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Pocket-Sized Ultrasonic Nebulizer For Inhalation Drug Delivery

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***Abstract*—Silicon-based MHz ultrasonic multiple Fourier horns in resonance are capable of producing high-throughput micrometer-sized droplets at low drive power. The centimeter-sized nozzles together with low power requirement enabled most recent realization of the first pocket-sized ultrasonic nebulizer (8.6 x 5.6 x 1.5 cm^3) that contains nozzle, IC electronic driver, cell-phone battery, micro pump, drug reservoir, and liquid feed. A variety of common drugs for asthma, chronic obstructive pulmonary disease (COPD), diabetics, cyanide poisoning, pulmonary fibrosis, etc. such as albuterol, Humulin U-100, cobinamide, interferon-γ, and budesonide suspension have been nebulized with desirable aerosol size and throughput.**

Keywords— MEMS; Fourier-horn Nozzle; Pocket-Sized Ultrasonic Nebulizer; Inhalation Drug Delivery; Aerosol

I. INTRODUCTION

Droplet generation has continued to be an area of broad interest with many applications [1, 2] among which is inhalation (pulmonary) drug delivery. Inhalation is a vitally important route for non-invasive drug delivery for both systemic and local applications [3]. Control of aerosol (particles or droplets in air) size to the optimum range (2 to 5μm) and throughput plays a critical role in the efficient and effective delivery of inhaled medications to the lung. Current commercial devices are metered dose inhalers (MDI), dry powder inhalers (DPI), and wet nebulizers. All these devices suffer from broad particle size (polydisperse) distributions (with large geometrical standard deviation GSD >1.5) and relatively low throughput (0.16 to 0.42 ml/min), making it difficult to deliver often expensive drug of desirable particle sizes and sufficient amount to targeted sites precisely and rapidly. The silicon-based MHz multiple-Fourier horn ultrasonic nozzle we reported recently [1, 2] has demonstrated capability of producing high-throughput micrometer-sized monodisperse droplets at low drive power and, thus, fulfilling the unmet needs, e.g., detoxification of cyanide poisoning [4, 5]. Here we report realization of the first pocket-sized ultrasonic nebulizer for inhalation drug delivery using such nozzles.

II. NOZZLE ARCHITECTURE AND WORKING PRINCIPLE

Each basic nozzle consists of a drive section and a resonator section (Fig. 1a). A lead zirconate titanate (PZT) piezoelectric 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 [6]. The nozzle is designed to vibrate in a single longitudinal mode (along the nozzle axis) at the resonance frequency of the three Fourier horns. The liquid to be atomized is externally transported to the nozzle end face using a fused silica tube. The resonance effect greatly enhances the vibration displacement of the nozzle endface (by a factor of 8) and, hence, readily facilitates generation and subsequent temporal instability of Faraday waves on the liquid layer resting on the nozzle end face. Droplets are ejected from the liquid surface when the vibration displacement of the nozzle end face exceeds the onset threshold. Importantly, the single vibration mode at the single resonance frequency ensures single-mode Faraday wave excitation and amplification and, thus, production of monodisperse droplets at very low electrical drive power [2].

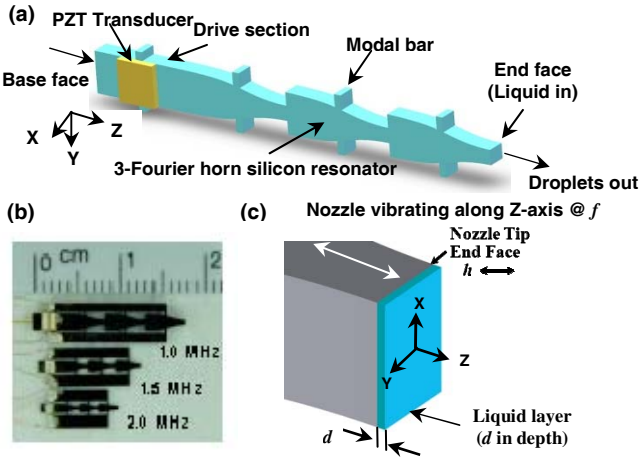

Fig. 1(a) 3-D architecture of the MHz multiple-Fourier horn ultrasonic nozzle; (b) Photograph of the 1.0 MHz and 1.5 MHz nozzles; (c) Geometry of nozzle endface and liquid layer *d* in depth.

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This is in stark contrast to all other ultrasonic devices that simultaneously involve various atomization mechanisms such as cavitation, impinging, and jetting in addition to capillary wave mechanism [7-9]. These various atomization mechanisms require much higher electrical drive power (by 2 to 3 orders of magnitude) and produce broad droplet size distribution. The significance of such low drive power (due to resonance) for the proposed device should be emphasized because it will eliminate the temperature rises that may damage the medications to be aerosolized.

III. Nozzle Performance and Comparison to Commercial Devices

Nebulization (atomization) of water or medicine is carried out by applying a voltage at MHz resonance frequency across the PZT transducer and the liquid to be nebulized transported upon the nozzle end face via a fused silica tube. Droplets are ejected from the liquid free surface when the vibration displacement of the nozzle end face exceeds the onset threshold. Fig. 2 shows the measured size distributions of the droplets produced by atomization with the 1.0, 1.5 and 2.0 MHz nozzles (plots (a), (b), (c), and (d)). The corresponding geometric standard deviations (GSD) of the droplets are shown to be as small as 1.18, 1.16, 1.18, and 1.18, respectively. Note that GSD of 1.0 corresponds to single size and that an aerosol with GSD up to 1.22 is commonly accepted as monodisperse in aerosol medicine [10]. For comparison, the size distributions of polydisperse droplets with GSDs of 1.85 (Omron published data sheet) and 1.51 [11] generated by two most advanced commercial nebulizers, Omron NE-U22V and Pari e-Flow, are also shown in Fig. 2, plots (e) and (f), respectively. In Fig. 2, MMD and MMAD stand for mass median diameter and mass median aerodynamic diameter, respectively. MMD was obtained in ambient air using the Malvern/Spraytec System while MMAD was obtained in the presence of high-velocity air (15-30L/min) using a commercial cascade impactor for plots (e) and (f). Generally speaking, MMAD is significantly smaller than MMD for aqueous aerosols.

The throughput of such commercial devices ranges from 160 to 420 µl/min, but with very broad droplet size distributions as described. The Pari e-Flow, which utilizes vibrating mesh technology, is capable of high throughput but suffers from broad droplet size distribution (GSD > 1.5) and clogging of the orifices that are considerably smaller in diameter than the droplets produced [12]. Clearly, the size distribution of the droplets produced by the ultrasonic nozzles is much narrower than that produced by the current commercial devices. Furthermore, since no mesh is used, the new device is less prone to clogging that severely impacts on the reliability and robustness of commercial devices.

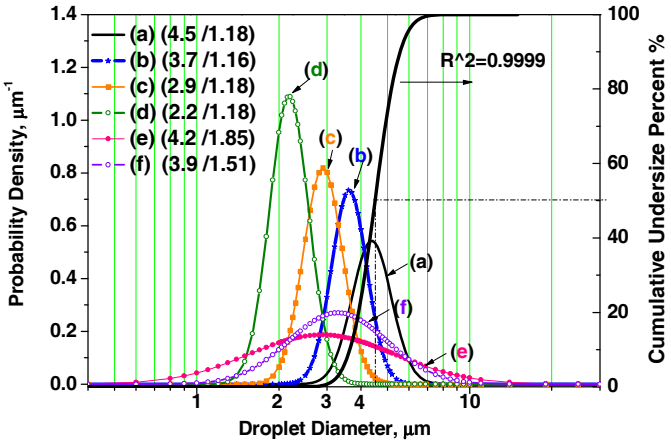

Fig. 2 Comparison of measured droplet sizes and size distributions in logarithmic scale (with MMD/GSD in parentheses for (a) to (d), and MMAD/GSD for (e) and (f)) among: (a) 1.0 MHz nozzle with a central channel for water (4.5 µm/1.18), (b) 1.5 MHz nozzle with water (3.7 µm/1.16), (c) 2.0 MHz nozzle with water (2.9 µm/1.18), (d) 2.0 MHz nozzle with alcohol (2.2 µm /1.18), (e) Omron NE-U22V (4.2 µm/1.85), and (f) Pari e-Flow (3.9 µm/1.51).

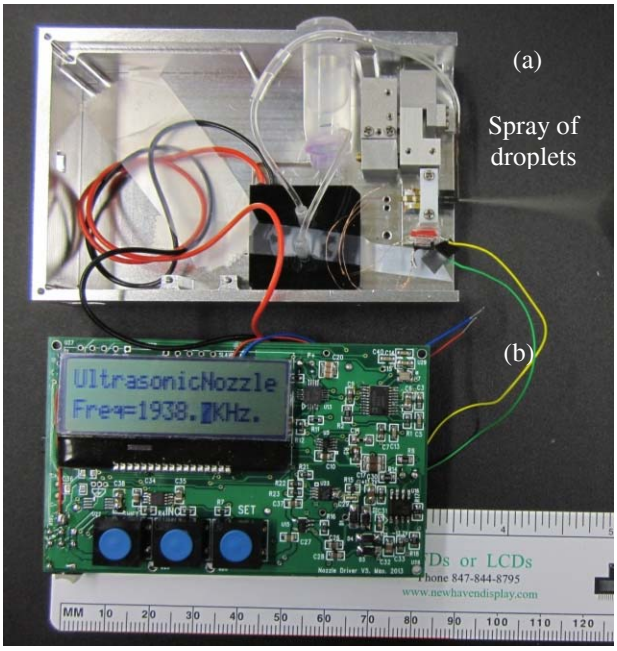

Fig. 3 MEMS-based pocket-size ultrasonic nebulizer (8.8 cm x 5.9 cm x 1.9 cm): (a) Mechanical components layout; (b) Battery-powered electronic driver

IV. Pocket-Size Ultrasonic Nebulizer and Nebulization of Common Drugs

A. *Pocket-Sized Nebulizer*

Monodisperse medicinal aerosols of diameter range 2.2 to 4.6µm have been produced at throughput as high as 200µl/min and electrical drive power as low as 0.3 watt. The centimeter-sized nozzles together with low power requirement enabled most recent realization of the first pocket-sized ultrasonic nebulizer (8.6 x 5.6 x 1.5 cm^3) as shown in Fig. 3. The

nebulizer contains nozzle, IC electronic driver, cell-phone battery, micro pump, drug reservoir, and liquid feed.

B. Nebulization of common Drugs

A variety of common drugs for asthma, chronic obstructive pulmonary disease (COPD), diabetes, pulmonary fibrosis, cyanide poisoning, etc. such as albuterol (isoproterenol), Humulin U-100, cobinamide, interferon-γ [13] and budesonide suspension [14] have been nebulized using either the bench-scale unit [2] or the pocket-size nebulizer with desirable aerosol size and output rate as summarized in Table I. It is to be noted that the demonstrated moderate output rate of 100 – 150μl/min by the pocket-sized nebulizer would provide a higher effective dosage over the current commercial nebulizers in light of the higher aerosol monodispersity produced by the former.

V. CONCLUDING REMARKS

A low-power, mesh-less pocket-sized ultrasonic nebulizer has been realized for the first time. The core of the nebulizer is the MEMS-based multiple-Fourier horn nozzle. The nebulizer is based on temporal instability of Faraday waves generated on the surface of medicine liquid resting on the nozzle end face. No mesh with micrometer-sized holes is used as in the commercial ultrasonic nebulizers based on the advanced vibrating mesh technology. Therefore, this new- type of ultrasonic nebulizer is less prone to clogging.

In addition, the external liquid feed offers advantage of easy control of on-off liquid flow to facilitate breath-actuation in inhalation drug delivery. The output can be increased by increasing the area of the nozzle end face and/or array of nozzles packed together sharing a single liquid feed system.

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TABLE I. SUMMARY OF DRUGS NEBULIZED

Medicine	Medicine Conc.	Ultrasonic Drive Freq. MHz	Nebulizer Unit	Droplet Diameter μm	Output Rate *μl*/min	Disease
Albuterol (isoproterenol)	25mg/ml	1.0	Bench-scale	4.5	150	Asthma
Humulin, U100	100 units/ml	1.0	Bench-scale	4.5	100	Diabetes
Cobinamide	100 mM	1.5	Pocket-size	3.9	130	Cyanide poisoning
Budesonide suspension*	0.5mg/2.0 ml	2.0	Pocket-size	3.1	200	Asthma

*Prevention of lung cancer in clinical trial