Computer Evaluation of Hydrogel-Based Systems for Diabetes Closed Loop Treatment

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Hydrogels provide the multifunctionality of smart materials and the applicability to medical regulatory systems. Hydrogel membranes that incorporate glucose oxidase for the closed loop treatment of type 1 diabetes mellitus are characterized and modeled. The Sorensen compartmental model is extended to represent the treatment system of a diabetic patient. The performance of the system closed by a hydrogel-based device is explored and compared to the dynamic behavior of a conventional scheme with an explicit controller element. Anionic and cationic hydrogels are discussed for insulin delivery application. Simulations demonstrate limitations in the range of swelling and contraction of hydrogels in a physiological environment due to the Donnan equilibrium effect. Results show the reduction of peak glucose levels and a basal insulin delivery from a hydrogel membrane system. The evaluation of ionic hydrogel membrane macrosystems prompts the consideration of detected pros and cons using different hydrogels, structures and scales. © 2008 American Institute of Chemical Engineers *AIChE J,* 54: 1901–1911, 2008

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Introduction

The International Diabetes Federation estimates that the number of adults (between 20 and 79 years of age) with diabetes will increment in more than 50% from the year 2007 to the year 2025, reaching 380 millions or 7.3% of the expected adult population.[1] Proper and extended treatment of diabetes mellitus is important for the quality of life of patients and families, optimal use of hospital resources, and the reduction of the impact in other social and economical aspects health related.

Diabetes treatment has evolved with technological and scientific advances. Traditional treatment is based in medical prescription of insulin injections based on glucose measurements performed manually with a certain low-frequency. The development of glucose sensors and insulin delivery devices has helped to approach a more continuous and opportune insulin administration.[2,3] Automatic continuous control systems

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offer the possibility of a precise blood glucose regulation in a diabetic patient.[4]

Desirable portability, reliability and comfortability of closed loop systems impose implementation challenges. Different insulin delivery routes[5,6,7,8] and control algorithms[9,10,11] have been proposed for the closed loop treatment of diabetes. Practical implementation of some of these systems has been done in hospital installations[9] due to the volume, complexity and supervision requirements of the instrumentation involved. Integration of the functional elements of a control system in a single device is necessary for an efficient closed loop treatment.

Hydrogels are ionic polymers that expand or contract in response to the pH of the medium. The hydrophilicity of the polymer allows for the absorption of drugs in solution. The change of intra and intermolecular spaces affects the diffusion resistance of the hydrogel, which modulates the drug release. Hydrogels have been evaluated as a competitive alternative for open loop treatment of diabetes mellitus.[12] This work analyzes systems to provide insulin to diabetic patients based on two approaches: (1) the use of separate controller, actuator and sensor units, and (2) the use of glucose sensitive hydrogels as smart materials that integrate the functions of the previously mentioned units in a single device (Figure 1).

The evaluation of hydrogel-based systems in this investigation considers the simulation of the interaction of the smart material with a localized physiological medium, which participates in the glucose-insulin metabolism in a diabetic patient. Poly(methacrylic acid-grafted-ethylene glycol) hydrogel membranes are synthesized and used as an experimental reference for the static and dynamic characterization of ionic hydrogel materials. The synthesis method and the swelling behavior are correlated with the diffusion transport through the gel. The experimental enzymatic oxidation of glucose in the polymer matrix is studied to provide a means to feedback the regulation system. Insulin delivery tests before different glucose concentrations are analyzed as preliminary demonstrations of the hydrogel performance. A hydrogel compartment is defined within the Sorensen model for the simulation of the diabetes closed loop treatment system. A simulation scenario consisting of three daily meals is proposed. Results are contrasted against the open loop response and the use of a mathematical controller. The performance of the hydrogel-based closed loop system is explained in terms of physicochemical characteristics of the hydrogel and the medium. Finally, some conclusions are presented, and some comments are made for other types of hydrogels and structures.

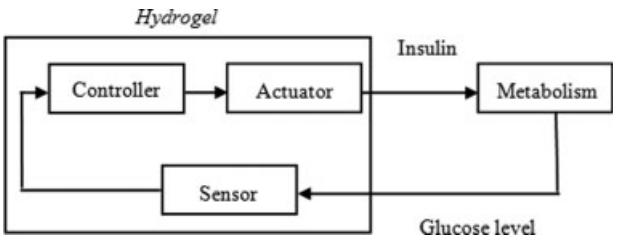

Figure 1. Closed loop approaches for diabetes mellitus treatment.

Hydrogel Membrane Synthesis

Materials and preparations

An anionic film is used as a reference for modeling and simulation of hydrogel systems. A poly(methacrylic acid-grafted-ethylene glycol) hydrogel or P(MAA-*g*-EG) is synthesized by a photoinitiated radical polymerization process. Methacrylic acid, MAA, (Sigma-Aldrich, Milwaukee, WI) and poly(ethylene glycol) monomethylether monomethacrylate with molecular weight of 1000 g/mol, PEGMA-1000, (Polysciences, Warrington, PA) are used in a 1:1 feed molar ratio of monomer repeating units. Tetraethylene glycol-dimethacrylate, TEGDMA, (Sigma-Aldrich) is used as a crosslinking agent in 1 mol % of total monomer mixture. Irgacure 184® (Sigma-Aldrich) is added in 1 wt % of total monomer mixture to initiate photopolymerization. Equal volumes of ethanol and water are used as solvent, which keeps a 1:1 volume ratio with respect to the monomer mixture. The pH is lowered to an approximate value of 2.5 using 1N chlorhydric acid (Fischer Scientific, Fair Lawn, NJ). The reactive mixture is purged with nitrogen and poured in a mold formed with glass slides separated by a Teflon® spacer. UV light is applied in the absence of oxygen for 30 min. The film formed is washed in deionized water for seven days, and then cut into small discs for its characterization. For storage purposes, the discs are dried at room-temperature for 24 h, and then inside a vacuum oven at 60°C for 3 h.

A glucose sensitive hydrogel is synthesized by substituting water by an enzyme solution of 380 units of glucose oxidase per mL in the previous preparation. Glucose oxidase and catalase are used in a 1:6.4 units ratio (a unit of glucose oxidase oxidizes 1 μmol of β-D glucose per min into D-gluconolactone, and hydrogen peroxide at pH 5.1 at 35°C, and a unit of catalase corresponds to the amount of enzyme which decomposes 1 μmol of hydrogen peroxide per min at pH 7 and 25°C). Catalase breaks the peroxide molecules, providing oxygen for the regeneration of the cofactor of glucose oxidase. The excess of catalase is intended to assure oxygen availability. The enzymes are dissolved in an acetate buffer with pH of 5.1 and acryl oil chloride is added for the functionalization reaction in an ice-water bath with continuous mixing. The enzyme containing membranes are washed and stored in refrigeration.

Polymerization kinetics and mesh size

The polymerization kinetics comprises the UV initiation, propagation and termination processes, and determines the size of the polymer molecule.[13] The average number of monomer units per polymer molecule ($\overline{X}_n$) considers the light intensity absorbed (I_{abs}), the concentration of the monomer ([M]) and termination by equally probable combination and deprotonation mechanisms

$$\overline{X}_n = \frac{0.75 k_p [M]}{(f k_t I_{abs})^{1/2}}, \tag{1}$$

where k_p and k_t are the propagation and termination rate constants, f is the efficiency of the initiator, [M] is the concentration of the monomer, and I_{abs} depends on the intensity and energy of the incident light, and the concentration and molar

Table 1. Parameters for the Estimation of the Mesh Size of P(MAA-*g*-EG) Hydrogel Network

Parameter	Value
Molar volume of swelling agent[15]	18 mL/mol
Density of water[15]	1 g/mL
Density of ethanol[15]	0.789 g/mL
Density of PMAA[16]	1.0153 g/mL
Density of PEG[16]	1.1135 g/mL
Density of heptane[15]	0.6837 g/mL
PMAA-solvent interaction parameter[17]	0.5987
PEG-solvent interaction parameter[17]	0.55
Characteristic ratio of PMAA[16]	14.6
Characteristic ratio of PEG[16]	3.8
Molecular weight of MAA repeating unit[16]	86 g/mol
Concentration of monomer	3.574 mol/L
Concentration of Irgacure 184® photosensitizer	0.0257 mol/L
Initiator efficiency	0.5
Molar absorption coefficient of Irgacure 184 at 365 nm[18]	10 L/mol·cm
Propagation rate constant of MAA chain radicals[17]	670 L/mol·s
Termination rate constant of MAA polymerization[17]	2.1×10^6 L/mol·s

absorptivity of the photoinitiator. The molecular weight of the uncrosslinked polymer M_n, is obtained as $\overline{X}_n$ times the molecular weight of the monomer.

The crosslinked structure of the hydrogel is characterized by the mesh size, which depends on the viscoelasticity of the material. The Peppas-Merrill equation [14] for the molecular weight of the crosslinked polymer considers the viscoelastic behavior described by volume fractions in the swollen and relaxed states

$$\frac{1}{\overline{M}_c} = \frac{2}{\overline{M}_n} - \frac{\frac{V}{V_1}\left[\ln(1-\upsilon_{2,s}) + \upsilon_{2,s} + \chi_1 \upsilon_{2,s}^2\right]}{\upsilon_{2,r}\left[\left(\frac{\upsilon_{2,s}}{\upsilon_{2,r}}\right)^{1/3} - 0.5\left(\frac{\upsilon_{2,s}}{\upsilon_{2,r}}\right)\right]}, \quad (2)$$

where $\overline{M}_c$ is the average molecular weight between crosslinks, V is the specific volume of the polymer, V_1 is the molar volume of the swelling agent, $\upsilon_{2,s}$ is the volume fraction of the polymer in the swollen state, $\upsilon_{2,r}$ is the volume fraction of the polymer in the relaxed state after synthesis, and χ_1 is the Flory polymer-solvent interaction parameter. The mesh size ξ, is calculated by

$$\xi = CN^{1/2}Q^{1/3}, \quad (3)$$

where C is the bond length along the polymer chain (1.54 Å for carbon-carbon bonds) multiplied by the square root of the Flory characteristic ratio of the polymer (C_n), N is the number of links per chain between crosslinks or $2\overline{M}_C$ divided by the molecular weight of the monomer, and Q is the volume swelling ratio or inverse of $\upsilon_{2,s}$. Although the reaction really consists of a copolymerization process due to the presence of the crosslinking agent, the consideration of the polymerization kinetics may be appropriate since the concentration of the crosslinking agent is generally low. The grafts of poly (ethylene glycol) affect the properties of the material, therefore the parameters C_n and χ_1 of the hydrogel are assigned the mean values of those for poly(ethylene glycol) and poly (methacrylic acid). Table 1 contains the parameters used for mesh size calculations.

Characterization of Hydrogels

Swelling behavior of hydrogels

The essential pH sensitivity of a hydrogel is characterized. Although a quantitative characterization of an anionic hydrogel is presented, the parameters for a cationic hydrogel are proposed based on the order of magnitude of the parameters of the first, and the qualitative behavior of the latter.

Step inputs are proposed in the pH range from 3.2 (approximate pH of products from enzymatic glucose oxidation) to 7.2 (close to neutral physiological pH) at 37°C to analyze the volume swelling ratio response Q, which is defined as the volume of the swollen hydrogel over the volume of the dry hydrogel. The structure of the model is given by a first-order ordinary differential equation

$$\tau\frac{dQ(t)}{dt} + Q(t) = K\ pH(t), \quad (4)$$

where a gain K, and a time constant τ are obtained in different operation zones for both ascending and descending directions. The gain is interpreted as a three-dimensional (3-D) mechanochemical compliance that relates a change in Q with respect to a change in pH. The time constant represents the relaxation time of the material. The sensitivity and the dynamics of the volume swelling ratio before pH variations are described by the values of these two parameters in each operation range.

Figure 2 shows the step experiments and the evaluation of the corresponding model with the structure given by Eq. 4, and the parameters listed in Table 2. Each step experiment requires the sample to have a steady volume before the pH change is applied. The volume swelling ratio is monitored constantly (through weight measurements) during the first 8 h to capture two thirds of the transitory response approximately. The final measurements are done 24 h from the start of the experiment to determine the new steady-state volume swelling ratio, which corresponds to the initial condition for the next step. The set of first-order models reproduces the experimental results.

The critical pH is where the hydrogel shows the highest sensitivity. For the case of the anionic gel under experimentation, the critical pH is 5.6. Around the critical pH, the con-

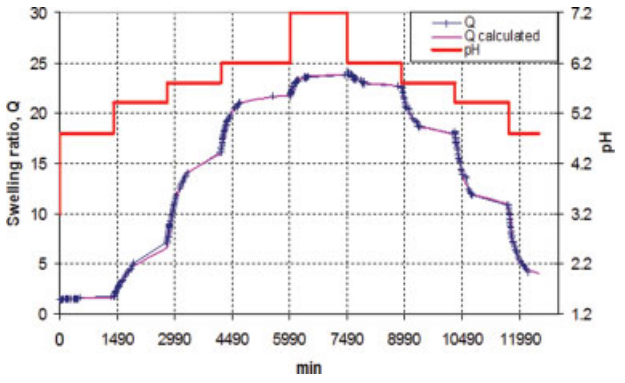

Figure 2. Swelling behavior of P(MAA-g-EG) hydrogel.

[Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Table 2. Parameters for Swelling Behavior Model of P(MAA-g-EG) Hydrogel

pH range and change direction	3D Mechanochemical Compliance	Relaxation Time (min)
3.2 to 4.8	0.15	625
4.8 to 5.4	8.96	588
5.4 to 4.8	11.46	170
5.4 to 5.8	22.46	333
5.8 to 5.4	17.75	238
5.8 to 6.2	13.92	222
6.2 to 5.8	11.63	256
6.2 to 7.2	2.12	167
7.2 to 6.2	1.32	357

traction response is faster than the swelling response, while the opposite occurs in other operations zones.

The characterization of P(MAA-*g*-EG) gives insight of the behavior of hydrogels. Cationic materials may be represented by considering a negative gain since a decrement in pH would cause the volume of the cationic membrane to augment. A cationic hydrogel is simulated with gains of the same magnitude and opposite sign than those calculated for the anionic gel.

Diffusion through hydrogel membranes

The diffusion through the gel of different species of interest, like glucose, insulin and hydrogen ions, depends on the hydrodynamic radius r, of the solute as well as on the degree of swelling of the membrane Q. Diffusion coefficients D, can be estimated as a fraction of the diffusion coefficient of the solute in pure water D_0. Such fraction depends on the relative size of the solute with respect to the mesh size of the polymeric network and the volume of solvent absorbed with respect to volume of the dry polymer, as expressed in

$$D = D_0\left(1 - \frac{r}{\xi}\right)e^{-1/Q-1}. \tag{5}$$

The Stokes-Einstein equation gives the hydrodynamic radius of a solute

$$r = \frac{k_B T}{6\pi\eta D_0}, \tag{6}$$

where k_B is the Boltzmann constant, T is the absolute physiological temperature, and η is the viscosity of the water at this temperature.

Alternatively, the diffusion coefficient can be determined experimentally using a diffusion cell, where two reservoirs are interfaced with a hydrogel membrane.[19] A hydrogel sample at equilibrium at pH 7 is fixed between the two reservoirs. The donor reservoir is loaded with a pH 7 solution with a specific concentration of the solute of interest. The receptor reservoir is filled with pure pH 7 buffer. Temperature is maintained at 37°C by the circulation of water through the jackets of the reservoirs. Small volume samples are taken from the receptor side and replaced by buffer during the experiment. The samples are analyzed to determine the solute concentrations on the receptor cell. The data are fitted to the following equation to calculate the permeability of the solute

$$ln\left(1 - \frac{2c_t}{c_0}\right) = -\frac{2A}{V}Pt, \tag{7}$$

where c_t is the concentration of the solute in the receptor reservoir at time t, c_0 is the initial concentration on the donor side, V is the volume of a half cell, *A* is the transfer area, and P is the permeability coefficient that can be estimated from the slope of the logarithmic function with respect to time. The partition coefficient of the solute is necessary to relate the permeability with the diffusion coefficient. A partition experiment consists of immersing a membrane at equilibrium at pH 7, in a solution with a certain initial concentration c_i, of the solute and the same pH. The final steady-state concentration c_f, in the solution is determined to do the following calculation

$$K_d = \left(\frac{V_{sol}(c_i - c_f)}{V_m}\right)\left(\frac{1}{c_f}\right), \tag{8}$$

where V_m is the volume of the membrane, V_{sol} is the volume of the solution, the first factor constitutes the concentration of the solute in the membrane, and the partition coefficient k_d is the ratio of the concentration of the solute in the membrane over the concentration in the solution. The diffusion coefficient D, is

$$D = \frac{P}{k_d}b, \tag{9}$$

where b is the thickness of the membrane.

At a pH of 7 and 37°C, the diffusion coefficient for insulin through a P(MAA-*g*-EG) film is determined in a diffusion cell experiment as 1×10^{-10} m^2/s. Insulin has a diffusion coefficient in water of 2×10^{-10} m^2/s,[20] and a Stokes radius of 16.4 Å. The hydrogel film under the mentioned pH and temperature conditions has an equilibrium volume swelling ratio of 23.93, and a mesh size of 416 Å, which gives a theoretical diffusion coefficient of 1.86×10^{-10} m^2/s. Therefore, the calculations of diffusivities with Eq. 5 show agreement with those that can be obtained from a diffusion experiment, despite experimental error. Equation 5 is conveniently used for the determination of diffusion coefficients for smaller species, such as glucose and hydrogen ions.

Enzymatic reaction within the hydrogel

The glucose sensitivity of the hydrogel is attained by the reactions promoted by the enzyme complex. Glucose oxidase interacts with its substrate to produce gluconolactone and hydrogen peroxide. The gluconolactone hydrolizes immediately and converts into gluconic acid. The presence of the gluconic acid lowers the pH of the membrane, which causes a change in its volume, and, therefore, in the diffusivity of the solutes of interest. As glucose oxides, the cofactor of the glucose oxidase enzyme reduces and becomes inactive. The catalase reaction over the hydrogen peroxide produces oxygen, which allows the reactivation of the cofactor of glucose oxidase by returning to the oxidized state.

The kinetics of the enzymatic glucose oxidation depends on the conditions of the reaction environment. In order to determine a characteristic kinetic constant for the glucose ox-

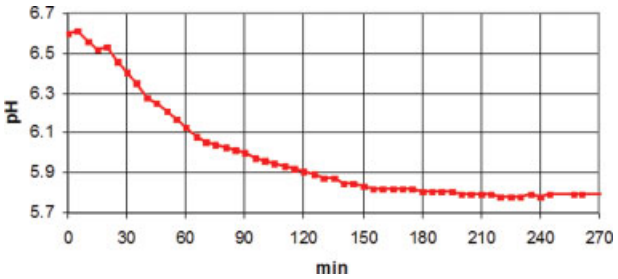

Figure 3. Variation of pH by enzymatic oxidation of glucose in hydrogel.

[Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

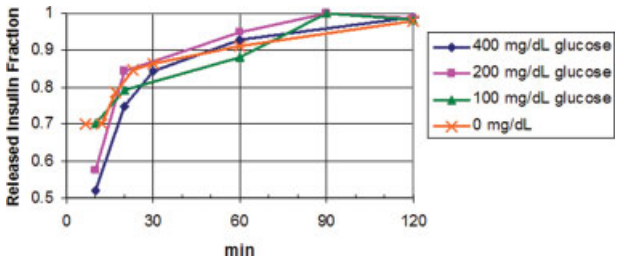

Figure 4. Insulin release in different glucose concentration solutions.

[Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

idation in the hydrogel, resultant from glucose oxidase and catalase reactions, a disc sample was immersed in 6 mL of a 200 mg/dL of glucose solution in deionized water, and the pH was monitored during the reaction (Figure 3).

The hydrogen ion concentration in the local environment of the gel is due to the chemical dissociation of water and part of the produced gluconic acid. The excess of proton concentration from the initial pH of 6.6 quantifies the dissociated gluconic acid, which is molarly equivalent to the hydrogen and gluconate ions produced. The pK_a of gluconic acid is used to determine the molar concentration of undissociated gluconic acid during the reaction. The sum of dissociated and undissociated gluconic acid gives the total reacted glucose, since there is a 1 to 1 stoichiometric relation of glucose to gluconic acid in the enzymatic reaction, assuming that the D-glucono-1,5-lactone is completely and instantaneously hydrolyzed to gluconic acid. The rate of glucose reaction is obtained by the time derivation of the consumed glucose. The inflection point that can be noticed in the curve of Figure 3, leads to a velocity profile with an early maximum, that is, the initial velocity is not the highest despite the highest glucose concentration in solution due to the delay of the diffusion process through the membrane. Finally, the glucose concentration during the reaction is determined by subtracting the reacted glucose from the initial total glucose. A plot of velocity of reaction with respect to the concentration of the glucose substrate, disregarding the initial raise of velocity, allows the determination of an average reaction rate constant k of 0.008 min^{-1}. This constant is specific for the enzymatic reaction system in the hydrogel, and differs from the constant of the glucose oxidase reaction in solution.[21]

Insulin delivery from hydrogel

The integration of sensor, controller and actuator functionalities in a hydrogel-based system can be explored preliminarily by insulin release experiments in solutions with different glucose concentration at neutral pH and 37°C in a dissolution apparatus. Insulin is loaded into a hydrogel sample at a pH of 5, below the isoelectric point (pI) of insulin, close to the pI of the enzymes present in the hydrogel system, and close to the critical or transition pH of the gel. The chosen loading pH is intended to produce a positive charge for insulin, a negative charge for the enzymes, as well as a partial ionization of the anionic hydrogel. In this way, a favorable electrostatic attraction between insulin and the hydrogel system is produced. The amount of insulin absorbed in the hydrogel from a 50 mg/dL insulin loading solution corresponds to an average of 10% of the dry weight of the sample. Figure 4 shows that when glucose sensitive hydrogel membranes are set into different glucose concentration solutions, the initial released fraction is lower for the higher glucose content.

Modeling of Hydrogel Interaction with Glucose-Insulin Metabolism

Modification of the Sorensen model

The glucose-insulin dynamics is represented by the high-order nonlinear model contributed by Sorensen.[22] This model represents the main organs of the human body involved in the glucose-insulin metabolism through compartments described by mass balances and kinetic effects. This model has been the base for research on meal and exercise effects on glucose-insulin metabolism and investigation on blood glucose control.[10] This work modifies the Sorensen's model with the inclusion of a hydrogel system, which is proposed to be implanted in the peritoneum (Figure 5). The physiolog-

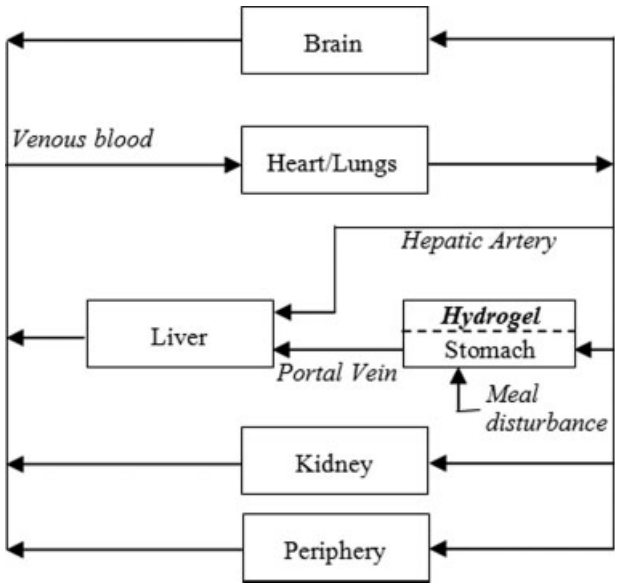

Figure 5. Sorensen glucose-insulin model with the addition of hydrogel subcompartment.

ical parameters available in the literature[10,22] are complemented with the hydrogel parameters from the experimental characterization.

A hydrogel subcompartment is defined in the stomach compartment of the Sorensen model. Diffusion terms link the glucose and insulin balances in the stomach and the hydrogel system. The equations for glucose transport are

$$G_s'(t) = (G_H(t) - G_s(t))\frac{q_s}{v_s} + \frac{\Gamma_{meal}(t)}{v_s} - \frac{\Gamma_{SU}}{v_s} - \frac{D_G(t)A_M(t)}{bv_S}(G_S(t) - G_M(t)), \quad (10)$$

$$(G_m(t)V_M(t))' = \frac{D_G(t)A_M(t)}{b}(G_s(t) - G_M(t)) - V_M(t)kG_M(t), \quad (11)$$

where G is glucose concentration in the compartment indicated by the subscript *S*, *H* and *M* for stomach, heart and gel membrane, respectively; glucose convective transport is effected by the blood flow q_S, through the capillary volume v_S in the stomach subsystem; Γ_{meal} and Γ_{SU} represent absorption of glucose from food and stomach glucose uptake, in the order given; V_M is the volume of the membrane, whose changes are reflected mainly in variations of the cross area $A_M(t)$; *b* is the thickness of the membrane assumed constant; D_G is the diffusion coefficient of glucose, and *k* is the estimated first-order reaction rate constant for the glucose oxidation reaction.

The glucose concentration in the membrane can be obtained by integrating the accumulation given by Eq. 11, and dividing over the volume of the hydrogel membrane

$$G_M(t) = \frac{\int_0^t (G_M(t)V_M(t))'dt}{V_M(t)} \quad (12)$$

The insulin balance is given by

$$I_s'(t) = (I_h(t) - I_s(t))\frac{Q_s}{V_s} + \frac{D_I(t)A_M(t)}{bV_s}(I_M(t) - I_s(t)), \quad (13)$$

$$(I_M(t)V_M(t))' = \frac{D_I(t)A_M(t)}{b}(I_s(t) - I_M(t)) = -\Gamma_{ID}(t), \quad (14)$$

where I is insulin concentration in the compartment indicated by the subscripts *S*, *H* and *M* for stomach, heart and gel membrane, respectively; insulin is transported convectively by the blood flow Q_S, through the capillary volume V_S in the stomach subsystem; insulin delivery Γ_{ID}, is realized by diffusion from the hydrogel membrane with an effective diffusion coefficient D_I.

The insulin depletion in the hydrogel is modeled by the integration of the delivery rate, Γ_{ID}. Therefore, the insulin concentration in the membrane is given by

$$I_M(t) = \frac{I_{Load} - \int_0^t \Gamma_{ID}(t)dt}{V_M(t)}, \quad (15)$$

where I_{Load} is the amount of insulin previously loaded in the hydrogel membrane.

Hydrogel membrane pH

The hydrogen ion concentration in the microenvironment of the hydrogel, H_M in mol/L, is determined from the next molar balance

$$(H_m(t)V_M(t))' = \frac{D_H(t)A_M(t)}{b}(H_P - H_M(t)) + x(t)V_M(t), \quad (16)$$

where D_H is the diffusion coefficient of hydrogen ion through the membrane; H_P is the molar hydrogen ion concentration in the peritoneum, considered at a constant pH of 6.5, and x(t) is the rate of production of moles of hydrogen ions per volume unit, and H_M gives the pH of the membrane.

The production of hydrogen ions depends on the dissociation of the produced gluconic acid, characterized by the dissociation constant K_a

$$K_a = \frac{[H^+][Gluconate^-]}{[Gluconic\ acid]}, \quad (17)$$

where the rectangular parenthesis indicate molar concentration. Since there is an equimolar relation between the consumed glucose and the produced gluconic acid and between the dissociated gluconic acid and each ionic species, the previous equation can be transformed into a quadratic function of hydrogen ion molar concentration by substituting

$$[Gluconate^-] = [H^+] \quad (18)$$

and

$$[Gluconic\ acid] = [Glucose]_M - [H^+], \quad (19)$$

where $[Glucose]_M$ is the molar concentration of glucose in the membrane. The production rate of hydrogen ions is assumed to be determined by the same rate constant for glucose oxidation and is expressed as

$$x(t) = k[H^+]. \quad (20)$$

Hydrogel volume model

Hydrogen ion concentration in the hydrogel determines the volume response of the membrane as already described. In order to represent not only the swelling dynamics and sensitivity before pH changes, but also the pH-volume operation points, the swelling process is represented as a closed loop system, as shown in Figure 6. The volume swelling ratio set point is interpolated for a specific value of pH in the membrane resulting from Eq.16, using the steady-state pH-volume points from Figure 2. The pH-volume operation points at equilibrium fit a hyperbolic tangent function with four constant parameters a, b, c and d

$$Q = a + b\tan h(c(pH) + d). \quad (21)$$

The function G(s) is determined to attain the characteristic time constant and reach the volume swelling ratio corresponding to the pH calculated in the microenvironment of the membrane

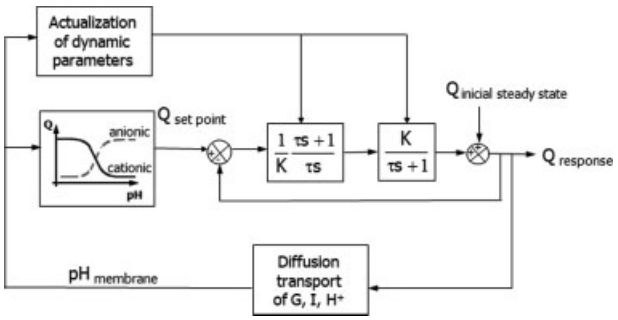

Figure 6. Model of hydrogel volume swelling ratio.

$$G(s) = \frac{1}{K}\left(1 + \frac{1}{\tau s}\right), \tag{22}$$

where G is defined in the domain of the Laplace variable s, K and τ are the parameters of the first-order dynamic model in a specific operation zone, and the integration represented by s^{-1} is reset when the parameters K and τ change.

A dynamic interaction between the pH and glucose effects on the hydrogel system exists since there is a bidirectional dependence between them. The glucose concentration in the medium causes a change a pH, which in turn produces a volume change of the hydrogel. Simultaneously, the glucose concentration in the gel is affected by its degree of swelling, which affects the hydrogen concentration inside and in the close vicinity of the gel.

Simulation of Closed Loop Treatment Systems

Simulation test

The performance of a hydrogel-based system for the regulation of blood glucose is evaluated by the simulation of three daily meals until significant insulin diffusion from the hydrogel stops. The meals are represented by pulse functions for the carbohydrates consumption rate. The pulse duration is fixed in 30 min, and the pulse area represents the ingestion of 66 g of carbohydrates. The carbohydrates total in three meals accounts for 53% of the energy from a 1,500 kcal diet, close to the minimum daily recommended energy percentage from carbohydrates.[23] In the case of a higher caloric content diet, low-carbohydrate meals are considered for the simulation.

Several assumptions complete the simulation conditions for hydrogel structures for insulin delivery in a diabetic patient. The meal absorption process in the stomach compartment is simulated by a filter with a constant time of 60 min, as proposed in the literature.[10] The hydrogel membrane is allowed to reach equilibrium at the physiological pH previous to its implantation. The hydrogel is loaded with insulin in 5% of the dry gel weight to prevent an abrupt descend of glucose level upon implantation. Moreover, the patient is assumed to have a meal after 100 min from implantation to avoid low glucose levels. The meals are programmed at 7:00, 12:00 and 17:00 h, considering implantation at 5:20. Finally, the insulin therapeutic effect is supposed not to decrease with time and implantation conditions, and the activity of the enzymes and the hydrogel itself are preserved beyond insulin depletion.

Comparison references

The effect of insulin delivery from a hydrogel-based device is contrasted against the open loop response of the physiological model of the diabetic patient, and the potential performance of a conventional closed loop system with an explicit controller.

The open loop response before the previously defined test offers a reference to determine when the hydrogel-based system stops being useful for blood glucose control. The glucose metabolism dynamics with the Sorensen model shows the highest glucose deviations and a slow recovery of a normal level when meal disturbances are considered. The differentiation from the open loop response indicates an advantage for the treatment system.

An explicit controller is defined to close a feedback glucose loop, since the action of the hydrogel-based system is reactive to the blood glucose concentration, i.e., no anticipation or adaptive features are considered in the conventional loop for better analogous conditions with respect to the hydrogel closed loop. The controller algorithm is proposed according to the linear quadratic regulatory problem formulation,[24] to minimize the following cost function J

$$J(x_1, u) = \int_0^\infty [\eta {x_1}^2(t) + \rho u^2(t)]dt \tag{23}$$

where x_1 is the deviation of glucose level from the desired value, u is the insulin delivery rate, and η and ρ are positive weighting factors. The tuning parameters of the controller or weight factors in the cost function are fixed during the simulation of the closed system. The separate sensor and actuator units are considered ideal systems with negligible effect on the overall process dynamics. The controller is simulated assuming that insulin availability is not interrupted.

Simulation results

A cationic gel is functionally more adequate for insulin delivery, since a decrement in pH caused by the enzymatic glucose oxidation opens the mesh and eases the liberation of the preloaded insulin. Figures 7 and 8 show the performance of a cationic hydrogel-based system. The diffusion delivery mechanism produces a decreasing release rate with time. Most of the loaded insulin is released upon exposure to glucose in physiological fluids or implantation as shown by the release profile and the first valley of glucose concentration. The insulin hydrogel-based delivery system reduces the glucose concentration relative maximums in the first days. The comparison with the open loop response (Figure 7) suggests that the hydrogel membrane would be effective for a three day treatment considering only the amount of insulin loaded. The preloaded drug may be limited to reduce a hypoglycemic reaction upon implantation. In a three day time frame (Figure 8), the hydrogel action achieves the same speed of response in the first day or series of three meals, with a significant and higher reduction of glucose levels with respect to the use of the controller. In the second day, the glucose concentration range is similar for both closed loop systems,

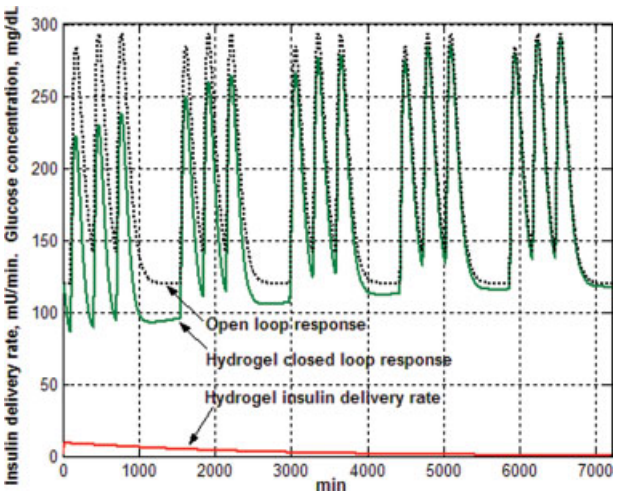

Figure 7. Cationic hydrogel and open loop performances.

[Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

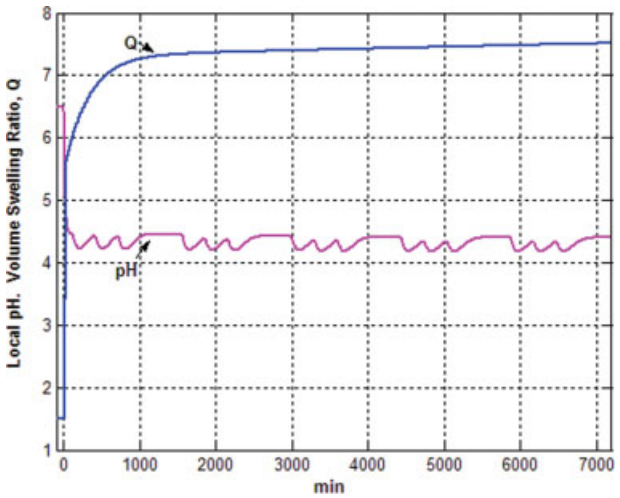

Figure 9. Volume swelling ratio and pH of implanted cationic hydrogel membrane system.

[Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

but the slope of recovery of normoglycemia is smaller in magnitude for the hydrogel system. In the third day, the response of the hydrogel closed loop is as slow as the open loop response, and the peak glucose levels are raised above the uniform peaks of the controller closed loop glucose response.

The behavior of the cationic hydrogel can be observed in Figure 9. The meal disturbances are reflected in the pH of the microenvironment of the hydrogel, but the produced variations are small and unable to cause an appreciable change in the volume swelling ratio. The initial interaction with the glucose containing physiological fluids dominates the volume response of the membrane over the pH changes caused by the meals. The continuous presence of glucose impedes the full range hydrogel action explored in the laboratory (Figure 2). These observations explain the monotonous release rate profile obtained for the implanted hydrogel membrane system.

An anionic gel may be used to store insulin and allow its diffusion out to the surroundings. However, the pH dependence of the volume is expected to hinder diffusion when insulin is most needed (or glucose level is high). This disadvantage can be overcome if the contraction of the hydrogel can squeeze out enough insulin to compensate the posterior hindered diffusion at the low pH caused by glucose oxidation. The squeezing effect is stronger with macroporous materials.[25] Macropores can be formed if the hydrogel is synthesized with excess of solvent by adjusting the pH of the reactive mixture as in the aforementioned P(MAA-*g*-EG) preparation procedure. The simulation of a P(MAA-*g*-EG) membrane, shown in Figures 10 and 11, gives similar results

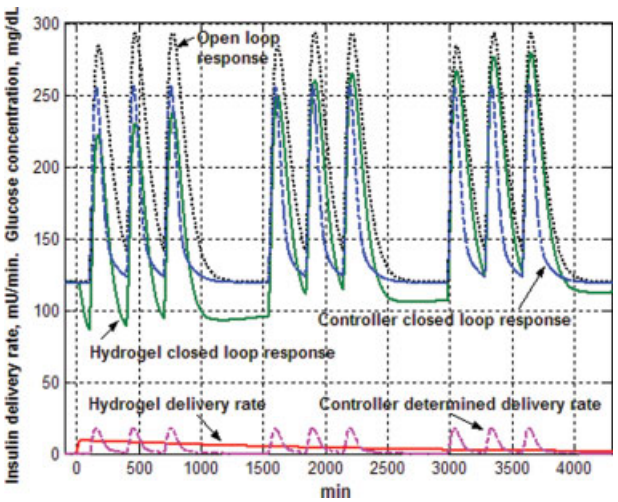

Figure 8. Cationic hydrogel, controller and open loop performances.

[Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

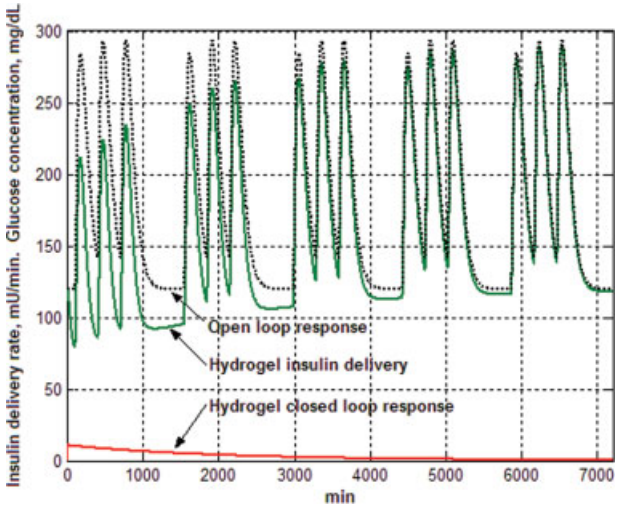

Figure 10. Anionic hydrogel and open loop performances.

[Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

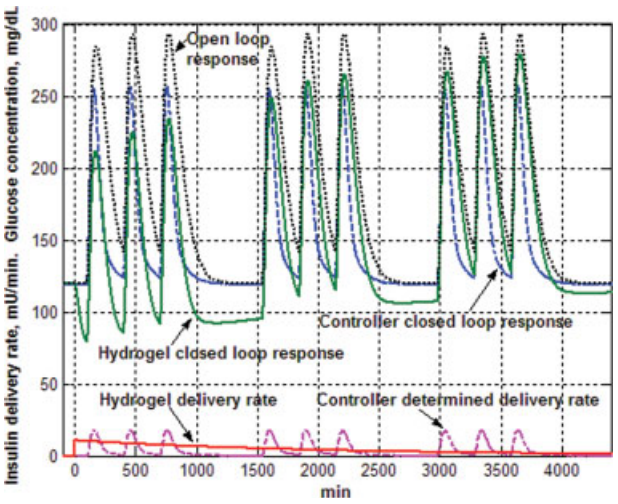

Figure 11. Anionic hydrogel, controller and open loop performances.

[Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

for the case of a cationic gel membrane. The difference is only noticed in the early interaction causing lower glucose concentration with respect to the initial glucose response with a cationic gel. The high initial insulin release is due to both the squeezing delivery by the contraction of the gel, [26] and the diffusion through wide molecular openings despite the volume reduction (Figure 12). The quantitative simulation results restrict the qualitative appreciation of a hindered diffusion from the anionic membrane in the presence of gluconic acid to relative terms with respect to the diffusion from the same anionic membrane at high pH. This means that the different ranges for the volume swelling ratio of cationic and anionic membranes do not allow establishing an advantage for insulin delivery for a particular type of hydrogel under the conditions of evaluation in this study.

The observed limitation of volume changes of the hydrogel (Figures 9 and 12) corresponds to the small variations of pH due to a combination of the buffer effect of the blood and its glucose composition. The recovery of a high pH in the hydrogel after a meal implies the diffusion of hydrogen ions out of the membrane that would promote a change of pH in the peritoneum. However, such change may be damped or practically avoided by the buffer characteristic of the blood. Therefore, the hydrogen ion gradient would be fixed on the side of the physiological pH, and limit the output of hydrogen ions from the hydrogel (Eq. 16). The high concentration of hydrogen ions, or low pH on the side of the hydrogel results from the generation of hydrogen ions by chemical dissociation of the produced gluconic acid. Even at the fasting glucose level, glucose would tend to diffuse into the gel causing a sustained production of gluconic acid that would oppose the recovery of the higher physiological pH.

The short variability of the pH input and volume swelling ratio output of a hydrogel system can be explained in terms of Donnan equilibrium. The crosslinked backbone of the polymer supports uniformly charged chemical groups that affect the local concentration of ionic species creating an electric bilayer.[27] Ionic species with the same charge of the pending groups of the polymer or coions are kept from entering the hydrogel because of electrostatic resistance. The exclusion of coions, increases the concentration of counterions. In consequence, species with equal electrochemical potential can be present at different concentrations inside and outside of the hydrogel membrane, which explains the conservation of a local pH different from the pH of the physiological environment.

The controller output in the conventional closed loop scheme is potentially more versatile and adequate to regulate blood glucose concentration before meal disturbances, while the insulin delivery through a hydrogel system provides the benefits of a low continuous decreasing dose. The behavior of the insulin delivery determined by the mathematical controller would only be possible for the hydrogel release profile if volume changes were faster and bigger. The insulin delivery by the hydrogel membrane may be considered more similar to a basal insulin supply, although there is a limited responsiveness to the particular physiological environment.

Conclusions

The simulations results are backed with experimental evidence obtained from insulin release studies, despite the different scenarios. In the treatment of diabetes mellitus, the insulin release rate from the hydrogel is more effective to correct glucose levels during the first meals after implantation. The high initial release in neutral pH buffer solutions at 37°C in a dissolution apparatus is also observed and differentiated for each glucose concentration (Figure 4). The later coincidence of the experimental profiles of insulin released fractions in the different glucose concentration solutions, indicate that glucose in the delivery medium is in enough excess to maintain the same constant local pH allowing for no difference in diffusivities. This observation in the laboratory supports the pH and volume behavior with little variations despite the meal disturbances in the simulation.

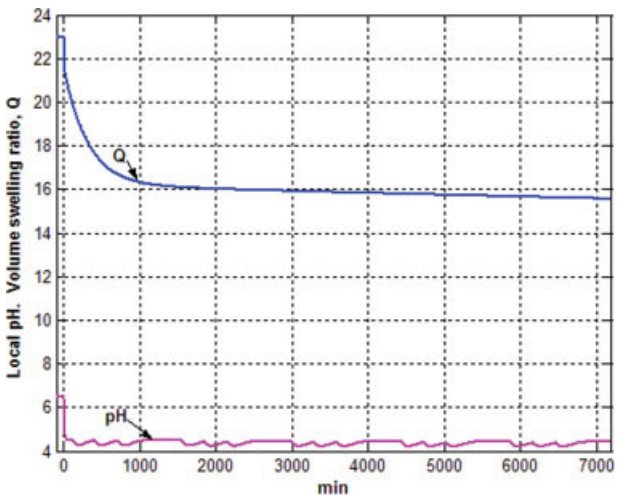

Figure 12. Volume swelling and pH of implanted anionic hydrogel membrane system.

[Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

The evaluation of the potential of hydrogel-based systems for closed loop insulin delivery highlights some limitations linked to particular characteristics of the synthesis of the hydrogel material, as well as to general conditions of the application context. Regardless of the type of hydrogel used for the membrane or monolithic system, the mesh size of the hydrogel material needs to show variations around the size of insulin at a physiological medium in order to produce a flexible delivery profile similar to the one obtained with the optimal controller. Synthesis parameters can be varied in order to obtain a more effective molecular valve coupled to the glucose sensitivity granted by the enzymatic system (glucose oxidase and catalase). In the case of ionic hydrogels, the mesh size, as well as the critical pH can be affected by the number, type and concentration of monomers. Even if the critical pH of an ionic hydrogel were adjusted closer to a neutral value, the buffer characteristic of physiological fluids would offer a resistance to the volume changes of the membrane. Hydrogel materials with temperature and glucose sensitivity can be suggested from the possibility to couple the energy produced by the enzymatic reaction of glucose to the modulation of molecular openings and drug delivery. Hydrogels without pH sensitivity would eliminate the limitations due to the buffer environment and the Donnan equilibrium effect, however, they would also be subjected to the saturation of the glucose oxidase enzyme due to the constant presence of glucose in the physiological environment.

The arguments given about the effects of the buffer physiological medium, the continuous presence of glucose and the Donnan equilibrium suggest that the discussed limitations may be present irrespective of the size of the ionic hydrogel system. Hydrogel microparticles show very low-time constants,[28] but the local pH variations may be restricted in magnitude as in the membrane systems.

Limitations of hydrogel monolithic systems or membranes for continuous blood glucose regulation may be overcome by hydrogel based devices. Hydrogels may be synergically used in composite systems[29,30] for a more effective insulin delivery. Such composite systems could be engineered to expose the hydrogel membrane to the physiological release medium, and to a washing medium alternately for a more differenciated response before body glucose levels. Another scheme could be based on the use of glucose permeable membranes (out of cellulose acetate for example) in an assembly that would separate glucose from the origin buffer physiological solution allowing for a nonbuffer microenvironment of the hydrogel system. The nonhydrogel membrane would prevent possible interferences and impose a diffusional resistance for glucose to reach the hydrogel-based system, which would help to avoid the saturation of the enzymes. The structure of such device should provide a path for insulin delivery. These are examples of design approaches that could take advantage of the combination of hydrogels with other types of materials and fluidic mechanisms to serve the application of interest.

The comparison of closed loop systems based on a single smart material device, and on a traditional scheme of a device per function serves the purpose of setting a reference for the discussion of hydrogel-based systems and alternatives of diabetes treatment. The short-range of actuation of the ionic hydrogel due to the small changes in the local pH limits the dynamic performance of a hydrogel membrane in comparison with a controller closed loop system. Nevertheless, both closed loop systems share issues regarding insulin availability and effectiveness. The higher-level of integration offered by a hydrogel based system is potentially more advantageous for implantation and, ultimately, for the comfort of the patient.

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