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Ultrasonic nebulisers for pulmonary drug delivery

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Abstract

Nebulisers are widely used to generate therapeutic aerosols for inhalation therapy. In this paper the factors determining aerosol size and drug output from ultrasonic nebulisers are discussed. The mechanism of droplet formation is described in relation to capillary wave production on the surface of the liquid being atomised and the implosion of cavitation bubbles near its surface. There are many commercially available ultrasonic nebulisers, and their design is a major factor determining aerosol characteristics and output, in particular the operating frequency of the devices (usually 1–3 MHz), the presence of a fan to assist droplet output and the positioning of baffles. The size of aerosols produced and the rate of fluid output is often larger than comparable jet nebulisers. They also have less tendency to increase the concentration of dissolved solutes. However, the residual or 'dead' volume of fluid is usually larger. The physicochemical properties of fluids for nebulisation significantly affect nebuliser performance. Viscosity is particularly important, with an increased viscosity increasing aerosol size but reducing output. Fluids of high viscosity cannot be efficiently atomised. Although most preparations for nebulisation are solutions, some suspension formulations are also commercially available. Suspensions are generally less efficiently delivered by ultrasonic than jet nebulisers with an inverse relationship between the size of suspended particles and their output. During use, the temperature of fluids in the reservoir of ultrasonic nebulisers increases. This may result in the degradation of heat sensitive materials. However, potentially heat sensitive such as proteins and liposomes have been successfully delivered using such devices. © 1997 Elsevier Science B.V.

Keywords: Aerosol; Drug delivery; Formulation; Nebuliser; Particle size; Ultrasonic

1. Introduction

Nebulisers deliver relatively large volumes of drug solutions and suspensions for inhalation. Whilst nebulisers may be used simply as an alternative to metered dose inhalers (MDIs) or dry

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powder inhalers (DPIs) for inhalation therapy, they are frequently used to deliver drugs, such as proteins, which cannot be conveniently formulated into MDIs or DPIs, or where the therapeutic dose is too large for delivery (e.g. pentamidine isethionate) by these alternative systems. During nebulisation, drug is inhaled during normal tidal breathing, through a mouth-piece or face-mask, and consequently nebulisers are useful for patients who experience difficulties when using MDIs or DPIs.

There are two categories of commercially available nebulisers. Jet nebulisers are most commonly used clinically and utilise compressed gases to produce aerosol droplets in the respirable size range. The use of such nebulisers for pulmonary drug delivery has recently been reviewed (Flament et al., 1995; McCallion et al., 1996a; Niven, 1996). Ultrasonic nebulisers use ultrasonic energy to convert liquid into a spray and have been less extensively studied and characterised than jet devices.

2. Mechanism of aerosol generation

In ultrasonic devices, the energy required to atomise a liquid comes from a piezoelectric crystal, usually a man-made ceramic material, vibrating at high frequency (usually 1–3 MHz). The base of the crystal is held firm such that the vibrations are transmitted from its front surface to the nebuliser fluid, either directly or via a coupling liquid, usually water. When the ultrasonic vibrations are sufficiently intense, a fountain of liquid is formed at the surface of the liquid in the nebuliser chamber. Large droplets are emitted from the apex and a 'fog' of small droplets is emitted from the lower part (Fig. 1). Ultrasonic nebulisers produce a large number of droplets per unit volume, which in the absence of air circulation through the nebuliser will tend to aggregate and settle. Some models have a fan to blow the respirable droplets out of the device (e.g. Medix Electronic, Easimist), whilst in others the aerosol only becomes available to the patient during inhalation (e.g. DeVilbiss Pulmosonic). Reduction in the power to the fan (e.g. Fisoneb, Medix Electronic) or the fan and vibrating crystal (e.g. Sonix 2000) is used to modify the speed of fluid output from the nebuliser. For instance the fluid output from the Sonix 2000 ultrasonic nebuliser can be varied between 1 ml/min to 1 ml in 6 min by changing the fan speed setting (Baker and Stimpson, 1994).

Two theories have been developed which describe the mechanism of liquid disintegration and aerosol production in ultrasonic devices. The capillary wave theory describes droplet formation as resulting from the production of capillary waves on the surface of the excited liquid. When the amplitude of the applied energy is sufficiently great, the crests of the capillary waves break off and droplets are formed. The rate of generation of capillary waves is dependent on the intensity of the ultrasonic vibration and the physicochemical properties of the liquid being atomised. Mercer (1981) calculated that the threshold amplitude for generation of capillary waves is given by Eq. (1):

$$A = 4\upsilon/f\lambda \quad (1)$$

where A is the threshold amplitude, υ is the kinematic viscosity of the liquid, f is the acoustic frequency and λ is the capillary wavelength. Droplets begin to be formed at the crests of capillary waves when the amplitude exceeds the threshold value by a factor of approximately four (Mercer, 1981). Lang (1962) observed that the mean droplet size generated from thin liquid lay-

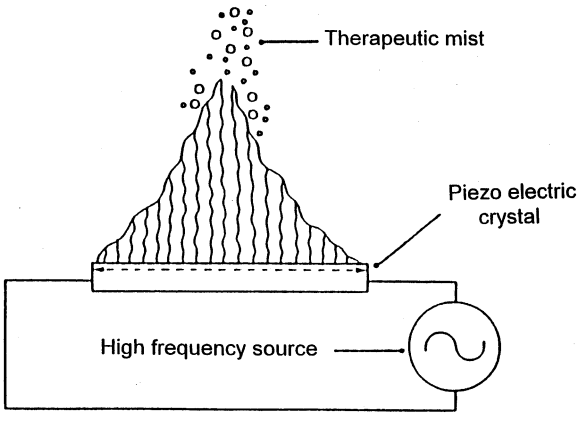

Fig. 1. Schematic diagram of an ultrasonic nebuliser (Reproduced with permission from Atkins et al., 1992).

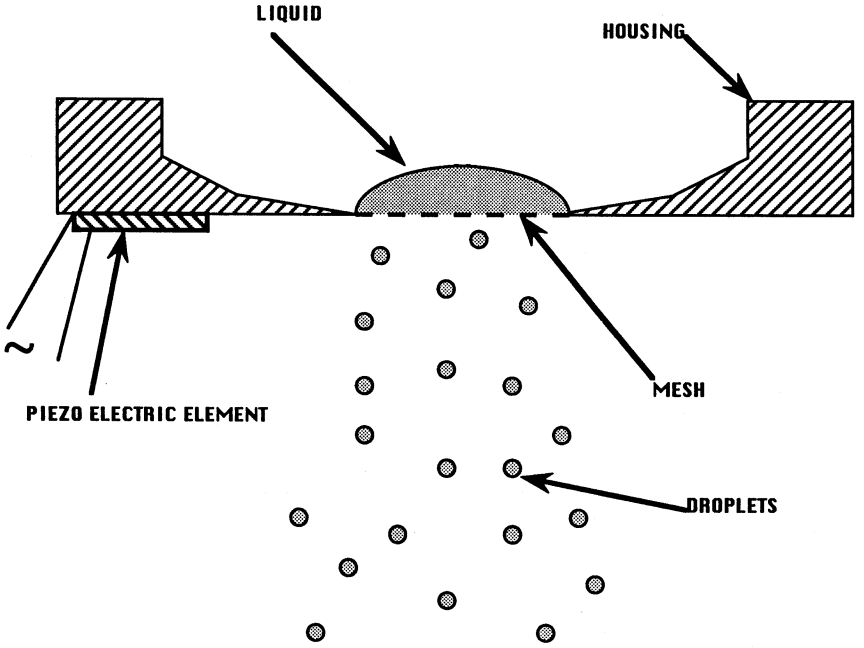

Fig. 2. Schematic diagram of the spray head of the Bespak Piezo Electric Actuator (Reproduced courtesy of Bespak plc, UK).

ers was proportional to the capillary wavelength on the liquid surface. Using an experimentally determined factor of 0.34, the droplet diameter, D is given by Eq. (2):

$$D = 0.34\lambda \quad (2)$$

where D is the number median diameter and λ is the capillary wavelength. Lobdell (1968) has calculated a theoretical value of 0.36 for the proportionality constant.

The capillary wavelength can be calculated (Eq. (3)) from Kelvin's equation where:

$$\lambda = (8\pi\gamma/\rho f^2)^{1/3} \quad (3)$$

where γ is the surface tension, ρ is the density and f is the acoustic frequency. If γ is in dynes/cm, ρ is in g/cm^3 and f is in megacycles/s then D calculated from Eq. (2) is given in μm. Such calculated diameters correlate well with experimentally derived values (Mercer et al., 1968).

The alternative cavitation theory (Sollner, 1936) postulates that liquid is atomised by hydraulic shocks produced by implosion of cavitation bubbles near its surface. The dependence of atomisation on cavitation phenomena has been demonstrated for frequencies between 0.5 and 2.0 MHz (Gershenzon and Eknadiosyants, 1964; Il'in and Eknadiosyants, 1966). The capillary wave and cavitation theories have been combined by Boguslavskii and Eknadiosyants (1969) who propose that droplet formation results from capillary waves initiated and driven by cavitation bubbles.

Commercially available ultrasonic nebulisers generally require access to mains supplied electricity, limiting their portability. However, rechargeable battery packs are becoming available for use with recently marketed nebulisers, such as the Sonix 2000, enhancing their portability and a small, portable battery powered device has been described (Zierenberg, 1992).

Recently, an aerosol delivery system based on a piezoelectric crystal combined with an electroformed mesh (Bespak Piezo Electric Actuator) has become available. This device produces droplets of 'adjustable' size from a single metered drop or fluid reservoir (Baker and Stimpson, 1994). The spray head of this device is shown in Fig. 2. The mesh hole size (which can be as small as 3 μm) determines the size of droplets produced, whilst the size and density of the holes controls the rate

at which fluid is delivered. The size and density of the holes in the mesh can be varied dependant on the formulation. Solutions are best nebulised, although suspensions can be delivered if the particle size of suspended particles are 2–3 times smaller than the mesh size. The optimal dose volume for droplets in the size range 5–8 μm to be produced, in the time in which they can be readily inhaled (approximately 1 second), is 20–50 μl (Baker and Stimpson, 1994).

3. Aerosol droplet size

For a pharmaceutical aerosol to exert a therapeutic effect, it must first be deposited at the appropriate site within the respiratory tract. Particle size is the principal factor determining aerosol deposition. To penetrate to the peripheral (respirable) regions of the lung, aerosols require a size less than approximately 5 or 6 μm, whilst a size less than 2 μm is optimal for alveolar deposition (Stahlhofen et al., 1980; Newman and Clarke, 1983). Penetration to the peripheral airways is particularly desirable in the treatment of conditions such as cystic fibrosis (Newman et al., 1988) and *Pneumocystis carinii* pneumonia (Smalldone et al., 1988; Thomas et al., 1991). Larger particles or droplets may deposit in the mouth and throat, possibly causing local effects, or following deposition in the upper respiratory tract and subsequent clearance by the mucociliary clearance process, drug will become available for systemic absorption, with the potential for resultant adverse effects.

Most reported studies of medical ultrasonic nebulisers which have considered the aerosol size, comprise comparisons with air-jet nebulisers as aerosol delivery devices (e.g. Ferron et al., 1976; Mercer, 1981; Ryan et al., 1981; Sterk et al., 1984; Newman et al., 1987; Smalldone et al., 1988; Phipps and Gonda, 1990; Cipolla et al., 1994).

Devices with an operating frequency of 2–3 MHz generate droplets of comparable size to jet nebulisers, whilst devices with frequencies less than 0.5 to 1 MHz generate droplets outside the respirable range (Boucher and Kreuter, 1968; Sterk et al., 1984). Droplet size is inversely proportional to acoustic frequency and thus smaller droplets are generated at higher frequencies (Eq. (3)). This has been demonstrated in study of nine ultrasonic nebulisers (Sterk et al., 1984). Increasing the airflow through the devices did not alter the rate of solution output or droplet size (Sterk et al., 1984).

Commercially available ultrasonic nebulisers, usually have an operating frequency between 1 and 2 MHz and produce aerosol droplets which are often significantly larger than those produced by jet nebulisers (Mercer, 1981; Sterk et al., 1984; Baker and Stimpson, 1994), but which are less polydispersed (Mercer, 1981; McCallion et al., 1996b). The generation of relatively large droplets with low polydispersity, and in particular the absence of droplets with size less than 2 μm suggests that such nebulisers may be inappropriate for applications requiring that drug penetrates to the most peripheral lung regions (Newman et al., 1987).

4. Nebulisation time, drug output and residual volume

The duration of nebuliser therapy is likely to be an important determinant of patient compliance. Preparations for nebulisation may be atomised for a set period of time, or more usually a measured volume is nebulised to 'dryness'. The time taken to nebulise a liquid to dryness may be decreased by decreasing the initial fill volume. However, not all the fluid in the nebuliser can be atomised and some fluid remains associated with the baffles, internal structures and walls of the nebuliser as the 'dead' or 'residual' volume (Clay et al., 1983). The proportion of fluid remaining as the 'dead' volume and hence unavailable to patients is greater for smaller fill volumes.

Generally ultrasonic nebulisers produce a much larger fluid output per unit time than jet nebulisers, however due to higher airflow through the devices droplet concentrations per unit volume of air are lower (Sterk et al., 1984).

Ultrasonic nebulisers may retain a higher residual or 'dead' volume than comparable jet nebulisers (Newman et al., 1987) but show less tendency

Table 1
Mean (± S.E.) nebulisation time and output for DeVilbiss Pulmosonic ultrasonic and DeVilbiss 646 jet nebulisers used to atomise 4 ml of sodium chloride solution (70 mg/ml)

	Ultrasonic	Jet (6 l/min)	Jet (12 l/min)
Nebulisation time (min)	11.7 (0.9)	32.4 (1.1)	14.6 (0.7)
Final sodium chloride concentration (mg/ml)	140 (6)	185 (4)	200 (5)
Mass of sodium chloride released (g)	125 (17)	146 (9)	184 (5)

Adapted from Newman et al., 1987.

than jet nebulisers to increase the concentration of solutes within the nebuliser chamber during use (Ferron et al., 1976; Newman et al., 1987). Newman et al. (1987) compared eight DeVilbiss ultrasonic and jet nebulisers. Their results (Table 1) illustrate the shorter time required to nebulise solutions to dryness, reflecting a high fluid output but also an increased dead volume as shown by the smaller mass of drug released. The DeVilbiss Pulmosonic ultrasonic nebuliser tended to increase the concentration of drug in the nebuliser reservoir to a lesser extent than the DeVilbiss 646 jet nebuliser operated at high or low flow rates. The output from a jet nebuliser comprises droplets of drug solution and solvent vapour, which saturates the outgoing air causing solute concentration to increase during atomisation (Ferron et al., 1976). Ultrasonic nebulisers generally have higher fluid output and a larger droplet size, so that there is more solvent available within the dense aerosol cloud to saturate the outgoing air and thus changes in solute concentration within the remaining solution are much smaller than for jet nebulisers (Ferron et al., 1976; Phipps and Gonda, 1990).

5. Formulation of nebuliser fluids

The earliest clinical uses for ultrasonic nebulisers was in the production of aqueous aerosols for the humidification of air in respiratory care units, where they had the advantage over steam in that air temperature was not increased (Tovell and D'Ambruoso, 1962) and for introducing humidity into the inspired air for volume controlled respirator systems (Herzog et al., 1964). Nebuliser fluids for inhalation therapy are formulated in water, with the inclusion of co-solvents such as ethanol or propylene glycol if necessary and surfactants in suspension formulations. Anti-oxidants and antimicrobial preservatives may also be included in nebuliser formulations, although these may cause paradoxical effects (i.e. excipients in solutions of beta-agonists may cause bronchoconstriction in some individuals rather than the intended bronchodilation) (Beasley et al., 1988). Iso-osmotic solutions of pH 4 or greater are usually employed, although osmolarity and pH may change in use, resulting in bronchospasm (Schöni and Kraemer, 1989). Whilst chemically preserved multidose preparations are available, nebuliser formulations are generally presented as sterile, isotonic, preservative free unit doses.

The viscosity and surface tension of a liquid being nebulised may affect the properties of the aerosol produced by nebulisers since energy is required to overcome viscous forces and to create a new surface. However, the size-selectivity of the nebuliser design, for instance the inclusion of baffles, results in the recycling of the majority of the primary aerosol mass into the bulk reservoir liquid. Consequently, changes in the size distribution of the primary aerosol resulting from changes in fluid properties will not necessarily be reflected in the size distribution of the aerosol emitted from the nebuliser (Mercer, 1981).

If, as proposed, capillary theory contributes in part to ultrasonic atomisation, the droplet size will be proportional to the liquid's surface tension and inversely proportional to its density (Eq. (3)). Additionally, variations in liquid properties increasing the threshold amplitude (e.g. increased viscosity) will tend to slow or suppress the rate of

Table 2
Mass median diameter (MMD) and total output (% of initial fluid delivered) for fluids nebulised in the Medix Electronic nebuliser

Fluid	Viscosity (mN/m^2 per s)	Surface tension (mN/m)	MMD (μm)	Output (%)
Water	1.00	72.80	4.5	68.3
Ethanol	1.19	24.10	4.7	92.7
Glycerol 10%	1.31	72.90	4.4	45.7
Glycerol 20%	1.92	72.54	4.5	26.5
Glycerol 25%	2.09	72.21	4.7	19.6
Glycerol 30%	2.74	71.73	4.8	15.8
Glycerol 35%	3.36	71.32	5.3	12.6
Glycerol 40%	4.09	70.61	5.6	8.6
Glycerol 45%	4.94	70.35	6.1	8.2
P.glycol 10%	1.50	62.00	4.6	65.3
P.glycol 30%	3.00	52.00	4.7	19.1
P.glycol 40%	4.32	47.65	4.7	12.6
P.glycol 45%	5.09	46.00	5.0	12.0
P.glycol 50%	6.50	45.00	5.6	8.9
S.F. 200/0.65cs	0.49	15.90	2.8	96.8
S.F. 200/1cs	0.82	17.40	2.9	93.5
S.F. 200/1 + 5cs	2.45	18.25	4.1	37.5
S.F. 200/5cs	4.60	19.70	4.8	1.5

P.glycol, propylene glycol; S.F., silicone fluid.
Reproduced with permission from McCallion et al., 1995.

atomisation. Thus, low viscosity liquids offer low resistance to fountain disintegration and produce a better output of droplets (Gershenzon and Eknadiosyants, 1964), whilst fluids with viscosities greater than 10 cP have proved difficult to aerosolise ultrasonically (Boucher and Kreuter, 1968).

Gershenzon and Eknadiosyants (1964) found that for a wide range of fluids, with the exception of water, the atomisation rate in mg/second could be related to certain physicochemical properties of the fluid (Eq. (4)).

$$A^2 \propto \pi p/\eta\sigma \quad (4)$$

where A is the atomisation rate, p is the liquid vapour pressure, η is the viscosity and σ is the surface tension.

Il'in and Eknadiosyants (1966) found the dynamic viscosity coefficient to be the most important variable determining the rate of nebulisation. For solutions of Alevaire (a drug used for Mucus clearance) or Mucomyst (*N*-acetyl-L-cysteine) the rate of nebulisation decreased progressively as the viscosity of the solution increased. When certain oily and viscous liquids, such as Lipiodal (a radio-opaque diagnostic agent) were nebulised a fountain of liquid was generated which did not subsequently disintegrate to generate an aerosol (Il'in and Eknadiosyants, 1966).

In a study of the atomisation of a range of materials with different physicochemical properties from jet and ultrasonic nebulisers, McCallion et al. (1995) demonstrated that for two ultrasonic nebulisers (Medix Electronic and Easimist) increasing the viscosity of nebuliser fluids resulted in the generation of larger droplets (Table 2, Fig. 3). This contrasted to jet nebulisers where increasing viscosity resulted in smaller droplets. However, no clear correlation was observed between surface tension and median aerosol size (Table 2, Fig. 4) with viscosity being the most important variable within the different classes of fluids atomised. The ultrasonic nebulisers could not efficiently atomise the more viscous liquids, and produced poor total fluid outputs (Table 2). In some instances aerosol production was poor from the beginning of the nebulisation process, whilst in other instances output was suppressed towards the end. The Medix Electronic nebuliser only

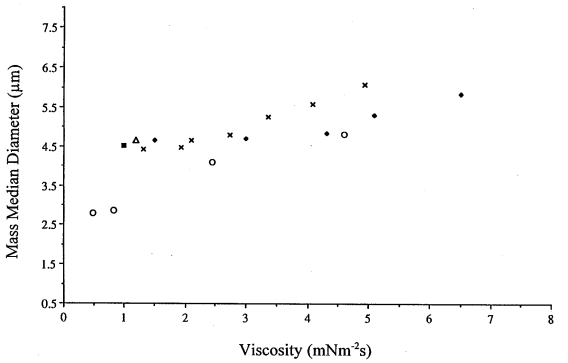

Fig. 3. Correlation plot of droplet size against fluid viscosity for fluids nebulised in Medix Electronic nebuliser at mid-power setting. Fluids nebulised were: water (■); ethanol (△); glycerol solutions (x); propylene glycol solutions (◆) and silicone fluids (○) (Reproduced with permission from McCallion et al., 1995).

delivered 1.5% of the 200/5 cs. silicone fluid (viscosity = 4.6 mN/m^2 per s) in 10 min, and unlike jet nebulisers would not atomise the more viscous (> 4.6 mN/m^2 per s) silicone fluids. The Easimist nebuliser would not nebulise any of the silicone fluids, even those with comparable viscosities to propylene glycol and glycerol solutions which were nebulised, suggesting that surface tension may also be important.

Reduction in liquid surface tension, through addition of surfactants, may decrease nebulisation rate, possibly due to a reduction in capillary wavelength causing an increase in threshold amplitude (Boucher and Kreuter, 1968) or through their influence on the diffusion of gas into cavitation bubbles (Kapustina, 1969). However, when the surface tension of nebuliser fluids was modified by the addition of the surfactants sodium lauryl sulphate, Tween 20, Tween 80 and Span 85, above and below their critical micelle concentration, the size of droplets produced tended to increase whilst the total fluid output was largely unchanged (McCallion et al., 1996b; Table 3).

Table 3
Mass median diameter (MMD) and total output (% of initial fluid delivered) for surfactant solutions nebulised in the Medix Electronic nebuliser

Fluid	Surface tension (mN/m)	MMD (μm)	Output (%)
Water	72.80	4.73	69.8
SLS 0.0001%	65.70	4.83	68.0
SLS 0.001%	60.60	4.97	63.0
SLS 0.01%	56.00	4.32	68.7
SLS 0.1%	43.80	4.31	71.9
SLS 1.0%	37.10	4.28	76.1
T80 0.0001%	65.17	4.43	68.0
T80 0.001%	55.56	4.48	63.5
T80 0.01%	50.54	4.86	63.0
T80 0.1%	45.27	4.96	73.1
T80 1.0%	43.20	4.73	75.0
T20 0.0001%	66.90	4.47	69.8
T20 0.001%	60.56	4.68	70.1
T20 0.01%	48.44	5.01	64.9
T20 0.1%	42.40	5.33	61.8
T20 1.0%	39.60	4.58	69.2
S85 0.0001%	56.90	4.67	72.4
S85 0.001%	50.90	4.69	69.8
S85 0.01%	35.40	4.74	66.7
S85 0.1%	32.50	5.09	68.6
S85 0.2%	31.80	5.95	47.1

SLS, sodium lauryl sulphate; T80, Tween 80; T20, Tween 20; S85, Span 85.
Adapted from McCallion et al., 1996b.

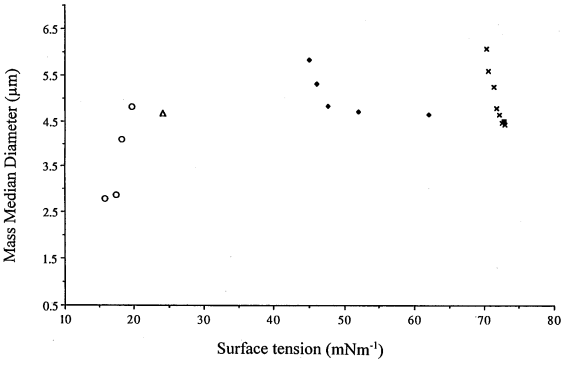

Fig. 4. Correlation plot of droplet size against surface tension for fluids nebulised in Medix Electronic nebuliser at mid-power setting. Fluids nebulised were: water (■); ethanol (△); glycerol solutions (x); propylene glycol solutions (◆) and silicone fluids (○) (Reproduced with permission from McCallion et al., 1995).

Although most nebuliser formulations are solutions, poorly aqueous soluble drugs such as corticosteroids may be formulated as suspensions of micronised drug. Those currently available are

Becotide® (beclomethasone dipropionate) and Pulmicort® (budesonide) formulations. Lin et al. (1974) successfully used an ultrasonic nebuliser to deliver radio-labelled sulphur and tin colloids for lung imaging, although soluble radiopharmaceuticals may be more appropriate for delivery from such devices (Istiman et al., 1974). In general, ultrasonic nebulisers are less efficient and more variable in delivering suspensions than jet nebulisers. McCallion et al. (1996c) demonstrated that the Medix Electronic nebuliser was able to deliver 27–33%, 20–25% and 7–8% of available 0.605, 2.97 and 6.40 μm latex spheres respectively. However 1.16 μm spheres were not released from the nebulisers, whilst large 11.90 μm spheres were apparently degraded in the nebuliser reservoir. The concentration of spheres within the nebuliser increased due to the more efficient delivery of continuous rather than disperse phase.

6. Temperature effects

Only a small fraction of the energy available in the nebuliser is used to generate the new surface necessary in the production of droplets. The excess energy is converted to heat causing the temperature of the liquid within the nebulisers to increase until the input energy balances the energy removed by evaporating solvent molecules and by conduction to the surroundings and circulating air (Mercer et al., 1968). Thus, the temperature of drug solutions in medical ultrasonic nebulisers may increase by up to 20°C above ambient temperature during use (Phipps and Gonda, 1990; Taylor and Hoare, 1993; Fig. 5). This will result in changes in the surface tension and viscosity of the liquid. For instance, increasing the temperature of water from 20 to 40°C decreases surface tension from 72.75 to 69.56 mN/m (Weast, 1988a) and viscosity from 1.00 to 0.65 mN/m^2 per S (Weast, 1988b). Such changes may produce changes in the aerosol size characteristics and overall drug output, although little variation was seen during the prolonged operation per s of Medix Electronic or Easimist nebulisers (McCallion et al., 1995) or when the temperature of the solution in a DeVilbiss Aerosonic nebuliser was increased using a heating coil (Niven et al., 1995). The increase in temperature may be advantageous. For instance, the reduction in temperature of therapeutic nebuliser solutions by approximately 10–15°C in jet nebulisers (Clay et al., 1983; Taylor et al., 1992) may cause bronchoconstriction in some asthma sufferers (Lewis, 1983). This bronchoconstriction, which is most marked at 5°C, is abolished at 37°C and is thus less likely to occur when ultrasonic devices are employed. Further, when drugs having poor aqueous solubility are nebulised at, or near their limit of solubility, the decrease in temperature that occurs in jet nebulisers may cause precipitation and poor nebuliser performance in terms of variable droplet size and drug output (Taylor et al., 1992). In such instances, ultrasonic nebulisers that warm, rather than cool, drug solutions may be a more appropriate alternative (Taylor and Hoare, 1993). However, the heat generated may cause chemical degradation of heat labile materials such as ^{99m}Tc-DTPA (Waldman et al., 1987), proteins (Cipolla et al., 1994) and some antibiotic solutions (Dennis and Hendrick, 1992), limiting their use in such applications. For instance, ultrasonic nebulisers are specifically prohibited for the delivery of the enzyme recombinant human deoxyribonuclease (rhDNase) for this reason (British National Formulary, 1996).

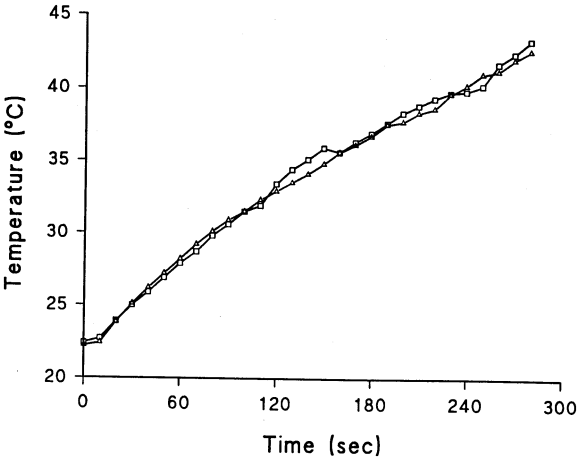

Fig. 5. Temperature increases in pentamidine isethionate solutions (300 mg/ 6 ml) nebulised in Medix Electronic nebuliser at maximum (□) and mid-power (△) settings (Reproduced with permission from Taylor and Hoare, 1993).

7. Delivery of novel drug delivery systems: peptides and liposomes

Published studies of liposome delivery to the human lung have employed nebulisers for the production of liposomal aerosols (Farr et al., 1985; Taylor et al., 1989; Barker et al., 1994; Vidgren et al., 1995). Nebulisers have been the preferred delivery system because they deliver large dose volumes and the liposomes can be produced by conventional techniques (Taylor and Farr, 1993). However, although jet nebulisers have been the devices of choice for such delivery, they may structurally damage some liposome formulations due to the shearing forces and recycling of liquid that occurs within the nebuliser (Niven and Schreier, 1990; Taylor et al., 1990).

Since ultrasonic nebulisers increase the temperature of fluid in the reservoir during use they have generally been avoided for delivering liposomes, which exhibit temperature dependent drug release. Barber and Shek (1989) reported that egg phosphatidylcholine (EggPC) liposomes, with a mean size of 281 nm or smaller were stable to nebulisation in a DeVilbiss Ultra-Neb 99 ultrasonic nebuliser. However, although small dipalmitoylphosphatidylcholine liposomes were stable to nebulisation, vesicles of 499 nm increased in size within the nebuliser reservoir, suggesting fusion of vesicles, which could result in loss of entrapped hydrophilic materials. A later study (Leung et al., 1996) showed that, the size of large multilamellar Egg PC liposomes remaining in a Medix Electronic nebuliser decreased markedly during nebulisation, suggesting vesicle disruption, whilst there was a good correlation between the size of liposomes deposited in each stage of a two-stage impinger and the size of aerosols collected in that stage. The size of cholesterol containing liposomes in the nebuliser reservoir was less markedly reduced, whilst the size of liposomes deposited on either stage of the impinger was independent of the size of aerosol droplets.

Ultrasonic nebulisers would also appear to be less suitable than jet nebulisers for the generation of aerosols for the delivery of proteins to the airways, because of the heat sensitivity of such materials. In a comparison of 8 jet and 2 ultrasonic nebulisers for the delivery of rhDNase a wide variation in the droplet size of the aerosols generated was demonstrated (Cipolla et al., 1994). With all the jet nebulisers the enzymatic activity of rhDNase was preserved in both the collected aerosol and fluid remaining in the reservoir. However, with the ultrasonic nebulisers there was evidence of some thermal denaturation of the enzyme, occurring towards the end of the nebulisation period when the volume of liquid was minimal and its temperature the greatest. The maximum temperature of the rhDNase solution was 58°C which was near to the thermal transition temperature (approximately 65°C) of the enzyme (Cipolla et al., 1994).

Ip et al. (1995) investigated the stability of recombinant consensus α-interferon to nebulisation in DeVilbiss Aerosonic, Mountain Medical Microstat and Medix Easimist nebulisers. The protein aggregated during atomisation, the extent of aggregation being dependent on the nebuliser used, the Easimist causing the least and Microstat the most aggregation. This was related to the heating of the solutions and could be minimised by cooling the nebuliser solution during use. When the Aerosonic nebuliser was used to atomise lactate dehydrogenase, the enzyme was completely inactivated after 20 minutes operation (Niven et al., 1995). The profile of inactivation was different from that observed with a jet nebuliser (Fig. 6) and was associated both with the heating of the nebuliser fluid during use and with aerosol production. The activity of the enzyme was almost completely retained if 0.01% w/v Tween 80 or 1% w/v PEG 8000 was included in the nebuliser fluid.

8. Conclusion

Ultrasonic nebulisers are established devices for the administration of therapy to the lungs. Published reports of their use for the delivery of bronchodilators suggest that they produce comparable bronchodilator responses to jet nebulisers and metered dose inhaler formulations (Ballard et al., 1991; Pallares et al., 1996). However, ultra-

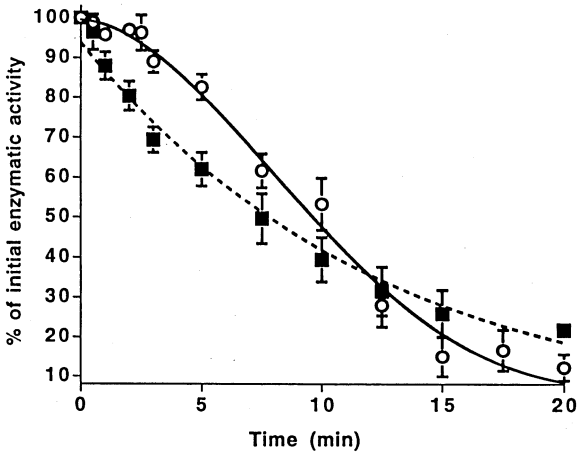

Fig. 6. Inactivation of lactate dehydrogenase in a 3 jet Collison jet nebuliser (■) and DeVilbiss Aerosonic ultrasonic nebuliser (○) (Reproduced with permission from Niven et al., 1995).

sonic nebulisers are less frequently used for pulmonary drug delivery than jet nebulisers. This may be due to their greater cost and less comprehensible mechanism of aerosol generation. Further, whereas jet nebulisers are made from injection moulded plastics and are usually disposable or sterilisable in an autoclave, ultrasonic nebulisers are not disposable and are used repeatedly (Greenspan, 1996). Cleaning nebulisers and connecting tubing is difficult and the spread of Gram negative bacteria from contaminated nebulisation equipment to patients and from infected patients to nebulisers has been reported (Rhoades et al., 1971).

Many different models of nebuliser are commercially available and it has not been the purpose of this paper to describe or compare models. Such devices cannot be considered equivalent having varying operational frequencies, baffles and fans. In addition to factors relating to the design of nebulisers, the dead and fill volumes, the warming of fluids during use and the physicochemical properties of the fluid should be considered, alongside patient-related factors, when considering therapeutic efficacy which is related to both the size of the aerosols produced and drug output.

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