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Ultrasonic nebulization platforms for pulmonary drug delivery

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Importance of the field: Since the 1950s, ultrasonic nebulizers have played an important role in pulmonary drug delivery. As the process in which aerosol droplets are generated is independent and does not require breath-actuation, ultrasonic nebulizers, in principle, offer the potential for instantaneously fine-tuning the dose administered to the specific requirements of a patient, taking into account the patient's breathing pattern, physiological profile and disease state. Nevertheless, owing to the difficulties and limitations associated with conventional designs and technologies, ultrasonic nebulizers have never been widely adopted, and have in recent years been in a state of decline.

Areas covered in this review: An overview is provided on the advances in new miniature ultrasonic nebulization platforms in which large increases in lung dose efficiency have been reported.

What the reader will gain: In addition to a discussion of the underlying mechanisms governing ultrasonic nebulization, in which there appears to be widely differing views, the advantages and shortcomings of conventional ultrasonic nebulization technology are reviewed and advanced state-of-the-art technologies that have been developed recently are discussed.

Take home message: Recent advances in ultrasonic nebulization technology demonstrate significant potential for the development of smart, portable inhalation therapy platforms for the future. Nevertheless, there remain considerable challenges that need to be addressed before such personalized delivery systems can be realized. These have to be addressed across the spectrum from fundamental physics through to *in vivo* device testing and dealing with the relevant regulatory framework.

Keywords: aerosol, microfluidics, nebulizer, pulmonary, ultrasonic

Expert Opin. Drug Deliv. (2010) 7(6):663-679

1. Inhalation therapy

Drug delivery to the lung can be viewed from the perspective of two distinctive objectives: (i) 'topical' treatment of the pulmonary tract (whereby the drug is applied locally to the surfaces along the respiratory tract); and (ii) a route for systemic delivery (whereby the drug enters into and is transported by the bloodstream). The former has grown enormously over the past 50 years, with the realization that where even relatively inefficient topical treatment is conducted, the level of effective dose required (compared with oral/systemic delivery) is drastically reduced, accompanied by an associated reduction in side effects and toxicity issues. The large surface area of the lung, its thin epithelium lining and highly vascularized nature, and its potential to be accessed also make it ideal for non-invasive systemic drug delivery, and a patient-friendly alternative to the needle. The human respiratory system has nevertheless evolved to trap and stop aerosolized material from entering such delicate and sensitive tissue, and hence controlled delivery to the lungs is far from simple. The nasal passages are, in particular, very effective traps to capture

10.1517/17425247.2010.485608 © 2010 Informa UK Ltd ISSN 1742-5247

Article highlights.

- Historically, cavitation and capillary wave destabilization have been proposed as possible mechanisms responsible for the generation of aerosol droplets owing to ultrasonic vibration; this paper, however, advocates that the latter should rather be viewed as a route towards aerosol generation as a consequence of some means by which the interface is perturbed, be it cavitation, acoustic streaming, or even a combination of several processes.
- There is evidence to suggest that the classical theories that have been widely adopted so far to predict aerosol size may be inadequate for providing a full understanding of the mechanics by which capillary waves destabilize and break up to form droplets; specifically, recent experimental observations of capillary wave vibration under strong acoustic forcing have demonstrated the absence of the narrowband subharmonic frequency selection predicted by the classical theory.
- A scaling argument based on capillary-viscous resonance is proposed to address this controversy by providing a possible explanation for the experimental observations, although a more rigorous theory that captures the inherent nonlinearity of the process is urgently needed to provide a complete fundamental understanding of the governing mechanisms that underpin capillary wave destabilization.
- There are many difficulties associated with both generic *in vitro* and *in vivo* comparisons of ultrasonic nebulizers with other nebulization or inhalation therapy platforms in terms of their performance and applicability; assessments should rather be carried out within the conditions and context of a specific case.
- Compared with portable inhalers, nebulizers, in general, nevertheless, provide a more consistent means for delivering droplets with very specific diameters and at controlled flow rates through normal tidal breathing.
- Recent advances in microfluidics and ultrasonic nebulization technology therefore offer tremendous possibilities for the development of miniature inhalation therapy devices with the ability to tune the administered dose to a patient's specific requirements.

This box summarizes key points contained in the article.

particulate matter and hence the following discussion is restricted to lung delivery through the oral route, which poses a lesser challenge, but still a formidable one nonetheless. The structure of the human respiratory system is well described for these purposes. The passage through the oropharangeal region provides the first barrier to aerosol delivery. Further barriers are imposed as the airways subsequently bifurcate in a manner resembling a 'tree'-like structure with passages dividing and narrowing from the central to the peripheral regions [1].

Despite these obstacles, man has always been aware of the 'benefits' of inhalation therapy, or pulmonary drug delivery. For example, the ancient Greeks in the first century were reported to breathe in sulfuric fumes from volcanic eruptions. It was also common practice among North American Indians to smoke pipes containing leaves and roots of native plants to treat asthma. The first account of commercial inhaled mist sprays, however, were not recorded until the nineteenth century, when compressed air systems were used to generate fine vapor mists from thermal water spas, which were touted to treat pulmonary ailments [2].

Thus, although it is generally accepted that inhalation therapy constitutes the ideal way to deliver therapeutic agents to the lung, the aerosolization process, which requires the drug compound or the solvent it is dissolved within, to be broken into small particles or droplets to form an aerosol that can be inhaled, is fundamentally difficult. This is because attractive intermolecular forces (such as hydrogen bonds or van der Waals forces) binding the molecules of a compound or solution together need to be overcome to create new surfaces that constitute the smaller particles or droplets. For solutions, this means that the capillary stress associated with the surface tension of the parent liquid needs to be overcome such that it can be broken up or atomized into smaller droplets. The energy that is required to do so is related to the difference in surface energy of the parent drop and the atomized droplets, and is proportional to the increase in surface area associated with the nebulization process. It is now known that an optimum respirable droplet aerodynamic diameter < 3 μm (coupled with suitable breathing maneuver) is typically required for systemic administration of a drug to the lung, in which droplets are successfully transported through the complex and efficient barrier posed by the oropharyngeal region (the first trap being imposed by the laryngeal jet), and then through the highly bifurcated airways of the lung where they can be absorbed [3-5]. Further, it is also known that for specific topical delivery targets, rather different but still highly dispersed and controlled narrow aerosol aerodynamic size ranges may be required; see, for example, [6-8]. Given the necessity for these small aerosol sizes, the surface energy is typically large, thereby demonstrating the inherent difficulty of the process.

The two most common clinically used methods for pulmonary drug administration are portable unit-dose or multi-unit-dose inhalers and nebulizers. The former (i.e., portable inhalers) can be subdivided further into two broad categories, namely, metered-dose inhalers (MDIs) [9] and dry powder inhalers (DPIs) [10]. Generally, the working principle of MDIs has varied little from the original push-and-breathe concept developed in the 1950s [11], in which a metered dose of the drug, suspended as colloid or dissolved in solution, in a pressurized gas (propellant) within the metering chamber is released on atmospheric depressurization through push-actuation. The drug-laden propellant droplets then evaporate to leave behind a residual drug-laden particle core that is inhaled. On the other hand, most DPIs are passively actuated, in that they utilize the respiratory intake of air of the patient to entrain and disintegrate the drug, which is in the form of dry powder particles. DPIs first appeared in 1940, with the first commercially successful product being introduced in

1969, and are now seeing an increase in use at the expense of the pressurized MDI (pMDI). A significant factor for this has been the 1987 Montreal Protocol, as DPIs circumvent the use of environmentally detrimental chlorofluorocarbon (CFC) propellants [12]. Alternative hydrofluoroalkane (HFA) propellants have been developed, but these suffer from challenges associated with solubility and stability, as well as the prospective risk of future government regulations surrounding their use [13,14]. In any case, there has been a wide range of reported efficiencies with the use of passive DPIs in comparison with MDIs [15]. In recent years, active DPIs have been developed, which have led to increased efficiencies [16], but these devices can be both complex and costly.

Compounding these limitations are several other issues. MDIs have typically been associated with a high level of patient misuse, notably owing to problems with breath coordination (up to 90%, as reported in some studies [17,18]). These highlight the necessity for training the patient in the correct technique, especially for coordinating device actuation with inspiration [19,20], which is a particular challenge for young children, the elderly, and those who suffer from severe forms of respiratory diseases [21-23]. Coordination difficulties can be minimized with the use of spacers [24], but are not without other issues. For example, the use of spacers has been reported to result in a change in the droplet diameter at the point of inhalation [25]. They are also large and cumbersome to use. In addition, if the dose is not administered immediately, a proportion of the drug is deposited on the inner chamber of the spacer and is thus lost. DPIs are not constrained by coordination problems but are well known to vary in efficiency with regards to patient inspiratory flow [26-28], and also have significant potential for misuse.

Consequently, a significant proportion of the asthmatic and chronic obstructive pulmonary disease (COPD) patient population is unable to use conventional MDIs or DPIs effectively owing to damaged lung function, poor manual dexterity, visual limitations, cognitive deficits and/or muscular weakness – DPIs are reportedly misused by 42% of patients above the age of 60 years [27]. The same study indicated that 83% of patients older than 80 years suffering from moderate to severe airway obstruction were using ineffective inhalation techniques. Moreover, aerosolization and delivery from such inhalers are notoriously variable depending on patient inhalation profiles and can be very poor in age-specific or compromised patient groups [29]; there is also little opportunity for tuning the device to a patient's need as the aerosol generation mechanisms are too primitive to permit any real degree of control, the aerosol size control being fundamentally predetermined by the drug and device.

By contrast, traditional nebulizers do not provide delivery to a single unit breath, but a continuous or regularly prolonged intermittent delivery over a period of minutes. Such nebulizers utilize an external energy source to overcome the capillary stress and hence destabilize the interface of the parent liquid volume containing the drug solution or suspension. Nebulization then ensues on break-up of the interface, thereby producing drug-laden aerosol droplets that are subsequently inhaled. As the ability to aerosolize is not dependent on the patient's inhalation ability, nebulizers, in principle, provide a more consistent means of delivering droplets with very specific diameters and at specific flow rates through normal tidal breathing. Nebulizers are hence more suitable for young children or patients with severe broncho-obstruction, who either do not have sufficient inspiratory flow rates to activate the MDIs or passive DPIs, or cannot, for one reason or another, be sufficiently trained to use these devices; they can also be used especially when a drug is unsuitable for use with MDIs or DPIs. In addition, nebulizers are generally perceived as a practical means for delivering large doses as well as off-label drugs not formulated for use with other devices.

Examples of common nebulizer formulations marketed at present and the excipients included in the formulation, which function as surfactants, stabilizers (e.g., EDTA), or preservatives (e.g., benzalkonium chloride, EDTA, ethanol, propylene glycol), can be found in [30,31]. Given the delicate and sensitive nature of the tissue comprising the pulmonary tract, toxological effects of both the drug and the excipient used are key limiting factors, not just for nebulizers, but for any pulmonary drug formulation. Specific limitations of nebulizers, nevertheless, include relatively long treatment times, which could potentially result in poor patient compliance, and the instability of drug solutions owing to hydrolysis.

Recently, the market has seen the introduction of a third alternative to the MDI and DPI in the unit-dose portable inhaler market, in the form of the Respimat® (Boehringer Ingelham GmbH, Ingelheim Rhein, Germany), which can be viewed as a non-pressurized MDI [32-34]. This system creates a respirable liquid aqueous spray, targeted to a single breath, through the collision of two liquid jets. There are other proposed systems for single unit-dose delivery that are, as yet, not on the market, such as those developed by Aradigm Corp., Sheffield Pharmaceuticals or Ventaira Pharmaceuticals. In addition, a technology that provides an intriguing return to man's original interest in pulmonary drug delivery is the condensation aerosol generator, such as that proposed by Chrysalis [32].

Generally, traditional continuous nebulizers fall into two broad categories depending on their operating principle. *Jet nebulizers,* which are also known as pneumatic nebulizers, use a high-speed velocity air flow through a nozzle to draw liquid containing the drug from side feed tubes into the nozzle region as a consequence of suction arising from the expansion of the jet at the nozzle orifice (**Figure 1A**). Owing to the large kinetic energy of the air jet, the liquid immediately breaks up into aerosol droplets as it emanates from the feed tubes. Baffles located downstream then provide a means to trap the significant mass of droplets above the required size distribution and to return them to the bulk liquid. In addition, the baffles provide a secondary mechanism to create smaller droplets on impact, although this could lead to drug wastage resulting from liquid adhesion on the baffle surface [33]. It should be

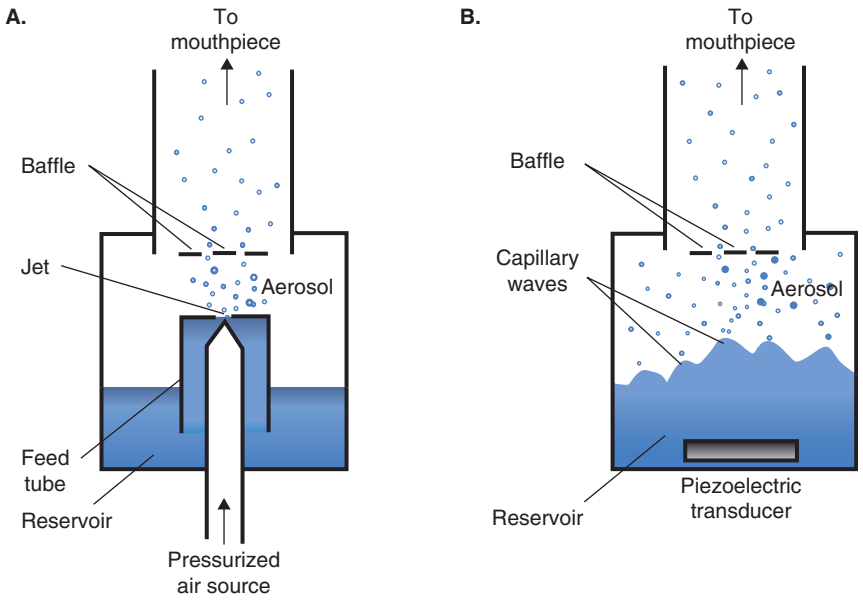

Figure 1. Schematic illustration of a typical (A) jet nebulizer and (B) ultrasonic nebulizer.

noted that the pressurized air jet is inadequate in itself to supply sufficient air flow to comprise the full inhalation flow volume, hence more air has to be inhaled by the patient through a mouthpiece [34]. This renders the jet nebulizer and hence the delivered drug dose dependent on the patient's inhalation profile, as with other inhalation devices [35]. Moreover, the requirement for compressed air or oxygen to generate the high-velocity jet requires a compressed gas cylinder, electrical compressor, hospital reticulated air system or bulky battery-operated compressor, which confines jet nebulizers to home or hospital use [36]. Jet nebulizers are also fairly inefficient; for example, only ~ 12% of the drug reaching the lung has been reported; the remaining drug is wasted, being trapped in the baffles and residual nebulizer volume, exhaled or deposited in the oropharynx and swallowed [33,37].

Ultrasonic nebulizers [38] utilize acoustic waves at moderate-to-high frequencies as an energy source in place of the high-pressure air jet to overwhelm the stabilizing capillary stresses and hence to break the liquid source into aerosol droplets (**Figure 1B**). The earliest ultrasonic nebulizers, produced mainly as humidifiers, date back to 1949 when electronic oscillators became widely available as an oscillating electric field source to the piezoelectric transducer at frequencies between 10 kHz and 1 MHz [2]. Nevertheless, they were expensive and large, and hence were quickly superseded by the smaller and cheaper MDI, which made its appearance in 1956. It was only in the 1980s that compact ultrasonic nebulizers with the ability to operate over several days on a single battery charge regained popularity owing to technological improvements that enabled them to be sufficiently small and simple for home use.

This paper briefly reviews ultrasonic nebulization technology until now and, in particular, discusses their performance compared with conventional MDIs and DPIs. Recent state-of-the-art improvements are then discussed with regards to ultrasonic nebulization and some perspectives are provided on the future of the technology in the context of pulmonary drug delivery. Before proceeding, some clarification is appropriate concerning the terminology commonly used when characterizing output from continuous, intermittent, or unit-dose ultrasonic nebulizers. For unit-dose delivery, the term *metered dose* (MD) refers to the total active load metered within the device, whereas the *delivered dose* (DD), which is often termed the *emitted dose* (ED), is the quantity of drug entering the patient. Thus, the DD is inherently lower than the MD as some material will remain as residue within the device. For continuous or intermittent ultrasonic devices, the DD terminology is potentially more confusing, but should similarly refer to the dose entering the patient, although there may be a significant proportion of the aerosol that leaves the device but that does not enter the patient: for example, during the exhalation cycle. Finally, terms such as *respirable* or *fine particle dose* (and fractions of these relative to the MD or DD) are often used, and refer to the proportion of the aerosol cloud generated that is measured below a specific size cut. The *in vitro* measurement of these is a potentially complex task, and may require different approaches to that used for portable inhalers, as outlined in Section 3.

2. Ultrasonic nebulizers

2.1 Operating principle and governing mechanisms

Sound waves are pressure disturbances that occur in and propagate through the medium of a material (owing to its elasticity) in the form of compression and rarefaction oscillation cycles.

Ultrasound generally encompasses all sound wave phenomena that occur at frequencies above those discernible to the human ear. The lower frequency limit of ultrasound is therefore ~ 20 kHz. Ultrasonic nebulizers work by applying an alternating electric field to a piezoelectric transducer, which converts the electrical signal into a periodic mechanical vibration, in contact with the liquid to be nebulized. Oscillatory pressure disturbances are then generated in the liquid – these sound waves subsequently propagate throughout the entire medium giving rise to instantaneous oscillations of the fluid molecules, which results in local temperature and density fluctuations on a timescale associated with the excitation frequency. The fluid as a whole, nevertheless, responds much more slowly, and hence the effects of the acoustic excitation of the fluid on its bulk properties can be obtained by time averaging these local oscillations over a timescale dependent on the viscosity, surface tension and density of the fluid.

Broadly, there appear to be two mechanisms to suggest how ultrasonic vibration can give rise to interfacial destabilization, which, if unabated by stabilizing stresses such as capillarity, eventually results in the break-up of the interface to produce aerosol droplets [39]. The first, originally proposed by Söllner [40], involves *cavitation,* which occurs when vapor bubbles are formed in the liquid as the pressure in a localized region of the fluid suddenly decreases owing to the periodic disturbances introduced by the sound excitation [41]. If the local pressure falls below the vapor pressure during the negative half cycle of the oscillation, the liquid in that region essentially 'boils' to form a vapor pocket. On the positive half cycle of the oscillation, these bubbles suddenly collapse with such intensities that extremely high instantaneous pressures and accelerations are generated in the form of a shock wave. The shock waves arising from the implosion of bubbles convected sufficiently close to the interface then lead to its destabilization [42,43]. Boguslavskii and Éknadiosyants [44] have proposed a theory in which the disturbance shock waves resulting from the implosion of the bubbles during cavitation lead to the excitation of finite amplitude capillary waves that result in droplet ejection. Physically, the rim of the collapsing bubble is stretched radially downward and initially outwards, and subsequently inwards, under the action of capillarity (**Figure 2A–C**), until it contracts on itself to form an elongated thread that eventually pinches off to form an aerosol droplet (**Figure 2D, E**). If these violent and transient collapse events near the interface occur simultaneously and periodically, finite amplitude standing capillary waves are excited on the interface [45] that destabilize beyond a critical vibration threshold to produce simultaneous pinch-off events along the interface. Mechanisms that describe the formation of the droplet from the break-up of interfacial capillary waves [46-48] have been discussed in various articles [49-51].

Even if cavitation were absent, interfacial capillary waves could still be excited and destabilized to produce nebulization owing to the growth of small disturbances introduced to the interface; indeed, nebulization has been widely observed even when the liquid is degassed. This was claimed to be an alternative mechanism for ultrasonic droplet production [52-54]. Other studies have suggested that this capillary wave destabilization mechanism is responsible for droplet formation at low powers that are inadequate for producing cavitation, whereas the cavitation mechanism dominates at higher powers [55]. Although there is considerable debate about these mechanisms, it is the authors' opinion that capillary wave destabilization should not constitute an alternative mechanism for ultrasonic droplet production as the source of the disturbance is not specified. For example, cavitation effects near the free surface can constitute such a disturbance source that results in the destabilization of capillary waves, which subsequently break-up to form aerosol droplets [40,42], as alluded to above. Capillary wave destabilization should rather be viewed simply as a pathway towards the generation of droplets as a consequence of cavitation or an alternative mechanism; some possible mechanisms have been discussed by Yule and Al-Suleimani [49].

One possible alternative mechanism that could give rise to the interfacial disturbances that lead to the destabilization of capillary waves is bulk *acoustic streaming.* In this case, the bulk fluid flow arising as a result of viscous absorption of the sound energy within the liquid (the time-averaged flow of the local oscillation of fluid molecules arising as a consequence of the compression and rarefaction events as the sound wave propagates through the liquid) gives rise to vibration of the entire liquid body at its natural resonant frequency [51]. A full coupled theory between the equations of motion in the transducer substrate and the hydrodynamics governing the acoustic streaming to produce the free surface evolution has yet to be developed. Nevertheless, a further discussion based on scaling arguments of the characteristic frequencies associated with the natural resonant frequency is provided below. Similar to that due to cavitation, however, capillary waves are excited at the free surface owing to the vibration of the liquid body, and destabilize beyond a threshold amplitude, resulting in break-up to form aerosol droplets.

This subject area is, nevertheless, still controversial, and considerable debate persists within the community. In addition to the excitation power, the dominance of one mechanism over the other could also depend on the film thickness, although these effects have yet to be carefully examined. It is also possible that both mechanisms can be present simultaneously – Topp [56] notes that the generation of droplets in the latter two mechanisms takes place at the crests of the interfacial capillary waves, whereas cavitation occurs with more statistical spatial and temporal randomness along the free surface. Such randomness is also speculated to lead to considerable variation in the droplet size distribution, although quantitative evidence for this has yet to be provided – the absence of such non-uniformity in the data is suggested by some to support the postulation that despite the random cavitation process, a modulation effect may arise if cavitation does not give rise directly to droplet ejection but to the excitation of capillary waves [57].

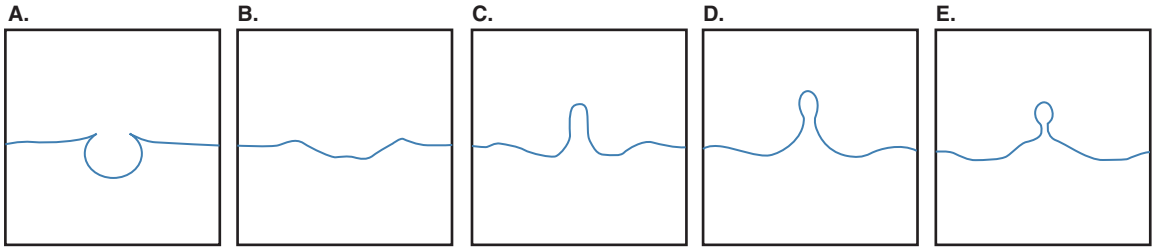

Figure 2. Schematic illustration of the interfacial profile as a cavitation bubble near the interface leads to its destabilization and hence the pinch-off of an aerosol droplet (after [119]).

2.2 Aerosol droplet generation owing to interfacial destabilization

Whichever mechanism is responsible for the excitation of capillary waves on the interface, namely, cavitation or acoustic streaming, a critical threshold amplitude of the waves must be exceeded before the onset of nebulization resulting from their destabilization. Such a threshold arises from a competition between the destabilizing stresses from the acoustic forcing and the stabilizing capillary stresses, which can be described by an acoustic Bond (or capillary) number,

$$\mathrm{Bo}_{a,c} \equiv \frac{\rho A^2 \omega^2 L}{\gamma}. \tag{1}$$

where ρ is the fluid density, A and $\omega = 2\pi f$ the vibration amplitude and frequency, L the characteristic length scale of the liquid and γ the surface tension. Equation 1, however, considers only a dominant balance between the surface tension and the acoustic forcing. Eisenmenger [52], on the other hand, allows for capillary wave damping and hence the liquid viscosity μ through a linear stability analysis to obtain

$$a_c = \frac{2\mu}{\rho}\left(\frac{\rho}{\pi\gamma\omega}\right)^{1/3}, \tag{2}$$

the onset of nebulization occurring around three to six times the critical amplitude a_c [49]. Note that the amplitude of forcing does not alter the droplet size [51], as discussed below, although it does influence the velocity at which the droplets are ejected as well as the nebulization rate [53].

The size of the ejected droplets produced on destabilization of the interface can be derived from an instability analysis of the free surface of the liquid in which a small amplitude disturbance is imposed on the free surface. By linearizing the equations that govern the spatiotemporal evolution of the free surface, a dispersion relationship can then be derived from which a prediction of the instability growth rate as a function of the disturbance wavenumber k as well as the wavenumber at which the growth rate is maximum, more commonly referred to as the 'most dangerous wave number', k_{max}, can be obtained. It is widely accepted that the average droplet diameter D correlates strongly with $k_{max} = 1/\lambda$, that is,

$$D_{32} \sim \frac{1}{k_{max}} \approx C\lambda, \tag{3}$$

where λ is the wavelength and

$$D_{32} \equiv \frac{\sum_i D_i^3}{\sum_i D_i^2} \tag{4}$$

is the droplet surface area moment mean (or Sauter mean) diameter (i = 1, 2, 3,…, n, where n is the total number of aerosol droplets in the statistical data set). An empirical coefficient C is commonly used to fit the experimental data to the predictions. The limitations of the linear stability theory, however, are evident from the wide range of values for C proposed in the literature that vary by an order of magnitude, for example, 0.34 [54], $1/\pi$ [53], and between 1 and 3.8 [58].

The wavelength λ can be specified by an expression known as the Kelvin equation, which is obtained through a linear stability analysis for the case of the excitation of free surface waves induced by periodic vertical forcing [47]:

$$\lambda \sim \left(\frac{2\pi\gamma}{\rho f_c^2}\right)^{1/3}. \tag{5}$$

As expected, this bears some resemblance to Equation 1 for Bond numbers of order unity. Although it has not been specified whether the frequency and amplitude in Equation 1 refer to that of the excitation (i.e., the surface of the ultrasonic transducer) or the liquid interface, for reasons that will be apparent below, the frequency f_c in Equation 5 refers specifically to that of the liquid interface, that is, the vibration of the free surface capillary waves. It should be noted that Kelvin's theory does not provide a mechanism to couple the velocity at which the free surface undulates in relation to the forcing; consequently, the film thickness and excitation amplitude do not enter into Equation 5, although a more elegant theory was later proposed to account for these parameters [59].

To relate f_c to the acoustic excitation frequency f, Lang [54] assumed that the capillary waves are excited at a subharmonic frequency that is half the acoustic forcing frequency, that is, $f_c = f/2$, such that Equation 5 becomes

$$\lambda \sim \left(\frac{8\pi\gamma}{\rho f^2}\right)^{1/3}. \quad (6)$$

Since then, Equation 6 has been wholly and widely adopted in the literature (see, for example, [49,53,58,60,61]). The half-frequency subharmonic assumption appears to originate from the theory of Faraday waves [46], in which a liquid is vertically excited from beneath by a vibrating plate, wherein the motion of the plate is perpendicular to the liquid free surface. Drawing the analogy with the motion of a pendulum, it is then possible to construct an elegant theory for the parametric excitation of the free surface using the Mathieu equation [62], from which it can be shown through a weakly nonlinear analysis that the lowest-order, and hence dominant, frequency from the theoretically infinite number of available resonant frequencies $nf/2$ (n = 1, 2, 3,…) is the $f/2$ subharmonic [63,64].

Nevertheless, there appears to be some controversy surrounding the adoption of the subharmonic frequency in Equation 5 [51]. Until recently, accurate measurements of the frequency at which capillary waves vibrate, at least > 10 kHz order, have been difficult. Moreover, the conventional way in which liquids are excited by ultrasound is typically in phase across the width of the fluid and perpendicular to the free surface, similar to the reciprocating piston motion of Langevin transducers [65]. Nevertheless, Equation 6 has been universally adopted, even when the mode of vibration is considerably more complex than the simple piston-like motion of Faraday waves, or when the excitation frequencies are higher than that used in conventional ultrasound, for example, in surface acoustic wave (SAW) nebulization [58] (the use of SAWs for nebulization and, in particular, for pulmonary drug delivery, is discussed in Section 4). Recent measurements of capillary wave vibration under acoustic forcing, admittedly at these higher frequencies and for SAW excitation, using advanced laser Doppler vibrometry reveal the absence of any subharmonic excitation. **Figure 3** shows the absence of a dominant subharmonic resonant peak at $f_c = f/2$ = 10 MHz when the substrate underneath the fluid is excited at f = 20 MHz. Instead, broadband excitation of the capillary waves at 10 kHz order is observed [51].

Qi *et al.* [51] argue that capillary waves are excited at a frequency given by the natural resonant frequency of the liquid, which is dependent on the characteristic length scale of the liquid geometry L. For a drop or a thick liquid film lying on the undulating substrate, in which the drop radius or film height is significantly larger than the viscous penetration depth, that is, the length over which the oscillation of the liquid molecules arising from the acoustic excitation of the substrate decays,

$$\delta \sim \left(\frac{\mu}{2\pi\rho f}\right)^{1/2}, \quad (7)$$

the inertia associated with the acoustic streaming of the fluid can be assumed to be negligible, and hence the natural resonant frequency of the drop or film is driven by acoustic streaming arising from viscous drag. In this case, the natural resonant frequency is the capillary-viscous resonant frequency,

$$f_c \sim \frac{\gamma}{\mu L}. \quad (8)$$

Qi *et al.* [51] then suggest that it is not necessary to apply the questionable subharmonic frequency assumption first proposed by Lang [54] and widely adopted by others to arrive at Equation 6. Instead, it is sufficient to use the capillary vibration frequency given by Equation 8 directly in Kelvin's equation, that is, Equation 5, to obtain a prediction for the capillary wavelength and hence an estimate of the droplet size. Their hypothesis is supported by the fact that a proper assignment for the characteristic length scale is shown to predict correctly the 1 – 10 kHz order capillary vibration frequencies measured (**Figure 3**) and the correct order of magnitude agreement of the droplet sizes obtained from Equations 3 and 5.

In hindsight, this result is not entirely surprising because it is expected that a significant proportion of the acoustic energy in the fluid is dissipated in the bulk by the viscosity of the fluid and manifests as acoustic streaming. It is likely that the subtlety in the subharmonic frequency assumption may have been historically overlooked given the difficulties in accurately measuring the vibration of capillary waves, especially at high megahertz-order frequencies where the discrepancy is most obvious. Until recently, most studies on capillary wave excitation resulting from periodic vibration have been carried out at kilohertz-order frequencies – that the subharmonic frequencies are then of the same order as the capillary-viscous resonant frequencies may have led to the confusion and hence the correct order of magnitude (although erroneous) prediction for the droplet sizes using Equation 6. At high frequencies, there is also some evidence to suggest that the droplet sizes are independent of the excitation frequency [61].

There are other reasons to suggest why the subharmonic frequency assumption may not be appropriate and why it fails to predict the experimental measurements obtained for the capillary vibration frequency data in **Figure 3**. The weakly nonlinear theory invoked in [62-64] requires the assumption of infinitesimally small amplitude oscillations, which is often invalidated by the violent and large amplitude capillary wave oscillations that lead to complete destabilization such that nebulization ensues. Moreover, there is little obvious reason to believe that the highly nonlinear effects associated with the acoustically driven free surface phenomenon can be accurately described by linear or weakly nonlinear theory.

Further, given the dispersive nature of capillary waves, it is hard to accept that the free surface vibration is always excited with a sharp subharmonic response regardless of the choice of fluid and its physical properties (e.g., viscosity, surface tension and density) [51]. This is also contrary to experimental data, where considerable dependence of the viscosity and flow rate

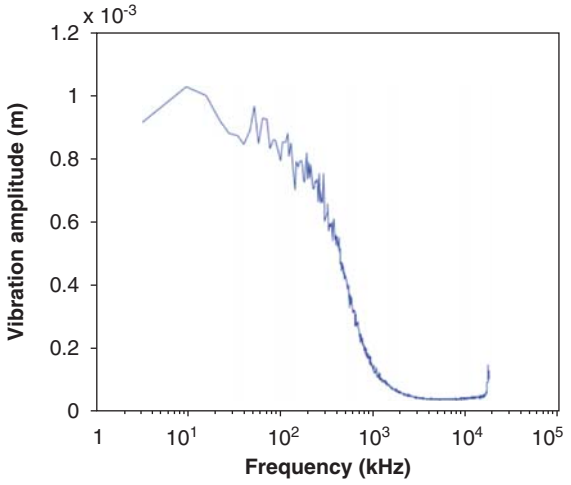

Figure 3. Capillary vibration amplitude and frequency of a sessile drop placed on a substrate excited by surface acoustic waves at 20 MHz (after [51]). Measurements of the capillary wave frequency were carried out using laser Doppler vibrometry.

has been observed [57]. It should be mentioned that attempts have been made to develop empirical correlations to predict the droplet sizes that capture the dependence of these parameters (see, for example, [57,60]), although these arise from a dimensional analysis and depend crucially on empirical fitting parameters, thus lacking a rigorous physical and fundamental basis. Despite claims otherwise, the agreement between these predictions and experimental data is modest, at best.

From a scaling analysis of the axial capillary stress, it is possible to extend Equations 5 and 8 for a continuous liquid film, giving rise to an expression for the droplet size that is dependent on the film thickness [51]; further corrections for the geometry, as required in [59], are therefore unnecessary. Moreover, as both film thickness and flow rate are interrelated [57], the physical model in Qi *et al.*'s study [51] therefore captures the effects of both liquid viscosity and flow rate absent in Lang's study [54]. In addition, the capillary-viscous resonant frequency in Equation 8 also addresses the concern developed that viscosity and surface tension are often considered in isolation in the various droplet size correlations [57]. Nevertheless, the limitation of experimental data to a specific high-frequency system in [51] suggests that more careful measurements of the capillary vibration frequency at lower frequencies commensurate with ultrasound and with conventional ultrasonic vibration modes are required before their theory can be claimed to be universal and conclusive; it should also be noted that cavitation was not present in Qi *et al.*'s experiments.

The concept of a capillary-viscous resonant frequency such as that given by Equation 8 may not be entirely obvious. As both capillary and viscous stresses, taken in the usual context, are generally stabilizing, there is no apparent destabilizing stress present. However, in the case of ultrasonic nebulization, it is simplistic to view the role of viscosity as solely damping fluid motion and hence dissipating the instability. Instead, the viscosity of the fluid also absorbs the acoustic energy, which, in turn, can drive the bulk liquid recirculation associated with acoustic streaming that can induce the capillary waves at the interface. It is therefore entirely possible that the viscosity provides a nonlinear mechanism in which the sharp narrowband high-frequency acoustic excitation is modulated to produce a wide broadband response of the fluid at lower frequencies.

3. Performance comparison between nebulizers

In a recent review arising from a workshop on regulatory issues pertaining to nebulizer technology, it was reported that 'device evaluation and comparison is not a trivial issue' [66]. Further, it was pointed out that both the nature of recent innovations in nebulizer technology coupled with the way in which nebulizers may be sold and used (i.e., in isolation or in combination with a host of drug products) lead to significant complexities and regulatory challenges in carrying out direct comparisons of different aerosol generation device types. Out of this there has arisen widespread recognition that nebulizer performance testing strategies require further effort to improve methodology robustness and to ensure harmonization.

In this context, it is perhaps not surprising that although several studies have reported comparison between the relative performances of different nebulizers as well as between that of nebulizers and portable inhalers, the findings that can be drawn appear to be inconclusive. Understandably, such an objective is complicated by the many and often interrelated factors that affect nebulizer performance, not least the physicochemical properties of the drug and that of the associated excipient to be administered [67,68], dose, fill volume and concentration [26,69-71], respiratory flow rate [72,73], measurement method (*in vitro* or *in vivo*) [26,74], *in vitro* aerosol collection and measurement method [70,75,76], ambient conditions (e.g., relative humidity) [77] and environmental context (hospital or point-of-care; availability of trained respiratory therapists to administer treatment) [21,78], as well as patient-related factors such as breathing mode (nasal or oral) and pattern (tidal or deep breathing; breath-holding) [67,79-81], severity of illness [21], age group [35,82-84], and physiological profile (e.g., lung morphology) [26,85,86]. Other patient factors such as gender and ethnicity as well as environmental and occupational exposure [87], both past and present, could also be important, although their effects have yet to be studied extensively. A systematic parameter study, wherein the effects of a parameter on the system's performance are examined in isolation to the other parameters, therefore poses a significant challenge.

The authors have found, in addition, that it is difficult to make any definitive statements about the performance of generic classes of nebulizers (e.g., jet nebulizers as opposed to ultrasonic nebulizers), or different commercial nebulizer

types in the same class, as each nebulizer type differs widely in design; this was also the conclusion of other researchers – see, for example, Katial *et al.* [70]. For example, whereas some have found that more efficient delivery could be obtained with ultrasonic nebulizers [71], there are other reports that suggest otherwise (see, for example, [88,89]). Further, even a comparison between a single type of commercial nebulizer could pose difficulties owing to production variability [90]. Considerable variability has also been found in lung deposition measurements owing to normal tidal breathing inhalation in healthy patients using the same nebulizer. This was attributed to variability in breathing patterns, the variability being exacerbated further with the acuteness of the disease owing to the increasing airway obstruction [67].

Several *in vivo* studies, both in animals and humans, have also been carried out to assess the performance of ultrasonic nebulizers (see, for example, [8,21,72,89,91-96]). A distinction between animal and human testing must be made as the correlation between results obtained from *in vitro* and *in vivo* studies remain tenuous, at best. For example, Le Brun *et al.* observed that the variations in the performance between jet and ultrasonic nebulizers were not apparent in two clinical studies conducted separately [97-99]. It is therefore important that *in vivo* studies are conducted to account for patient factors before a specific nebulizer is recommended or adopted clinically [26]. Although these studies are ideally performed in the human target population, animal models play an important role for detailed optimization and mechanistic studies, and need to be selected carefully for their translational potential [91,92,100].

There are also other issues regarding study design parameters that complicate comparisons further. For example, when comparisons are carried out, it is common (and widely accepted, though without adequate justification) to compare the performances based on equal drug doses regardless of the dosage form or delivery route. Kisch and Paloucek [21], however, argue that, given the wide range of effective dose and dose frequencies, it is perhaps more pertinent to adopt the relief of acute symptoms as the measurement (primarily for bronchodilators), with the total dose and time required to achieve symptom relief and restoration of regular pulmonary function as milestones. Temperature differences can also affect results drastically, although this could be exploited to alter the nebulization rate through the incorporation of temperature control measures such as a heat sink [87]. Given the tendency of acoustic energy dissipation to heat the liquid, the increase in temperature could result in concentration of the drug solution, which, in turn, could lead to an increase in the osmolality and hence the potential for denaturing of the drug [93]. Changes in osmolality can also trigger coughing or bronchoconstriction in patients [94]. Nevertheless, the concentration effect was not always observed [70]. Thus, Steckel and Eskandar [93] suggest that in addition to temperature and concentration effects, the nebulization period should also be taken into account when comparing the performance of nebulizers.

For the reasons discussed above, the authors will refrain from making specific and direct comparisons between:

- portable inhalers and ultrasonic nebulizers,
- different types of nebulizers, and,
- different commercial ultrasonic nebulizers.

The authors believe it to be more appropriate to assess their relative performance on a specific case-by-case basis for the relevant conditions and context. Nevertheless, an attempt will be made to summarize the *generic* advantages and limitations of ultrasonic nebulizers.

Perhaps the most significant advantage of ultrasonic nebulizers, although this has yet to be exploited fully in the current line-up of commercial devices available, is that they afford the possibility for tuning the administered dose because they are not breath-actuated (the aerosolization process is independent of the patient's breathing) and hence this arguably simplifies the breath training required for proper use. The ability to incorporate electronic control to adjust the droplet size (and hence the target deposition region), nebulization rate, total dose and spray pattern (with appropriate geometry design in the piezoelectric substrate [57]) offers considerable flexibility for obtaining equivalent drug efficacy across a wide variation of breathing patterns (e.g., one of the main advantages of ultrasonic nebulizers is that they can be used under relaxed tidal breathing conditions [3]) in a real physiological environment as well as for providing a means to tailor the device to a specific patient profile.

Such possibilities for control inherent in ultrasonic nebulizers can be exploited further to achieve other pharmacokinetic and pharmacodynamic outcomes; for example, it is possible to time the actuation and termination of the device to coincide with the onset of the inhalation and exhalation process, respectively (see Section 4) [87]. Furthermore, ultrasonic nebulization does not lead to as much evaporation compared with jet nebulizers (which occurs during recycling of the liquid from the baffle), resulting in less drug wastage from concentration effects, and hence ensuring more consistent drug doses [88]. The lower droplet ejection velocities generated, in addition, do not give rise to as much splashing during inertial impaction as jet nebulizers, which is a significant reason for lung deposition inefficiency [57].

Ultrasonic nebulizers also have been argued to be capable of producing smaller droplets (especially at higher frequencies) and more uniform droplet size distributions (through control of the applied frequency and/or use of a mesh) than jet nebulizers and can be adopted for drug formulations that may not be suitable for delivery with inhalers [57]. Recent developments in the fabrication of high-frequency transducers leading to their reduction in size have also increased the attraction of silent, simple-to-use ultrasonic nebulizers for portable consumer applications [95]. A limitation with smaller devices, however, is the reduction in the aerosol production rate, which is proportional to the surface area of the substrate.

Unfortunately, ultrasonic nebulizers, in general, also suffer from some other limitations. Most conventional systems tend to be large and cumbersome to use, have difficulty in the aerosolization of suspensions [96,101], and are too primitive in design to permit any real degree of dose control. Micronebulizers (to be discussed more specifically in Section 4), which allow for portability, on the other hand, require nozzles, orifices or meshes for droplet production (see, for example, [95,102]), and hence involve intricate micro- and nanofabrication procedures, which drives up cost and complexity considerably. In addition, they are prone to clogging owing to solute precipitation and have to be either regularly cleaned or replaced. As these ancillary surfaces are directly involved in the droplet production process, careful cleaning is also necessary to avoid the possibility of inhaling bacteria, which results in increased risks of respiratory infections [87]. In addition, heat is usually generated in ultrasonic nebulizers, which could lead to the denaturing of biomolecules and thermolabile formulations, odor changes in the case of antibiotics, and concentration effects, which have a direct effect on the quality of droplet production and dose administration.

In terms of cost, nebulizers can be developed and used for specific applications such that costs are comparable to or even cheaper than MDIs, but other issues associated with institutional budgets and governmental policies may factor into the decision of technology implementation in hospitals and healthcare service providers [21]. Although jet nebulizers may, as a single unit, cost less than an ultrasonic nebulizer, the need for pressurized air sources, which are both costly to install as well as to maintain, means that they are only cost-effective in hospital settings. The rapidly reducing costs of fabricating ultrasonic transducers at the microscale by exploiting the economies of scale associated with large-scale photolithographic processes may therefore mean that miniaturized ultrasonic nebulizers could become a cost-effective portable device of choice for point-of-care pulmonary drug delivery. The issue of cost is, however, highly complex, and should be considered specifically on a case-by-case basis.

In any case, the nebulizer–drug–patient interface is a critical issue for commercial development, and has arguably been a neglected area in terms of regulation. The complexities discussed above, in terms of a strict comparison of devices, reflect this. A recent review has highlighted such issues and has outlined a recent focus in efforts to harmonize standards and development guidelines at a global level in this area [66].

4. Next-generation advanced ultrasonic nebulizers

Conventional ultrasonic nebulizers generally use either Langevin transducers (vibration along the length of the transducer in thickness-extension mode), sandwiched between a support and a horn over which the liquid flows and is hence atomized, or single lead zirconium titanate piston (in-phase thickness mode vibration across the entire transducer surface) atomizers [51]. These nebulizers have traditionally been relatively inefficient, often requiring tens of watts of power and hence a fairly large power source. There is also some evidence that heating could lead to the denaturing of the drug molecules. Cavitation can also lead to similar molecular damage – to avoid cavitation, it is necessary to reduce the power or to operate at higher frequencies where the power required to induce cavitation is lower than that required for the onset of nebulization. Nevertheless, ultrasonic nebulizers are typically limited by a maximum frequency of ~ 3 MHz owing to the resonance modes and limitations of the piezoelectric crystal [103]. In addition, ultrasonic nebulizers have been found to be less efficient for use with drug suspensions and viscous solutions [104]. This is primarily because of the large amounts of energy dissipated, associated with the increase in the effective viscosity in the case of suspensions; as a result of the inefficiency, the power requirement is large, and the heating that occurs as a consequence could potentially lead to denaturing of the drug. Further, Kisch and Paloucek [21] have also found that there is little advantage of such nebulizers over portable inhalers in the treatment of patients with acute respiratory diseases. Consequently, the popularity of ultrasonic nebulizers has been in decline in recent years [104].

The next generation of new advanced ultrasonic nebulizers, however, could potentially reverse this trend, or, at the very least, offer new perspectives for local and systemic drug delivery [105]. A promising approach uses a vibrating perforated mesh or array of micro-orifices (**Figure 4**) [99,105,106], which originated from the concept of a single vibrating orifice proposed by Berglund and Liu [107], better known as the vibrating orifice aerosol generator. These nebulizers use the same piezoelectric element as conventional ultrasonic nebulizers but the vibration is applied to the mesh or orifice array. Vibrating mesh nebulizers are reported to provide a more uniform droplet size defined by the dimension of the orifices without subjecting the drug to the large shear stresses and temperature increases common with conventional nebulizers [106]. Given the narrower droplet size distributions produced, baffles are not required, and hence residual drug loss is minimized. With the higher doses administered, patient compliance is then improved owing to shorter nebulization times [104]. These battery-powered devices can also be made relatively compact and can operate quite silently. A severe limitation, however, is that the meshes require careful cleaning to avoid the clogging of the orifices; the large surface area of the orifice array also poses some problems with bacterial contamination if they are not thoroughly cleaned [104]. The complex fabrication required for the laser-assisted drilling of the mesh orifices also adds significantly to the cost of manufacturing these devices, which has to be justified through improved pharmacokinetic and pharmacodynamic outcomes as well as patient compliance.

Adaptive delivery devices (the term 'Adaptive Aerosol Delivery' [AAD™] has been used by Philips Respironics to refer to a specific approach [108], although the term adaptive

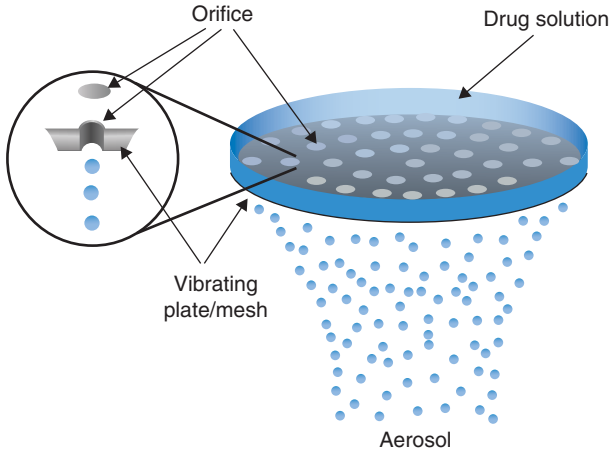

Figure 4. Schematic illustration of a vibrating mesh nebulizer (after [105]).

delivery is used more generically in the present context) have also been developed to deliver precise amounts of drug to a patient so as to minimize the amount of drug wasted during exhalation, which, in conventional nebulizers, is primarily due to constant aerosol delivery, thereby subjecting the efficiency of the drug inhalation to the patient's breathing pattern [108]. Adaptive devices therefore vary the delivery according to the patient's breathing pattern with the use of advanced in-built sensors to monitor the inhalation of the patient over a sequence. This information is coupled to an electronic control system to synchronize the pulsed release of the aerosol with the patient's inspiration such that the aerosol generation is subsequently terminated after the first half of the next inspiratory maneuver of the patient. Some nebulizers, independent of the mechanism (i.e., jet or ultrasonic) by which the aerosols are generated, have incorporated such technology; there are claims (see [108] and references therein) that adaptive nebulizers have been able to achieve greater lung deposition than conventional nebulizers.

More recently, a new miniature ultrasonic nebulization platform for pulmonary drug delivery based on SAWs has been developed [109]. SAWs are nanometer-order amplitude sound waves that propagate on the surface of a piezoelectric single crystal substrate. Unlike conventional ultrasound where the sound waves propagate through the entire *bulk* of a medium, most of the acoustic energy associated with the SAW is confined to a localized region three to four wavelengths thick (devices driven at 10 MHz frequencies have typical wavelengths on the order of 100 µm) along the substrate *surface* until the surface comes into contact with the liquid, at which point the acoustic energy refracts into the liquid, as depicted in the top image in **Figure 5** [110,111]. The SAW is therefore an extremely efficient energy transfer mechanism from the piezoelectric crystal to the fluid. In fact, it is possible sufficiently to destabilize the liquid interface to generate nebulization at ~ 1 W of power, which is at least one order of magnitude smaller than that required with conventional ultrasonic nebulizers. The low power requirement therefore allows the device to be miniaturized for portable, battery-powered use, as shown in the bottom images in **Figure 5**.

The SAW technology demonstrates considerable promise. Preliminary results using a standard twin stage impinger *in vitro* test report stage two deposition in the region of 70 – 80% of the emitted dose without requiring nozzles or orifices [109]. Moreover, the high frequencies typically used (> 10 MHz) and low power required ensure that no cavitation occurs in the fluid – recent tests with the SAW have shown almost negligible denaturation of proteins or biomolecules during nebulization [112]. It has also been shown that there is little damage to the viability as well as proliferation and differentiation capabilities of mesenchymal stem cells by the acoustic irradiation arising from the SAW [113]. The dose can also be tuned to specific individual requirements [114], and the advanced electronic detection and control for adaptive delivery could be incorporated into such a generic platform.

This new droplet synthesis technology has been discussed in the context of a potential new portable nebulizer system, but the technology is also applicable for use in the category of the unit-dose portable non-pressurized MDI market. In that case, a single metered volume of liquid would be nebulized such that it is coordinated with the single breath of a patient, albeit with a much lower dose range. Another significant possibility with the SAW device is its ability to rapidly synthesize nanoparticles comprising biodegradable polymeric excipients and to encapsulate therapeutic drug molecules within the polymer nanoparticles through a simple one-step procedure without requiring the cumbersome laboratory-based techniques associated with nanoparticle production methods that are available at present [115-117]. The SAW nebulizer platform therefore provides an enabling technology for *in situ* simultaneous nanoparticle carrier synthesis, drug encapsulation and pulmonary delivery in a portable palm-sized device.

5. Conclusions

Much has been made about the possibility of a generic device that has the ability to deliver universally an idealized aerosol distribution of any drug to any patient. However, it should be recalled that every patient's respiratory physiology is unique and is dependent on the disease state and inhalation profile. Consequently, different aerosol size distributions may be needed as treatment may dictate deposition at different sites in the lung. Moreover, the aerosol characteristics are governed by the physical properties of the specific drug to be administered (see Section 2.2). Arguably, therefore, such a 'universal' device does not exist. Instead, what is required is a personalized delivery system that is capable of delivering a dose specifically for a particular patient's physiological make-up and needs.

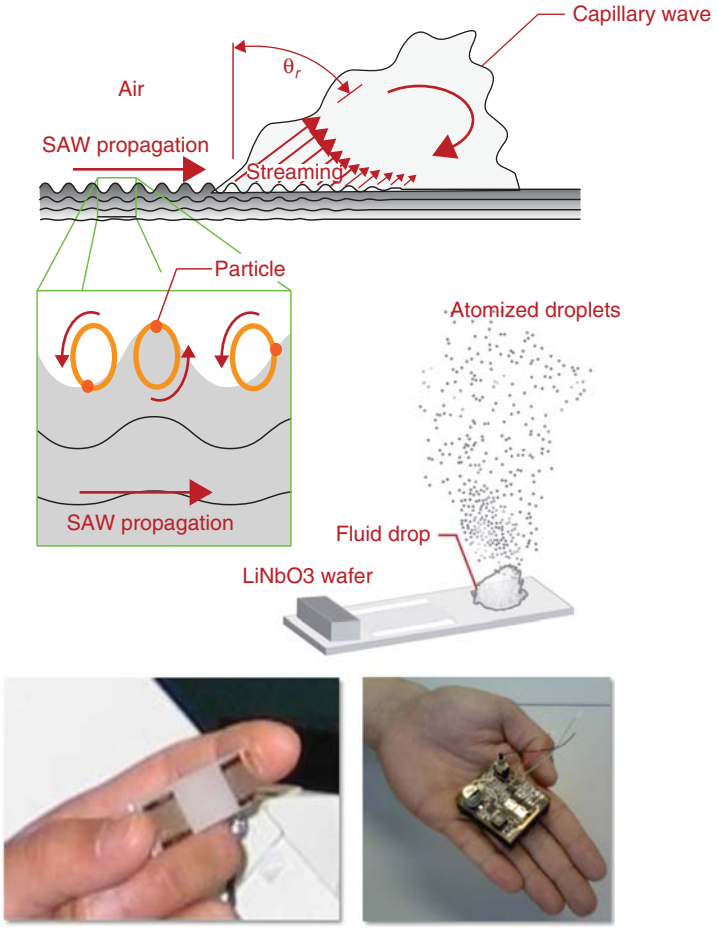

Figure 5. Ultrasonic nebulization using a SAW nebulization device (after [51,109]). The top image shows a schematic depiction of the fluid-structural coupling that arises from the SAW as it propagates along the piezoelectric substrate with a sessile drop placed atop the substrate. The efficient transfer of acoustic energy into the drop generates strong fluid streaming (recirculation) and rapid interfacial destabilization, which results in the generation of micrometer-sized aerosol droplets. The bottom images show the piezoelectric substrate on which the SAW is generated (left) and the portable battery-powered circuit used to provide the electrical input to generate the SAW (right).
SAW: Surface acoustic wave.

Despite the limitations associated with ultrasonic nebulizers, therefore, there are perceived advantages of this technology over unit-dose or multi-unit-dose portable inhalers or traditional jet nebulizers, particularly in their practical ability to adapt aerosol delivery to the breathing patterns of specific individuals through simpler and more precise electronic signal control rather than air pump control, as well as their potential flexibility to tune dosing to the specific requirements of individual patient profiles. These arguably warrant further evaluation of their use in both clinical and point-of-care settings, especially the advanced ultrasonic nebulizer technologies discussed in Section 4. Caution has to be exercised, however, when carrying out a comparison of these devices, or any device for that matter, with other devices or technologies, as there is a large number of complex and often interrelated factors arising from the device and formulation itself, the limitations of current nebulizer test methods, and the matching of devices to specific patient groups and their environmental context (see Section 3). These significantly complicate the evaluation to a point where generic statements about the superiority of one device over another cannot be made. Conclusions derived from comparative evaluations should therefore be specific and limited to individual cases without being loosely extrapolated to other systems and contexts. Device selection should be based on careful examination of all the above-mentioned factors affecting the efficacy of delivery. In the end, however, the decision for the implementation of a particular technology over others, at least for the average patient, may simply be down to factors such as cost, simplicity in the administration technique, ease-of-use, and smart, convenient design [118].

6. Expert opinion

A survey of the literature so far reveals that although a significant number of attempts have been made to compare the performance of inhalation therapy platforms, there remains wide variability in intra-platform comparisons (i.e., comparisons between MDIs, DPIs and nebulizers) as well as intra-nebulizer comparisons (i.e., comparisons between different nebulizer types, for example, jet and ultrasonic nebulizers). It is the authors' opinion that generic conclusions derived from such tests, for example, generalized statements such as 'ultrasonic nebulization is no more effective than jet nebulization', are unhelpful and often misleading, even if the assessments were carried out for specific drugs and patient age groups. There are simply many other factors, both device and patient-related, which are variable, which make a generalized conclusive statement too simplistic. This is compounded by the fact that the term ultrasonic nebulization covers a wide range of devices that could differ widely in terms of the fundamental aerosol-generating mechanism, resulting in widely different performances. Moreover, even tests on the same nebulizer device can yield very different results owing to variations inherent in current test practice as well as those at the device production stage. The appropriate delivery technology must therefore be selected within the context of a specific patient condition and profile, the formulation to be administered, and other factors, which can be determined only by specific *in vitro* tests carried out under those particular conditions and subsequent *in vivo* and clinical evaluations and comparisons.

The concept of matching the choice of the delivery platform to specific patient conditions and profiles can be extrapolated further to tailor the chosen device to deliver optimum efficacy for an individual patient's requirements. Indeed, the authors envisage a potential future in which personalized drug delivery becomes the norm. This is where advanced ultrasonic nebulizer platforms possess a distinct advantage over most other competing technologies – their ability to be adaptively tuned to administer a specific dose (by varying the aerosol size distribution and aerosol generation rate, or through coordination with respiratory maneuver, etc.) according to the patient's particular requirement at a given instance, without requiring considerable training in its use. The authors therefore anticipate a resurgence in the development and subsequent adoption of advanced ultrasonic nebulizers with integrated adaptive sensing and electronic control. The surface acoustic wave nebulization platform is potentially one such candidate.

History has, nevertheless, demonstrated that advanced technologies and delivery efficiency may not result in successful commercialization and uptake of the technology. Instead, the success stories seem to suggest that it is device simplicity, in terms of its cost, ease of use, as well as design (lightweight, portable, silent, convenient, attractive aesthetics, etc.), that determines to some extent whether or not a technology is widely adopted. If the advanced computer-aided industrial design and intelligent electronics that have revolutionized smart personal data assistant (PDA) phone technology together with the possibility of miniaturization through advances in microfluidic technology can be exploited synergistically in the design of advanced ultrasonic nebulizers, there might be a significant chance of a wave of state-of-the-art devices replacing the current conventional portable inhaler technologies that have become commonplace in today's society.

Little yet, however, is understood about the fundamental mechanisms that govern the physicochemical hydrodynamics associated with the interfacial destabilization and nebulization process. Decades of research have so far failed to satisfactorily produce a coherent theory for ultrasonic nebulization let alone address the controversies and debate that have arisen. Further efforts to fundamentally examine and understand the complex physics associated with the underlying processes that lead to nebulization are therefore urgently required before further significant progress in the developments of advanced nebulization technology can be achieved.

Acknowledgements

The authors gratefully acknowledge funding from the National Health and Medical Research Council under Development Grant 1000513.

Declaration of interest

E Meeusen is involved in Allergenix Pty Ltd, which commercializes sheep asthma and respiratory delivery models. The other authors state no conflict of interest and have received no payment in preparation of this manuscript.

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