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MEMS-Based Silicon Ultrasonic Twin-Nozzle Nebulizer for Inhalation Drug Delivery*

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Abstract— A versatile silicon-based ultrasonic nebulizer that utilizes a twin-nozzle of multiple Fourier horns at 1—2 MHz drive frequencies has been realized to perform simultaneous aerosolization of cobinamide and magnesium thiosulfate drug solutions. The drive frequency of the individual nozzle for a desirable aerosol diameter was individually designed. Using the 2.0 MHz 4-Fourier horn twin-nozzle aerosols of the two drug solutions with mass median diameter (MMD) of $3.0\pm0.1\mu m$ and geometrical standard deviation (GSD) of 1.18 ± 0.02 and total flow rate up to $400\mu L/min$ were produced.

Keywords— *MEMS, Multiple Fourier-horn Nozzle, Twin-Nozzle Ultrasonic Nebulizer, Inhalation Drug Delivery, Medicinal Aerosol Mixing*

I. INTRODUCTION

The innovation and potential applications of megahertz (MHz) MEMS-based multiple-Fourier horn ultrasonic nozzles that utilize temporal instability of Faraday waves for formation and ejection of monodisperse micro droplets were highlighted in a new journal most recently [1]. In fact, the resulting ultrasonic nebulizer module using a single nozzle was used successfully to aerosolize a number of common pulmonary drugs [1, 2]. Controllability of particle (aerosol) size range (2 to 6µm) and much narrower size distribution achievable by the new device will improve targeting of treatment within the respiratory tract and improve delivery efficiency. For example, a recent in-vitro experiment with Technetium (T_c)-tagged saline solution using the new nebulizer module has demonstrated potential of higher delivery efficiency than typical commercial nebulizers [3]. Therefore, it may constitute a desirable device for inhalation delivery of expensive medicines such as gamma interferon [4]. Short treatment time is a critical requirement in situations such as massive cyanide poisoning [5]. Clearly, the treatment time can be shortened by increased aerosol output rate of an array of such nozzles. Furthermore, nozzle arrays with individual nozzles operating at identical or different drive frequency will provide the unique capability for formation and subsequent mixing of medicinal aerosols of the same or different medicines at identical or different aerosol sizes. Note that such strategy is essential in order to avoid instability of mixed drug solutions prior to aerosolization. Here we report the realization of a pocket-size 2 MHz twin-nozzle nebulizer for simultaneous nebulization of cobinamide and magnesium thiosulfate drug solutions.
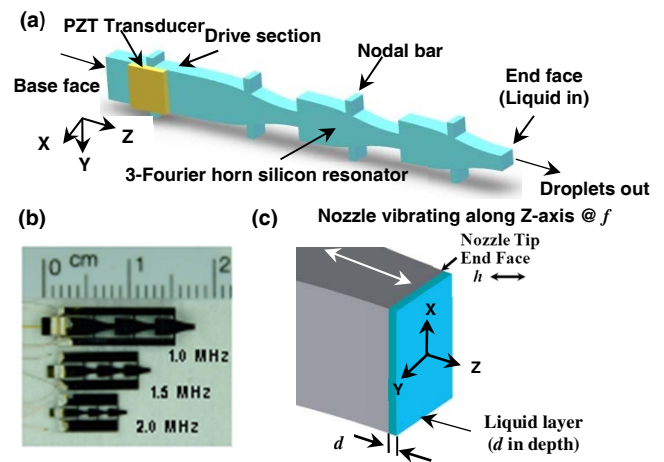

Fig. 1(a) 3-D architecture of the MHz multiple-Fourier horn ultrasonic nozzle; (b) Photograph of the 1.0, 1.5, and 2.0 MHz nozzles; (c) Geometry of nozzle end face vibrating at nozzle drive frequency *f* with displacement *h* and liquid layer *d* in depth.

II. TWIN-NOZZLE ULTRASONIC NEBULIZER

A. Architecture of Element Nozzle and Working Principle

Each basic (element) nozzle consists of a drive section and a resonator section (Fig. 1a). A lead zirconate titanate (PZT) transducer is bonded on the drive section to excite mechanical vibrations along the nozzle axis. The resonator section is made of multiple (3 in the example) Fourier horns in cascade [1]. The nozzle is designed to vibrate in a single longitudinal mode at the resonance frequency of the multiple Fourier horns. The resonance effect greatly enhances the vibration displacement (*h*) of the nozzle end face (by a factor of approximately 8 for three Fourier horns) and, hence, readily facilitates excitation and subsequent temporal instability of Faraday waves on the liquid layer resting on the nozzle end face. Droplets are formed and ejected from the nozzle end face when its longitudinal vibration displacement exceeds the onset threshold [6]. The

liquid to be atomized is externally transported to the nozzle end face using a fused silica tube. Importantly, the single vibration mode at the single MHz resonance frequency ensures single-mode capillary wave atomization mechanism, namely, temporal instability of Faraday waves, and production of micron-size monodisperse droplets at very low electrical drive power [1]. The diameter (D_p) of the resulting droplets is equal to four tenth of the wavelength ( ) of the Faraday waves excited as follows [6]:

$$D_p = 2(2/\pi^2)^{1/3}(\sigma/\rho)^{1/3} f^{-2/3} = 0.40\,\lambda \;, \tag{1}$$

where σ, ρ, and f designate surface tension, liquid density, and the nozzle drive frequency (resonance frequency), respectively.
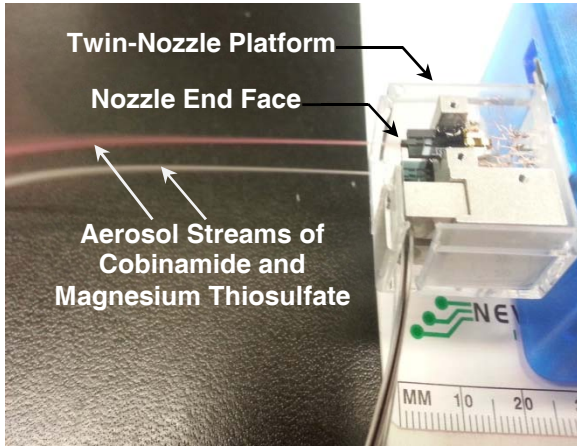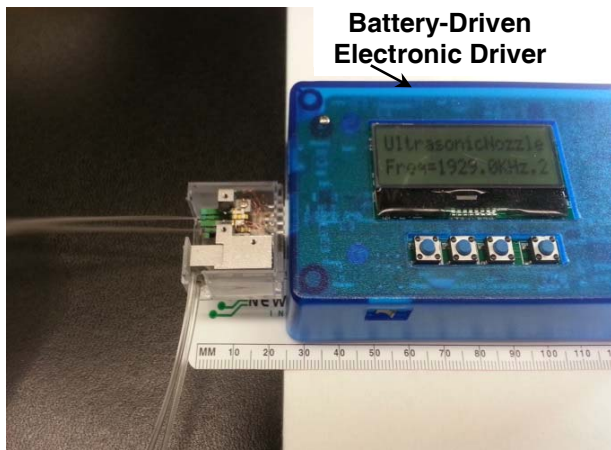

Fig. 2 Twin-nozzle platform

Fig. 3 Pocket-size MEMS-based ultrasonic twin-nozzle nebulizer

B. Platform of Twin-Nozzle and Pocket-Size Nebulizer

Fig. 2 shows the platform for installation of the twin-nozzle array with identical or separate design specifications for the aerosol size (or drive frequency). The twin nozzles were driven by a pair of independent electronic drivers with controllable frequency and power together with separate fused silica tubes for transport of drug solutions to the nozzle end faces. Fig. 3 shows the resulting battery-run pocket-size ultrasonic nebulizer.

III. Simultaneous Nebulization of Identical or Different Medicines

Separate aerosolization of 100mM cobinamide solution [7] and 1.0 M magnesium thiosulfate solution as well as simultaneous aerosolization of the two drug solutions at varying flow rates were carried out using the nebulizer shown in Figs. 2 and 3 with 2 MHz 4-Fourier horn twin-nozzle and established equipment and characterization procedures [8]. Fig. 2 shows the two streams of aerosols produced simultaneously at respective flow rates of 200μL/min and 250μL/min.
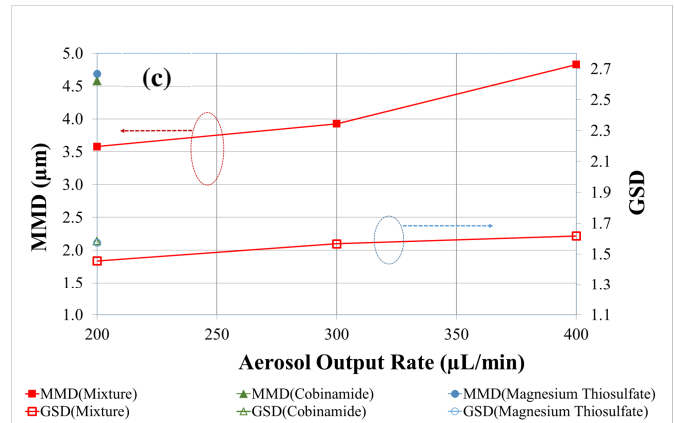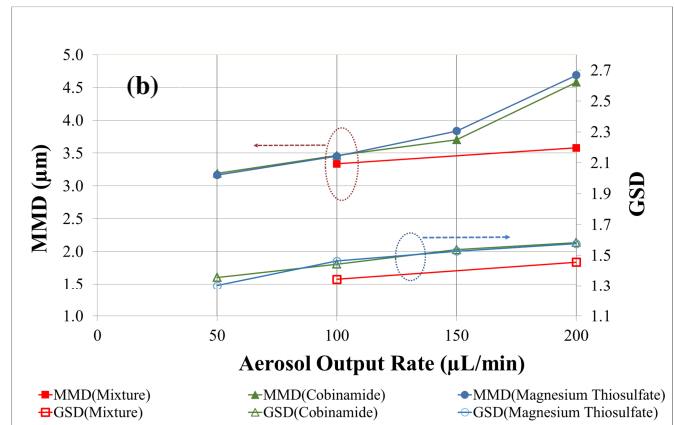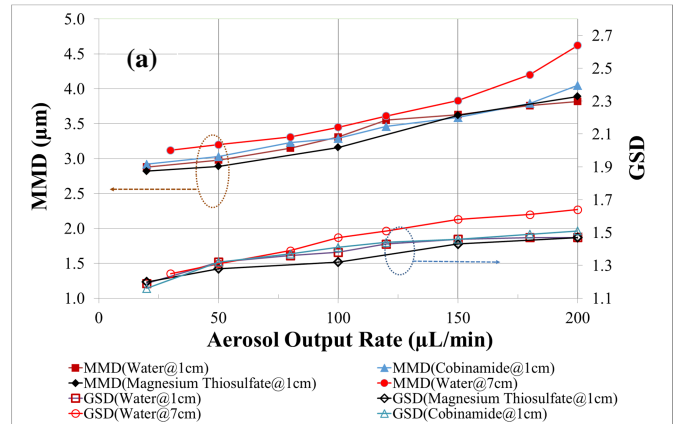

Fig. 4 Measured aerosol sizes in mass median diameter (MMD)/geometrical standard deviation (GSD) versus output rate for 100mM cobinamide solution and 1 M magnesium thiosulfate solution using the 2 MHz 4-Fourier horn ultrasonic nebulizers with (a) single-nozzle, and (b) and (c) twin-nozzle. Note that all data in (b) and (c) were obtained at a distance of 7 cm from the nozzle end face.

The sizes and size distributions of the aerosols produced were measured using Malvern/Spraytec system (Model #STP 5311) which is a well-established non-invasive particle sizing instrument based on laser light diffraction. The streams of aerosol traveled from the nozzle end faces (as depicted in Figs. 2 and 3) and passed the laser beam of the instrument. Fig. 4(a) shows that the sizes of aerosols produced using the 2 MHz single-nozzle nebulizer and measured at 1 cm from the nozzle end face are within the experimental errors in sizes for all three liquids including water (reference liquid), cobinamide solution, and magnesium thiosulfate solution. Specifically, the measured mass median diameters (MMDs) of the aerosols of water and the two aqueous drug solutions are in good agreement with the predicted value of 3.1µm for water based on Eq. (1). The MMDs are seen in Fig. 4(a) to increase from 2.8±0.1 to 3.8±0.2µm as the aerosol output rate (liquid flow rate) increases from 20 to 200µL/min. The corresponding geometrical standard deviation (GSD) increases from 1.18±0.02 to 1.49±0.02. Fig. 4(a) also shows that the sizes of the water (reference liquid) aerosols measured at a distance of 7 cm are larger than those measured at a distance of 1 cm. The increase in aerosol sizes with increased output rate may be caused by aerosol coalescence in the dense sprays.

A comparison of Fig. 4(b) with Fig. 4(a) shows that like the water aerosols, the aqueous medicinal aerosols measured downstream at 7 cm from the nozzle end faces of the 2 MHz twin-nozzle nebulizer are larger than those measured at 1 cm from where they were produced (liquid layer on the nozzle end face). The two streams of aerosols ensuing from the two nozzle end faces overlapped (mixed) at 7cm downstream. Note that the aerosol MMD and GSD were measured at both 1 and 7 cm from the nozzle end faces.

Furthermore, Figs. 4(b) and 4(c) show that when the two streams of aerosols overlapped at 7 cm from the nozzle end face, the total aerosol output rate was doubled to about 400µL/min, and the MMD and GSD of the mixed aerosols were slightly larger than those of the individual aerosol streams at half the total output rate.

IV. Concluding Remarks e

A pocket-size ultrasonic nebulizer with 2 MHz twin-nozzle of silicon multiple-Fourier horn has been realized to demonstrate the capability of doubling the aerosol output of same drug solution and simultaneous aerosolization of different drug solutions. Specifically, for 100mM cobinamide and 1 M magnesium thiosulfate drug solutions, simultaneous and continuous aerosolization at respective flow rates of 200µL/min and 250µL/min for 7 min. delivered 430mg thiosulfate and 152mg cobinamide that would be nearly sufficient antidote dosages for effective detoxification of cyanide poisoning.

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