

Glucose-driven Monolithic Polydimethylsiloxane Decompression Unit for Drug Release Device Using Plasma-activated Bonding Technology

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A new enzymatic chemomechanical actuator that can convert the chemical energy of glucose into mechanical energy for an autonomous drug release system without electrical power was developed and demonstrated. The glucose-oxidase-immobilized membrane recognized glucose and converted the chemical energy found in glucose to the mechanical energy of actuation. The decompression unit of the system consisted of an enzyme co-immobilized dialysis membrane, an ultraviolet cross-linkable polymer of polyvinyl alcohol (PVA-SbQ), and polydimethylsiloxane (PDMS) microfluidic channels. According to the evaluation of the bonding condition between PVA-SbQ and PDMS, direct bonding with different polymer materials was realized without damage to glucose oxidase (GOD). The optimized plasma treatment conditions were a sweep rate of 400 mm/s and an applied electric power of 140 W. The decompression unit had an appropriate decompression rate (2.16 Pa/s) at the glucose concentration of the blood sugar level, which was achieved by increasing the enzyme membrane area per gas phase volume. The monolithic PDMS decompression unit is promising for the development of a chemomechanical device driven by human blood sugar for diabetes treatment in the future.

1. Introduction

Diabetes mellitus is a well-known serious and chronic disease and a global health problem. Approximately 422 million adults were living with diabetes in 2014, compared with only 108 million in 1980.⁽¹⁾ When the effect of insulin secretion decreases and a hyperglycemic state persists in diabetic patients,⁽²⁾ an insulin pump⁽³⁾ and self-injection by a syringe⁽⁴⁾ and insulin

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therapy can stabilize blood sugar levels.⁽⁵⁾ It is necessary for diabetic patients to stabilize their glucose concentration at a suitable level. An artificial pancreas has been developed, which is based on blood glucose information obtained by continuous glucose monitoring (CGM), in which the insulin dosage is controlled by feedback.^(4,6) However, there are some problems such as complicated operations, the need for an external power supply, and the risk of infection.^(7–10) There are certain important risks in daily insulin use and the measurement of glucose concentration, with hypoglycemia a possible result of errors in the insulin dosing volume or blood sugar measurements.

On the other hand, our group has developed and demonstrated chemomechanical organic engine-based drug release systems for an autonomous drug release device for glucose control.^(11–13) In our previous work, we developed a glucose-driven chemomechanical autonomous drug release system using an enzymatic reaction that reduces the chamber pressure in an acrylic cell due to oxygen consumption accompanying the oxidation of glucose using glucose oxidase (GOD) (Fig. 1). The GOD reduces the pressure according to the concentration of glucose, which is a blood sugar component. Subsequently, the performance of the organic engine was enhanced by physical and chemical modifications and multi-enzymatic amplification techniques.⁽¹²⁾ The glucose-driven decompression unit reduces the pressure of the gas phase cell according to the concentration of glucose, which is a blood sugar component. However, since the operation of the existing system requires a glucose concentration of about 2.5 times the blood glucose level of the diabetic patient, it is necessary to improve the decompression performance to operate this system at the blood sugar level. In addition, silicone seals for enhancing the airtightness of the gas phase cell and mechanical bonding with screws and nuts also complicate the structure.

Polydimethylsiloxane (PDMS) is a well-known biocompatible material and high-performance polymer having both inorganic and organic properties owing to its inorganic siloxane skeleton and organic skeleton of methyl groups.^(14–17) PDMS also has high permeability, flexibility, self-adsorption, biocompatibility, and chemical resistance and can be microfabricated.^(18–22)

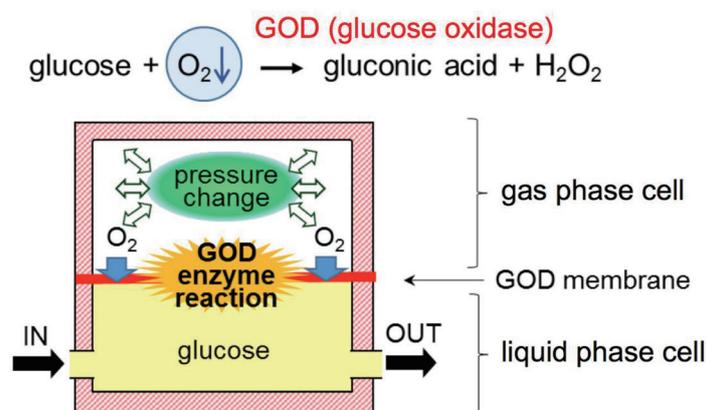


Fig. 1. (Color online) Working principle of glucose-driven decompression unit using GOD in enzyme-immobilized membrane and glucose solution.

It can be bonded at room temperature using plasma surface treatment, and its bonding with dissimilar materials such as a glass substrate has been reported.^(16,19) PDMS can be bonded at room temperature by a method using atmospheric pressure plasma, which is one of the joining methods, and bonding with dissimilar materials such as a glass substrate has been reported.^(16,23,24) By bonding PDMS with other materials, we have developed a PDMS unit with an enzyme-immobilized membrane without damage to enzymes to enable the construction of a monolithic PDMS decompression device.

In this research, we constructed a pressure decompression unit using PDMS, which also has steric workability, as a new cell material. The unit has superior flexibility and self-adsorption to a conventional device. We describe the new monolithic PDMS decompression system with an enzyme-immobilized dialysis membrane using a plasma-activated bonding method to enable the actuation of autonomous drug release according to the blood glucose concentration.

2. Experimental Methods

2.1 Bonding of dissimilar polymers by atmospheric-pressure plasma treatment

Firstly, PVA-SbQ [polyvinyl alcohol, Biosurfine SPH (10.2 wt%), Toyo Gosei Co., Ltd.],^(25,26) which is a polymer for immobilizing PDMS and the enzyme, and a dialysis membrane (UC 36-32-100, MWCO 14000, pore size 5 nm, EIDIA Co., Ltd.) were examined by plasma treatment. To construct a decompression mechanism using PDMS as a cell structural material, the PDMS and an enzyme-immobilized PVA-SbQ film on a dialysis membrane by plasma treatment were directly bonded. The optimum bonding conditions were examined. For the PVA-SbQ film, a mixed solution (PVA-SbQ: PB = 100:50 weight ratio) of PVA-SbQ and a phosphate buffer solution (PB, pH 7.0, 50 mmol/l) was spread on a dialysis membrane that was prepared by drying in a cool dark place (1 h, 4 °C) and curing with ultraviolet irradiation (5 min). Also, PDMS (SILPOT 184, Dow Corning Toray Co., Ltd.) was mixed with a base elastomer and a curing agent in a weight ratio of 9:1, poured into a mold having a depth of 1 mm, then heated in a thermostatic chamber (1 h, 55 °C) and cured. After that, the PDMS pieces (20 × 53 mm²) were released from the mold. Air pressure plasma pretreatment (APP) (sweep rate 400 mm/s, applied electric power 140 W) was applied to the surface of a PDMS piece and the surface of PVA-SbQ using an APP cleaning apparatus (Aiplasma, Panasonic Co.). Furthermore, a sample piece for the peeling test was prepared by a similar method of processing the dialysis membrane surface on the back side of the PVA-SbQ film (Fig. 2).

Peeling tests were performed using a tensile tester (SV-55C-20H, Imada Seisakusho Co., Ltd.) (Fig. 1S). A specimen was opened at 180 degrees, the grip width was separated by 50 mm, and the specimen was fixed to the jig. The tensile speed was set to 50 mm/min, and loading was applied until the bonded PDMS peeled off from the PVA-SbQ film or fractured. The PDMS samples were subjected to various APP processing conditions: a sweep rate of 50–400 mm/s and an applied plasma power of 40–180 W. The maximum bonding strength (N/20 mm) was set as the load at the peeling and breaking of the bonded surface, and the optimum APP treatment conditions for maximizing the bonding strength were thus obtained.

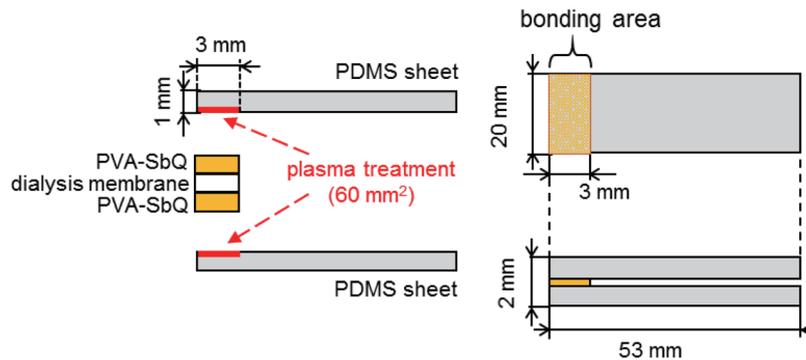


Fig. 2. (Color online) Method of preparing sample piece for peeling test using atmospheric-pressure plasma.

2.2 Construction of decompression unit by atmospheric-pressure plasma pretreatment bonding

Figure 2S shows the decompression unit ($50 \times 50 \text{ mm}^2$), which has a two-layer structure made of gas and liquid phase cells prepared using PDMS with a GOD membrane as a diaphragm. Along with the liquid and gas phase cells, an area with a width of 5 mm from the edge of the PDMS substrates is bonded with the GOD membrane. In the gas phase part, an arrangement of supporting structures at intervals of 2.0 mm for hexagonal injection was constructed to reduce pressure loss due to the deflection caused by the wetting of the enzyme film.

To prepare the decompression unit, PDMS (base elastomer:curing agent = 9:1) was poured into a mold of an acrylic plate and a Si wafer to prepare liquid and gas phase cells of PDMS. Precision machining was applied to the acrylic plate ($t = 1.0 \text{ mm}$) to fabricate the beam structure mold by using a CO_2 laser processing machine (ML-G9320, Keyence Co.).

To prepare the enzyme membrane, a PVA-SbQ and GOD membrane was formed on a dialysis membrane, and then the PDMS liquid phase cell was subjected to APP under optimum conditions and bonded with the enzyme membrane. A mixed solution of PVA-SbQ:PB:GOD = 100:50:1 (GOD: G7141-250 kU, 155 units/mg, Sigma-Aldrich) was added to the dialysis membrane surface, and the GOD was trapped and immobilized by ultraviolet irradiation. Also, the surface of the GOD-immobilized membrane was bonded with the gas phase cell using APP. In the experimental system, the decompression unit was made of PDMS. PB and a glucose solution (5–50 mmol/l) were injected to the liquid phase cell using a syringe pump (Nexus 3000, ISIS Co., Ltd.), and the pressure of the gas phase part was measured with a differential pressure gauge (PA-100-500 DW, Nidec Copal Electronics Co.).

2.3 Improvement of structure for pressure reduction

To achieve the miniaturization and high performance of the decompression unit, improved cells were fabricated and evaluated. A high output can be achieved by simultaneously increasing

the area of the enzyme membrane and decreasing the volume of the gas phase to efficiently reduce the pressure. Therefore, the height of the gas phase part was reduced from 1.0 to 0.1–0.3 mm, and the output was increased by reducing the volume of the gas phase part to improve the pressure reduction. Reducing the beam height of the gas phase cell could cause the beam to come into contact with the inner wall of the gas phase cell owing to the deflection of the membrane, which could reduce the effective enzyme membrane area. Therefore, the length of the front side of the hexagonal prisms placed in the beam structure was changed to 1.5 mm, the interval between the prisms was changed to 1.0 mm, and a circular cavity with an inner diameter of 1.7 mm and an outer diameter of 2.7 mm was incorporated inside each hexagonal prism (Fig. 3S). This prevented the thin PDMS membrane from bonding with the flow channel due to deflection.

2.4 Drug release system with PDMS cell

The drug release system fabricated in this study was composed of a decompression unit and a drug release unit (Fig. 3). The drug release unit was designed to be actuated by the pressure of the decompression unit in two main steps (Fig. 4S). Firstly, the pressure in the decompression unit is reduced by the consumption of oxygen in the GOD reaction. The PDMS diaphragm between the chambers starts moving upward and the suction causes the drug to simultaneously be drawn into the drug chamber. Secondly, the upward movement of the diaphragm pushes a rod and opens a valve, releasing air at a release pressure determined by the distance of the release hole. After that, the diaphragm returns to its initial position, inducing drug release from the drug chamber in the process. This cyclical process repeats intermittently in the system and is sustained by the pressure reduction and release. In the drug release system, the operation of the pressure relief valve to intermittently relieve pressure was evaluated. A duckbill-type check valve (IMCB 8057, ISIS Co., Ltd.) was used as a pressure relief valve via a three-way stopcock (R-1, TOP Co.), which was attached to the improved PDMS decompression unit whose gas phase part was optimized to enable intermittent depressurization. A glucose solution (10 mmol/l) was

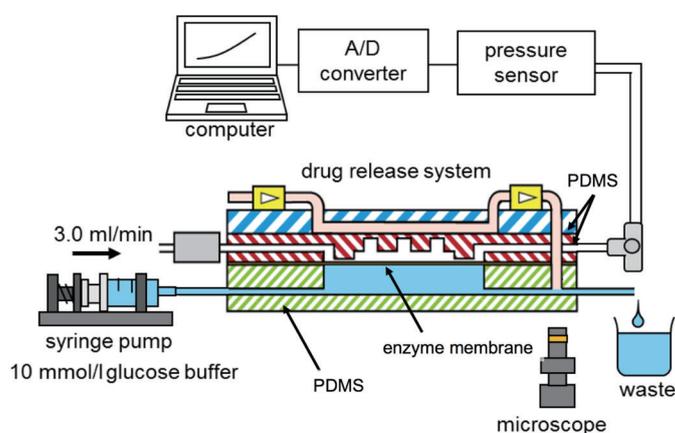


Fig. 3. (Color online) Experimental setup for characterization of drug release system.

injected into the liquid phase cell, and the pressure change of the gas phase part was measured with a differential pressure gauge. After that, the acrylic plate (3 mm thickness) and the cutting sheet were processed precisely, and the drug release system was prepared by molding the PDMS using the combined mold. The drug release and decompression units were bonded using APP. A duckbill check valve was incorporated as a pressure relief valve and a check valve into the drug release system. The drug release system was filled with blue PB as a pseudodrug. The glucose solution was injected into the liquid phase cell, and the state of the pseudodrug was observed while measuring the pressure change of the gas phase part with a differential pressure gauge.

3. Results and Discussion

3.1 Evaluation of bonding dissimilar materials using APP

The experimental results of the peeling test were evaluated at each plasma sweep rate (50–400 mm/s) to examine the bonding condition of APP-treated PDMS and a PVA-SbQ film. The bonded surfaces did not peel away from each other, but the PDMS structure was fractured. As a result, the bonding between PDMS and PVA-SbQ has sufficient strength for microfluidic operation. Figure 4 shows a schematic of the surface modification of PDMS and the bonding principle using APP. PDMS is a polymeric organosilicon compound having siloxane bonds composed of Si–O bonds as the main chain and Si–CH₃ bonds as side chains. Reactive oxygen atomic species (O·) are generated by the irradiation of APP on this PDMS surface, and Si–CH₃ becomes Si–CH₃O· as a reaction intermediate. Since this Si–CH₃O· is unstable, it is immediately desorbed from the PDMS surface. It reacts with OH groups such as those of water molecules present in the environment to form Si–OH groups (silanol groups), and finally, the PDMS surface is oxidized.

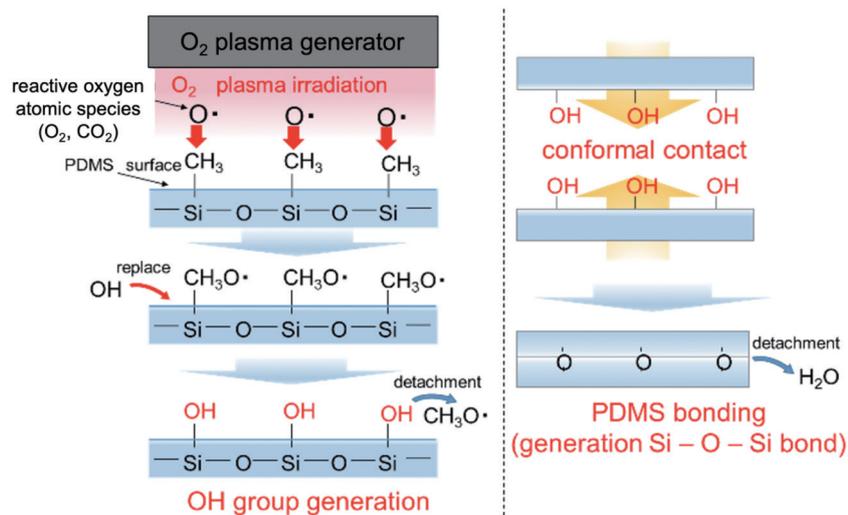


Fig. 4. (Color online) Surface modification of PDMS using atmospheric-pressure plasma (left) and principle of bonding (right).

When the oxidized PDMS surfaces were bonded with each other, the silanol groups were accompanied by the formation of water molecules, resulting in Si–O–Si bonds. The bonding between the PDMS surfaces is covalent. Compared with the van der Waals force, which is a coupling by an electrostatic attractive force, strong bonding is generated. The irreversible bonding of PDMS by oxidation treatment with APP can also be used for the oxidation of hydroxyl (OH), ketone (C=O), and carboxyl (COOH) groups.^(18,27–29) Since PVA-SbQ has an OH group in the backbone polyvinyl alcohol [basic skeleton: C-C(OH)], we considered that O₂-plasma-activated PVA-SbQ forms covalent bonds with PDMS.

In the bonding by APP, it is considered that the formation of OH groups by the oxidation treatment contributes to the bonding property, and the generation of the OH groups is affected by the irradiation time (speed) and the applied electric power of the plasma. However, there was no difference in tensile stress on the test piece with the plasma sweep rate. This is the main reason why a sufficient number of OH groups to enable bonding were formed on the PDMS surface by APP regardless of the sweeping rate.

Next, we investigated the effect of the power of the applied plasma on PDMS (Fig. 5). A PDMS test piece did not bond at a plasma power of less than 40 W. The PDMS surface bonded with APP of 80 and 180 W peeled off. PDMS test pieces with APP from 100 to 160 W fractured. As the applied power was increased from 40 to 100 W, the tensile stress increased. Therefore, the power of the applied plasma affected the bonding strength of PDMS. From the above results, it is possible to construct a PDMS pressure decompression unit by direct bonding to the enzyme membrane using PDMS as the cell material. A simple and flexible pressure decompression unit can thus be constructed. For the bonding of PDMS to PVA-SbQ, the sweep rate of plasma was selected to be 400 mm/s, enabling rapid processing. The applied power was selected to be 140 W, which provides a stable bonding strength between PDMS substrates. A maximum bonding strength of 2.0 N/20 mm was obtained under the optimized bonding conditions.

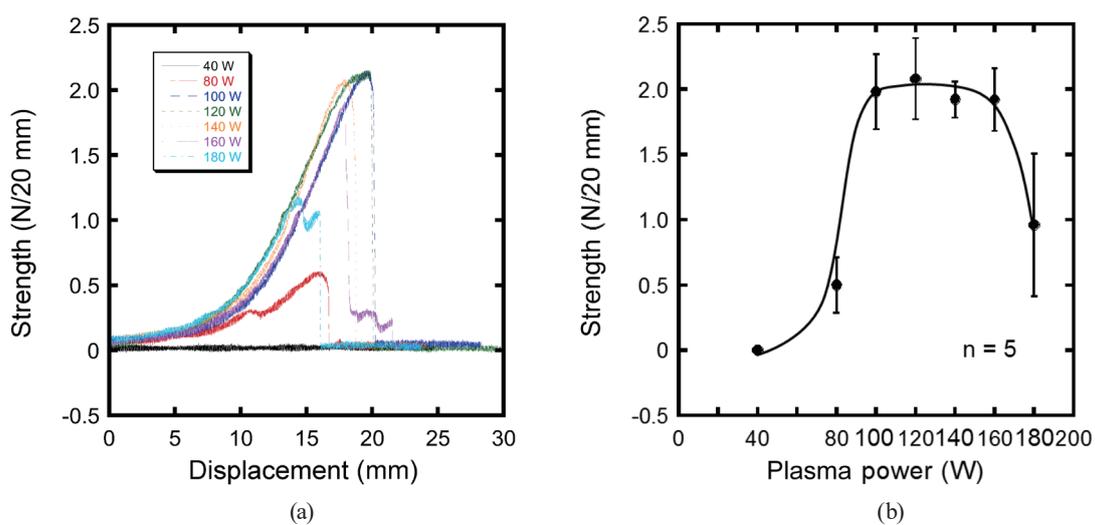


Fig. 5. (Color online) Effects of applied plasma power on junction between PDMS and PVA-SbQ film. (a) Strain-stress curve. (b) Maximum tensile stress plotted against power of applied plasma.

3.2 PDMS decomposition unit using APP process bonding

Figure 6 shows the appearance of the decomposition unit. We fabricated a decomposition unit in which a PDMS cell and an enzyme membrane for dialysis were directly bonded. The volume of the gas phase part of the improved PDMS decomposition unit was increased, and the area of the enzyme membrane was considerably increased compared with that of the conventional system, and the enzyme membrane area ratio per volume of the gas phase part was set to 8.3 cm^{-1} (1.7 times that of the conventional system).

To investigate the pressure reduction characteristics of the PDMS decomposition unit, glucose solutions of different concentrations were introduced into the liquid phase cell. The pressure change and decompression rate in the gas phase cell were examined. As shown in Fig. 7(a), when the glucose solution was injected, a continuous decrease in pressure in the gas phase

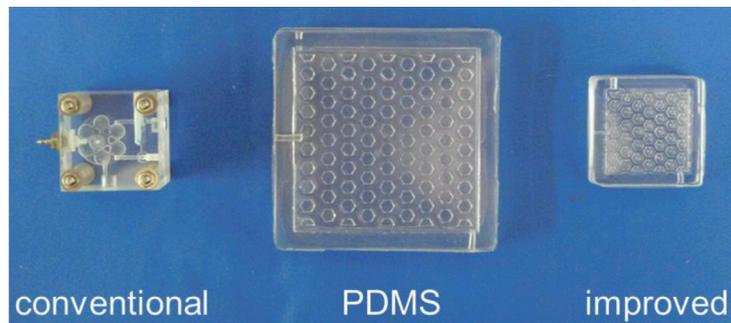


Fig. 6. (Color online) Photograph of decomposition mechanism heterojunction with conventional system (left: conventional unit made from acrylic resin, center: PDMS decomposition unit, right: improved PDMS decomposition unit).

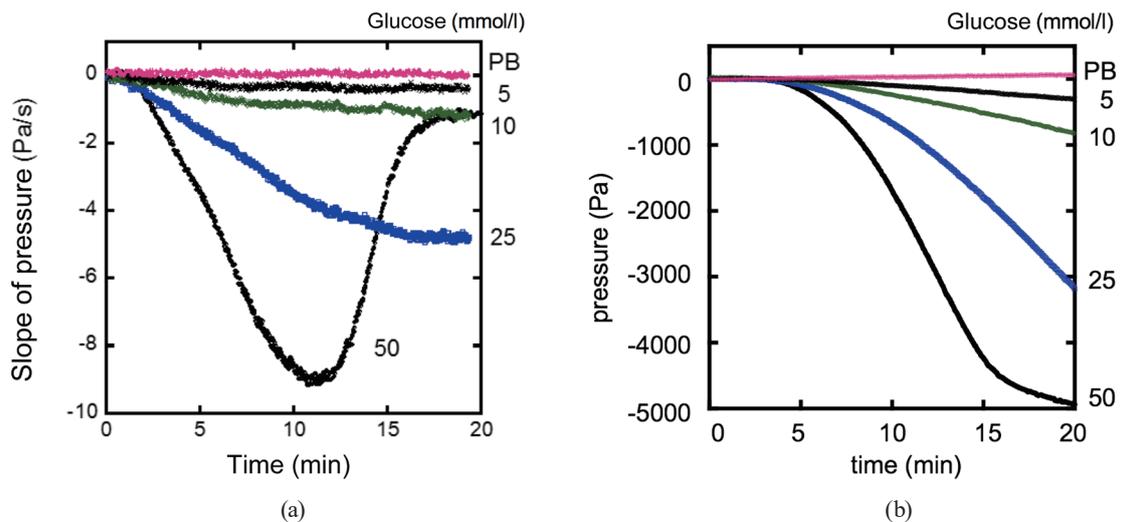


Fig. 7. (Color online) (a) Characteristics of decompression rate for glucose solution in PDMS decomposition unit, and (b) pressure response characteristics in gas phase cell at each glucose concentration.

cell and an increase in slope corresponding to the concentration were observed. On the basis of this result, the time-dependent change in decompression rate (inclination) was examined. The decompression rate increased with the introduction of the glucose solution [Fig. 7(b)]. Note that with a glucose solution of 50 mmol/l, the output dropped 12 min after the injection of the solution. Since the pressure at the time of pressure reduction is about -4000 Pa, which corresponds to the oxygen partial pressure at atmospheric pressure (20% O_2 ; about 20000 Pa), the oxygen consumption in the gas phase cell is considered to be the rate-limiting factor in the catalytic reaction of GOD. By comparing the pressure reduction characteristics, it was found that the pressure reduction rate of the conventional system was improved to 1.4–1.8 times that of the conventional PDMS decompression unit. The rate of decompression (1.39 Pa/s) at the glucose concentration of 10 mmol/l, corresponding to the blood sugar level of diabetic patients, was about 1.7 times.

3.3 Improvement of PDMS decompression unit

In the improved PDMS decompression unit, the volume of the enzyme membrane per gaseous phase volume was increased by 1.8–2.1 times compared with that of the conventional system from its original volume to decrease the volume of the gas phase. The pressure change and pressure reduction rate were measured when glucose solutions of various concentrations were injected into the improved PDMS decompression unit. Figure 8 shows the decompression characteristics for each glucose concentration in the gas pressure cell of the decompression unit for different beam heights. Even in the improved type, a continuous pressure reduction was observed with a glucose solution. A decrease in pressure with increasing glucose concentration was confirmed. By improving the PDMS decompression unit, the time to reach the maximum decompression rate at a high glucose concentration was shortened. We consider that the deflection of the enzyme membrane was suppressed by miniaturizing the beam structure. As

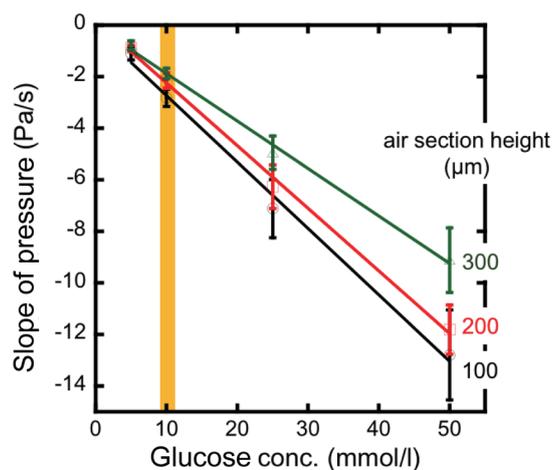


Fig. 8. (Color online) Dependence of glucose concentration on slope of pressure for beam height of gas phase of improved PDMS decompression unit.

the beam height of the gas phase cell decreases, the pressure reduction rate improves at all glucose concentrations. However, at a beam height of 0.1 mm, the enzyme membrane deflected when the glucose solution was introduced, then the structure of the gas phase cell did not allow stable actuation. Since the decompression unit with a beam height of 0.1 mm is not suitable for long-term actuation, the beam height of this improved device was set to 0.2 mm.

In the improved PDMS decompression unit with a beam height of 0.2 mm, a pressure reduction rate of 2.16 Pa/s was obtained with 10 mmol/l glucose solution (human glucose concentration), which was 2.6 times greater than that of the conventional system. In the conventional system, stable intermittent drug release was confirmed at the glucose concentration of 25 mmol/l (decompression rate: 2.82 Pa/s). These results indicate the possibility of drug release at a glucose concentration equivalent to the blood sugar level of diabetic patients.

3.4 Construction and characterization of a drug release system

We investigated a new drug release system by incorporating a pressure release valve, a drug release unit, and the improved PDMS decompression unit. Firstly, a pressure relief valve was attached to the improved PDMS decompression unit, and the capability of intermittent decompression and actuation was investigated. Figure 4S shows the pressure change in the gas phase cell with a glucose solution for the improved PDMS decompression unit fitted with a pressure relief valve. A pressure change inside the gas phase cell was induced by the introduction of the glucose solution. As a result, the pressure was reduced by approximately -500 Pa; thereafter, intermittent decompression was induced by the PDMS decompression unit. The difference between the opening and closing pressures was 230 Pa, and the pressure decompression rate was 1.01 Pa/s.

Finally, the intermittent decompression operation by the drug release system was confirmed. Intermittent pressure relief was observed, but the difference in pressure before and after opening was as small as 220 Pa, and the pressure reduction rate also decreased to 0.69 Pa/s (Fig. 9),

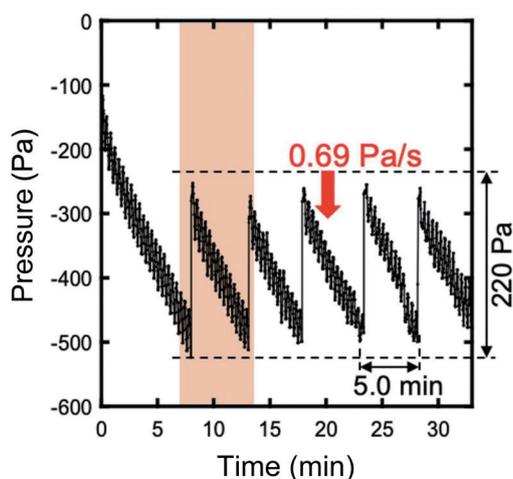


Fig. 9. (Color online) Intermittent decompression of drug release system containing 10 mmol/l glucose solution.

about half that when using the PDMS decompression unit alone. This was because the cell and the release valve are connected to a three-way stopcock and a pressure relief valve, which increased the volume of the gas phase. In the future, incorporating the pressure relief valve inside the decompression unit will improve the pressure reduction efficiency and downsize the system.

4. Conclusion

We developed a drug release system driven by glucose with superior flexibility and self-adsorptivity. The glucose-driven pressure decompression unit, which consisted of PDMS and an enzyme-immobilized membrane, was fabricated by a direct bonding method with atmospheric-pressure plasma pretreatment. The direct bonding of different polymer materials, PVA-SbQ and PDMS, was realized without damage to GOD. The decompression unit had an appropriate decompression rate (2.16 Pa/s) for a glucose solution corresponding to the blood sugar level, which was obtained by increasing the enzyme membrane area per gas phase volume. The output was improved by 2.6 times compared with that of a conventional decompression unit. In future work, we hope to develop high-performance devices based on chemomechanical energy conversion technology and the monolithic PDMS drug release system.

Acknowledgments

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Supporting information

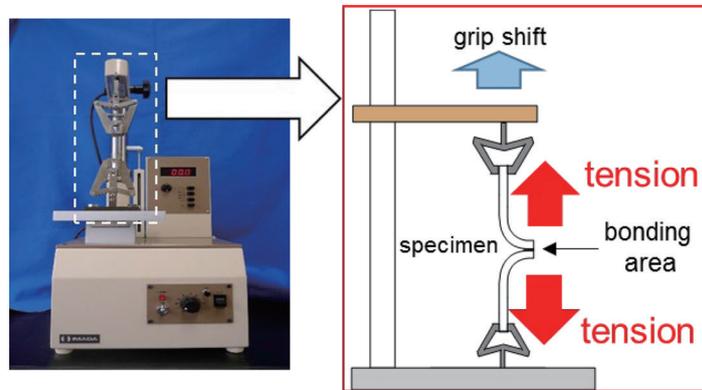


Fig. 1S. (Color online) Schematic image of peel test system at bonding between PDMS and PVA-SbQ film by air plasma pretreatment (APP).

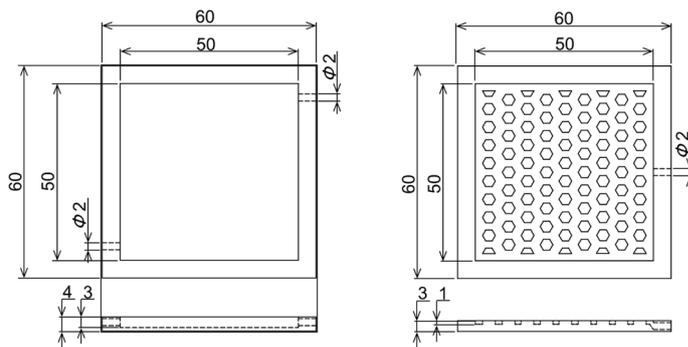


Fig. 2S. Structural view of PDMS pressure reduction mechanism (left: liquid phase cell, right: vapor phase cell).

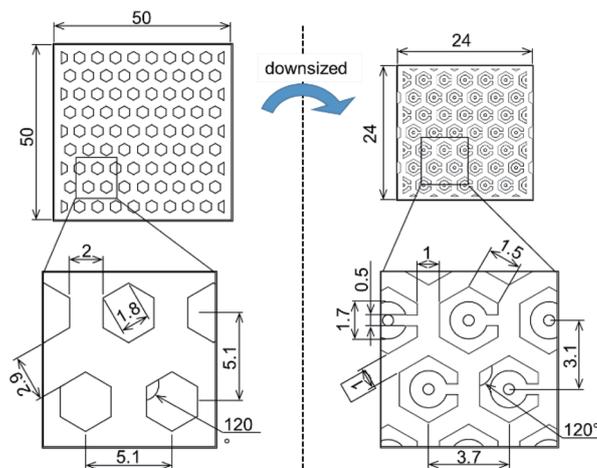


Fig. 3S. (Color online) Pattern of deflection prevention structure before and after improvement (left: before improvement, right: after improvement).

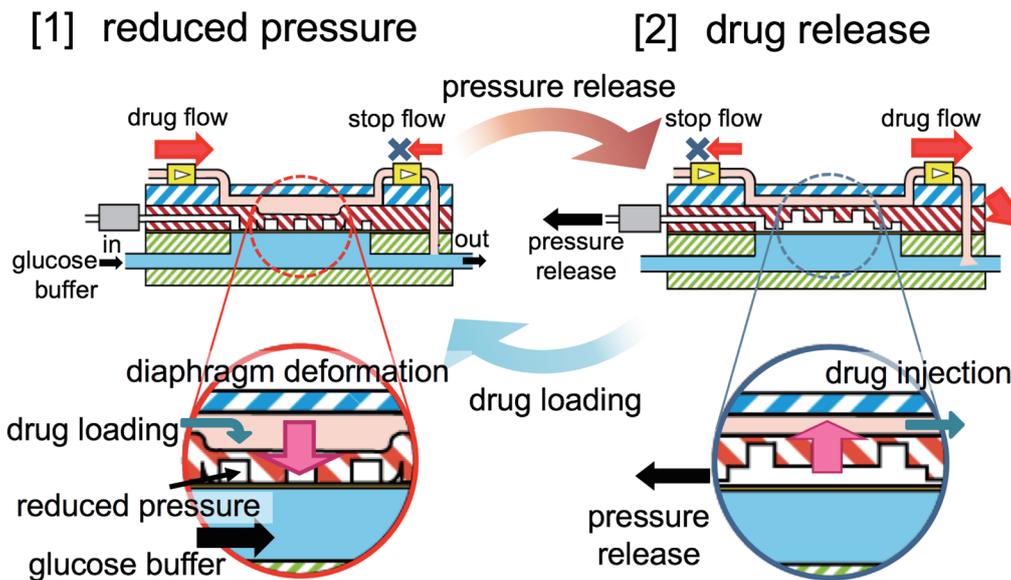


Fig. 4S. (Color online) Schematic of drug release unit and its release mechanism. (1) The drug release unit was fabricated by assembling PDMS cells, PDMS membrane, and enzyme membrane. (2) The drug release unit was designed to actuate by pressure changes (reduce, release) of the decompression unit in four main steps.

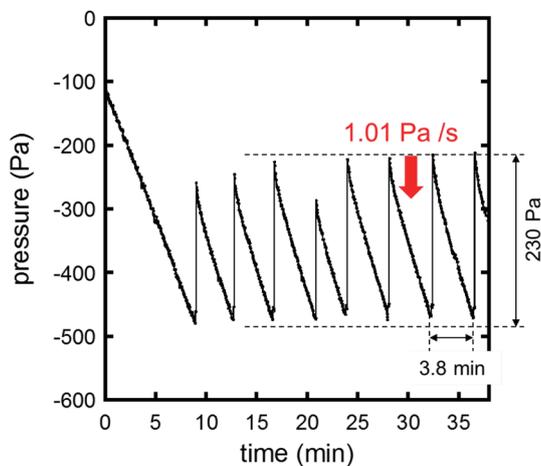


Fig. 5S. (Color online) Pressure changes of decompression unit in drug release system. Pressure released at same interval at -490 Pa under applied constant glucose concentration (10 mmol/l).