2D Photonic Crystal Hydrogel Sensor for Tear Glucose Monitoring

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ABSTRACT: Photonic crystal (PC) materials have huge potentials as sensors for noninvasive and real-time monitoring glucose in tears. We developed a glucose-sensitive PC material based on monolayered colloidal crystals (MCCs). Polystyrene nanoparticles were first self-assembled into a highly ordered MCC, and this two-dimensional (2D) template was then coated by a 4-borobenzaldehyde-functionalized poly(vinyl alcohol) hydrogel. Such a sensor efficiently diffracts visible light, whose structural color could change from red through yellow to green, as the glucose concentration altered from 0 to 20 mM, covering both tears’ and bloods’ physiological ranges. The sensor also represents a rapid response within 180 s at each titration of glucose, combining the characteristics of high accuracy and sensitivity in detecting the glucose concentration in tears, and this intelligent sensing material presents certain possibility for the frontier point-of-care glucose monitoring.

INTRODUCTION

Global burden of diabetes mellitus is increasing worldwide year by year, and nearly 422 million patients have been diagnosed.1 Abnormalities of glycemic control usually produce other diseases and cause a series of complications that may even endanger life.2 Currently, instantaneous blood glucose self-monitoring sensors require collecting blood samples several times a day and thus are unable to warn of hypoglycemic and hyperglycemic events in advance. Such an intermittent and minimally invasive approach is inconvenient and results in poor patient compliance. Hence, noninvasive and real-time detection devices were designed for the painless and convenient reporting of the blood sugar level.3 Most of the tear glucose sensor devices rely on the use of glucose oxidase (GOD) and production—detection process of hydrogen peroxide (H2O2).4 During reduction—oxidation (redox) reactions, GOD can be enzymatically converted to H2O2, which was then detected with a chromogenic reagent or electrode to determine the glucose concentration. Unfortunately, GOD and H2O2 could be affected by other components of the tear, especially the electrolyte, and thus considerable efforts have been made for the developing of nonenzymatic glucose sensors.5,6 Because interstitial fluids including saliva,7 urine,8 tears,9,10 and sweat5,11 are easier to get from the body surface, they have become the hotspot in the study of nonenzymatic glucose monitoring. Among them, it has been confirmed that the glucose concentration of tears is closely related to the blood glucose level, and there is a ca. 30 min’s delay, as glucose is transported from the blood level to the tear fluid level.12 Although the real-time tear glucose information might be later than that in blood, there are still many advantages for tear glucose monitoring, such as stability and accessibility of tear fluid, painless detecting, and being pollution-free. To accomplish tear glucose monitoring, the sensitivity and accuracy of the senor should be well controlled because the amount of glucose in tear (0.16 ± 0.03 mM by mean in normal individuals, and 0.35 ± 0.04 mM by mean in diabetics) is much lower than that in blood (3.90−6.20 mM in normal individuals, 7.10−11.10 mM in postprandial normal individuals, and 11.10−30.00 mM or even higher in diabetes).13 Moreover, as a complex composition of the body fluid, aside from water and electrolyte, tear also contains nitrogenous compounds, sugars, oligonucleotides, steroids, organic acids, vitamins, enzymes, and lipids,14 which can influence the detection of glucose, and the total volume of a tear is as small as 7 ± 2 μL15,16 meanwhile the update rate of a tear is as slow as 1.2 μL/min.17,18

The photonic crystal (PC) is an ideal material to prepare point-of-care type tear glucose sensors to provide vast visual
detection because of its special performance.\textsuperscript{3,19,20} Such a material possesses a periodically dielectric structure, which selectively modulates electromagnetic waves with a certain frequency according to Bragg’s law. One type of PC sensor was developed by combining three-dimensionally (3D) charged crystalline colloidal array (CCA) and hydrogels, where CCA is the array with a face-centered cubic structure that Bragg diffracts visible light, which is electrostatically self-assembled by monodisperse colloids, and the hydrogels were commonly in situ polymerized of the monomer solution surrounding the CCA. Thus, the Bragg diffraction of the 3D PC sensors shifts because of the swelling or shrinkage of the functionalized hydrogel matrices in response to certain external stimuli such as humidity,\textsuperscript{21} pH, and metal cations,\textsuperscript{22} and the color changes accordingly. Various 3D PC sensors were developed based on this method for the detection of specific analytes such as nitroaromatic molecules,\textsuperscript{23} glucose,\textsuperscript{19} and ionic strength.\textsuperscript{24} The major limitation of 3D PC materials is the fragility of the unstable matrices because of the low polymer content and species. Only nonionic polymers were utilized to fabricate 3D PC materials because the ionic force would disorder the assembly of CCA. Recently, physically gelated hydrogel has been employed to form an ionic 3D PC sensor.\textsuperscript{25} The physical hydrogel has a robust matrix, and thus, harsh chemical functionalization could be done to make such materials multisensitive. Most recently, a contact lens-based 3D PC glucose sensor has been developed using such a physical hydrogel; however, the sensing ability was limited because the volume change of the hydrogel was restricted by the lens.\textsuperscript{10}

Meanwhile, two-dimensionally (2D) constructed PCs can be prepared by self-assembling monodisperse colloids into an ordered monolayer.\textsuperscript{26} After being attached to stimuli-responsive hydrogels, the diffraction from the 2D array can be used to monitor the hydrogel volume change according to analytes.\textsuperscript{27,28} Hence, by attaching glucose recognition molecules, the concentration of the tear glucose could be visually read out by observing the perceptible color change.\textsuperscript{29} The advantages of 2D PC sensors include (1) independent fabrication of 2D arrays and hydrogels, the 2D array could be either attached onto the hydrogel surfaces or embedded into the hydrogel during polymerization; (2) the response of the sensor can be determined by measuring the Debye ring instead of using a spectrometer; and (3) the readout of the 2D PC sensor is reliable because the diffracted light from the 2D material is independent of the refractive index.\textsuperscript{30} The first 2D PC pH sensor utilized carboxylates to immobilize counter-ions within the hydrogel. The diffraction red shifts from 620 to 668 nm between pH 3.22 and 7.91 as the carboxyl groups ionization increases the free energy of mixing and swells the hydrogel.\textsuperscript{31} A 2D inverse opal polyvinylpyridyne hydrogel sensor was also developed for pH sensing via a facile spin-coating method.\textsuperscript{32} For the glucose-sensing motif, a 2D PC sensor was prepared by attaching a monolayer of polystyrene (PS) particles with a diameter of 950 nm onto the surface of polyacrylamide-co-acrylic acid hydrogel,\textsuperscript{33} which exhibits a rapid response to glucose and reached the binding equilibrium within 3 min, and the structure color of the sensor shifted from red to green as the glucose concentration changed from 0 to 20 mM. However, the response in the physiological range could not be distinguished by naked eye, which limited its application in tear glucose sensing. Another 2D PC material for urine glucose sensing was reported, which can avoid the urine-interfering elements, but the diffraction color change could not be distinguished in low glucose concentration.\textsuperscript{34} It’s crucial to fabricate a sensor that reports the glucose level in the tear glucose range with good accuracy and repeatability.

Herein, as inspired by Asher’s previous work,\textsuperscript{20,26−28} we present a novel gelated monolayered colloidal crystal (GMCC) PC material to monitor glucose in the tear fluid. Briefly, two-dimensionally assembled PS colloids were embedded in a 4-boronobenzaldehyde (4-BBA)-modified poly(vinyl alcohol) (PVA) hydrogel (see Figure 1). During detection, as the glucose molecule binds to borate, the PVA diols and borate ions alter their proportion that change the hydrogel volume and thus shift the Bragg diffraction of the GMCC. The accompanying structure color change of the GMCC could be easily distinguished within 180 s once the glucose concentration changed, especially in the physiological range. Furthermore, we can also measure the size of the Debye ring to determine the change in the lattice constant of the 2D PC. Compared with the dry chemistry method for qualitative analysis, such a GMCC sensor is more accurate and cost-effective. Moreover, this novel sensor provides a new approach to detect tear glucose, which is far superior to the previously reported PC sensors with higher sensitivity and less interference.

![Figure 1. Illustration of the construction of GMCCs.](image)

**RESULTS AND DISCUSSION**

The work presented here describes the combination of 4-BBA-modified PVA hydrogel and monolayered colloidal crystal (MCC) to form a GMCC photonic material. The MCC is constructed by spherical PS colloids that are assembled into a generally hexagonal close-packed lattice. A more stable GMCC was then formed via an in situ physical gelation to couple the MCC and the PVA hydrogel. The hydrogel volume transmission causes the MCC lattice distance change and thus accordingly the diffraction wavelength shifts.

The monodisperse PS colloids (∼600 nm) are shown in Figure 2a; they readily self-assembled into an ordered close-packed hexagonal monolayer structure (Figure 2b). Figure 2c shows a 2D MCC covered with freshly prepared PVA hydrogel; the structure of the MCC stayed stable after gelation and a GMCC was thus formed. The interstices between neighboring colloids are filled with PVA hydrogel, which indicates that the MCC was embedded in the hydrogel matrix. In Figure 2d, a non-close-packed MCC with PVA hydrogel was observed, and the distance between the colloids enlarged because of the swollen hydrogel.

Because 2D MCC has ordered repeating units around hundreds of nanometers, this periodic structure is able to strongly diffract visible light. Alternatively, the diffracted light could easily be observed by illuminating the 2D crystal with a flashlight at a normal angle, a convenient method to confirm the 2D array and its interparticle spacing. A diffraction of 6-spot symmetry will be shown when illuminated with monochromatic
laser light if the colloids form a perfect hexagonal MCC. Actually, the MCC exposed in laser beam is randomly oriented because the crystallites are significantly smaller than the beam; thus, many symmetry spots with the same diffraction diameter will form a ring, and such pattern is called a Debye diffraction ring. We excite the GMCC along its normal with a 445 nm laser pointer. As expected, the 2D PC diffracts the laser light, and a sharp circle was observed (Figure 3a). The spacing of the colloids in the GMCC can be calculated by the following formula, and the related parameters can be clarified in Figure 3b.

\[
d = \frac{4\lambda_{\text{laser}} \sqrt{(D/2)^2 + h^2}}{\sqrt{3} D}
\]

where \(\lambda\) is the incident wavelength, \(d\) is the nearest-neighboring colloids spacing, \(h\) is the distance between the GMCC sample and the screen, and \(D\) is the diameter of the Debye diffraction ring on the screen. Hence, we can easily determine the concentration of the analytes by measuring the spacing of the colloids embedded inside the GMCC hydrogel. The method only requires a laser pointer and a ruler, as illustrated in Figure 3b.

Tear is a complex solution containing various components which can influence the detection of specific analytes; artificial tear fluid (ATF) was prepared according to the constituents of human tear; and the prepared ATF was adjusted to pH 7.4 to simulate the real detection conditions. We noticed that the diffraction of the PVA GMCC film blue-shifted as the cross-linking reaction time was extended because the cross-link density strongly influences the equilibrium hydrogel volume, that is, the sensitivity of the hydrogel sensor. In this study, the GMCCs were cross-linked in GA solutions for 0 to 4 h. The obtained GMCCs were immersed in ATF solutions with different glucose concentrations for 15 min to reach the swelling equilibrium; the hydrogel films were taken out; and the diameters of the Debye diffraction ring were measured. The spacing of the PS colloids can be calculated according to eq 1.

Figure 4 shows the dependence of the GMCC sensitivity on the gelation time. After 15 min of adsorption in the ATFs with different glucose concentrations, the GMCCs were taken out and placed directly beneath a 445 nm laser pointer. By measuring the diameter of the Debye ring and calculating the interparticle spacing according to eq 1, the response for different GMCCs was traced out. For the original GMCC hydrogel, without GA cross-linking, the spacing of the colloids changed 5 nm as the glucose concentration increased from 0 to 1 mM; however, the hydrogel could not maintain its mechanical strength for further detection. For the GMCC cross-linked for 0.5 and 1 h, the interparticle spacing narrowed from 915 to 784 nm (131 nm) and from 867 to 775 nm (92 nm), respectively, as the glucose concentration increased from 0 to 10 mM. While the GMCC cross-linked for 2 and 4 h, the spacing of the colloids changed from 792 to 767 nm (25 nm) and from 740 to 731 nm (9 nm), respectively. It is worth noticing that for the GA cross-linked GMCCs, there is an inflexion point at around 10 mM glucose with a narrowest
interparticle spacing, before which the spacing narrowed as the glucose concentration increased and after which the spacing enlarged following the increase of the concentration of glucose. However, it’s not a disturbing result considering that the physiological concentration of tear glucose range is from 0.1 to 0.6 mM, far to reach the inflexion point of our GMCCs. The result indicated that the GA cross-linking strengthened the PVA hydrogel matrix so that the GMCC could shift its volume in complex chemical solutions, and the hydrogel sensors’ glucose response decreased as the cross-linking time increased. The inset of Figure 4 plots the interparticle spacing change of original GMCC to the cross-linking time. It is found that the nearest spacing of the GMCC sample revealed a substantial decrease over the first 2 h, indicating that the formation of cross-linking points by GA shrank the system volume. Such shrinkage leveled off after 2 h, and the cross-linked hydrogels stopped decreasing after 4 h of gelation, which probably indicates that the GMCC reached its highest cross-linking density within 4 h. Thus, we chose the 0.5 h cross-linked GMCC hydrogel as the optimal material to measure the glucose concentration, whose glucose sensitivity and mechanical strength were satisfactory.

For the optimized GMCC, we further investigated its glucose response ability in the tear glucose range (ca. 0.1–0.6 mM). As described in Figure 5a, the particle spacing narrowed from 915 to 878 nm as the glucose concentration increased from 0.1 to 0.6 mM, where a 37 nm linear spacing shifting was found with the increased glucose concentration (inset of Figure 5a). The corresponding visible color change is also displayed in Figure 5a, where we found that initially the GMCC was red, which gradually blue-shifted with the changing glucose concentration. As the glucose concentration increased to 0.6 mM, a reddish yellow diffraction was observed, while the color could change to green with the concentration of glucose increased to 10 mM. Figure 5b shows the diffraction wavelength shifting of the GMCC recorded by a fiber optic spectrometer; the diffraction wavelength shifted from 623 to 598 nm when titrated by glucose, which matches the interparticle spacing change (from 915 to 878 nm) measured from the Debye diffraction diameter in Figure 5a correspondingly (cf. eq 1). Obviously, there is a linear correlation between the diffraction wavelength and the glucose concentration at the settled physiological range. Figure 5b also claimed the stable intensity of the diffraction wavelength detected at a settled distance as the diffraction wavelength shifted. Considering the 2D structure of GMCCs, only 20% energy of the incident light was lost as it went through the particles and then diffracted.

According to Flory’s theory,58 during the swelling process of the polymer network, the total osmotic pressure $\pi_t$ of a gel is the sum of three contributions.

![Figure 5. Glucose concentration dependence of GMCC in ATF. (a) Interparticle spacing change of GMCC with different glucose concentrations, the photographs show the forward-diffraction color changed from red, through yellow, to green, and the scale bars are 1 cm in length. The inset shows a linear stop-band shifting with the increasing glucose concentration (0.1–0.6 mM). (b) GMCC response to glucose in the diffraction wavelength. A linear stop-band shifting with the increasing glucose concentration (0.1–0.6 mM) is also shown in the inset figure.](image)

![Figure 6. (a) Reversibility of GMCC interparticle spacing changes to glucose concentration of 10 mM. (b) Time dependence of spacing of colloids in response to different concentrations of glucose.](image)
boric acid process is reversible. We consider the following equilibrium of molecules. Therefore, the response of the whole sensing complexes, which could be easily hydrolyzed in acidic solution involves (Scheme S2) (1) boronic acid bind glucose both in its practical application. Similar response kinetics was observed for 200 s under gentle agitation, which was appropriate for the wavelength was recorded at different times. For 0.6 mM glucose ATF, the binding equilibrium can be reached within 200 s under gentle agitation, which was appropriate for the practical application. Similar response kinetics was observed for 10 mM glucose ATF, and the sensor may find other applications beyond tear glucose. Furthermore, in contrast to traditional 3D PC sensors, the 2D GMCC readout is intrinsically more sensitive and reliable because the 2D diffracted wavelength is independent of the refractive index.

## CONCLUSIONS

In summary, a novel GMCC sensor for the semiquantitative detection of tear glucose was constructed by embedding 2D PS MCC into a 4-BBA-functionalyzed PVA hydrogel. Such a sensor had a fantastic glucose detective sensitivity by a facile preparation. The volumetric change of GMCC, actually the spacing of the PS colloids relating to glucose combination, could be predicted by both Debye diffraction ring and diffracted color. Present results indicate that increasing the glucose concentration can induce the shrinking of GMCC, which is a boundary for certain degrees of tear glucose under physiological conditions. Because of its reaction mechanism, GMCC can specifically aim at glucose molecule though interfered by other analytes in the tear. It has great potential in replacing finger-prick diabetes test, and it might inspire the design of other intelligent sensors.

## EXPERIMENTAL SECTION

### Chemicals and Materials

PVA (99% hydrolyzed, DP = 1750 ± 50) was purchased from Shanghai Chemical Agent Co., Ltd. Monodisperse PS latex (≈600 nm, 20 wt % in water) was purchased from Aladdin Co., Ltd. All other reagents were of analytical grade and obtained from Sigma-Aldrich. Ultrapure water (18.2 MΩ·cm) is used in all experiments. The glassware used in experiments was cleaned with RCA solution (5:1 mixture of water, hydrogen peroxide (30%) and ammonia (28%)) at 75 °C for 30 min. All materials were used as received without further purification.

**Preparation of Monolayer Colloidal Crystal (MCC).** The PS latex was mixed with 1-propanol at a ratio of 1:3 in volume. The resultant suspension was then injected onto the pure water surface through a 10 μL micropipette in a Petri dish, and PS self-assembled into MCC rapidly on the air–liquid interface. Then, the MCC was gently lifted up with a glass slide. After the solvent was removed by evaporation, the sample was treated in an oven at 80 °C for 2 h.

**Preparation of Glucose-Responsive GMCC.** Typically, a 10 wt % homogeneous solution was prepared by dissolving PVA powder (10.0 g) in dimethyl sulfoxide (DMSO) at 100 °C for 2 h in the atmosphere of N₂. Then, 4-BBA (0.4 g) and drops of HCl were added for reaction (cf. Scheme S1). The resulting 4-BBA–PVA solution was cooled down and poured onto the MCC containing glass slide, and another glass slide was covered onto the sample with a two-layer Parafilm (~250 μm thick) spacer. This set of slides was frozen at −20 °C for 2 h to form physical hydrogel and thawed at 25 °C for 1 h, and then the upper slide was removed and the hydrogel-MCC was peeled off and stored in 40 mL DMSO. After that, 10% glutaraldehyde (GA, 1.5 mL) was added as a cross-linker and the pH of the system was adjusted to 1 by adding concentrated sulfuric acid (H₂SO₄). The cross-linking reaction lasted for 4 h under slight stirring, and the resultant glucose-detective GMCC was washed with water to remove unreacted molecules.

**Characterization of PC Materials.** To observe the microstructure of the GMCC, the samples were cut into 1 × 1 cm pieces as required and quenched in liquid nitrogen and...
sputter-coated a thin layer of Au; structural and morphological characterizations of the crystals were conducted using a scanning electron microscope (SEM, Hitachi, S-4800) operating at an acceleration voltage of 10 kV. Optical micrographs of the GMCC are taken by using a digital camera (Canon, EOS 6D). We quantify the stop-band of GMCC by measuring the diffraction spectra using a fiber optic spectrometer (Ocean Optics, USB 4000-XR1-ES). Spectra were captured between the wavelengths of 400 and 900 nm. The diffraction characteristic could be accurately predicted through Bragg’s relationship
\[ m\lambda_0 = \sqrt{3} d \sin \theta \]  
(7)

where \( m \) is the order of diffraction, \( \lambda_0 \) is the diffracted wavelength in air, \( d \) is the nearest spacing of the monolayered colloids, and \( \theta \) is the angle between the diffracted light and the normal to the GMCC; during detection, the \( \theta \) is adjusted to \( \sim 19^\circ \) so that the observed diffraction is located in the visible spectral range. Also, Debye diffraction rings were analyzed by a laser pointer to prove its 2D ordering. To characterize the in normal to the GMCC; during detection, the colloids, and wavelength in air, samples under the same condition.

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**ASSOCIATED CONTENT**

- Supporting Information
The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.7b02046.

Additional information about FTIR result of GMCC, schematic represent of the reactions, and glucose measurements at physiological conditions (PDF)

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**Notes**
The authors declare no competing financial interest.

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