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Short communication

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.

1. Introduction

In recent years, there has been a considerable effort to develop enzyme-free glucose-sensitive hydrogels (GSHs) 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* 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

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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]:

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

In Eq. (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 [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*-methylene-bisacrylamide (BIS, Sigma–Aldrich), 3-acrylamidophenylboronic acid (3-APB, Frontier Scientific, Logan, UT), and N-(3-dimethyl-aminopropyl acrylamide (DMAPAA Polyscience). 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 min, after which the pregel solution was rapidly injected into a cavity (thickness 400 μm) between two square plates (polycarbonate and poly(methyl methacrylate)) of surface area 60 cm^2. The total monomer concentration in the pregel solution was 12.7 wt%. After approximately 12 h 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 pregel solution was 30.2 wt%. 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 wt% water, and GSH (composition 2) contains 58 wt% 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 Eq. (1)) which must at equilibrium equal the mechanical pressure measured by the pressure transducer. Fig. 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 ≈400 μm. 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

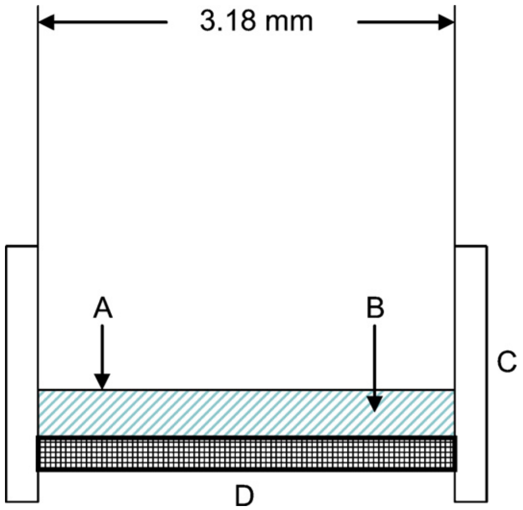

Fig. 1. Preliminary version of the chemomechanical sensor used in this study. A piezoresistive pressure transducer with a cylindrical sensing area (A) is completely covered with a disc-shaped hydrogel film (B) of approximate thickness 400 μm. The hydrogel is held in place by a cap (C) that has a top surface which is a replaceable wire mesh/porous membrane (D) (from Ref. [28]).