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Authors

Tsai, CS
Mao, RW
Zhu, Y
[et al.](#)

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Hand-Held High-Throughput Ultrasonic Monodisperse Aerosol Inhalers for Detoxification of Massive Cyanide Poisoning

Chen S. Tsai*, Rong W. Mao, Yun Zhu, Eric Chien,
James Maduzia

University of California, Irvine
Dept. of Electrical Eng. and Comp. Science
Irvine, CA 92697, USA
*e-mail: cstsai@uci.edu

Shirley C. Tsai
Dept. of Chem. Eng. and Materials Science
University of California, Irvine

Matthew Brenner, Sari Mahon, David Mukai,
Jangwoon Lee, David Yoon, Tanya Berney

University of California, Irvine
Division of Pulmonary and Critical Care Medicine
Beckman Laser Institute and Medical Clinics
Irvine, CA 92612 USA

Gerry Boss
Department of Medicine, Univ. of California, San Diego
La Jolla, CA 92093
Steve Patterson
Dept. of Pharmacology and Center for Drug Design, Univ.
of Minnesota, Minneapolis, MN 55455

Abstract— Detoxification of massive cyanide (CN) poisoning by inhalation of antidotes is recognized to be superior to intravenous (IV) or intra muscular (IM) treatment with regard to ease of administration, self-administration, and rapidity of onset. However, there are currently no effective, portable, high-throughput inhalers that can be produced in large quantities and distributed for such purpose. A hand-held inhaler has been realized using silicon-based ultrasonic nozzle to produce high-throughput of monodisperse cobinamide antidote solution for detoxification of CN poisoning in a rabbit model.

Keywords- cyanide poisoning and detoxification, cobinamide antidote, Fourier-horn ultrasonic nozzles, monodisperse aerosol inhaler

I. INTRODUCTION

Currently, all effective cyanide (CN) antidotes must be administered intravenously (IV). This is not possible for mass CN poisoning resulting from disasters such as terrorist attack and major fires. There is currently no available intramuscular (IM) treatment or agents that can be applied rapidly for the mass CN poisoning either. Meanwhile, inhalation modes may be superior with regard to ease of administration, self-administration, and rapidity of onset. However, current commercial inhalers or nebulizers all suffer from polydisperse (broad-size) aerosol distribution and/or low throughput, making it difficult to deliver sufficient amount of drugs to the lung rapidly and precisely. Thus, there is no effective portable, high-throughput, low-power inhalers that can be produced in large quantities and distributed for such purposes.

Aerosol particles (or droplets) greater than $5\mu\text{m}$ in mass median aerodynamic diameter (MMAD) or mass median diameter (MMD) impact primarily in the oropharynx and thus do not enter the respiratory system. Particles between 5 and $1\mu\text{m}$ (the “respirable” fraction) enter the respiratory system [1,

2] and deposit in progressively smaller airways [2]. Particles between 3 and $1\mu\text{m}$ deposit optimally in the alveolar region [3-5], while particles smaller than $1\mu\text{m}$ remain airborne and are exhaled. Droplet size distribution, as measured by geometrical standard deviation (GSD), is also an important determinant of inhaled drug delivery. Human deposition images from the same patient inhaling from two different wet nebulizers both with MMAD below $5\mu\text{m}$ but with different size distributions (GSD >4.0 versus 3.0 - 4.0) illustrate how small changes in the polydispersity or GSD of the aerosol distributions result in markedly different deposition patterns [6, 7].

Fig. 1 (a) 1.5 MHz nozzle with water ($3.6\mu\text{m}/1.14$), (b) 2.0 MHz nozzle with water ($2.9\mu\text{m}/1.18$), (c) 2.0 MHz nozzle with alcohol ($2.2\mu\text{m}/1.18$), and commercial nebulizers (d) Omron NE-U22V ($4.2\mu\text{m}/1.85$) and (e) Pari eFlow ($3.9\mu\text{m}/1.51$). Note: Numbers in parenthesis designate NMD and GSD which stand for number mean diameter and geometrical standard deviation, respectively.

As shown in Fig. 1 plots (d) and (e), even the most advanced vibrating mesh technology-based ultrasonic

nebulizers produced very broad drop-size distributions. In contrast, the MHz multiple-Fourier horn ultrasonic nozzle reported recently [8-10] has demonstrated its capability of producing high-throughput micrometer-sized monodisperse droplets (see plots (a) to (c) of Fig. 1) at very low electrical drive power and thus fulfilling the unmet needs. This paper reports utilization of a hand-held inhaler with 1.5 MHz 4-Fourier horn nozzle to produce high-throughput of aerosolized monodisperse cobinamide antidote solution for detoxification of CN poisoning in a rabbit model.

II. SILICON-BASED ULTRASONIC NOZZLE

Figure 2(a) shows the silicon-based multiple-Fourier horn ultrasonic nozzle that enables controlled excitation of single-mode MHz Faraday waves and production of micrometer-sized monodisperse droplets from the nozzle end face. Fig. 2(b) shows photographs of the 1.5 MHz four-Fourier horn nozzle used in this study. The nozzle was designed to vibrate in a single longitudinal vibration mode at the single resonance frequency (f) of the multiple-Fourier horns [8]. Electrical activation of the PZT transducers at this resonance frequency creates a standing acoustic wave through the nozzle body in the direction perpendicular to the nozzle end face [Z-axis in Figs. 2(a) and 2(c)] with a maximum vibration displacement (h) on the end face. The greatly enhanced h due to the multiple-Fourier horns in resonance (with a displacement gain of 2^n for a n -Fourier-horn nozzle) [8, 9] facilitates the critical excitation displacement (h_{cr}) required to form Faraday waves on the free surface of the planar liquid layer resting on the nozzle end face and, subsequently, initiates temporal instability of the waves, resulting in the ejection of monodisperse droplets at low electrical drive power. Specifically, high-throughput of aerosolized micrometer-sized monodisperse cobinamide antidote solution was produced for the CN detoxification experiments.

Fig. 2 (a) MHz silicon ultrasonic nozzle with central channel dimensions of $150\mu\text{m} \times 150\mu\text{m}$ for 1.5 MHz four-Fourier horn nozzle, and the corresponding end face dimensions of $482\mu\text{m} \times 1060\mu\text{m}$. (b) Photograph of the 1.5 MHz nozzle; (c) Geometry of nozzle end face and liquid layer d in depth.

III. CYANIDE DETOXIFICATION EXPERIMENTS WITH RABBITS

We proceeded with the animal experiments using the 1.5 MHz nozzle just described with relatively low throughput (0.15 ml/min) of cobinamide antidote (100 mM or ~ 100 mg in saline solution) [11-13]. Four rabbits were studied using CN infusion continuously for 60 min as shown in Fig. 3. Nebulized cobinamide was administered beginning 40 min into the CN infusion and continuing for 10 min. As is evident from Fig. 4, the rate deterioration and tissue oxygen extraction defect was immediately stabilized as the nebulization started. The process was further reversed after the CN infusion was discontinued at 60 min. Cobinamide was readily seen in the plasma samples drawn serially following initiation of the cobinamide nebulization (Fig. 5). These results clearly show the significant effect of nebulized cobinamide for reversing CN poisoning even at low dose (~ 100 mg) and thus, demonstrate the high potential of the hand-held high-throughput ultrasonic monodisperse aerosol inhalers for detoxification of massive CN poisoning.

IV. CONCLUSIONS

Significant effect of aerosolized cobinamide for reversing CN poisoning even at low dose (~ 100 mg) has demonstrated the high potential of a hand-held MHz ultrasonic monodisperse aerosol inhaler for detoxification of massive CN poisoning. Furthermore, the micrometer-sized (2.2 to $4.6\mu\text{m}$) monodisperse aerosols produced at high throughput and very low electrical drive power (<1.0 W) will have broad applications to delivery of both inhalation solution and suspension drugs to the lung.

Fig. 3 Rabbit Model Experiment

Fig. 4 Diffuse optical spectroscopy (DOS) measurements of oxyhemoglobin (OHb) and deoxyhemoglobin (RHb) during induction of cyanide poisoning and reversal using monodisperse aerosol cobinamide administration. OHb increases during cyanide poisoning due to inability of tissue to extract oxygen. As antidote drug is absorbed, OHb returns to normal rapidly.

Fig. 5 Appearance of active drug, cobinamide, in the plasma of rabbits following trans-pulmonary drug administration. In other words, cobinamide is seen as CN toxicity has been reversed with aerosol administration

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REFERENCES

- [1] W. H. Finlay and A. R. Martin, "Recent advances in predictive understanding of respiratory tract deposition," *J Aerosol Med Pulm D*, vol. 21, pp. 189-205, Jun 2008.
- [2] J. Heyder, "Deposition of inhaled particles in the human respiratory tract and consequences for regional targeting in respiratory drug delivery," *Proc. Am. Thorac. Soc.*, vol. 1, pp. 315-20, 2004.
- [3] J. S. Patton and P. R. Byron, "Inhaling medicines: delivering drugs to the body through the lungs," *Nat. Rev. Drug Discovery*, vol. 6, pp. 67-74, Jan 2007.
- [4] J. Heyder, J. Gebhart, G. Rudolf, C. F. Schiller, and W. Stahlhofen, "Deposition of Particles in the Human Respiratory-Tract in the Size Range 0.005-15 μ m," *J. Aerosol Sci*, vol. 17, pp. 811-825, Oct 1986.
- [5] P. R. Byron, "Prediction of drug residence times in regions of the human respiratory tract following aerosol inhalation," *J. Pharm. Sci.*, vol. 75, pp. 433-8, May 1986.
- [6] S. Sangwan, R. Condos, and G. C. Smaldone, "Lung deposition and respirable mass during wet nebulization," *J. Aerosol. Med.*, vol. 16, pp. 379-386, Win 2003.
- [7] M. Solomita and G. C. Smaldone, "Reconciliation of Cascade Impaction during Wet Nebulization," *J. of Aerosol Medicine and Pulmonary Drug Delivery*, vol. 22, pp. 11-18, Mar 2009.

- [8] S. C. Tsai, Y. L. Song, T. K. Tseng, Y. F. Chou, W. J. Chen, and C. S. Tsai, "High-frequency silicon-based ultrasonic nozzles using multiple Fourier horns," *IEEE Trans. Ultrason. Ferroelectr. Freq. Control*, vol. 51, pp. 277-285, Mar 2004.
- [9] S. C. Tsai, C. H. Cheng, N. Wang, Y. L. Song, C. T. Lee, and C. S. Tsai, "Silicon-based Megahertz ultrasonic nozzles for production of monodisperse micrometer-sized droplets," *IEEE Trans. Ultrason. Ferroelectr. Freq. Control*, vol. 56, pp. 1968-1979, 2009.
- [10] C. S. Tsai, R. W. Mao, S. K. Lin, N. Wang, and S. C. Tsai, "Miniaturized multiple Fourier-horn ultrasonic droplet generators for biomedical applications," *Lab. Chip*, vol. 10, DOI: 10.1039/c005262k, pp. 2733-2740, 2010.
- [11] K. E. Broderick, P. Potluri, S. Zhuang, I. E. Scheffler, V. S. Sharma, R. B. Pilz, and G. R. Boss, "Cyanide detoxification by the cobalamin precursor cobinamide," *Exp Biol Med (Maywood)*, vol. 231, pp. 641-649, May 2006.
- [12] K. A. Kreuter, J. Lee, S. B. Mahon, J. G. Kim, D. Mukai, O. Mohammad, W. Blackledge, G. R. Boss, B. J. Tromberg, and M. Brenner, "Rapid reversal of cyanide toxicity using a novel agent, cobinamide, assessed non-invasively using diffuse optical spectroscopy," *Chest*, vol. 134, pp. 124001, 2008.
- [13] M. Brenner, J. G. Kim, S. B. Mahon, J. Lee, K. A. Kreuter, W. Blackledge, D. Mukai, S. Patterson, O. Mohammad, V. S. Sharma, and G. R. Boss, "Intramuscular cobinamide sulfite in a rabbit model of sublethal cyanide toxicity," *Ann. Emerg. Med.*, vol. 55, pp. 352-363, Apr 2010.