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Osmotic Swelling Pressure Response of Smart Hydrogels Suitable for Chronically-Implantable Glucose Sensors

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Abstract

In the last few years, a new type of glucose-sensitive hydrogel (GSH) has been developed that shrinks with increasing glucose concentration due to the formation of reversible crosslinks. The first osmotic swelling pressure results measured for any member of this new class of GSH are reported, so that their suitability for use in sensors combining pressure transducers and smart gels can be evaluated. Comparison is also made with results obtained for an older type of GSH that expands with increasing glucose concentration due to an increase in the concentration of counterions within the gel. The newer type of GSH exhibits both faster kinetics and weaker fructose interference, and therefore is more suitable for *in vivo* glucose sensing.

Keywords

glucose sensor; hydrogel; piezoresistive sensor; smart material

1. Introduction

In recent years, there has been a considerable effort to develop enzyme-free glucose-sensitive hydrogels (GSH) with enhanced selectivity for glucose relative to fructose [1–8]. A GSH is a crosslinked polymer network that reversibly changes its volume in response to changes in environmental glucose concentration [9]. By coupling a GSH of micron-scale thickness to a method for detecting the volume change, such as optical or pressure measurements, one can obtain an implantable glucose sensor suitable for diabetic patients [1,4,7–8,10]. If the GSH is enzyme free, then the sensor response will be independent of blood oxygen level. By contrast, the widely-studied electrochemical glucose sensors that rely on the enzyme *glucose oxidase*

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require special measures to overcome the blood oxygen deficit [11], such as the use of glucose-restrictive membranes [12]. The vast majority of enzyme-free GSH developed to date employ the glucose-binding moiety phenylboronic acid (PBA). The first generation of PBA-containing GSH, of a type first synthesized about 15 years ago, have volumes that increase with increasing glucose concentration [13–22]. This increase occurs because glucose binding favors the charged form of boronic acid. Hence when the environmental glucose concentration increases, the fraction of charged boronic acid groups increases, thereby increasing the osmotic contribution of counterions that swell the hydrogel. Unfortunately, PBA will bind any molecule containing a cis diol, and in fact the binding affinity of PBA for fructose exceeds that for glucose by a factor of 40 [23]. Hence finding a means for enhancing the glucose-selectivity of enzyme-free GSH is considered a high priority, even though physiological glucose concentrations far exceed those of fructose [24].

The second generation of GSH, of a type first synthesized about 5 years ago, have volumes that decrease with increasing glucose concentration [1–8,25]. This decrease occurs because glucose simultaneously binds to two PBA moieties within the gel, thereby forming a reversible crosslink (bis-boronate-sugar complex) that increases the entropic penalty associated with chain stretching [7]. This penalty can be reduced by chain contraction, hence the gel shrinks with increasing glucose-mediated crosslinking. Fructose, unlike glucose, contains only one set of cis diols and thus cannot bind to two PBA moieties simultaneously. However, PBA must have the correct stereochemistry for glucose to reversibly crosslink the gel. This correct stereochemistry is achieved by attaching PBA to the hydrogel in the ortho position [1,4–5], or by incorporating protonated tertiary amines in the hydrogel adjacent to the PBA [3,7–8,25]. The cationic tertiary amines stabilize the charged form of boronic acid, even in the absence of sugars, so that almost all of the added glucose participates in reversible crosslinking [23]. Fructose molecules can still bind to PBA moieties in the gel, one at a time, but this has a relatively minor effect on the swelling pressure because most of the boronic acid groups are already charged. Hence the glucose-selectivity of the second generation of GSH greatly exceeds that of the first.

Surprisingly, as far as we know, there have been no reports of the osmotic swelling pressure Π for any member of the second generation of GSH. The osmotic swelling pressure Π is defined as the derivative of the hydrogel free energy of swelling ΔF_{tot} with respect to moles of water [26–27]:

$$\Pi = -(\partial \Delta F_{\text{tot}} / \partial n_1) / V_1 = (\mu_{1,0} - \mu_1) / V_1 \quad (1)$$

In Equation (1), V_1 is the molar volume of water, n_1 is the number of moles of water, μ_1 is the chemical potential value for water in the hydrogel *at ambient pressure*, and $\mu_{1,0}$ is the chemical potential value for water in the reference solution that surrounds the hydrogel. The value of ΔF_{tot} includes contributions from the boronic acid counterions and the glucose crosslinks mentioned above. As discussed in detail in a recent publication within this journal [28], Π is a measure of the force that a given GSH can exert on a pressure sensor, or equivalently, of the force that a given GSH can exert when used as an autonomous actuator [19]. Hence, in the following, we report for the first time the glucose-dependent Π value in physiological saline solution (PBS buffer) for one particular member of the second generation of GSH, namely the hydrogel with composition developed by Tierney et al. [7]. The goal is to evaluate the suitability of this GSH for use in chemomechanical sensors that combine smart hydrogels and pressure transducers. It should be noted that Tierney et al. have already shown that this GSH exhibits adequate glucose response in blood plasma [8]. We also investigate Π for a hydrogel with composition developed by Gu and co-workers [23], a hydrogel belonging to the first generation of GSH.

2. Experimental Methods

2.1 Materials

The monomers used for preparation of the gels were obtained as follows: acrylamide (AAM, Fisher Scientific), *N,N*-methylenebisacrylamide (BIS, Sigma-Aldrich), 3-acrylamidophenylboronic acid (3-APB, Frontier Scientific, Logan, UT), and *N*-(3-dimethylaminopropyl) acrylamide (DMAPAA). The monomers were used as received. Ammonium peroxydisulfate (APS, Sigma-Aldrich), *N,N,N',N'*-tetramethylethylenediamine (TEMED, Sigma-Aldrich), D(+)-glucose (Mallinckrodt Chemicals), D(−)-fructose (Sigma-Aldrich), dimethyl sulfoxide (DMSO, Sigma-Aldrich), 4-(2-Hydroxyethyl)piperazine-1-ethanesulfonic acid (HEPES, Sigma-Aldrich), and Delbecco's phosphate-buffered saline solution (PBS, Sigma-Aldrich) were also used as received. Market grade wire cloth mesh (type 304 stainless steel, 80 mesh, wire opening 178 μm , open area 31%) was obtained from Small Parts, Inc., Miramar, FL, USA.

2.2 Hydrogel Synthesis

A GSH (composition 1) containing AAM/3-APB/DMAPAA/BIS at a nominal mole ratio of 80/8/10/2 was prepared by free radical crosslinking copolymerization. This composition and the synthesis procedure followed were the same as in Tierney et al. [7], with the exception that we used a different reaction initiator and accelerator, namely thermal free radical initiator APS and TEMED. This use of APS and TEMED is not expected to markedly change hydrogel properties. In brief, stock solutions were prepared of AAM and BIS in 1 mM HEPES buffer. Appropriate amounts of the two stock solutions were mixed in a vial with DMAPAA and TEMED. In order to dissolve 3-APB into the pregel solution, 10 vol% of DMSO was added into the vial. The free radical initiator APS was introduced after purging the vial with N_2 gas for 10 minutes, after which the pregel solution was rapidly injected into a cavity (thickness 400 microns) between two square plates (polycarbonate and poly(methyl methacrylate)) of surface area 60 cm^2 . The total monomer concentration in the pre-gel solution was 12.7 wgt%. After approximately 12 hours of reaction at room temperature, the hydrogel slab was removed from the mold and washed for at least two days with deionized water and PBS buffer (pH 7.4, ionic strength 0.15 M) before testing. A similar procedure was used to prepare a GSH (composition 2) containing AAM/3-APB/BIS at a nominal mole ratio of 80/20/0.25, with the principal difference being the replacement of HEPES buffer/DMSO with 1 M NaOH. The total monomer concentration in the pre-gel solution was 30.2 wgt%. This GSH has a composition very similar to a hydrogel studied by Gu [23]. In sugar-free PBS buffer at physiological pH and ionic strength, GSH (composition 1) contains 88 wgt% water, and GSH (composition 2) contains 58 wgt% water.

2.3 Sensor Construction and Sensor Response Tests

As analyzed in detail in a recent publication in this journal [28], the osmotic swelling pressure Π of a smart hydrogel can be obtained by confining it between a porous membrane and the diaphragm of a miniature pressure transducer. In such a sensing scheme, a change in the environmental glucose concentration, as sensed through the pores of the membrane, changes Π (see Equation 1) which must at equilibrium equal the mechanical pressure measured by the pressure transducer. Figure 1 shows a sketch of the chemomechanical sensor that was used. The sensor consists of a piezoresistive pressure transducer (model EPB-501-5P, Entran, Inc., Fairfield, NJ, USA) with a cylindrical stainless steel sensing area (diameter 3.18 mm) completely covered with a hydrogel film of thickness $\approx 400 \mu\text{m}$. The hydrogel is held in place in the sensor by a cap with a top surface that consists of a replaceable porous membrane through which mass transfer can occur. In our previous work [28], we investigated membranes having various pore sizes and porosities, and found that use of a stainless steel wire cloth mesh (mesh size 80, wire opening 174 μm , 31% open area) gave acceptable results for Π measurements in

PBS buffer. Therefore the same porous mesh was used to obtain all the results presented here. A GSH was synthesized and cleaned as described above, a circular biopsy tool was used to cut a disc-shaped sample of appropriate diameter, and the sample was then transferred from sugar-free PBS buffer (pH 7.4, ionic strength 0.15 M) to the sensing surface of the pressure transducer using tweezers. The sensor cap with wire mesh was attached to the sensor base by tightening three screws that were adjusted to impose an axial compressive stress on the hydrogel in the sensor. The sensor was then inserted into a large covered environmental bath containing PBS buffer at room temperature and physiological pH and ionic strength. This bath also contained a magnetic stirrer used to minimize external mass transfer resistance to the sensor. Sensor response tests were performed by either injecting solutions of glucose with or without fructose into the environmental bath and then noting the time-dependent response of the pressure transducer, or by rapidly switching the sensor into another environmental bath at the same ionic strength and pH but with no sugar. The time-dependent pressure signal was captured with an Agilent data acquisition system.

3. Results and Discussion

3.1 The Glucose-Dependent Swelling Pressure Response: Magnitude and Kinetics

In order to ensure good mechanical contact with the pressure transducer at all glucose concentrations, GSH (composition 1) was transferred from sugar-free buffer into the sensor at a high loading pressure of approximately 20 kPa, which is approximately 60% of the transducer full-scale value. From measurements of the change in optical path length by Tierney et al. [7], this hydrogel is expected to shrink with increasing glucose concentration. Figure 2 shows the measured change in swelling pressure Π when the hydrogel is exposed to a cyclic variation in glucose concentration between zero and 5 mM at physiological pH and ionic strength. As expected, Π is lower at higher glucose concentration, and the change in Π is observed to be reversible and surprisingly large, almost 9 kPa or 1750 Pa per mM of glucose. We are aware of only one previous Π measurement for a GSH, in this case for a GSH that swells with increasing glucose concentration. Lei et al. subjected this first generation GSH to an increase in glucose concentration from 0 to 20 mM, and measured an increase in Π of only 3 kPa [29]. For GSH (composition 1), Figure 3 contains a plot of the equilibrium Π response vs. glucose concentration over the range of physiological interest for diabetic patients, 0 to 20 mM. The swelling pressure increases monotonically with glucose concentration, but unfortunately the equilibrium response curve appears to saturate near 20 mM glucose. Presumably this occurs because all of the glucose binding sites become occupied at high external glucose concentration. This is unsurprising, given that the mole fraction of PBA in this hydrogel is only about 0.08. Figure 4 shows the fit of the time-dependent swelling curve in Figure 2 to a first-order-kinetics model. The fit is excellent, and this was observed to be the case (R-squared values 0.92 – 0.98) for all of the time-dependent swelling and deswelling curves for this GSH (composition 1). There was no obvious dependence of the first-order time constant τ on glucose concentration. The average values were $\tau = 60 \pm 15$ min for deswelling, and $\tau = 75 \pm 15$ min for swelling. Though the relative uncertainty in the τ values is large, nonetheless deswelling appears to be slightly faster than swelling, probably because the membrane and the piezoresistive diaphragm exhibit mechanical forces that oppose swelling and accelerate deswelling.

3.2 Interference by Fructose

The normal physiological level of fructose is approximately 500 times smaller than that of glucose (8 μ M vs. 5.5 mM, respectively) [24]. Nonetheless, potential interference is important because the affinity of PBA for fructose is 40 times greater than that for glucose [23], hence normal fructose levels could cause a glucose-measurement error of ca. 10%. Figure 5 compares the measured response of Π for GSH (composition 1) to PBS solutions containing 5 mM

glucose and PBS solutions containing 5 mM glucose plus 0.1 mM fructose. As noted previously, this GSH shrinks with increasing glucose-concentration due to the formation of reversible crosslinks formed when glucose binds simultaneously to two PBA moieties, whereas fructose cannot mediate crosslinks. Hence addition of 0.1 mM fructose has no discernible effect on the sensor response in Figure 5. Figure 5 also shows the measured response of Π for GSH (composition 2) to PBS solutions containing 5 mM glucose. In contrast to GSH (composition 1), this hydrogel does not contain pendant tertiary amines and hence is expected to swell with increasing glucose concentration. One observes in Figure 5 that the measured Π value of GSH (composition 2) responds to the increase in glucose concentration in a direction which is opposite to that of GSH (composition 1). The magnitude of the equilibrium response is slightly greater for GSH (composition 2) than for GSH (composition 1) (9.2 kPa vs. 8 kPa). However, the response time of GSH (composition 2) in Figure 5 is clearly larger than that of GSH (composition 1). The time-dependent response curve of GSH (composition 2) in Figure 5 does not fit a first- or second-order model. Defining τ_{60} as the time at which hydrogel response reaches 60% of its final value, and τ_{90} as the time at which hydrogel response reaches 90% of its final value, then $\tau_{60} = 140$ min and $\tau_{90} = 260$ min for GSH (composition 2) in Figure 5. In comparison, $\tau_{60} = 60$ min and $\tau_{90} = 175$ min for GSH (composition 1). Furthermore, the measured Π value of GSH (composition 2) is much more responsive to fructose than to glucose, as shown in Figure 6. Figure 6 contains the time-dependent response of Π for both types of GSH to PBS solutions containing 5.0 mM fructose. After one hour, the Π response of GSH (composition 1) in Figure 6 has already reached an equilibrium value of 1.9 kPa, which is four times smaller in magnitude than the equilibrium response of the same gel to an equivalent concentration of glucose (Figure 3). On the other hand, after one hour, the Π response of GSH (composition 2) is still increasing in Figure 6, and the magnitude of the response of this gel to 5.0 mM fructose is already at least 1.6 times greater than the response to an equivalent concentration of glucose (Figure 5). We speculate that the small short-time drop in Π observed for GSH (composition 2) in Figure 6 arises from the osmotic effect of fructose on the environmental solution that occurs immediately after fructose injection and before fructose diffuses into the gel and binds.

4. Conclusions and perspectives

For both glucose-sensitive hydrogels studied (GSH composition 1 and GSH composition 2), the magnitude of the osmotic swelling pressure response to glucose is surprisingly large, and easily detectable using custom-designed microfabricated pressure sensors. For example, near the normal glucose level in the body (5.5 mM), the sensitivity of GSH (composition 1) is approximately 1750 Pa per mM of glucose. Since microfabricated pressure sensors are available with resolutions of order 1 mbar, this implies a chemomechanical glucose sensor resolution of 0.06 mM (1.2 mg/dl), which is more than adequate for a chronically-implantable glucose sensor [11,30]. GSH (composition 1) also exhibits minimal fructose interference and reasonably fast kinetics, with a first-order time constant of about 65 minutes at room temperature. GSH (composition 2), an older-type of hydrogel that swells rather than shrinks with increasing glucose concentration, has slower kinetics and much greater fructose interference. GSH (composition 1) was first developed by Tierney et al.[7], who placed it on the tip of a fiber optic sensor and measured glucose-dependent changes in optical path length in PBS buffer and in blood plasma. Tierney et al. report that the swelling kinetics of GSH (composition 1) are four times faster at body temperature than at room temperature [8], so we can expect a similar reduction in the first-order-time constant of our chemomechanical glucose sensor. Additional reduction in response time can no doubt be obtained by reducing the thickness of the GSH in the sensor from 400 μ m or by introducing pores. In the future, we plan to construct a MEMS glucose sensor [29,31] which is a microfabricated chemomechanical sensor and that will use the same or a similar GSH. The only deficiency of GSH (composition 1) is the reduction in sensitivity observed at higher glucose concentrations, near 20 mM. This

can probably be rectified by synthesizing a hydrogel with a greater mole fraction of glucose-binding moieties.

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Figure 1.

Preliminary version of the chemomechanical sensor used in this study. A piezoresistive pressure transducer with a cylindrical sensing area (A) is completely covered with a disc-shaped hydrogel film (B) of approximate thickness 400 microns. The hydrogel is held in place by a cap (C) that has a top surface which is a replaceable wire mesh/porous membrane (D) (from reference 28).

Figure 2.

Time-dependent response of the osmotic swelling pressure in response to change in glucose concentration from zero to 5 mM then back to zero. Measurements were made at room temperature in PBS buffer at physiological pH and ionic strength using GSH (composition 1) in the sensor of Figure 1.

Figure 3. Magnitude of the equilibrium change in swelling pressure vs. glucose concentration, as measured at room temperature in PBS buffer at physiological pH and ionic strength using GSH (composition 1) in the sensor of Figure 1 (average error bar magnitude 0.6 kPa). The dashed curve is given as a guide to the eyes only.

Figure 4. Fit of the time-dependent decrease in swelling pressure in Figure 2 to an exponential decay. The value of the first-order-time constant is 54 min.

Figure 5.

Time-dependent response of the swelling pressure measured at room temperature in PBS buffer at physiological pH and ionic strength using the sensor of Figure 1 with GSH (composition 2) (upper curve) and GSH (composition 1) (two lower curves). At time equal zero, the sugar concentration was suddenly increased from zero to: 5 mM glucose (unfilled symbols); 5 mM glucose plus 0.1 mM fructose (filled symbols).

Figure 6.

Time-dependent response of the swelling pressure to 5 mM fructose as measured in PBS buffer at room temperature and at physiological pH and ionic strength with sensor of Figure 1 using: GSH (composition 1) – filled symbols; GSH (composition 2) – open symbols