ELSEVIER

International Journal of Pharmaceutics 130 (1996) 1–11

international journal of pharmaceutics

Invited Review

Jet nebulisers for pulmonary drug delivery

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Received 8 March 1995; revised 28 April 1995; accepted 20 June 1995

Abstract

Nebulisers are widely used clinically to produce aerosols for a range of applications. This paper reviews the many factors which determine the particle size of the aerosol and drug output and describes their potential usefulness for novel drug delivery.

There are numerous commercially available nebulisers, and their design is an important factor governing aerosol size and fluid output. Recent designs have included developments to reduce the proportion of drug lost during exhalation with traditional continuous output nebulisers.

The rate of gas flow driving atomization is a major determinant of aerosol size; there being an inverse relationship between droplet size and flow rate, due to the increased shearing forces at higher flow rates. Although droplet size is largely independent of fill volume, the proportion of available drug increases with increased fill volumes, since some fluid is invariably retained within the nebulisation chamber at the end of atomization. During use the temperature of the fluid within the nebuliser significantly decreases. This may result in precipitation of poorly soluble drugs and produce variability in droplet size due to changes in the physicochemical properties of nebuliser fluids. Mean aerosol size is inversely proportional to viscosity. However, although high viscosity fluids produce small droplets, they require longer to nebulise to dryness and are retained to a greater extent. Reducing the surface tension of fluids tends to produce aerosols of smaller size. Thus, the size and dose of aerosol available for inhalation by a patient is a complex function of all these factors, whilst the dose inhaled and deposited in the airways is highly dependent on patient-related factors.

Keywords: Aerosol; Drug delivery; Formulation; Nebuliser; Respiratory tract

1. Introduction

Although pressurised metered dose inhalers (MDIs) are the most commonly used inhalation drug delivery system, other delivery systems, such as dry powder inhalers (DPIs) and nebulisers, are widely used as propellant-free alternatives to MDIs.

Nebulisers use ultrasound or compressed gas to produce aerosol droplets in the respirable size range from liquids, usually aqueous solutions of drugs. They are widely used therapeutically to deliver β_2 agonists, corticosteroids, anti-allergics, anticholinergics, antibiotics, mucolytics and other

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SSDI 0378-5173(95)04233-2

agents to the respiratory tract (British National Formulary, 1994). They also have other medical uses, including the production of aerosols for ventilation scanning (Francis et al., 1981), bronchial challenge (Ryan et al., 1981) and for measuring epithelial permeability (Minty et al., 1981).

Nebulisers have the advantage over MDIs and DPIs that the drug may be inhaled during normal tidal breathing through a mouth-piece or face-mask. Thus, they can be employed to deliver aerosolized drug to patients, such as children, the elderly and patients with arthritis, who experience difficulties using other devices. Nebulisers can also deliver relatively large volumes of drug solutions and suspensions. They are frequently used for drugs that can not be conveniently formulated into an MDI or DPI or where the therapeutic dose is too large for delivery with the alternative systems.

Jet nebulisers use compressed gas (air or oxygen) from a compressed gas cylinder, hospital air-line or electrical compressor to convert a liquid (usually an aqueous solution) into a spray (Mercer, 1981). The jet of high velocity gas is passed either tangentially (concentric nebulisers, e.g. Turret, Respirgard II) or co-axially (Inspiron Mini-neb) through a narrow Venturi nozzle, typically 0.3–0.7 mm in diameter. An area of negative pressure, where the air jet emerges, results in liquid being drawn from a fluid reservoir up a feed tube by the Bernoulli effect (Fig. 1). Liquid emerges as fine filaments that collapse into droplets under the influence of surface tension (Green and Lane, 1964). A proportion of the resultant (primary) aerosol leaves the nebuliser directly, the remaining, large, non-respirable droplets impact on baffles or the walls of the nebuliser chamber and are recycled into the reservoir fluid.

Mercer, 1981 derived an equation relating the primary droplet diameter (d) with diameter of the venturi nozzle:

$$d = 0.64D[1 + 0.011(G_l/G_g)^2][2\gamma/(\rho v^2 D)]^{0.45}$$

where D = diameter of liquid inlet orifice; G_l = mass flow-rate of liquid; G_g = mass flow rate of gas; γ = surface tension of liquid; ρ = density of the gas and v = velocity of air.

The equation indicates the dependency of the primary aerosol size on gas and liquid flow rates, air and liquid inlet orifices and the surface tension of the liquid.

The aerosol leaving the nebuliser is diluted by atmospheric air and inhaled through a face-mask or mouth-piece. The droplet size of this secondary aerosol is significantly modified within the nebuliser by the 'filtering' effect of the baffles and due to droplet aggregation, solvent evaporation and condensation. Nebulisers are operated continuously and since the inspiratory phase of breathing

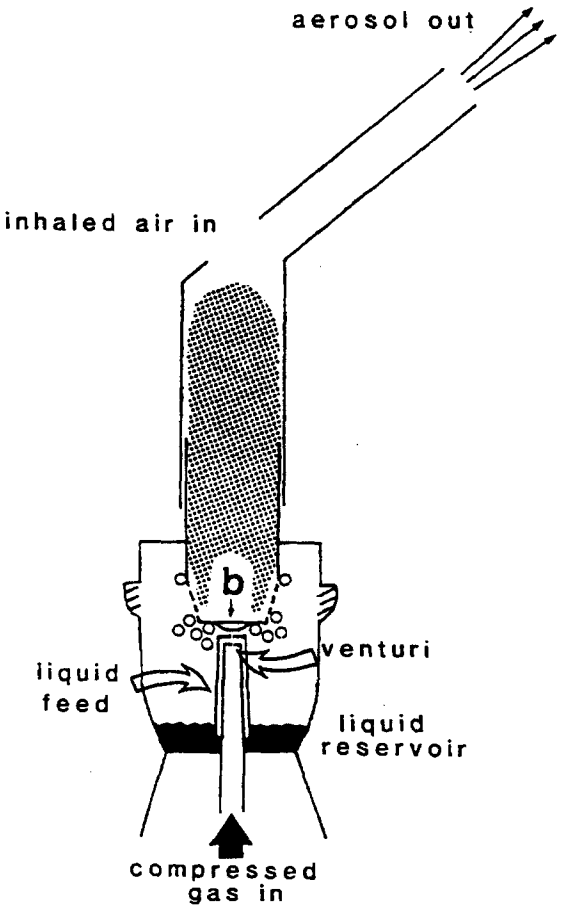

Fig. 1. Operation of a jet nebuliser. Compressed gas passes through a venturi nozzle where an area of negative pressure is created. Liquid is drawn up a feed tube and is fragmented into droplets. Large droplets impact on baffles (b) while small droplets are carried away in the inhaled airstream. (Reproduced with permission from Newman, 1989).

constitutes approximately 1/3 of the breathing cycle, a large proportion of the emitted aerosol is not inhaled. The mouth-piece may be connected to a T-piece with a finger-activated triggering device (manual interruptor) to divert the aerosol during exhalation, reducing wastage of exhaled aerosol. Alternatively, the aerosol may be released into a chamber (volume 0.1–1.0 litres), equipped with valves, such that the aerosol is stored during exhalation (Thomas et al., 1988).

Open vent systems (e.g. Pari LC and Ventstream) incorporating inhalation and exhalation valves have recently been developed. These systems avoid the inconvenience of manually interrupting aerosolization, whilst reducing wastage of aerosol during continuous operation. Inhaled air is drawn through a ventilation tube past the point of aerosol generation. In these nebulisers the patient's own breath boosts nebuliser performance, such that aerosol production matches the patient's tidal volume, greatly enhancing drug delivery. On exhalation, the aerosol being produced is generated only from the compressor gas source, such that drug wastage is minimal and saved for delivery on inhalation. Breath-enhanced nebulisers have improved drug output characteristics compared to conventional constant output jet nebulisers (Dennis, 1994, Knoch and Wunderlich, 1994) and ultrasonic nebulisers (Dennis, 1994) and may be designed to give lung deposition comparable to that achieved by nebulisers fitted with a manual interruptor (Newman et al., 1994).

Knoch and Wunderlich, 1994 compared the Pari LC Plus open vent nebuliser with two conventional nebulisers: Whisper-Jet and Hudson Updraft II. The amount of aerosol delivered from the Pari LC Plus after 5 min (31% continuous and 34% intermittent operation) was approximately twice that achieved with the conventional systems, 15% and 17% for the Whisper-Jet and Hudson respectively.

2. Aerosol size and drug delivery

The efficacy of a clinical aerosol is dependent on its ability to penetrate the respiratory tract. The most important property of a particle or droplet governing penetration and deposition in the airways is its size. To penetrate to the peripheral (respirable) regions, aerosols require a size less than about 5 or 6 μm, with a size < 2 μm preferable for alveolar deposition (Stahlhofen et al., 1980; Newman and Clarke, 1983). Larger particles or droplets deposited in the upper respiratory tract are rapidly cleared from the lung by the mucociliary clearance process, with the effect that drug becomes available for systemic absorption and potentially adverse effects (Lippman and Schlesinger, 1984). Similarly, steroid aerosols of sufficiently large size may deposit in the mouth and throat, with the potential to cause oral candidiasis. It has been suggested that close attention to the droplet size of the aerosolized drug may be particularly important in the treatment of certain conditions, where penetration to the peripheral airways is particularly desirable, for instance the antibiotic treatment of cystic fibrosis (Newman et al., 1988) and the treatment and prophylaxis of *Pneumocystis carinii* pneumonia (Smalldone et al., 1988; Thomas et al., 1991a).

In vitro measurements of aerosol droplet size are frequently employed to predict clinical performance. The principle methods employed for size characterisation of nebulised aerosols have been based on the principles of cascade impaction or laser diffraction. Cascade impactors, comprise a series of progressively finer jets and collection plates, allowing fractionation of aerosols according to their mass median aerodynamic diameter (MMAD) (Hallworth and Andrews, 1976). However, the use of cascade impaction for determining the droplet size of nebulised aerosols has a number of disadvantages. The high flow rates employed (typically 30–60 l/min) result in rapid solvent evaporation and droplet re-entrainment (Ho et al., 1987). Both these effects can result in a significant decrease in the measured aerosol size. Further, cascade impaction is an invasive, laborious and time consuming technique. Currently, the most popular methods for sizing nebulised aerosol are based on the principle of laser diffraction.

Droplets are sized as they are atomised into a laser beam to give a volume diameter or mass median diameter (MMD) which can be converted to the aerodynamic diameter if the liquid density is known (Farr et al., 1994). The optical properties of the atomized liquid may influence the computed size distributions, most medical nebuliser solutions do not absorb light at the wavelength of the laser used for diffraction analysis (Clarke, 1995) and thus for such studies computed size is independent of optical properties of the liquid being nebulised. Spraying droplets into a beam exposes them to ambient conditions of temperature and humidity, which may result in solvent evaporation (Niven and Brain, 1994). Thus, the distance between beam and nebuliser output should be standardised, usually at 25 mm.

Patient variables such as size (Alderson et al., 1974), variations in depth of breathing (Pavia et al., 1977) and breathing patterns (Dickenson and Smalldone, 1990) can influence the deposition of inhaled aerosols. However, attempts have been made to correlate droplet size with the deposition or therapeutic efficacy of nebulised aerosols. Some studies have failed to demonstrate a correlation between clinical effect and droplet size (Douglas et al., 1986; Hadfield et al., 1986), possibly due to the problems of inter-subject variability mentioned above, the production of polydispersed aerosols, or because commonly nebulised drugs such as bronchodilators are administered at super-therapeutic doses (Reilly et al., 1983). Other studies have demonstrated a relationship between droplet size and the regional deposition or clinical effect. For instance, a greater bronchodilator response was produced when patients with asthma received terbutaline from nebulisers producing small droplets (Clay et al., 1986). This was later demonstrated to correlate with an enhanced pulmonary deposition for smaller droplets of ^{99m}Tc-DTPA (diethylenetriamine pentaacetate) solution in a similar group of patients (Clay and Clarke, 1987). Recent gamma scintigraphic studies of the deposition of ^{99m}Tc-DTPA solution nebulised to healthy volunteers correlated pulmonary deposition from five nebuliser models to the

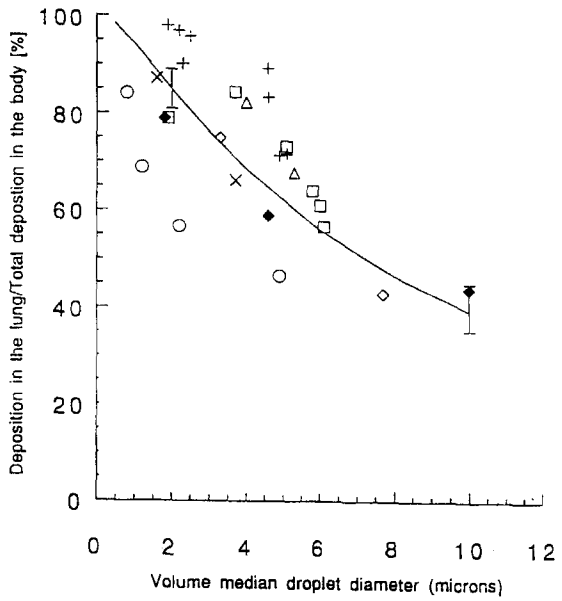

Fig. 2. Correlation between the volume median diameter of a nebuliser cloud, measured by laser diffraction analysis, and % thoracic deposition: ◆ Clay and Clarke, 1987; □ Ho et al. (1988); ◇ Johnson et al. (1989); × O'Doherty et al. (1990); +Thomas et al. (1991a); △ Thomas et al. (1991b); ○ Hardy et al. (1993)—Theory. (Reproduced with permission from Clarke, 1995).

proportion of aerosol < 5 μm (Farr et al., 1994). Although investigation of the regional distribution was limited by the low levels of activity used and the polydispersity of the aerosols it was reported that a greater penetration of aerosol to the peripheral airways was achieved with nebulisers producing the smallest droplet sizes. In a similar study of ^{99m}Tc-DTPA deposition, three jet and one ultrasonic nebuliser were studied (Hardy et al., 1993). The median lung depositions expressed as a percentage of the dose initially loaded into the nebulisers were 19% (Pari IS-2), 13% (PariBoy 37.80), 9% (Respirgard II) and 2% (Penta-sonic Ultrasonic nebulizer). The Pari IS-2 (MMAD = 1.2 μm) delivered the highest peripheral aerosol dose to the lungs, although the peripheral to central lung ratios were greater for the Respirgard II (MMAD = 0.8 μm) and Penta-sonic (MMAD = 2.2 μm) nebulisers. The peripheral to central ratio for the PariBoy (MMAD = 4.9 μm) was

significantly less than for the other three nebulisers.

Clarke, 1995 recently plotted the amount of aerosol deposited in the lung as a percentage of body deposition versus the volume median diameter for a number of deposition studies where aerosol size was measured by laser diffraction (Fig. 2). A good correlation exists between me-dian size and thoracic deposition. The data also correlated well with a theoretical model relating size to deposition (Rudolph et al., 1990).

3. The influence of gas flow rates on aerosol size

The rate of gas flow driving atomization is the major determinant of the aerosol droplet size produced by a jet nebuliser.

Clay et al. (1983) in a laser diffraction analysis of four jet nebulisers, showed that a 50% reduction in the MMAD was produced when the flow rate was increased from 4 to 8 l/min. This was accompanied by a linear increase in the proportion of droplets less than 5 μm and an increase in the polydispersity of the aerosol. Increasing the flow rate increases the shearing forces to which the fluid filaments and the surface of droplets are exposed, resulting in smaller droplets. Newman et al., 1986 also demonstrated the inverse relationship between aerosol size and flow rate for five nebulisers (Fig. 3). Droplet size was largely independent of the fill volume. The wide range of aerosol sizes produced by the different models were due to variations in the diameter of the air inlet, resulting in variations in the pressure drop for a given flow rate. Differences in construction of the devices, including the orientation of the baffles may also be responsible for the dissimilarity of the measured sizes.

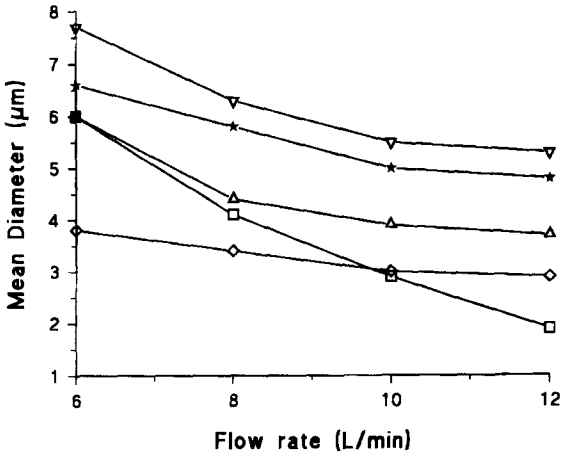

Fig. 3. The relationship between mean droplet size and gas flow rate for various jet nebulisers: Bird (✱), cirrus (□), De Vilbiss 646 (△), Inspiron (▽) and Turret (◇). (Adapted from Newman et al., 1986).

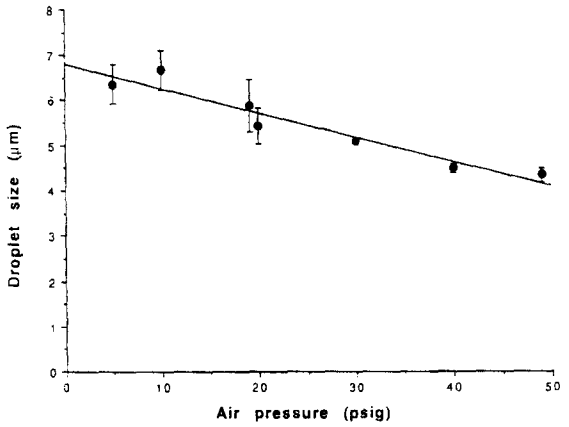

Fig. 4. The relationship between droplet size and driving air pressure for the Whisper-jet nebuliser. Each point represents the mean and range. (Reproduced with permission from Niven and Brain, 1994).

Recently, Niven and Brain, 1994 used cascade impaction to determine the mass median aerosol size produced by nebulising sodium chloride solutions in nine models of air-jet nebulisers operated at between 10 and 40 psi and 6 l/min. Increasing the driving pressure decreased the MMAD as previously described in studies employing laser diffraction size analysis. A linear relationship between droplet size and driving pressure was observed (Fig. 4). The extent of change in the droplet size was dependent on the individual nebuliser. For the Acorn II nebuliser there was only a

decrease of 0.3 μm (< 15%) between 10 and 40 psi, whereas the MMAD for aerosols produced by the Cirrus nebuliser decreased by 2.6 μm (> 40%) over the same pressure range.

4. Properties of the solution being nebulised

Viscosity and surface tension might be expected to affect the output characteristics of nebulisers, since energy is required to overcome viscous forces and to create a new surface. Atomization theory suggests that the mean diameter of aerosol droplets will increase as viscosity increases (Marshall, 1954; Mercer, 1973).

There have been few systematic studies with medical nebulisers to assess the effect of changes in the physicochemical properties of liquids being nebulised on the emitted aerosol. Walkenhorst and Dautrebande, 1964 manipulated the properties of solutions containing propylene glycol and concluded that surface tension, although influencing the number of droplets produced did not alter the size or size distribution of the droplets. Later studies with Maximyst and Bird nebulisers indicated that the MMAD of aerosols increased when propylene glycol was present in water at 10–20%, but decreased as the propylene glycol content (and viscosity) was further increased (Davis, 1978). Addition of increasing proportions of ethanol to water, reducing surface tension, resulted in a marked increase in total output from nebulisers, which comprised primarily alcohol-water vapour (Davis et al., 1978). Ethanol increases solution viscosity up to a maximum of 40% v/v after which viscosity decreases. The maximum in viscosity did not significantly alter the aerosol output. Addition of ethanol to water or water-propylene glycol mixtures resulted in a decrease in mean aerosol size (Davis et al., 1978), which probably reflected reduction of the droplets due to solvent evaporation during measurement with a cascade impactor. Newman et al., 1987 studied the properties of aerosols produced by the Bird, DeVilbiss and Upmist nebulisers. There was a tendency, though not significant, for smaller droplets to be produced when solutions of highest viscosity were nebulised. There was no clear correlation between droplet size and surface tension of the solution being nebulised, although the ranges of surface tensions and viscosities studied was not great.

McCallion et al., 1994 nebulised fluid systems of different surface tensions (15.9–72.9 dynes/cm) and viscosities (0.49–97.00 cP) from Cirrus, Pari LC and Sidestream Durable jet nebulisers. For all nebulisers the droplet size was inversely proportional to viscosity. Although the fluids of highest viscosity produced the smallest droplets, they required longer times to nebulise to dryness and nebulisers retained greater volumes of the fluids. With more viscous liquids there is reduced liquid flow through the feed tubes. The energy supplied (by the air-jets) remains constant, but since less fluid is presented the nozzles may operate more efficiently and generate aerosols of smaller mean size. Although fluids with lowest surface tension tended to produce aerosols with smallest mass median diameters, there was no clear correlation between surface tension and droplet size.

Changes in size distribution of the primary aerosol resulting from changes in the properties of the solution being atomised may not always be reflected in the size distribution of the emitted aerosol (Mercer, 1981). Within nebulisers > 99% of the primary aerosol mass is recycled back into the reservoir liquid, with < 1% (the smaller droplets) being emitted as the secondary aerosol, resulting from the size-selectivity of the nebuliser design and dimensions (Newman et al., 1987). Consequently, the relationship between aerosol output, droplet size and size distribution and the viscosity and surface tension of the fluid is a complex function of the design and orientation of baffle systems and walls of the nebuliser.

5. The effect of temperature on droplet size and output

The aerosol output from a jet nebuliser comprises drug solution and solvent vapour which saturates the outgoing air (Ferron et al., 1976). This causes solute concentration to increase with time (Ferron et al., 1976) and results in a rapid decrease in the temperature of the liquid being

nebulised by approximately 10–15°C (Clay et al., 1983; Taylor et al., 1992; Fig. 5).

These effects are more pronounced for dry air delivered from a cylinder than for partially humidified air from a compressor (Wood et al., 1986). The temperature of the fluid within the nebuliser is also determined by the ambient temperature and the initial temperature of the solution and may be manipulated by warming the nebuliser, pre-heating nebuliser fluids or by holding the nebuliser chamber in the hand during use (Stelliou et al., 1993). The cooling effect within the reservoir fluid will reduce drug solubility and result in increased surface tension and viscosity of the liquid. Precipitation is uncommon with bronchodilators, which have high aqueous solubility, but problems may arise with less soluble drugs such as mucolytics and antimicrobials (Taylor et al., 1992). In such instances the use of an ultrasonic nebuliser may be appropriate, since operation of such devices result in warming of solutions, eliminating the problems of drug solubility associated with operation of jet nebulisers (Taylor and Hoare, 1993).

Where drug solubility is not a consideration the changes in viscosity and surface tension occurring with time do not seem to be reflected in the droplet size of emitted aerosols (Newman et al., 1987), although an increase in ambient temperature by

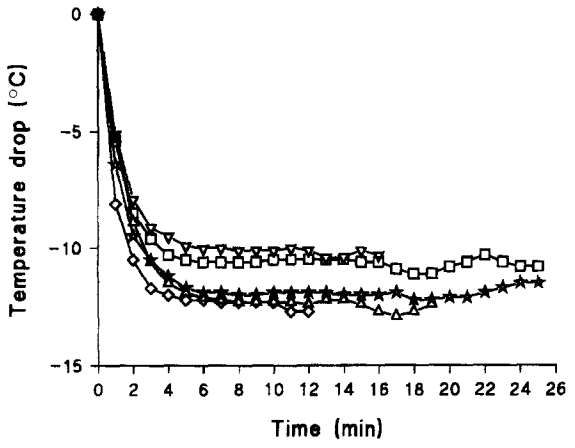

Fig. 5. Mean temperature decreases occuring in pentamidine isethionate (300 mg/5 ml) solutions during nebulisation in the Respirgard II nebuliser at 5 l/min (★), 6 l/min (□), 7 l/min (△), 8 l/min (▽) and 10 l/min (◇). (Reproduced with permission from Taylor et al., 1992).

5°C has been reported to significantly increase solution output (Kongerud et al., 1989).

The decrease in temperature occurring during use of jet nebulisers may be important clinically, in the airways response to inhaled solutions, since some asthma sufferers experience bronchoconstriction on inhalation of cold solutions (Lewis, 1983). This constriction is most marked at 5°C, but is abolished at 37°C.

6. Nebulisation time, fill volume and dead (residual) volume

Clinically, liquids may be nebulised for a specified period of time, or alternatively, liquids may be nebulised to 'dryness'. Different investigators have interpreted nebulisation to dryness differently. Kradjan and Lakshminarayan, 1985 have suggested three categories of nebulisation time:

(1) Sputtering Time - the point at which air is drawn up the feed tube and nebulisation becomes erratic. Agitation of nebuliser permits treatment to be continued;
(2) Clinical Time - the time at which therapy is ceased following sputtering;
(3) Total Time - the time at which production of aerosol ceases.

Since consistent quantification of sputtering and clinical times is difficult, Newman et al., 1986 defined nebulisation time as the time 30 s after the last visible release of aerosol. In all cases, the amount of drug delivered for a given formulation will depend on the device employed, operating conditions and ambient temperature.

The nebulisation time is likely to be an important determinant of patient compliance and within hospitals has implications for staff time. The time taken to nebulise a liquid to dryness may be decreased by increasing the gas flow rate or by decreasing the initial fill volume (Hess et al., 1989; (Table 1).

Regardless of nebulisation time, not all the fluid in the nebuliser can be atomised. Some liquid remains as the 'dead' or 'residual' volume, associated with the baffles, internal structures and walls of the nebuliser (Clay et al., 1983). When the aerosol output rate is plotted against the volume of fluid remaining in the nebuliser, there is an

Table 1
Mean times (min) to nebulise solutions of orciprenaline at various combinations of air flow rate and diluent volume

	Flow rate (6 l/min)			Flow rate (8 l/min)		
	2 ml	3 ml	4 ml	2 ml	3 ml	4 ml
Acorn	9	13	20	8	10	13
DeVilbiss	12	18	28	9	14	19
Fan Jet	15	19	25	13	17	20
Hudson	8	12	17	8	12	13
Raindrop	11	17	23	7	10	16
Seamless	10	17	21	4	7	11
WeeNeb	15	21	29	10	16	19
Whisper-Jet	7	12	18	10	14	19
Mean (± S.D.)	11 (3)	16 (3)	23 (5)	9 (2)	12 (3)	14 (5)

Adapted from Hess et al., 1989.

initial slight decrease in rate as the liquid temperature drops. Subsequently, output (and temperature) remain constant until the fluid level falls below the bottom of the feed tube. With the uptake of air bubbles, the output becomes initially intermittent, then falls to zero, leaving the 'dead' volume (usually 0.5–1 ml) in the nebuliser. Gentle periodic tapping of the nebuliser walls may help dislodge droplets adhering to the walls, allowing them to return to the reservoir for re-atomization (Steventon and Wilson, 1986). The proportion of drug retained as 'dead' volume is more marked for smaller fill volumes and may be decreased by increasing the flow rate (Hess et al., 1989; Table 2). Where the solubility of the drug is a major determinant of drug output from a nebuliser, it has been reported that a more efficient output of drug may be achieved with smaller rather than larger fill volumes (Taylor et al., 1992).

7. Nebulisers for novel drug delivery: peptides and liposomes

Since formulations for delivery by jet nebulisers can be prepared with relative ease, nebulisers are frequently the first delivery devices employed when delivering a new entity to the lung. Recent studies have investigated the applicability of nebulisers for the aerosolization of peptides and liposomes.

Jet nebulisers have been used successfully to atomize recombinant human deoxyribonuclease (Cipolla et al., 1994). The activity and structural integrity of the enzyme was maintained, when jet nebulisers were employed, although ultrasonic nebulisation caused denaturation of the protein, probably as a result of the elevated temperatures. However, studies with lactate dehydrogenase have suggested that during aerosolization in air-jet nebulisers there was an irreversible time-dependant loss of enzyme activity (Niven and Brain, 1994). The volume of fluid and rate of aspiration were reported to be major determinants of the stability of the enzyme to nebulisation. Niven and Brain, 1994 have suggested that by increasing the efficiency of nebulisation, such that the number of times a fluid is recycled in the nebuliser is reduced, the potentially damaging effects of nebulisation can be minimised.

Nebulisers are the only delivery devices which have so far been used for delivery of liposomes to the human lung (Farr et al., 1985; Taylor et al., 1989; Barker et al., 1994; Vidgren et al., 1995). Nebulisers have a number of advantages over MDIs and DPIs, since liposomes can be prepared by conventional techniques and following removal of non-vesicle associated material, usually require no further processing. However, jet nebulisers may damage liposomes containing entrapped hydrophilic materials (Niven and Schreier, 1990; Taylor et al., 1990) due to the shearing forces within the nebuliser. The size of the liposomes

Table 2
Mean percentage of orciprenaline solutions nebulised at various combinations of air flow rate and diluent volume

	Flow rate (6 l/min)			Flow rate (8 l/min)		
	2 ml	3 ml	4 ml	2 ml	3 ml	4ml
Acorn	72	80	85	77	82	86
DeVilbiss	57	64	67	64	72	81
Fan Jet	84	89	91	92	93	96
Hudson	74	78	83	72	81	85
Raindrop	66	77	85	68	75	81
Seamless	47	61	67	53	62	68
WeeNeb	74	73	85	72	78	82
Whisper-Jet	52	56	65	81	83	85
Mean (± S.D.)	66 (12)	72 (11)	79 (10)	72 (11)	78 (9)	83 (8)

Adapted from Hess et al., 1989.

(Taylor et al., 1990, Niven et al., 1991) and the air pressure used to generate the aerosols (Niven et al., 1992) are the major determinants of liposome stability to nebulisation.

The rise in reservoir temperature with ultrasonic nebulisers has been associated with the chemical breakdown of labile materials such as ^{99m}Tc-DTPA (Waldman et al., 1987) and the fusion of liposomes (Barber and Shek, 1989).

8. Conclusion

Many different models of nebuliser and compressors are commercially available. It has not been the purpose of this paper to describe or compare models (for such comparisons see Newman et al., 1986; Ho et al., 1988; Cipolla et al., 1994; Waldrep et al., 1994). Such devices cannot be considered equivalent. For instance, in a study of 18 different commercially available jet nebulisers, operated according to the manufacturers guidelines, aerosols were produced with MMADs ranging from 0.9 to 7.2 μm (Waldrep et al., 1994). Clearly, the regional deposition within the lung of aerosols generated from such devices will vary enormously. Variability may not only exist between different nebulisers but also between individual nebulisers of the same type (Alvine et al., 1992) whilst repeated use of a single nebuliser may cause variability due to baffle wear and non-uniformity of assembly (Massey et al., 1982). In addition to factors relating to the design of nebulisers, gas flow rate, fill volume and the physicochemical properties of the fluid must be considered, alongside patient-related factors, when considering both the size of the aerosols produced and drug output.

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