Permeation of Drug and Swelling Agent Through Polymeric Membranes

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The permeation of drug (benzocaine) and swelling agent (ethanol) through the polymeric [poly(ethylene-co-vinylacetate) and polyurethane] membranes was investigated theoretically and experimentally. Based on the Flory-Huggins and Yasuda theories, the swelling effect on permeant diffusivity was described by expressing the permeant diffusivity in powers of the activity of the swelling agent. The experimental results suggest that the leading-order term (first order of activity) is accurate enough to describe the diffusivities of benzocaine and ethanol in the poly(ethylene-co-vinylacetate) and polyurethane membranes. The linear dependence of permeant diffusivity on swelling-agent activity was further used to analyze the drug diffusion in a membrane subject to a swelling gradient. With the knowledge of the dependence of benzocaine and ethanol diffusivities on ethanol activity, the activity profile of ethanol across the membrane can be calculated, and the effective diffusivity of benzocaine can then be predicted. Experiments carried out to determine the variation in the effective benzocaine diffusivity corresponding to different swelling gradients agreed well with the calculated results.

Introduction

In a membrane-controlled reservoir system, the drug is usually dissolved in medium and surrounded with a rate-controlling membrane (Baker, 1987). It is well known that the physical and chemical properties of the membrane play important roles in determining the drug release rate (Flynn et al., 1974). Besides, it has also been reported that the medium used to dissolve the drug can also have a dramatic effect on the drug release rate (Theeuwes et al., 1976; Gelotte and Lostritto, 1990).

It is widely accepted that the solution-diffusion model can be used to describe the permeation of drugs through dense (nonporous) membranes (Lee et al., 1985; Wijmans and Baker, 1995). On the basis of this model, the medium can affect the drug permeation either by affecting the drug partition or by influencing the drug diffusion. When there is no interaction between the medium and the membrane (the medium cannot swell the membrane), the effect of medium on drug permeation is mainly contributed by the effect on drug partition (Garret and Chemburkar, 1968; Theeuwes et al., 1976). On the other hand, when the medium contains a swelling agent of the membrane, the effect of medium on drug diffusion would play an important role in determining the drug permeability through the membrane. Investigation on the effect of medium on drug diffusion is the major aim of the present work.

When the medium contains a swelling agent of the membrane, the medium can swell the rate-controlling membrane and can then alter the diffusivity of drugs through the membrane (Peppas, 1984). Generally speaking, a higher degree of swelling results in higher drug diffusivity (Chen and Lostritto, 1996). It is believed that the increase in the drug diffusivity is mainly caused by the increase in free volume due to the swelling effect. On the basis of this point, a theory was proposed by Yasuda et al. (1968) to correlate the relationship between drug diffusivity and the degree of swelling. Peppas and Reinhart (1983) have extended the theory to describe the

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effect of swelling on the drug permeability through cross-linked polymeric membranes. Experimental evidence supporting Yasuda's theory has also been reported (Yasuda et al., 1971; Peppas and Moynihan, 1985; Chen and Lostritto, 1996).

The Yasuda model (Yasuda et al., 1968) describes the effect of swelling in terms of the dependence of permeant diffusivity (D) on the volume fraction of swelling agent in the swollen membrane (H). The Yasuda model can be simplified in the limit of very small H, and a linear dependence of the logarithm of diffusivity ($\ln D$) on H can then be obtained. However, the data presented in this work indicate that the linear dependence of $\ln D$ on H cannot accurately describe the experimental results in the range of $H < 0.2$. The present work suggests that, to obtain a linear relationship, the effect of swelling should be expressed in terms of the relationship between the diffusivity and the activity of the swelling agent (a_E). The relationship between D and a_E can be derived by combining the Yasuda model and the Flory-Huggins theory (Flory, 1953), which has been widely used to describe the relationship between the volume fraction of liquid in the swollen membrane (H) and the activity of the swelling agent (a_E). The dependence of D on a_E will be expressed in powers of a_E. It will be shown that the leading order term (linear term) is accurate enough to describe the experimental data of the dependence of $\ln D$ on a_E. The linear dependence can reduce the numbers of the required parameters for describing the effect of swelling and is more convenient for further calculation.

An application of the relationship between D and a_E is that it can be used to analyze the drug diffusion in a membrane subject to a swelling gradient. In measuring the drug diffusivity through the swollen membrane, the degree of swelling across the membrane should be kept uniform to prevent the nonuniformity of drug diffusivity across the membrane. However, for real application, the drug is released from the reservoir (containing drug medium) to the interstitial fluid, which is basically water. Since both sides of the membrane surface contact solutions with different swelling abilities, the degree of swelling is not uniform and a swelling gradient occurs across the membrane. Under this situation, the degree of membrane swelling and the drug diffusivity are dependent on the position across the membrane. We will show that, with the obtained relationship between the permeant diffusivity and the activity of the swelling agent, the distribution profile of the degree of swelling can be determined and the effective diffusivity of drugs through the membranes subject to the swelling gradient can also be calculated.

The membranes used in the present work were the poly(ethylene-*co*-vinylacetate) (EVAc) and polyurethane (PU) membranes that can swell in ethanol (the volume fraction of ethanol in the swollen membrane is about 0.2). The swelling agent was ethanol, and water was added to adjust the activity of ethanol and the ability to swell. The model drug used was benzocaine. Experiments of uniform swelling were performed by placing solutions with equal ethanol concentration in both donor and receptor cells (see Figure 1). On the other hand, an ethanol solution was placed in the donor cell and water in the receptor cell to generate a swelling gradient. For such a system, we can vary the ethanol concentration in the medium to vary the swelling of the membrane, and the effect of swelling on drug diffusivity can then be studied.

Theoretical Analysis

Determining drug diffusivity in polymeric membranes

The transport of drug (benzocaine) and swelling agent (ethanol) through the polymeric membrane are shown in Figure 2. We only consider the drug flux in the initial period when the drug concentration in the receptor (C_L) is essentially zero. Then, the drug permeation flux (J_D, kg/m^2·s)

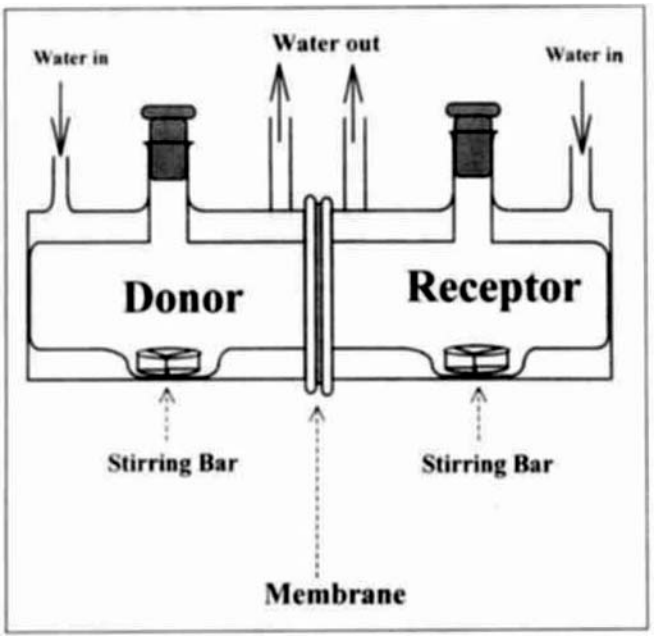

Figure 1. Setup of side-by-side cells .

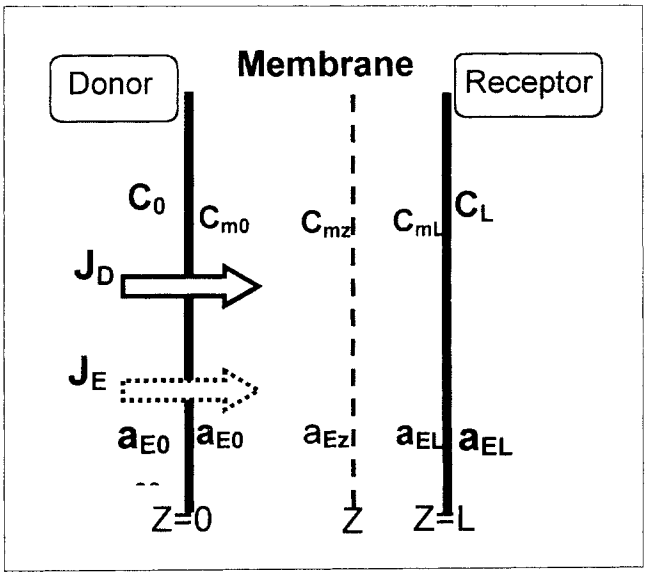

Figure 2. Transport of the drug (benzocaine) and the swelling agent (ethanol) through the polymeric membrane.

through the membrane can be expressed as (Baker, 1987)

$$J_D = \frac{KD_{\text{eff}}}{L} C_0, \tag{1}$$

where D_{eff} (m^2/s) denotes the effective diffusivity of the drug; L (m) represents the membrane thickness; C_0 (kg/m^3) is the drug concentration in the donor cell; and K is the partition coefficient (C_{m0}/C_0). The permeability of the drug through the membrane is defined as $P = KD_{\text{eff}}$. With Eq. 1, the effective diffusivity can be determined by measuring J_D, L, C_0, and K.

The measured effective diffusivity is a bulk averaged property. When the ethanol concentrations in the donor and receptor cells are the same (the case of uniform swelling), the drug diffusivity is independent of the position in the membrane. Therefore, the measured diffusivity is the drug diffusivity for the degree of swelling corresponding to the ethanol composition in the donor and receptor cells. However, when the ethanol concentrations in the donor and receptor cells are different, a distribution of ethanol concentration is developed across the membrane. Hence, the degree of swelling and the drug diffusivity are position-dependent. Obviously, analysis of the transport-of-swelling agent (ethanol) is required to understand the dependence of the diffusivity of the drug (benzocaine) on the position across the membrane and to calculate the effective diffusivity in a membrane subject to a swelling gradient.

Determination of the diffusivity of swelling agent in polymeric membranes

According to Fick's law, the ethanol mass flux through the membrane can be described by

$$J_E = -\frac{\rho_E}{a_E} D_E \frac{da_E}{dZ}, \tag{2}$$

where J_E ($kg/m^2 \cdot s$) is the ethanol flux through the membrane; a_E represents the activity of ethanol; ρ_E (kg/m^3) is the mass concentration of ethanol in the membrane; D_E (m^2/s) denotes the diffusivity of ethanol in the membrane; and Z (m) is the coordinate in the direction across the membrane. The relationship between ρ_E and a_E and J_E is measurable. Then, once the dependence of a_E on Z is known, D_E can be determined.

The dependence of a_E on Z can be determined implicitly as described in the work of Helfferich (1962) and Dinh et al. (1992). The steady ethanol flux (J_{E0}) across a membrane between two solutions of ethanol composition a_{E0} ($Z = 0$) and 0 ($Z = L$) can be obtained by integrating Eq. 2 either from $Z = 0$ to $Z = L$ or from $Z = Z$ to $Z = L$:

$$J_{E0} = \int_0^{a_{E0}} \frac{\rho_E D_E}{a_E L} da_E = \frac{1}{1 - Z/L} \int_0^{a_{EZ}} \frac{\rho_E D_E}{a_E L} da_E, \tag{3}$$

where a_{EZ} is the ethanol activity at position Z. In addition, the term $\int_0^{a_{EZ}} (\rho_E D_E / a_E L) da_E$ is the steady ethanol flux (J_{EZ}) across a membrane with thickness L when the ethanol activity is a_{EZ} in the donor cell and 0 in the receptor cell. Therefore, Eq. 3 can be rewritten as

$$\frac{J_{EZ}}{J_{E0}} = 1 - \frac{Z}{L}, \tag{4}$$

which can be used to determine implicitly the position Z corresponding to where the ethanol activity is a_E. By placing ethanol–water solutions with ethanol activities a_{EZ} and a_{E0} in the donor cell and pure water in the receptor cell, the associated ethanol fluxes J_{EZ} and J_{E0} can be measured. The position Z corresponding to where $a_E = a_{EZ}$ can then be calculated from Eq. 4. Hence, the dependence of a_E on Z can be determined.

Calculating effective diffusivity in a membrane subject to swelling gradient

On the basis of Fick's law, the drug flux through the membrane can be described by

$$J_D = -D_D \frac{dC_m}{dZ}, \tag{5}$$

where C_m (kg/m^3) is the drug concentration in the membrane, and D_D (m^2/s) is the drug diffusivity in the membrane. It should be noted that the use of Eq. 5 requires that the permeant concentration in the membrane be small. The drug concentration (weight percent) in the medium was maintained at 0.005, and the corresponding drug concentration in the membrane was about 0.01. Since the concentration in the membrane is small, the use of Eq. 5 can be justified. However, the ethanol concentration (volume percent) in the membrane can be as high as 0.2, and the assumption of low concentration in the membrane might not be valid. Hence, the ethanol flux is expressed in terms of activity gradient (Eq. 2). Integrating Eq. 5 from $Z = 0$ to $Z = L$ and comparing the result with Eq. 1, we obtain

$$D_{\text{eff}} = \frac{1}{\int_0^1 \frac{1}{D_D} d\left(\frac{Z}{L}\right)} = \frac{1}{\int_0^1 \frac{1}{D_D \frac{da_E}{d(z/L)}} da_E}. \tag{6}$$

The dependence of D_D on a_E can be determined by using the data from experiments of uniform swelling. In addition, by assuming that the transport of ethanol is not influenced by the existence of drugs, the dependence of a_E on Z can be determined by using Eq. 4 after the ethanol fluxes corresponding to various ethanol activity in the donor cell are measured. Then, the effective diffusivity can be calculated by Eq. 6.

Modeling permeant diffusivity dependence on swelling agent activity

It has been shown (Chen and Lostritto, 1996) that the dependence of the benzocaine diffusivity on the volume frac-

tion of swelling agent in the swollen EVAc membrane can be well described by the Yasuda's free-volume theory (Yasuda, 1968):

$$\ln D = \ln D_\infty - \frac{b(1-a)x}{1+ax}, \tag{7}$$

where $x = (1-H)/H$; H is the volume fraction of the swelling agent in the swollen polymeric membrane; D_∞ is the drug diffusivity when $H \to 1$; a represents the ratio of the free volume in the dry membrane (V_{fm}) to that in the swelling agent (V_{fL}); and b denotes the ratio of the characteristic volume of drug (V_D^*) to the free volume in the swelling agent (V_{fL}).

In addition to Eq. 7, an equation describing the relationship between H and a_E is needed to determine the dependence of D on a_E. It is widely accepted that the absorption of liquid into polymer can be described by the Flory-Huggins theory (Flory, 1953). The original Flory-Huggins theory was developed for the binary system and has been extended to the ternary system by Tompa (1956). In our system, three components are involved in the swelling process (assuming that the drug has no effect on membrane swelling): polymer, ethanol, and water. Hence, it requires use of the extended Flory-Huggins theory. To simplify the analysis, the following assumption is made. The membranes used in this work are only a little swollen in water, indicating that the polymer is hydrophobic. Due to the hydrophobicity of the polymer, the water concentration in the swollen membrane is very low. Then, in the swollen membrane, most liquid contained in the membrane is ethanol; hence, the volume fraction of the swelling agent can be approximated by the volume fraction of ethanol contained in the membrane. Therefore, the swollen membrane can be treated as a binary system. By using the Flory-Huggins theory, the relationship between the volume fraction of ethanol and the activity of ethanol can be expressed as

$$\ln a_E = \ln H + 1 - H + \chi(1-H)^2, \tag{8}$$

where χ is the interaction parameter between polyurethane and ethanol. With Eqs. 7 and 8, the relationship between the drug diffusivity and the ethanol activity can be obtained. Similarly, the relationship between the ethanol diffusivity (D_E) and the ethanol activity (a_E) can also be modeled by using the Flory-Huggins and the Yasuda theories as described earlier.

Approximate solution of permeant diffusivity dependence on swelling agent activity

On the basis of Eq. 7, the diffusivity of permeant in the dry membrane (membrane does not swell at all, $H \to 0$, $x \to \infty$) can be expressed as

$$\ln D_m = \ln D_\infty - \frac{b(1-a)}{a}, \tag{9}$$

where D_m represents the diffusivity of permeant in the dry membrane. With Eqs. 7 and 9 and $x = (1-H)/H$, the following equation can be obtained:

$$\ln \frac{D}{D_m} = \frac{b}{a}\frac{H(1/a-1)}{1+H(1/a-1)}. \tag{10}$$

The preceding equation can be written in terms of the power series of H

$$\ln \frac{D}{D_m} = \frac{b}{a}(1/a-1)H[1-(1/a-1)H+\cdots]. \tag{11}$$

In the preceding equation, the ratio of the second-order term to the first-order term is $(1/a-1)H$. When $(1/a-1)H$ is small, higher-order terms are negligible and a linear dependence of $\ln D$ on H can be obtained.

When H is very small, Eq. 8 can be approximated by $H = e^{-(1+\chi)}a_E$. Hence, $e^{-(1+\chi)}$ must be small to make H small. When H is not very small, higher-order terms of $e^{-(1+\chi)}$ are needed to describe the dependence of H on a_E. By using ϵ to represent $e^{-(1+\chi)}$, the expansion of H can be expressed as

$$H = H_1\epsilon + H_2\epsilon^2 + \cdots \tag{12}$$

By substituting Eq. 12 into Eq. 8, expanding the equation in powers of ϵ, and equating the terms with the same power of ϵ, the solutions of H_1 and H_2 can be obtained. Then Eq. 12 can be written as

$$H = a_E\epsilon + (1+2\chi)a_E^2\epsilon^2 + \cdots \tag{13}$$

Substituting the preceding equation into Eq. 10, it follows that

$$\ln \frac{D}{D_m} = \frac{b}{a}(1/a-1)\epsilon a_E\{1-[(1/a-1)-(1+2\chi)]\epsilon a_E + \cdots\}. \tag{14}$$

In the preceding equation, the ratio of the second-order term to the first-order term is $[(1/a-1)-(1+2\chi)]\epsilon a_E$. When $[(1/a-1)-(1+2\chi)]\epsilon a_E$ is small, higher-order terms are negligible and a linear dependence of $\ln D$ on a_E can be obtained.

The condition required to obtain a linear dependence of $\ln D$ on H is that $(1/a-1)H$ be small, and the condition for linear dependence of $\ln D$ on a_E is that $[(1/a-1)-(1+2\chi)]\epsilon a_E$ be small. Since $(1/a-1)-(1+2\chi)$ is smaller than $(1/a-1)$ and ϵa_E is smaller than H (see Eq. 13), it is easier to obtain a linear dependence by expressing $\ln D$ in terms of a_E than in terms of H. Experimental evidence supporting this point is provided in the present work.

Model the effective diffusivity in a membrane subject to swelling gradient

We will show later that the relationship between the activity of ethanol and the diffusivities of benzocaine and ethanol in the EVAc and PU membranes can be accurately described by linear equations. On the basis of Eq. 14, the dependence

of benzocaine diffusivity on ethanol activity can be approximated by $D_D = D_{Dm}e^{\gamma_D a_E}$, where $\gamma_D = (b/a)(1/a - 1)e^{-(1+\chi)}$. On the basis of Eq. 9, D_{Dm} is the diffusivity of benzocaine in the dry (nonswollen) membrane. However, from Eq. 14, D_{Dm} can be interpreted as the diffusivity of benzocaine at $a_E = 0$ (pure water). Since the membranes we used (EVAc and PU) have a very low degree of swelling in water (see Tables 2 and 4), the diffusivity in water-swollen membrane should be very close to that in the dry membrane; hence, we assume they are the same. Similarly, the relationship between ethanol diffusivity and ethanol activity can be written as $D_E = D_{Em}e^{\gamma_E a_E}$, where $\gamma_E = (b_E/a)(1/a - 1)e^{-(1+\chi)}$, D_E is the ethanol diffusivity in the swollen membrane, and D_{Em} is the ethanol diffusivity in the dry membrane. The ratio of the characteristic volumes of benzocaine (V_D^*) and ethanol (V_E^*) to the free volume in the swelling agent (V_{fL}) is denoted by b and b_E.

Following the assumption that most liquid contained in the swollen membrane is ethanol, the relationship between ρ_E and H can be expressed as $\rho_E = d_E H$, where d_E is the density of ethanol. For simplicity, in the following calculation, we only consider the drug transport in the PU membrane, in which the relationship between H and a_E can be described as a linear function $H = \beta a_E$ (see Figure 8). With the preceding relationships and $D_E = D_{Em}e^{\gamma_E a_E}$, Eq. 2 can be written as

$$J_E = -P_{Em}e^{\gamma_E a_E}\frac{da_E}{dZ}, \tag{15}$$

where $P_{Em} = \beta d_E D_{Em}$. Integrating Eq. 15 from $Z = Z(a_E = a_{EZ})$ to $Z = L(a_E = 0)$ gives

$$J_E\left(1 - \frac{Z}{L}\right) = \frac{P_{Em}}{\gamma_E L}(e^{\gamma_E a_{EZ}} - 1). \tag{16}$$

By using the condition that at $Z = 0$ $a_{EZ} = a_{E0}$ (the ethanol activity in the donor cell), it can be derived that $J_E = P_{Em}(e^{\gamma_E a_{E0}} - 1)/(\gamma_E L)$. Substituting this relationship into Eq. 16, it follows that

$$a_{EZ} = a_{E0} + \frac{1}{\gamma_E}\ln\left[(1 - e^{-\gamma_E a_{E0}})\left(1 - \frac{Z}{L}\right) + e^{-\gamma_E a_{E0}}\right], \tag{17}$$

which can be used to describe the distribution of ethanol activity across the membrane. Differentiating a_{EZ} with respect to Z and expressing the results in terms of a_{EZ}, we can obtain the dependence of da_{EZ}/dZ on a_{EZ}. Plugging this relationship and $D_D = D_{Dm}e^{\gamma_D a_E}$ into Eq. 6, one can obtain

$$D_{\text{eff}} = D_{Dm}\left(1 - \frac{\gamma_D}{\gamma_E}\right)\frac{1 - e^{\gamma_E a_{E0}}}{1 - e^{(\gamma_E - \gamma_D)a_{E0}}}, \tag{18}$$

which can calculate the relationship between the drug effective diffusivity and the activity of ethanol in the donor cell.

Experimental Studies

Preparation of membranes

The EVAc polymer was purchased from the Aldrich Company, and the content of vinyl acetate in the copolymer is 40%. The polyurethane polymer was synthesized by 4,4-dicyclohexylmethane diisocyanate (H_{12}MDI; Mobay Co.), hydroxyl-terminated polybutadiene (HTPB; ARCO Co.), and 1,4-butanediol (1,4-BD; Merck Co.), under the catalysis of dibutylzinn-dilaurat (DBTDL; Merck Co.). One can refer to the work of Huang and Lai (1995) for more details of the synthesis process. A dry process (Mulder, 1991) was used to fabricate the membranes. The casting solutions were prepared by dissolving 5 g of EVAc in 45 g of chloroform, and dissolving 5 g of PU in 62.5 g of chloroform. The homogeneous solutions were kept at room temperature for 24 h and were then cast on glass plates to a predetermined thickness of 500 μm with a Gardner knife. Next, the casting films were put in an oven at 60°C for 24 h to remove the remaining solvent. On the basis of the SEM analysis, the prepared membranes are homogeneously dense and the membrane thickness ranges from 35 μm to 45 μm for the PU membrane, and 30 μm to 40 μm for the EVAc membrane.

Measurement of drug permeation rate

Side-by-side cells (Figure 1) were used to measure the benzocaine permeation rate through the polyurethane membrane. The volume of the donor and receptor cells is 13 mL, and the permeation area is 2.9 cm^2. Both cells were well stirred by magnetic bars and were temperature-controlled at 37°C. The initial benzocaine concentration in the donor cell is 0.5 wt. %, and there is no benzocaine in the receptor cell initially. Membranes were swollen in the medium and clamped between the donor and receptor cells. Samples in the receptor were taken at different times to determine the time dependence of the benzocaine concentration in the receptor. The concentration of benzocaine was assayed spectrophotometrically at 292 nm. After the measurement of benzocaine concentration, the cumulative amount of benzocaine per unit area in the receptor (Q) can be calculated. Then, the drug permeation flux can be determined by differentiating Q with respect to time.

Measurement of ethanol permeation rate

Similarly, we used side-by-side cells to measure the ethanol permeation rate. Ethanol–water solutions with various ethanol compositions were placed in the donor cell and pure water was put in the receptor cell. Samples in the receptor were taken at different times to determine the time dependence of the ethanol concentration in the receptor. The concentration of ethanol was assayed by gas chromatography (China Chromatography, GC-8700T). The cumulative amount of ethanol per unit area in the receptor can be calculated and the permeation flux of ethanol can then be determined.

Partition coefficient between membrane and medium

Benzocaine was dissolved in an ethanol–water solution containing various ethanol concentration (10, 20, 35, 47, 65, 80 and 95 wt. %). The benzocaine concentration was kept at 0.5 wt. %. Discs of membrane were immersed in a large volume of benzocaine solution, which was temperature controlled at 37°C. After waiting for 24 h to let the drug parti-

tion between the medium and the membrane reach equilibrium, the membranes were removed from the solution and were rinsed with 95 wt. % of ethanol to remove the benzocaine on the membrane surface. The benzocaine contained in the polyurethane membranes was then extracted from the membrane by immersing the membranes in a fresh ethanol solution (95 wt. %) for 24 h. To make sure that the benzocaine was completely removed from the membrane, the membranes were immersed in a second bath of fresh ethanol solution for another 24 h. The amount of benzocaine in the membrane could then be calculated from the volume of the extract and the associated concentration. The partition coefficient could be obtained by calculating the ratio of the drug concentration equilibrium in the membrane to the drug concentration equilibrium in the solution.

Swelling of membranes

Dry membranes were weighed first and were then immersed in the ethanol–water solutions. After 24 h, the swollen membranes were removed from the solution, quickly blotted dry on the surface, and weighed. To make sure that 24 h were enough for the swelling experiment to reach equilibrium, data from swelling for 48 h were also obtained. No detectable difference between the data from the 24- and 48-h experiments was observed. The volume fraction of the medium in the swollen membrane can then be calculated by

$$H = \frac{\dfrac{(W_s - W_d)}{d_E}}{\dfrac{W_d}{d_P} + \dfrac{(W_s - W_d)}{d_E}}, \qquad (19)$$

where W_s and W_d represent the weight of swollen and dry membranes, and d_P and d_E represent the densities of polymer and ethanol. The density of ethanol is 0.78 g/mL. The densities of EVAc and PU membranes are 1.00 and 0.99 g/mL, respectively.

Experimental Results vs. Theoretical Analysis

Swelling of EVAc membranes

First, media containing different ethanol compositions (0, 10, 20, 35, 47, 65, 80 and 95 wt. %) were prepared. The EVAc membrane was immersed in these media and the volume fraction of liquid in the swollen membrane was measured. The results are presented in Figure 3. It can be seen that the volume fraction of liquid in the swollen membrane increases with increasing ethanol concentration. It should be noted that in Figure 3 the composition of ethanol is expressed in terms of ethanol activity. The activity was determined by using the vapor–liquid equilibrium data of the ethanol–water solution. It can also be seen from Figure 3 that the EVAc membrane almost cannot swell in water, indicating that the EVAc membrane is hydrophobic.

Due to the hydrophobicity of the EVAc polymer, it is reasonable to assume that most liquid contained in the swollen membrane is ethanol; therefore, the relationship between the volume fraction of ethanol and the activity of ethanol can be described by the original Flory-Huggins theory. By taking $\chi = 1.3$, the dependence of the volume fraction of ethanol on the activity of ethanol can be calculated from Eq. 8, and the results are presented in Figure 3. It can be seen that the theoretical calculation agrees well with the experimental measurement.

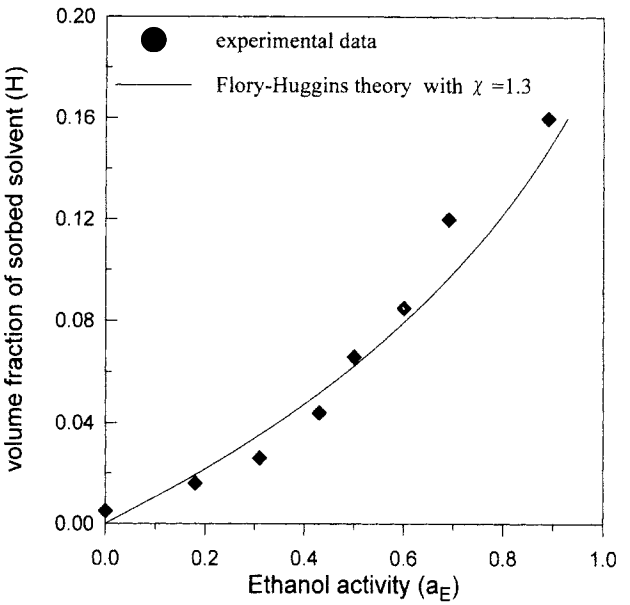

Figure 3. Dependence of the volume fraction of medium in the swollen membrane (H) on the activity of ethanol (a_E) in the EVAc membrane.

Dependence of benzocaine diffusivity on membrane swelling in EVAc membranes

Benzocaine was dissolved in media containing different ethanol compositions, and the drug solutions were placed in the donor cell. The receptor cell was filled with medium containing the same ethanol composition as that in the donor cell, but without benzocaine. The results of the drug accumulation in the receptor cell are plotted vs. time, as shown in Figure 4. The initial slopes of the lines depicted in Figure 4 are the initial drug fluxes corresponding to different ethanol compositions in the medium. With the drug flux, the initial drug concentration in the donor cell, and the membrane thickness, the permeability can be calculated by using Eq. 1. The calculated permeabilities corresponding to different ethanol activity in the medium are presented in Table 1. It can be seen that the permeability of benzocaine does not increase monotonously with increasing ethanol concentration in the medium. A minimum occurs at the ethanol concentration of about 47 wt. %. This observation can be accounted for by the competition between swelling and partition (Wang et al., 1998). Because the benzocaine is a hydrophobic drug, its solubility in the medium increases with increasing ethanol concentration. Therefore, the partition coefficient decreases accordingly. On the other hand, the degree of membrane swelling and the drug diffusivity increase with increasing ethanol concentration. The effects of increasing ethanol concentration on partition and on diffusion have an opposite ef-

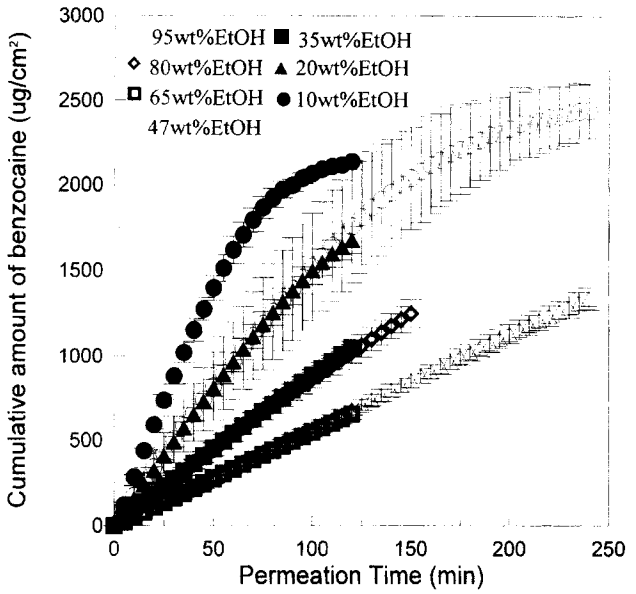

Figure 4. Time dependence of the cumulative amount of benzocaine in the receptor cell for media with various ethanol concentrations (EVAc membranes).

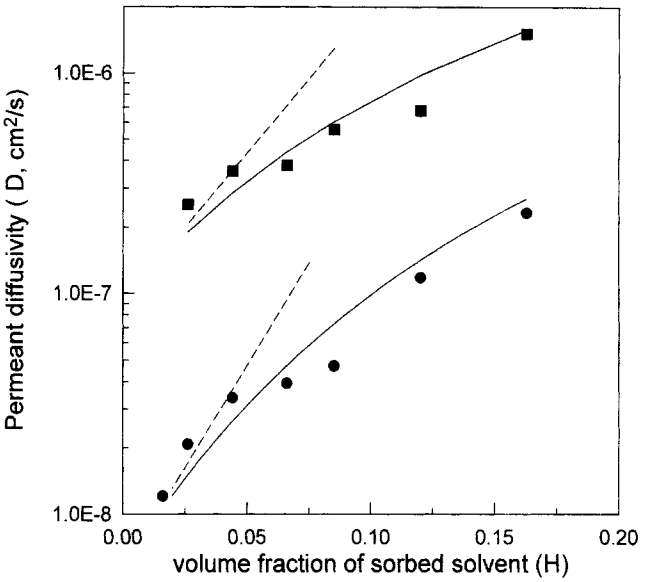

Figure 5. Dependence of the diffusivities of benzocaine (D_D) and ethanol (D_E) on the volume fraction of the medium in the swollen membrane (H) in the EVAc membrane.

● Experimental measurement of D_D; —— Yasuda model (Eq. 10, with $D_m = 5.7\times10^{-9}$ cm²/s, $a = 0.17$, and $b = 1.49$); --- linear approximation for Yasuda model (ln $D = -19.0 + 42.8H$). ■ Experimental measurement of D_E, —— Yasuda model (Eq. 10, with $D_m = 9.2\times10^{-8}$ cm²/s, $a = 0.17$ and $b = 1.08$); --- linear approximation for Yasuda model (ln $D = -16.2 + 31.1H$).

fect. Since the permeability is the product of the partition coefficient and diffusivity, the competition between the increasing diffusivity and the decreasing partition coefficient results in the observation discussed earlier.

To calculate the drug diffusivity, we need the information about the partition coefficient of benzocaine between the membrane and the medium. The partition coefficients corresponding to different ethanol activities were measured, and the results are shown in Table 1. With the results of the permeability and the partition coefficient, the diffusivity of benzocaine in the polyurethane membrane can be calculated by using the solution-diffusion model ($P = K * D_{\text{eff}}$). The relationship between the diffusivity and the volume fraction of the medium in the swollen EVAc membrane is depicted in Figure 5.

By taking $D_m = 5.7\times10^{-9}$ cm²/s, $a = 0.17$, and $b = 1.49$, it can be seen from Figure 5 that the Yasuda model (Eq. 11) can well describe the experimental results. On the basis of the preceding parameters, the diffusivity of benzocaine at $H \to 1$ ($D_{D\infty}$, the diffusivity in the swelling agent) can be calculated, and the result is $D_{D\infty} = 8\times10^{-6}$ cm²/s. It should be noted that the same system (benzocaine in EVAc membrane and the swelling agent is ethanol–water solution) has been investigated by Chen and Lostritto (1996). The parameters they obtained are $D_{D\infty} = 7\times10^{-6}$ cm²/s, $a = 0.084$, and $b = 0.65$. Our $D_{D\infty}$ value is similar to the value reported in the literature, but the values of a and b are higher than those reported. The discrepancy could stem from the difference in the system temperature between the work of Chen and Lostritto (1996) (25°C) and the present work (37°C).

Table 1. Ethanol Concentration Effect on Benzocaine Transport through EVAc Membranes

Ethanol Conc. (wt. %)	Activity of Ethanol	Permeability $\times10^{-8}$ (cm²/s)	Partition Coeff.	Effective Diffus. $\times10^{-8}$ (cm²/s)
95	0.89	22.02	0.94	23.36
80	0.69	11.89	1.01	11.81
65	0.60	7.03	1.49	4.70
47	0.50	7.00	1.78	3.95
35	0.43	11.28	3.33	3.38
20	0.31	20.24	9.74	2.08
10	0.18	34.31	28.32	1.21

Benzocaine: 0.5 wt. %; $n \geq 4$.

Dependence of benzocaine diffusivity on ethanol activity in EVAc membranes

By using the data presented in Figures 3 and 5, the relationship between the diffusivity of benzocaine and the activity of the swelling agent (ethanol) can be obtained, and the results are depicted in Figure 6. It can be seen that the logarithm of the diffusivity of benzocaine increases linearly with increasing a_E. The result suggests that only the first term in Eq. 14 is needed to describe the dependence of the diffusivity of benzocaine on the ethanol activity.

On the basis of the parameters obtained from Figures 3 and 5 ($\chi = 1.3$, $D_m = 5.7\times10^{-9}$ cm²/s, $a = 0.17$ and $b = 1.49$), the linear dependence of ln D on H in the limit of small H can be expressed as ln $D = -19.0 + 42.8\ H$ (from Eq. 11), and the linear dependence of ln D on a_E can be written as ln $D = -19.0 + 4.2\ a_E$ (from Eq. 14). These two linear equations

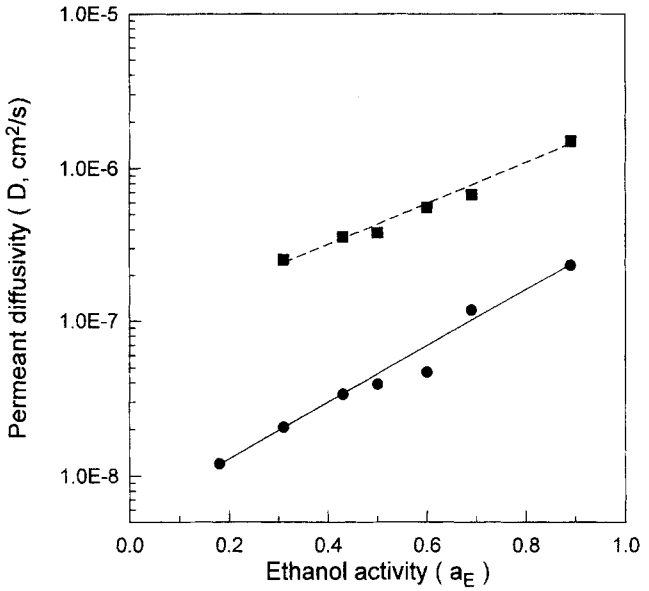

Figure 6. Dependence of the diffusivities of benzocaine (D_D) and ethanol (D_E) on the activity of ethanol in the membrane (a_E) in the EVAc membrane.

● Experimental measurement of D_D; —— theoretical calculation ($\ln D = -19.0 + 4.2a_E$). ■ Experimental measurement of D_E; --- theoretical calculation ($\ln D = -16.2 + 3.1a_E$).

are plotted in Figures 5 and 6, respectively. It can be seen that the linear equation can accurately describe the data presented in Figure 6, but can only match the data in the range of $H < 0.05$ in Figure 5. On the basis of the discussion in the section on theoretical analysis, the ratio of the second-order term to the first-order term in the dependence of $\ln D$ on H is $(1/a-1)H$ (Eq. 11), and is $[(1/a-1)-(1+2\chi)]e^{-(1+\chi)}a_E$ in the dependence of $\ln D$ on a_E (Eq. 14). The maximum H in the system of EVAc is about 0.17 and the maximum a_E is 0.89. By using these values and the values of χ, D_m, a, and b, it can be estimated that the error of neglecting the second-order term is 83% in the dependence of $\ln D$ on H and is 11% in the dependence of $\ln D$ on a_E. The preceding analysis can account for why nonlinear dependence is required for the dependence of $\ln D$ on H, while linear dependence can be obtained for $\ln D$ on a_E.

Dependence of ethanol diffusivity on swelling ratio and on ethanol activity in EVAc membranes

Experiments on the permeation of ethanol through the EVAc membrane were performed. Ethanol–water solutions with various ethanol compositions (20, 35, 47, 65, 80, and 95 wt. %) were placed in the donor cell and pure water was put in the receptor. The corresponding ethanol flux was measured and the results are presented in Table 2. With these data the activity profile of ethanol across the EVAc membrane can be calculated by Eq. 4, and the results are also presented in Table 2. The activity profile can be well fitted by $a_{EZ} = 0.89 + (1/3.1)\ln[(1-(Z/L)) + 0.063]$. Differentiating this equation, and expressing the results in terms of a_E, we obtain

$$\frac{da_{EZ}}{d(Z/L)} = -\frac{1}{3.1}e^{3.1(0.89-a_{EZ})},$$

which can be used to calculate the activity gradient corresponding to various activities in the membrane. By accepting the assumption that most liquid contained in the swollen membrane is ethanol, the relationship between ρ_E and H can be expressed as $\rho_E = d_E H$, where d_E is the density of ethanol. The relationship between H and a_E was presented in Figure 3. In addition, the ethanol flux (J_E) through the EVAc membrane was measured as 51.8 mg/(cm^{2}h) [ethanol activity is 0.89 (95 wt. % of ethanol) in the donor cell and 0 (pure water) in the receptor cell]. Substituting the preceding relationships and

$$\frac{da_{EZ}}{d(Z/L)} = -\frac{1}{3.1}e^{3.1(0.89-a_{EZ})}$$

into Eq. 2, the diffusivity of ethanol can be calculated, and the results are presented in Table 2 and depicted in Figures 5 and 6.

Table 2. Ethanol Activity Dependence on the Position in EVAc Membranes

a_E	H	J_E (mg/cm^2 × h)	Z/L	D_E × 10^{-6} (cm^2/s)
0.89	0.163	51.77	0	1.52
0.69	0.120	31.31	0.40	0.68
0.60	0.085	16.23	0.69	0.56
0.50	0.066	10.44	0.80	0.38
0.43	0.044	8.26	0.84	0.36
0.31	0.023	3.89	0.92	0.25
0	0	0	1.00	—

$n \geq 4$.

The dependence of ethanol diffusivity on the swelling ratio (H) presented in Figure 5 can be well described by the Yasuda model (Eq. 10) with $D_m = 9.2\times10^{-8}$ cm^2/s, $a = 0.17$, and $b = 1.08$. The fitted parameter D_m is close to the value (6×10^{-8} cm^2/s) obtained in the work of Dinh et al. (1992). Our result is larger than the reported value for two reasons: the polymer has a higher vinyl acetate content (40% in this work and 37% in Dinh et al.) and the system temperature is higher (37°C in this work and 32°C in Dinh et al.). Parameter a represents the ratio of the free volume in the dry membrane (V_{fm}) to that in the swelling agent (V_{fL}). Hence, the value of a should be independent of the permeant. The fitted values of a for both systems of benzocaine and ethanol are the same ($a = 0.17$), indicating that the results are quite reasonable. Besides, b denotes the ratio of the characteristic volume of drug (V_D^*) to the free volume in the swelling agent (V_{fL}). Hence, the obtained b value for the permeation of benzocaine should be larger than for the permeation of ethanol, since the molecular weight of benzocaine (165 g/mol) is larger than that of ethanol (46 g/mol). The b value obtained is 1.49 for benzocaine and 1.08 for ethanol, which is consistent with the earlier discussion.

Table 3. Ethanol Concentration Effect on Transport of Benzocaine through PU Membranes

Ethanol Conc. (wt. %)	Activity of Ethanol	Permeability $\times 10^{-8}$ (cm^2/s)	Partition Coeff.	Effective Diffus. $\times 10^{-8}$ (cm^2/s)
95	0.89	15.9	1.37	11.64
80	0.69	3.28	1.50	2.19
65	0.60	2.43	1.39	1.75
47	0.50	1.58	1.98	0.80
35	0.43	1.59	3.2	0.50
20	0.31	3.19	11.0	0.29
10	0.18	4.48	34.4	0.13

Benzocaine: 0.5 wt. %; $n \geq 4$.

From Figures 5 and 6, it can be seen that the linear relationship can well describe the dependence of ln D on a_E, but cannot accurately describe the dependence of ln D on H, which is similar to the behavior of benzocaine. By using the fitted parameters $\chi = 1.3$, $D_m = 9.2 \times 10^{-8}$ cm^2/s, $a = 0.17$, and $b = 1.08$, it can be estimated that the contributions of the second-order terms in Eqs. 11 and 14 are 83% and 11%, respectively. Hence, neglecting the second-order term would not introduce much error on the dependence of ln D on a_E, but would have a dramatic effect on the dependence of ln D on H. By using the parameters just listed, and neglecting the second-order term, Eq. 14 can be written as $\ln D = -16.2 + 3.1 a_E$, which can well describe the experimental data shown in Figure 6.

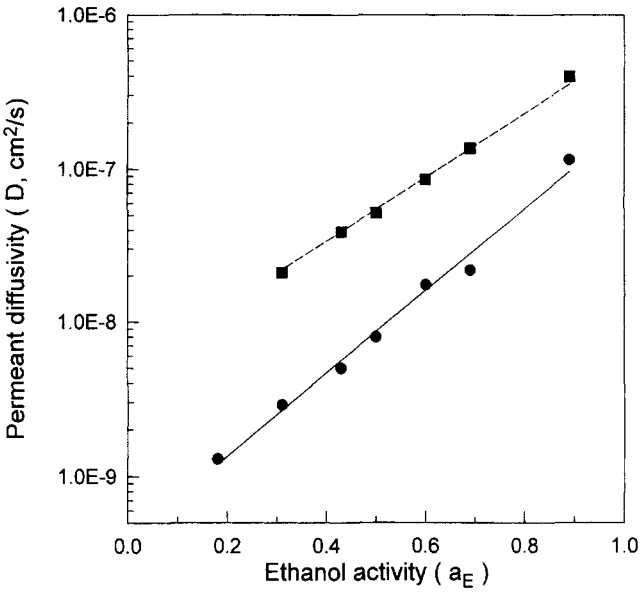

Figure 7. Dependence of the diffusivities of benzocaine (D_D) and ethanol (D_E) on the activity of ethanol in the membrane (a_E) in the PU membrane.

● Experimental measurement of D_D; —— theoretical calculation ($\ln D = -21.6 + 6.0 a_E$). ■ Experimental measurement of D_E; --- theoretical calculation ($\ln D = -19.0 + 4.8 a_E$).

Dependence of diffusivities of benzocaine and ethanol on ethanol activity in polyurethane membranes

On the basis of the previous discussion, it is known that, in EVAc membranes, the dependence of the logarithm of the diffusivity of the permeant on the activity of ethanol can be well described by a linear relationship, as shown in Figure 6. In this section, the diffusion of benzocaine and ethanol in the polyurethane membrane is examined to see if linear dependence between ln D and a_E can still be observed.

Experiments on the permeation of benzocaine and ethanol through the PU membrane were performed. The diffusivities of benzocaine and ethanol in the polyurethane membrane were obtained by using the same procedures discussed earlier for the EVAc membrane. The results are presented in Tables 3 and 4. The dependence of the permeant diffusivity on ethanol activity is shown in Figure 7. It can be seen that the logarithm of the diffusivity of permeants increases linearly with increasing ethanol activity. Obviously, the linear relationship between the permeant diffusivity and the ethanol activity is not limited to the EVAc membrane. It can also apply to the PU membrane.

Table 4. Ethanol Activity Dependence on the Position in PU membrane

a_E	H	J_E (mg/cm^2 $\times$h)	Z/L	D_E $\times 10^{-6}$ (cm^2/s)
0.89	0.189	12.41	0	0.40
0.69	0.164	7.22	0.42	0.14
0.60	0.149	3.59	0.71	0.09
0.50	0.125	1.78	0.86	0.05
0.43	0.102	1.08	0.91	0.04
0.31	0.078	0.41	0.97	0.02
0	0.012	0	1.0	—

$n \geq 4$.

Dependence of permeant diffusivity on membrane swelling in PU membranes

The dependence of permeant diffusivity on ethanol activity in PU membranes can be well described by a linear equation, similar to that of the EVAc membrane. However, the Flory-Huggins and Yasuda theories, which can well describe the swelling and permeation behavior in EVAc membrane, as shown in Figures 3 and 5, cannot reasonably describe the behavior in the PU membrane.

The volume fraction of liquid in the swollen PU membrane was measured, and the results are plotted vs. ethanol activity in Figure 8. It can be seen that the volume fraction of liquid in the swollen membrane increases linearly with increasing ethanol activity. The linear dependence in the limit of small H suggests a value of 0.56 for χ. With $\chi = 0.56$, however, the Flory-Huggins theory (Eq. 8) can only describe the data for $H < 0.05$, but cannot match the data for $H > 0.05$, as shown in Figure 8. On the other hand, by using the data $H = 0.21$ at $a_E = 1$ (swelling in the aqueous solution with 99 wt. % of ethanol), $\chi = 1.24$ can be calculated from Eq. 8. By using $\chi = 1.24$, however, discrepancies between theoretical calculation and experimental data are still observed in Figure 8.

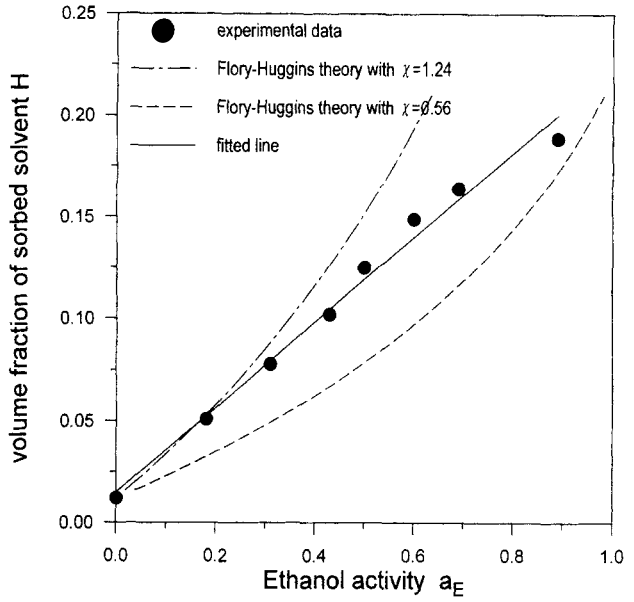

Figure 8. Dependence of the volume fraction of the medium in the swollen membrane (H) on the activity of ethanol (a_E) in the PU membrane.

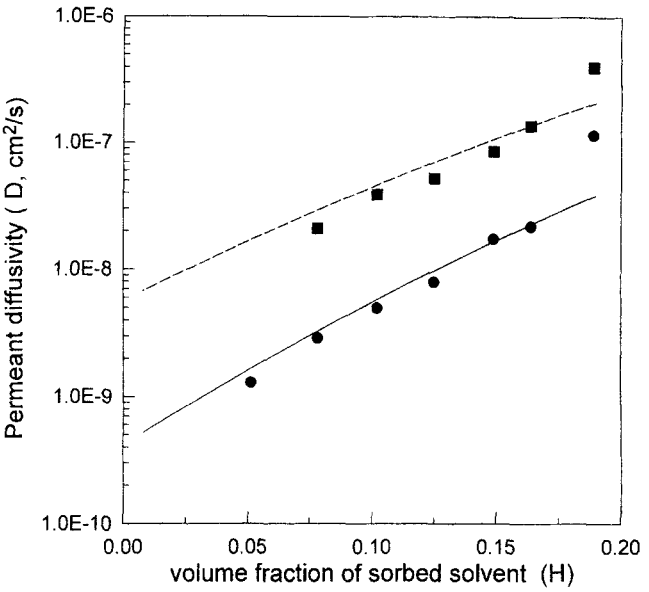

Figure 9. Dependence of the diffusivities of benzocaine (D_D) and ethanol (D_E) on the volume fraction of medium in the swollen membrane (H) in the PU membrane.

● Experimental measurement of D_D; —— Yasuda model (Eq. 10, with $D_m = 4.0\times10^{-10}$ cm²/s; $a = 0.49$, and $b = 13.3$).
■ Experimental measurement of D_E; – – – Yasuda model (Eq. 10, with $D_m = 5.6\times10^{-9}$ cm²/s, $a = 0.49$, and $b = 10.8$).

These discrepancies are believed to originate from the assumption that the swollen membrane contains only polymer and ethanol. In reality, there are three components involved in the swelling process: polymer, ethanol, and water. A detailed discussion in this respect is given in the discussion section.

The dependence of the diffusivities of ethanol and benzocaine on the liquid volume fraction in the swollen membrane is depicted in Figure 9. It can be seen that the logarithm of the diffusivities of benzocaine and ethanol increases linearly with increasing H. By taking that $D_m = 4.0\times10^{-10}$ cm²/s, $a = 0.49$, and $b = 13.3$, the experimental data of the benzocaine diffusivity shown in Figure 9 can be reasonably predicted by using Yasuda theory. With these parameters, however, the calculated $D_{D\infty}$ (the diffusivity in the swelling agent) is 4.8×10^{-4}, which is unreasonably higher than the value reported in the literature ($D_{D\infty} = 7\times10^{-6}$ cm²/s). The previous observation indicates that Yasuda's theory cannot reasonably describe the measured diffusivity in PU membranes. The reason why Yasuda's theory is believed to be invalid is strongly related to the water contained in the swollen PU membrane. A detailed discussion about the validity of the Yasuda theory is given in the Discussion section.

Effective diffusivity of benzocaine in PU membranes subject to swelling gradient

The linear dependence of the logarithm of permeant diffusivity on ethanol activity presented in Figure 7 suggests that the relationship between the benzocaine diffusivity and ethanol activity in the PU membrane can be described by $D_D = 4.0\times10^{-10}e^{6.0a_E}$, and the relationship between the ethanol diffusivity and ethanol activity by $D_E = 5.6\times10^{-9}e^{4.8a_E}$. The linear dependence of the permeant diffusivity logarithm on ethanol diffusivity strongly suggests that the effective diffusivity of benzocaine through the polyurethane membrane subject to a swelling gradient can be described by Eq. 18. To verify the adequacy of Eq. 18, experiments of benzocaine permeation with nonuniform swelling were carried out. Benzocaine was dissolved in media containing various ethanol compositions. The drug solutions were put in the donor cell and pure water was put in the receptor cell. The drug permeation rate corresponding to different ethanol composition in the donor cell was measured and the associated drug permeability was calculated. Then, with the help of the partition coefficients presented in Table 3, the effective diffusivities corresponding to different ethanol activities in the donor cell were determined. The results are shown in Figure 10. It can be seen that the experimental results agree well with the theoretical calculation, indicating that Eq. 18, derived on the basis of the linear dependence of the permeant diffusivity on the activity of the swelling agent, can accurately describe the drug transport through membranes subject to the swelling gradient.

Discussion

In the present work, on the basis of the Flory-Huggins and Yasuda theories, the effect of swelling on permeant diffusivity was described by expressing the permeant diffusivity in powers of the activity of the swelling agent. The experimental results suggest that the leading-order term (first order of the activity of the swelling agent) is accurate enough to describe the diffusivities of benzocaine and ethanol in the EVAc and PU membranes. For the EVAc membrane, the Yasuda theory and the Flory-Huggins theory can well describe the de-

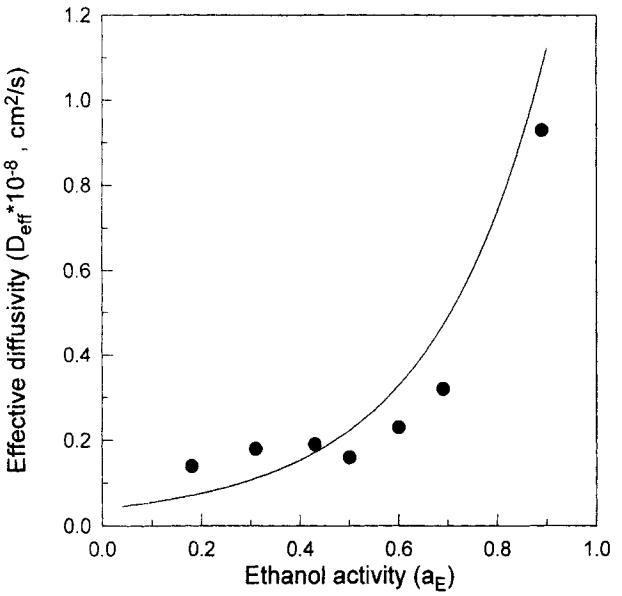

Figure 10. Dependence of the effective diffusivity on the ethanol activity in the donor cell (the ethanol activity in the receptor is zero).

● Experimental measurement; —— theoretical calculation (Eq. 18, with $\gamma_E = 4.8$, $\gamma_D = 6.0$, and $D_{Dm} = 4 \times 10^{-10}$ cm^2/s).

pendence of D on H and the dependence of H on a_E, respectively. Hence, it is reasonable to see that the derived equation (Eq. 14) can describe the dependence of D on a_E. According to the obtained parameters for the Yasuda and Flory-Huggins models, the contribution of the high-order terms in Eq. 14 is small, which can account for the linear dependence of $\ln D$ on a_E. For the PU membrane, although the linear dependence of $\ln D$ on a_E can also be obtained, the Yasuda and Flory-Huggins models cannot reasonably describe the experimental results. For the system that can be well described by the Flory-Huggins and Yasuda theories, the linear dependence of $\ln D$ on a_E can be explained by the analysis presented in the present work. However, for the system in which the Flory-Huggins and Yasuda theories are not valid, it is not clear why the linear dependence of $\ln D$ on a_E can still be obtained.

Since the Flory-Huggins and Yasuda theories are the basis of our theoretical analysis, we discuss the validity of these two models below. The Flory-Huggins theory used in the present work (Eq. 8) is only valid for the binary system. In the swelling experiment, however, there are three components involved in the swelling process: polymer, ethanol, and water. Although the EVAc and PU polymers used in this work are hydrophobic, water can still swell the polymer a little. Swelling of the EVAc membrane in water is very low ($H = 0.005$), and not much error has been introduced by using the Flory-Huggins theory for the binary system (see Figure 3). On the other hand, the swelling ratio of the PU membrane in water ($H = 0.012$) is higher than that of the EVAc membrane, indicating that PU is less hydrophobic than EVAc. Because PU is not so hydrophobic, water may play roles in the swelling process. We have used the extended Flory-Huggins theory developed by Tompa (1956) to describe the equilibrium of the ternary system: PU, ethanol, and water (Young et al., 2000). Good agreement between the theoretical prediction and experimental data can be observed, indicating that the discrepancies shown in Figure 8 do stem from the simplification of a ternary system by assuming that it is binary. The preceding discussion indicates that, although the swelling ratio of PU in water is small (only 1.2%), the role of water in the swelling process is not negligible. However, to use the extended Flory-Huggins theory, a numerical solution is required. Therefore, a detailed discussion is not given here.

Similarly, the validity of using the Yasuda model is also related to the water content in the swollen membrane. The development of the Yasuda model requires the assumption of the additivity of the free-volume contributions of liquid and polymer: $V_f = HV_{fL} + (1 - H)V_{fm}$, where V_f is the free volume in the swollen membrane, V_{fL} represents the free volume in the liquid, and V_{fm} is the free volume in the dry membrane (polymer). In order for this assumption to hold, the specific volumes and molecular weights of the liquid and the polymeric jumping unit should be equal. For organic solvents, it is reasonable to expect that the molecular weight of the solvent is close to that of the polymeric jumping unit, because the polymer is often formed from a monomer that itself is an organic solvent (Vrentas and Duda, 1979). The agreement between the Yasuda model and the experimental data, given in Figure 5, indicates that the assumption of the additivity of free volumes is reasonable for the EVAc membrane. As mentioned earlier, however, for the PU membrane, the water may play roles in the swelling process. For small molecules, like in water, the molecular weight of liquid is smaller than that of the polymeric jumping unit. Hence, the assumption of free-volume additivity might not be valid and the Yasuda model cannot be used to describe the relationship between the permeant diffusivity and the swelling ratio.

Another important assumption made in this work is that the interaction between membrane and drug is assumed to be negligible. If interaction exists between drug and membrane, the drug would influence the membrane swelling. We have compared the swelling ratios of membranes with (0.5 wt. %) and without benzocaine in the medium, and no detectable difference was observed. The effect of drug on membrane swelling might not be negligible when the drug concentration in the medium is high, but it can be neglected in systems presented in the present work, in which the benzocaine concentration is 0.5 wt. %. In addition, if there is interaction between drug and membrane, the diffusivity of the drug would depend on its concentration. We have data showing that there is no detectable difference in the benzocaine diffusivity when the benzocaine concentration in the donor cell is raised from 0.5 wt. % to 1.5 wt. %, indicating that the diffusivity is not sensitive to the change in benzocaine concentration in the range we studied. On the basis of the preceding discussion, it seems reasonable to neglect the interaction between permeant and membrane in our system. Therefore, in the present work, we only considered that dependence of the diffusivity on the activity of the swelling agent, but did not take into account the dependence on the drug concentration.

Besides, it should be noted that we assumed that the relationship between the degree of swelling and the ethanol activity is the same for both uniform and nonuniform swelling. In the case of uniform swelling, the relaxation of polymer

chains due to the swelling effect is uniform across the membrane. On the other hand, in the case of nonuniform swelling, the relaxation of polymer chains is different from position to position. In this case, the local relaxation of polymer chains might be affected by the polymer chains in the neighborhood that have a different relaxation status. Therefore, when the local ethanol activity is the same for both uniform and nonuniform swelling, the local relaxation of polymer chains and the local degree of swelling might not be the same. On the basis of the good agreement between the calculated and experimental results (Figure 10), however, it seems that the effect on local swelling introduced by nonuniformity is not severe.

Conclusion

On the basis of the Flory-Huggins and Yasuda theories, a perturbation procedure was used to expand the logarithm of diffusivity in powers of the activity of the swelling agent. Experiments were performed to measure the diffusion of drug and swelling agent in polymeric membranes. The experimental results suggest that the linear term in the derived equation is accurate enough to describe the diffusivities of benzocaine and ethanol in EVAc and PU membranes. With the linear dependence of benzocaine and ethanol diffusivities on ethanol activity, the effective diffusivity of benzocaine in the membrane subject to a swelling gradient can be calculated. Experiments were also carried out to verify the calculation procedure. Good agreement between the calculated and experimental results was obtained.

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