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Drug Release Mechanisms from Composite Matrices I. Theoretical Issues

M.J. Abdekhodaie* and Y.L. Cheng[1]

In this paper, composites containing hydrophilic particles uniformly dispersed within a hydrophobic network have been studied. Theoretical issues governing the release characteristics have been defined. When the hydrophilic content is below the percolation threshold, either equilibrium swelling or osmotic rupturing would occur. Theoretical criteria to determine whether equilibrium swelling or osmotic rupturing would occur are defined and a model for predicting the extent of equilibrium swelling in the presence of mechanical constraint is offered. Different drug release mechanisms can be achieved by choosing different materials and various formulation factors.

INTRODUCTION

Development of a biocompatible material with good mechanical properties and flexible transport rate has been a challenge for quite a few years. Hydrophobic and hydrophilic polymers are two important groups of polymeric materials for biomedical applications.

Due to the poor permeability of some drugs, e.g. high molecular weight drugs, through the hydrophobic polymers, this group of polymers has long been recognized as inadequate for administration of high molecular weight drugs [1]. However, there has been a lot of effort to promote the release of numerous drugs with very different physicochemical properties [2-8], including proteins [6-8], from matrices based on hydrophobic polymers. These efforts can be classified into two groups: 1) Those that require loading the drug beyond the percolation threshold and 2) Those using osmotic agents or fillers. There are some disadvantages to using monolithic-type delivery systems based on hydrophobic polymers. Loading drugs beyond the percolation threshold involves using a high percentage of drug in the monolith [9]. This feature is undesirable for drugs that are expensive or require very low dosage. If osmotic agents or other fillers are used, they can be released along with the drug and may cause harmful effect in some therapies such as wound healing [10].

The disadvantages of hydrophilic polymers are: poor mechanical properties, large volume change responsible for variations in permeability, difficulty in controlling transport rate and the very limited fabrication potential [11-13]. Furthermore, they cannot be processed and shaped by currently used processing technologies for plastics, such as extrusion, molding, etc.

It seems that by using composites of hydrophilic and hydrophobic polymers, the disadvantages of monolithic-type delivery systems, based on either hydrophilic polymers or hydrophobic polymers, can be reduced. Composite materials containing two phases can be prepared, where the discontinuous phase (hydrophilic polymer and drug particles) is randomly dispersed within the continuous phase (hydrophobic polymer). The hydrophilic phase in the swollen state is more permeable to hydrophilic drugs than the hydroph obic phase. Composite materials may, therefore, provide well-controlled and efficient drug release without releasing undesired substances. In addition, since hydrophilic particles are dispersed within hydrophobic matrices, the composite materials may have good mechanical properties and less limitation in fabrication compared to hydrophilic polymers [11,12]. Previously, several silicone rubber hydrogel composites have been prepared and their permeation and release rates have been studied [11,12,14,15].

The presence of hydrophilic agents in a composite can affect both the swelling and drug release kinetics.

*. *Corresponding Author, Department of Chemical Engineering, Sharif University of Technology, Tehran, I.R. Iran.*

1. *Department of Chemical Engineering and Applied Chemistry, University of Toronto, Toronto, Ontario, Canada, M5S 3E5.*

When the hydrophilic content in a dry matrix is beyond the percolation threshold, hydrophilic particles form clusters which span the matrix thickness and form continuous pathways in the swollen state. Drug release may be governed by either diffusion or swelling kinetics. When the hydrophilic content is below the percolation threshold, most of the particles remain trapped within the hydrophilic polymer and only a small number of hydrophilic particles are connected to the releasing surface. Equilibrium swelling in the presence of the constraint provided by the hydrophobic polymer may be observed, or if the swelling forces exceed the cohesive forces in the hydrophobic polymer, osmotic rupturing will occur. Release may be governed by diffusion or swelling kinetics, or may be controlled by osmotic rupturing.

In this study, the theoretical criteria for either equilibrium swelling or osmotic rupturing are defined and a model for predicting the extent of equilibrium swelling in the presence of mechanical constraint is presented. To explore these issues, the osmotic pressure of the hydrophilic phase and the retractive pressure of the hydrophobic phase are needed. Flory model is modified to obtain the ionic osmotic pressure of the hydrophilic phase. An equation is developed to calculate the retractive pressure of the hydrophobic phase. Finally, different drug release mechanisms are discussed in detail with respect to the occurrence of either equilibrium swelling or osmotic rupturing.

OSMOTIC PRESSURE OF THE HYDROPHILIC PHASE

Hydrogels can be divided into two groups: neutral gels and ionic gels. When an ionic gel is placed in a swelling agent, three contributions can affect the osmotic pressure of the system: 1) Mixing 2) Elastic-retractive and 3) Ionic osmotic pressures. In the neutral gels, only the mixing and the elastic-retractive contributions can influence the osmotic pressure. Therefore, by combining the mixing and elastic-retractive contributions as the network osmotic pressure, osmotic pressure of neutral gels is equal to π_{net} and osmotic pressure of ionic gels is equal to $\pi_{net} + \pi_{ion}$, where π_{ion} and π_{net} are the network and ionic osmotic pressures, respectively.

Various models have been developed to find the osmotic pressure of polymeric networks under different experimental conditions [16]. The earliest theory was developed by Flory and Rehner [17] for a neutral cross-linked polymer system prepared from macromolecular chains reacted in the solid state, when the macromolecular chains exhibit a Gaussian distribution. Peppas and Merrill [18] presented a model, similar to the Flory-Rehner model, which is applicable to systems prepared by the cross-linking of macromolecular chains, in solutions. To take into account the non-Gaussian distribution of macromolecular chains, observed at high cross-linking ratios, Peppas and Lucht [19] provided another model. In a similar manner, Peppas et al. [20], provided an expression for describing the swelling of a highly cross-linked moderately swollen polymeric network. Based on the reaction conditions (with or without the solvent) and molecular weight between cross-links (assuming a Gaussian or non-Gaussian distribution of the macromolecular chains), one of the above mentioned equations can be used to obtain the network osmotic pressure of the gels in composites.

Numerous attempts have been made to accurately model the ionic contribution to the osmotic pressure of gels [21-31]. Flory [24] presented the most basic model for the ionic osmotic pressure π_{ion}, arising from the difference in mobile ion concentration in the gel and outer solution, by assuming Donnan-type equilibrium in polyelectrolyte gels. The concentration of the ions inside the gel is the sum of the contributions of the mobile ions from the electrolyte (νC_s) and from the polymer dissociation ($i\upsilon_{2,s}/z\_V_u$).

When the hydrophilic content in a composite is below the percolation threshold, most of the hydrophilic particles are isolated by the hydrophobic polymer. Since most hydrophobic polymers are impermeable to the electrolyte salts, they act as a barrier for the exchange of ions between the swollen ionic particles and the surrounding electrolyte. The electrolyte ions cannot get into the gel; therefore, the concentration of the mobile ions in the gel is limited to that contributed by dissociation of the polymer. Since, in the existing models, the mobile ions in the gel were considered to be provided by both electrolyte solution and polymer dissociation, these models cannot be used for composites. Therefore, a method for calculating the ionic osmotic pressure of the gel surrounded by a hydrophobic polymer is required.

Assuming Donnan-type equilibrium in the polyelectrolyte gel, using the most basic equation from Flory model and eliminating the electrolyte ion contribution term in the gel provides:

$$\pi_{ion} = RT\left[\frac{i\upsilon_{2,s}}{z\_V_u} - \nu C_s^*\right], \tag{1}$$

where R is the ideal gas constant, T is the absolute temperature, $\upsilon_{2,s}$ is the polymer volume fraction in the swollen gel, i is the degree of ionization, $z\_$ is the charge of the gel, V_u is the molar volume of a structural unit, $\nu = \nu_+ + \nu_-$ (where the electrolyte is completely dissociated into ν_+ cations and ν_- anions) and C_s^* is the mobile electrolyte concentrations in the external solution. For a more convenient form of Equation 1, the ionization, i, might be expressed in terms of other variables in the polymer-solvent systems. For anionic monomer gels, there is an equilibrium such that:

$$HA \rightleftarrows H^+ + A^- \tag{2}$$

and hence:

$$K_a = \frac{[A^-][H^+]}{[HA]}, \tag{3}$$

where $[HA]$ is the concentration of undissociated polymer chains, $[A^-]$ is the concentration of the dissociated polymer chain and $[H^+]$ is the concentration of the hydrogen ion. The degree of ionization, i, is defined as:

$$i = \frac{[A^-]}{[HA]+[A^-]} = \frac{[A^-]/[HA]}{1+([A^-]/[HA])}. \tag{4}$$

Using Equation 3, Equation 4 may be rewritten as:

$$i = \frac{K_a/[H^+]}{1+(K_a/[H^+])} = \frac{K_a}{K_a+[H^+]} = \frac{K_a}{K_a+10^{-\mathrm{pH}}}. \tag{5}$$

Substituting Equation 5 into Equation 1 gives:

$$\pi_{\mathrm{ion}} = RT\left[(\frac{\upsilon_{2,s}}{z\_V_u})(\frac{K_a}{K_a+10^{-\mathrm{pH}}}) - \nu C_s^*\right]. \tag{6}$$

By using Equation 6, the ionic osmotic pressure of the gel in the composite in terms of polymer-solvent variables can be calculated. Furthermore, by adding this value to the network osmotic pressure, the osmotic pressure of the ionic gels in the composites can be obtained.

RETRACTIVE PRESSURE OF THE HYDROPHOBIC PHASE

The retractive pressure or resisting pressure is the pressure in an isolated enlarged cavity of radius r in the hydrophobic polymer when the cavity is enlarged from an initial radius r_0. To calculate the retractive pressure, P, of hydrophobic polymers, Briggs et al. [32] presented a model. It was assumed that the original internal force is equal to the force producing deformation at the inflated state. However, because of equilibrium at the inflated sate, the internal force at the inflated state should be equal to the force producing deformation at this state. Therefore, the main assumption for obtaining this model appears to be in error. Gent and Lindley [33] presented an equation, which was followed by Fedors [34] and Schirrer and Thepin [35] for calculating the retractive pressure of a spherical cavity in a large block of rubber. Their equation is strictly valid for an isolated cavity in an infinite block of polymer. This will be true when the volume fraction of inclusion is less than approximately 1% [33]. In composites, when the hydrophilic content is more than 1% Gent-Lindley model is not valid. Therefore, developing a method for calculating retractive pressure of the hydrophobic polymer is required.

To develop an equation for calculating the retractive pressure of the hydrophobic polymer, the following assumptions are made: 1) Hydrogel particles have spherical shapes, 2) Spherical particles are distributed through a simple cubic lattice, 3) There is no interaction between particles, 4) Each cube has the same behavior as the spherical particle which is surrounded symmetrically by the hydrophobic polymer with thickness h, the minimum thickness of the hydrophobic polymer wall in each cube. Therefore, the system can be simplified as an encapsulated hydrophilic polymer or a balloon of the hydrophobic polymer. The schematic diagram of the simplification of the system is shown in Figure 1. After immersion in an aqueous medium, water permeates through the hydrophobic phase and is absorbed by the hydrophilic phase. The swelling of the hydrophilic phase produces the cohesive forces in the hydrophobic polymers. The force balance for the balloon of the hydrophobic polymer (Figure 2) can be written as:

$$P\pi r^2 = \sigma\pi[(r+h)^2 - r^2], \tag{7}$$

and hence:

$$P = \sigma[(\frac{h}{r})^2 + 2(\frac{h}{r})], \tag{8}$$

where h is the hydrophobic polymer wall thickness and σ is the biaxial tension stress (force per unit strained cross-sectional area).

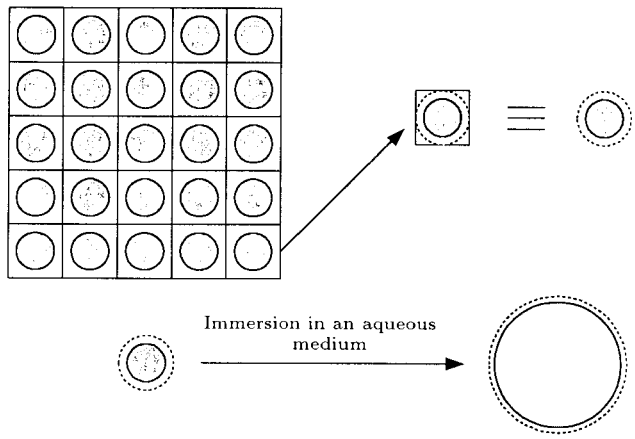

Figure 1. Schematic diagram of the simplification of composites and the approximation used in the developed model.

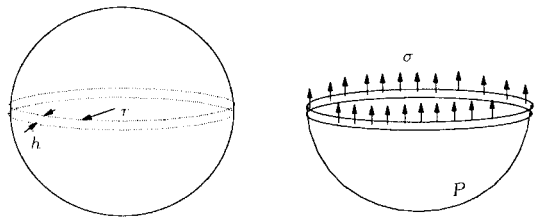

Figure 2. Schematic diagram of force balance for a balloon.

Assuming that the volume of the hydrophobic polymer remains constant:

$$(h+r)^3 - r^3 = (h_0 + r_0)^3 - r_0^3. \tag{9}$$

Equation 9 can be rewritten as:

$$\frac{h}{r} = \left\{ \frac{1}{\lambda^3}[(1 + \frac{h_0}{r_0})^3 - 1] + 1 \right\}^{1/3} - 1, \tag{10}$$

where $\lambda = r/r_0$. For the particle distribution in the simple cubic lattice:

$$\frac{h_0}{r_0} = (\frac{\pi}{6\varphi})^{1/3} - 1, \tag{11}$$

where φ is the volume fraction of the hydrophilic particles in the dry matrix.

By substituting Equations 10 and 11 into Equation 8, the following equation can be obtained:

$$P = \sigma\Big\{[\frac{1}{\lambda}(\frac{\pi}{6\varphi} - 1 + \lambda^3)^{1/3} - 1]^2 + 2[\frac{1}{\lambda}(\frac{\pi}{6\varphi} - 1 + \lambda^3)^{1/3} - 1]\Big\}. \tag{12}$$

Through running a biaxial tension test for the hydrophobic polymer, the stress-strain profile $\sigma(\lambda)$ can be obtained. Substituting $\sigma(\lambda)$ into Equation 12 gives the retractive pressure profile. When the hydrophobic polymer behaves as a rubber, rubber elasticity theory gives the following expression for biaxial tension:

$$\sigma = G(\lambda^2 - \frac{1}{\lambda^4}). \tag{13}$$

When the hydrophobic polymer behaves as a Hookean polymer, $\sigma(\lambda)$ can be obtained by:

$$\sigma = E(\lambda - 1), \tag{14}$$

where E is the Young's modulus of hydrophobic polymer.

By using Equations 12 to 14, the retractive pressure profiles in terms of the mechanical properties of the hydrophobic polymer and the content of the hydrophilic polymer in the matrix can be obtained.

PREDICTING EQUILIBRIUM SWELLING OR OSMOTIC RUPTURING

In a composite, when the hydrophilic content is below the percolation threshold, most of the particles are isolated by the hydrophobic polymer. After immersion in an aqueous medium, water permeates through the hydrophobic phase and is absorbed by the hydrophilic phase. The swelling of the hydrophilic phase produces local stresses. Therefore, if no opening exists, the retractive pressure increases until either equilibrium is reached or osmotic rupturing occurs. Equilibrium swelling will be reached if the osmotic pressure in the capsule is balanced by the retractive pressure of the hydrophobic polymer. The encapsulating membrane will be ruptured if the osmotic pressure exceeds the mechanical strength of the hydrophobic polymer. The criteria to determine whether equilibrium swelling or osmotic rupturing would occur can be defined with respect to the osmotic pressure and retractive pressure profiles and the mechanical strength of the hydrophobic polymer.

The mechanical strength of the hydrophobic polymer can be expressed by a critical value for the retractive pressure, P_c, or for the extension ratio, λ_c, at which the hydrophobic polymer is ruptured. The value of the critical elongation should be obtained by running a biaxial tension test. However, for the materials where the failure point is very close to the yield point, by running a uniaxial tension test, the characteristics of the critical point can be obtained. Using the experimental value of the yield point stress in uniaxial tension, and the relationship between yield stress in uniaxial and biaxial tensions, yield point stress in biaxial tension can be obtained and then the characteristics of the critical point can be determined. In developing a general yield criterion for plastics [36,37] and polymer melt continuous phases [38,39], the more general approach for yielding under multiaxial loading adopted is the von Mises criterion. Based on the von Mises criterion, yield occurs when the function of all the components of stress reaches a critical value for different combinations of stresses. The von Mises criterion can be expressed mathematically as [40]:

$$(\sigma_{11} - \sigma_{22})^2 + (\sigma_{22} - \sigma_{33})^2 + (\sigma_{33} - \sigma_{11})^2 + 6(\sigma_{12}^2 + \sigma_{13}^2 + \sigma_{23}^2) \geq 6C^2, \tag{15}$$

where σ_{ij} are components of the stress matrix. If the left-hand side exceeds $6C^2$, yielding has occurred. C is a function of hydrostatic pressure, material, temperature and strain rate. By running a simple test and finding the components of the yield stress, C can be obtained and applied to other situations. Applying the von Mises criterion gives the same yielding criterion for uniaxial stress and symmetric biaxial stress, when the effects of parameters influencing C are neglected. By using the yield criterion, the stress-strain profile and the retractive pressure equation (Equation 12), the characteristics of the critical point (P_c and λ_c) can be obtained for the materials in which the yield point is very close to the failure point.

In the case of equilibrium swelling, the osmotic pressure in the capsule is balanced by the retractive pressure; therefore, the osmotic pressure and retractive

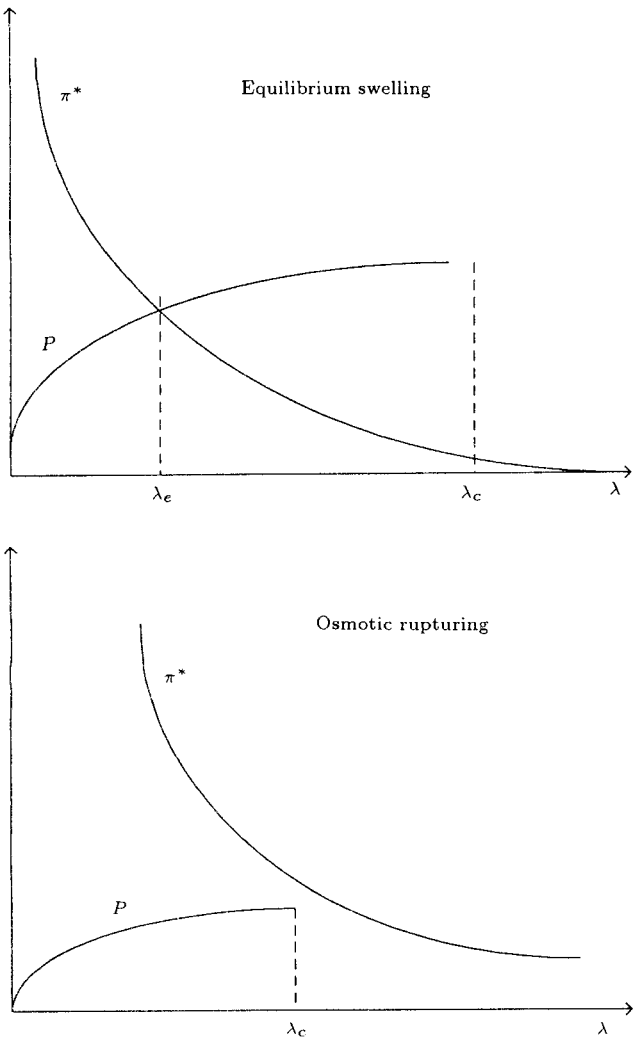

Figure 3. Behavior of osmotic pressure and retractive pressure profile versus elongation of the hydrophobic polymer in systems with either equilibrium swelling or osmotic rupturing.

pressure profiles intersect before the critical point of the hydrophobic polymer ($\lambda_E < \lambda_c$). In the case of osmotic rupturing, the osmotic pressure exceeds the mechanical strength of the hydrophobic polymer; therefore, the osmotic pressure and retractive pressure profiles do not intersect before the critical point of the hydrophobic polymer ($\lambda_E > \lambda_c$). Schematic diagrams of the osmotic pressure and retractive pressure profiles in the systems with equilibrium swelling and osmotic rupturing are shown in Figure 3.

PREDICTING THE EXTENT OF EQUILIBRIUM SWELLING

In equilibrium swelling, the osmotic pressure of the hydrophilic phase is balanced by the retractive pressure of the hydrophobic phase. Therefore, the osmotic pressure of the hydrophilic phase should be equal to the retractive pressure of the hydrophobic phase. By calculating the osmotic pressure of the hydrophilic phase and the retractive pressure of the hydrophobic phase, the extent of equilibrium swelling in the presence of a mechanical constraint can be obtained. Graphically, Figure 3 gives the rubber elongation at the intersection of the osmotic pressure and retractive pressure profiles, λ_E. By using the relationship between the swelling ratio of the gel Q, and the rubber elongation ($Q = \lambda^3$), the swelling ratio of the gel in the composites can be obtained.

DRUG RELEASE MECHANISMS

The drug release mechanism in a composite, when the hydrophilic content is below the percolation threshold, consists of two stages. The first stage involves drug particles which are at or very near the surface, or connected to the hydrophilic particles connected to the surface. These particles are released quickly after immersion in an aqueous medium (initial burst). In the second stage, in which dispersed particles are isolated by the hydrophobic polymer walls, either equilibrium swelling or osmotic rupturing may occur.

When the osmotic pressure profile of the hydrophilic polymer and the retractive pressure profile of the hydrophobic polymer intersect before the critical elongation of the hydrophobic polymer ($\lambda_E < \lambda_c$), equilibrium swelling occurs. In this case, no material is released if the drug cannot permeate through the hydrophobic phase. If the drug is permeable through the hydrophobic phase and Deborah number is much different from one, drug release will be controlled by diffusion. Since the hydrophilic particles remain isolated within the hydrophobic polymer and drug permeability through the hydrophobic phase is much smaller than that through the hydrophilic phase, drug diffusion through the hydrophobic phase is the rate-controlling step. On the other hand, the hydrophilic content in the matrix affects the effective diffusion coefficient. Therefore, as the hydrophilic content in the matrix increases, the drug release rate also increases.

When the osmotic pressure and retractive pressure profiles do not intersect before the critical elongation of the hydrophobic polymer ($\lambda_E > \lambda_c$), osmotic rupturing occurs. It is proposed that the release of solute during osmotic rupturing occurs in the following fashion. Water partitions into and diffuses through the hydrophobic polymer and is imbibed osmotically by the hydrogel and drug particles. This influx of water results in dissolution of the drug particles and swelling of the hydrophilic particles until rupture occurs. The capsules rupture, creating small fractures in the hydrophobic polymer which lead to the external aqueous environment. The dissolved drug particles which are connected to these cracks or that are able to produce enough osmotic pressure to rupture the

hydrophobic walls themselves, can diffuse out of the matrix. Meanwhile, water continues to be imbibed into the interior of the device to repeat the process. Therefore, a serial rupturing mechanism can be considered. This mechanism allows the system to be broken into two regions: the zone of ruptured capsules and the zone of intact capsules [5,35,41,42]. The zones are separated by the front of imbibing-rupturing capsules. In view of the mechanism described, the drug release rate is given by:

$$\frac{dM}{dt} = \frac{M_L}{t_b + t_d}, \tag{16}$$

where M_L is the mass of drug per layer, t_b is the time for the capsule to imbibe water and rupture, and t_d is the time required for the drug to diffuse out through the created channels. In any monolithic osmotic system, three major phenomena may occur: 1) Osmotic imbibition of water into the layer of intact capsules, 2) Osmotic imbibition of water into the layer of capsules that have ruptured but can still absorb water, and 3) Diffusion of solute through the ruptured capsule network. Phenomena (1) and (2) deal with the influx of water, and phenomenon (3) concerns the efflux of solute from the system. The drug release rate will be determined by the slower step: the influx of water or the efflux of solute. If the influx of water is the rate-controlling step, t_b dominates the overall duration of the drug release while t_d contributes insignificantly to the total release time. By considering the serial rupturing mechanism, the osmotic pressure gradient, which is the driving force for penetrating water from the layer of ruptured capsules to the layer of intact capsules, is independent of the moving front position. Therefore, the value of t_b for all layers is similar and the release kinetics will be zero order. If the efflux of solute is the rate controlling step, t_d dominates the overall duration of the drug release. Therefore the release kinetics will be controlled by diffusional release.

CONCLUSION

In this paper composites having hydrophilic particles dispersed uniformly within a hydrophobic network have been investigated. The important requirements for understanding release mechanisms for composite materials have been defined theoretically. When the hydrophilic content in a dry matrix is beyond the percolation threshold, drug release is governed by diffusion or swelling kinetics. When the hydrophilic content is below the percolation threshold, equilibrium swelling or osmotic rupturing may occur. By presenting a model for calculating the retractive pressure of the hydrophobic phase, theoretical criteria to determine whether equilibrium swelling or osmotic rupturing would occur were defined. A model for predicting the extent of equilibrium swelling in the presence of mechanical constraint was also presented. When the osmotic pressure and retractive pressure profiles intersect before the critical elongation of the hydrophobic polymer ($\lambda_E < \lambda_c$), the osmotic pressure in the capsules is balanced by the retractive pressure. Therefore, equilibrium swelling should occur, and the intersection of the osmotic pressure and retractive pressure profiles gives the extent of equilibrium swelling. When the osmotic pressure and retractive pressure profiles do not intersect before the critical elongation of the hydrophobic polymer ($\lambda_E > \lambda_c$), the osmotic pressure exceeds the mechanical strength of the hydrophobic polymer. Therefore, osmotic rupturing should occur. In the case of equilibrium swelling, drug release may be governed by diffusion or swelling kinetics. In the case of osmotic rupturing, drug release may be controlled by diffusion or osmotic rupturing kinetics.

NOMENCLATURE

C_s^*	mobile electrolyte concentration in the external solution
G	shear modulus
h	wall thickness of an inflated sphere
h_0	original wall thickness of a hollow sphere
i	degree of ionization
P	retractive pressure of the hydrophobic polymer
P_c	critical value for the retractive pressure of the hydrophobic polymer
r_0	original internal radius of a sphere
t	release time
t_b	time for the capsule to imbibe water and rupture
t_d	time required for drug to diffuse out of the matrix
T	temperature
V_u	molar volume of a structural unit of a polymer
z_-	charge of the gel
φ	volume fraction of the hydrophilic particles in a dry matrix
λ	extension ratio ($= r/r_0$)
λ_c	critical value for the extension ratio
λ_E	equilibrium extension ratio of the hydrophobic polymer
ν	number of ions
π_{ion}	ionic osmotic pressure
π_{net}	network osmotic pressure

π^*	osmotic pressure of the hydrophilic polymer
σ	biaxial tension
σ_{ij}	components of the stress matrix
σ_y	yield point stress
$v_{2,s}$	polymer volume fraction in the swollen gel

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