Selective Micro Preconcentration of Propofol for Anesthetic Depth Monitoring by using Seedless Electroplated Gold as Adsorbent

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Abstract—This communication presents selective preconcentration of the anesthetic agent (Propofol) and the elimination of unwanted species from a representative sample of human breath. In this approach, a micro preconcentrator (µPC) consisting of embedded high-aspect-ratio pillars (30 µm × 120 µm × 240 µm), an outer dimensions of 7 mm × 7 mm (encompass more than 3500 micro pillars), total inner surface area of ~10 m^2, and a total inner volume of ~6.5 µL was used to selectively preconcentrate Propofol. The µPC has on-chip thermal desorption capability and was coated by electrodeposited gold as an adsorbent material. Experimental evaluations showed successful preconcentration of trace level of Propofol from a mixture containing several volatile organic compounds diluted in water-like solvent (1-propanol) and the efficient removal of non-polar compounds present in the mixture.

I. INTRODUCTION

DEPTH of anesthesia assessment is a persistent challenge for anesthesiologists [1]. Conventional clinical signs of inadequate anesthetic depth include changes in blood pressure, heart rate, movement, lacrimation, sweating, and pupil size which often are inconsistent and unreliable [2-4]. More accurate methods of assessing depth of anesthesia is needed especially when using newer intravenous anesthetic compounds such as Propofol (2,6-diisopropylphenol) whose effective dosages vary greatly across patients [5]. Propofol is an aromatic compound with a distinct smell used for induction and maintenance of anesthesia in the intensive care unit [6]. It has been reported that the expiratory measurement of Propofol in human breath is a suitable procedure for non-invasive monitoring of patients undergoing anesthesia [7]. However, normal human breath contains a complex mixture of more than 1200 volatile organic compounds (VOCs) [8] at very low concentrations typically in the parts per billion (ppb) range [9] which are hardly detectable by conventional sensors. Consequently, sample preconcentration along with gas chromatographic (GC) analysis are used for accurate and precision detection of complex gas mixtures [10]. However, current GC systems are large, require highly trained technicians and intensive maintenance, and are expensive table-top instruments with high power consumptions [11].

Miniaturization of GC systems was enabled by microelectromechanical systems (MEMS) technology and, recently, various designs of micro separation columns and preconcentrators (PC) for sensing and monitoring applications have been reported [11-17]. Nevertheless, the success of micro analytical systems (µTAS) in breath analysis applications rely on the ability to remove water vapor from the sample and selectively preconcentrate analytes of interest in the mixture that can later be processed µGC column and micro detector [18]. The use of selective adsorbent is one possible way to attain selective micro preconcentration (µPC). This article reports, for the first time, electrodeposited-gold thin films as a selective adsorbent for Propofol in µPCs.

II. EXPERIMENTAL

A. Fabrication of µPC

The µPCs used in this study contain an array of 3D micro pillars and is similar to our previously reported work [19]. Fig. 1 summarizes the fabrication process of the µPC. First, the single mask design pattern was transferred to a silicon wafer via standard photolithography as shown in Fig. 1(a). Second, the silicon wafer was etched by deep reactive ion etching (DRIE) process (Fig. 1(b)) followed by oxygen plasma clean step to remove any residual fluorocarbon on the etched surface. The devices were then coated with the adsorbent material via electrodeposition technology as shown in Fig. 1(c). Pulsed electroplating technique was used to directly deposit a thin layer of gold on heavily phosphorous-doped (n^+) silicon microstructures. Seedless gold electroplating of silicon surfaces provides simple method of realizing large surface area gold films (Fig. 2 inset) with low adhesion strength. The weak gold-to-silicon adhesion is advantageous at this step as it allows post deposition patterning of the gold films as reported previously [20] and shown in Fig. 2. The film can be stabilized by thermal annealing at a later stage. The pulse duration and time period for pulse electroplating were adjusted to achieve a desired thickness (350 nm) on the

micro pillars. Phosphorous diffusion was done at 950 ºC for 6 hours to achieve 2 µm-deep doped region below the silicon surface. The electroplating bath was maintained at 55 ºC with a stirring rate of 200 rpm to provide a uniform distribution of gold ions in the bath. Acidic gold electroplating solution and a platinized Ti grid (anode) were used to complete the electroplating circuit. The anode is placed at a distance of 2 cm from the cathode and has a size at least twice that of the cathode to afford a uniform electric field on the silicon wafer.
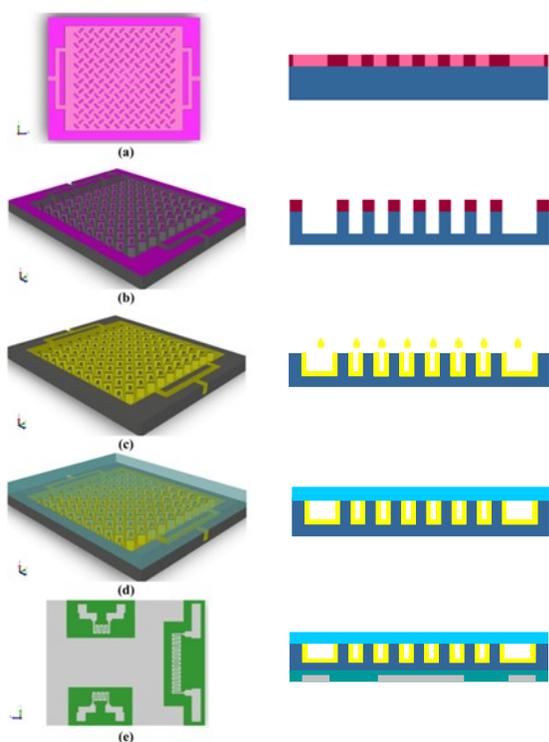
Fig. 1. (a) Photolithography (b) Deep reactive-ion etching (DRIE) (c) Electrodeposition and patterning of the adsorbent material (d) Sealing the device with Pyrex by anodic bonding (e) Patterning of resistive heaters and temperature sensors over PECVD oxide at the back of the device.

The current between the platinized Ti grid anode and doped silicon cathode was controlled by a square current pulse. After gold deposition and patterning, the silicon wafer was anodically bonded to the Pyrex 7740 substrate (Fig. 1(d)). The bonding temperature and pressure were 350 ºC and 2 kPa, respectively. Thermal annealing during the bonding process at temperatures less than the Si-Au eutectic temperature (365 ºC) stabilizes the electroplated gold by significantly improving its adhesion to the doped silicon surface. The gold coating was proved to be stable under GC operating temperature (350 ºC) and flow conditions (1 mL/min) [21]. The final step of µPCs fabrication was patterning thin film Ti/Pt resistive heaters and temperature sensors over plasma enhanced chemical vapor deposition (PECVD) oxide on the backside of the silicon wafer as shown in Fig. 1(e). The wafer was then diced and fused silica capillary tubing with 167 µm O.D. and 100 µm I.D.

was attached to fluidic ports.

The fabrication process described above produced high quality µPCs. The silicon-glass chips have outer dimensions of 7 mm × 7 mm × 1 mm, specific surface area of 10 m^2/g (gas sorption method), and an inner volume of about 6.5 µL. The dimensions of the high-aspect-ratio pillars were 30 µm × 120 µm × 240 µm. Fig. 3 illustrates the top and bottom views of the µPC placed in front of a resistor to give a size prospective.
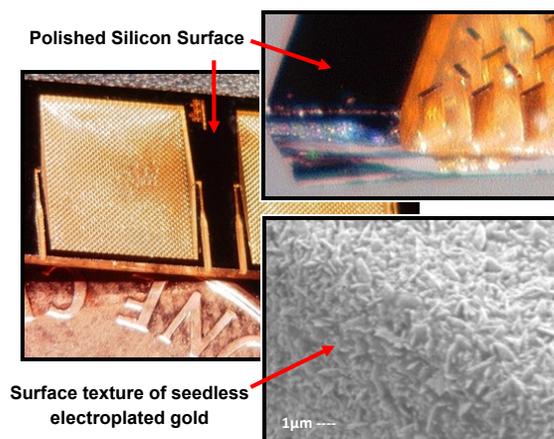
Fig. 2 Optical images showing the the uniform and conformal coverage coating of electroplated gold. The top flat surfaces including the top of the posts are polished and smooth for anodic bonding. The porous surface texture of the gold layer maximizes the adsorbent surface area.
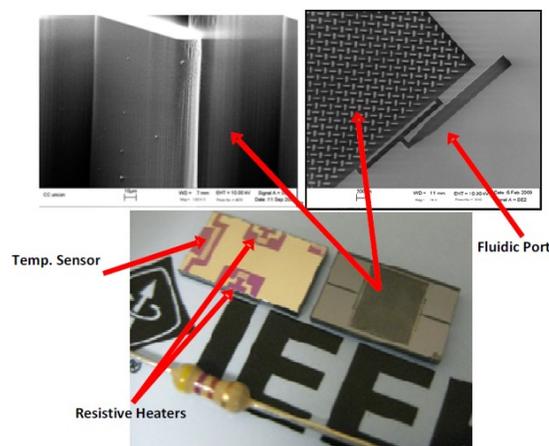
Fig. 3 Optical images of the µPC showing the front and back sides of the device, insets are SEM monographs of the etched microstructures and the fluidic ports.

B. Testing Setup

To maintain isothermal temperature conditions, the testing setup was installed inside the oven of a commercial dual inlet and dual detector GC system. Moreover, the built-in auxiliary systems such as a gas flow controller and flame ionization detectors (FIDs) were also utilized to ensure consistent testing parameters. Carrier gas was supplied via the GC inlets and controlled by the flow controller. The

testing setup consisted of a six-port zero-dead-volume valve, commercial methylpolysiloxane phase GC column, and deactivated fused silica transfer lines configured as shown in Fig. 4. The inlet pressure was adjusted to achieve 1mL/min flow rate through the µPC and column. During the loading stage the valve is set in the "loading position" to load the µPC as shown in Fig 4(a). The loading was done by supplying the breath representative mixture into the GC inlet-B and monitored by FID-A. Fig. 4(b) illustrates the valves set in the "injection position." In this configuration, the GC column was connected to the preconcentrator. The µPC was then heated rapidly to 250 °C at 100 °C/sec to inject the collected sample into the column. As soon as the injection step was completed, the valves set back to the "separation position" (Fig 4(a)). Here, the column was heated to 150 °C from 35 °C at 30 °C/min to separate the injected sample.

(a)

(b)
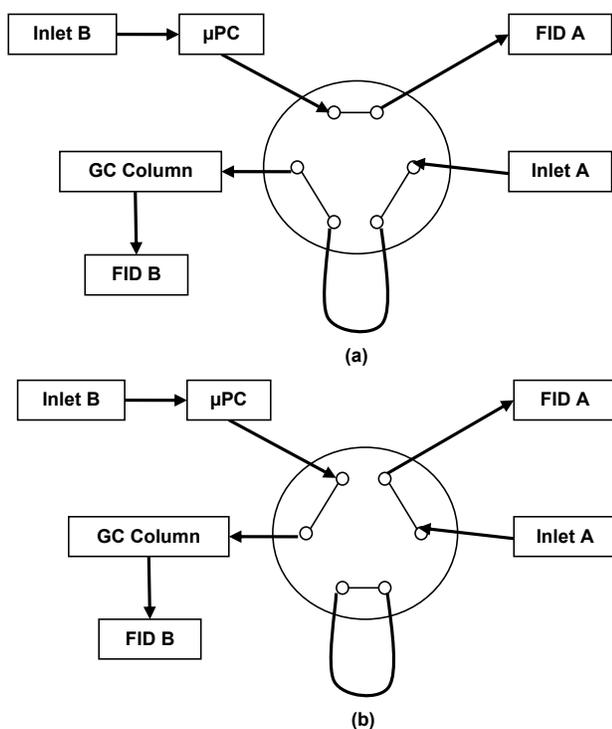
Fig. 4 µPC test setup with the valves set in the (a) loading or seperation position (b) injection position

III. RESULTS AND DISCUSSIONS

For the preliminary evaluation of the presented device, a 125 ppm of Propofol was added to a mixture of n-heptane (C_7) at 250 ppm, n-octane (C_8) at 250 ppm, n-nonane (C_9) at 500 ppm, and n-decane (C_{10}) at 750 ppm, which are some of the VOCs found in normal human breath [8] diluted in 1-propanol. The choice of 1-propanol as solvent instead of water vapor present in breath was dictated mainly by the available water insensitive detector (FID).

Fig. 5 shows the separation of the breath representative mixture without preconcentration as a reference. The large

1-propanol content in injected sample is evident. 1-propanol (or water vapor in breath) could impose premature saturation in the collection process by saturating the adsorbent material. It can also saturate the detector as well during the detection process. It should be noted that most gas detectors are sensitive to water [22]. As a result, eliminating any interfering compounds by means of selective preconcentration is essential for high performance analysis.
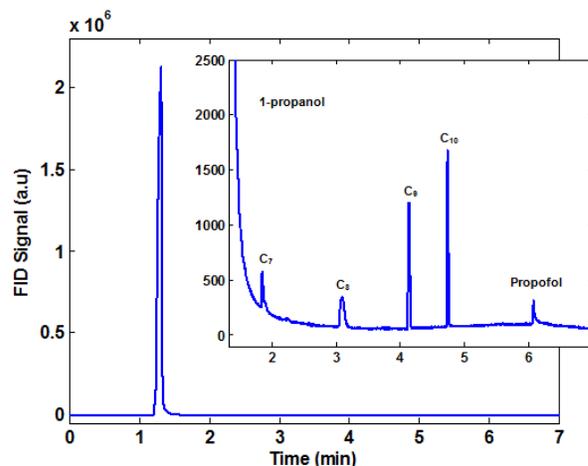
Fig. 5 Chromatogram of breath representative mixture without µPC showing the large amount of 1-Propano, inset is zoom-in of the separated VOCs

Fig. 6 demonstrates the results of selective preconcentration of trace Propofol in the breath representative mixture. The electrodeposited gold thin film demonstrated preferential adsoption characteristics over the other compounds which are non-polar. We considered polar adsorption as possible mechanism since the electrodeposited gold showed high affinity to polar compounds. Thus, the adsorption of Propofol on the electrodeposited gold could be attributed to the polar nature of both the phenol derivative anesthetic agent [23] and the gold film. The polar nature of the electrodeposited gold can be explained by the formation of gold oxide layer on the gold electrode surface [24]. Gold oxides are known to be polar [25]. Determining the exact mechanism responsible for Propofol adsorption on electrodeposited gold films will be the subject of future investigation.

The performance of the presented adsorbent can be evaluated by a figure of merit known as the preconcentration factor (PF). This figure of merit can be defined as the ratio of peak height of the detector's signal with and without the presence of the µPC. Using the gold electroplated µPC and under the testing conditions presented here, the PF factor for Propofol was determined to by about 100.

IV. CONCLUSIONS

Propofol measurements in human breath, which are not yet possible to monitor on-line, could be used to monitor depth of anesthesia to prevent accidental awaking of patients during surgery. Additionally, the demand for cost-effective

Propofol monitoring devices is expected to increase as many surgical procedures are now being shifted from hospitals to outpatient surgical centers and physician's offices.

This paper reported the utilization of MEMS technology to develop µPCs which is selective to a target chemical species for breath analysis. The elimination of unwanted species by selective preconcetration allowed more adsorption surface for the target compound on the adsorbent material and alleviated stringent requirements on the separation and detection stages.
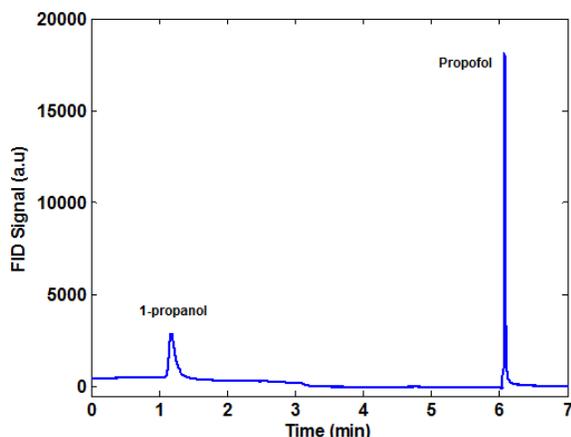
Fig. 6 Chromatogram of selective preconcentration of propofol. VOCs were not preconcentrated in the µPC.

REFERENCES

[1] H. L. Kaul, and N. Bharti, "Monitoring Depth of Anaesthesia," *Indian Journal of Anaesthesia,* vol. 46, no. 4, pp. 323-332, 2002.

[2] N. Moerman, B. Bonke, and J. Oosting, "Awareness and recall during general anesthesia. Facts and feelings," *Anesthesiology,* vol. 79, no. 3, pp. 454–464, 1993.

[3] J. Bruhn, P. S. Myles, R. Sneyd, and M. M. R. F. Struys, "Depth of anaesthesia monitoring: what's available, what's validated and what's next?," *Br. J. Anaesth.,* vol. 97, no. 1, pp. 85-94, 2006.

[4] C. J. D. Pomfrett, "Monitoring depth of anaesthsia," *Bulletin of The Royal College of Anaesthetists* vol. 4, 2000.

[5] R. Flaishon, A. Windsor, J. Sigl, and P. S. Sebel, "Recovery of consciousness after thiopental or propofol. Bispectral index and isolated forearm technique," *Anesthesiology,* vol. 86, no. 3, pp. 613–619, 1997.

[6] C. Hornuss, S. Praun, J. Villinger, A. Dornauer, P. Moehnle, M. Dolch, E. Weninger, A. Chouker, C. Feil, J. Briegel, M. Thiel, and G. Schelling, "Real-time Monitoring of Propofol in Expired Air in Humans Undergoing Total Intravenous Anesthesia," *Anesthesiology,* vol. 106, no. 4, pp. 665-674, 2007.

[7] E. D. Kharasch, "Every Breath You Take, We'll Be Watching You," *Anesthesiology,* vol. 106, no. 4, pp. 652-654 2007.

[8] M. Phillips, "Method for the Collection and Assay of Volatile Organic Compounds in Breath," *Analytical Biochemistry,* vol. 247, no. 2, pp. 272-278, 1997.

[9] P. Spanel, K. Dryahina, and D. Smith, "The concentration distributions of some metabolites in the exhaled breath of young adults," *Journal of Breath Research,* vol. 1, no. 2, pp. 026001, 2007.

[10] D. Helmig, "Air analysis by gas chromatography," *Journal of Chromatography A,* vol. 843, no. 1-2, pp. 129-146, 1999.

[11] M. Agah, and K. D. Wise, "Low-Mass PECVD Oxynitride Gas Chromatographic Columns," *Journal of Microelectromechanical Systems,* vol. 16, no. 4, pp. 853-860, 2007.

[12] B. Alfeeli, M. Ashraf-Khorassani, L. T. Taylor, and M. Agah, "Multi-inlet/outlet Preconcentrator with 3-D µ–structures Coated by Inkjet Printing of Tenax TA " in Solid-State Sensors, Actuators, and Microsystems Workshop, Hilton Head Island, South Carolina, 2008, pp. 118-121.

[13] I. Gràcia, P. Ivanov, F. Blanco, N. Sabaté, X. Vilanova, X. Correig, L. Fonseca, E. Figueras, J. Santander, and C. Cané, "Sub-ppm gas sensor detection via spiral µ-preconcentrator," *Sensors and Actuators B: Chemical* vol. 132, no. 1, pp. 149-154, 2008.

[14] S. Li, J. C. Day, J. J. Park, C. P. Cadou, and R. Ghodssi, "A fast-response microfluidic gas concentrating device for environmental sensing," *Sensors and Actuators A: Physical,* vol. 136, no. 1, pp. 69-79, 2007.

[15] F. Blanco, X. Vilanova, V. Fierro, A. Celzard, P. Ivanov, E. Llobet, N. Cañellas, J. L. Ramírez, and X. Correig, "Fabrication and characterisation of microporous activated carbon-based pre-concentrators for benzene vapours," *Sensors and Actuators B: Chemical,* vol. 132, no. 1, pp. 90-98, 2008.

[16] M. A. Zareian-Jahromi, M. Ashraf-Khorassani, L. T. Taylor, and M. Agah, "Design, Modeling, and Fabrication of MEMS-Based Multicapillary Gas Chromatographic Columns," *Microelectromechanical Systems, Journal of,* vol. 18, no. 1, pp. 28-37, 2009.

[17] B. Alfeeli, S. Ali, V. Jain, R. Montazami, J. Heflin, and M. Agah, "MEMS-based gas chromatography columns with nano-structured stationary phases," in The 7th IEEE Conference on Sensors, Lecce, Italy 2008, pp. 728-731.

[18] B. Alfeeli, and M. Agah, "Selective Preconcentration by Temperature Manipulation of Cascaded Micro Preconcentrators," in 15th International Conference on Solid-State Sensors, Actuators and Microsystems, Denver, CO, 2009 In press.

[19] B. Alfeeli, D. Cho, M. Ashraf-Khorassani, L. T. Taylor, and M. Agah, "MEMS-Based Multi-Inlet/Outlet Preconcentrator Coated by Inkjet Printing of Polymer Adsorbents," *Sensors and Actuators B: Chemical* vol. 133, no. 1, pp. 24-32, 2008.

[20] M. A. Zareian-Jahromi, and M. Agah, "Micro Gas Chromatography Multicapillary Columns with Mono-Layer Protected Gold as a Stationary," in 22nd Annual IEEE Conference on Micro Electro Mechanical Systems, Italy, 2009, pp. 288-291.

[21] M. A. Zareian-Jahromi, and M. Agah, "Self-Patterned Seedless Gold Electroplating in High-aspect-ratio Channels for GC Application," in 15th International Conference on Solid-State Sensors, Actuators and Microsystems, Denver, CO, 2009 In press.

[22] S. M. Cho, Y. J. Kim, G. S. Heo, and S.-M. Shin, "Two-step preconcentration for analysis of exhaled gas of human breath with electronic nose," *Sensors and Actuators B: Chemical,* vol. 117, no. 1, pp. 50-57, 2006.

[23] M. Barann, I. Linden, S. Witten, and B. W. Urban, "Molecular Actions of Propofol on Human 5-HT3A Receptors: Enhancement as Well as Inhibition by Closely Related Phenol Derivatives," *Anesth Analg,* vol. 106, no. 3, pp. 846-857, March 1, 2008, 2008.

[24] K. Juodkazis, J. Juodkazyte, V. Jasulaitiene, A. Lukinskas, and B. Sebeka, "XPS studies on the gold oxide surface layer formation," *Electrochemistry Communications,* vol. 2, no. 7, pp. 503-507, 2000.

[25] N. Cioffi, I. Farella, L. Torsi, A. Valentini, and A. Tafuri, "Correlation between surface chemical composition and vapor sensing properties of gold-fluorocarbon nanocomposites," *Sensors and Actuators B: Chemical,* vol. 84, no. 1, pp. 49-54, 2002.