Drug Release Mechanisms
From Composite Matrices
II. Experimental Issues

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In this paper, the theoretical issues governing release characteristics of a solute of composite materials are validated experimentally, using composites of cross-linked poly (hydroxyethyl methacrylate) (PHEMA) particles dispersed within ethylene vinyl acetate copolymer (EVAc) matrices, and composites of cross-linked poly (methacrylic acid) (PMAA) particles dispersed within poly (dimethyl siloxane) (PDMS) networks which were prepared. Using theophylline and caffeine as the model drugs, the results of release, permeation and swelling experiments were employed to validate the theoretical issues. In PHEMA-EVAc matrices, due to equilibrium swelling, Fickian diffusional release kinetics was observed. In PMAA-PDMS matrices, which contained 19%wt, 23.7%wt, 28.5%wt, 33.2%wt and 38%wt PMAA, because of osmotic rupturing, pseudo-zero-order release kinetics preceded by a marked burst effect was observed. In all the cases, the experimental results were in good agreement with the theoretical criteria for equilibrium swelling versus osmotic rupturing. For the model predicting the extent of equilibrium swelling, the maximum deviation of the swelling ratio compared to the experimental results for different matrices was only 8.4%.

INTRODUCTION

Theoretical issues governing the release characteristics of a solute of composites of hydrophilic and hydrophobic polymers have been investigated in the preceding paper [1]. In that paper, theoretical criteria for determining whether equilibrium swelling or osmotic rupturing would occur were defined and a model for predicting the extent of equilibrium swelling in the presence of mechanical constraint was proposed. In this paper, these theoretical issues are validated experimentally.

Composites of cross-linked poly (hydroxyethyl methacrylate) (PHEMA) particles dispersed within Ethylene Vinyl Acetate copolymer (EVAc) matrices and composites of cross-linked poly (methacrylic acid) (PMAA) particles dispersed within poly (dimethyl siloxane) (PDMS) networks were fabricated. Using

theophylline and caffeine as the model drugs, the results of permeation, release and swelling experiments were used to validate the presented models.

MATERIALS AND METHODS

The materials used to prepare poly (hydroxyethyl methacrylate) gel particles and films include 2-hydroxyethyl methacrylate (Sigma Chemical Co., St. Louis, MO), benzoyl peroxide (Fluka Chemika Inc., Ronkonkoma, NY) and ethylene glycol dimethacrylate (Aldrich Chemical Co., Milwaukee, WI). The materials for the hydrophobic networks were Elvax-40, a copolymer of ethylene and vinyl acetate containing 40% vinyl acetate, (Du Pont Canada Inc., Mississauga, Ont.) and dichloromethane (Aldrich Chemical Co., Milwaukee, WI). Theophylline (Sigma Chemical Co., St. Louis, MO) was used as the model drug.

The materials for poly (methacrylic acid) gel particles and films include methacrylic acid and triethylene glycol dimethacrylate (Polyscience Inc., Warrington, PA), ethylene glycol (Fisher Scientific, Fairlawn, NJ) and ammonium persulfate and sodium metabisulfate (Sigma Chemical Co., St. Louis, MO). For preparation of the hydrophobic networks, Sylgard 184 silicon elas-

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tomer, base and curing agent (Dow Corning, Midland, MI) was used. Citrate and phosphate buffer solutions were prepared from citric acid monohydrate, sodium citrate, sodium hydrogen phosphate, sodium dihydrogen orthophosphate and sodium azide (Sigma Chemical Co., St. Louis, MO). Caffeine (Aldrich Chemical Co., Milwaukee, WI) was considered as the model drug.

There are two steps involved in making composite materials; hydrogel preparation and dispersion of the hydrogel in the hydrophobic network. Hydrogels were prepared through free radical solution polymerization with simultaneous cross-linking. PHEMA and PMAA films were prepared according to the methods described by Peppas et al. [2] and Sefton and Nishimura [3]. Ethylene glycol dimethacrylate with 0.005 nominal cross-linking ratio (mole EGDMA/mole PHEMA) and triethylene glycol dimethacrylate with 0.5 %wt were used as the cross-linking agents for PHEMA and PMAA, respectively. The resultant gel films were washed using distilled water for three weeks, with the wash liquid being changed daily. The gel films were ground using a laboratory mixer and then the gel particles were lyophilised. The lyophilised gel particles and drugs were ground and sieved to the same particle size and dispersed into the hydrophobic networks.

The solvent casting method was used to prepare PHEMA-EVAc monoliths. Theophylline was ground and sieved to the same particle size as the PHEMA particles ($< 38\ \mu$m). Suspensions of PHEMA and theophylline particles, with different fractions of PHEMA and various levels of theophylline (Table 1), in a 10 %wt EVAc / dichloromethane solution were prepared. Constant stirring for one hour agitated the mixtures, to disperse the particles through the polymer solution. The resulting suspensions were poured quickly in precooled glass moulds, under a liquid nitrogen bath. After a few minutes, they were placed in a vacuum oven at room temperature for 5 hours to evaporate the solvent. Then, the temperature of the vacuum oven was increased to 80°C and was maintained at this temperature for two weeks to degas the resultant mixtures. The resulting matrices were melt-pressed to form monoliths of 6 mm thickness. To complete the degassing procedure, the monoliths were put again in the vacuum oven at 80°C for two more weeks. The degassed monoliths were melt-pressed to form a

Table 1. Composition of PHEMA-EVAc matrices.

#	EVAc (g)	PHEMA (g)	Theophylline (g)
I1	3.25	1.75	0.165
I2	3.25	1.75	0.270
I3	3.25	1.75	0.572
I4	3.75	1.25	0.270
I5	2.75	2.25	0.270

Table 2. Composition of PMAA-PDMS matrices.

#	PDMS(g)	PMAA(g)	Caffeine (g)
1	2.800	0.700	0.185
2	2.625	0.875	0.185
3	2.450	1.050	0.185
4	2.275	1.225	0.185
5	2.100	1.400	0.185

monolith of 5 ± 0.1 mm thickness. Disks of 1.4 cm diameter were cut from the monoliths.

PMAA-PDMS matrices were prepared using the following procedure. Caffeine was ground and sieved to the same particle size as the PMAA particles (120 – 180 μm and 255 – 350 μm). Sylgard 184 silicon elastomer, base and curing agents in a ratio of 10 parts base to 1 part curing agent by weight, were mixed and then the PMAA and caffeine particles with different compositions were added (Table 2). The resultant mixtures were mixed and then cast in a Teflon mould and degassed for 4 hours in the vacuum oven. The polymer mixtures were then placed at room temperature for 24 hours to complete the hydrosilyation reaction. The cured PMAA-PDMS matrices were approximately 5 mm in thickness and were die cut to a diameter of 1.4 cm.

To minimize the effect of release from the sides and to increase the effective thickness of the disks, the sides and one end of the disks were sealed using the following procedure. Poly Vinyl Chloride (PVC) tube with 1.4 cm diameter was cut into 3 cm lengths and the disks were fitted into the PVC tubes. These devices were put into test tubes filled with 20 ml distilled water for PHEMA-EVAc matrices, and phosphate buffer solution for PMAA-PDMS matrices. Therefore, the monoliths only were in contact with the release medium from the bottom side. The containers were stirred at a constant rate (750 rpm) to reduce boundary layer effects. The tubes were placed in a bath that provided temperature control (37°C). At 24 hour intervals, the tubes were removed from the bath, the liquid was replaced with fresh water or phosphate buffer solution, and then the tubes were again placed in the bath. The concentration of each sample was determined by measuring the optical density at the wavelength of maximum absorbance, 274 nm for theophylline and 272 nm for caffeine, using a Hewlett Packard model 8452A UV - Vis spectrophotometer.

EQUILIBRIUM SWELLING OR OSMOTIC RUPTURING

PHEMA-EVAc Matrices

In this section, the occurrence of either equilibrium swelling or osmotic rupturing in PHEMA-EVAc ma-

trices which contain 23.7%wt, 33.2%wt and 42.7%wt PHEMA is predicted using the theoretical criteria for equilibrium swelling versus osmotic rupturing presented in the preceding paper [1]. Then, the experimental results, obtained from the release and permeation studies, are used for the experimental validation of the theoretical issue.

Theoretical Prediction

To predict whether equilibrium swelling or osmotic rupturing would occur, the profiles of the osmotic pressure, π^*, and the retractive pressure, P, versus polymer volume fraction in the swollen gel, v_{2s}, or elongation of the hydrophobic polymer, λ, were obtained. Since PHEMA is a neutral gel, the osmotic pressure π^* is equal to the network osmotic pressure, π_{net}. Because of assuming a non-Gaussian distribution of macromolecular chains and the presence of the solvent during the cross-linking of PHEMA, the model presented by Peppas et al. [4] was chosen to calculate the osmotic pressure of PHEMA:

$$\pi_{net} = -\frac{RT}{V_1}\left\{[\ln(1 - v_{2,s}) + v_{2,s} + \chi v_{2,s}^2][1 - \frac{1}{N}v_{s,r}^{2/3}]^3 \right.$$
$$\left. +\frac{V_1}{vM_c}(1 - \frac{2M_c}{M_n})v_{2,r}(v_{s,r}^{1/3} - \frac{v_{s,r}}{2})(1+\frac{1}{N}v_{s,r}^{1/3})^2\right\},$$
$$(1)$$

where R is the ideal gas constant, T is the absolute temperature, V_1 is the molar volume of the swelling agent, $v_{2,s}$ is the polymer volume fraction in the swollen gel, χ is the Flory polymer-solvent interaction parameter, M_c is the molecular weight between cross-links, M_n is the number average molecular weight before cross-linking, v is the specific volume of the polymer, $v_{2,r}$ is the polymer volume fraction in the relaxed polymer state, i.e., immediately after cross-linking but before swelling; the term $v_{s,r}$ denotes the ratio $v_{2,s}/v_{2,r}$ and N is the number of links per chain and is given by $N = 2M_c/M_r$, where M_r is the molecular weight of the monomer repeating unit.

To obtain the osmotic pressure profile based on Equation 1, the interaction parameter, the molecular weight between cross-links and the number average molecular weight of PHEMA are needed. The interaction parameter depends on both temperature and polymer volume fraction in the swollen gel, $v_{2,s}$. Janacek et al. [5] proposed the following equation to obtain χ for PHEMA at 37°C:

$$\chi = 0.32 + 0.904\, v_{2,s}. \qquad (2)$$

Using $v_{2,s} = 0.573$ in Equation 2, obtained from the swelling of the unconstrained PHEMA gel, χ was calculated ($\chi = 0.838$). Using the reciprocal

of the equilibrium-swelling ratio of the unconstrained PHEMA gel, the molecular weight between cross-links, M_c, was obtained. For the unconstrained PHEMA gel at equilibrium swelling, Equation 1 can be written as:

$$\frac{1}{M_c} = \frac{2}{M_n}$$
$$-\frac{\frac{v}{V_1}[\ln(1 - v_{2,s}) + v_{2,s} + \chi v_{2,s}^2][1 - \frac{1}{N}v_{s,r}^{2/3}]^3}{v_{2,r}(v_{s,r}^{1/3} - \frac{1}{2}v_{s,r})(1 + \frac{1}{N}v_{s,r}^{1/3})^2}. \qquad (3)$$

As the polymerization of the HEMA occurred simultaneously with cross-linking, determining the number average molecular weight of PHEMA, M_n, is very difficult. Following other studies [6], it has been assumed that M_n is large enough to neglect the term $2/M_n$ in Equation 3. Substituting $v = 0.785$ cm^3/g, $V_1 = 18$ cm^3/mole, $N = 2M_c/130$, $v_{2,r} = 0.6$ in Equation 3 gives $M_c = 2795$. Using the suitable values in Equation 1 and considering $1 - (2M_c/M_n) \approx 1$, π^* versus $v_{2,s}$ was determined. Considering the relationship between $v_{2,s}$ and $\lambda, [\lambda = (1/v_{2,s})^{1/3}], \pi^*$ versus λ was obtained.

To calculate the retractive pressure of the hydrophobic phase P, the method presented in [1] was used. Since EVAc has extremely high extensibility generated by low mechanical stress and complete recovery after mechanical deformation, it was considered to be a rubber. Introducing the stress-strain profile for rubbers in the general equation for calculating retractive pressure gives:

$$P = G\left\{\lambda^2 - \frac{1}{\lambda^4}\right\}\left\{[\frac{1}{\lambda}(\frac{\pi}{6\varphi} - 1 + \lambda^3)^{1/3} - 1]^2\right.$$
$$\left. + 2[\frac{1}{\lambda}(\frac{\pi}{6\varphi} - 1 + \lambda^3)^{1/3} - 1]\right\}. \qquad (4)$$

To obtain P versus rubber elongation λ based on Equation 4, the shear modulus, G, of EVAc and the volume fraction of the hydrophilic agents in the matrix, φ, are needed. Using a Sintech Testing machine, the Young modulus of EVAc (average of five specimens) was measured as 0.365 ± 0.025 MPa (mean $\pm$ standard deviation). Young modulus is related to shear modulus by:

$$G = \frac{E}{2(1 + \nu)}, \qquad (5)$$

where ν is Poisson ratio equal to 0.5 for rubbers. Therefore, G for EVAc was determined to be 0.122 MPa. Using the weight fraction of different components in the matrix, φ is obtained as:

$$\varphi = \frac{w_{PHEMA} + w_{Drug}\frac{\rho_{PHEMA}}{\rho_{Drug}}}{w_{PHEMA} + w_{Drug}\frac{\rho_{PHEMA}}{\rho_{Drug}} + w_{EVAc}\frac{\rho_{PHEMA}}{\rho_{EVAc}}}, \qquad (6)$$

where w_i is the weight fraction of the ith component and ρ_i is the density of the ith component. Using the values of G and φ in Equation 4, P versus λ was obtained.

The critical value for the extension ratio λ_c was estimated using the yield point stress, the von Mises criterion [7,8] and the stress-strain profile for rubbers. Using Sintech Testing machine, the yield point of EVAc for uniaxial stress was obtained ($\sigma_y = 10.6 \pm 0.5$ MPa). The von Mises criterion has been expressed mathematically as [9]:

$$(\sigma_{11} - \sigma_{22})^2 + (\sigma_{22} - \sigma_{33})^2 + (\sigma_{33} - \sigma_{11})^2$$
$$+ 6(\sigma_{12}^2 + \sigma_{13}^2 + \sigma_{23}^2) \geq 6C^2. \tag{7}$$

For uniaxial stress and symmetric biaxial stress, Equation 7 is reduced to $2\sigma_u^2 = 6C^2$ and $2\sigma_b^2 = 6C^2$, respectively, where σ_u and σ_b are the yield point stresses for the uniaxial and biaxial tests, respectively. Therefore, applying the von Mises criterion (Equation 7) provides the same yielding criterion for uniaxial stress and symmetric biaxial stress. Using the yield criterion and the stress-strain profile for biaxial tension of rubbers:

$$\sigma = G(\lambda^2 - \frac{1}{\lambda^4}), \tag{8}$$

the critical value for the extension ratio was obtained ($\lambda_c = 9.33$).

Figure 1 shows the osmotic pressure π^* and the retractive pressure P, versus λ of PHEMA-EVAc matrices with different PHEMA contents (23.7%wt,
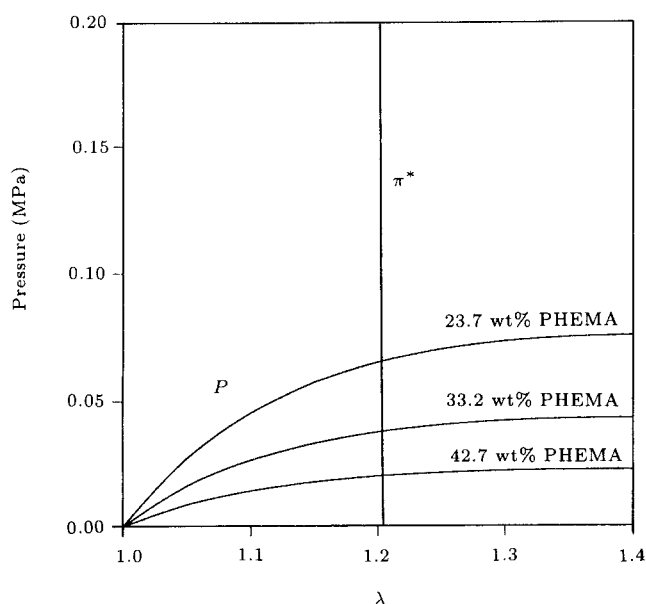
33.2%wt and 42.7%wt). Since osmotic pressure and retractive pressure profiles intersected before the critical elongation of the hydrophobic polymer ($\lambda_E < \lambda_c$), the osmotic pressure in PHEMA capsules would be balanced by the retractive pressure of EVAc. Therefore, the theoretical criteria of equilibrium swelling versus osmotic rupturing predicts that equilibrium swelling should occur.

Experimental Results

In composites, several parameters can influence the drug release rate. Some of these parameters, such as the cross-linking density of the hydrophilic phase and the mechanical properties of the hydrophobic phase, depend on the characteristics of one phase, while other properties, such as the hydrophilic content in the matrix and the drug loading level, depend on formulation factors. Here, effects of two formulation factors, the hydrophilic content and the drug loading level, on the cumulative release of theophylline from PHEMA-EVAc matrices have been studied. The cumulative release profiles of theophylline versus $t^{1/2}$ over 100 days for three PHEMA-EVAc monoliths with different content of PHEMA (I2, I4 and I5 in Table 1) are shown in Figure 2. Initial drug loading was 5 %wt and PHEMA particle size was less than 38 μm. These results are consistent with the expectation that as the content of PHEMA gel in the monolith increases, the cumulative release increases. Figure 3 illustrates the effect of drug loading on the release profiles of PHEMA-EVAc monoliths with different contents of theophylline (I1-I3 in Table 1). The PHEMA particle size was less than 38 μm.

The release mechanism can be ascertained by fitting the cumulative release profiles to kt^n. Values of n and k were calculated from both the linear regression of $\{\ln M_t = \ln k + n \ln t\}$ and the nonlinear regression of $\{M_t = kt^n\}$. The values of n and k from both methods were very close and in the
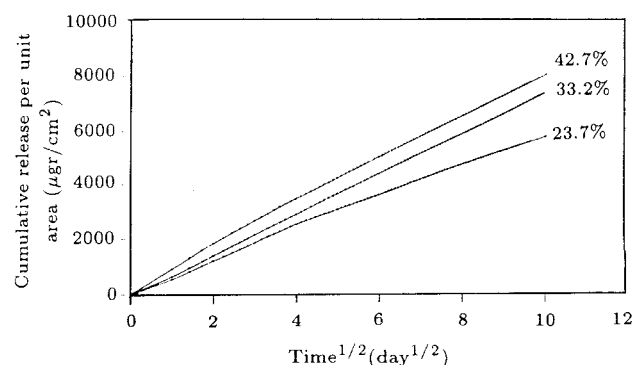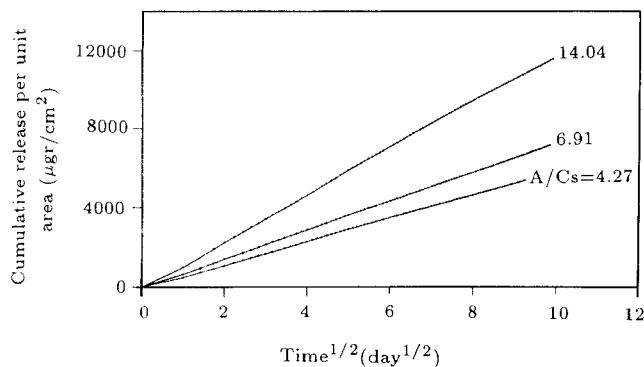

Figure 1. Osmotic pressure and retractive pressure profiles versus elongation of EVAc for PHEMA-EVAc matrices with different PHEMA content of λ_c (critical elongation) $= 9.3$.

Figure 2. Effect of PHEMA content on the cumulative release of theophylline from PHEMA-EVAc monoliths ($n = 2$, range < graph resolution).

Figure 3. Effect of drug loading level on the cumulative release of theophylline from PHEMA-EVAc matrices ($n = 2$, range < graph resolution).

worst case, the deviation was only 2.1%. For the sake of simplicity and since in the worst case when using linear regression the residual was only 0.3% of the estimated value, the linear regression method was chosen. The exponents in the time dependence, n, and the regression coefficients, R^2, for the cumulative release profiles of theophylline for different PHEMA-EVAc matrices are given in Table 3. For diffusional release, the cumulative release profile is expected to vary as $t^{1/2}$. To determine if the values of n are statistically equal to 0.5, the 95% joint confidence region for the linear regression was obtained. In all cases, the point corresponding to the values of n and k, where k was obtained by linear regression with n fixed at 0.5, is inside the 95% joint confidence region. Therefore, in all cases the values of n are statistically equal to 0.5 at the 95% confidence level. Experimentally, it is difficult to satisfy all model assumptions such as perfect sink conditions and constant diffusion coefficient. This may cause slight deviations of n from 0.5. However, the release behavior appears to be Fickian and diffusional release was likely the rate-controlling step.

Drug release may be governed by diffusional release even when osmotic rupturing occurs. Therefore, permeation studies have been undertaken to determine whether osmotic rupturing has occurred or not. Theophylline can permeate through both

Table 3. Linear regression analysis of $\{\ln M_t = \ln k + n \ln t\}$ for cumulative release profiles of theophylline from PHEMA-EVAc matrices.

#	n	R^2
I1	0.517	0.99981
I2	0.525	0.99959
I3	0.529	0.99949
I4	0.482	0.99792
I5	0.490	0.99996

n: the exponent in the time dependence,
R^2: the regression coefficient.

Table 4. Results of permeation of theophylline through PHEMA-EVAc membranes.

#	$\eta_{swollen}$	P cm^2/s $*10^8$	D cm^2/s $*10^8$	k
III 1	0.361	0.574	0.910	0.631
III 2	0.465	0.862	1.079	0.799
III 3	0.559	1.111	1.170	0.949
III 4	0.653	2.337	2.171	1.077
III 5	1	19.677	11.236	1.751

$\eta_{swollen}$: PHEMA weight fraction in the swollen state,
P: permeation coefficient,
D: diffusion coefficient,
k: partition coefficient of the given compound at 37°C.

PHEMA and EVAc, but the permeability of theophylline through PHEMA is much higher than that through EVAc. The values of the permeability of theophylline through PHEMA and EVAc are $19.7*10^{-8}$ cm^2/sec and $0.271*10^{-8}$ cm^2/sec, respectively. When the permeability of theophylline through the composite membranes is very close to that through EVAc, diffusion through EVAc is likely the rate controlling step, implying that no rupturing occurs. To obtain permeability, diffusion coefficient and partition coefficient, "time lag" method [10] was used. The results of the permeation studies are presented in Table 4. Since the permeability of theophylline through composite membranes was much smaller than that through PHEMA and close to the permeability of theophylline through EVAc (which was $0.271*10^{-8}$ cm^2/sec), diffusion through EVAc was likely the rate controlling step and rupturing most likely did not occur.

Comparison Between Theory and Experiment

Theoretically, since osmotic pressure and retractive pressure profiles of PHEMA-EVAc matrices with different contents of PHEMA (23.7%wt, 33.2%wt and 42.7%wt) intersected before the critical elongation of EVAc (Figure 1; $\lambda_E < \lambda_c$), equilibrium swelling should occur. Experimentally, the release behavior appears to be Fickian and diffusional release is likely the rate-controlling step. In addition, the permeability of theophylline through PHEMA-EVAc membranes was much smaller than that through PHEMA and was close to the permeability of theophylline through EVAc. For this reason, permeation experiments indicate that rupturing has not occurred. Therefore, experimental results are in agreement with the model for the theoretical criteria of equilibrium swelling versus osmotic rupturing.

PMAA-PDMS Matrices

In this section, the occurrence of either equilibrium swelling or osmotic rupturing in PMAA-PDMS ma-

trices is predicted using their respective theoretical criteria. Then, the experimental results are used to validate the theoretical predictions.

Theoretical Prediction

To predict whether equilibrium swelling or osmotic rupturing would occur, the osmotic pressure profile of PMAA and the retractive pressure profile of PDMS should be obtained. Since PMAA is an ionic gel, the osmotic pressure, π^*, was calculated by:

$$\pi^* = \pi_{net} + \pi_{ion}. \tag{9}$$

Due to the fact that Gaussian distribution has been assumed for the macromolecular chain and the presence of the solvent during the cross-linking of PMAA, the network osmotic pressure π_{net} was obtained using the model presented by Peppas and Merill [11]:

$$\pi_{net} = -\frac{RT}{V_1}[\ln(1 - v_{2,s}) + v_{2,s} + \chi v_{2,s}^2$$
$$+ \frac{V_1}{\bar{v}M_c}(1 - \frac{2M_c}{M_n})v_{2,r}[(\frac{v_{2,s}}{v_{2,r}})^{1/3} - \frac{1}{2}(\frac{v_{2,s}}{v_{2,r}})]. \tag{10}$$

The ionic osmotic pressure, π_{ion}, was calculated by [1]:

$$\pi_{ion} = RT[(\frac{v_{2,s}}{z_- V_u})(\frac{K_a}{K_a + 10^{-pH}}) - \nu C_s^*], \tag{11}$$

where 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 concentration in the external solution, respectively.

To calculate π_{net}, two terms χ and $[(1 - 2M_c/M_n)/(vM_c)]$ are needed. Hasa and co-workers [12,13] proposed the following equation to obtain the value of χ for non-ionized PMAA:

$$\chi = 0.44 + 0.6 \, v_{2,s}. \tag{12}$$

When the pH of the swelling medium is equal to 3, PMAA behaves as a non-ionized gel; therefore, $\pi^* = \pi_{net}$. For equilibrated unconstrained PMAA, the osmotic pressure is equal to zero. Thus, using the reciprocal of the equilibrium swelling ratio of unconstrained PMAA in this medium [$v_{2,s}$(pH = 3) = 0.207] and applying Equations 10 and 12, [$(1 - 2M_c/M_n)/(vM_c)$] was obtained. The value of [$(1 - 2M_c/M_n)/(vM_c)$], equal to $1.252{*}10^{-4}$ mole/cm^3, is independent of the pH of the swelling medium. Since it was assumed that most of the PMAA particles were isolated by PDMS and electrolyte salts could not permeate through PDMS, the value of χ for swelling of encapsulated PMAA should be equal to the χ value for swelling of

PMAA in deionized water. Using the reciprocal of the equilibrium swelling ratio of unconstrained PMAA in deionized water [$v_{2,s}$(pH = 5.5) = 0.145] and [$(1 - 2M_c/M_n)/(vM_c)$] = $1.252{*}10^{-4}$ mole/cm^3, $V_u = 66$ cm^3/mole [14] , $z_- = 1$, $K_a = 6.19$ [15] and Equations 9 to 11, χ was calculated ($\chi = 0.634$). Using these values in Equations 9 to 11 and taking the concentration of the mobile ion in the external solution (phosphate buffer solution) as $\nu C_s^* = 2.846{*}10^{-4}$ mole/cm^3, the osmotic pressure profiles versus $v_{2,s}$ were obtained. Using the relationship between $v_{2,s}$ and λ, π^* versus λ was obtained.

Since PDMS also has high extensibility generated by low mechanical stress and complete recovery after mechanical deformation, it was considered as a rubber. Therefore, Equation 4 was used to calculate the retractive pressure. Young modulus of PDMS, obtained from uniaxial tensile testing of 5 samples, is 3.73 ± 0.18 MPa. Using the relationship between Young modulus and shear modulus (Equation 5), the shear modulus of PDMS was calculated to be 1.24 MPa.

Based on the load-extension profile of PDMS in uniaxial tension test, the failure of PDMS point was very close to the yield point. Therefore, the critical value for extension ratio λ_c was obtained from the yield point stress, the von Mises criterion and the stress-strain profile for rubbers. Using the yield point stress of PDMS ($\sigma_y = 2.33 \pm 0.12$ MPa, from five specimens) and the stress-strain profile for rubbers, the critical value for the extension ratio was obtained ($\lambda_c = 1.45$).

Figures 4a and 4b show the osmotic pressure, π^*, and retractive pressure, P, versus rubber elongation, λ, of PMAA-PDMS matrices with different fractions of PMAA (3%wt, 5%wt, 10%wt, 19%wt, 23.7%wt, 28.5%wt, 33.2%wt and 38%wt). When osmotic pressure and retractive pressure profiles intersect before the critical elongation of PDMS ($\lambda_E < \lambda_c$), (Figure 4a; PMAA-PDMS matrices which contain 3%wt, 5%wt and 10%wt PMAA), the osmotic pressure in the PMAA capsules is balanced by the retractive pressure of PDMS. Therefore, the model for criteria of equilibrium swelling versus osmotic rupturing predicts that equilibrium swelling should occur. When osmotic pressure and retractive pressure profiles do not intersect before the critical elongation of PDMS ($\lambda_E > \lambda_c$), (Figure 4b; PMAA-PDMS matrices which contain 19%wt, 23.7%wt, 28.5%wt, 33.2%wt and 38%wt PMAA), the osmotic pressure in PMAA capsules exceeds the mechanical strength of PDMS. Therefore, osmotic rupturing is expected.
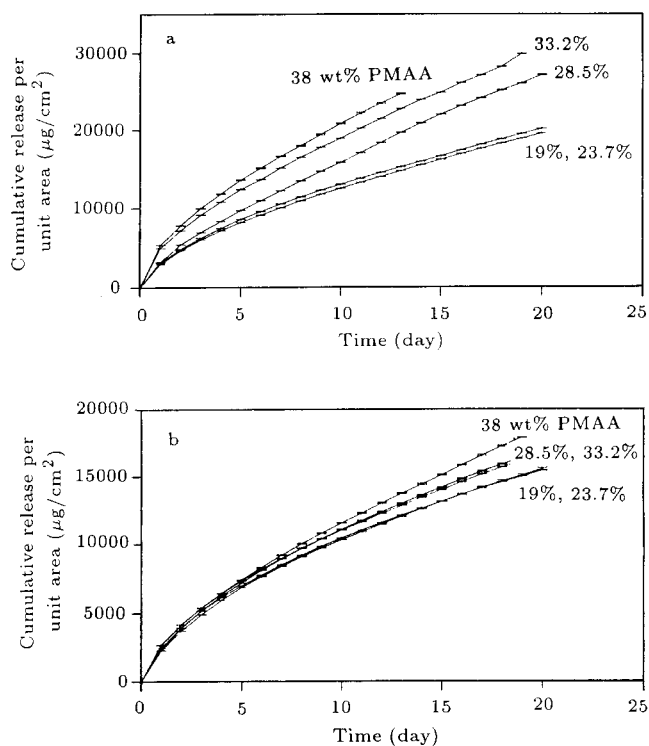
Experimental Results

To determine whether equilibrium swelling or osmotic rupturing would occur in PMAA-PDMS matrices which contain 3%wt, 5%wt and 10%wt PMAA,
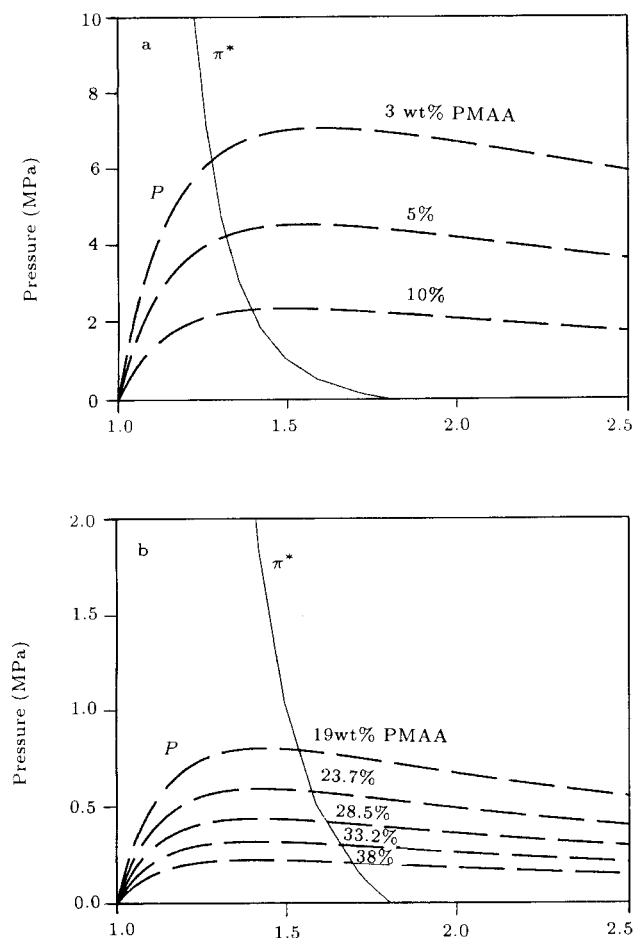
Figure 4. Osmotic pressure and retractive pressure profiles vs elongation of PDMS for PMAA-PDMS matrices with different contents of PMAA λ_c (critical elongation of PDMS) = 1.45.

Figure 5. Effect of PMAA content on the cumulative release of caffeine from PMAA-PDMS matrices with different PMAA particle sizes, a) dp = 255-350 μm, b) dp = 120-180μm, ($n = 3$, error bars represent standard deviations).

permeation studies were carried out. PMAA gel is permeable to FITC-Dext (Mw = 4400) but PDMS is not. In composites, when osmotic rupturing occurs, aqueous pathways are produced. Therefore, high molecular weight drugs can permeate through these aqueous channels. When rupturing does not occur, the PMAA particles are isolated by the hydrophobic walls. Since high molecular weight drugs cannot permeate through PDMS, these drugs cannot permeate through these composite membranes. In the permeation experiments, FITC-Dext (Mw = 4400) did not permeate through PMAA-PDMS membranes which contained 10%wt PMAA, thus indicating that no rupturing occurred.

Figures 5a and 5b demonstrate the cumulative release profiles of caffeine from PMAA-PDMS monoliths with different fraction of PMAA (19%wt, 23.7%wt, 28.5%wt, 33.2%wt and 38%wt) and various particle size of PMAA (120-180 μm and 255-350 μm). Initial drug loading was 5%wt. As mentioned earlier, the drug release mechanism consists of two stages: the first stage

involves drug particles that are at, or very near, the surface or connected to the hydrophilic particles that are connected to the surface. These drug particles are released quickly after immersion in an aqueous medium (initial burst). In the second stage, which controls the release behavior, dispersed particles are isolated by the hydrophobic polymer walls. To eliminate the effect of initial burst, release profiles should be analyzed after the first day of release. To determine the release behavior, the time dependence of each drug release profile should be obtained. For this purpose, each drug release profile was fitted to kt^n after the first day of release. Values of n and k from both the linear regression of $\{\ln M_t = \ln k + n\ln t\}$ and the non-linear regression of $\{M_t = kt^n\}$ were very close and in the worst case, the deviation was only 1.9%. Again, for the sake of simplicity and since in the worst case, using linear regression, the residual was only 0.5% of the estimated value, the linear regression method was chosen. The exponents in the time dependence, n, and the regression coefficients R^2, for the cumulative release profiles of caffeine from different PMAA-PDMS matrices are presented in Table 5. For osmotic rupturing, the cumulative release profile is expected to vary directly with t. To determine if the values of n are statistically equal to 1, the 95% confidence region for the linear regression was obtained. In all

Table 5. Linear regression analysis of $\{\ln M_t = \ln k + n \ln t\}$ for cumulative release profiles of caffeine from PMAA-PDMS matrices after the first day of release.

φ	dp: 255-350 μm		dp: 120-180 μm	
	n	R^2	n	R^2
19%	0.971	0.988	0.940	0.987
23.7%	0.962	0.992	0.957	0.986
28.5%	1.004	0.998	0.956	0.988
33.2%	1.007	0.993	0.978	0.989
38%	1.035	0.991	1.014	0.993

φ: the PMAA content in the matrix,

n: the exponent in the time dependence,

R^2: the regression coefficient.

cases, the values of n are statistically equal to 1 at the 95% joint confidence level. Experimentally, it is difficult to satisfy all model assumptions such as solute release by convection and not diffusion and perfect sink conditions. This may cause slight deviations of n from 1. In any osmotic monolithic system, a fraction of the solute will be released by dissolution and diffusion [16,17]. Capsule rupturing and osmotic release dominate the overall release mechanism, while dissolution/diffusion may contribute to the release profile. Therefore, the presence of a slight curvature in the release profiles shown in Figures 5a and 5b is an indication that these other effects may be present. However, the release kinetics is very close to zero-order, suggesting that osmotic rupturing is the dominated release mechanism following the marked initial burst.

Comparison Between Theory and Experiment

In PMAA-PDMS matrices which contained 3%wt, 5%wt and 10%wt PMAA, the osmotic pressure and retractive pressure profiles intersected before the critical elongation of PDMS, (Figure 4a; $\lambda_E < \lambda_c$). Therefore, the model for the theoretical criteria of equilibrium swelling versus osmotic rupturing predicts that equilibrium swelling should occur. Experimentally, FITC-Dext (Mw = 4400) did not permeate through PMAA-PDMS membranes which contained 10%wt PMAA, thus indicating that no rupturing occurred. Therefore, the results of the permeation experiments agreed with the prediction of equilibrium swelling.

In PMAA-PDMS matrices which contained 19%wt, 23.7%wt, 28.5%wt, 33.2%wt and 38%wt PMAA, osmotic pressure and retractive pressure profiles did not intersect before the critical elongation of PDMS (Figure 4b; $\lambda_E > \lambda_c$). Therefore, osmotic rupturing was predicted. Experimentally, because of osmotic rupturing, pseudo-zero-order release kinetics preceded by a marked burst effect was observed. There-

fore, experimental results agreed with the theoretical prediction.

EXTENT OF EQUILIBRIUM SWELLING

PHEMA-EVAc Matrices

Theoretically, in equilibrium swelling, the osmotic pressure of the hydrophilic phase should be equal to the retractive pressure of the hydrophobic phase. To predict the extent of equilibrium swelling of the gel, the rubber elongation at the intersection of the osmotic pressure and retractive pressure profiles, λ_E, is needed. The values of λ_E for PHEMA-EVAc matrices which contain 23.7%wt, 33.2%wt and 42.7%wt PHEMA were obtained from Figure 1. Using the relationship between the swelling ratio of the gel, Q_{model}, and the rubber elongation ($Q_{model} = \lambda_E^3$), the swelling ratios of PHEMA gel in PHEMA-EVAc matrices, Q_{model}, were predicted.

In Table 6, the experimental data are compared with the equilibrium swelling ratio of the hydrophilic phase of PHEMA-EVAc matrices based on the model presented in [1], which predicts the extent of equilibrium swelling. The maximum percentage deviation of the predicted swelling ratio from the experimental results for PHEMA-EVAc matrices with different contents of PHEMA was only 8.4%. The predicted equilibrium swelling ratio of the gel is not very sensitive to the PHEMA content, but experimentally, a slight dependence of the swelling ratio on PHEMA content was observed. The high slope in the osmotic pressure profile (Figure 1) causes less sensitivity of the predicted swelling ratio on the PHEMA content. However, the slight changes in the swelling ratio, which are given in Table 6 do not seem to affect the important parameters such as the diffusion coefficient [18]. In another study, by Lopour et al. [19], swelling experiments regarding PHEMA-PDMS composites with different contents of PHEMA were carried out. The equilibrium swelling ratios for PHEMA based on the results of Lopour et al. were also not very sensitive to the PHEMA content. Because Lopour et al. did not report the required parameters, the extent of equilibrium swelling cannot be predicted theoretically. Therefore, a comparison

Table 6. Comparison of equilibrium swelling ratios of PHEMA in PHEMA-EVAc matrices based on the model predicting the extent of equilibrium swelling and the experimental data.

PHEMA Content in Composites (%wt)	Model	Experiment	Error %
23.7	1.750	1.615	8.39
33.2	1.755	1.655	6.05
42.7	1.759	1.692	3.85

could not be made between the data of Lopour et al. and the theoretical predictions of the swelling ratio.

PMAA-PDMS Matrices

In PMAA-PDMS matrices, which contained 3%wt, 5%wt and 10%wt PMAA, equilibrium swelling occurred. The values of λ_E for these matrices were obtained from Figure 4a. Using the relationship between the swelling ratio of the gel, Q_{model}, and λ_E, $(Q_{model} = \lambda_E^3)$, the swelling ratios of constrained PMAA in different matrices were predicted.

Swelling experiments with PMAA-PDMS matrices which contained 3%wt, 5%wt and 10%wt PMAA, with two different particle sizes of PMAA (120-180 μm and 255-350 μm) have been completed.

The predicted equilibrium swelling ratio of the hydrophilic phase was compared with the experimental results in Table 7. The model for predicting the extent of equilibrium swelling cannot account for the particle size and, based on experimental observations, the particle size is not an important parameter in swelling. The maximum percentage deviation of the predicted swelling ratio from the experimental results for PMAA-PDMS matrices with different contents of PMAA was 6.9%.

CONCLUSION

The occurrence of either equilibrium swelling or osmotic rupturing in different matrices was predicted using their respective theoretical criteria. Then, the experimental results were used to validate the theoretical predictions. For PHEMA-EVAc matrices with different PHEMA contents (23.7%wt, 33.2%wt and 42.7%wt), the theoretical criteria for equilibrium swelling versus osmotic rupturing predicts that equilibrium swelling should occur. The results of permeation and release experiments are in agreement with the theoretical prediction. In PHEMA-EVAc matrices, because of equilibrium swelling, Fickian diffusional release kinetics were observed. For PMAA-PDMS matrices, the theoretical criteria for equilibrium swelling versus osmotic rupturing predicts that equilibrium swelling should occur in matrices which contain 3%wt, 5%wt and 10%wt PMAA and osmotic rupturing should occur

when the PMAA content is 19%wt, 23.7%wt, 28.5%wt. 33.2%wt or 38%wt. The results of permeation and release experiments are also in agreement with the theoretical prediction. In PMAA-PDMS matrices, which contained 19%wt, 23.7%wt, 28.5%wt, 33.2%wt and 38%wt PMAA, because of osmotic rupturing, pseudo-zero-order release kinetics preceded by a marked burst effect were observed.

To validate the model for predicting the extent of equilibrium swelling, swelling experiments with PHEMA-EVAc matrices which contained 23.7%wt, 33.2%wt and 42.7%wt PHEMA, and PMAA-PDMS matrices which contained 3%wt, 5%wt and 10%wt PMAA were conducted. For the presented model, which predicts the extent of equilibrium swelling, the maximum percentage deviation of the swelling ratio compared to the experimental results was only 8.4%.

NOMENCLATURE

C_s^*	mobile electrolyte concentration in the external solution
E	Young modulus
G	shear modulus
M_c	molecular weight between cross-links
M_n	number average molecular weight before cross-linking
M_r	molecular weight of the monomer repeating unit
n	exponent in the time dependence
N	number of links per chain
P	retractive pressure of the hydrophobic polymer
P_c	critical value for the retractive pressure of the hydrophobic polymer
R	ideal gas constant
t	release time
T	temperature
V_1	molar volume of the swelling agent
V_u	molar volume of a structural unit of a polymer
w_i	weight fraction of the ith component in the matrix
z_-	charge of the gel

Table 7. Comparison of swelling ratio of PMAA in PMAA-PDMS matrices based on the model, predicting the extent of equilibrium swelling and the experimental results; φ is the PMAA content in the matrix.

		dp: 255-350 μm		dp: 120-180 μm	
φ	Model	Experiment	Error%	Experiment	Error%
3%	1.99	2.13	-6.89	2.09	-5.11
5%	2.17	2.19	-1.28	2.14	1.31
10%	2.46	2.63	-6.46	2.56	-3.75

χ	Flory polymer-solvent interaction parameter
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, Poisson's ratio
π_{ion}	ionic osmotic pressure
π_{net}	network osmotic pressure
π^*	osmotic pressure of the hydrophilic polymer
σ_y	yield point stress
v	specific volume of the polymer
$v_{s,r}$	$= v_{2,s}/v_{2,r}$
$v_{2,r}$	polymer volume fraction in the relaxed polymer
$v_{2,s}$	polymer volume fraction in the swollen gel

REFERENCES

1. Abdekhodaie, M.J. and Cheng, Y.L. "Drug release mechanisms from composite matrices. I. Theoretical issues", *J. of Scientia Iranica*, **91**, Sharif university of technology, Tehran, Iran.

2. Peppas, N.A., Moynihan, H.J. and Lutch, L.M. "The structure of highly cross-linked poly (2-hydroxyethyl methacrylate) hydrogel", *J. Biomedical Material Research*, **19**, pp 397-411 (1985).

3. Sefton, M.V. and Nishimura, E. "Insulin permeability of hydrophilic polyacrylate membranes", *J. Pharm. Sci.*, **69**, pp 208-209 (1980).

4. Peppas, N.A., Moynihan, H.J. and Lutch, L.M. "The structure of highly cross-linked poly (2-hydroxyethy methacrylate) hydrogel", *J. Biomed. Mat. Res.*, **19**, p 397 (1985).

5. Janacek, J. and Hasa, J. "Structure and properties of hydrophilic polymers and their gels; VI equilibrium deformation behavior of PHEMA and PHEMA networks prepared in the presence of a diluent and swollen with water", *Col. Czech. Chem. Commun.*, **31**, p 2186 (1966).

6. Migliaresi, C., Nicodemo, L., Nicolais, L. and Passerini, P. "Physical characterization of PHEMA gel", *J. Biomed. Mater. Res.*, **15**, p 307 (1981).

7. Ward, I.M., Ed., *Mechanical Properties of Solid Polymers*, Wiley Interscience, NY, p 278 (1971).

8. Williams, J.G., Ed., *Stress Analysis of Polymers*, Longman, London, UK, p 64 (1973).

9. McCrum, N.G., Buckley, C.P. and Bucknall, C.B., Eds., *Principles of Polymer Engineering*, Oxford University Press, NY, p 177 (1986).

10. Crank, J., *The mathematics of Diffusions*, 2nd Ed., Clarendon press, Oxford, p 50 (1975).

11. Peppas, N.A. and Merrill, E.W. "PVA hydrogels: Reinforcement of radiation cross-linked network by crystallization", *J. Polym. Sci.: Chem.*, **14**, p 441 (1976).

12. Hasa, J., Ilavsky, M. and Dusek, K. "Deformational, swelling, and potentiometric behavior of ionized poly (methacrylic acid) gels: I. Theory", *J. Polym. Sci.*, **13**, p 253 (1975).

13. Hasa, J. and Ilavsky, M. "Deformational, swelling, and potentiometric behavior of ionized poly (methacrylic acid) gels: II. Experimental results", *J. Polym. Sci.*, **13**, p 263 (1975).

14. Katchalsky, A. and Micheli, I. "Polyelectric gels in salt solutions", *J. Polym. Sci.*, **15**, p 69 (1955).

15. Brannon-Peppas, L. and Peppas, N.A. "Equilibrium swelling behavior of dilute ionic hydrogels in electrolytic solutions", *J. Controlled Release*, **16**, p 319 (1991).

16. Schirrer, R. and Thepin, P. "Water absorption, swelling, rupture and salt release in salt-silicon rubber compounds", *J. Material Sci.*, **27**, p 3424 (1992).

17. Amsden, B.G., Cheng, Y.L. and Goosen, M.F.A. "A mechanistic study of the release of osmotic agents from elastomeric monoliths", *J. Controlled Release*, **30**(1), p 45 (1994).

18. Korsmeyer, R.W. and Peppas, N.A. "Effect of the morphology of hydrophilic elastomeric matrices on the diffusion and release of water soluble drugs", *J. Membrane Sci.*, **9**, p 211 (1981).

19. Lopour, P., Vodracek, P., Janatova, V., Sulc, J. and Vacik, J. "Silicone rubber-hydrogel as polymeric biomaterials: II. Hydrophilicity and permeability to water-soluble low-molecular-weight compounds", *Biomaterials*, **11**, p 37 (1990).