Drug Release Studies on an Oil–Water Emulsion Based on a Eutectic Mixture of Lidocaine and Prilocaine as the Dispersed Phase

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Abstract □ The in vitro drug release properties of a topical anesthetic formulation known to be effective on intact skin, based on a 1:1 eutectic mixture of lidocaine and prilocaine emulsified in water, were investigated with a poly(dimethylsiloxane) membrane partition model. Aqueous solutions and solubilized systems of lidocaine and prilocaine in a 1:1 ratio by weight were also included in the study as well as the eutectic mixture itself. Two identical sets of samples were used, one of which was gelled with carbomer 934 P. Drug solubilities in the membrane, partition coefficients between membrane and water, and diffusion coefficients in the membrane and the formulations were determined. As in the case of an aqueous medium, lidocaine and prilocaine in combination had lower solubilities in the membrane than they did separately. However, in the aqueous phase or in the membrane, the diffusion coefficients were mutually independent. Carbomer 934P, when neutralized totally with sodium hydroxide, did not decrease the aqueous diffusivities of the local anesthetic bases. The major advantages of using the emulsion formulation based on a eutectic mixture rather than more conventional formulations are: (*a*) the local anesthetic bases are present in their permeable uncharged forms; (*b*) the use of a poor solvent, water, as the vehicle provides a saturated system at low concentrations; (*c*) lipophilic solvent is absent in the dispersed phase, the presence of which would decrease the effective distribution coefficients of the active substances between the skin and the formulation; (*d*) the droplets consist of dissolvable drug and act as reservoirs to obtain steady-state release; and (*e*) the fluid state of the excess drug provides a higher dissolution rate than from a solid state.

Many attempts have been made to anesthetize intact skin without the use of invasive methods. To achieve this effect, high concentrations of the active substance,[1] penetration enhancers,[2] or iontophoresis[3] have been used. Lidocaine is one of the most frequently used local anesthetics. Broberg[4] has formulated a lidocaine–prilocaine emulsion system (EMLA) which anesthetizes intact skin to such an extent that minor surgery can be performed.[5] This formulation represents a pharmaceutical–technological method which overcomes the limitations of commonly used vehicle systems. It combines the high thermodynamic activity of saturated systems with a high escaping tendency of molecules from a liquid drug phase. This is achieved by mixing the chemically related local anesthetics lidocaine and prilocaine in a 1:1 ratio to form a eutectic mixture having a eutectic temperature of 18°C.[6] This liquid has been emulsified in water with a surfactant consisting of ethoxylated esters of fatty acids to produce a cream that is thickened by neutralized carbomer 934P. In contrast to conventional oil–water emulsions of local anesthetic bases,[7] the lidocaine–prilocaine emulsion system does not contain any lipophilic solvent.

The distribution conditions of prilocaine and lidocaine in lidocaine–prilocaine emulsions were investigated in a previous study.[8] The goals of the present work were to study: (*a*) the influence of the active substances on the diffusivities of each other; (*b*) the effect of the concentrations of the active substances, the surfactant, and the thickening agent, and (*c*) the importance of the droplet and micellar phases on drug release.

To simulate the lipophilic character of biological membranes, especially that of the stratum corneum, a poly(dimethylsiloxane) membrane was used. This membrane is nonpolar, lacks pores, and is permeable only to the uncharged forms of lidocaine and prilocaine.

Experimental Section

Materials and Formulations—Lidocaine (L), prilocaine (P) (Astra Pharmaceutical Production AB, Sweden), ethoxylated hydrogenated castor oil (Arlatone 289, Atlas Chemie GmbH, Essen, F.R.G.), and carbomer 934P (carboxypolymethylene, Carbopol 934P, Goodrich Chem. Co., U.S.A.) were used as obtained. Sodium hydroxide was of analytical grade.

An L–P eutectic mixture was prepared by mixing lidocaine and prilocaine in a 1:1 weight ratio while heating gently. If not otherwise stated, this eutectic mixture was used to prepare the L–P formulations studied, i.e., solutions, micellar solutions, and emulsions.

Two series of lidocaine–prilocaine–surfactant systems, I and II, were prepared by diluting an L–P emulsion concentrate with water or an aqueous solution of ethoxylated hydrogenated castor oil (surfactant), respectively. The emulsion concentrate contained lidocaine, prilocaine, and surfactant in a 1:1:0.76 weight ratio, and water as the continuous phase. The preparation of the emulsion concentrate has been described elsewhere.[8] Series I contained L–P in a concentration range of 0.55–10%. Series II contained 1.0, 2.5, and 5.0% L–P and 0.38–5.0, 0.95–10, and 1.0–15% surfactant, respectively. No creaming or settling out of the emulsions were observed during the course of the experiments. Two sets of each sample series were prepared, one of which was gelled with carbomer 934P. The carbomer 934P was dispersed in the diluting media, the mixture was adjusted to a pH of 9.0–9.5 with 2 M NaOH, and then was mixed with the emulsion concentrate.

Solubilities—Segments of 16 cm^2 of poly(dimethylsiloxane) membrane (Silastic sheeting, nonreinforced, Dow Corning Corp., Midland, MI) were immersed in the L–P eutectic mixture and agitated in a shaker water bath at 32°C for 64 h. Upon removal from the eutectic mixture, the segments were thoroughly cleaned by wiping with paper tissues. Lidocaine and prilocaine were extracted from themembrane with 0.1 M HCl and were measured separately using HPLC. The solubilities of lidocaine and prilocaine were determined individually and that of L–P was determined by adding the two separate solubilities. The volumes of the membrane segments were calculated using the data on membrane thickness provided by the supplier.

Partition Coefficients—Segments of known sizes of poly(dimethylsiloxane) membrane were immersed in a 0.5% L–P aqueous solution and the samples agitated in a water bath at 32°C. The concentrations of prilocaine and lidocaine in the aqueous phase were determined separately using HPLC. The partitioned amounts of local anesthetics in the membrane were calculated from the initial and the equilibrated aqueous concentrations. Membrane volume was estimated from the data on membrane thickness provided by the supplier.

Equal volumes of poly(dimethylsiloxane) oil (Silicone Oil MS 200, 1cSt, Kebo Grave, Sweden), saturated with pH 9.4 borate buffer and

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0.3% lidocaine, and 0.5% prilocaine and 0.5% L–P, respectively, in the same buffer saturated with poly(dimethylsiloxane) oil were equilibrated at 32°C while being agitated with a magnetic stirrer. The partition coefficient was obtained in the same way as with the membrane. The pH of the aqueous phase, measured before and after the experiment, was found to be unchanged.

Viscosity—The viscosity measurements were performed at 32°C using a Rheomat 30 rotational viscometer with MS-O and MS-C_b measuring systems and a Rheoscan 30 recorder (Contraves AG, Switzerland).

Diffusion Coefficients in Water—The shear cell used to determine the aqueous diffusion coefficients of lidocaine and prilocaine, individually and in combination, was described by Sundelöf.[9] Briefly, the apparatus consisted of four cylinders. Each cylinder contained two diffusion cells and was made of two teflon blocks with a common vertical axis of rotation. The two diffusion cell compartments in the upper block were filled with distilled water and the two compartments in the lower block with 2.5 mg/mL lidocaine or prilocaine, or 5.0 mg/mL of L–P. Each compartment contained 0.2 mL. The boundary between solvent and solution was formed by rotating the blocks with respect to each other. The diffusion process was terminated in two cylinders after 2, 4, and 6 h to obtain four data points at each time. The contents of the upper compartments were removed and the amount of the diffused drug species measured as described elsewhere.[6] The square of the amount of drug diffused (Q) was plotted against time (t) and the diffusion coefficient (D) was calculated according to:

$$Q^2 = \frac{A^2 D C_0^2}{\pi} t \qquad (1)$$

where A and C_0 denote the cross-sectional area and the initial concentration, respectively.

Drug Release Studies—Two-compartment diffusion cells were used. The top (donor) and the bottom (receptor) compartments had volumes of 8 and ~600 mL, respectively.

The medical grade poly(dimethylsiloxane) membrane, 0.127-mm thick, was placed between the formulation and the sink compartment giving an interfacial area of ~7.10 cm^2. Except when otherwise stated, 0.1 M HCl was used as the receptor phase to ensure sink conditions for the local anesthetic bases within the receptor compartment. The cell was submerged in a 32°C water bath. In addition, experiments with aqueous solutions were carried out at 25 and 37°C. The sink solution was pumped through a spectrophotometer (Zeiss DM4 double-beam spectrophotometer) by a peristaltic pump (Gilson Minipuls II, Isoversing tubing). All tubing was made of teflon and the sink was agitated with a magnetic stirrer at a calibrated speed of 600 rpm. When the temperature of the sink had been regulated, 8 mL or grams of the formulation was placed in the donor compartment, and the automatic recording of the absorbance of the sink at 230 nm was started. When the ratio of lidocaine and prilocaine in the sink was not known, an HPLC method was used to determine lidocaine and prilocaine individually. The L–P flux was calculated by summing the fluxes of the individual species.

The release studies were carried out with and without stirring of the formulations. The stirring was carried out with a glass blade at a precalibrated speed of 140 rpm, the speed at which the release rate reached its maximum when tested up to 200 rpm.

Results and Discussion

Partition Coefficient and Solubility Determinations—A direct measure of the partitioning into and the solubility in a poly(dimethylsiloxane) membrane is difficult to obtain due to the uncertainties in the measurement of the membrane volume and because of the presence of silica filler in the membrane. Poly(dimethylsiloxane) oil has proved, however, to be a useful model for the membrane in partitioning experiments.[10,11]

In the present study, both poly(dimethylsiloxane) membrane and oil were used, and the partition coefficients are given in Table I. The values for the membrane are higher than those for oil. Except for lidocaine in L–P, where no significant difference was obtained, the higher values might be explained by the presence of the silica filler. The pK_a values of lidocaine and prilocaine are 7.86 and 7.89, respectively.[12] At pH 9.4, ~3% of the lidocaine and prilocaine are in the ionized form. Thus, calculating the partition coefficients by taking into account only the un-ionized fraction of L–P resulted in values only slightly higher than those without correction for the ionization (Table I).

Table I—Partition Coefficients[a] of Lidocaine and Prilocaine Between Poly(dimethylsiloxane) Membrane and Oil, Respectively, and Borate Buffer (pH 9.4)

Substance	Membrane (pH = 9.4)	Oil	
		pH = 9.4	pH >> pK_a[b]
Lidocaine	—	7.1(7.06, 7.22)	
Prilocaine	—	3.5(3.52, 3.57)	
Lidocaine in L–P[c]	9.1 ± 1.32 (4)	7.7 ± 0.20 (3)	7.93 ± 0.208 (3)
Prilocaine in L–P[c]	4.4 ± 0.40 (4)	3.5 ± 0.02 (3)	3.59 ± 0.027 (3)
L–P[d]	6.6 ± 0.71 (4)	5.1 ± 0.05 (3)	5.29 ± 0.076 (3)

[a] Mean ± SD (n) or mean (single values). [b] Calculated based on pK_a. [c] Individual substance data determined in experiments with the lidocaine–prilocaine (L–P) eutectic mixture. [d] Calculated from the individual substance data obtained in L–P experiments.

The solubilities of L–P in poly(dimethylsiloxane) membrane are summarized in Table II. Due to its more lipophilic character, lidocaine was more soluble in the membrane than was prilocaine. The poly(dimethylsiloxane) solubilities can also be estimated from the partition coefficients and the aqueous solubilities[6] according to the equation:

$$S_m = S_w K \qquad (2)$$

where S is the solubility, K is the partition coefficient, and the subscripts m and w denote membrane or oil, and water, respectively. The aqueous solubility of the L–P eutectic mixture was determined in 1 mM NaOH to be 0.52% w/v at 32°C.[6] As shown in Table II, the calculated values for the membrane were 17–27% lower than those determined experimentally and ~20% higher than those calculated for the oil. As in the case of an aqueous medium,[6] a combination of lidocaine and prilocaine appears to have lower solubility in poly(dimethylsiloxane) than L and P do separately, as indicated by the calculated values of the non-L–P drugs.

Diffusion Coefficients in Water—The diffusion coefficients in water, D_{aq}, for lidocaine and prilocaine can be estimated from the aqueous diffusion coefficient of benzoic acid using the equation:

$$D_a = \left[\frac{M_b}{M_a}\right]^{1/3} D_b \qquad (3)$$

where M is the molecular weight of the solute denoted by the subscripts a and b for the local anesthetic and benzoic acid,

Table II—Solubility (mg/mL) of Lidocaine and Prilocaine in the Poly(dimethylsiloxane) Membrane and Oil

Substance	Membrane		Oil
	Exp.	Calc.[a]	Calc.[a]
Lidocaine	—	—	25
Prilocaine	—	—	23
Lidocaine in L–P[b]	24	20	17
Prilocaine in L–P[b]	18	13	10
L–P[c]	42	33	27

[a] Calculated according to eq. 2. [b,c] Individual substance data and their sum determined in experiments with the lidocaine–prilocaine (L–P) eutectic mixture.

respectively. Using a D value of 1.113×10^{-5} cm^2/s at 30°C for benzoic acid,[13] the estimated values for lidocaine and prilocaine become 8.96×10^{-6} and 9.14×10^{-6}, respectively. For L–P (1:1 ratio), the weighted mean molecular weight gives an estimated D_{aq} of 9.05×10^{-6} cm^2/s.

The experimental D_{aq} values for lidocaine and prilocaine determined in the shear cell diffusion model were $(7.6 \pm 1.6) \times 10^{-6}$ and $(7.2 \pm 0.8) \times 10^{-6}$ cm^2/s (± 95% confidence intervals). Similar D_{aq} values, $(7.8 \pm 2.5) \times 10^{-6}$ and $(7.4 \pm 0.9) \times 10^{-6}$ cm^2/s, were obtained for lidocaine and prilocaine determined separately in an L–P solution. As expected from their similar molecular weights and chemical structures, the aqueous diffusion coefficients for lidocaine and prilocaine are practically the same. No interaction between lidocaine and prilocaine in L–P solution that would affect the diffusion coefficients was observed.

Even though molecular weights instead of molecular volumes were used in the estimation of D values, the values obtained by eq. 3 are almost the same as those determined experimentally.

Characterization of Membrane Transport—The maximum combined flux of lidocaine and prilocaine through the poly(dimethylsiloxane) membrane was achieved when the L–P eutectic mixture was used as the donor system. Due to the absence of any other solvent in the system, L and P could permeate directly into the membrane without any aqueous diffusion layer reducing the diffusional flux, a situation quite opposite to that of ordinary oil–water systems. The steady-state rate of transfer of L and P (J) per cm^2 can be described by the equation:

$$J = \frac{D_m S_m}{h_m} \tag{4}$$

where D_m, S_m, and h_m denote the membrane diffusion coefficient, the solubility in the membrane, and the thickness of the membrane, respectively.

The following assumptions were made: (*a*) the membrane solubility values determined experimentally were not influenced substantially by the silica fillers; and (*b*) the adsorption of the penetrants onto the silica fillers has only a minor effect on the permeability of the membrane.[14]

The experimental J values for lidocaine and prilocaine from the L–P eutectic were $(2.12 \pm 0.036) \times 10^{-3}$ and $(1.96 \pm 0.033) \times 10^{-3}$, respectively, which gives a total flux of $(4.08 \pm 0.086) \times 10^{-3}$ μmol/(cm^{2}s) (± 95% confidence interval). The corresponding D_m values for lidocaine and prilocaine were calculated from eq. 4 to be 2.6×10^{-7} and 3.0×10^{-7} cm^2/s, respectively, using the solubilities in the membrane determined experimentally (Table II). The differences are well within experimental error and, thus, in accordance with what can be expected in view of the similar molecular weights of these local anesthetics. The higher steady-state flux of lidocaine results from its higher solubility in the membrane. The D_m values of lidocaine and prilocaine are in good agreement with reported data for 4-aminopropiophenone.[15]

Characterization of Combined Membrane and Aqueous Diffusion Layer Transport—A drug release experiment was carried out with a 0.23% L–0.30% P aqueous solution without stirring at 32°C. These concentrations were chosen on the basis that they were close to the aqueous solubility of the L–P eutectic mixture, which is equal to the freely dissolved L–P concentration in the L–P emulsions. Lidocaine and prilocaine were assayed individually using HPLC. The permeabilities were calculated for the 0–40 and the 50–150 min intervals, which correspond to constant and changing donor-side concentrations, respectively. In the calculations, the following equations were used:

$$M_t = P_{T,i} A C t \tag{5}$$

$$-\ln \frac{(M_0 - M_t)}{M_0} = \frac{P_{T,q} A}{V_d} t \tag{6}$$

where M_0 and M_t are the amounts of penetrant in the donor phase at time 0 and in the sink at time t, respectively, C is the initial concentration in the donor phase, V_d is the volume of the donor phase, A is the area of the membrane, P is permeability, and the subscripts T, i, and q refer to total, initial, and quasi- steady-state, respectively. The total diffusion resistance ($1/P_T$) may be written as:

$$\frac{1}{P_T} = \frac{1}{P_m} + \frac{1}{P_{aq}} \tag{7}$$

$$\frac{1}{P_T} = \frac{h_m}{D_m K_{m/aq}} + \frac{h_{aq}}{D_{aq}} \tag{8}$$

where the subscripts T, m, and aq refer to total, membrane, and aqueous, respectively. It was assumed that, due to the use of 0.1 M HCl as the sink, no aqueous diffusion layer existed on the receptor side of the membrane. The initial total permeabilities for lidocaine and prilocaine were found to be $(8.44 \pm 0.81) \times 10^{-5}$ and $(6.19 \pm 0.5) \times 10^{-5}$ cm/s, respectively (95% confidence intervals). The corresponding quasi-steady-state total permeabilities were $(9.31 \pm 0.62) \times 10^{-5}$ and $(6.39 \pm 0.65) \times 10^{-5}$ cm/s (statistically not different from the initial values).

The membrane resistance, $h_m/(D_m K_{m/aq})$, was calculated to be 5376 s/cm for lidocaine and 9615 s/cm for prilocaine. The $K_{m/aq}$ values used in the calculations were obtained with the silicone membrane (Table I). The aqueous resistance (h_{aq}/D_{aq}), calculated according to eq. 7, was found to be 6450 (5360) and 6490 (6030) s/cm for lidocaine and prilocaine, respectively (quasi-steady-state values within parentheses). Using D_{aq} determined in the shear cell diffusional model, the thickness of the aqueous diffusion layer was estimated to be ~460 μm, the mean of the lidocaine and prilocaine values under initial and quasi-steady-state conditions. This value, however, seems to be larger than generally expected under these conditions. When using the most unfavorable 95% confidence limits of the experimental data in the calculations, h_{aq} was found to be ~200 μm, indicating a large uncertainty in the estimate of the aqueous diffusion layer. The unexpectedly high h_{aq} value might be due to an overestimation of the membrane diffusion coefficients. The use of 100% L–P in the donor compartment may have resulted in too high a concentration of the individual substances in the membrane on the donor side and, consequently, in a nonlinear, curved concentration gradient. This would mean that the observed effective thickness of the membrane would appear smaller than the actual thickness of the membrane (127 μm).

From the point of view of formulation development, the combined flux, rather than the individual fluxes of the two local anesthetics, is of major interest. The possibilities of investigating the combined flux of lidocaine and prilocaine from different formulations by determining the two drugs together were examined. Initially, when the concentrations in the donor phase can be assumed to be constant, the two fluxes can be added:

$$J_L + J_p = P_L C_L + P_P C_P \tag{9}$$

$$J_L + J_P = \frac{dM_L}{dt} + \frac{dM_P}{dt} \tag{10}$$

The combined flux will be:

$$J_{L-P} = d\frac{(M_L + M_P)}{dt} \quad (11)$$

where M denotes the amounts of lidocaine and prilocaine in the sink per unit membrane area at different time intervals. P_L and P_p are the individual permeabilities of lidocaine and prilocaine, respectively. The concentration of prilocaine may be written as:

$$C_P = \alpha C_L \quad (12)$$

and the total concentration as:

$$C_T = C_L + C_P = C_L + \alpha C_L = (1 + \alpha)C_L \quad (13)$$

The combined permeability can be written as:

$$\frac{J_{L-P}}{C_T} = \frac{P_L + \alpha P_P}{1 + \alpha} = P_{L-P} \quad (14)$$

If $\alpha = 1$, as for the aqueous solutions discussed later, then:

$$\frac{J_{L-P}}{C_T} = \frac{P_L + P_P}{2} = P_{L-P} \quad (15)$$

Substituting the experimental data for the 0.23% L–0.30% P solution into eq. 11 and the first term of eq. 14 gives a combined permeability of 7.17×10^{-5} cm/s for L–P of a ratio of 1:1.3, by weight; the same as the weighted mean total permeabilities for L and P calculated according to the second term of eq. 14.

To measure the combined amount of L–P in the sink by UV spectrophotometry, the ratio of the single components had to be known. Initially, for equal initial donor concentrations and in the absence of an aqueous diffusion layer, a 1.8 ratio of lidocaine to prilocaine in the sink could be expected, which would correspond to the difference in their membrane permeabilities. However, due to the impact of an aqueous diffusion layer on the donor side that is equally permeable to both L and P, the difference in the effective permeabilities and, consequently, in the sink concentrations, will be less.

The ratios of lidocaine to prilocaine in the sink and the corresponding combined UV absorptivities were determined experimentally for the different L–P formulations. For example, in the case of the 0.23% L–0.30% P aqueous solution, the prilocaine fraction of the combined amount of L–P was 0.47 ± 0.019 (16) at early times (≤40 min) and 0.49 ± 0.014 (18) during the following 140 min of the experiment [mean ± SD (n)]. With 100% L–P in the donor compartment, the prilocaine fraction in the sink was 0.45 ± 0.018 (29). In release experiments with the L–P–surfactant system series I (unstirred conditions), the prilocaine fraction in the sink was found to be 0.45 ± 0.023 (93), and for series II (stirred conditions) 0.48 ± 0.014 (39), during the steady-state interval.

Thus, the ratio of the single components was relatively unchanged. Consequently, it is possible to use the combined flux of lidocaine and prilocaine instead of the individual fluxes in these determinations. However, for more precise determinations of the true diffusion parameters, lidocaine and prilocaine should be determined individually.

Drug Release from Aqueous Lidocaine–Prilocaine Solutions—The aim of this series of experiments was to investigate the relationship between the release parameters and the concentrations of L–P under experimental conditions where only the solutions in the receptor compartment or both compartments were stirred.

To study the influence of L–P present as the dispersed phase on the release rate, droplet-containing systems were prepared by raising the temperature. Since the temperature dependence of L–P solubility in water is exothermic,[6] excess L–P will separate as small drops when the temperature is increased. The L–P concentration used ranged from 0.1 to 0.7% where the ratio of L to P was 1:1 by weight, and the temperatures were 25, 32, and 37°C.

The initial release rate calculated using eq. 11 continued to increase above that found for saturated concentrations when a dispersed phase was present. However, it was no longer directly proportional to the initial concentration. The corresponding combined permeabilities calculated from the first term in eq. 14 are given in Fig. 1. A maximum at or close to the saturated concentration appears to exist. At a low concentration, the slight increase in P could be explained in part by a slight increase in pH which increases the un-ionized, diffusable fraction of the local anesthetics.

The permeabilities above the saturated concentration in Fig. 1 are apparent values, since the total concentration instead of the effective one was used in the calculations. On the other hand, assuming that the effective concentration is equal to the aqueous solubility of L–P (0.52%) when droplets are present, a permeability of 1.24×10^{-4} cm/s was calculated for a 0.7% L–P concentration at 32°C under stirred conditions. This value seems to be too high compared with the value of a 0.5% solution (1.02×10^{-4} cm/s) shown in Fig. 1. This suggests some contribution of the droplets to the effective permeability, either by increasing the effective concentration of L–P or by decreasing the thickness of the aqueous diffusion layer, or both.

When the solution in the donor compartment was stirred, the effective permeabilities were twice those determined under unstirred conditions due to expected differences in aqueous diffusion resistance (Fig. 1). Using unstirred conditions with water as the sink, aqueous diffusion layers were present on both sides of the membrane. Using stirred conditions, the total resistance (R_T) for a 0.5% L–P solution at 32°C was calculated to be 9770 s/cm. If the contribution of the aqueous diffusion layer to the total resistance can be neglected, as the release rate did not increase by increasing the

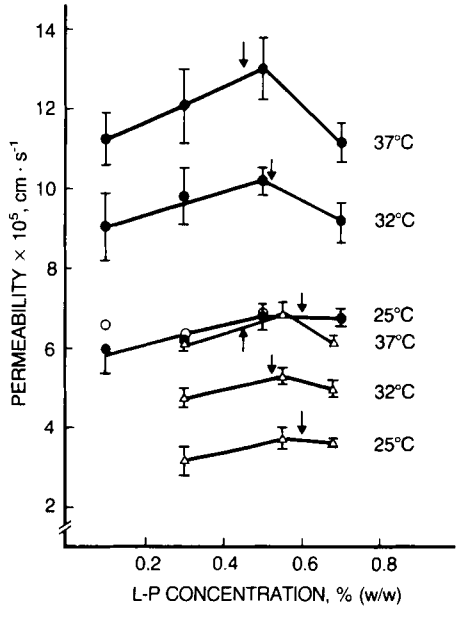


Figure 1—*Combined effective permeability of lidocaine–prilocaine (L–P) in aqueous solution at different temperatures as a function of initial concentration. Key: (●) stirring in the donor compartment; (○) permeability calculated on the un-ionized fraction of L–P; (△) no stirring in the donor compartment, water as sink. The arrows indicate the solubility concentrations of the L–P eutectic mixture. The bars represent 95% confidence intervals.*

stirring speed, R_T will be equal to R_m. In that case, D_m can be calculated from the term $h_m/(D_m K_{m/aq})$. Using the combined K value determined for the membrane (Table I) and 127 μm for h_m, results in a D_m value of 2.0×10^{-7} cm²/s. This would support the view that the D_m values obtained with 100% L–P appear to be too large (2.6×10^{-7} for lidocaine and 3.0×10^{-7} cm²/s for prilocaine).

An activation energy of 40 kJ/mol for the permeation process was calculated from an Arrhenius-type plot of the values in Fig. 1, and is in the range of previously reported data for poly(dimethylsiloxane) membranes.[15]

Drug Release from Lidocaine–Prilocaine Emulsions—The amount released versus time curves for L–P emulsions have an initial steady-state portion, the length of time of which depends on the initial total concentration of L–P (Fig. 2). All release rates from the emulsions were calculated from this portion of the release curves.

When stirring was employed in both the donor and receptor compartments, no significant difference in the initial release rates was observed for emulsion series I (Fig. 3). This suggests that the emulsions contained the same effective concentration of L–P. This effective concentration (C_{eff}) can be calculated from the release experiments with stirring in both compartments, using the equation:

$$C_{eff} = \frac{J}{P} \qquad (16)$$

where J is the steady-state flux from the emulsion per square centimeter and P is the combined effective permeability in centimeters per second for an aqueous L–P solution close to saturation (0.5% was used; Fig. 1).

The following assumptions were made: (*a*) the thickness of the aqueous diffusion layers is the same in both cases; and (*b*) only freely dissolved active substances are transported through the membrane. The results are shown in Table III. Except for the 0.55% solution containing no visible drops, the calculated effective concentrations are similar to the plateau values of the gel filtration studies which were assumed to give the concentrations of the dissolved L–P in the emulsions.[8] These values are somewhat higher than the aqueous solubility of the L–P eutectic, 0.52% w/v at 32°C.[6] However, assumption (*a*) is probably not completely valid due to the presence of droplets.

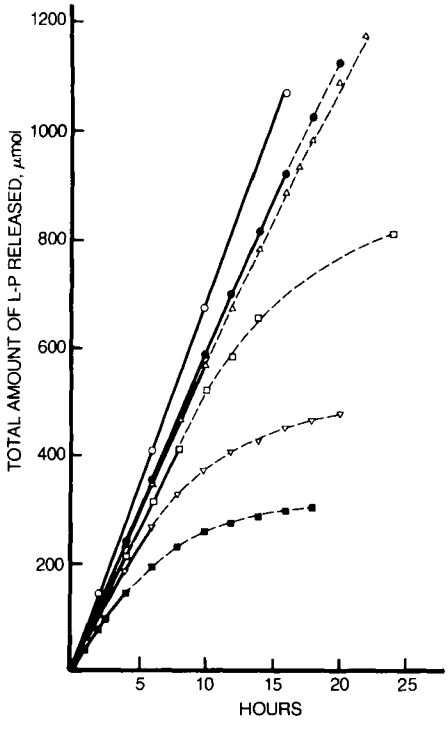


Figure 2—*Drug release profiles for lidocaine–prilocaine (L–P) emulsions of different concentrations at 32 °C. As a comparison, data for the pure L–P eutectic mixture are also shown. The experiments were carried out without stirring in the donor compartment. Key: (■) 1%; (▽) 1.5%; (□) 2.5%; (△) 5%; (●) 10%; (○) 100%. The solid lines indicate the linear portions of the release profiles.*

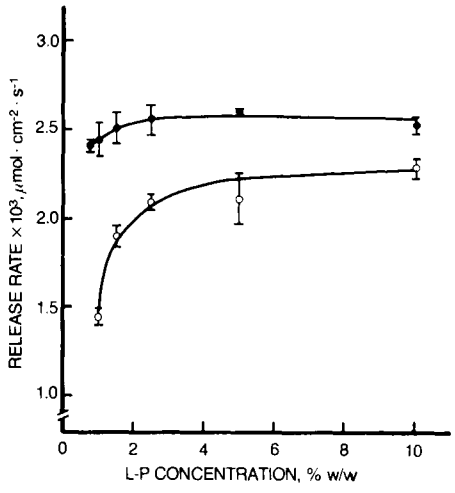


Figure 3—*Release rate at 32 °C as a function of lidocaine–prilocaine concentration in the emulsions. Key: (○) no stirring in the donor compartment; (●) stirring in the donor compartment. The bars represent 95% confidence intervals.*

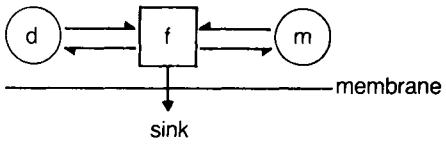
Table III—The Effective Total Concentrations (C_{eff}) in the Lidocaine–Prilocaine (L–P) Emulsions[a]

Conc. of L–P, % w/w	$J \times 10^3$, μmol/cm² · s	C_{eff}, % w/v
0.55	1.87	0.42
0.75	2.41	0.54
1.0	2.44	0.55
1.5	2.51	0.56
2.5	2.56	0.57
5.0	2.60	0.58
10.0	2.53	0.57

[a] Calculated from release data at 32°C according to eq. 16.

A plot of the release rates from an unstirred L–P emulsion as a function of the total concentration resulted in a steep curve which leveled off at a concentration of ~2.5% (Fig. 3). The difference between the curves representing stirred and unstirred systems is probably due to the presence of a thicker aqueous diffusion layer on the donor side of the membrane in the unstirred system. In addition, some batch variation in membrane permeabilities between the two series cannot be excluded. The fact that the difference in release rates gradually decreases as the emulsion concentration increases, points to the involvement of L–P fractions other than those which are freely dissolved.

Recently, Amidon et al.[16] showed that in saturated surfactant solutions, micelles act as carriers across the aqueous diffusion layer, and thereby, depending on the concentration, diminish or even eliminate diffusion layer resistance. The L–P emulsion also represents, in part, a saturated micellar solution. In addition, it contains the emulsified droplet phase as another reservoir of the diffusant. A dynamic equilibrium exists between them and the dissolved L–P according to Scheme I:



Scheme I—Schematic representation of drug release from lidocaine–prilocaine emulsion system. Emulsified, freely dissolved, and surfactant-solubilized fractions of L–P are denoted by d, f, and m, respectively.

At $t = 0$, the formulation in the donor compartment is homogenous and saturated due to an equilibrium between the dissolved, solubilized, and emulsified fractions of L–P. At $t > 0$, the loss of solute due to transport across the membrane is replenished by rapid dissolution of droplets as long as a substantial number of droplets are present. Across the diffusion layer, a constant concentration gradient of the dissolved L–P is maintained for several hours, as the steady state of the initial release rate suggests (Fig. 2). Droplets from the bulk are transported to the boundary layer and supply the solute which diffuses through the membrane. It is assumed that saturation conditions still exist in the bulk and that the transport between the different forms of L–P (dissolved, surfactant-solubilized, and emulsified) takes place instantaneously, thus not influencing the rate of the overall diffusion process.

The surfactant does not diffuse through the membrane to any significant degree. Thus, due to the dissolution of the droplets, the surfactant concentration and, consequently, the solubilized fraction of L–P increases in the aqueous phase of the emulsion. As long as a large number of droplets are present, this is not reflected in the release curves.

As the initial concentration of droplets increases, the number found in the aqueous diffusion layer increases. The diffusion limiting effect of this layer decreases, since the droplets too can act as carriers of L–P to the membrane surface. Presumably, this is reflected in the leveling off and the approach of the curves for the stirred and unstirred emulsions as the initial L–P concentration in the emulsions increased (Fig. 3).

Due to these features of the drug release process, the L–P emulsion system actually resembles a suspension more than an emulsion. In the latter case, if an emulsion is formulated with an inert oil, the distribution of an active substance between the phases would result in a decreased thermodynamic activity. Though both a suspension and the L–P emulsion system theoretically have a high thermodynamic activity due to the saturation of the external phase, the dissolution rate of solid particles in a suspension could be a limiting factor. By contrast, the fluid state of the L–P "particles" may promote a higher dissolution rate.

The total amount of L–P in the formulation can be written:

$$C_T V_T = C_f V_f + C_m V_m + C_d V_d \qquad (17)$$

where subscripts T, f, m, and d denote the total, dissolved, surfactant-solubilized, and emulsified fractions of L–P, respectively. With the emulsions of series I, both $C_m V_m$ and $C_d V_d$ increased as the total concentration of the emulsified phase increased, while $C_f V_f$ remained fairly constant. Thus, it is difficult to distinguish between the influence of droplets and micelles on the increase in drug release rate from the unstirred emulsions. However, as was shown earlier,[8] the droplet fraction of L–P increased rapidly as the total L–P concentration increased while the micelle fraction remained constant.

To further study the role of the two reservoirs in the L–P emulsion, L–P–surfactant system series II was prepared. In this series, the ratio of the concentration of surfactant to the concentration of L–P was increased.

The ratios cover a range of emulsions and clear solubilized solutions. The relationship between L–P (y) and surfactant (x) concentration in the external, clear, aqueous phases of the L–P emulsions at 32°C was found to be: $y = 0.56x + 0.39$.[8] Thus, the droplet phase of the 1.0, 2.5, and 5.0% L–P emulsions should disappear at surfactant concentrations of ~1, 4, and 8%, respectively. In reality, these surfactant concentrations proved to be the minimum amounts necessary to change the appearance of the emulsions from white and opaque to grey-white and translucent. At higher surfactant concentrations the systems became clear.

The drug release rates when no stirring was used in the formulation compartment as a function of the surfactant concentration are shown in Fig. 4. These values are higher than those found in series I, and they can be explained by the batch variation in the membrane permeability. The curves for the 2.5 and 5.0% L–P systems consist of two portions. The first portion of the curves has a small negative slope. A common parameter for the formulations of different surfactant concentrations is that the fraction of the droplet phase decreases and that of the micellar phase increases with increasing surfactant concentration. The slight decrease in the release rate suggests that the depot effect of both the droplets and the micelles is important. When droplets are present, the micelles are saturated with L–P, and thus their carrier function, rather than their inhibiting effect due to partitioning, predominates. However, in the aqueous diffusion layer the latter phenomenon may be responsible for the decrease in the release rate. When the droplets are dissolved in the aqueous diffusion layer, the micellar concentration may increase and thus further decrease the release rate.

The second portion of the curves for the 2.5 and 5% emulsions, as well as the curve for the 1% L–P systems, show a substantial decrease in drug release rate as the concentration of the surfactant is increased. This behavior can be explained by a decrease in the concentration ratio of freely dissolved drug to micellar drug, since these mixtures were primarily solubilized systems that contained only a negligible amount of an emulsified phase.

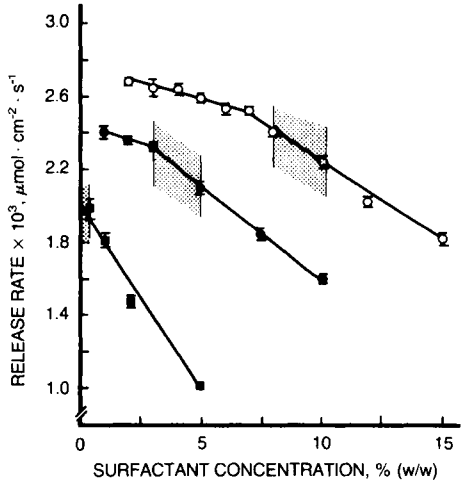


Figure 4—*Drug release from lidocaine–prilocaine–surfactant systems at 32°C as a function of surfactant concentration using unstirred conditions. Key: (■) 1.0%; (●) 2.5%; and (○) 5.0% L–P. The bars represent 95% confidence intervals. The shaded intervals mark the surfactant concentrations where the appearance of the formulations changed from white and opaque to greyish-white and translucent, and then, to clear.*

As changes in physicochemical parameters due to increased surfactant concentration may influence drug release rate, the pH and the viscosity of the L–P formulations were measured and compared with those of surfactant solutions of the same concentrations. Aqueous solutions of the surfactant have an acidic pH, presumably due to the presence of water-soluble acidic components. The pH versus concentration curve shows a rather rapid decrease in pH at lower surfactant concentrations, which then levels off (Fig. 5, insert). The similarity between this plot and that for the L–P emulsions (Fig. 5) would suggest that the decrease in pH of the L–P emulsions is due to the chemical nature of the surfactant. According to the pH-partition theory, this may decrease the membrane transport of the local anesthetics only to a minor extent, as the ionized fraction of the solute is <10% in this pH range. Furthermore, in the case of the 5% L–P systems, the change in pH was greater at the lower surfactant concentrations, while the release rate decreased more rapidly at higher surfactant concentrations.

With an increasing concentration of the surfactant, the viscosity of the formulations increased (Fig. 6). The nonlinearity of the curves at higher surfactant concentrations suggests an interaction between the micelles, especially in the L–P formulations. However, the viscosities were still Newtonian. The viscosity increase due to the surfactant may decrease the drug release rate in two ways: by an increase in the microviscosity of the system due to the presence of the water-soluble components; or by hindrance of micelle diffusion due to interaction between the micelles.

When comparing the viscosity with the drug release profiles for the 5% L–P formulations (Figs. 4 and 6), a relationship seems to exist. That is, diffusion of the micelles in the formulations may be hindered due to steric effects. On the other hand, a substantial decrease in the release rate from the 1% L–P formulations occurred with an increasing surfactant concentration. This occurred even though the viscosity did not change remarkably in this surfactant concentration range.

It can be concluded, therefore, that changes in both pH and viscosity due to the increase of surfactant concentration

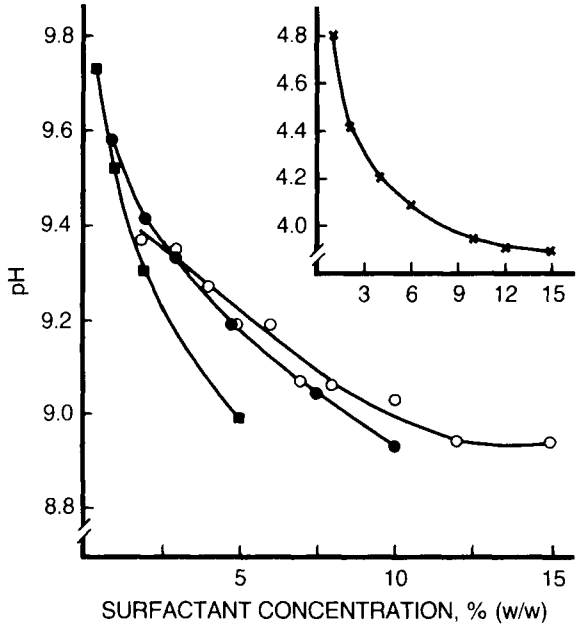


Figure 5—*Effect of the surfactant concentration on the pH of lidocaine–prilocaine emulsions at 23 °C. The insert shows the pH without L–P. Key:(■) 1.0%; (●) 2.5%; and (○) 5% L–P.*

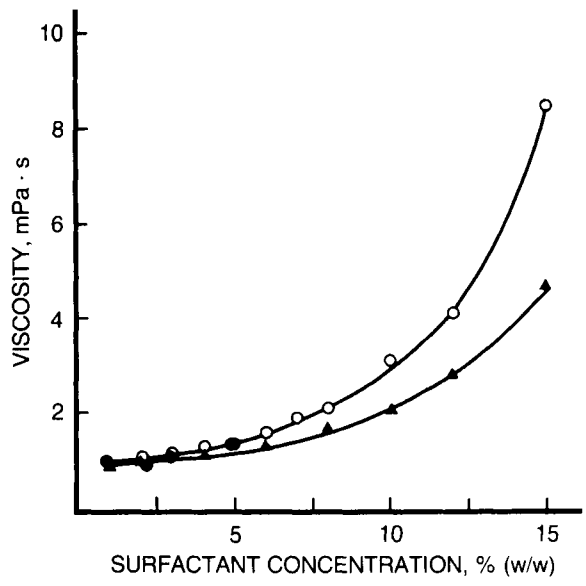


Figure 6—*Viscosity of lidocaine–prilocaine–surfactant systems and surfactant solutions (▲) at 32 °C as a function of surfactant concentration. Key: (●) 2.5% and (○) 5.0% L–P.*

apparently were not responsible for the decrease in drug release rates. Rather, partitioning of the active substances into the micelles as well as disappearance of the droplets in the diffusion layer account for the altered rates.

Drug Release from Lidocaine–Prilocaine Gels—The L–P formulations were thickened with neutralized carbomer 934P. The resulting solution, emulsion, or micellar gels had a pH of ~9.4, and thus contained the local anesthetics mainly in their uncharged form. The release profiles for an emulsion gel containing 1% carbomer 934P and that for a non-thickened emulsion are shown in Fig. 7. The initial release rates were similar for both systems. During the initial release, the process is assumed to be controlled by the membrane and the adjacent aqueous diffusion layer. With time, the release rate from the gel decreased continuously; after 4 h, the amount of L–P released was only about half of that from the non-thickened emulsion. This can be explained by the formation of a depletion zone in the gel. The thickness of this stagnant

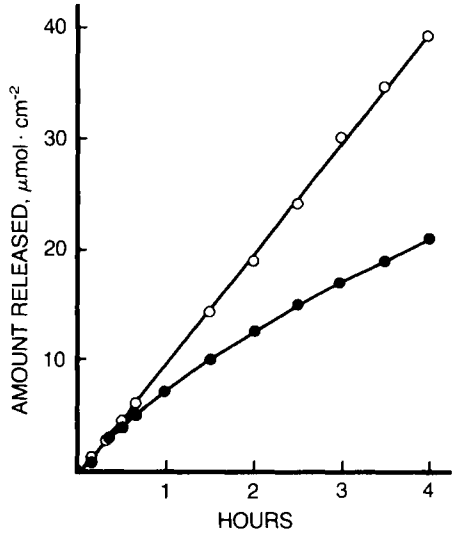


Figure 7—*Drug release profile at 32 °C for a non-thickened emulsion (○) and an emulsion-gel (●) containing 5% lidocaine–prilocaine and 1.9% surfactant.*

diffusion layer next to the membrane increased to such a degree that the release process became vehicle-controlled. This was the case for time intervals > 1 h, as suggested by the linearity of a square root of time plot of this data.

The effect of the concentration of carbomer 934P on the macroviscosity and the drug release rate from 0.5% L–P solutions containing 0.19% surfactant is shown in Fig. 8. The apparent diffusion coefficients were calculated according to:[17]

$$D = \left(\frac{k_{qs}}{2C_0}\right)^2 \pi \qquad (18)$$

where k_{qs} is the slope of amount released per squared centimeters versus the square root of time and C_0 is the initial concentration. The apparent diffusion coefficients were 34.6×10^{-6}, 17.2×10^{-6}, and 7.4×10^{-6} cm^2/s for solutions with 0, 0.1, and 0.2–1.3% carbomer 934P, respectively. The value of 7.4×10^{-6} cm^2/s is the same as that determined for aqueous solutions of the local anesthetics in the shear cell diffusion model. The higher D values at lower carbomer 934P concentrations indicate the existence of processes other than diffusion in the formulation promoting the drug release. At these polymer concentrations, the gel structure might not be developed sufficiently to hinder convective mass transport. The physical entrapment of the L–P droplets at >0.2% polymer concentration can be compared with that of the 0.3-μm latex particles being entrapped at a concentration of 0.3% carbomer 934P.[18] For benzocaine,[19] the diffusivities in carbomer 934P gels were essentially the same as in the non-gelled liquid phase of the gels. Our data shows that this is true also for basic substances such as lidocaine and prilocaine which form salts with carbomer 934P unless the acidic groups on the polymer, as in this case, are neutralized in advance.

To study the release of lidocaine and prilocaine from gels, the lidocaine–prilocaine–surfactant systems of series I and II were thickened with 1.0 and 0.4% neutralized carbomer 934P, respectively. According to Fig. 8, this difference in the carbomer 934P concentration should not influence the drug release rate.

The initial release rates, as discussed above, were similar to those from the non-thickened emulsions, and could only be calculated for the first 30–60 min of the release process. For the thickened emulsion series I, the plot of the quasi-steady-state release rates versus the square root of the total concentration of L–P resulted in a straight line (Fig. 9). This is in agreement with the theory for a matrix-controlled diffusion process where the active substance is only partly dissolved.[20]

The effect of surfactant concentration on release from a thickened system is shown in Fig. 10. For this series of lidocaine–prilocaine–surfactant systems (II) a successive decrease of the release rate was observed as the concentration of the surfactant increased. No clear difference can be distinguished between the emulsion and the completely solubilized systems, as was the case for the non-thickened formulations (Fig. 4).

Apparent diffusion coefficients in the emulsion gels were calculated according to an equation derived by Higuchi for suspension ointments:[20]

$$D = \frac{k_{qs}^2}{2C_T C_s} \qquad (19)$$

where the symbols are the same as in eq. 18 and the subscripts T and s refer to the total and solubility limit concentrations of L–P in the vehicles, respectively. For C_s, the aqueous solubility of the L–P eutectic mixture, 0.52%, (w/v) was used. The increase in the amount of solubilized L–P

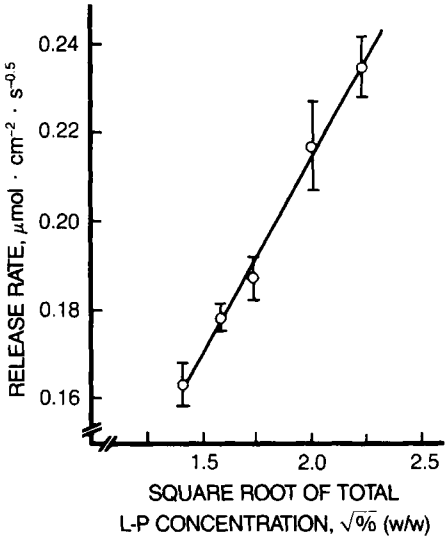


Figure 9—*Relationship between the quasi-steady-state drug release rate at 32 °C and the total lidocaine–prilocaine concentration in the emulsion-gel series I. The bars represent 95% confidence intervals; r = 0.997.*

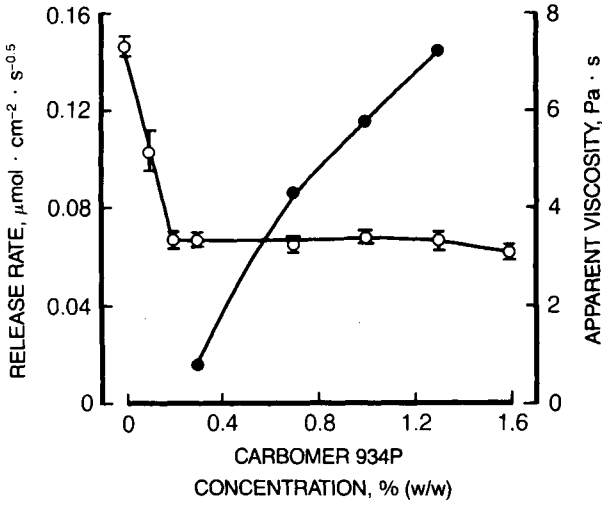


Figure 8—*Effect of the carbomer 934P concentration on the apparent viscosity at a shear rate of 36 s^{-1} (●) and drug release rate (○) at 32 °C from solutions containing 0.5% lidocaine–prilocaine and 0.19% surfactant.*

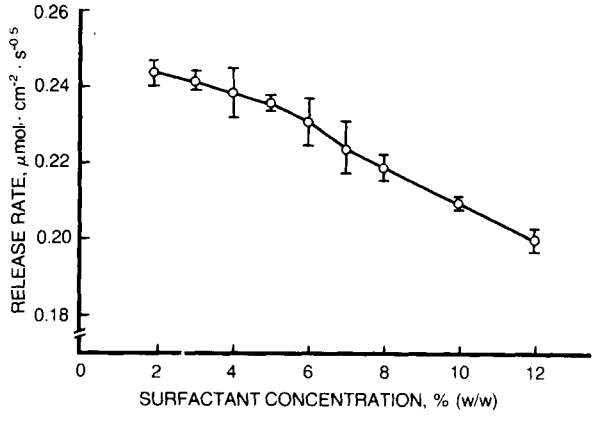


Figure 10—*Effect of surfactant concentration on the quasi-steady-state drug release rate at 32 °C from the 5% lidocaine–prilocaine emulsion and micellar gels. The bars represent 95% confidence intervals.*

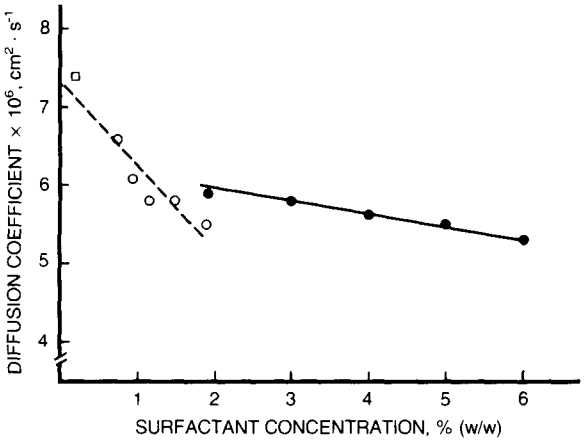


Figure 11—*Apparent diffusion coefficients at 32°C in lidocaine–prilocaine gels as a function of surfactant concentration. Key: (□) solution-gel containing 0.5% L–P (eq. 18); (○) emulsion-gel series I with 2.0, 2.5, 3.0, 4.0, and 5.0% L–P (eq. 19); (●) emulsion-gel series II wit 5% L–P (eq. 19). Since the L:P:surfactant ratio in the 0.5% L–P solution-gel was the same as in emulsion-gel series I, this solution has been included in the line of this series.*

with increasing surfactant concentrations was not taken into consideration, i.e., a distinction was not made between the solubilized and emulsified fractions of L–P. Further, as C_T was about four to ten times larger than C_s, it was not corrected for the freely dissolved fraction of L–P. The apparent D values as functions of surfactant concentration are shown in Fig. 11. The experiments with the two series were carried out at different dates and by different operators, which probably accounts for the slightly higher values for series II. It can be seen that the decrease of D due to increasing surfactant concentration was larger for series I, where the L–P concentration increased at the same time. The increase of L–P concentration also resulted in a proportional decrease of the macroviscosity. This might be due to a breakdown of the gel structure which would decrease its entrapping capacity, and in turn, increase rather than decrease the D values in the system. However, these changes were relatively small; the viscosity of a 1% carbomer 934P gel decreased by only 1.0 Pa·s on the addition of 5% emulsified L–P.

The microviscosity being the important factor, the decrease of the values for series I could, at least partly, be explained by the presence of free, water-soluble acidic components in the surfactant as discussed above in connection with the non-thickened emulsions. However, just increasing the surfactant concentration and thereby solubilizing more L–P, as in the series II systems, has a minimal effect on the values. The difference in sensitivity to the surfactant concentration between the series I and series II systems (Fig. 11) might depend on the increased presence of micellar-bound L–P within series II, since eq. 19 does not consider the solubilized L–P. To explain this, the diffusion of micellar L–P, at least partly, has to counteract the effect of a possible increase in microviscosity. However, the observed decrease in the apparent diffusion coefficients is small and the studied systems are complicated, since direct interactions between the three components (drug, surfactant, and polymer) may influence the observed D values.

Conclusions

The release process was both membrane and aqueous layer controlled for non-gelled systems. For the gelled systems, this was the case for the initial release but later, at $t > 1$ h, the release became formulation-controlled. There was no difference in the effective permeability whether calculated from the initial or the quasi-steady-state phase of the release process up to the solubility limit of L–P.

The diffusion coefficients in water for lidocaine and prilocaine individually and in combination, were found to be the same, i.e., $\sim 7.5 \times 10^{-6}$ cm^2/s, suggesting no interaction between the active substances. Diffusion coefficients of the same magnitude were obtained from release data on L–P emulsion gels which indicates that the dissolution rate of the droplets did not influence drug delivery.

The release rates from aqueous solutions were directly proportional to the initial L–P concentration up to the solubility limit with and without stirring in the donor compartment. For the non-gelled L–P emulsions, the steady-state release rate versus total L–P concentration curve reached a plateau at a concentration of ~2.5%. The quasi-steady-state release rate from L–P emulsion gels was directly proportional to the square root of the total L–P concentration.

Both the emulsified and surfactant-solubilized fractions of L–P in a lidocaine-prilocaine-surfactant system acted as reservoirs. However, from a drug release point of view, the droplets were superior to the micelles in this respect. As long as a large number of droplets were present, the inhibiting effect of the surfactant on the drug release rate was not prevalent.

Gels produced by carbomer 934P concentrations >0.2% physically entrapped not only the L–P droplets but also bulk water. Thus, streaming in the formulation was prevented. No interaction between the local anesthetic bases and the neutralized carbomer 934P occurred at the investigated concentrations. Up to concentrations of at least 1.3%, the gel structure of carbomer 934P does not appear to inhibit diffusion.

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