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Micro-patterning and characterization of PHEMA-co-PAM-based optical chemical sensors for lab-on-a-chip applications

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Abstract

We report a novel method for wafer level, high throughput optical chemical sensor patterning, with precise control of the sensor volume and capability of producing arbitrary microscale patterns. Monomeric oxygen (O_2) and pH optical probes were polymerized with 2-hydroxyethyl methacrylate (HEMA) and acrylamide (AM) to form spin-coatable and further crosslinkable polymers. A micro-patterning method based on micro-fabrication techniques (photolithography, wet chemical process and reactive ion etch) was developed to miniaturize the sensor film onto glass substrates in arbitrary sizes and shapes. The sensitivity of fabricated micro-patterns was characterized under various oxygen concentrations and pH values. The process for spatially integration of two sensors (Oxygen and pH) on the same substrate surface was also developed, and preliminary fabrication and characterization results were presented. To the best of our knowledge, it is the first time that poly (2-hydroxyethyl methacrylate)-co-poly (acrylamide) (PHEMA-co-PAM)-based sensors had been patterned and integrated at the wafer level with micron scale precision control using microfabrication techniques. The developed methods can provide a feasible way to miniaturize and integrate the optical chemical sensor system and can be applied to any lab-on-a-chip system, especially the biological micro-systems requiring optical sensing of single or multiple analytes.

Keywords

Optical chemical sensor; PHEMA; Microfabrication; Lab-on-a-chip

1. Introduction

Fluorescent optical chemical sensors have been widely used for applications in aerospace, oceanography, biology, meteorology, agricultural industry, environmental science, and life science [1-7]. Compared to other types of sensors, optical chemical sensors show the clear advantages in term of high sensitivity, non-invasiveness, disposability, and remote sensing capability. This is especially attractive for biological applications requiring in-situ detection of very small change (pico-mol to femto-mol per min) of analytes, such as single cell physiological phenotype studies [5, 8]. To perform the measurement in liquids which is the

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most common case for biological analysis, the optical chemical sensors are usually either physically or chemically dispersed into various hydrophobic polymer matrices including silicon rubbers, silica gels, polystyrene, and hydrogels [9-12]. Recently, our group has developed a series of new optical chemical sensors using poly (2-hydroxyethyl methacrylate)-co-poly (acrylamide) (PHEMA-co-PAM) as polymeric matrices for oxygen and pH measurements. PHEMA-co-PAM has been selected because it is permeable to both dissolved oxygen and ions [12-15]. These sensors are in thin films states, which are generated by polymerization of monomeric fluorescent oxygen and/or pH probes with other monomers (e.g. HEMA and AM).

There has been an extensive need to spatially separate optical sensors and integrate them with microfeatures such as micro-channels and micro-wells [5-6]. This is especially important for multi-parameter sensing application which requires multi-spot sensor array structures. By today, various patterning techniques have been reported. the most straightforward approach is to have optical sensor dye embedded into photosensitive matrix materials such as SU8 [6], photo-PDMS [16] and photoresist [17], and patterned onto the flat glass substrate surface using standard photolithography techniques. Another approach is to spin-coat polystyrene based optical sensor to form thin film, then use reactive ion etch [18-19] to pattern the thin film into various features. However, these approaches are not suitable for pH sensor patterning since the ion permeability of the aforementioned matrices is very limited, highly reducing the sensor's sensitivity. Furthermore, they are developed for single sensor patterning only. Integrating additional sensors onto the same device for multi-sensor development using the same method is still very challenging. On the other hand, we have developed an alternative optical sensor deposition (patterning) method using automatic non-contact piezoelectric liquid dispensing robot (au301, Aurigin Technology Inc, Phoenix, AZ). This technique can deposit 100-200 pL of various sensor materials into selected microstructures [8]. However, the problem with limited pattern shapes, sensor overflowing, and difficulty in controlling the sensor volume prevents it from being used for multi-spot sensing application especially when the device is scaled down below 80 μm . In this paper, we report a microfabrication technique based approach to micro-pattern both oxygen and pH sensors on glass substrates, and present our results from materials developments, process development, sensor characterization, and multi-sensor integration. The goal of this project is to overcome the technical bottleneck of current sensor patterning methods, and to develop a feasible way to produce arbitrary micro-features with precise control of the sensor volume and sensitivity for lab-on-a-chip sensing applications.

2. Experimental

2.1. Materials and reagents

Four-inch double side polished fused silica wafers (Markoptics, Santa Ana, CA) were used as the substrate material because it is optically transparent and flat, and will generate minimum auto-fluorescence noise during the fluorescence intensity measurement. The *N,N'*-dimethyl formamide (DMF), azobisisobutyronitrile (AIBN), acrylate-containing silane, and trimethylsilylpropyl acrylate (TMSPA) were acquired from Sigma-Aldrich (St. Louis, MO). AZ3312 positive photoresist and AZ 300MIF developer were purchased from Capital scientific, CA. The microstripper 2001 was purchased from Columbus Chemical Industries, Columbus, WI. Britton-Robinson (B-R) buffers composed of acetic acid, boric acid, phosphoric acid, and sodium hydroxide were used for tuning pH values. Calibration gases (nitrogen and oxygen, each of 99.9% purity) were purchased from Air Liquide America, LP (Houston, TX). The exact gas percentage was controlled using a homemade gas manipulator. All measurements of sensing behaviors were carried out at atmospheric pressure (760 mmHg, or 101 kPa) at room temperature ($23 \pm 2^\circ\text{C}$) unless specified.

2.2. Instruments

A portable precision spin coater (P-6708, Specialty coating systems, Indianapolis, IN) was used to spin coat the sensor solution and photoresist onto the substrate surface. A plasma etch system (G1000, YES engineering, Livermore, CA) was used to pre-treat the substrate surface or etch the sensor film. Nitrogen purged vacuum oven (ADP21, Yamato, Santa Clara, CA) was used to thermally polymerize the sensor solution. Hotplate (Model 1000-1, Electronic Micro Systems Ltd, Wiltshire) was used to soft-bake the photoresist layer. Maskless photolithography system (SF-100, Intelligent Micropatterning LLC, St. Petersburg, Florida) was used to expose the photoresist masking layer at 435 nm wavelength. The optical microscope, equipped with image capturing module (LV150, Nikon, Melville, NY), was used to visualize the feature surface and measure the lateral dimensions of the micro-pattern. The stylus profiler (Dektak 150, Veeco, Tuscon, AZ) was used to characterize the substrate surface and measure the thickness of the resulted pattern. Confocal fluorescence microscope (Eclipse TE2000E, Nikon, Melville, NY) was used for fluorescence imaging of the fabricated patterns surface. Fused silica glass was cut into squares of 1.31 cm $\times$ 1.31 cm using a dicer (Microautomation, Billerica, MA) for fluorescence intensity measurement. A spectrofluorophotometer (RF 5301, Shimadzu Scientific Instruments, Columbia, MD) was used to measure the fluorescence intensity.

3. Results and discussion

3.1. Preparation of the sensors' stock solutions

Detailed synthesis of the spin-coatable polymeric pH and oxygen sensors were given in the supplementary data. 500 mg of P2 or P4 and 10 mg of AIBN were dissolved in 12.5 mL of DMF as the stock solutions for spin coating. The solutions were filtrated using a 0.25 μ m Nylon microfilter and were stored at 4 $^{\circ}$ C under darkness before use (Fig. 1A). In order to develop a spin-coatable sensor, we polymerized two monomeric probes with HEMA and AM to synthesize two new polymers P1 and P3. To get stable thin films with chemical binding on substrate, the two polymers were further modified with polymerizable methacrylate units (P2 and P4). After spin-coating of P2 and P4, the methacrylate units enabled the crosslinking of the two polymers with the TMSPA modified glass substrate to form stable polymer thin layers on the fused silica surfaces.

3.2. Thin film formation

The fused silica wafer was RCA cleaned first to free the substrate of any organic and inorganic contamination. The substrate was then treated by oxygen plasma for ~30 min (Fig. 1B) to generate active hydroxyl groups and followed by 20 hour vapor silianization using TMSPA (Fig. 1C) to modify the substrate surface [12-15], enabling the sensors to be chemically grafted onto the surface. The fresh sensor stock solution was dispensed onto the wafer surface via pipette and spun at a selected spin speed. The completed sample was cured in nitrogen purged vacuum oven for 48 hours to completely polymerize the sensor films.

Fig. 2 shows the spin curve resulted from spin-coating of oxygen and pH sensors after the polymerization. The film thickness linearly decreases with the spin speed. The maximum thickness acquired from single spin-coating is around 0.15-0.17 μ m (at 1000 rpm). The thickness can be increased by additional layer coating, and the maximum thickness of 0.6 μ m was acquired by coating the substrate for three times at 1000 rpm each. However, thicker film requires subsequent longer etch process, which makes the masking layer process very challenging and is not our focus in this study. The Optical inspection of the samples showed the formation of smooth, continuous film on the glass substrate with high thickness uniformity and repeatability. A quantitative test by blowing the pressurized nitrogen onto the

film demonstrated good adherence of the sensor without the need of increasing the film adhesion by adhesion promoter.

3.3. Single sensor micro-patterning

After the sensor thin film was formed and polymerized on the substrate, AZ3312 was spun onto the sensor film surface as the etch mask layer (Fig. 1E). AZ 3312 was selected because it is easy to be removed after the process, and has high aspect ratio for fine feature fabrication. The thickness of this photoresist after single spin-coating is in the range of 1-2 μm depending on the spin speed. The double-coating process was used to form 4 μm AZ3312 masking layer on top of the sensor film (1000 rpm/30s for each layer). The sample was then soft baked at 100 $^{\circ}\text{C}$ for 2 min for best photo-exposure results and exposed for 1.5 seconds at 435 nm wavelength UV light (Fig. 1F).

The subsequent developing process is the most critical part of this patterning process. Since PHEMA-co-PAM matrix is hydrophilic and tends to get dissolved in TMAH based photoresist developers, to protect the matrix from getting in contact with the developer directly, the sample was immerse-developed for 10-15 seconds to partially dissolve the exposed pattern. The developing time is carefully controlled to maintain the measured step height (thickness difference between the protected area and developed area) at 2-3 μm which will leave sufficiently thin protection layer between the patterns. When the developing time increased from 15 to 30 seconds, the TMAH component inside the developer started to penetrate into and dissolve the PHEMA-co-PAM matrix causing the whole pattern to be peeled off. The optical images of the pattern after different developing time can be found in supplementary materials. Since the developing time varies with the processing temperature and humidity, a calibration sample was used every time before the developing to calibrate the developing time for real sample. Typically, the developing time was selected to ensure the exposed photoresist layer to be as thin as possible to avoid making the subsequent process especially the etch process time-consuming.

After the developing process, the sample was hard-baked at 110 $^{\circ}\text{C}$ for 2 min to eliminate the remaining solvent and moisture inside the photoresist and sensor film. The sample was then placed into a plasma etch chamber for directional reactive ion etch (RIE) (Fig. 1G). Fig. 3 shows the etch depth characterization under 50 sccm Ar, 150 mT and 100 W plasma etch condition. The sensor film was observed to get etched much faster than the AZ3312 masking layer, and the etch rate was determined to be 0.28 $\mu\text{m}/\text{h}$ for AZ 3312, 0.9 $\mu\text{m}/\text{h}$ for pH sensor, and 0.6 $\mu\text{m}/\text{h}$ for oxygen sensor. To compensate the measurement error, 10 min additional etch was used to clear any remaining sensor residue and the overall etching was determined to be complete at 40 min for oxygen sensor and 50 min for pH sensor film.

Other etch conditions were studied as well to compare the etch performance. Oxygen plasma led to higher etch rates compared to argon plasma, but it potentially introduced active oxygen radicals into the sensor film which could interfere with the resulted sensitivity. Higher plasma power also increased the etch rate, but the chamber temperature was observed to increase significantly which makes the resulting masking layer very hard to remove especially for long time etch. Therefore, in this study, we selected the 100 W, 50 sccm Ar at 150 mT as the best etch condition and patterned all the samples under this condition.

After the sensor film was fully etched, the remaining 3312 masking layer was stripped using the microstripper 2001 (5 min at 65 $^{\circ}\text{C}$). To confirm there is no sensor residue left after etch, confocal fluorescence microscopy was used to take images of the sensor pattern. For the oxygen sensor, a 561 nm laser was used to excite the sensor and the emission light was collected using a 605/75 nm filter. For the pH sensor, 402 nm laser was used to excite the

sensor and the emission light was collected using a 515/30 nm filter set. The Z-height was scanned from the top of the sample surface to the glass surface to collect potential emission light from possible residue. Fig. 4B-C shows the resulted fluorescence image of 50 μm oxygen and pH sensor micro-pattern. There was no fluorescence emission detected between each microfeatures, and the surface was smooth and uniform. This concluded our patterning process was successful.

3.4. Single sensor characterization

The sensors' sensitivity before and after the pattern formation was characterized to evaluate their sensing performances. The finished samples (1.31 cm $\times$ 1.31 cm) were placed in a quartz cuvette with a 45° angle facing to the excitation laser and immersed in Britton-Robinson (B-R) buffer. The dissolved oxygen concentration was adjusted through flushing oxygen and nitrogen mixtures at different volume ratios. The sample was then allowed to equilibrate for 10 minutes before the luminescence measurement. Fig. 5A and 5C shows the typical pH and oxygen responses of the patterned 50 μm diameter sensor dots. For oxygen sensor, both the thin film and patterned sensor dots follows the linear Stern-Volmer equation (Fig. 5D) as shown in equation 1.

$$\frac{I_0}{I} = 1 + K_{SV} [O_2] \quad (1)$$

where K_{SV} is the Stern-Volmer quenching constant and $[O_2]$ is the dissolved oxygen concentration. I_0 and I are the steady state fluorescence signals measured at various dissolved oxygen concentration, respectively. For the pH sensor, both the thin film and patterned sensor dots follows the sigmoidal function (Boltzmann fitting) (Fig. 5B) as shown in equation 2.

$$\frac{I}{I_0} = \frac{m1 - m2}{1 + \exp\left(\frac{pH - pK'_a}{p}\right)} + m2 \quad (2)$$

Where I is the fluorescence intensity measured at varying pH values and I_0 is that at the highest pH value (pH=10) used during the measurement. $m1$, $m2$, pK'_a , and p are empirical parameters describing the initial value ($m1$), the final value ($m2$), the point of inflection (pK'_a), and the width (p) of the sigmoidal curve. The pK'_a value was calculated to be 7.6 for thin film and reduced to 6.5 for patterned sensor dots. Our results showed that the sensitivity decreased for both pH sensor and oxygen sensors after the patterning. This can be explained as high energy radicals and electrons generated in the plasma etch penetrated into the underlying sensor film, and destructed the chemical bond between the matrix molecules and sensing probe molecules. The plasma induced heating is another possible factor that leads to reduced sensitivity. The maximum sensitivity acquired is 6 for patterned pH sensor (pH varied from 2-10) and 3 for patterned oxygen sensor (oxygen concentration varied from 0-25 ppm). The damage to the fluorescent responses of the probes in the matrices during the patterning process is the drawback of the present method. The alternative patterning methods using photodegradable matrix and/or photo-patterning method are under study aimed to alleviate these problems.

3.5. Multi-sensor integration and characterization

Based on the single sensor patterning methods developed above, multiple sensors can be integrated on the same chip with selected spatial separation. Fig. 1I-N shows the process flow for patterning the second sensor (pH sensor) spatially on the substrate which already

has oxygen sensor pattern on. Before the remaining photoresist layer was removed after the oxygen sensor patterning is completed (Fig. 1G), the wafer was plasma treated and silianized again to re-anchor the Si-O bonds back to the surface which was destructed during the oxygen sensor patterning process (Fig. 1I). The plasma treatment will also reduce the remaining photoresist layer thickness down to 1-2 μm . The pH sensor solution was then spun onto the surface to form a thin layer both on top of oxygen sensor pattern and on the area between the oxygen sensor patterns (Fig. 1J). After the sensor is thermally polymerized, double coating process was performed to form 4 μm AZ 3312 on top of the substrate as an etch mask layer. Thickness of 4 μm was selected to ensure the coated layer was fully planarized for optimized photo-exposure performance. Then the digital mask file for the second layer was loaded, and manual alignment was performed to ensure the pH sensor patterns did not overlap with the existing oxygen sensor patterns. By following the same exposure and developing protocol, the sample was partially developed which left thicker photoresist on top of oxygen sensor and thinner photoresist on top of pH sensor pattern (Fig. 1L). Ar plasma etch was used to etch away the additional photoresist between these two sensor pattern first, and then used further to etch away remaining sensor films between the patterns (Fig. 1M). The total etch time of 60-70 min was used to ensure the pH sensor on top of the oxygen sensor features was completely etched away. The final rinse using microstripper was performed to strip all remaining photoresist to complete the fabrication process (Fig. 1N). Since this process is not selective to sensor types, the order of patterning is not critical. In other words, either the oxygen sensor or the pH sensor can be patterned in an interchangeable order because it will not affect the fabrication results.

Fig. 4D shows the image of fabricated oxygen and pH sensor on the same chip using the developed process techniques. Each sensor feature is 50 μm big and separated by 20 μm . The induced fluorescence emission of oxygen sensor (red) was much weaker than that of pH sensor (green). To further characterize the dynamic range, we varied only one parameter (oxygen concentration or pH value) each time, and measured the emission intensity from 450 nm to 700 nm. For example, for oxygen sensor spectra measurement, we use the buffer with a fixed pH value (pH = 7.0), and oxygen bubble the medium to have a tunable oxygen concentration. And for pH sensor spectra measurement, we fixed the oxygen concentration at 8 ppm (or atmosphere condition), and then immersed the sample into a different pH buffer medium. The results are shown in Fig. 5E-F. At atmosphere condition, the emission peak at 515 nm decreased as the pH value increased, while the emission peak at 650 nm stayed constant. On the other hand, when the pH value was fixed at pH = 7.0, and the oxygen concentration decreased from 40 ppm to 0 ppm, the emission peak at 650 nm decreased as the oxygen concentration decreased, while the emission peak at 515 nm stayed constant. The emission peak of the pH sensor is much higher than that of oxygen sensor which explains the reason of having dimmer image of the oxygen sensor pattern from Fig. 4D. The future work will be optimizing the sensor synthetics process to improve the emission light intensity and the working dynamic range.

4. Conclusions

We have developed a novel method for wafer level, high throughput optical chemical sensor patterning with precise control of the sensor volume and capability of producing arbitrary patterns. PHEMA based oxygen and pH sensor were successfully patterned, integrated and characterized. It is the first time PHEMA based sensor film was successfully patterned at the wafer level with micron precision control. The result implies the developed methods can provide a feasible way to miniaturize the optical sensor system and allow for fast statistical data collection during the lab-on-a-chip application requiring optical sensing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

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Figure 1.

Schematic illustration of the sensor micro-patterning and characterization process: (A) sensor immobilization and chemical synthesis, (B) oxygen plasma wetting to generate active hydroxyl group, (C) vapor deposition of thin TMPSA layer, (D) spin-coating of oxygen sensor solution to form thin film (E) double spin-coating of AZ 3312 to form masking layer, (F) broadband UV exposure and partial developing of the AZ3312 layer, (G) reactive ion etch using Ar plasma to etch the sensor film, the remaining AZ3312 was removed afterwards, (H) surface contact profiling and fluorescence imaging of the finished sample, then diced into 13 mm × 13 mm chip if single sensor characterization is needed, (I) plasma treatment and vapor deposition of TMPSA layer for pH sensor grafting, (J) pH sensor thin film formation by spin-coating, (K) AZ 3312 double layer formation by spin-coating, (L) broadband UV exposure and partial developing, (M) reactive ion etch and photoresist stripping, (N) surface contact profiling and fluorescence imaging, (O) sensitivity measurement. The processes connected by red arrows were used to pattern oxygen sensor, and the processes connected by black arrows were used to integrate the pH sensor onto the same substrate.

Figure 2.

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Figure 2.
Spin-curve characterization for pH and oxygen sensor film

Figure 3.

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Figure 3.

Etch process characterization. The etch condition was selected to be 150 mT, 100 W, 50 sccm Ar. T_0 is the film thickness before the etch, and T is the thickness after etch for selected timeframe

Figure 4.

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Figure 4. Confocal bright field image of patterned pH and oxygen sensor features (A) and fluorescence image of oxygen (B) and pH (C) sensor patterns. (D) shows the fluorescence image of both pH and oxygen sensor features which were integrated on the same substrate. Both sensors were excited at 405 nm. The oxygen sensor emits red emission peaked at 650 nm, and the pH sensor emits green emission peaked at 515 nm.

Figure 5.

Fluorescence emission spectral changes (A) and the sigmoidal fitting at emission intensity of 525 nm (B) for single pH sensor features. (C) and (D) show the fluorescence emission spectral changes and Stern-Volmer fitting at emission intensity of 650 nm for single oxygen sensor features respectively. After integrating the pH and oxygen features onto the same substrate, the emission spectra was measured again by first tuning the buffer's pH values at fixed oxygen concentration (8 ppm) (E), and then by bubbling the buffer solution at different oxygen concentrations at a fixed pH value (pH=7.0) (F). For all above measurements, the excitation wavelength was fixed at 405 nm.