Development of an Orientation-independent Handheld Nebulizer

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ABSTRACT

This work aimed to develop and evaluate a miniaturized handheld vibrating mesh nebulizer (MHVMN) that functions equally well in any orientation. The MHVMN, which comprises a power supply unit, a vibrating mesh plate, and a liquid reservoir equipped with either a flat end orifice tube (FEOT) or a traditional wick for delivery, was primarily tested using deionized water and a 0.9% sodium chloride solution. Since our study focused on optimizing the dimensions of the FEOT, which utilizes capillary action to deliver the solution, we examined the effects of the operating parameters, viz., the gap between the reservoir wall and the FEOT ($L_{LR-FEOT}$), the diameter of the FEOT's orifice ($D_{orifice}$), the orientation of the nebulizer, and the size of the aperture, on the performance of the device. The output rate and the residual volume were determined gravimetrically, and both the concentration and the mass distribution of the aerosolized particles were measured with an aerosol size spectrometer (welas digital 3000) and a Micro-Orifice Uniform Deposit Impactor (MOUDI). The results revealed an optimal $L_{LR-FEOT}$ of 0.225 mm, which achieved similar output rates and residual volumes across various orientations. Additionally, a $D_{orifice}$ exceeding 0.8 mm was necessary to ensure continuous nebulization, thereby yielding a residual volume of less than 4%. Using the FEOT instead of a traditional wick also significantly decreased the residual volume—a major advantage in delivering costly drugs. The consistently high efficiency of the MHVMN regardless of orientation demonstrates its suitability for administering aerosolized medication, especially to patients lying in bed.

Keywords: Vibrating mesh nebulizer, Orientation-independent, Flat end orifice tube

1 INTRODUCTION

For several decades, nebulizers, which convert liquid drugs into tiny airborne particles, have been used for medication through inhalation (McCallion *et al.*, 1996; Dhand, 2002; Martin and Finlay, 2015; Mansour, 2018). Aerosol therapy through nebulizers is a well-established method for treatment of patients with pulmonary diseases, including, but not limited to, asthma (Zimo *et al.*, 1989; O'Driscoll *et al.*, 1992; Demoly *et al.*, 1998; Hess, 2008), chronic obstructive pulmonary disease (COPD) (O'Driscoll *et al.*, 1992; O'Driscoll, 1997; Alhaddad *et al.*, 2015) and cystic fibrosis (Bos *et al.*, 2016; Baravalle-Einaudi *et al.*, 2017) in both hospital and home settings. The role of nebulizers in treating acute lung injury (Tuinman *et al.*, 2012), ventilation-associated pneumonia (Rouby *et al.*, 2012), dyspnea (Boyden *et al.*, 2015), as well as for systemic administration of macromolecules (Siekmeier and Scheuch, 2008) has also been reviewed. As a consequence of an aging population and increased occurrence of respiratory diseases (Maio *et al.*, 2006; Burney *et al.*, 2015; Khakban *et al.*, 2017), the market for nebulizers is expected to grow (Mansour, 2018; Pritchard *et al.*, 2018). There exist many types of nebulizer, including jet, ultrasonic, and vibrating mesh nebulizers, with many commercially available models (Martin and Finlay, 2015; Tashkin, 2016; Mansour, 2018). The jet nebulizer was developed according to the Bernoulli principle to

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provide suction by forcing drug solution through a constriction and to reduce the liquid into a fine spray. Early jet nebulizers were clumsy, noisy, and inefficient due to high amounts of drug left in nebulizer reservoir (referred to as *residual*) (Rau, 2002; Fischer *et al.*, 2009). Although new jet nebulizers either utilize baffles that remove large droplets or have breath-enhanced aerosol production that leads to less drug loss during expiration to improve drug delivery efficiencies, the generated particle size distributions can vary significantly due to the changes of temperature and concentration of the nebulizing solution over the nebulization time (Phipps *et al.*, 1990). Ultrasonic nebulizers incorporate a piezoelectric crystal vibrating at high frequencies to generate aerosol particles (Ari, 2014). Early ultrasonic nebulizers have many limitations compared with jet nebulizers, such as large residual, degradation of heat-sensitive materials (Taylor and McCallion, 1997; Watts *et al.*, 2008), and not suitable for atomizing suspensions and viscous solutions (Taylor and McCallion, 1997; Elhissi and Taylor, 2005).

Vibrating mesh technology is a significant innovation for drug delivery. A vibrating mesh nebulizer (VMN) is composed of a piezoelectric mesh disk, a piezoelectric mesh driver, a circuit board with batteries, and a liquid reservoir unit. The piezoelectric material vibrates at a very high frequency, pushing the liquid drug through the mesh to form aerosol particles (Dhand, 2002; Vecellio, 2006). Compared with other types of nebulizers, VMNs offer many advantages, such as ease of use, high portability, low power consumption, low noise during operation and high efficiency with minimal residual (Waldrep *et al.*, 2007; Waldrep and Dhand, 2008; Pitance *et al.*, 2010). The details of new types of VMN have recently been reviewed (Pritchard *et al.*, 2018).

Most VMNs are designed to work with a liquid drug reservoir aside, normally placed in the vertical position. For some current commercially available models, the position of nebulizer is an important factor affecting run time and variability in particle distribution (Skaria and Smaldone, 2010). Although it has been shown that the dose delivery of some VMNs were not significantly affected by orientation angle (Hardaker and Hatley, 2010), they are not allowed to tilt over 45° off vertical. In fact, medical nebulizers currently available are sensitive to orientation. When a nebulizer is operated in improper orientation, drug aerosols may be prevented from being generated as the solution inside the nebulizer cannot be effectively transported; it might also lead to spillage of the solution. Therefore, it will be ideal if solution transport mechanisms, such as capillary force, can be employed to carry the liquid drug, thus reducing or eliminating the effect of nebulizer orientation.

Capillarity described below is the phenomenon of a liquid rising or falling inside a narrow tube without external force. It is the result of adhesion and cohesion between liquid molecules and the capillary material. The relative strength of adhesion and cohesion affect the contact angle, θ , which is the angle between the free surface of a liquid and the capillary edge. The liquid surface will be raised if the angle is less than 90°. The height of liquid rise, H , has been mathematically derived (Batchelor, 1967), given as:

$$H = \frac{2\gamma \cos \theta}{\rho g a} \quad (1)$$

where γ is the surface tension (J m^{-2}); θ is the contact angle between the liquid surface and wall (°); ρ is the density of the liquid (kg m^{-3}); g is the acceleration (m s^{-2}); and a is the capillary radius (m).

To make the devices more user-friendly, especially for patients lying on bed, it will be ideal to remove the nuisance restriction of nebulizer orientation. Therefore, the main goal of this work is to develop and improve the solution storage and delivery unit and make the vibrating mesh nebulizer more compact, portable, quiet, and operable in any orientation.

2 METHODS

The MHVMN consists of two major parts: the power supply-frequency generator unit and the vibrating-mesh-liquid-delivery unit, as shown in Fig. 1. The MHVMN is powered by a rechargeable lithium-ion battery (DC of 3.7 V). The power consumption of this device is about 0.93 watt. The external dimensions of the MHVMN are $6 \times 4 \times 4 \text{ cm}^3$, with weight of 60 g. The stainless vibrating mesh plate is 40 μm thick and 16 mm in diameter, and is mounted on top of the solution reservoir

Fig. 1. Prototype of MHVMN: (A) assembly view of vibrating mesh and liquid delivery unit, and (B) three passive liquid delivery materials.

by using a fixing cap (Fig. 1(A)). The technical specifications of the mesh plates provided by the manufacturer are presented in Table 1. There are 2375 apertures on each mesh plate and the distance between neighboring apertures (D_{ap-ap}) is 160 μm . The aperture is tapered. The narrower end of the two aperture sizes used in this work are 6.5 and 9.5 μm . The volume of the home-made solution reservoir is about 3.3 mL (Ø of $9.3 \times 35 \text{ mm}^2$). A unique flat end orifice tube (FEOT) or traditional polyester (PE) porous materials (Fig. 1(B)) can be inserted into the reservoir to deliver solution by the force of capillary action. In present study, FEOTs with different outer diameters (OD_{FEOT}) and orifice sizes ($D_{orifice}$) are used to investigate in more detail how liquid output rates and residual have changed. Fig. 2 gives a schematic representation of the FEOT-based MHVMN. The gap size between the liquid reservoir and a FEOT, $L_{LR-FEOT}$ (mm), is given by:

$$L_{LR-FEOT} = \frac{(9.3 - OD_{FEOT})}{2} \quad (2)$$

The major operating parameters and ranges are listed in Table 2. The $L_{LR-FEOT}$ and $D_{orifice}$ values range from 0.15–0.35 mm and 0.5–2.0 mm, respectively. The effect of nebulizer orientations (upright (0°), horizontal (90°), and inverted (180°)) on output rate and residual is of particular interest. The diameter of orifice on FEOTs is important for solution delivery, especially when the MHVMN is operated in an inverted position. The packing density of the PE wicks used in this study is about 20%. At a rough estimate, the contact areas formed between the mesh-wick structure for strip and rod wicks are 18 and 35 mm^2 , respectively. Besides the passive capillary liquid transport method, a syringe pump (KDS 200; KD Scientific Inc., Holliston, MA, USA) is used to deliver liquid actively to explore the maximum liquid consumption rate of the MHVMN and the effect of liquid feeding rate on the size distribution of generated aerosol particles.

In order to characterize the particle size distributions, the MHVMN is operated in an acrylic chamber. The aerosol flow tube system is shown schematically in Fig 3. The flows in the experiments are generated from compressed air passed through particle filters and a dryer prior to use. The total air flow through the chambers is regulated by a mass flow controller (MFC; Teledyne Hastings Instruments, Hampton, VA, USA). A flow divider valve is used downstream of the MFC to split the total flow into two parts: a dispersion flow and a dilution flow. The generated droplets are first mixed with a dispersion flow of 1.0 L min^{-1} and then passed through a 10 mCi ^{241}Am neutralizer positioned immediately downstream of the MHVMN. The charge-neutralized droplets are then mixed with 159 L min^{-1} of dilution air to evaporate the solvent and to obtain a stable particle size distribution. The number concentration and size distribution of the aerosol

Table 1. Technical information of MHVMN.

Handheld nebulizer	
Battery voltage (V)	3.7
Power consumption (W)	0.93
External dimensions (cm)	6 (L) × 4 (W) × 4 (H)
Weight (g)	60
Vibrating mesh plate	
Aperture diameter (mm)	6.5, 9.5
Distance between neighboring apertures (D_{ap-ap} ; mm)	160
Number of apertures	2375

Fig. 2. Schematic diagram of FEOT-based MHVMN. Right plot is the blown-up figure of the mesh plate, showing the orifice on top of the inner tube.

Table 2. Operating parameters and ranges.

Nebulizer orientation	
Upright (0°)	
Horizontal (90°)	
Inverted (180°)	
Liquid delivery method	
<i>Passive</i>	
Outer diameter of FEOTs (OD_{FEOT} ; mm)	8.6–9.0
Gap between coaxial tubes ($L_{LR-FEOT}$; mm)	0.15–0.35
Diameter of orifices on FEOT ($D_{orifice}$; mm)	0.5, 0.8, 1.0, 1.4, 2.0
Shape of PE wicks	Strip, rod
<i>Active</i>	
Syringe pump (mL min^{-1})	0.1–1.0

particles are monitored using an aerosol size spectrometer (welas digital 3000; Palas GmbH, Karlsruhe, Germany), covering particle size ranging from 0.3 to 40 μm and aerosol number concentration up to $10^5 \text{ count cm}^{-3}$. Polystyrene latex spheres (Duke Scientific Corporation, Palo Alto, CA, USA) are used to check the size accuracy of the welas digital 3000. Moreover, a Micro-Orifice Uniform Deposit Impactor (MOUDI Model 110; MSP Corp., St. Paul, MN, USA), is employed

Fig. 3. Schematic diagram of experimental system set-up.

to measure aerosol mass concentrations and size distributions, covering particle size ranging from 0.056 to 18 μm . Silicone-grease-coated aluminum foils (47 mm) are used as collection media and are weighed on an analytical balance (92SM-202A; Precisa, Dietikon, Switzerland) before and after each sampling run to determine the mass distribution. Then, the mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD), defined by the following equations, of aerosol are calculated on a log-probability plot with the cut-off diameter as the abscissa and the cumulative percent less than the cut-off size as the ordinate.

$$\text{MMAD} = 50^{\text{th}} \text{ percentile size } (d_{50\%}) \quad (3)$$

$$\text{GSD} = \frac{d_{84\%}}{d_{50\%}} = \frac{d_{50\%}}{d_{16\%}} = \left(\frac{d_{84\%}}{d_{16\%}} \right)^{1/2} \quad (4)$$

Other important characteristics of nebulizer performance include output rate and residual. In this study, these characteristics of the MHVMN are determined by gravimetric methods. The MHVMN weight is measured before and after each nebulization experiment, and the nebulization time is also recorded. The output rate and residual (percentage of the retained nebulizer charge at the cessation of nebulization) are calculated according to the equations below. This process is repeated at least three times for each test run.

$$\text{Output rate} = \frac{\text{Postweight} - \text{Prewrite}}{\text{duration of nebulization} \times \text{solution density}} \quad (5)$$

$$\text{Residual} = \frac{\text{Postweight} - 60}{\text{Prewrite} - 60} \times 100\% \quad (6)$$

The MHVMN is mainly evaluated with deionized (DI) water and 0.9% sodium chloride (NaCl) solution. The 0.9% NaCl solution has a surface tension of 72.5 mN m^{-1} , a density of 1.005 g cm^{-3} , and a viscosity of 1.019 $\text{mPa}\cdot\text{s}$ (Masoodi and Pillai, 2012).

3 RESULTS AND DISCUSSION

3.1 Effect of $L_{\text{LR-FEOT}}$ on FEOT-based MHVMN Performance

The gap between two coaxial tubes is a critical factor influencing the output rate of the

MHVMN, as shown in Fig. 4, with the D_{orifice} of 1 mm, and DI water as the test agent. The output rate of the upright MHVMN is the most typical case. As shown in Fig. 4, the output rate increases with increasing $L_{\text{LR-FEOT}}$ up to 0.225 mm, and then decreases as the $L_{\text{LR-FEOT}}$ kept increasing, indicating that the gravity gradually dominate the flow process when the $L_{\text{LR-FEOT}}$ increase. The effect of gravity on liquid delivery in the MHVMN is more obvious when the MHVMN is in inverted position. The output rate increases with increasing $L_{\text{LR-FEOT}}$, apparently due to more weight and less drag on the liquid as the $L_{\text{LR-FEOT}}$ widens. As expected, the output rate of the horizontal case is almost unaffected by $L_{\text{LR-FEOT}}$.

The residual is also an important performance index, especially for expensive medicines. The lower the residual, the better the nebulizer performs. The residual of this MHVMN is less than 10% for all positions, as shown in Fig. 5, with the same D_{orifice} (1 mm), and DI water as the test agent. The residuals of both upright and inverted positions decrease slightly with increasing $L_{\text{LR-FEOT}}$. This is because the inner tube tended to tilt when the gap is too wide, as observed in the laboratory, and thus the capillary transport capability dropped. When the MHVMN is operated in horizontal position, the gap between the two coaxial tubes tend to become non-uniform because the inner tube would fall and make contact with the inner wall of the outer tube, and the orifice on top of

Fig. 4. Effect of $L_{\text{LR-FEOT}}$ on output rate of FEOT-based MHVMN in different orientations.

Fig. 5. Effect of $L_{\text{LR-FEOT}}$ on residual of FEOT-based MHVMN in different orientations.

the inner tube is not on the center of the vibrating mesh. Therefore, the residual is slightly higher than the others. The residual of the inverted MHVMN is the lowest due to the influence of gravity. In general, the upright MHVMN with $L_{LR-FEOT}$ of 0.225 mm has the highest output rate of 0.24 mL min^{-1} and a residual of 3.5%. When this design is placed inverted, the output rate is 0.27 mL min^{-1} , with a residual of 2.3%.

3.2 Effect of D_{orifice} on FEOT-based MHVMN Performance

The D_{orifice} has significant influence on the performance in all MHVMN positions. The effect of orifice size on MHVMN output rate and residual is shown in Figs. 6 and 7, respectively. The $L_{LR-FEOT}$ of 0.225 mm is chosen for the highest output rate shown in Fig. 4. For the upright case, the output rate is only 0.1 mL min^{-1} when the smallest orifice, 0.5 mm, is used, and the residual is as high as 90%, because the siphon function is frequently stopped by the solution film. The residual decreases sharply when D_{orifice} increases from 0.5 to 0.8 mm, indicating that the chance of film formation to cover the orifice also decreases abruptly. The output rate reaches the maximum when D_{orifice} is 1.0 mm, followed by gradual decrease in output rate with increasing D_{orifice} . This is because of less contact areas formed between the mesh-orifice structure for upright MHVMN with larger D_{orifice} . For the inverted MHVMN, the residual is similar to that of the upright

Fig. 6. Effect of D_{orifice} on output rate of FEOT-based MHVMN in different positions.

Fig. 7. Effect of D_{orifice} on residual of FEOT-based MHVMN in different positions.

case. Yet, the output rate increases linearly with increasing D_{orifice} . The output rate for a 2.0 mm orifice is 0.72 mL min^{-1} , indicating dominant influence of gravity.

3.3 Performance Comparison of FEOT-based and Wick-based MHVMN

Without considering the issues of cleaning and maintenance, it has been shown in a previous study (Kuo *et al.*, 2019) that porous materials can be used for solution delivery in a VMN. Therefore, two types of PE wicks, strip and rod, are used in this work to deliver the solution to the vibrating mesh plate for further atomization. The PE strip and PE rod have the same packing density (20%), but different contact areas formed between the mesh-wick structure. As shown in Fig. 8, MHVMN with PE rod has higher output rate and higher residual than the one with PE strip due to larger contact area and larger wick volume, respectively. Although the output rates of the two PE wicks used in this work are comparable to that of FEOTs, the FEOT-based MHVMN is superior to the wick-based one for much lower residual. The effect of wick properties on output rate and residual is not within the scope of the present study but merits further exploration.

3.4 Effect of Solution on the Performance of FEOT-based MHVMN

Aerosol therapy may be carried out using an undiluted drug solution or it may require dilution beforehand. Isotonic sodium chloride (0.9% NaCl) solution is widely used for dilution purposes. Thus, two types of liquid, DI water and 0.9% NaCl solution, are used in this study to examine whether different solutions would have different output rates and residual. The tests are conducted using MHVMNs with $L_{\text{LR-FEOT}}$ of 0.225 and 0.350 mm, respectively. Fig. 9 shows negligible differences in output rate, probably because both solutions have about the same surface tension.

3.5 Effect of Liquid Feeding Rate on the Performance of Vibrating Mesh

The maximum output of this vibrating mesh is determined using a syringe pump, as shown in Fig. 10. The output concentration increases linearly with increasing 0.9% NaCl solution feeding rate, and reaches the maximum when the feeding rate is 0.8 mL min^{-1} . The maximum number

Fig. 8. Performance comparison of FEOT-based and wick-based MHVMNs.

Fig. 9. Effect of solution on performance of FEOT-based MHVMN with different $L_{LR-FEOT}$.

Fig. 10. Output aerosol concentration as function of solution feeding rate.

concentration is 19,500 count cm⁻³ in the mixing chamber. Aerosol generation terminated when feeding rate exceeds 0.8 mL min⁻¹, because the mesh plate is overloaded to change the resonance frequency. Fig. 11 shows the number concentrations and size distributions of aerosol particles, with 0.9% NaCl solution feeding rates varying from 0.1 to 0.8 mL min⁻¹. As can be seen, the concentration increases linearly with feeding rate while the size distribution remained unchanged, with count median diameter (CMD) of 0.65 μ m and GSD of 2.3.

3.6 Effect of Orientation and Aperture Size on the Performance of FEOT-based MHVMN

Since the aerosol size spectrometer might have detection efficiency problem for particles too large or too small, mass concentration and size distribution of the generated droplets after being dried are also validated using the MOUDI. Fig. 12 shows the aerosol mass concentration as function of aerodynamic diameter for the FEOT-based MHVMN with the best reservoir design ($L_{LR-FEOT}$ of 0.225 mm and $D_{orifice}$ of 1.0 mm) operated at different orientations. With 0.9% NaCl solution and aperture size of 9.5 μ m, the generated particle size distributions under three

positions shows the same MMAD of 4.41–4.55 μm and GSD of 2.39–2.93. The aerosol output is expected to show a log-normal distribution, if the MOUDI is equipped to further separate aerosols larger than 18 μm . The effect of aperture size on size distribution of nebulized aerosols is shown in Fig. 13. When smaller aperture size of 6.5 μm is used instead of 9.5 μm , the MMAD shrinks from 4.5 μm to 3.3 μm . Therefore, the particle size distribution of MHVMN could be tailored to suit specific requirements by altering the aperture size of the mesh plate.

Fig. 11. Effect of feeding rate on particle size distribution.

Fig. 12. Aerosol mass concentration as function of aerodynamic diameter for FEOT-based MHVMN with the best reservoir design operated at different orientations.

Fig. 13. Effect of aperture size on particle size distribution of FEOT-based MHVMN.

4 CONCLUSIONS

In this study, we developed and fabricated an AFEOT-based MHVMN that performs equally well in any orientation. Furthermore, we investigated the effects of the operating parameters, namely, $L_{LR-FEOT}$, $D_{orifice}$, the nebulizer's orientation, and the aperture's size, on the efficacy of this device.

We found that not only $L_{LR-FEOT}$ and $D_{orifice}$ but also the orientation played potential roles in the output rate and residual volume of the MHVMN. Although the output rate remained unaffected by $L_{LR-FEOT}$ in the horizontal position, it increased with $L_{LR-FEOT}$ in the inverted position owing to the dominant effect of gravity. An $L_{LR-FEOT}$ of 0.225 mm, which achieved similar output rates and residual volumes across various orientations, appeared to be optimal. Furthermore, continuous nebulization and thus a low residual volume was guaranteed only when $D_{orifice}$ exceeded 0.8 mm, with a diameter of 1.0 mm achieving the maximum output rate and the minimum residual volume in the upright position. The residual volume was also reduced by employing an FEOT instead of a traditional wick.

Overall, when the FEOT-based MHVMN was configured with the optimal parameters (an $L_{LR-FEOT}$ of 0.225 mm and a $D_{orifice}$ of 1.0 mm), the generated aerosolized particles exhibited a consistent size distribution regardless of the orientation of the nebulizer. Therefore, this device is ideal for administering drugs in aqueous and normal saline solutions, particularly to patients lying in bed.

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