A Cylindrical Ion Sensor Tip with a Diameter of 1.5 mm for Potentially Invasive Medical Application

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ABSTRACT: A fine cylindrical chemical sensor tip is developed with optical fiber in the core, surrounded by a transparent cylinder of photopolymer Norland Optical Adhesive 61 (NOA 61), and covered by a polymer hydrogel mixed with sensing molecules. The overall diameter is as small as 1.5 mm. pH response is demonstrated using two approaches of sensing materials: (i) absorbing probe Phenol Red mixed with Rhodamine 6G fluorescent dye and (ii) 8-hydroxypyrene-1,3,6-trisulfonic acid fluorescent probe. Both the optical excitation and fluorescence signal collection are through the optical fibers. A time resolution of 10 s is achieved for pH variations. Good linearity is observed in the physiological range from pH 7.0 to pH 8.6 with reversible and reproducible outcomes. For in vitro urea measurement, the sensor tip can distinguish 1, 3, and 5 mM urea solution, which is a crucial range in saliva urea concentration. The miniaturized tip with such simple cylindrical symmetry is designed to detect vital signs during minimally invasive surgeries and can be potentially accompanied with endoscopes to enter human bodies.

INTRODUCTION

Minimally invasive surgery (MIS) has been an emerging field in the past decades. During the surgery, small incisions of 5–15 mm are made in order to do less damage to the body compared to an open surgery. Providing less recovery time, less pain, and minimal scarring, MIS has become a popular choice in operating rooms worldwide. Due to the strict limitation of the incision size, fiber-optic-based technology (endoscopy, laparoscopy, etc.) is developed to help the MIS procedure. New techniques are also being proposed because there are still some restrictions in MIS. For example, force sensors have been introduced to help replace the traditional palpation because the surgeons lose almost completely the haptic perception of the manipulated tissue. The invasive sensor size is strictly confined to fit the incisions, making it a challenge to be both small and precise. Besides the haptic perception, other vital sign monitoring is important to ensure the best surgical outcome. Signals such as blood pressure and end-tidal carbon dioxide can be detected either in an invasive or non-invasive way. However, there are some vital signs that depend only on invasive monitoring. Patients who have severe neurological dysfunction require the monitoring and management of multiple aspects of brain physiology including pressure, perfusion, oxygenation, cellular metabolism, and electrical activity. In such cases, invasive monitoring can provide the real-time information of the brain during or after surgery to help obtain the best possible functional neurological outcome. So far, there are few reports on the chemical probes that focus on miniaturizing the probe’s cross-sectional area for potential application in such surgery with small incision.

A zinc ion sensor has also been proposed in our previous work, for which zinc ion concentration is related with brain injury. However, the overall sensor size and their planar geometry are not perfect for an invasive device.

In this work, we provide a simple cylindrical sensor structure with minimized size that may be a solution for real-time invasive monitoring during brain surgery and MIS. The sensor tip has a transparent plastic cylinder with diameters as small as 1 mm built on the end of 1 or 2 optical fibers. Hydrogel sensing layers are then dip-coated onto the cylinder surface. The overall diameter of the finished sensor tip has a cylindrical symmetry with a diameter no greater than 1.5 mm. It is flexible but strong, perfectly suitable for body penetration over a long distance. In addition to fixing the fibers, the cylinder enlarges the sensing film area and broadens the optical excitation from the fiber.

The sensing layers are transducers that can transform certain chemical signals into light signals. As an example, we chose the sensing materials that respond to pH values, but the cylindrical sensor structure here can be further extended to a wide range of chemical signals. Although optical pH sensors and pH meters have been developed for decades, there are restrictions. Some of them are built in the form of planar film contained in
a cuvette, being tested for spectroscopic measurement only.12,13 Some built the sensing film directly onto the optical fiber, but in this way, the leaching and photobleaching issue of the fluorophore may not be solved.14 Even a 2D imaging technique was developed to monitor the in vivo tissue pH value.15 More importantly, none of them are designed as a fine medical device for an invasive monitoring purpose.

Figure 1 shows the schematic diagram for implementing the sensor. To prove the versatility of the tip structure, we verify two sensing approaches: mixture of fluorescent dye with an absorbing probe and direct fluorescence sensing (DFS) by a fluorescent probe. In mixture sensing, we have only one fiber in the cylinder and use a 1-to-2 fiber coupler (Y fiber) to separate excitation and photoluminescence (PL) away from the tip; while in DFS, we bury two optical fibers into the transparent plastic cylinder to collect the excitation and the emission signal independently. For mixture sensing, an absorbing probe Phenol Red (PR) and the fluorescent dye Rhodamine 6G (R6G) are mixed in polyvinyl alcohol (PVA) or poly(2-hydroxyethyl methacrylate) (PHEMA) to form a hydrogel. Such a sensing tip shows rapid response to changing pH values in a few seconds. On the other hand, 8-hydroxypyrene-1,3,6-trisulfonic Acid (HPTS) is chosen for the sensing probe in DFS because HPTS is a pH indicator and fluorescent at the same time. Here, we chose the water-soluble PVA to immobilize HPTS for which it is only soluble in water. The hydrogel with probes is then dip-coated onto the cylindrical tip, forming a sensing layer that can respond to pH values. We also show in DFS results that a second covering layer made of polyacrylonitrile (PAN) can eliminate the leaching of HPTS and prevent the PVA sensing layer from swelling when immersed in water. Thus, DFS experiment performs a great linearity in the physiological range from pH 7 to pH 8.6 with highly reversible and reproducible outcomes. We further apply the DFS sensor into in vitro urea detection using its pH sensing ability by adding urease into urea solution. The urease-urea sensing method has been well developed but usually in an electrical way.16 Here, we apply it in an optical tip, and results show that it can clearly distinguish 1, 3, and 5 mM urea solution, a crucial range in the saliva urea level.17 The success of pH detection suggests that the fine cylindrical sensing tip can be generalized to other chemical signals needed for the...

Figure 1. Components of the sensor tip and the hardware setup.

Figure 2. (A) Fabrication diagram of a cylindrical tip. (B) Optical microscopy image of the fabricated cylindrical tip. (C) Bird’s-eye view and cross section of a PR-R6G mixture in PVA/PHEMA sensor, where (a), (b), and (c) represent the Y fiber, cylindrical tip, and PR-R6G-PVA/PHEMA mixed sensing layer, respectively. (D) Bird’s-eye view and cross section of a HPTS-PVA sensor, where (1), (2), (3), and (4) represent the optical fibers, cylindrical tip, HPTS-PVA sensing layer, and PAN covering layer, respectively. (E) Optical microscopy image of the fabricated sensor coated with the sensing layer and covering layer. There is a reflection of the light on the surface. (F) PR-R6G sensor under 532 nm excitation. (G) HPTS sensor under 430 nm excitation.
invasive medicine as long as there exist absorbing or fluorescent probe molecules.

**SENSOR TIP DESIGN AND FABRICATION**

**Optical Fiber in Plastic Cylinder.** The transparent cylinder was fabricated as shown in Figure 2A. First, a pipette was used to dispense 3 μL of NOA 61 into a silicone tube with an inner diameter of 1 mm and the optical fibers were inserted into the adhesive with the help of a 21G needle. The NOA 61 resin was then hardened by exposure to 365 nm 3 W LED light, burying the fiber inside. The cylinder containing the fiber has a diameter of about 1 mm and a length of 3 mm as shown in Figure 2B.

**Sensor with Absorbing Probe/Fluorescent Dye Mixture.** The PVA hydrogel solution was prepared by dissolving 0.01 weight percent (w %) of PR, 0.001 w % of R6G, 0.02w % of NaOH, and 13 w % of PVA in deionized water (DI water). NaOH is added to neutralize the initial pH value. The mixtures are then heated and stirred at 135 °C for 30 min. The preparations of PHEMA hydrogel were similar to PVA: the same weight concentrations of PR, R6G, and NaOH are mixed accompanied with 20 w % of PHEMA and dissolved in 95% ethanol. The mixture is heated and stirred at 60 °C for 40 min. These resulting hydrogel solutions were cooled at room temperature when sealed tightly. To fabricate the PR/R6G-based sensing tip, one layer of PVA or PHEMA hydrogels containing the sensing molecules was coated over the cylinder surface by dipping into the hydrogel solution followed by slowly pulling out. The sensor tip is completed after drying at room temperature for 5 h, with the schematic structure shown in Figure 2C and the real picture shown in Figure 2F. When the tip is immersed in water for a long time, the small molecules inside PVA may diffuse out of the hydrogel, which is the leaching effect. The tip can therefore be used and measure the pH value only in a short time to be discussed below.

**Sensor with Fluorescent Probe.** HPTS immobilized in the PVA hydrogel is selected as the fluorescent sensing layer due to its high resolution in the physiological pH range. A 13 w % PVA solution in DI water is prepared and stirred at 150 °C for 10 min to completely dissolve PVA. Then, 1 mg of HPTS is added into the solution, kept stirring at 60 °C for 20 min. The HPTS-PVA hydrogel solution is dip-coated onto the cylinder and left to dry for 2 h at room temperature. The sensing layer is formed after DI water evaporates. Furthermore, PAN is also dip-coated as the second covering layer. PAN is denser than PVA so that it acts as a reverse-osmosis film, only letting water and hydrogen ions come in and out, which prevents the leaching effects and largely enhances sensor lifetime. A 12 w % PAN solution is dissolved in 1-methyl-2-pyrrolidone (NMP) at 60 °C and under stirring conditions. The covering layer is achieved using a phase inversion method to remove the solvent. The cylindrical tip is placed under DI water for 6 min after coating the PAN sol–gel. NMP and DI water will exchange at the surface of the film; meanwhile, PAN will shrink and lock the HPTS-PVA film inside. The PAN layer is further dried for 1 h at room temperature to evaporate the remaining water; at the same time, the film keeps shrinking. The sensor tip coated with the PAN layer is shown in Figure 2E under an optical microscope. The finalized schematic structure and the real picture of the DFS sensor are shown in Figure 2D and 2G, respectively.

**EXPERIMENTAL METHODS AND OPTICAL SYSTEM SETUP**

The experimental setup for the optical measurement is sketched in Figure 3A,B. It consists mainly of a light source (430 nm LED or 532 nm laser), a lens, and fiber adaptors. The collection system uses a CCD spectrometer to record the emission spectrum. (C) PR-R6G sensor tip placed in a Petri dish's cap. (D) HPTS sensor tip placed in a Petri dish.

Besides the optical setup on the sensor, spectroscopic analysis on the sensing molecules is also made. Absorbance measurements for the sensing film and solutions were conducted on a Cary 50 UV–Visible Spectrophotometer with the sensing film coated on a glass slide and the test solution placed in a 1.0 cm path length glass cuvette. A Hitachi F-4500 Spectrophotometer was used to record the fluorescence emission spectra. pH value measurements were performed on the waterproof ExStik PH100 pH meter (Extech) calibrated with standard pH buffers of 4, 7, and 10. All measurements were carried out at room temperature.

**RESULTS AND DISCUSSION**

**Spectroscopic Characteristics of Sensing Molecules.** Figure 4 shows the spectroscopic properties of the sensing molecules: HPTS and PR-R6G. Figure 4A,B shows the absorption and fluorescence spectrum of PR-R6G solution, respectively, revealing that PR-R6G solution’s fluorescence would change versus pH value due to its absorption change under 500 nm excitation. Such energy transfer characteristics could be applied into a pH detecting method; thus, in the mixture sensing implementation, we applied PR-R6G immobilized either in PVA or PHEMA using a 100 mW continuous wave laser with a peak of 532 nm as the excitation. On the
other hand, Figure 4C,D shows the absorption of the HPTS-PVA film and the fluorescence of the HPTS solution, respectively. Spectroscopic results reveal that the fluorescence of HPTS can respond to pH values under an excitation of around 460 nm. Therefore, in the DFS sensor implementation, we select a 3 W LED having a peak wavelength of 430 nm as the excitation light source.

Sensor with Absorbing Probe in PVA. Figure 5A shows the average PL intensity of the PR/6G mixture in PVA versus time with various buffer solutions. A 30 μL of buffer solution with pH 9.1 is dropped onto the sensing tip for the reaction. It is then sucked away and replaced by the next drop in pH of 5.1. In this way, the pH values are varied in a sequence, showing the PL response versus the pH variation of the sensor. The PL intensity starts to increase/decrease within 10 s when the environmental pH is changed, which is a good time resolution for a pH sensor. Unluckily, the probe PR and dye R6G will diffuse out of the hydrogel after about 6 min because PVA cannot lock them well. Also, at about the same time, the PVA will suffer from swelling because PVA itself is water-

Figure 4. Spectroscopic properties of the sensing probe. (A) Absorption spectrum of PR-R6G in buffer solutions of different pH values. (B) Fluorescence spectrum of PR-R6G in buffer solutions under 500 nm excitation. (C) Absorption spectrum of HPTS-PVA film of different pH values. (D) Fluorescence spectrum of HPTS in buffer solutions of different pH values under 430 nm excitation.

Figure 5. (A) Average fluorescence intensity of the PR-R6G mixture in PVA over the PL wavelength range of 550–575 nm at various pH buffers. (B) Reproducibility of the PR-R6G mixture in the PVA sensor by relative PL slope versus pH values. (C) Average fluorescence intensity of the PR-R6G mixture in PHEMA in a range of 550–575 nm in different buffer solutions. (D) Reproducibility of the PR-R6G mixture in PHEMA by relative PL slope versus pH values.
soluble. The advantage of PVA is the rapid diffusion of the ions through the hydrogel and fast response of the sensor tip, but it cannot work for a long time. There is only one optical fiber in the cylinder so that the sensor tip has a perfect cylindrical symmetry. The optical excitation at 532 nm is sent from one end of the Y fiber, and the PL is collected through the other end of the Y fiber shown in Figure 3A. The PR can be tuned from a dark state to a transparent state as the pH value decreases, so the illumination over R6G is also tuned as a result. Figure 6B presents the reproducibility of the sensor. The slope is defined as the relative change of PL intensity per second. The slope is considered as the indicator for the pH value for the tip. Three samples undergo the same behavior in the PL slope versus pH plot.

Sensor with Absorbing Probe in PHEMA. To deal with the problem of leaching and long-time stability of PVA, we studied a water-stable hydrogel PHEMA also containing the PR-R6G mixture. PHEMA is a water-insoluble but ethanol-soluble polymer. Luckily, PR and R6G are also soluble in 95% ethanol. A PHEMA sensor tip is then built using the same recipe and process. As expected, the sensor can last longer in the measurement without swelling, having the same time resolution of 10s. The leaching, i.e., diffusion of the small molecules out of the wet hydrogel, is negligible with the PHEMA hydrogel host. There is no visible color change of the water due to leaching. Figure 5C illustrates the average PL intensity of the PR+R6G PHEMA sensor in different pH values of buffer solutions, while Figure 5D shows the reproducibility. In principle, the absorbing probe PR can be

Figure 6. pH and urea response of the fluorescent probe. (A) Average PL intensity versus time in buffer solutions of different pH values. (B) Normalized saturated intensity versus pH with line fitting. Mean and SEM values are collected from five samples, where the SEM values are 0, 0.030, 0.057, and 0.048. (C) Average PL intensity versus time in pH 7 buffer, different concentrations of urea solutions without/with adding 0.01 mg of urease. (D) Normalized saturated intensity versus urea concentration with line fitting. (E) The reversibility of the DFS sensor is shown for the pH sequence 7.21/7.86/8.10 /8.51/9.88/7.21/7.86.
replaced by any kind of chemical probe as long as they can be dissolved in water or alcohol. Such a mixture sensing approach is therefore a platform for general chemical targets on demand. It transforms the absorbing signal to the fluorescence signal, which is readily collected by the y fiber.

**Sensor with Fluorescent Probe.** When applying HPTS as the pH indicator and fluorescent dye itself, the PL signal of HPTS is weaker compared with the absorbing probe case involving the highly fluorescent R6G. As a result, two optical fibers instead of one are inserted in the plastic cylinder for optical excitation and PL collection. In such way, there is no optical loss at the Y fiber coupler. The sensor tip still has a cylindrical shape even with two fibers buried inside. The two fibers are placed tightly together inside a syringe needle when they are inserted into the resin before UV curing as shown in Figure 3B. Also, the fluorescent probe does not work well in PHEMA, so only PVA is used as the hydrogel.

Figure 6A shows the fluorescence intensity change, integrated over 500–550 nm, versus time of the DFS sensor when switching between different pH values. The fluorescence increases and then saturates in about 6 min when the environmental pH is changed. The leaching of PVA is eliminated after the covering layer of PAN is coated. As a result, compared to the absorbing type sensor in PVA, the DFS sensor can last longer, measuring time up to 3 h, which is enough for a normal surgery. A calibration curve of normalized fluorescence intensity versus pH is constructed as shown in Figure 6B, where the mean ± deviation values are collected from five samples. The performances for different tips are quite reproducible, and the line fitting gives good linearity with pH value. The DFS sensor performs well in the physiological range of pH 7.0 to pH 8.6, proving the potential of invasive pH measurement. Even though not perfect, the DFS sensor show a reversible saturation value as the pH value goes up and down in Figure 6E.

The DFS sensor is further applied to detect in vitro urea concentration by adding urease into the prepared urea solution. It can be achieved by a pH sensor because the generated ammonia will dissolve in water and gradually increase the pH value. Figure 6C shows the fluorescence intensity versus time when changing the environment of the sensor. The intensity increases after the addition of urease and reaches stability in about 6 min. A pH 7 buffer is inserted in the interval of each concentration in order to eliminate the remaining urea in the previous measurement, also proving that the sensor outcome is reversible. The calibration curve of normalized fluorescence intensity versus urea concentration is constructed as shown in Figure 6D. With a clear normalized intensity difference in 1, 3, and 5 mM, the sensor may also be applied to the practical implementation of saliva urea detection.

**CONCLUSIONS**

A fine cylindrical chemical sensor tip with a diameter of 1.5 mm is developed. The optical excitation and fluorescence collection are through the optical fiber inside the transparent cylinder, and the sensing materials cover the outside. pH detection with a short response time of 10 s and reproducible PL responses are demonstrated in the absorbing probe. The sensor is also applied to urea detection with good results. Both absorbing or fluorescent type probes can be applied, and the sensor structure can be extended to general chemical probes. Due to the small cross-sectional area, such a cylindrical sensor can be potentially used to obtain crucial chemical information in surgery as it can pass through small incisions or body openings.

**MATERIALS**

Figure 7 shows the main molecules used in this work. The fluorescent pH probe HPTS and absorbing pH probe PR were purchased from Alfa Aesar. The hydrogel polymers PHEMA and PVA, the fluorescent dye R6G, urease, and the covering polymer PAN were purchased from Sigma-Aldrich. Urea and buffering agent TRIS hydrochloride were purchased from Fisher Scientific. The optical fibers for the fluorescent probe were purchased from Onset EO Corporation. The fiber has an outer jacket of 500 μm, cladding of 225 μm, and silica core of 200 μm. The range of the optical wavelength is 300–1200 nm. The 1-to-2 Y fiber with a cladding of 220 μm and silica core of 200 μm was obtained from FIPOS. The optical fibers are inserted in the transparent plastic cylinder, which is made by curing the resin inside a silicone tube under ultraviolet (UV) irradiation. The UV resin is Norland Optical Adhesive 61 (NOA 61), purchased from Norland Products Incorporated.

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Notes

The authors declare no competing financial interest.

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