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## Improving the *in vivo* stability and sensor lifetime with new blend membranes on CGM sensors†

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Continuous glucose monitoring (CGM) is essential for managing diabetes, including closed-loop (artificial pancreas) technology. However, the current lifetime of commercial glucose sensors used in CGM based on the electrochemical method is limited to 3–15 days. The instability or failure of implanted electrochemical glucose sensors caused by tissue reactions, outer membrane degradation, calcification, and delamination can decrease *in vivo* sensor accuracy and lifetime. Durable outer membrane materials with good biocompatibility are crucial to improve the accuracy and durability of long-term implantable electrochemical glucose sensors *in vivo* and overcome these obstacles. This study used PDMS/HydroThane as the outer membrane of the glucose sensors to demonstrate long-term *in vivo* stability in non-diabetic dogs for 28 days. The good biocompatibility and stability of the outer membrane contributed to the extended sensor lifetime. Additionally, the study evaluated the effect of oxygen on the performance of glucose sensors coated with PDMS/HydroThane blending membranes containing different PDMS contents. The results showed that glucose sensors coated with blending membranes of PDMS/HydroThane with a weight ratio of 10 : 50 were essentially independent of environmental PO<sub>2</sub> while blending membranes of PDMS/HydroThane with a weight ratio of 5 : 50 coated glucose sensors were affected by oxygen fluctuation. This new membrane was developed to increase the *in vivo* lifetime of CGM sensors with quick response time and good *in vivo* stability and provide valuable insights into the design and development of new glucose sensors for long-term CGM applications.

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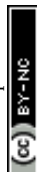
## Introduction

Diabetes mellitus, a metabolic disease affecting millions worldwide, can lead to impaired blood glucose control.<sup>1–4</sup> It is characterized by persistent hyperglycemia caused by imbalances in insulin secretion. The management of diabetes primarily relies on monitoring blood glucose levels to prevent complications such as cardiovascular diseases, neuropathy, and retinopathy. Continuous glucose monitoring (CGM) systems have emerged as a transformative technology in diabetes management, offering real-time observation of blood glucose fluctuations and enabling timely interventions. Unlike traditional finger-prick methods, CGM sensors provide continuous blood glucose monitoring data, which is crucial for optimizing therapy and improving glycemic control.<sup>5–7</sup> The application of CGM sensors has been shown to reduce glycated hemoglobin (HbA1c) levels, lower the risk of hypoglycemia, and enhance the overall quality of life for diabetic patients.<sup>8–10</sup>

The outer membranes of CGM sensors play a critical role in determining their functionality, affecting glucose permeability, oxygen permeability, biocompatibility, and stability.<sup>11</sup> The primary function of these membranes is to regulate the transport rate and proportion of glucose and oxygen to the sensor's active site while protecting the sensor from biofouling and enzymatic degradation.<sup>12,13</sup> Commercially available CGM sensors use various membrane formulations and strategies to enhance their performance and longevity. For example, polyurethane is one of the most commonly used materials in CGM sensor membranes due to its good biocompatibility, adjustable ratios of soft and hard segments, hydrophilic and hydrophobic properties, and mechanical properties.<sup>14</sup> The structure of polyurethane consists of soft and hard segments, and by adjusting their ratios, the flexibility and mechanical strength of polyurethane can be regulated. Polyurethane can also be modified by adjusting the ratios of hydrophilic and hydrophobic segments and incorporating PDMS for oxygen permeability, thereby controlling the sensor's biocompatibility, glucose and oxygen permeability, ultimately altering the sensor's stability and accuracy.<sup>15–17</sup>

Our research focuses on developing and applying a new blend membrane composed of polydimethylsiloxane (PDMS) and Hydrothane (HT) for CGM sensors. Hydrothane is a com-

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Technology Co. Ltd). The surface morphology of the membrane was observed using a FEI Inspect F scanning electron micrographs (SEM) device operating at a 2 kV acceleration voltage, and the membrane was sputtered with gold before observation. To perform the strain–stress experiments, polymer samples with a thickness of 2 mm were made from a polymer solution in THF. They cut into the dimensions of a dumbbell (115 mm in length and 25 mm in breadth, with a narrow segment measuring 33 mm in length and 6 mm in width). These samples were tested utilizing a Single Column Motor Table (Shenzhen Suns Technology Stock Co. Ltd) with an upper force limit of 50 N and a force ramp rate of 5 N min<sup>−1</sup>. In the water sorption test, the membrane was submerged in PBS (0.1 M) for 72 hours, surplus water was blotted using filter paper, and the amount absorbed was calculated by weighing the films. Using the following formula, the water sorption rate was calculated as a percentage of membrane weight gain or  $D_w$ :

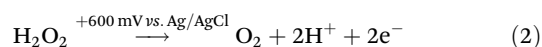
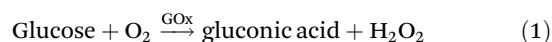
$$D_w = \left( \frac{W_s - W_d}{W_d} \right) \times 100\%$$

Using a metallographic microscope to compare the membrane thickness before and after water adsorption allowed researchers to calculate the membrane expansion rate. The following formula was used to calculate the membrane expansion rate as a percentage of membrane thickness gain, or  $D_e$ :

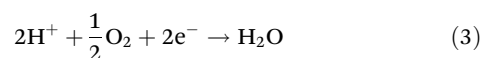
$$D_e = \left( \frac{E_s - E_d}{E_d} \right) \times 100\%$$

The response time was defined as the time needed to increase the glucose concentration from 5.0 to 10.0 mM and achieve 90% of the maximum response.

The amperometric sensor converts glucose molecules into hydrogen peroxide ( $\text{H}_2\text{O}_2$ ), using glucose oxidase (GOx). Through a series of reactions, the concentration of  $\text{H}_2\text{O}_2$  is detected on the surface of the working electrode (WE) when a bias of +0.6 V is applied anodically;<sup>18,19</sup>



The reduction reaction balances the current flow at the counter electrode (CE).



## Material characterization

RSC Appl. Polym., 2024, **2**, 880–890 | 881

brane fabrication processes are as follows. First, tetrahydrofuran (THF) solution containing 5 wt% HydroThane (HT) and 5 wt% PDMS, respectively, were prepared, and they were mixed at different ratios to obtain the PDMS/HT blending polymer solution. Second, a film coating apparatus was used to fabricate the outer membrane for the CGM. The liquid film of the outer membrane polymer started from the distal end of the sensor, and by passing the sensor through a wire loop, the entire sensor was uniformly coated with the outer membrane. The sensor was then allowed to dry in the air for 5 minutes. The outer membrane fabrication process was halted until the sensor sensitivity reached 2.0–4.0 nA mM<sup>-1</sup>.

### Biocompatibility test

Rat skin tissue samples were taken after the sensor was implanted for 28 days to assess the tissue reactions to the implanted glucose sensor during continuous monitoring. The biocompatibility experiments used male Sprague-Dawley rats (SIVZ, Tierspital, Zurich, Switzerland) weighing 150–200 g. The glucose sensors were implanted under the rats' skin using a half-wall needle. The control and experimental groups were identified as the skin tissue surrounding the silicone and PDMS/HT blended membrane-coated glucose sensors, respectively. In contrast, the sham group was identified as the skin tissue surrounding the glucose sensors without an outer membrane.<sup>27,28</sup> The biocompatibility tests were performed using hematoxylin and eosin (HE) and immunohistochemistry (IHC) stains, as previously reported.<sup>29,30</sup>

### *In vivo* glucose sensing

All animal experiments were carried out according to the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were approved by the Scientific Ethical Committee of Southeast University. For this experiment, three beagles weighing over 15 kg were utilized. Sensors were placed on each beagle's neck using the supplied applicator and following the manufacturer's recommended procedures (Yuwell CT2A CGM). It's important to note that, apart from modifying the outer membrane, all other steps were completed in the same manner as the commercially available Yuwell CT2A CGM sensors, including assembly, packaging, and sterilization. Therefore, these prepared glucose sensors were assembled and sealed in sterile packaging and sent to CGN Irradiation Technology Co. Ltd for sterilization using electron-beam radiation with a dosage of 25 kGy. Other necessary components for continuous glucose monitoring, such as transmitters, batteries, and tapes, are also available from Zhejiang POCTech Co. Ltd/Jiangsu Yuekai Biotech. Therefore, the sensor application process used in this experiment is identical to that of the commercial CT2A CGM sensors.

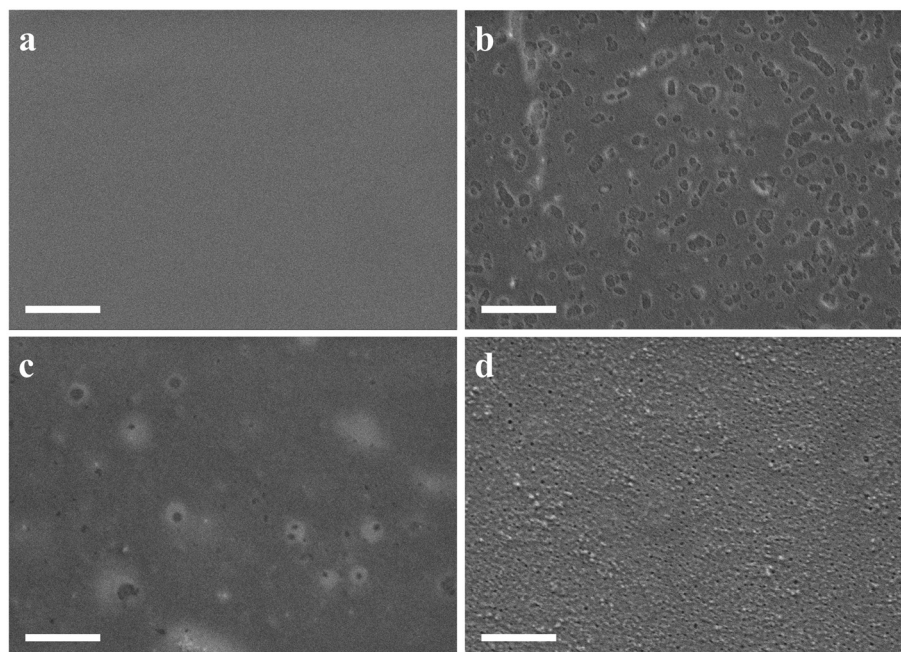
Before application, the hair around the beagle's neck was clipped, and the skin was cleaned with alcohol. A drop of tissue glue was placed on the skin-facing surface of the double-sided tape on glucose sensors. After the application, the transmitters with new batteries installed were used and connected to the app for continuous glucose monitoring. To

Zhejiang POCTech Co. Ltd/Jiangsu Yuekai Biotech provided the sensors without outer membrane coating. A polyimide (PI) substrate with a diameter of 250  $\mu\text{m}$  was used, with screen-printed platinum, Ag/AgCl, and gold as the working electrode, reference electrode, and counter electrode. The inner membrane and enzyme layer were formed according to previous reports.<sup>24,25</sup> Generally speaking, the enzyme layer was deposited on the electrode by spraying and crosslinked in glutaraldehyde vapor (produced from 25 wt% glutaraldehyde) for 15 min. The enzyme composition comprised 1.0 mL PBS (0.1 M), 50 mg GOx, and 36 mg BSA.<sup>26</sup>

The PDMS/HT outer membrane was added using a film coating apparatus (provided by Zhejiang POCTech Co. Ltd/Jiangsu Yuekai Biotech.). The procedures for the outer mem-







**Fig. 1** SEM images of the membrane: (a) HT; (b) PDMS/HT 5 : 50; (c) PDMS/HT 10 : 50; (d) PDMS/HT 20 : 50. Scale bar: 1  $\mu\text{m}$ , accelerating voltage: 2 keV.

PDMS. According to the data presented in Fig. S1,<sup>†</sup> it can be observed that the incorporation of PDMS resulted in a decrease in both the ultimate tensile strength and the elongation at break. This phenomenon can be attributed to the relatively low mechanical strength exhibited by PDMS compared with HT.<sup>33</sup>

#### ***In vitro* evaluation of oxygen effects on PDMS/HT outer membrane with different PDMS content coated glucose sensors**

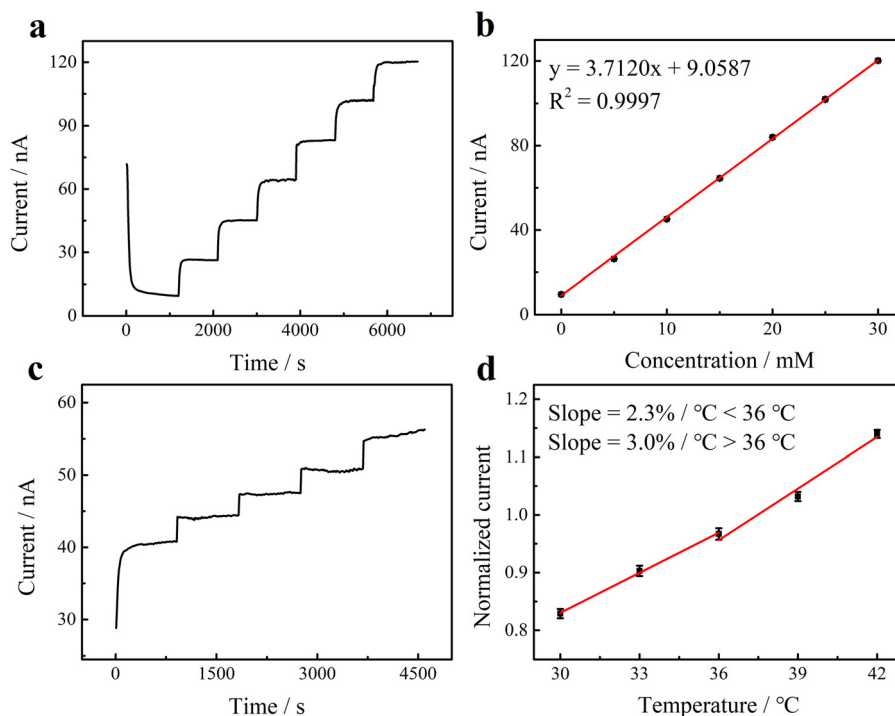
The glucose concentration in interstitial fluid is higher than the oxygen concentration. To obtain accurate sensor output results, the outer membrane of CGM sensors should regulate the diffusion ratio of glucose/oxygen at a proper rate based on the electrooxidation of hydrogen peroxide.<sup>18</sup> PDMS is permeable to oxygen,<sup>21</sup> it was usually used in the outer membrane of TPU by blending or partially replacing the soft segment of TPU with PDMS.<sup>17</sup> However, the output signal of the CGM sensor depends on the concentration of oxygen instead of glucose if the content of PDMS is too low. The system was initially brought to air equilibrium to elucidate the relationship between PDMS content and the oxygen effect, and the glucose sensor baselines were stabilized. 10.0 mM of glucose was added to the system in two sequential injections, each providing a 5.0 mM concentration. This was 3.0–5.0 mM higher than the usual blood glucose level. A steady stream of  $\text{N}_2$  gas was added to the solution to lower the oxygen tension once the glucose sensors showed signs of stable current. This operation was done slowly while constantly stirring the solution to guarantee an oxygen balance throughout the cell. The oxygen

sensor was used to track the partial pressure of oxygen. The  $\text{N}_2$  flow was partially stopped to allow for a slow accumulation of oxygen in the system once the oxygen effect was noticed at a low  $\text{PO}_2$  level. This permitted the glucose sensors to start operating normally again. To achieve an accurate  $\text{PO}_2$  measurement at extremely low oxygen tension, the numerical values of the oxygen tension were also recorded simultaneously (as shown in Fig. 2a). One of the common data sets seen in the experiment mentioned above is Fig. 2. The oxygen partial pressure measured using a calibrated oxygen sensor is shown in Fig. 2a. Fig. 2b displays the current output of the CGM sensor (sensitivity: approximately  $3.8 \text{ nA mM}^{-1}$ ) coated with PDMS/HT blending outer membrane with a weight ratio of 5 : 50 in response to 10.0 mM glucose. Fig. 2c displays the output of the CGM sensor (sensitivity: approximately  $3.7 \text{ nA mM}^{-1}$ ) coated with PDMS/HT blending outer membrane with a weight ratio of 10 : 50. Interestingly, Fig. 2b shows that the sensor did not show any oxygen effect until the oxygen tension dropped to 8 mm Hg. At that point, the sensor began to function. It rapidly turned over due to the accumulated glucose trapped inside the enzyme layer's lack of  $\text{O}_2$  supply, producing a peak current before returning to the normal steady state current. Fig. 2c's CGM sensor demonstrates that it did not indicate any oxygen effect, even when the oxygen tension fell to 5 mm Hg.

Above all, when the weight ratio of PDMS/HT is 5 : 50, the oxygen effect may affect the accuracy of the output signal of the CGM sensor. When the weight ratio of PDMS/HT is 10 : 50, the oxygen effect does not exist. According to the SEM results, the porosity was observed in the blending membrane when the weight ratio of PDMS/HT is 20 : 50, which is detrimental to







**Fig. 4** (a) Change in the sensor response with the sequential addition of glucose aliquots. Sensors were immersed in PBS (pH 7.4) at  $32.0 \pm 0.5$  °C while aliquots of glucose were added to produce step responses: 0, 5.0, 10.0, 15.0, 20.0, 25.0, and 30.0 mM. (b) Plot of calibrated sensor response as a function of glucose concentration. (c) Amperometric  $i-t$  curve of the sensor in 0.1 M PBS (pH 7.4) containing 10.0 mM glucose with different testing temperatures ( $30.0 \pm 0.5$ ,  $33.0 \pm 0.5$ ,  $36.0 \pm 0.5$ ,  $39.0 \pm 0.5$ , and  $42.0 \pm 0.5$  °C). (d) Temperature effect for glucose detection on PDMS/HT modified electrode.

temperature parameters of  $2.3\% \text{ } ^\circ\text{C}^{-1}$  ( $<36$  °C) and  $3.0\% \text{ } ^\circ\text{C}^{-1}$  ( $>36$  °C) were recorded. For the sake of comparison, the current was normalized to 37 °C.

In this work, acetaminophen (0.17 mM), bovine serum albumin ( $22 \text{ mg mL}^{-1}$ ),<sup>35</sup> physiological concentrations of L-ascorbic acid (0.11 mM)<sup>36</sup> and uric acid (0.48 mM)<sup>37</sup> are combined with 10.0 mM glucose in PDMS/HT-coated glucose sensors to examine the effects of recognized interferents. The PDMS/HT-modified glucose sensor demonstrates high selectivity for glucose detection, as shown in Fig. S3,† where the current change for glucose detection in the presence of possible interferents was less than 5%.

Electron beam radiation is a typical sterilizing procedure for implanted glucose sensors. The impact of electron beam radiation on sensor performance was thus investigated by contrasting the sensitivity variations before and after sterilization. The results are displayed in Table S3.† The results show that the sensitivity of the glucose sensors remained unchanged, indicating that the sterilizing procedure did not affect the polymer's permeability or the activity of the enzymes.

### Biocompatibility test

HE and IHC staining of rat tissues was used to assess the biocompatibility of the sensor. During prolonged use, the tissue reaction and sensor-associated fibrosis to electrodes are important variables influencing the sensor's accuracy and longevity.

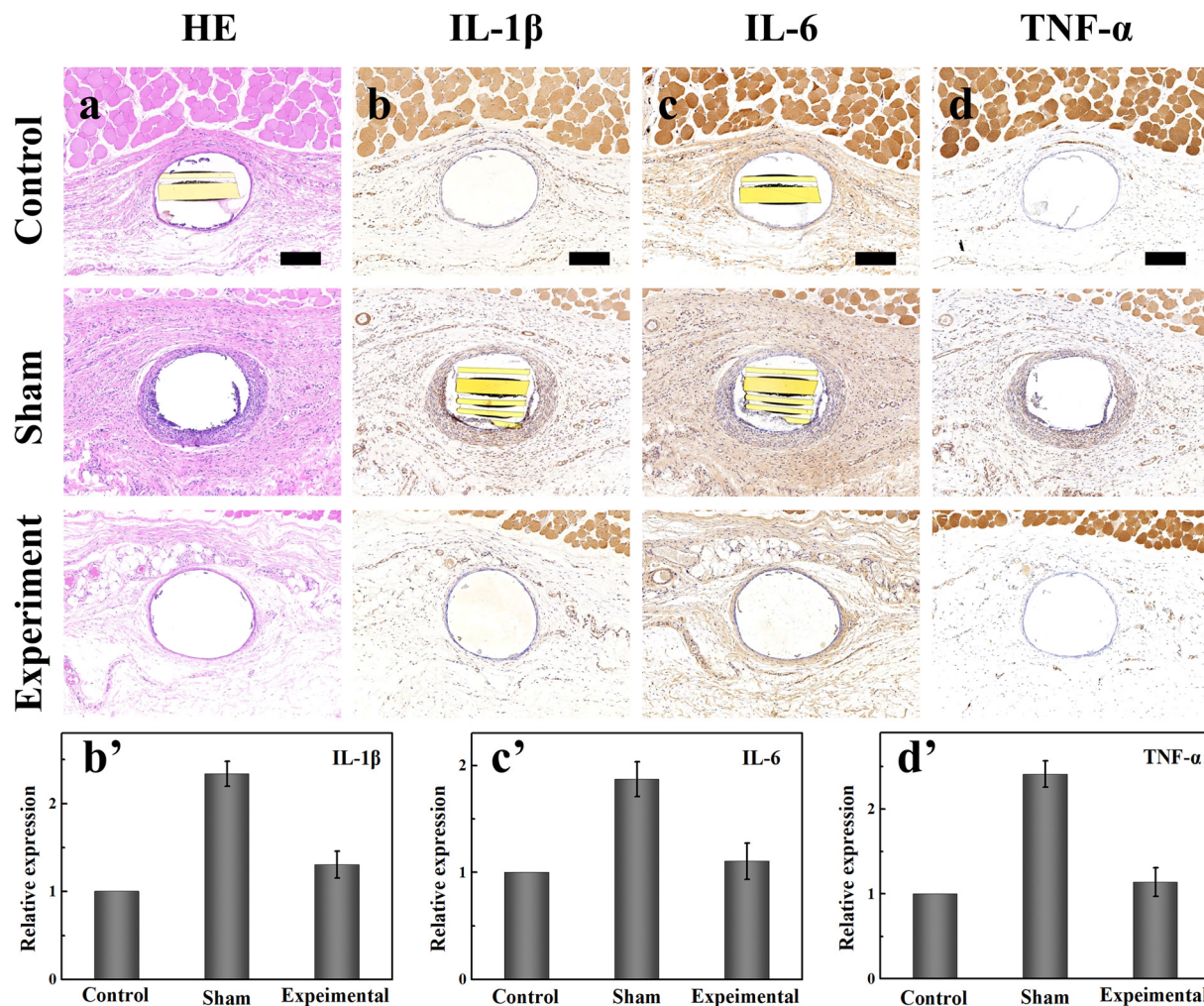
Skin tissues surrounding the implanted sensor without an outer membrane were studied as part of a sham control group. In contrast, skin tissues surrounding the implanted sensor with PDMS/HT and silicone outer membrane were evaluated as experimental and control groups, respectively. Hematoxylin and eosin (H&E) staining results after 28 days of implantation showed that the tissues surrounding sensors with PDMS/HT (experimental group) outer membrane had thinner fibrous capsules (20  $\mu\text{m}$ ) and milder inflammatory cell infiltration than the tissues surrounding sensors without outer membrane (sham control group, 80  $\mu\text{m}$ ). Fig. 5 illustrates these findings. The silicone-coated sensors in the control group showed the least inflammatory cell infiltration and the thinnest fibrous capsules (12  $\mu\text{m}$ ). Additionally, IHC staining of IL-1 $\beta$ , IL-6, and TNF- $\alpha$  was performed to assess the inflammation in the skin tissue. The IHC staining revealed lower expression areas of IL-1 $\beta$ , IL-6, and TNF- $\alpha$  in the experimental group than in the sham groups and slightly higher than in the control group, as shown in Fig. 5b'-d'. These findings suggest that the outer membrane coating on glucose sensors has good biocompatibility.

### *In vivo* electrochemical glucose sensing

The *in vivo* stability and sensor lifetime of nine prepared CGM sensors coated with PDMS/HT outer membrane was evaluated in beagles over 31 days, and the detailed sensitivity variation







**Fig. 5** (a) HE staining micrographs of the skin tissues of the rats. (b–d) IHC of the IL-1β (b), IL-6 (c), and TNF-α (d) in the skin tissues. Grey-dyed cytokines could be observed in the tissues. (b'–d') Relative expression of the IL-1β (b'), IL-6 (c'), and TNF-α (d'). Scale bars: 200 μm. Control group: silicone-coated glucose sensors. Sham group: glucose sensors without outer membrane. Experiment group: PDMS/HT coated glucose sensors.

of the nine sensors on days 3, 15, and 28 was presented in Fig. S4† and Table 1. These results indicate that these sensors can work stably *in vivo* for more than 28 days. After 28 days, the implanted sensors commonly exhibited a progressive loss of sensor sensitivity until complete failure. The failure of sensors was likely due to tissue reactions of the sensor–tissue interface.<sup>38</sup> The mean *in vivo* sensitivity variation of the 9 sensors over time is shown in Fig. 6a, which remained rela-

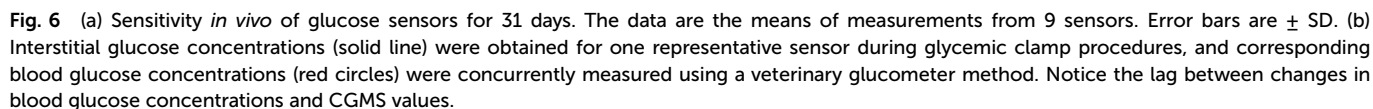
tively stable during days 3 to 28. The stable *in vivo* performance of the implanted glucose sensors facilitates more concise output results, which is beneficial for advancing CGM management of diabetes. The sensor lifetime is extended for two weeks compared to some commercial CGM sensors, which can be attributed to the following reasons. First, the excellent biocompatibility of the outer membrane can reduce tissue reactions and prevent sensor-associated fibrosis. Second, the

**Table 1** *In vivo* sensitivity data obtained on different days

| Sensor  | Dog 1 |      |      | Dog 2 |      |      | Dog 3 |      |      |
|---------|-------|------|------|-------|------|------|-------|------|------|
|         | 1     | 2    | 3    | 4     | 5    | 6    | 7     | 8    | 9    |
| Initial | 3.89  | 3.87 | 3.85 | 3.82  | 3.80 | 3.88 | 3.85  | 3.82 | 3.89 |
| Day 3   | 3.97  | 3.74 | 3.87 | 3.75  | 3.69 | 3.84 | 3.87  | 3.93 | 3.82 |
| Day 15  | 3.65  | 3.63 | 3.88 | 3.68  | 3.67 | 3.84 | 3.80  | 3.90 | 3.88 |
| Day 28  | 3.73  | 3.48 | 3.82 | 3.59  | 3.64 | 3.73 | 3.73  | 3.89 | 3.77 |
| Day 31  | 1.79  | 2.24 | 2.53 | 2.36  | 1.98 | 2.32 | 2.45  | 2.38 | 2.26 |







While previous reports have shown that the lifetime of glucose sensors has increased from 3 days to 15 days, there are few reports of sensors with reliable results beyond 15 days. In this work, the prepared CGM sensors can work *in vivo* for 28

In this study, the long-term storage stability of glucose sensors with an PDMS/HT outer membrane was thoroughly examined. The sensors typically exhibited a sensitivity range of 3.0–4.0 nA mM<sup>-1</sup> and maintained linearity between 5.0 and 30.0 mM, with a response time of 30 seconds following the injection of 5.0 mM glucose. The storage stability under ambient conditions (25.0 ± 0.5 °C, RH 45% ± 5%) was evaluated after storage periods of 15, 30, 45, and 60 days. Before testing in glucose concentrations ranging from 5.0 mM to 30.0 mM, the sensors were polarized in PBS (pH 7.4) until the background current was reduced to below 10.0 nA. The background current was defined as the intercept of the linear regression analysis for the dose–response equation. Table 2 illustrates the change in sensitivity for these sensors before and after specific storage durations in ambient conditions. The results indicated only

|     | Before<br>(nA mM <sup>-1</sup> ) | After<br>(nA mM <sup>-1</sup> ) | Time of<br>storage (day) | % change |
|-----|----------------------------------|---------------------------------|--------------------------|----------|
| 1#  | 3.87                             | 3.83                            | 15                       | -1.0%    |
| 2#  | 3.85                             | 3.81                            | 15                       | -1.0%    |
| 3#  | 3.89                             | 3.94                            | 15                       | +1.3%    |
| 4#  | 3.76                             | 3.82                            | 30                       | +1.6%    |
| 5#  | 3.88                             | 3.81                            | 30                       | -1.8%    |
| 6#  | 3.82                             | 3.73                            | 30                       | -2.4%    |
| 7#  | 3.84                             | 3.89                            | 45                       | +1.3%    |
| 8#  | 3.79                             | 3.68                            | 45                       | -2.9%    |
| 9#  | 3.86                             | 3.78                            | 45                       | -2.1%    |
| 10# | 3.85                             | 3.93                            | 60                       | +2.1%    |
| 11# | 3.86                             | 3.75                            | 60                       | -2.8%    |
| 12# | 3.88                             | 3.79                            | 60                       | +2.3%    |

minor signal changes ( $\leq 5\%$ ) within 60 days of storage in ambient conditions. These observations suggest that the bio-sensor possesses good storage stability, which can be attributed to the high chemical stability of the outer membrane and its protective effect on the electrode.

## Conclusion

This work demonstrated that PDMS/HT blending outer membrane can extend the sensor lifetime to at least 28 days with excellent *in vivo* stability when implanted subcutaneously in non-diabetic beagles, which extended the sensor life for 2 weeks compared with commercially used electrochemical implanted glucose sensors. It also evaluated the effect of oxygen on the blending membranes of PDMS/HT-coated glucose sensors with different PDMS content in the outer membrane. It demonstrated that glucose sensors coated with blending membranes of PDMS/HT with a weight ratio of 10:50 were essentially independent of environmental  $\text{PO}_2$  while blending membranes of PDMS/HT with a weight ratio of 5:50 coated glucose sensors were affected by oxygen fluctuation. This result is also important for developing a new outer membrane of implanted glucose sensors based on the electrochemical detection of hydrogen peroxide. This work provides a stable, protective membrane that can potentially be used for commercial long-term continuous glucose monitoring in diabetes management with an extended sensor lifetime.

## Author contributions

Yinxu Zuo: conceptualization, methodology, validation, investigation, data curation, writing – original draft, writing – review & editing. Lanjie Lei: methodology. Ke Huang: validation. Qing Hao: funding acquisition. Chao Zhao: funding acquisition. Hong Liu: conceptualization, data curation, supervision, funding acquisition.

## Data availability

The data supporting this study's findings are available from the corresponding author, upon reasonable request.

## Conflicts of interest

Authors have no conflict of interest to declare.

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