Self-Powered Glucose-Responsive Micropumps

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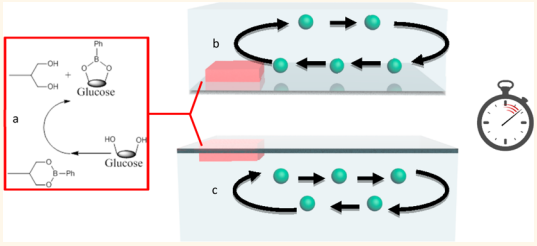
ABSTRACT A self-powered polymeric micropump based on boronate chemistry is described. The pump is triggered by the presence of glucose in ambient conditions and induces convective fluid flows, with pumping velocity proportional to the glucose concentration. The pumping is due to buoyancy convection that originates from reaction-associated heat flux, as verified from experiments and finite difference modeling. As predicted, the fluid flow increases with increasing height of the chamber. In addition, pumping velocity is enhanced on replacing glucose with mannitol because of the enhanced exothermicity associated with the reaction of the latter.



KEYWORDS: glucose · mannitol · self-powered · micropump · sensor · boronate chemistry

Micropumps are used for a wide range of applications, including *in vivo* drug dispensation systems[1,2] and miniaturized chemical and biological analysis systems.[3−5] These micropumps require an external power source and are generally too large for use in applications such as nanomanufacturing and self-assembly. Recently, we[6−15] and others,[16−18] have developed micropumps that directly convert energy derived from chemical fuel into fluid pumping, thereby eliminating the need for an external power source.[19,20] The design overcomes a critical barrier in the field, in which pressure-driven pumps are used to move fluids. However, many chemically powered pumps involve toxic chemicals, and for biomedical applications, it is desirable that the micropumps utilize molecules found in the physiological environment. Here, we describe the fabrication of self-powered soft micropumps that are triggered by the presence of glucose with the pumping velocity proportional to the ambient glucose concentration.

Traditionally, glucose-responsive drug delivery systems[21−33] are based on self-assembly of block copolymers with a boronate ester moiety,[28−32] gel−sol transition,[33] or glucose-induced surface charge alteration.[34] In the presence of glucose, the self-assembled micelles disintegrate, the polymer gels liquefy, or polymer particles change surface charge, releasing the trapped drug molecules. We will refer to this method of drug delivery as a passive mechanism because drug release is based solely on diffusion. Drug delivery in which the molecules are actively pumped out in response to specific stimuli, such as an insulin pump responding to blood sugar fluctuations, will be referred to as an active mechanism. The operation of a chemically powered micropump system requires a gradient,[35] either of density (to emerge buoyancy convection)[13] or chemical concentration (to give rise to electrophoretic and/or electroosmotic flows).[11,12,36] Compared to acyclic 1,2-diols, such as ethylene glycol, saccharides with *cis*-diol functionalities have higher affinity toward boronic acids, forming boronate esters.[31,37,38] Thus, a gradient can be created exploiting the transesterification of the boronate ester of *cis*-diols with glucose. On the basis of this phenomenon, we were able to successfully fabricate an active glucose-responsive self-powered fluidic pump.

RESULTS AND DISCUSSION

There are two essential parameters to consider in fabricating an effective glucose-responsive micropump: (1) The transesterification with glucose must occur at a

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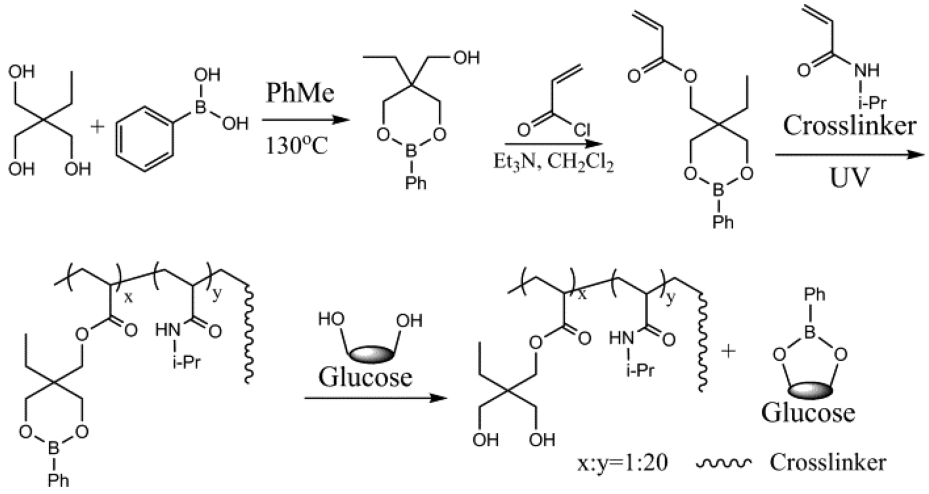

Scheme 1. Synthesis scheme for a hydrogel with a boronate moiety.

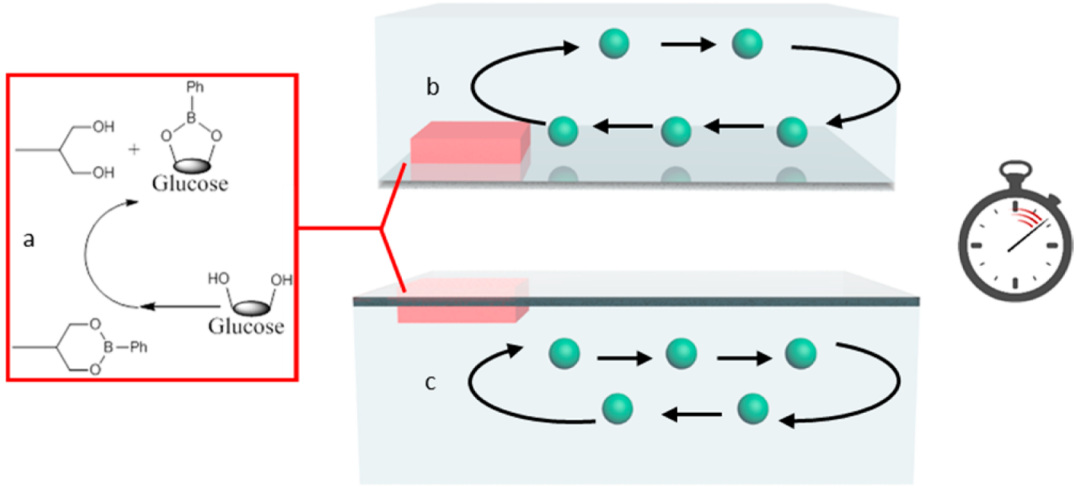

Figure 1. Schematic demonstration of the experimental setup. (a) Transesterification inside the micropump when exposed to glucose. (b) Normal configuration of the micropump: outward fluid flow on the top layer (near the horizontal boundary opposed to the pump) and inward flow on the bottom layer (near the glass slide). (c) When the micropump is flipped upside down, flow direction reverses: outward fluid flow on the top layer (near the glass slide) and inward flow on the bottom layer (near the horizontal boundary opposed to the pump).

physiological pH range, and (2) the micropump itself must be highly hydrophilic so that the glucose molecules in aqueous solution have sufficient access to the hydrophobic acyclic diol boronate moieties in the pump matrix. The first concern has been addressed in the literature.[28,29,31] To address the second issue, we used a hydrogel material to fabricate the micropump. The hydrogel incorporated a high loading ratio of *N-i*-propylacrylamide. In principle, *N-i*-propylacrylamide can be substituted by other hydrophilic monomers such as hydroxyethyl methacrylate. The hydrogel was obtained through UV-initiated radical copolymerization between *N-i*-propylacrylamide and (2-phenylboronic ester-1,3-dioxane-5-ethyl)acrylate monomer in the presence of a cross-linker (Scheme 1).

To test the pumping behavior, the hydrogel was cut into small cubes (1 mm × 1 mm), placed on a glass slide, and sealed with a silicone rubber gasket. The gasket was then filled with glucose buffer solution (pH = 7.4, glucose concentration from 0.01 to 0.1 M) and polystyrene tracer particles (5 μm, Invitrogen S37227). Pumping behavior was recorded by a microscope (Figure 1a,b). For the negative control, a phosphate buffer lacking glucose was used. The tracer particle speed was assumed to equal fluid flow speed and was analyzed using Tracker software and plotted *versus* glucose concentration (Figure 2a). In the control group, no pumping was observed with the tracer particles merely undergoing Brownian diffusion (Supporting Information video SV1). However, when glucose was present, a flow was generated with its speed increasing with glucose concentration. The tracer particles were pushed away (top layer, 40 μm above the top of the gel) from the micropump at approximately 7 μm/s when the glucose concentration reached 0.1 M (Figure 2a and Supporting Information video SV2).

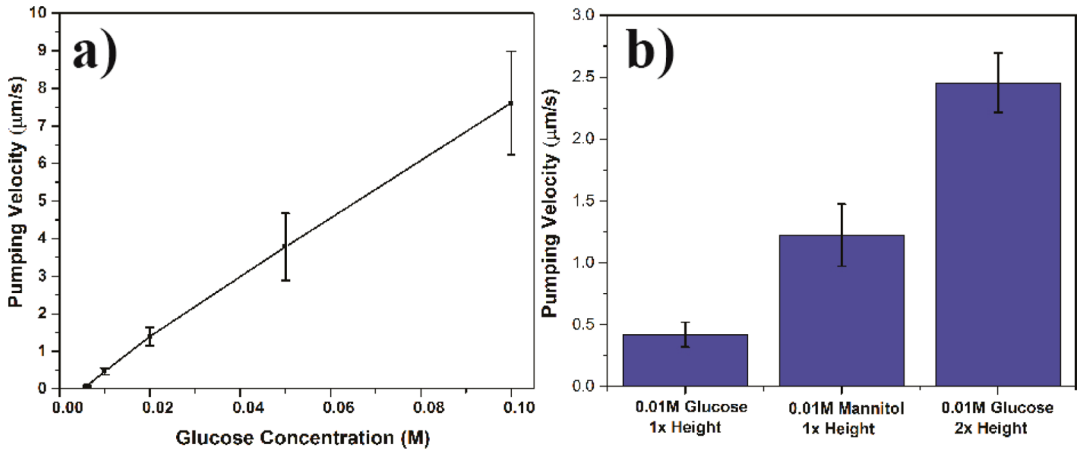

Figure 2. (a) Pumping speed *vs* glucose concentration at a distance of 200 μm from the gel surface. Control group only showed Brownian motion without directional movement. Unpaired two-tailed *t* test was performed to show that the pumping speeds are statistical different for each concentration. See Supporting Information. (b) Pumping speed comparisons for glucose trigger, mannitol trigger, and glucose trigger with double height of the fluidic layer.

Fluid pumping (approximately 0.1 μm/s) can be observed with a glucose concentration as low as 6 mM, which is around the mean normal blood glucose level in humans.[39,40] Due to fluid continuity, the fluid was pumped toward the gel in the bottom layer close to the glass substrate. The net result is a convective flow in a closed chamber.

We hypothesize that the observed pumping is a result of a thermoconvective flow[41] generated by the transesterification reaction. *cis*-Diols form more stable boronate esters than acyclic diols; the transesterification reaction produces more thermodynamically stable glucose boronate molecules with an estimated enthalpy of −3.52 kcal/mol.[42] This exothermic reaction increases the temperature near the pump and therefore decreases the density of the fluid in the vicinity. The lighter solution moves up and, eventually, away from the micropump, creating outward fluid flow. Due to fluid continuity, the bottom layer of fluid moves inward, toward the hydrogel (Figure 1b). When the micropump is flipped upside down, the lighter fluid spreads along the substrate away from the pump and, as a consequence, the fluid flow is reversed (Figure 1c).

The intensity of thermal convective flow in a horizontal layer of liquid in the presence of a temperature gradient is governed by the Rayleigh number (R_a), as defined by eq 1:

$$R_a = \frac{g\beta\Theta h^3}{\nu\chi} \quad (1)$$

where, g, h, β, ν, and χ represent the gravitational acceleration, thickness of the liquid layer, coefficient of thermal expansion, kinematic viscosity, and thermal diffusivity of the liquid, respectively. The typical temperature difference across the layer Θ can be estimated as $\Theta = qh/\kappa$, where κ is the thermal conductivity of the liquid and $q = r\Delta H/S_g$ is the rate of heat release per unit surface of gel (in J s^{-1} m^{-2}) with S_g, r, and ΔH being the area of the gel surface, rate, and enthalpy of the chemical reaction, respectively.

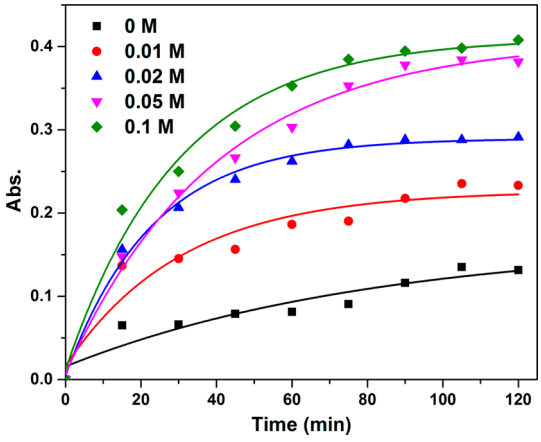

Figure 3. Fluorescein (model drug) release kinetics over time. In 0.1 M glucose solution, the drug release is about 5 times higher than that in the control experiment in 60 min.

For small-amplitude steady flow, we can calculate the fluid velocity by eq 2

$$V = \frac{\chi}{h} R_a f(a, b) \quad (2)$$

where the function $f(a,b)$ depends on the aspect ratios of the micropump, $a = R/h$ and $b = l/h$, where R and l are the radius and height of the gel, respectively (in calculations, we treat the gel as a circular cylinder of the same volume).

The flow, therefore, can be characterized by a speed given by eq 3

$$V = \frac{g\beta h^3 r\Delta H}{\nu\kappa\pi R(R+2l)} f(a, b) \quad (3)$$

Based on this derivation, when enthalpy doubles, the pumping speed should also increase by a factor of 2. Furthermore, doubling the layer thickness, h, should result in an increase in the flow velocity by

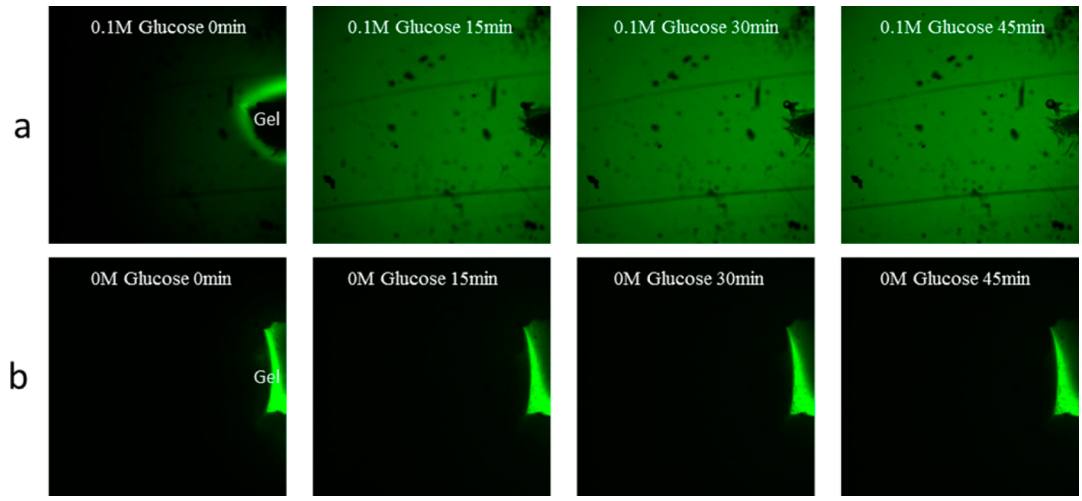

Figure 4. Confocal microscope images (5× magnification) of fluorescein release over time: (a) micropump in 0.1 M glucose solution; (b) micropump in 0 M glucose.

the factor of $8f(a/2,b/2)/f(a,b)$. For the experimental setup (h = 0.80 mm, l = 0.50 mm, R = 0.56 mm or a = 0.70, b = 0.63), the typical dimensionless velocity (the factor $f(a,b)$ in eq 3) is rather small, $f(a,b) \approx 10^{-3}$ (see Supporting Information for the details), which justifies the assumption of the creeping flow. The computations show that 2-fold decrease in both a and b leads to a decrease in $f(a,b)$ by the factor 1.6, $f(0.70,0.63)/f(0.35,0.31) \approx 1.6$. This results in net 5.0-fold increase in the speed ($h^3 \times f(a,b) = 8/1.6$) on doubling the chamber height. To test these assumptions, two additional experiments were carried out. First, we demonstrated that transesterification initiated by another *cis*-diol, mannitol (0.01 M), rather than glucose, creates an even stronger fluidic flow simply due to higher reaction enthalpy. The enthalpy for transesterification with mannitol is estimated to be −8.05 kcal/mol,[42] approximately 2.3 times the enthalpy of glucose transesterification. The pumping speed of the mannitol-triggered pump was measured to be 1.2 μm/s (2.7 times higher than the pumping speed with glucose) (Figure 2b). The pumping speed can also be tuned by changing the height of the fluidic layer. Using a 0.01 M glucose buffer, when the height of the fluid chamber was doubled, the pumping speed was observed to increase to 2.5 μm/s (5.6 times higher compared to the theoretical estimate of 5.0 times higher) (Figure 2b).

Since the reaction rate r is unknown, the direct comparison of the experimental and theoretical values for the pumping speed is complicated. We have estimated r roughly for 10 mM glucose solution as $r \approx 10^{-9}$ mol/s. This value gives a pumping speed of approximately 0.4 μm at 200 μm from the gel, in reasonable agreement with the experimental values (see Supporting Information).

This self-powered pumping action driven by enthalpy enables the design of biocompatible, nontoxic, active delivery systems. As proof of principle, we performed a small molecule release kinetics experiment using fluorescein. Hydrogel was cut into five pieces of equal size (1 cm × 1 cm × 5 mm) and loaded by soaking in an acetone solution of fluorescein (10 mg/mL). The hydrogel pieces were then rinsed with the glucose phosphate buffer solution (pH = 7.4, glucose concentration from 0.01 to 0.1 M) to remove any acetone in the hydrogels or any free fluorescein on the surface. After equilibration, each of the hydrogels was placed in 3 mL of glucose phosphate buffer solution (pH = 7.4, glucose concentration from 0.01 to 0.1 M). The release kinetics were measured by UV/vis spectroscopy (absorbance max = 494 nm). As shown in Figure 3, the dye release rate increased significantly with increasing concentration of the glucose trigger. In the first 60 min, the drug release in 0.1 M glucose solution was 5 times higher than the control.

The release of fluorescein was also visualized with a confocal microscope. The confocal microscope was used to capture 1 image per min for a total duration of 45 min. The results are shown in Figure 4. In Figure 4a, the release of fluorescein by the micropump in 0.1 M glucose is obvious: just after 15 min, the whole field of view was full of green fluorescence, indicating that fluorescein was rapidly released by glucose-triggered pumping. Figure 4b shows fluorescein release in the control, where no glucose was present. The presence of fluorescein in solution was negligible for the entire 45 min period.

CONCLUSION

We have successfully demonstrated a self-powered glucose-responsive fluidic delivery system employing the well-known transesterification reaction of acyclic diol boronate with glucose. Compared to conventional delivery systems, which generally operate by pure diffusion, our system has several distinct advantages. By actively pumping out fluid and small molecules, the

micropump is able to rapidly and evenly distribute the delivered cargo. Moreover, unlike a mechanical pump, the micropump system requires no external power source; it is capable of converting chemical energy into mechanical motion directly, providing additional value over traditional delivery systems. While the studies were carried out in a closed chamber, other pump architectures will allow the directed delivery of a desired payload in response to the presence and concentration of a specific sugar derivative.[14]

METHODS

(2-Phenylboronic ester-1,3-dioxane-5-ethyl)acrylate Monomer Synthesis. The monomer was synthesized according to previous literature.[32] First, phenylboronic acid (1 g) and trimethylolpropane (1.1 g) were mixed in dry toluene. The mixture was then heated at 130 °C for 3 h. Then, the solvent was removed, and the product was dissolved with dichloromethane in the presence of triethylamine and acryloyl chloride. This mixture was stirred for 12 h, while the temperature was maintained at 0 °C with an ice−water bath. The product was subsequently washed with brine, and the organic phase was dried with solid anhydrous $MgSO_4$. The product was then purified by using column chromatography. The pure monomer is a slightly yellow oily liquid.

Hydrogel Fabrication. The boronate monomer, *N*-*i*-propylacrylamide, cross-linker (*N*,*N*′-methylene bisacrylamide), and photoradical initiator (Ciba Darocure 1173) were mixed in DMSO (3 mL) and exposed under UV (365 nm) light for 3 h. The hydrogels then underwent dialysis with acetone to remove any unreacted monomers and initiators.

Micropump Experiments. The hydrogels were cut into small pieces (1 mm × 1 mm) and pre-equilibrated with glucose phosphate buffer solution (pH = 7.4, glucose concentration from 0.01 to 0.1 M) for 30 min to remove any acetone. This pre-equilibration step is necessary since any remaining acetone leaching out of the hydrogels will create undesirable flows which will interfere with flows caused by transesterification. After equilibration, the hydrogel was placed on a glass slide and sealed with a silicone rubber gasket (Grace-Bio Cat. No. 621501). Then the gasket was filled with glucose buffer solution (pH = 7.4, glucose concentration from 0.01 to 0.1 M) with polystyrene tracer particles (5 μm Invitrogen S37227). The pumping behavior was recorded at 20× magnification by a microscope (Zeiss Axiovert 200). The velocity of the tracer particles was tracked by the Tracker software and calculated in an Excel spreadsheet.

Confocal Microscopy. The hydrogel was cut and soaked in fluorescein acetone solution (10 mg/mL). Before the test, the gels were pre-equilibrated with the glucose phosphate buffer solution (pH = 7.4, glucose concentration 0 and 0.1 M). The gels were sealed in a rubber gasket (Grace-Bio Cat. No. 621501). The images were captured every 1 min for 45 min. The images were compiled into two videos (6 images per second).

Fluorescein Release Kinetics. The release kinetics of the micropumps were measured with a UV/vis spectrometer. Five equally sized gels (1 cm × 1 cm × 0.5 cm) were soaked in fluorescein acetone solution (10 mg/mL). Then the gels were washed and equilibrated with glucose buffer solution (0.01, 0.02, 0.05, and 0.1 M) for 30 min. Then these gels were immersed in glucose buffer solution (0.01, 0.02, 0.05, and 0.1 M), and the absorbance of the solution (494 nm) was measured with a UV/vis spectrometer. In the control experiment, the gel was equilibrated with just buffer solution and immersed in buffer solution during the kinetics test.

Conflict of Interest: The authors declare no competing financial interest.

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Supporting Information Available: Unpaired two-tailed *t* test, estimation of reaction rate, modeling results of pumping velocity, and supporting videos. This material is available free of charge *via* the Internet at http://pubs.acs.org.

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