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Report

Solvent Interaction with Polydimethylsiloxane Membranes and Its Effects on Benzocaine Solubility and Diffusion

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The effect of polar solvents and polar cosolvent mixtures on the transport properties of benzocaine in polydimethylsiloxane (PDMS) was studied. Methanol, ethanol, *n*-propanol, and *n*-butanol, as well as aqueous cosolvent mixtures of each *n*-alkanol, were used as vehicles for benzocaine. A constant activity gradient was maintained in all diffusion studies, with the membrane exposed to saturated donor suspensions of drug, and sink conditions maintained in the receiver. In spite of the constant activity gradient, steady-state benzocaine flux was substantially enhanced with increasing *n*-alkanol volume fraction and reached a maximum for the pure *n*-alkanol in each case. At any given composition, the degree of benzocaine flux enhancement generally increased with *n*-alkanol carbon number. In terms of the appropriate Fick's first law expression for this system, these observations were attributed to simultaneous changes in benzocaine concentration within the PDMS membrane, the diffusion coefficient of benzocaine in PDMS, fillerless membrane volume fraction, tortuosity, and the membrane thickness. These parameters were in turn correlated with the cosolvent composition in contact with the membrane. Both membrane solubility and diffusion coefficient were found to increase substantially, but decreases in tortuosity and increases in fillerless membrane volume fraction and membrane thickness were minor.

KEY WORDS: polymer swelling; polydimethylsiloxane; cosolvent; benzocaine diffusion.

INTRODUCTION

Polydimethylsiloxane (PDMS) membranes are commonly used as homogeneous hydrophobic barriers in drug diffusion studies (1) and as components in drug delivery devices (2). In many instances, permeants are dissolved in vehicles which are placed in contact with the membrane, and in pharmaceutical applications, polar solvents are often used. It is possible that the solvents may influence the transport properties of the diffusional barrier, thus they have been termed interacting or noninteracting (3). The transport characteristics of PDMS are essentially unaffected by contact with polar solvents such as propylene glycol, polyethylene glycol 400, glycerol, and binary mixtures of each with water (4). Low concentrations of phenol were also found to have no effect on PDMS permeability (5). However, other workers have detected slight changes in the diffusivity of a permanent in PDMS with propylene glycol and propylene glycol/water vehicles (6). In contrast to these essentially noninteracting systems, Twist and Zatz report that ethanol/water mixtures (4) as well as a number of pure alcohols (3) enhance the flux of paraben esters through PDMS membranes. They conclude that the enhancement is due primarily to an increase in paraben solubility in the membrane, with a smaller effect caused by an increase in the diffusion coefficient.

Cosolvent mixtures may be used as vehicles in the reservoir of diffusion-controlled drug delivery devices to alter the solubility of poorly water-soluble drugs. Cosolvents can thus be used to manipulate drug flux through the rate-controlling membrane, as well as total drug load in these devices. Polar solvents such as water and various lower alcohols may be good candidates for these formulations.

Although the manipulation of cosolvent composition can substantially alter drug solubility in the donor vehicle, the permeant activity gradient in the membrane and permeant flux will remain constant in the case of noninteractive polymer barrier/solvent pairs if drug saturation is maintained and the same solid form of the drug is used. An appropriate form of Fick's first law describing permeant flux through a rate-controlling membrane containing inert filler and under steady-state and sink conditions is given by:

$$\frac{J}{A} = \frac{C_m D \phi}{h\tau} \tag{1}$$

in which J/A is the permeant flux per unit area, C_m is the saturated concentration of permeant in the barrier membrane at the donor surface, D is the permeant diffusion coefficient in the membrane, ϕ is the fillerless membrane volume fraction, h is the barrier thickness, and τ is the toruosity.

A constant activity gradient of permeant may be main-

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tained using different vehicles when diffusion studies are conducted from a saturated donor solution to a receiver under sink conditions. By keeping the activity gradient constant and using the same type of membrane, it is possible to attribute any change in steady-state diffusion to membrane/solvent interaction. One method for quantifying the interaction is the measurement of equilibrium membrane swell upon exposure to a solvent. If the solvent does enter and swell the membrane, any or all of the five transport parameters, C_m, D, ϕ, h, and τ, may be altered, resulting in a change in drug flux. Therefore, under the same steady-state and sink conditions, Fick's first law may be modified to reflect these interactions:

$$\frac{J}{A} = \frac{C_{m(sw)}D_{(sw)}\phi_{(sw)}}{h_{(sw)}\tau_{(sw)}} \quad (2)$$

where C_m, D, ϕ, h, and τ may all be influenced by the degree of swell, sw.

It is important to understand the nature of membrane/vehicle interactions as they impact on drug transport behavior. Aside from modifying permeant solubility in the vehicle, the use of different solvents or manipulation of cosolvent composition may result in unexpected alterations in the properties of the membrane barrier. Therefore, the objectives of this investigation were to examine systematically the effect of cosolvent composition on both the solubility of benzocaine, a poorly water-soluble permeant, and its transport properties in PDMS. The full range of vehicle composition was studied using a homologous series of *n*-alkanols and water, a noninteractive solvent, in order to understand further the effect of water content on cosolvent/membrane interaction and to make comparisons among the *n*-alkanols. In this work, the effect of cosolvent/membrane interaction was quantitatively studied in terms of not only the permeant concentration in the membrane and diffusion coefficient, but also the remaining three transport parameters: unfilled membrane volume fraction, membrane thickness, and tortuosity.

EXPERIMENTAL

Materials

Benzocaine (Eastman Kodak Co., Rochester, N.Y.), methanol, *n*-propranol (J. T. Baker, Phillipsburg, N.J.), 200-proof ethanol (USI Chemicals Co., Newark, N.J.), and *n*-butanol (Allied Chemical Co., Morristown, N.J.) were reagent grade and used as received. Silastic Medical-Grade NRV sheeting (gift from Dow Corning Corp., Midland, MI) of 0.0127-, 0.0254-, 0.0508-, 0.1016-, and 0.1524-cm specified thickness was used after washing with mild soapy water followed by rinsing with double-distilled water. All PDMS membranes were pretreated by soaking in pure *n*-propranol for 24 hr to extract any leachable components and air-dried under ambient conditions. Membrane thickness was confirmed using an optical stereomicroscope (Wild M420, E. Leitz, Inc.) equipped with a scaled-filar eyepiece (Wild MMS 235 digital measuring set and printer) for size measurement. Instrument precision is within 0.001 mm. The measured values were within 5% of those specified for each thickness. Borosilicate glass apparatus and double glass-distilled water were used throughout this work.

Methods

Swelling

The swell of PDMS membranes upon exposure to various solvents was determined gravimetrically. The swelling solvents included methanol, ethanol, *n*-propanol, and *n*-butanol, as well as binary mixtures of each of these *n*-alkanols with water. The *n*-alkanol/water mixed systems ranged in composition from 0 to 100% (v/v) *n*-alkanol for methanol, ethanol, and *n*-propanol. Due to the limited mutual solubilities of *n*-butanol and water, a restricted composition range was investigated: up to 7.5% and over 85% (v/v) *n*-butanol. Accurately weighed portions of 0.1524-cm-thick membrane, approximately 1 g, were placed in sealed flasks containing solvent. These flasks were maintained at 32°C for at least 24 hr, after which the membranes were removed, quickly blotted dry of surface solvent, and immediately placed in sealed weighing vessels. The weight of solvent imbibed by each sample was calculated as the difference between the swollen and the initial dry weights. Triplicate swelling measurements were made, and solvent uptake was expressed as percentage (w/w) based on the initial dry weight. In the calculation of swell, the 27.15% (w/w) inert filler content (7) was subtracted from the dry weight of the PDMS sample. Sorption studies were also performed in a similar manner for PDMS swollen in the pure *n*-alkanols saturated with benzocaine.

Changes in membrane thickness upon exposure to each neat *n*-alkanol, as well as selected compositions of *n*-propanol/water and *n*-butanol/water, were determined. Measurements were made both in the absence of benzocaine and in the presence of saturated concentrations using the optical microscopy method described above. In these studies, rectangular portions of 0.1016-cm-thick membrane, approximately 1 by 1.5 cm, were glued on edge perpendicularly to glass microscope coverslips using a silicone adhesive. After measuring the initial dry thickness, the samples were swollen in the solvents for 24 hr at 32°C. Three to five measurements were made along the top edge of the swollen samples.

Solubility Determination

Benzocaine solubility in solution was determined in triplicate as a function of composition for each cosolvent system by equilibrating excess benzocaine with the solvent or cosolvent mixture for at least 24 hr. Samples were slowly rotated in a thermostated water bath maintained at 32°C. Aliquots were removed and, after appropriate dilution with water, assayed spectrophotometrically at 284 nm (Varian, Carey 2290).

Benzocaine solubility in the PDMS membrane was also measured as a function of cosolvent composition by exposing accurately weighed portions of 0.1524-cm-thick membrane to suspensions in each cosolvent system. After equilibration at 32°C, the membrane pieces were removed and blotted dry with absorbent tissue paper. Samples were rinsed twice by briefly dipping in 95% ethanol with blotting of surface excess following both immersions. Benzocaine

was then leached from the membrane at ambient temperature in 95% ethanol and assayed spectrophotometrically. Membrane concentration was calculated excluding the 27.15% (w/w) inert filler content and using 0.97 (g/cm^3) (7) as the density of PDMS. At least three determinations were made at each composition.

Diffusion Studies

Diffusion studies were conducted using Bellco (Vineland, N.J.) glass diffusion cells in the form of two cylindrical half cells, each with a volume of 5 cm^3. These half cells, separated by the PDMS membrane with a cross-sectional area of 2.01 cm^2 available for diffusion, were held together with a screw clamp. Agitation was provided in each side of the diffusion cell with a 1-cm magnetic stirring bar, rotated from below at 900 rpm. The diffusion cells were partially submerged in a water bath to maintain the temperature at 32°C. All diffusion studies were conducted in triplicate, and except as otherwise noted, 0.0127-cm-thick PDMS membranes were used. The donor chambers contained saturated benzocaine suspensions, and sink conditions were effectively maintained in the receiver chamber by replacement of the entire receiver volume at appropriate intervals. Receiver samples were diluted with water and assayed spectrophotometrically. The same cosolvent composition was used in both the donor and receiver chambers.

The influence of hydrodynamic boundary layers was evaluated with both flux measurements as a function of membrane thickness and stirring speed studies. The steady-state flux of benzocaine from water was directly proportional to the reciprocal of membrane thickness for 0.0127-, 0.0254-, and 0.1016-cm-thick membranes. Additionally, steady-state flux was found to be independent of stirring speed within the range tested (300 to 1500 rpm). For this study, water, the solvent offering the greatest membrane/solvent partition coefficient and the thinnest (0.0127 cm) membrane were used. These results strongly suggest that boundary layer hydrodynamic effects are negligible under the experimental conditions selected.

RESULTS AND DISCUSSION

Swelling

Because solvents may interact with a polymer barrier and possibly alter the mass transport of a permeant, it is important to identify and quantify these interactions. The extent of membrane/solvent interaction was quantified by swelling studies, in which the equilibrium swell of PDMS membranes was measured as a function of *n*-alkanol/water composition for methanol, ethanol, *n*-propanol, and *n*-butanol. The swelling results for each are presented in Fig. 1. It is apparent that the extent of swell increased with higher *n*-alkanol content for each of the four *n*-alkanols, with minimal swelling in pure water and maximal swelling in pure *n*-alkanol. For any particular composition, the extent of swell increased with higher carbon number. When benzocaine is added to the solvent or cosolvent mixture, the equilibrium solvent uptake is diminished, apparently due to lowered solvent activity. For example, the extent of PDMS membrane swell in the presence of the *n*-alkanols saturated

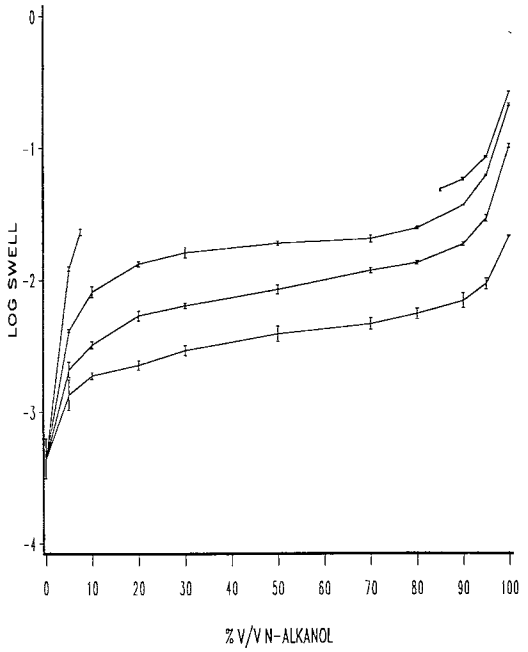

Fig. 1. Logarithm of fractional weight uptake of solvent by PDMS versus *n*-alkanol composition. Curves from bottom to top are methanol, ethanol, *n*-propanol, and *n*-butanol/water cosolvent systems. Error bars represent ±1 SE.

with benzocaine was 2.1, 4.6, 9.4, and 13.1% (w/w) for methanol, ethanol, *n*-propanol, and *n*-butanol, respectively, which was about one-half the extent measured in each drug-free solvent. PDMS swell has been reported as a function of ethanol/water composition (4) and in the presence of these same pure *n*-alkanols (3), with swelling results qualitatively similar to those shown here. In this work, however, the *n*-alkanol/water composition range was studied more completely and included each of the four cosolvent systems.

These findings are consistent with the solubility parameter concept, which when applied to cross-linked polymers, predicts the greatest degree of polymer swell with solvents whose solubility parameter most closely matches that of the polymer (8). There is a range of values reported for the solubility parameter of PDMS, but values near 7.5 (cal/cm^3)$^{1/2}$ are most often reported (9,10). The solubility parameters of water, methanol, ethanol, *n*-propanol, and *n*-butanol are 23.4, 14.5, 12.7, 11.9, and 11.4 (cal/cm^3)$^{1/2}$, respectively (11). Based on these values, the rank order of extent of PDMS swell upon exposure to these solvents is expected to be *n*-butanol > *n*-propanol > ethanol > methanol > water. The observed PDMS swelling values are consistent with the solubility parameter concept for this limited homologous series because the swell in the pure solvents increased as the difference in their solubility parameters became smaller. Similarly, for each *n*-alkanol/water system, PDMS swell also increased with a decrease in solubility parameter (lower water content).

As suggested by Eq.(2), the degree of membrane swell may affect the thickness of the barrier membrane, $h_{(sw)}$, and impact on permeant flux. Figure 2 demonstrates the change in membrane thickness upon exposure to the neat *n*-alkanols, both with and without saturated concentrations of

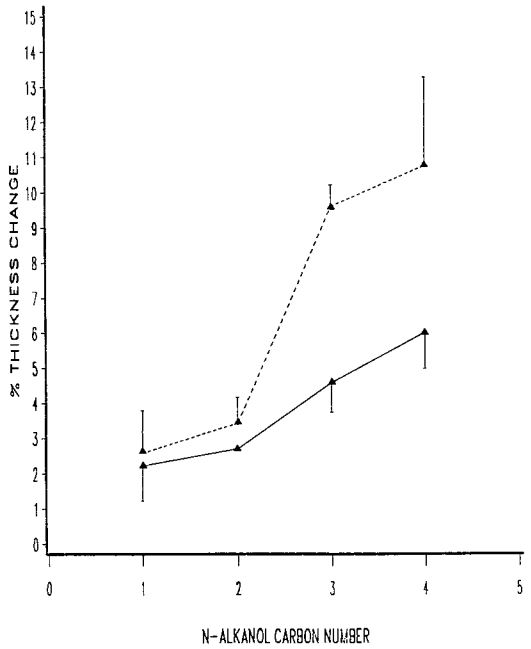

Fig. 2. Swelling-induced membrane thickness change versus *n*-alkanol carbon number. (-----) In the absence of benzocaine; (—) *n*-alkanol saturated with benzocaine. Error bars represent ±1 SE.

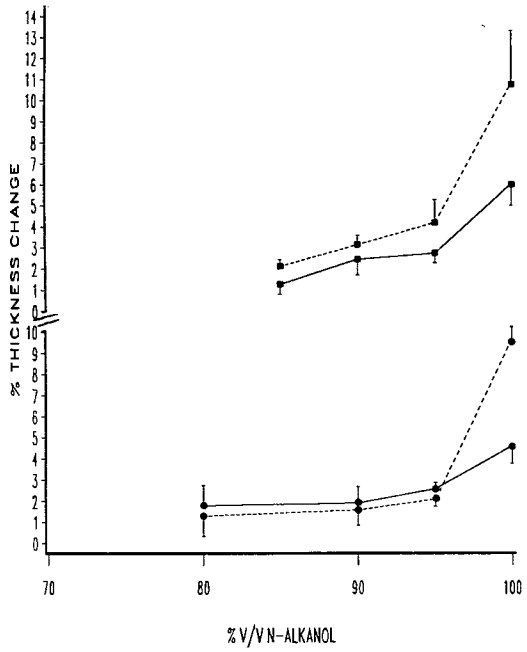

Fig. 3. Swelling-induced membrane thickness change versus selected *n*-butanol/water and *n*-propanol/water compositions. (■) *n*-butanol/water; (●) *n*-propanol/water; (------) in the absence of benzocaine; (—) saturated with benzocaine. Error bars represent ±1 SE.

benzocaine. As expected from the gravimetric swelling studies, the higher *n*-alkanols cause a more substantial increase in thickness. Similar to total membrane swell, the presence of benzocaine apparently lowers solvent activity and diminishes swelling-induced thickness changes. When water is included, the membrane thickness is further diminished, as illustrated with *n*-propanol and *n*-butanol in Fig. 3. The presence of benzocaine caused a statistically significant reduction in membrane thickness only for pure *n*-propanol, pure *n*-butanol, and 95% *n*-butanol (least significant difference test, $\alpha = 0.05$).

Benzocaine Diffusion

The results of three representative diffusion studies, each at a different *n*-propanol/water composition, are depicted in Fig. 4. Due to the thin (0.0127-cm) membranes used in the diffusion studies and the relatively high permeability of PDMS to benzocaine, steady-state was achieved rather quickly. Therefore, steady-state flux was calculated using the data collected after 15 min. As these linear slopes demonstrate, steady-state benzocaine flux increased with higher *n*-propanol content even though a constant activity gradient of drug across the PDMS membrane was maintained. The same trend of increasing flux with higher *n*-alkanol content was observed for the methanol, ethanol, and *n*-butanol systems as well.

Figures 5 and 6 summarize the effect of *n*-alkanol content on steady-state benzocaine flux throughout the entire composition range for each *n*-alkanol/water system investigated. Flux is expected to be independent of the applied donor vehicle composition for a noninteracting solvent as long as saturation is maintained. However, the flux values were not constant, and based on the sigmoidal shape of the curves, the flux is apparently related to the degree of membrane swell. To emphasize the correlation between steady-state flux and swell, the flux from each *n*-alkanol/water vehicle is plotted versus the logarithm of fractional weight uptake in Fig. 7. Although correlated with swell in the absence

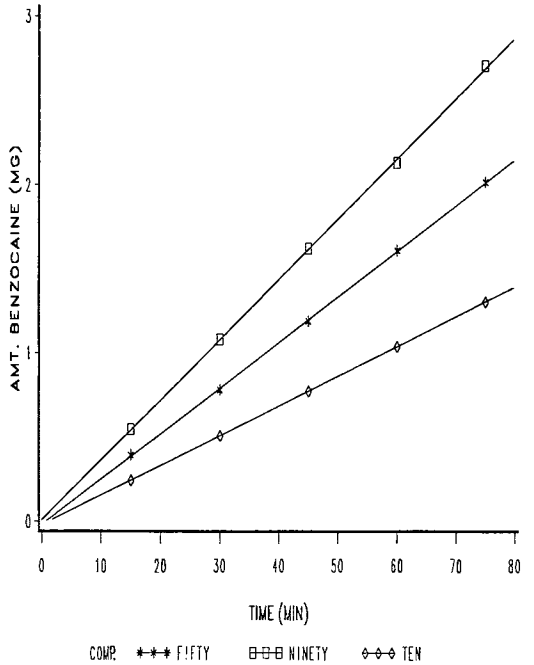

Fig. 4. Cumulative amount of benzocaine transported versus time for three different *n*-propanol/water vehicle compositions.

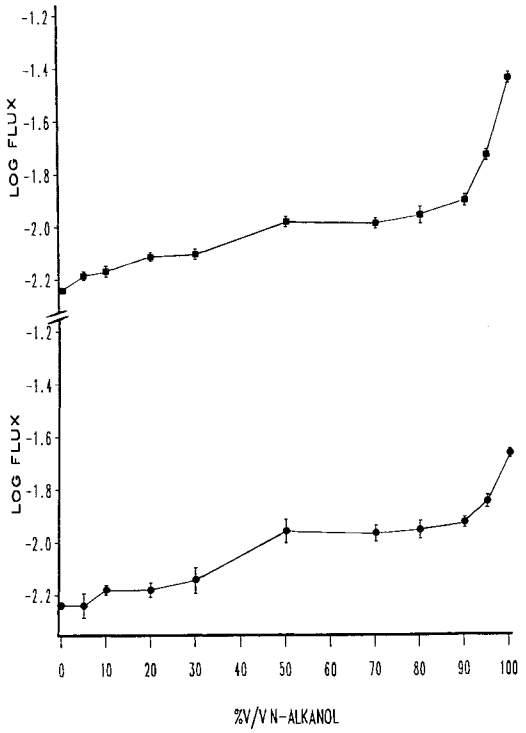

Fig. 5. Logarithm of steady-state benzocaine flux [mg/(min cm^2)] versus *n*-alkanol/water vehicle composition. (●) Methanol/water; (■) ethanol/water. Error bars represent ±1 SE.

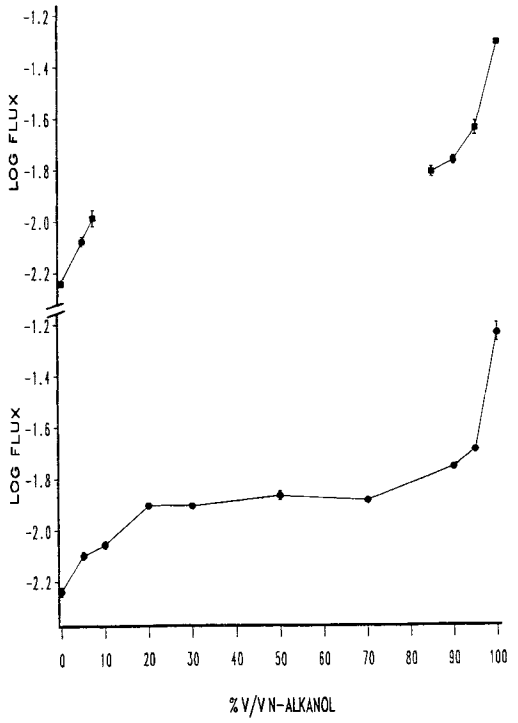

Fig. 6. Logarithm of steady-state benzocaine flux [mg/(min cm^2)] versus *n*-alkanol/water vehicle composition. (●) *n*-Propanol/water; (■) *n*-butanol/water. Error bars represent ±1 SE.

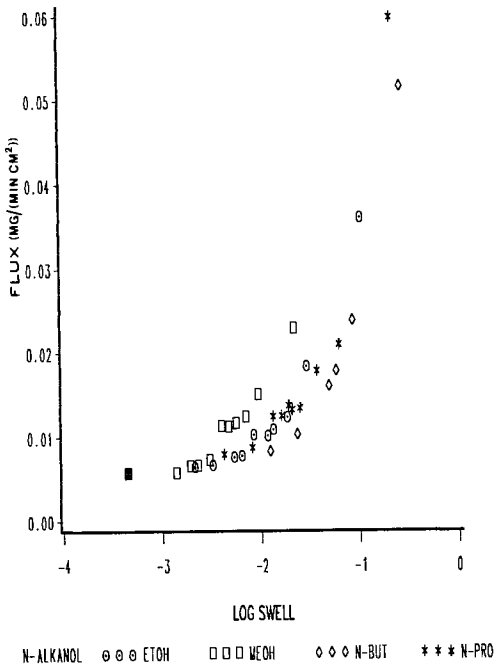

Fig. 7. Steady-state benzocaine flux from each *n*-alkanol/water composition versus the logarithm of PDMS swell (as fractional weight uptake).

of drug, this plot suggests that benzocaine flux is sensitive to the degree of swell and is not simply dependent on *n*-alkanol/water composition, because different degrees of swell are encountered at a single composition.

To illustrate the effect of cosolvent composition on the transport of benzocaine, a flux enhancement factor, defined as the ratio of the flux at a given composition to that from water, was calculated and values are listesd in Table I. This approach facilitates comparisons among the *n*-alkanols on the basis of cosolvent composition. Flux enhancement may be substantial, and for each individual *n*-alkanol, increases in *n*-alkanol content enhanced benzocaine flux. Although not

Table I. Benzocaine Flux Enhancement Factor as a Function of *n*-Alkanol/Water Vehicle Composition

Composition (%, v/v *n*-alkanol)	Flux enhancement factor			
	Methanol	Ethanol	*n*-Propanol	*n*-Butanol
0	1.0[a]	1.0	1.0	1.0
5	1.0	1.1	1.4	1.5
10	1.2	1.2	1.5	1.8[b]
20	1.2	1.3	2.2	—
30	1.3	1.4	2.2	—
50	2.0	1.8	2.4	—
70	2.0	1.8	2.3	—
80	2.0	1.9	2.3	2.8[c]
90	2.2	2.2	3.1	3.1
95	2.6	3.2	3.6	4.2
100	4.0	6.3	10.4	9.0

[a] flux from pure water = 5.76×10^{-2} mg/(min cm^2).
[b] 7.5% (v/v) *n*-butanol.
[c] 85% (v/v) *n*-butanol.

entirely consistent, there appears to be a general trend in which the longer-chain *n*-alkanols offer more effective flux enhancement at any particular composition.

These findings support the premise that solvent interactions with a polymer barrier may cause significant deviations from the ideal noninteractive model. Therefore, the operative mechanisms for overall flux enhancement were studied by isolating the effects of solvent interaction on permeant solubility in the membrane, $C_{m(sw)}$, permeant diffusion coefficient, $D_{(sw)}$, unfilled membrane volume fraction, $\phi_{(sw)}$, membrane thickness, $h_{(sw)}$, and tortuosity $\tau_{(sw)}$.

Solubility

Solution solubility of benzocaine, as well as benzocaine solubility in the PDMS membrane, were determined as a function of the cosolvent composition as one way to characterize more fully the effect of cosolvents on benzocaine transport in PDMS membranes. Figure 8 depicts the solubility in both media for each *n*-alkanol/water system. Cosolvent composition had a pronounced effect on benzocaine solution solubility, with a difference of more than two orders of magnitude between all maximum and minimum values.

In contrast to solution solubility, the solubility of benzocaine in PDMS was far less sensitive to the composition of the cosolvent vehicle. For a noninteracting system, saturated permeant concentration in the membrane is independent of vehicle composition. For *n*-alkanol/water mixtures, however, benzocaine concentration was relatively constant until the composition of the bathing solvent approached that of pure *n*-alkanol, after which there was at least a doubling of membrane concentration to the maximum values observed with the pure *n*-alkanols. This increase in membrane concentration may be attributed to larger degrees of membrane swell associated with higher *n*-alkanol compositions. The finding that benzocaine solubility in PDMS varied with cosolvent composition is another indication of solvent/membrane interaction. As proposed by Most (12), the imbibed solvent components likely act to shift the overall solubility parameter of the membrane phase. Therefore, the uptake of polar solvents by PDMS would increase its solubility parameter from an initial value of aplproximately 7.5 $(cal/cm^3)^{1/2}$ to a value closer to that of benzocaine, reported to be 12.2 (11).

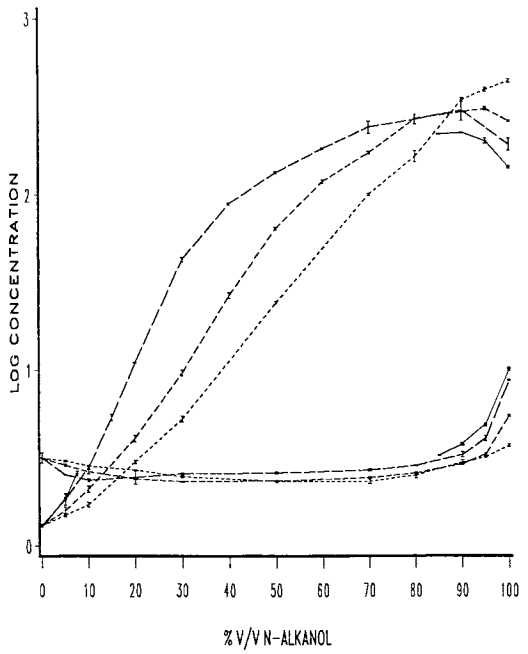

Fig. 8. Benzocaine solution and membrane solubilities (mg/cm^3) versus *n*-alkanol/water composition. (-----) Methanol/water; (---) ethanol/water; (– –) *n*-propanol/water; (—) *n*-butanol/water. Upper curves represent solution, and lower curves represent membrane solubilities. Error bars represent ±1 SE.

The apparent diffusion coefficient of benzocaine in the PDMS membrane was calculated for each cosolvent composition based on the applicable form of Fick's first law [Eq. (2)]. The experimentally determined flux and membrane concentration values at each composition were substituted into this expression. A constant value for membrane thickness of 0.0127 cm was assumed in the calculations, except for the pure *n*-alkanols, where the experimentally determined values in the presence of benzocaine were used. These adjustments were minor: 2.3, 2.7, 4.6, and 6.0% increases in thickness, $h_{(sw)}$, for benzocaine-saturated methanol, ethanol, *n*-propanol, and *n*-butanol, respectively. As stated previously, thickness changes diminish rapidly as the water content of the *n*-alkanol/water mixture increases. The fillerless volume fraction in the absence of swell, 0.86, was calculated on the basis of the content (27.15%, w/w) and density (2.2 g/cm^3) of inert filler and density of PDMS elastomer (0.97 g/cm^3) (7). When exposed to the saturated anhydrous *n*-alkanols, $\phi_{(sw)}$ was determined to be 0.88, 0.88, 0.89, and 0.89 for methanol, ethanol, *n*-propanol, and *n*-butanol, respectively. These were calculated based on the swelling results in the presence of drug, its membrane concentration, and the densities of all components. The density of benzocaine, 1.13 g/cm^3, was experimentally determined using a pycnometer and *n*-hexane as the solvent. Because these adjustments were minor, the value of 0.86 was assumed constant for all but the pure *n*-alkanol cases. Using the method of Higuchi and Higuchi (13), tortuosity, τ, was calculated for these membranes. Values of 1.12 were determined in the absence of swell, and 1.11, 1.10, 1.10, and 1.10 for the anhydrous methanol, ethanol, *n*-propanol, and *n*-butanol/benzocaine systems, respectively. Since the presence of water substantially reduces membrane swell, and because τ is influenced to only a minor extent by the experimentally encountered degrees of swell, the value of 1.12 was assumed constant for all but the anhydrous alcohol cases. Diffusion coefficient values are presented in Table II.

The diffusion coefficient of benzocaine in PDMS, $D_{(sw)}$, increased with higher *n*-alkanol content within the range of composition for each *n*-alkanol. At most lower compositions, the rank order of diffusion coefficient values among the *n*-alkanols was *n*-butanol > *n*-propanol > ethanol > methanol. These results may be interpreted as solvent/PDMS interaction in which the imbibed solvents plasticize the polymer. A plasticizer diminishes the cohesive forces between polymer chains and enhances their segmental mobility, resulting in the greater ease of diffusion of a third component through the polymer. In the simplest sense, therefore, the action of a plasticizer can be considered as a "lubricant" reducing the intermolecular friction between

Table II. Benzocaine Diffusion Coefficient as a Function of *n*-Alkanol/Water Vehicle Composition

Composition (%, v/v *n*-alkanol)	Benzocaine diffusion coefficient (cm^2/sec) times 10^7			
	Methanol	Ethanol	*n*-Propanol	*n*-Butanol
0	5.0	5.0	5.0	5.0
5	5.2	6.3	8.7	9.6
10	6.4	7.1	10.2	9.3[a]
20	6.8	8.8	13.5	—
30	8.1	9.3	13.3	—
50	13.4	12.2	14.5	—
70	13.2	11.5	13.5	—
80	12.7	11.6	12.9	13.5[b]
90	11.5	11.7	14.9	13.0
95	12.9	15.2	14.1	13.5
100	16.7	17.9	18.6	14.1

[a] 7.5% (v/v) *n*-butanol.
[b] 85% (v/v) *n*-butanol.

polymer molecules (14). The effectiveness of a material as a plasticizer depends on the interaction with the polymer by means of its solvent power for the polymer. Comparison of the polymer/plasticizer solubility parameters is one method of measuring the solvent power of a plasticizer and compatibility of a polymer/plasticizer system (15).

As evidenced by the relatively small degrees of PDMS swell by polar solvents and confirmed by the dissimilarity of solubility parameters, the lower *n*-alkanols and *n*-alkanol/water mixtures are thermodynamically poor solvents for PDMS. However, even at the modest degrees of swell observed, the effects on the transport parameters, $D_{(sw)}$ and $C_{m(sw)}$, were substantial. There is a consistent trend in which the effectiveness of plasticization, as reflected by an increase in the diffusion coefficient, is inversely related to the cosolvent solubility parameter for each *n*-alkanol/water system. This general trend remains when comparing different *n*-alkanol/water systems of lower *n*-alkanol compositions. In contrast, the effect of solvent swelling on the other transport parameters, $\phi_{(sw)}$, $h_{(sw)}$, and $\tau_{(sw)}$, was minor.

In conclusion, the findings of this report demonstrate that polar mixed solvents can substantially alter the drug diffusion characteristics of PDMS with only modest degrees of membrane swell. Since mixtures of polar solvents may be used as vehicles in diffusion-controlled drug delivery devices to modify drug solubility, their effects on the rate-controlling polymer barriers may need to be considered. Solvent/membrane interaction and its resultant effect on drug solubility in the membrane, diffusion coefficient, membrane thickness, and possibly unfilled membrane volume fraction and tortuosity may warrant examination in some of these systems.

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