a and d

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