

Mathematical Modeling and Simulation of Dissolvable Hydrogels

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Abstract: Hydrogels have a large number of potential applications in microelectromechanical technology as sensors and actuators. In this paper we try to understand the physics of dissolvable hydrogels and investigate the various parameters controlling the dissolution process. Hydrogels, crosslinked via disulfide bonds, when immersed in a solution containing the disulfide cleaving agent can break covalent cross links causing the hydrogel to dissolve and thereby indicating the presence of the cleaving agent. Such a concept can be used to develop biochemical sensors, sacrificial structures in microfluidic systems, and other applications. The mechanism of the hydrogel dissolution process has been studied in detail and a mathematical model has been developed. From the vanishing time of the dissolvable hydrogel, a significant amount of qualitative and quantitative information about the solution can be obtained. A large number of factors governing the hydrogel dissolution process were investigated by simulations and experiments.

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Introduction

The sensitivity of hydrogels to a large number of chemical and physical factors (Kost 1990) like temperature, light, electrical voltage, pH, ionic strength, biological, and chemical agents make them suitable for a broad range of applications. Miniaturized hydrogel objects are strong candidates for sensors and actuators in microelectromechanical systems (MEMS) technology. Their comparatively large volume changes and large force exertion combined with favorable scaling of their time response make them very suitable for application as microsensors and microactuators in MEMS devices. For example, electroresponsive ionic polymer gels (Cohen 2001) have been successfully employed for the design of a catheter steering element, a miniature manipulator, a dust wiper, a miniature robotic arm, and grippers. The application of such ionic electroactive polymers and other stimuli-sensitive polymer gels as actuators for manipulation, mobility, and robotic devices can have a significant impact in the aerospace and auto-

mobile industry. Hydrogels can also be used to regulate the flow of fluids in microchannels (Liu et al. 2002).

In this paper, we investigate the use of stimuli-responsive hydrogels as biochemical sensors, which can have numerous applications in the field of (BioMEMS) and microfluidics. Stimuli responsive hydrogels are three-dimensional cross-linked polymer networks that undergo volume transitions when exposed to a change in environment, such as pH, temperature, biochemical agents, and electric field. Microscopic (polyacrylamide) hydrogels, which are cross linked via disulfide linkages, can dissolve in the solution upon exposure to disulfide reducing agents like dithierythritol (DTT) and glutathione as a result of the decross-linking caused by the thiol-disulfide interchange reaction (Houk and Whitesides 1987). The mechanisms of the dissolution process have been studied in detail and a complete model has been developed for predicting the behavior of the hydrogels. Besides thiol other types of disulfide reducing agent [e.g., tris (2-carboxyethyl) phosphine hydrochloride (TCEP HCl)] can also be used as the cleaving agent. Dissolvable hydrogels can lead to the development of chemical and biological sensors and sacrificial structures for microfluidic systems. The rest of the paper is outlined as follows: The basic concepts and the structure of a hydrogel are first described. The underlying physics behind the initial swelling and dissolving of the chemically modified hydrogels is then explained. The mathematical model that has been developed to capture the various physical processes in dissolvable hydrogels is then described. The next sections dwell on details on numerical simulations and how the various fields have been coupled. Numerical results comparing with experiments are presented for several examples followed by the conclusions section.

Hydrogel Structure

Hydrogels are polymers with a cross-linked three-dimensional network (Chu et al. 1995). (See Fig. 1.) When the polymer network is immersed in a suitable solvent, the chains in the network

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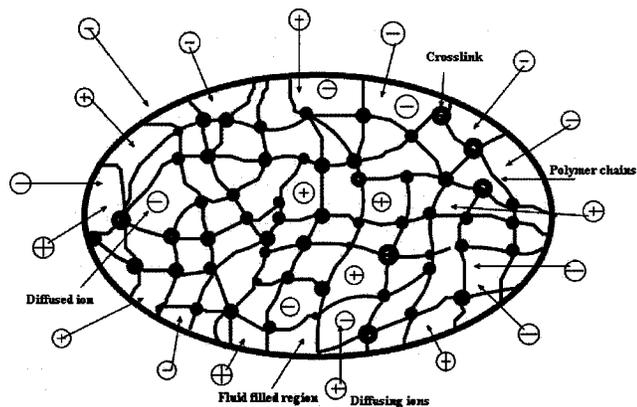


Fig. 1. Structure of hydrogel

mix with the solvent in the same way as two miscible liquids combine. Cross links prevent the complete mixing of the polymer chains and the solvent by providing an elastic restoring force that counters the expansion of the network. The liquid prevents the network from collapsing. On the other hand, the network retains the liquid and imparts solidity to the gel.

Hydrogels can be chemically modified to make them sensitive to certain specific species. In our paper, the monomers have been cross linked by a disulfide bond that can be cleaved by certain chemical or biological species. Once the polymer chains are decross linked, they become linear. Then, these linear polymer chains, which are of amorphous nature, can dissolve in the solvent by diffusion. Cleaving the disulfide bonds can be achieved by thiols through thiol-disulfide interchange reaction (Houk and Whitesides 1987) and by other types of reducing reagents. Thus, one can utilize the sensitivity of disulfide cross-linked hydrogels or other cleavable cross links to design a sensor that will indicate the presence of a cleaving agent in a solution by dissolving in it. Since the process is not reversible, hydrogels that dissolve in the solution whenever a cleaving agent is present act like chemical or biochemical fuses.

Theory

In the present work, PAAm (polyacrylamide) hydrogels cross linked via disulfide bonds have been used as biochemical sensors. These hydrogels can be used to sense any chemical agent that can cleave the disulfide bond, which acts as a crosslinker. A typical example of such a chemical agent is the thiol group, which can cleave the disulfide bond through a thiol-disulfide interchange reaction (Houk and Whitesides 1987). When the hydrogel is placed in a thiol solution, the thiol diffuses into the hydrogel, attacks the disulfide bond and a thiol-disulfide interchange reaction takes place (Szajewski and Whitesides 1980; Whitesides et al. 1983; Houk and Whitesides 1987). As a result of this interchange reaction, the disulfide bonds acting as cross links are cleaved as shown in Fig. 2. Due to the decross-linking, the modulus of the hydrogel decreases as the modulus of the gel is dependent on the cross linking density of the hydrogel (Franse et al. 2000). As the modulus of the gel decreases the gel swells. As time progresses, more diffusion and reaction takes place. As a result, after a certain time, the cross linking density decreases drastically and the polymer chains become linear or negligibly cross linked. At this instant, even though the polymer chains are decross-

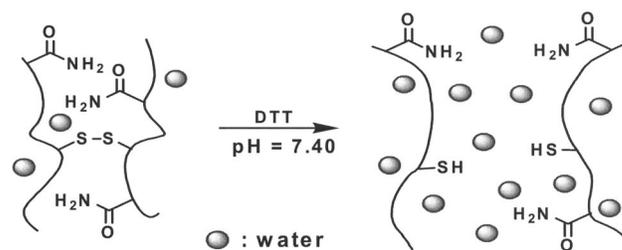


Fig. 2. Decrosslinking of polymer network due to cleaving of disulfide bond by DTT

linked, they are still entangled with each other. Therefore, before dissolving the polymer chains must become disentangled. Transport of the amorphous polymer chains into the surrounding solution results in mass loss from the hydrogel. The period during which the size of the hydrogel does not decrease is defined as the *induction period* and the period during which the size of the hydrogel decreases is defined as the *dissolving period*. It is important to note that some amount of gel dissolution (especially from the outer layer of the gel) may take place even during the induction period. However, since the internal portion of the gel is expanding, there is potentially a net increase in the size of the gel during the induction period.

The physical processes in the dissolution of hydrogels can be broken up into a number of phases: migration of ions, thiol-disulfide interchange reaction, swelling, disentanglement of the decross-linked polymer chains, and dissolving of the polymer chains. All of these processes may be occurring simultaneously in the hydrogel. Migration of the ions, thiol-disulfide interchange reaction, and dissolving of the linear polymer chains are essentially occurring in sequential manner. Thus, either diffusion, reaction, or dissolving can be rate limiting.

Depending on the type of the thiol, various situations can arise. For some thiols [e.g., DTT (dithierythritol)], the diffusion is fast while the reaction is slow. In this case, reaction is the rate limiting step. For some other cleaving agent [e.g. TCEP {tris (2-carboxyethyl) phosphine} at high pH] both the diffusion as well as the reaction is fast. Here the dissolving time may be the rate limiting factor. For some cleaving agents both diffusion and reaction may be slow. Here, both diffusion and reaction are rate limiting. Thus, depending on the type of the cleaving agent the induction period will vary. For some cases (e.g. where both diffusion and reaction are occurring fast), the induction period could be absent.

In this paper, the thiol has been considered as the cleaving agent. The present model of a disulfide cross-linked hydrogel can be considered as a prototype for understanding the mechanism of a cleaving process, which is more complicated than the thiol-disulfide interchange reaction. For example, the Botulinum toxin, which poses a major bioweapon threat because of its extreme potency, lethality, and the need for prolonged intensive care among the affected persons, can act as a cleaving agent and thus can be sensed. However, for sensing the Botulinum toxin the cross-linking agent in the hydrogel structure would be more complicated than a mere disulfide bond.

The hydrogel swelling during the induction period may be explained as follows: There are two types of stresses acting on the hydrogel. The first is the osmotic stress due to the difference in the concentration of the ions inside and outside the gel. The other type of stress is the residual stress. The residual stress develops as

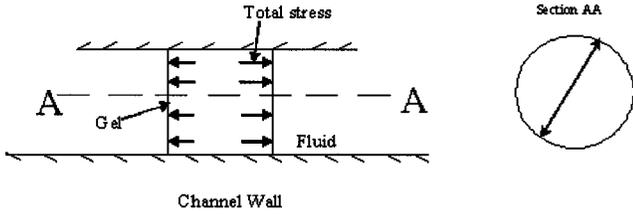


Fig. 3. Cylindrical hydrogel in microchannel. Cross section of cylindrical hydrogel is shown as AA.

the hydrogel is first swollen in water before it is placed in the thiol solution. Thus, initially the hydrogel is in a stretched condition. The residual stress is proportional to the product of the initial modulus (i.e., the modulus corresponding to the initial cross-link density and the fluid volume fraction) and the initial strain in the hydrogel. In those cases where the ions are diffusing fast, the concentration of the ions inside the gel is close to the outside concentration within a short time. Thus, the osmotic stress is very small and the residual stress is dominant. The presence of these stresses coupled by the decrease in the modulus of the hydrogel during decross-linking causes the hydrogel to swell.

A cylindrical hydrogel in a microchannel is considered as shown in Fig. 3. The displacement of the top and the bottom surfaces of the gel is restricted by the glass channel. It can be assumed that the hydrogel undergoes deformation only in the radial direction. As a result, the swelling/dissolving can be modeled by considering only a circular section as shown in Fig. 3. A one-dimensional model can be applied along the diameter of the circular cross section to investigate the swelling/dissolving aspects of the hydrogel.

Mathematical Model

Transport of Ions

The total flux of the ions can be predicted by using the Nernst-Planck equation which includes the fluxes due to the concentration gradient, electrical migration and convection (Malmivuo and Plonsey 1995; Tien and Leitmannova 2000) i.e.

$$\Gamma_k = \phi \left[-\bar{D}_k \frac{\partial c_k}{\partial x} - \bar{\mu}_k z_k c_k \frac{\partial \psi}{\partial x} \right] + c_k U \quad (1)$$

where Γ_k = flux of the k th ion; ϕ = gel porosity; \bar{D}_k = effective diffusivity of the k th ion inside the hydrogel; c_k = concentration of the k th ionic species inside the hydrogel; $\bar{\mu}_k$ = effective ionic mobility; Z_k = valence of the k th ion; ψ = electric potential; U = area-averaged fluid velocity relative to the polymer network; and x = coordinate system associated with the deformed hydrogel. The diffusivity is related to ionic mobility by the Einstein relationship i.e.,

$$\bar{D}_k = \frac{\bar{\mu}_k RT}{F} \quad (2)$$

where R = universal gas constant; T = absolute temperature; and F = Faraday's constant. Gel porosity is given by

$$\phi = \frac{H}{1+H} \quad (3)$$

where H = hydration state of the gel and is defined as the ratio of the volume of the fluid to the volume of the solid in the gel.

Transport of ions is limited to the regions containing fluid in the gel. The presence of polymer chains, which are impenetrable to mobile ions, increases the path length an ion travels, resulting in a slower diffusion rate. Mackie and Meares (Mackie and Meares 1955) introduced a statistical model for the diffusion of ions through a tortuous cross-linked polymer membrane. In this model, the effective diffusion rate inside the gel can be related to the diffusion in aqueous solution by an obstruction model

$$\frac{\bar{D}_k}{D_k} = \left(\frac{H}{2+H} \right)^2 \quad (4)$$

At the high-hydration state, a large amount of fluid is present between the polymer chains, and the diffusion rate approaches that of an aqueous solution. At low hydration, there is very little fluid between the polymer chains, and the effective path length an ion must travel to circumvent polymer chains lowers the diffusion rate of the ion.

Applying the continuity condition in one dimension leads to

$$\frac{\partial}{\partial t} (Hc_k) = - \frac{\partial (\Gamma_k)}{\partial X} \quad (5)$$

where, t = time and X = Lagrangian coordinate system associated with the solid frame of the hydrogel (Grimshaw 1990). x and X are related by the following relation:

$$x = (1+H)X \quad (6)$$

Combining Eqs. (1) and (5), the continuity equation for ion concentration is given by

$$\frac{\partial}{\partial t} (Hc_k) = \frac{\partial}{\partial X} \left[\left(\frac{H}{1+H} \right) \left(\bar{D}_k \frac{\partial c_k}{\partial x} + \bar{\mu}_k c_k \frac{\partial \psi}{\partial x} - \frac{1+H}{H} c_k U \right) \right] \quad (7)$$

If the convective velocity is not significant, then Eq. (7) can be rewritten as

$$\frac{\partial}{\partial t} (Hc_k) = \frac{\partial}{\partial X} \left[\left(\frac{H}{1+H} \right) \left(\bar{D}_k \frac{\partial c_k}{\partial x} + \bar{\mu}_k c_k \frac{\partial \psi}{\partial x} \right) \right] \quad (8)$$

Typically, buffers are used to minimize changes in pH and ionic strength. In our case, we have used a Tris buffer of 80 mM concentration. The presence of buffer affects the diffusion of the hydrogen ion. Using continuity condition for the hydrogen ion, the following expression is obtained:

$$\frac{\partial}{\partial t} (Hc_H + Hc_{HB}) = - \frac{\partial (\Gamma_H + \Gamma_{HB})}{\partial X} \quad (9)$$

where, c_{HB} = concentration of the hydrogen ions bound to the buffer; Γ_H = flux of the hydrogen ions; and Γ_{HB} = flux of the hydrogen ions bound to the buffer. Using a reaction isotherm (Berry et al. 1980), c_{HB} can be expressed in terms of c_H by

$$c_{HB} = \frac{c_T c_H}{K_B + c_H} \quad (10)$$

where, K_B = dissociation constant of the buffer and c_T = total concentration of the buffer's conjugate base. The flux of the buffer is proportional to the flux of the hydrogen ions, i.e.

$$\Gamma_{HB} = \frac{\bar{D}_{HB}}{\bar{D}_H} \frac{c_T}{K_B + c_H} \Gamma_H \quad (11)$$

\bar{D}_{HB} = diffusivity of the buffer in the hydrogel.

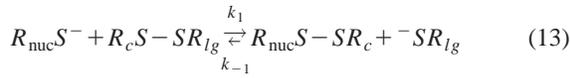
The Poisson's equation is employed to compute the electrostatic potential and the electric field (Jeans 1911)

$$\frac{\partial^2 \psi}{\partial x^2} = - \frac{F}{\epsilon \epsilon_0} \left(\sum_{k=1}^N z_k C_k \right) \quad (12)$$

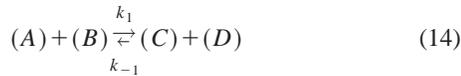
where N = number of ions; ϵ_0 = dielectric constant of vacuum; and ϵ = relative dielectric constant of the solvent.

Reactions

After the thiol diffuses into the hydrogel it attacks the disulfide bonds, which act as a cross link between the linear polymer chains. A thiol-disulfide interchange reaction (Szajewski and Whitesides 1980; Whitesides et al. 1983; Houk and Whitesides 1987) takes place, which in turn causes decross-linking of the polymer chains. Fig. 2 shows the decross-linking of the polymer network. The concentration profile of the species corresponding to the open chain and the cross-linked chain with time is obtained by making use of the following reaction (Whitesides et al. 1983).



Or



where $R_{nuc}S^-$ or (A) corresponds to the thiolate anion, $R_cS - SR_{lg}$ or (B) corresponds to the cross-linked polymer chains, $R_{nuc}S - SR_c$ or (C) corresponds to the decross-linked polymer chains and $^-SR_{lg}$ is the by-product.

From Eq. (14), the rate of formation of specie C is given by

$$\frac{\partial [C]}{\partial t} = k_1 [A][B] \quad (15)$$

As k_{-1} is negligible compared to k_1 the backward reaction has been neglected. Using the conservation of the complex group, i.e., R_c as in $R_cS - SR_{lg}$ or $R_{nuc}S - SR_c$, we get the following equation:

$$[B] + [C] = [B]_0 \quad (16)$$

where $[B]_0$ = initial concentration of specie B. From Eqs. (15) and (16) the concentration profile of species [B] and [C] can be obtained as a function of time.

Model for Modulus of Hydrogel

As the concentration of the product corresponding to the decross-linked species increases and the concentration of the reactant corresponding to the cross-linked species decreases, the cross-link density of the hydrogel decreases. This leads to a decrease in the modulus of the hydrogel (Franse and Nijenhuis 2000). The modulus of the hydrogel is related to the concentration of the cross-linked and decross-linked species and the fluid volume fraction of the gel by the following relation (Franse and Nijenhuis 2000; Okay and Durmaz 2002):

$$E = E_0 (1 - 2([C])/([C] + [B])) \left(\frac{1}{H+1} \right)^{1/3} \quad (17)$$

In the above relation, the term $(1 - 2([C])/([C] + [B]))$ is a correction term, which takes into account the effect of the variation

of the modulus of the gel with changing cross-linking density. The expression used in the present model is different from the expression that has been used in (Franse and Nijenhuis 2000; Okay and Durmaz 2002). However, these expressions turn out to be similar by applying conservation of mass of the polymer chains during the decross-linking reaction, i.e.

$$\bar{M}_c ([C] + [B]) = M ([C]) \quad (18)$$

where, \bar{M}_c = average molecular weight between the cross links and M = molecular weight of the polymer.

The term $(1/H+1)^{1/3}$ takes into account the change in the modulus of the dry gel due to the presence of the fluid in the swollen gel (Franse and Nijenhuis 2000; Okay and Durmaz 2002). The term $(1/H+1)^{1/3}$ has been obtained in an empirical way.

Mechanics

The mechanical equation balances the stress generated in the hydrogel with the residual stress and the osmotic stress. The quasi-equilibrium form of the mechanical equation is given by

$$\nabla \cdot \sigma = 0 \quad (19)$$

where σ = stress tensor. The components of σ are σ_r , the radial stress, and σ_t , the tangential stress, which can be obtained by the following relations:

$$\sigma_r = \frac{E}{(1+\nu)(1-2\nu)} \left[(1-\nu) \frac{\partial u}{\partial r} + \nu \frac{u}{r} \right] - (P_{osmotic} + \sigma_{residual}) \quad (20)$$

and

$$\sigma_t = \frac{E}{(1+\nu)(1-2\nu)} \left[(1-\nu) \frac{u}{r} + \nu \frac{\partial u}{\partial r} \right] - (P_{osmotic} + \sigma_{residual}) \quad (21)$$

where, ν = Poisson's ratio and E = modulus of the gel, which is a function of space and time due to the varying crosslink density.

The osmotic pressure, $P_{osmotic}$, is calculated by the following equation:

$$P_{osmotic} = RT \sum_{k=1}^N (c_k - c_k^0) \quad (22)$$

where c_k^0 = concentration of the k th ion in the stress-free state in the outside solution.

Hydration H , is defined as the ratio of the volume of the fluid to the volume of the solid inside the gel

$$H = \frac{V_f}{V_s} = \epsilon_r + \epsilon_t + \epsilon_r \epsilon_t \quad (23)$$

where, ϵ_r = strain in the radial direction and ϵ_t = strain in the tangential direction for the circular cross section. The radial strain ϵ_r is equal to $\partial u(r)/\partial r$ and the tangential strain, ϵ_t , is equal to $u(r)/r$. $\sigma_{residual}$ is the residual stress and is defined as the product of the initial modulus of the gel and the initial hydration, i.e.

$$\sigma_{residual} = E_0 \left(\frac{1}{H_0+1} \right)^{1/3} H_0 \quad (24)$$

where, E_0 = modulus of the dry gel and H_0 = initial hydration of the hydrogel. Using the above mechanical model, the volumetric strain or the hydration can be obtained. Once the hydration is known, the size of the gel can be determined.

In the theoretical model used in the present work, there are essentially $(N+2)$ unknowns. These are the concentrations of the

ions, c_k , ($k=1,2,\dots,N$) the electric potential ψ and the hydration H . To compute the $(N+2)$ unknowns, $(N+2)$ coupled equations need to be solved. The Nernst-Planck equation for each ion gives N equations. The Poisson's equation is the $(N+1)$ th equation. The $(N+2)$ th equation is the mechanical equation by which the hydration at any given time can be computed.

Gel Dissolution

As the proportion of the decross-linked polymer chains in the hydrogel network increases, the hydrogel at those portions (where it is primarily decross-linked) will start dissolving. Siepmann et al. (1999) have developed a mathematical model describing polymer dissolution based on the theory of macromolecular disentanglement and chain reptation theory. They showed that the dissolution can be disentanglement and/or diffusion controlled depending on the polymer molecular weight and the thickness of the diffusion boundary layer. The dissolution process can be divided into three phases, which occur sequentially. First, disentanglement of the cleaved macromolecule takes place. (See Fig. 4.) The time taken for this is called the Zimm time (Moore et al. 2000). The Zimm time is given by

$$\tau_R = \frac{\eta_s R_g^3}{kT} \quad (25)$$

where k =Boltzmann constant; η_s =viscosity of the solvent; T =temperature; and R_g =radius of the polymer chain.

After the individual macromolecules are disentangled and isolated, the dissolution of the macromolecular chains takes place. In the case of hydrogels, the macromolecular chains are purely amorphous in nature. As a result, the governing equation for the dissolution of the polymer chains is given by (Moore et al. 2000)

$$\frac{\partial v_2}{\partial t} = D_{12} \frac{\partial^2 v_2}{\partial x^2} \quad (26)$$

where D_{12} =mutual diffusion coefficient and v_2 =volume fraction of the polymer in the hydrogel. v_2 can be related to the hydration by the following relation:

$$v_2 = \left(\frac{1}{H+1} \right) \quad (27)$$

The mutual diffusion coefficient of the polymer in the solution has been obtained using the following model (Moore et al. 2000):

$$D_{12} = \frac{kT}{\eta_s R_g} \quad (28)$$

The third phase of the dissolution process is the convective mass transport, where the polymer particles which have diffused into the solution are carried away by the flow of the solution.

There are numerous mathematical models (Gopferich 1996; Mallapragada and Peppas 1997; Siepmann et al. 1999; Moore et al. 2000; Narasimhan 2001) that quantify the process of polymer dissolution. Most of them neglect convective transport within the well-stirred medium. As all the three processes (i.e. disentanglement, dissolution, and convective mass transport) take place sequentially, the faster one can be neglected as the slower ones determine the overall dissolution rate. Usually, the velocities of convective mass transfer processes in well-stirred media are much higher than the velocities of diffusional processes. Thus, it is reasonable to neglect the convective transfer to simplify the mathematical treatment.

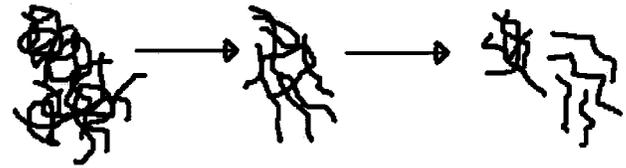


Fig. 4. Disentangling process of decross linked polymer chains

The factors that affect the dissolution rate are

- Diffusivity of the macromolecules,
- Concentration gradient within the unstirred layer, and
- Thickness of the unstirred layer.

Coupling of Different Fields

The Nernst-Planck Eq. (8), the Poisson's Eq. (12), the mechanical Eq. (19), and the equation for polymer dissolution (26) are all coupled to each other. Hence, an iterative process has to be used to obtain a self-consistent solution. Fig. 5 shows the iterative process used to solve the coupled equations. First, the Nernst-Planck Eq. (8) is solved to compute the concentration of the ions inside the hydrogel. Using the concentrations of the various ions, the Poisson's Eq. (12) is solved to compute the electrical potential and electrical field. Since these two equations (i.e. the Nernst-Planck equation and the Poisson's equation) are coupled they are

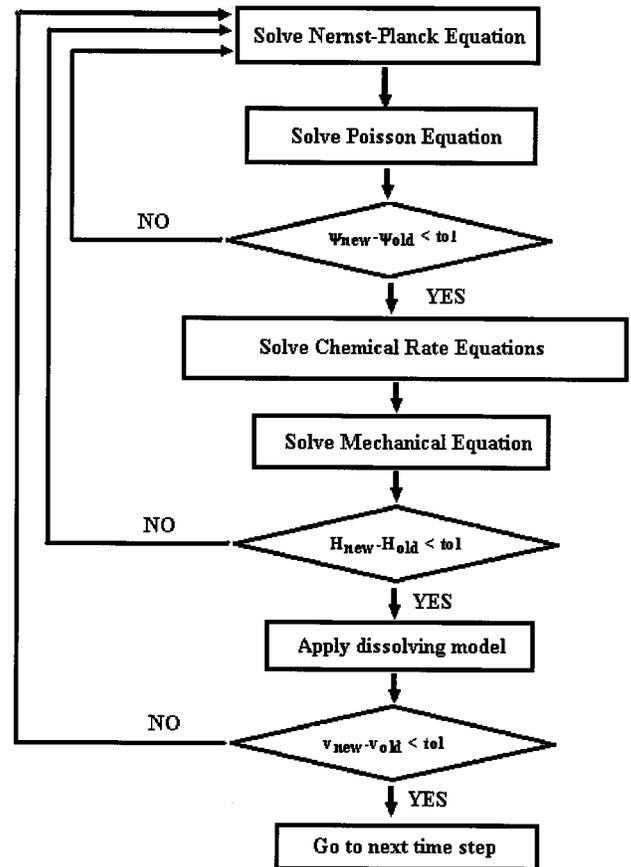


Fig. 5. Flow chart to solve coupled equations within time loop

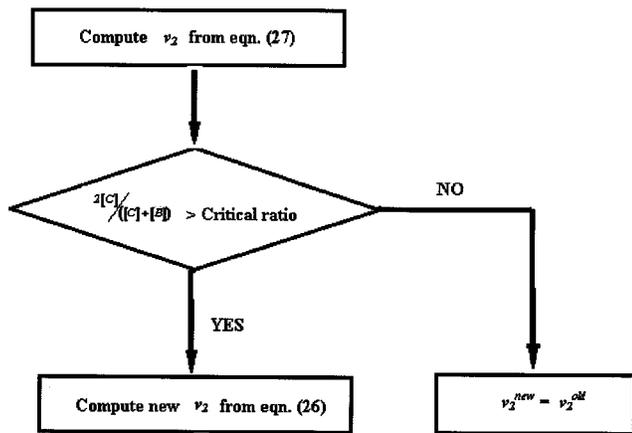


Fig. 6. Flow chart to implement dissolving model

solved iteratively to obtain a self-consistent solution for the electrical potential ψ and the concentration of the ions c_k . Then the concentrations of the species [B] and [C] are computed from the chemical rate Eqs. (15) and (16), using the concentration of the thiolate anion [A], computed from the self-consistent solution of the Nernst-Planck and the Poisson's equations. Once the concentration of [B] and [C] are determined, the modulus of the hydrogel is updated using Eq. (17). Using the updated modulus, the mechanical Eq. (19) is solved to compute the hydration H . To compute a self-consistent solution the Nernst-Planck equation, the Poisson's equation, and the mechanical equation are solved in an iterative manner as shown in Fig. 5. Finally, the dissolving model given in Eq. (26) is solved to compute the volume fraction of the polymer v_2 . Since v_2 may not be self consistent with the computed concentrations, potential and the hydration, coupled iterations as shown in Fig. 5 are performed to compute the self-consistent solution.

In Fig. 5, "tol" stands for the tolerance used to determine if the solution has converged. A tolerance of 10^{-5} is used.

Fig. 6 shows more details on the implementation of the dissolving model. First, the polymer volume fraction is computed using Eq. (27), which relates hydration H , to the polymer volume fraction v_2 . It is important to note that the gel starts dissolving when the majority of the polymer chains are de-cross-linked and have become linear. The ratio $2[C]/([C]+[B])$ is used to determine the de-cross-linking of the hydrogel.

If the ratio defined as critical ratio in Fig. 6 exceeds 0.85, then the polymer chains are said to be de-cross-linked. If the proportion of the de-cross-linked species is above the critical ratio at a given

Table 1. Values of Constant Parameters

D_{thiol}	$7.5 \times 10^{-9} \text{ m}^2/\text{s}$
D_H	$9.3 \times 10^{-9} \text{ m}^2/\text{s}$
ν	0.43
η_s	$0.46 \times 10^{-4} \text{ Ns/mm}$
R_g	0.3 nm
E_a	120 kJ/mol
k_1 (dithierythritol)	$4.95 \text{ M}^{-1} \text{ min}^{-1}$
k_1 (glutathione)	$0.32 \text{ M}^{-1} \text{ min}^{-1}$
E_0	0.2 Mpa
$[B]_0$	8.64 mM

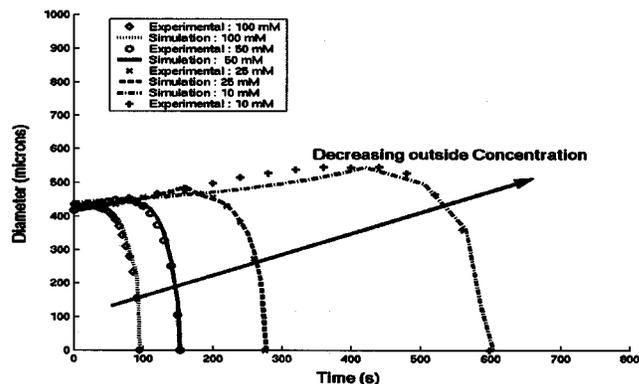


Fig. 7. Variation of diameter of hydrogel with time for various outside concentrations of thiol

location, then Eq. (26) is used to compute the new value of the polymer volume fraction v_2 . However, if the proportion of the de-cross-linked species at a location is below the critical ratio, then the polymer chains have not sufficiently de-cross-linked and the gel will not dissolve. In this case, the value of the polymer volume fraction v_2 stays unaltered at that location.

Numerical Solution

The mathematical model developed in the previous section contains coupled partial differential equations. Analytical solutions for these equations are impossible. The finite cloud method (Aluru and Li 2001; Jin and Aluru 2001) has been used for the numerical solution of the equations. The experimental conditions shown in Fig. 3 have been modeled in this paper. For the circular cross section, the concentration gradient and the ionic fluxes are in the radial direction and hence a one-dimensional model is used. For the particular case of a cylindrical hydrogel, the expression for the mechanical deformation Eq. (19) can be simplified by making use of an infinitesimal sector (Popov 1997). Using cylindrical coordinates, Eq. (19) becomes

$$\frac{\partial \sigma_r}{\partial r} + \frac{\sigma_r - \sigma_t}{r} = 0 \quad (29)$$

The expressions for σ_r , radial stress, and σ_t , tangential stress, are given in Eqs. (20) and (21), respectively. The hydrogel is

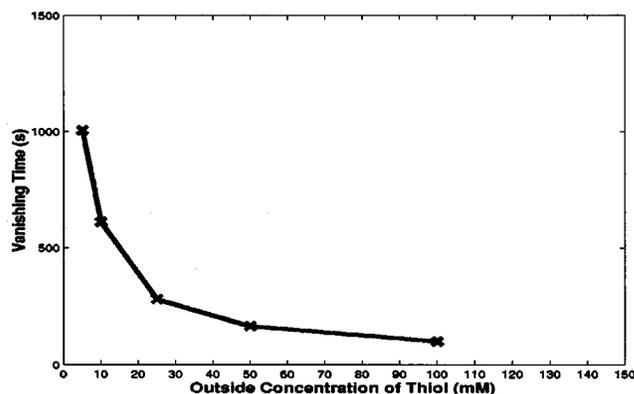


Fig. 8. Variation of vanishing time with outside concentration of thiol

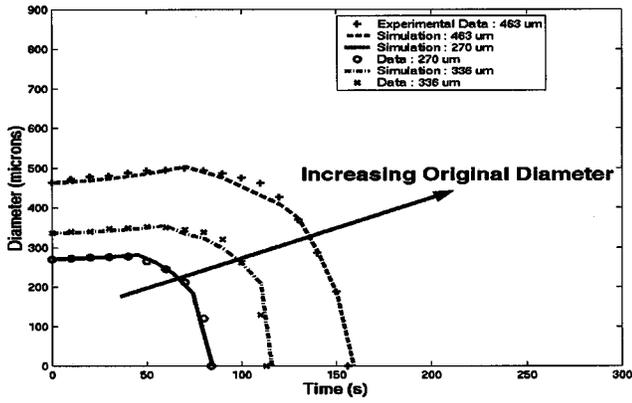


Fig. 9. Variation of diameter with time for various original diameters. Type of cleaving agent is DTT.

discretized into 41 points along the radial direction to apply the finite cloud method. The parameters used in the simulations are summarized in Table 1.

Results and Discussion

In this section we present results obtained from the numerical solution of the mathematical model. Numerical simulations are compared with experimental data for several cases. The results have been mainly categorized according to the various design parameters that impact the gel dissolution time. The important design parameters for a biofuse are

1. Outside concentration of the thiol;
2. Original diameter of the hydrogel; and
3. Cross linking density of the hydrogel.

Effect of Outside Concentration of Thiol

Fig. 7 shows the variation of the diameter of a dissolvable hydrogel with time for various bath concentrations of the thiol. Here, the thiol considered is DTT (dithierythritol). The vanishing time increases as the bath concentration of the thiol decreases.

Both the induction period as well as the dissolving period of the hydrogel increases with a decrease in thiol concentration. The

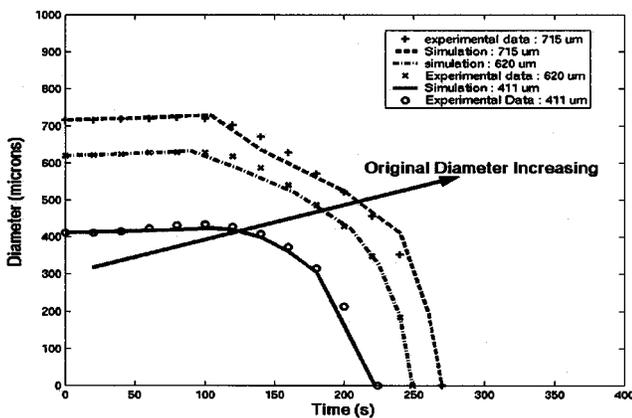


Fig. 10. Variation of diameter with time for various original diameters. Type of cleaving agent is glutathione.

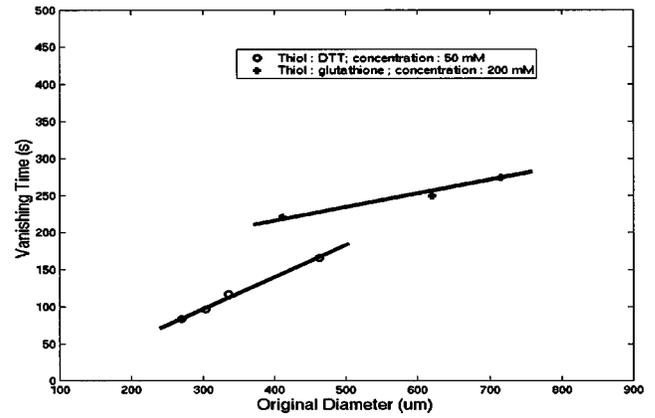


Fig. 11. Variation of vanishing time with original diameter

increase in the induction period with decreasing thiol concentration can be attributed to the fact that the lower the thiol concentration, the more time it will take to cleave the crosslinks. The higher dissolving period is due to the lower rate of dissolving, which in turn is due to the lower-concentration gradient of the polymer created by the low outside concentration.

Fig. 8 summarizes the variation of the vanishing time with the outside concentration of the thiol. Note that the vanishing time decreases nonlinearly with the increase in the outside concentration.

Effect of Original Diameter of Hydrogel

Figs. 9 and 10 show the variation of the hydrogel diameter with time for various original diameters. The results in Fig. 9 are for DTT as the cleaving agent and the results in Fig. 10 are for glutathione as the cleaving agent. The concentration of the cleaving agents has been kept fixed at 50 mM for all the cases. From the above results it can be observed that the vanishing time increases with the original diameter. Both the induction period as well as the dissolving period is found to increase with the original diameter. A larger diameter indicates that the number of cross links that need to be cleaved are more. So the time for decross-linking increases and the induction period increases with the increase in the original diameter. Also, a larger diameter means that a larger mass of polymer chains need to be dissolved. Thus, the dissolving time increases with increasing original diameter.

Fig. 11 summarizes the variation of the vanishing time with

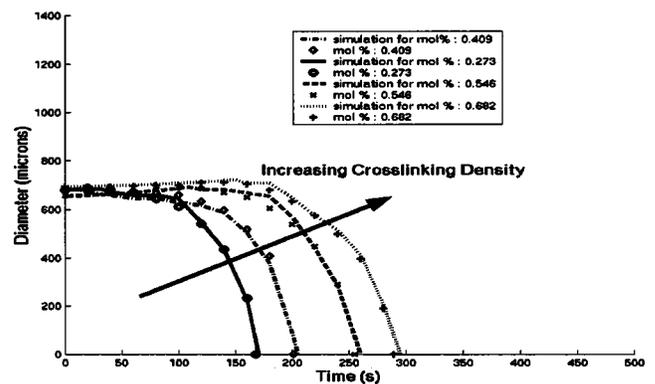


Fig. 12. Variation of hydrogel diameter with time for various cross-linking densities

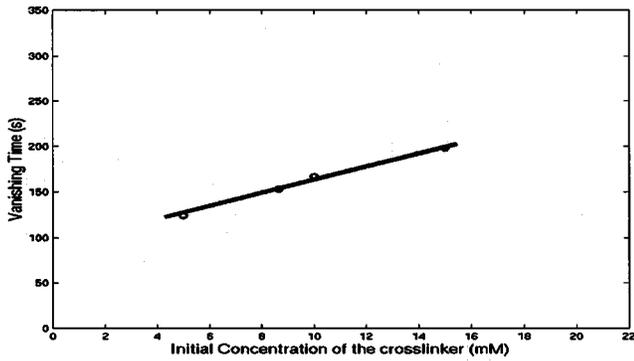


Fig. 13. Variation of vanishing time with varying cross-linking density

the original diameter for the two types of thiols. The variation turns out to be of a linear nature.

Effect of Cross-linking Density of Hydrogel

Fig. 12 shows the variation of the hydrogel diameter with time for various cross-linking densities. The thiol considered here is DTT. Bath concentration of 25 mM has been maintained in all the cases.

The above result shows that the vanishing time increases with increasing cross-linking density as other parameters (e.g. diameter, bath concentration, etc.) are kept constant. Cross-linking density is found to primarily affect the induction period. The induction period increases with cross-linking density, as the number of cross links that need to be cleaved during the induction period increases with the cross-linking density. The dissolving period is not affected as much as the induction period by the variation in cross-linking density.

Fig. 13 summarizes the variation of the vanishing time with crosslinking density.

Role of Temperature

In the case of DTT, the decross-linking reaction occurs slowly compared to the diffusion of the thiolate anion. Fig. 14 shows the time evolution of DTT along the radial direction.

In order to decrease the vanishing time (i.e., improve the response time) of the biofuse, the reaction rate of the decross-

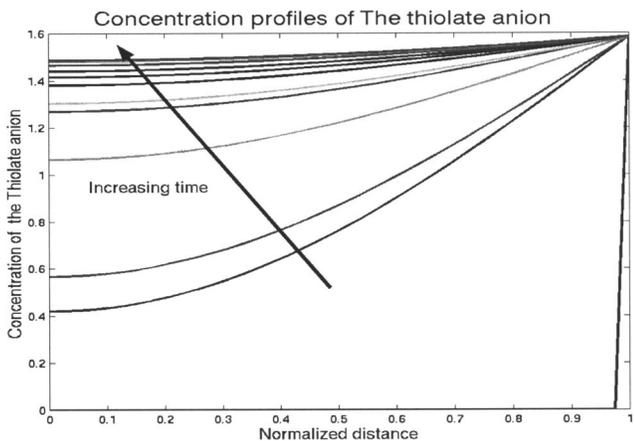


Fig. 14. Variation of thiolate anion concentration with time

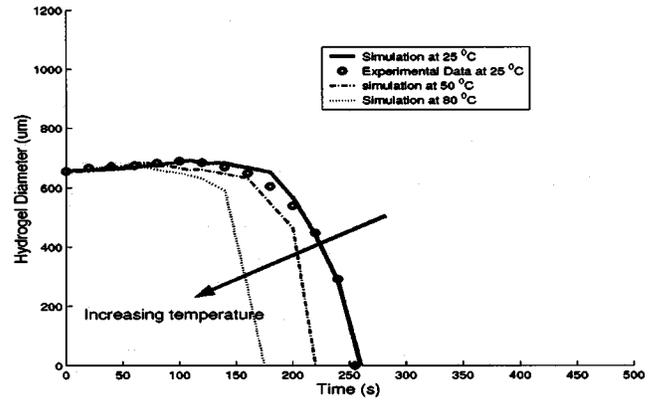


Fig. 15. Variation of hydrogel diameter with time for varying temperature of 25, 50, and 80°C

linking reaction needs to be increased. An increase in the reaction rate of the decross-linking reaction can be achieved by making use of the temperature. The reaction rate is related to the temperature by the arrhenius equation (Berry et al. 1980)

$$k_1 = A e^{-E_a/RT} \tag{30}$$

where, k_1 = reaction rate; A = constant; E_a = activation energy; R = universal gas constant; and T =temperature. Fig. 15 shows the variation in size of the dissolvable gel for various temperatures (25, 50, and 80°C). In this simulation, a hypothetical value of E_a (120 KJ/mole) has been chosen. It is important to note that the sensitivity of the system to temperature will be dependent on the value of E_a . The sensitivity of the system will be low for a high value of activation energy while it will be higher for a lower value of activation energy.

Diffusion Limiting Case

The mathematical model is also employed to investigate a diffusion limiting case. Such a situation is in contrast to the reaction limiting case of DTT. When diffusion is the rate limiting step the hydrogel dissolves layer by layer as shown by schematics in Fig. 16. Since the dissolution starts right from the time of exposure of the gel to the cleaving specie, the induction period will be very short. Fig. 17 shows the variation of the hydrogel diameter with time when diffusion is the rate limiting step. Note that there is no induction period in this case.

Conclusion

A mathematical model has been developed for dissolvable hydrogels. The model accounts for transport of ions into the hydrogel because of concentration gradient and electrostatic potential, chemical reactions for decross-linking, variation in the modulus

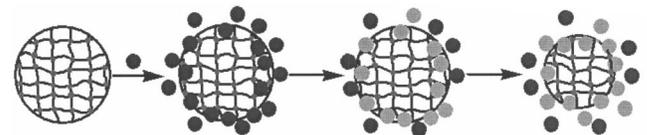


Fig. 16. Layer-by-layer dissolution of gel when diffusion is rate limiting step

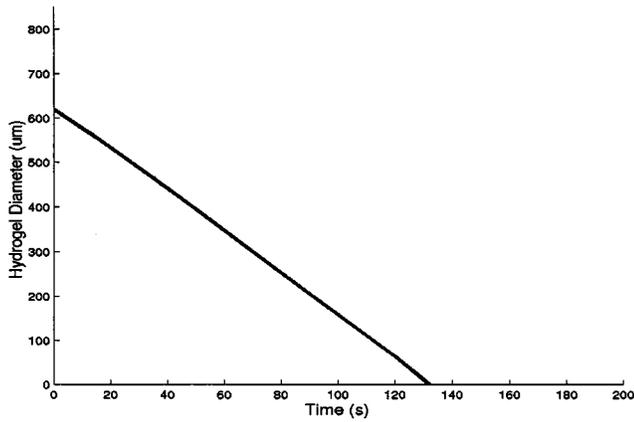


Fig. 17. Variation of hydrogel diameter with time for diffusion limiting case

of the hydrogel, swelling of the hydrogel, and dissolution of the linear polymer chains into the solution. Various parameters that influence the gel dissolution time have been identified. The following parameters were found to have a significant effect:

1. Concentration of the cleaving reagent;
2. Original diameter of the hydrogel; and
3. Initial cross-linking density of the hydrogel.

The vanishing time of the dissolvable hydrogel decreases with increase in the bath concentration, with a decrease in the original diameter of the hydrogel and with a decrease in the cross-linking density of the hydrogel. It was observed that the temperature can also have a significant effect on the behavior of the biofuse. It is important to note that depending on the type of the cleaving chemical specie, the significance of the parameters mentioned above can change. It was also observed that there may not be an induction period when diffusion is the rate limiting step.

A number of applications can be envisioned based on dissolvable gels. For example, dissolvable gels can be used as biosensors, chemical sensors, valves or as gates in microfluidic devices. The identification of various parameters influencing the device behavior will enable the design optimization of dissolvable hydrogels for various applications.

Notation

The following symbols are used in this paper:

- A = frequency factor in arrhenius equation;
- c_k = concentration of k th chemical specie; e.g., c_H is concentration of hydrogen ion;
- c_k^0 = concentration of k th ion in solution outside hydrogel;
- c_{HB} = concentration of hydrogen ion bound to buffer;
- c_T = total concentration of buffer's conjugate base;
- D_k = diffusivity of the k th ion in aqueous solution;
- \bar{D}_k = effective diffusivity of k th ion in porous gel;
- \bar{D}_H = effective diffusivity of hydrogen ion in porous gel;
- \bar{D}_{HB} = effective diffusivity of buffer;
- D_{12} = diffusion coefficient of polymer in solution;
- E = modulus of elasticity;
- E_0 = initial modulus of elasticity;
- E_a = activation energy;

- e = 2.718281828;
- F = Faraday's constant;
- H = hydration;
- H_0 = initial hydration;
- K_B = dissociation constant of buffer;
- k = Boltzman's constant;
- k_1 = reaction rate;
- M = molecular weight of polymer;
- \bar{M}_c = average molecular weight between crosslinks;
- N = total number of ions;
- $P_{osmotic}$ = osmotic pressure;
- R = universal gas constant;
- R_g = radius of the polymer chain;
- r = radial distance;
- T = temperature;
- U = convective velocity;
- u = displacement;
- V_f = volume fraction of fluid phase in hydrogel;
- V_s = volume fraction of solid phase in hydrogel;
- v_2 = volume fraction of polymer;
- X = Lagrangian coordinate system associated with solid frame of hydrogel;
- x = coordinate system associated with lab frame;
- z_k = valence of the k th ion;
- Γ_k = total flux of k th ion; e.g., Γ_H is flux of hydrogen ion;
- Γ_{HB} = Flux of the hydrogen ion bound to the buffer;
- ϵ = relative dielectric constant;
- ϵ_0 = dielectric constant of vacuum;
- ϵ_r = radial strain;
- ϵ_t = tangential strain;
- η_s = viscosity of solution;
- $\bar{\mu}_k$ = effective ionic mobility of k th ion;
- ν = Poisson's ratio;
- σ = stress;
- σ_r = radial stress;
- σ_t = tangential stress;
- $\sigma_{residual}$ = residual stress;
- τ_r = Zimm time;
- ϕ = porosity; and
- ψ = electric potential.

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