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# Physicochemical and release studies of naproxen in poloxamer gels

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**Abstract**

The solubility of naproxen at pH 2 was significantly increased as a linear function of PF-127 concentration at three temperatures. Naproxen was highly entrapped by the micelles as indicated by large partition coefficients. The micellar solubilization was a spontaneous ($\Delta G < 0$) and exothermic ($\Delta H < 0$) process which resulted in a less orderly state ($\Delta S > 0$). In the presence of PF-127, the release of naproxen across the membrane was significantly sustained at pH 2 and inversely proportional to the surfactant concentration. At pH 7, PF-127 had little effect on the membrane transport of naproxen. The release of naproxen from the PF-127 gel into isopropyl myristate was dependent on the medium pH. The highest release was observed at pH 6.3. The diffusion coefficients of naproxen were inversely proportional to drug loading and PF-127 concentration. The activation energy of 7.45 kcal/mol for the diffusion of naproxen in the gel was calculated using the Arrhenius equation.

*Keywords:* Naproxen; Micellar solubilization; PF-127; Membrane transport; Isopropyl myristate; Diffusion coefficient

## 1. Introduction

Naproxen, S-2-(6-methoxy-2-naphthyl) propionic acid, is a potent nonsteroidal anti-inflammatory drug with analgesic and antipyretic properties. Like other NSAIDs, the most common side effect of naproxen in oral dosage forms is gastrointestinal irritation. Thus, alternative routes of administration for these drugs are being currently investigated. Recent studies have shown significant drug levels in deep tissues such as fascia, muscle and synovium after topical application (Monteiro-Riviere et al., 1993; Rabinowitz et al., 1982; Singh and Roberts, 1994), which is a desirable feature for the relief of local symptoms with low dose, thereby reducing systemic side effects. Poloxamer 409 (PF-127), one of many polyoxyethylene-polyoxypropylene-polyoxyethylene type block copolymers, is a nonionic surfactant with an average molecular weight of 12 600, consisting of 70% polyoxyethylene units (BASF Company). Since it has many attractive characteristics (BASF Company; Henry and Schmolka, 1989) such as low toxicity, thermoreversibility, micelle formation and gelling property, PF-127 has been employed as a vehicle in various dosage forms such as injectable solutions (Collett et al., 1985) and

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semisolid formulations for dermatological (Nalbandian et al., 1972; Miyazaki et al., 1984) and ophthalmic (Saettone et al., 1988) use.

The drug delivery process from topical formulations is controlled by the physicochemical interactions between the drug and the vehicle which kinetically or thermodynamically govern the release of drug to the skin. Such interactions can become particularly important when the barrier function of skin is compromised. In vitro release study has been used as a means of evaluating the effects of formulation parameters on drug release from a semisolid formulation and further determining lot-to-lot variability. Method development includes selecting an appropriate receptor medium and optimizing the effects of formulation factors on release.

The purposes of this study were to investigate the physicochemical phenomena and thermodynamic properties of naproxen in PF-127 and to determine the effects of micellar solubilization on the release of naproxen from the vehicle into the receptor medium under various conditions.

## 2. Materials and methods

### 2.1. Materials

Naproxen and isopropyl myristate (Sigma Chemical Co., St.Louis, MO), PF-127 (BASF Wyandotte Corp., Parsippany, NJ), ethanol (Florida Distillers Co., Lake Alfred, FL), hydrochloric acid (EM Science, Gibbstown, NJ), sodium hydroxide, potassium dihydrogen phosphate, potassium hydrogen phthalate, boric acid and potassium chloride (all from J.T.Baker Chemical Co., Phillipsburg, NJ) were used as received from the manufacturers.

### 2.2. Solubility test

An excess amount of naproxen was added to 0.01 N HCL (pH 2) containing different amounts of PF-127 (0-10%, w/w) in glass vials which were continuously shaken for 48 h in a thermostatted water bath set at 25, 30, or 35°C ( ± 1°C). The properly diluted samples were assayed by U.V. spectrophotometer (Bausch and Lomb, Spectronic$^R$ 2000) at 230 nm after passing through 0.45 $\mu$m Millipore membrane filters. The solubility was established by analyzing serial samples. To minimize the effect of temperature change on solubility, filtration was performed in a temperature-controlled oven. PF-127 did not interfere with the assay.

### 2.3. Dialysis study

Dialysis bags, prepared from Visking Cellophane tubings (MWCO 3500 and diameter 2.4 cm), were filled with 3 ml of a saturated naproxen solution in 0.01 N HCL (pH 2) or 0.1 M phosphate buffer (pH 7) containing different amounts of PF-127. The bags were individually immersed in a beaker containing 500 ml of a receiver solution having the same pH as the donor phase. The temperature was maintained at 25°C ( ± 1°C) and the receptor medium was constantly stirred to maintain the sink condition. At appropriate time intervals, samples were taken from the receiver solution and assayed spectrophotometrically to quantitate the amount of naproxen released through the membrane. The samples were returned to the receiver solution after assay.

### 2.4. Preparation of PF-127 gels

PF-127 gels of naproxen were prepared by the cold method as described by Schmolka (Schmolka, 1972): an adequate amount of PF-127 was dissolved in a buffer solution or in distilled water for the study of the effect of initial drug concentration on release, and the solution was left in a refrigerator overnight. When the mixture became a clear solution, an ethanolic solution containing an appropriate amount of naproxen was thoroughly mixed into the PF-127 solution. The mixture containing 18% (w/w) ethanol was then left at room temperature until becoming a clear gel. Hydrochloric acid buffer (0.2 M) for pH 2–3, phthalate buffer (0.2 M) for pH 3–6 and phosphate buffer (0.2 M) for pH 6–8 were used to study the pH effect on the naproxen release from the poloxamer gel. The pH of the gels was measured with a Corning pH meter after liquifying

the gels in a refrigerator. The Brookfield digital viscometer (model DV-11) was used to measure the bulk viscosity of the gels at 20, 30, 40 and 50°C.

### 2.5. In vitro naproxen release

The release of naproxen from PF-127 gels into isopropyl myristate, a lipophilic medium, was determined using the membraneless diffusion cells described by Poulsen et al. (Poulsen et al., 1968). This method offered the advantage of measuring naproxen released directly into the receptor phase without crossing a barrier membrane. The liquified formulations were poured into a thermostatted jacket-beaker (3.4 cm i.d., 7 cm height) to the depth of 0.5 cm thick. After returning to the gel state at room temperature, 30 ml of isopropyl myristate which was preheated to the experimental temperature was poured over the gel. A three-blade stirrer (Arrow Engineering Co., 2.5 cm diameter) was placed at 0.7 cm above the gel surface in the diffusion cell and was rotated at 70 rpm continuously. At predetermined intervals, a 3-ml sample was removed from the receiver solution at the same location each time for the determination of naproxen released using the spectrophotometric assay. After measuring the absorbance, the sample was returned to the receiver solution.

### 2.6. Data treatment

For the release of drug from one side of a semisolid slab in which the drug is completely dissolved, Higuchi derived the following equation (Higuchi, 1962):$Q = 2\ C_0\ (D\ t\ /\ \pi)^{1/2}$where Q is the amount of drug released per unit surface area; $C_0$, the initial concentration of drug in vehicle; D, the diffusion coefficient; and t is the diffusion time. According to this equation, the amount released is a linear function of the square root of time, and the slope represents the diffusion coefficient of drug in the vehicle. Several assumptions were made for the use of this equation; (a) the total amount of drug released is less than 30% of the drug initially present, (b) only the drug diffuses out of the vehicle, not any other components, (c) D remains constant with respect to both time and position in the vehicle, and (d) the receptor phase is maintained in the sink condition. Since the naproxen gel prepared was a semisolid formulation in which the drug was uniformly dissolved, the Higuchi model was used for the analysis of naproxen release data from the gel.

## 3. Results and discussion

### 3.1. Solubility of naproxen in PF-127 solutions

For the development of a topical formulation, the solubility of the active ingredient in the vehicle is often an important factor to determine the applied dose. Naproxen is practically insoluble in water, thus limiting its use in aqueous preparations. Since surfactants have been successfully used to enhance the solubility of drugs in many pharmaceutical formulations, PF-127 was evaluated for its potential use in formulating an aqueous naproxen preparation in this study.

#### 3.1.1. Solubility profile

Fig. 1 shows a linear relationship between the amount of naproxen solubilized and the concen-

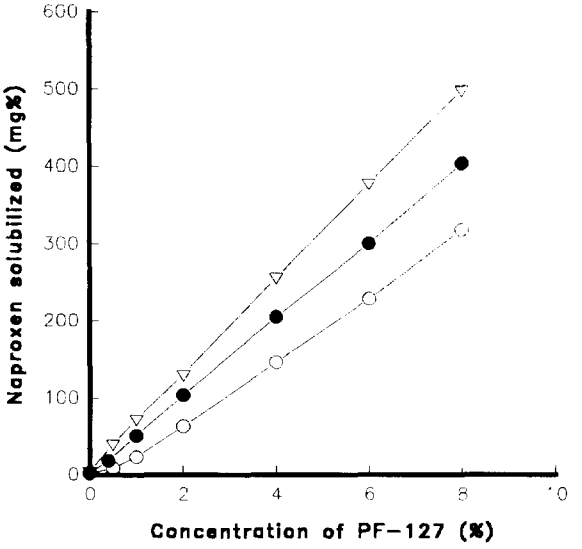



Fig. 1. Solubility profiles of naproxen in PF-127 solutions at 25°C (○), 30°C (●), 35°C (▽) ($n = 3$).

Table 1
Partition coefficients (Km) and thermodynamic parameters of naproxen in PF-127 solution at three temperatures < TB1 >

| | 25°C | 30°C | 35°C |
|---|---|---|---|
| Km | 1814 | 1683 | 1536 |
| $\Delta$G (kJ/mol) | -18.6 | -18.7 | -18.8 |
| $\Delta$H (kJ/mol) | -12.7 | | |
| $\Delta$S (J/K.mol) | +19.8 | +19.9 | +19.8 |

tration of the poloxamer in the medium at three temperatures. The solution properties of a surfactant including the solubilizing activity are generally known to change drastically near the critical micelle concentration (CMC). In the presence of 8% PF-127, the solubilities of naproxen increased nearly 100-fold at each of the three temperatures. However, due to the low CMC of PF-127 (Rassing and Attwood, 1983), the transition point in the solubility profiles was not clearly shown in this figure.

The solubilization of drugs in a surfactant solution has been suggested to occur due to the increased partitioning of solute molecules into the micelles which could be considered as a separate, pseudo-phase (McBain and Hutchinson, 1955). The linear increase in the solubility of naproxen as a function of PF-127 concentration observed in this study suggested that the total micellar volume into which naproxen partitioned was a linear function of the amount of PF-127 present.

*3.1.2. Partition coefficient*

The partition coefficient of naproxen (Km) between micellar and aqueous phases was determined by the ratio of the naproxen solubility in the micellar phase (Sm) to that in the aqueous phase (Sw) as shown in Table 1. The solubility of naproxen in the extramicellar phase was assumed to be equal to that in water since colloidal surfactants usually do not change the chemical potential of the solute (McBain and Hutchinson, 1955). The Sm values were estimated by extrapolating the solubility of naproxen to 100% (w/w) of PF-127 as previously reported (Humphreys and Rhodes, 1968). The large Km values observed in this study indicated that naproxen had highly partitioned into the micelles.

The partition coefficients of naproxen were found to be inversely related to temperature. When temperature was increased from 25°C to 35°C, the log Km values were decreased from 3.26 to 3.19, despite the higher solubilities of naproxen in both the micellar and aqueous phases. According to Elworthy and McDonald (Elworthy and McDonald, 1964), the size of micelles increased only slightly until a threshold temperature, approximately 20°C below the cloud point of the surfactants, was reached. They showed that beyond this temperature, the micellar volume expanded rapidly and asymmetrically, thus causing increased loading of the drugs into the micelles. In this experiment, the highest temperature used was 50°C, far below the cloud point of PF-127 which was reported to be beyond 100°C (BASF Company). Therefore, the reduction of Km at 35°C as compared to that at 25°C could be attributed to a smaller increase in the solubility of naproxen in the micellar phase than that in the external aqueous phase, probably due to a higher temperature coefficient of the aqueous solubility of naproxen.

*3.1.3. Thermodynamics*

Table 1 summarizes the thermodynamic parameters associated with the solubilization of naproxen in the PF-127 solution. These parameters are particularly useful in understanding the thermodynamic phenomena involved in the micellar solubilization of naproxen. The standard free energy change which indicates the spontaneity of the solubilization process was calculated using the equation: $\Delta G = - RT \ln Km$, where $\Delta G$ is the free energy change for the transfer of one mole of naproxen from the aqueous phase into the micellar phase; R, the gas constant; T, the absolute temperature; and Km is the partition coefficient. All the values of $\Delta G$ obtained at the three temperatures were found to be negative, indicating that naproxen molecules spontaneously partitioned into the micelles.

The standard enthalpy change, $\Delta H$, which was calculated from the slope of the Van't Hoff plot representing $d \ln Km / d(1/T) = -\Delta H/R$, was also negative, indicating that the micellar solubilization of naproxen was an energetically favored

exothermic process. The negative $\Delta H$ values for the solubilization of selected steroids in the non-ionic polyoxyethylene surfactant solution were previously reported (Barry and El Eini, 1976).

The standard entropy change for the micellar solubilization of naproxen which was calculated using $\Delta S = (\Delta H - \Delta G) / T$ was a positive value (Table 1). The observed increase in entropy can be explained by a loss of orderliness resulting from the redistribution of naproxen from an aqueous phase to a micellar pseudo-phase. During this process, a disruption of the water structure surrounding the hydrophobic naproxen molecules could increase the entropy of the system. Conversely, the entrapment of naproxen molecules within micelles could restrict their activity, causing a decrease in entropy of the system. However, the net increase in entropy suggests that the disruption of water structure was sufficient to compensate for the entropy loss due to the micellar entrapment of naproxen.

### 3.2. Release of naproxen across membrane

The effect of micellar solubilization of naproxen on the release profile was evaluated using the dialysis method. A cellophane membrane (Spectra/Por$^R$, MWCO 3500), which was permeable to naproxen while impermeable to the PF-127 micelles, was used as the barrier membrane. The rate of release across the membrane was measured both at pH 2 and 7 where naproxen was primarily unionized and ionized, respectively. As shown in Fig. 2 and Fig. 3, in the presence of 8% PF-127 in the donor phase, almost 90% of naproxen was released across the membrane within 5 h at pH 7, while only 6% of the drug was released at pH 2 during the same period. PF-127 micelles apparently served as a reservoir for the release of unionized naproxen, while ionized naproxen was released quickly without the influence of the surfactant. These results are clearly indicative of the potentially useful role of an amphiphilic compound such as PF-127 in sustaining the release of non-polar drugs from liquid or semisolid vehicles.

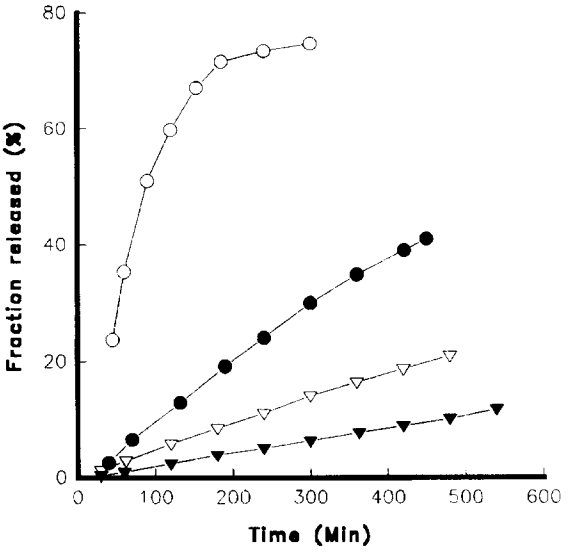



Fig. 2. Effect of PF-127 concentration (0%,○ ; 2%,●; 4%,▽; 8%,▼) on membrane transport of naproxen at pH 2, 25°C ($n = 3$).

### 3.3. Release of naproxen from PF-127 gel

The effects of various formulation factors on naproxen release into a lipophilic vehicle were investigated using membraneless diffusion cells.

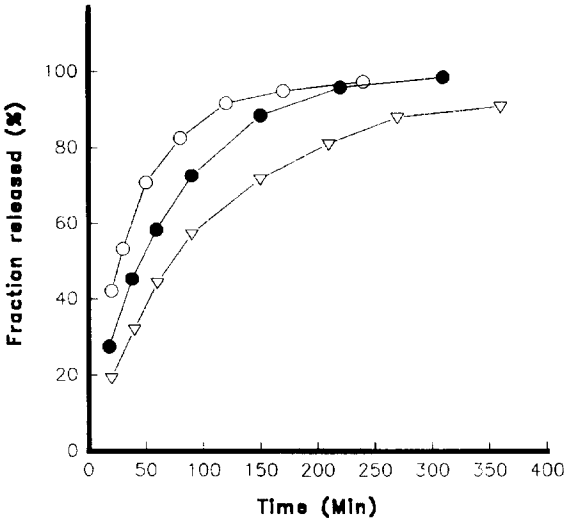



Fig. 3. Effect of PF-127 concentration (0%,○; 2%,●; 8%,▽) on membrane transport of naproxen at pH 7, 25°C ($n = 3$).

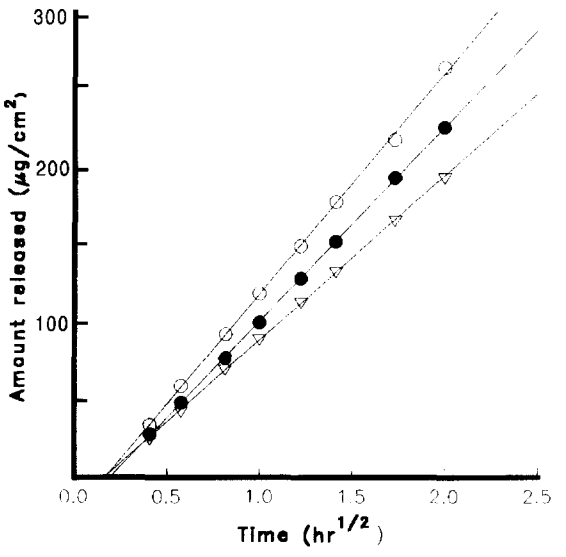


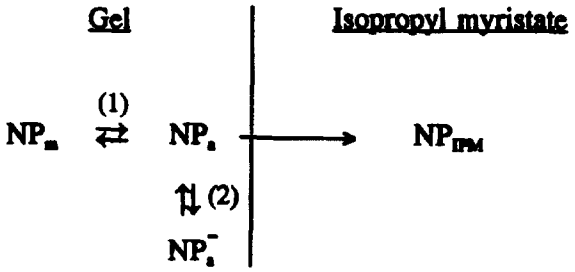

Fig. 4. Effect of PF-127 concentration (20%,○ ; 25%,●; 30%,▽) on release of naproxen (1% w/w) at 25°C ($n = 3$).

### 3.3.1. PF-127 concentration

In Fig. 4, the cumulative amounts of naproxen released from the PF-127 gels of different concentration were plotted as a function of square-root of time. The release was measured from the gels containing 1% of naproxen at 25°C. Highly linear responses ($r > 0.999$) observed in this figure indicated that the release of naproxen from the PF-127 gel was in full compliance with the Higuchi equation discussed earlier. The diffusion coefficients calculated, however, were decreased from $4.28 \times 10^{-8}$ to $3.53 \times 10^{-8}$ and $2.44 \times 10^{-8}$ $cm^2/sec$, as PF-127 concentrations were increased from 20% to 25% and 30%, respectively. The lower release rate with the higher PF-127 concentration was in agreement with Lauffer's diffusion theory in gels (Lauffer, 1961), which stated that the diffusion coefficient of solute is inversely proportional to the volume fraction occupied by the gel forming agent.

### 3.3.2. pH

The effect of pH on the release of naproxen ($pK_a = 4.2$) from the gel was studied at the gel pH of 2.9, 3.9, 5.5, 6.3, 7.0 and 7.7, and the highest release of naproxen was found from the gel pH of 6.3 (Fig. 5). It was possible that between the two immiscible phases of PF-127 gel and isopropyl myristate, naproxen could exist in several forms as




Scheme 1.

shown in Scheme 1 where NP and $NP^-$ represent the unionized and ionized naproxen, the subscripts a, m and IPM refer to the aqueous, micellar and isopropyl myristate phases, respectively. The unionized form of naproxen in aqueous phase ($NP_a$) represents the diffusible form of the drug into isopropyl myristate, which is in equilibrium with both ionized aqueous ($NP^-$) and unionized micellar forms of naproxen ($NP_m$) as shown in Scheme 1.

The pH effect on the release was probably due to the altered distribution of naproxen between the aqueous and micellar phases of the gel. The low release rates at pH values higher than 6.3 could be due to increased ionization of naproxen, since only the unionized drug was able to diffuse into the receiver phase used. However, the release of naproxen was also decreased at pH lower than 6.3,

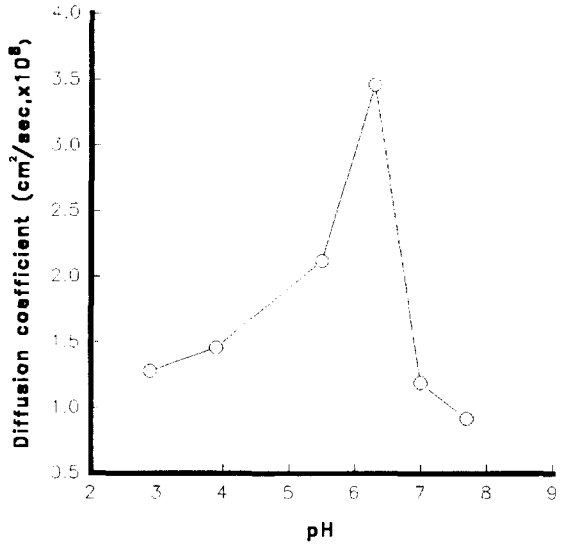



Fig. 5. Effect of pH on diffusion coefficients of naproxen in PF-127 gel (25% w/w) at 25°C ($n = 3 - 5$).

where naproxen was less ionized, thus presumably increasing micellar entrapment. At a lower pH value, a higher proportion of drug is in micellar phase, and diffusion is supported by a redistribution of unionized naproxen between aqueous and micellar phases (process 1 in Scheme 1). At a higher pH value, on the other hand, a higher proportion of drug is in ionized form, and diffusion is primarily supported by an equilibration between ionized aqueous and unionized aqueous forms (process 2 in Scheme 1). Therefore, the maximum diffusion rate of naproxen observed at pH 6.3 where naproxen was primarily ionized suggested that the rate of equilibration between ionized and unionized naproxen in aqueous phase exceeded the rate of redistribution of unionized micellar form into unionized aqueous form.

### 3.3.3. Drug loading

The Higuchi equation shown earlier assumes that the diffusion coefficient is independent of the initial drug concentration below the solubility of drug in the vehicle. However, the data obtained in this study showed that the release was significantly affected by the solute concentrations. When naproxen in the gel was increased from 0.25% to 1.0% at 30°C, the diffusion coefficient was decreased from $2.36 \times 10^{-8}$ to $1.59 \times 10^{-8}$ $cm^2/sec$, although each of the individual release profiles exhibited a good fit to the Higuchi equation. It is generally known that the diffusion coefficient can change, if the diffusant alters the properties of the diffusion medium. In this study, it was found that when drug concentrations in the gel increased from 0.25% to 1%, the pH of the gel decreased from 5.65 to 5.14 due to the acidic nature of naproxen, which probably explains the reduced diffusivity of naproxen due to higher drug content.

### 3.3.4. Temperature

The release of naproxen (1%, w/w) from the 25% PF-127 gel into isopropyl myristate was determined at 20, 30, 40, and 50°C using the membraneless diffusion cell described earlier. The cumulative amounts of naproxen released as a function of square-root of time at each temperature showed an excellent linearity ($r > 0.999$), indicating that the release was governed by the Higuchi diffusion model. As the temperature increased from 20 to

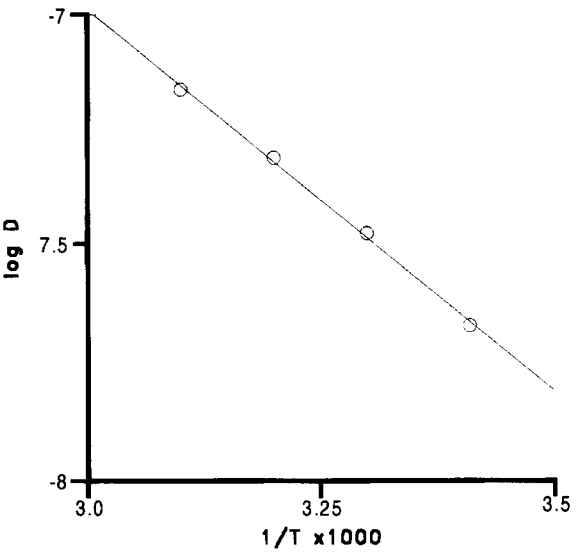



Fig. 6. Diffusion coefficients of naproxen in PF-127 gels (25% w/w) as a function of the reciprocal of absolute temperature.

50°C, the diffusion coefficient of naproxen increased from $2.16 \times 10^{-8}$ to $6.91 \times 10^{-8}$ $cm^2/sec$, despite the net increase of the bulk viscosity of the gel from 47 000 to 66 000 cps due to the thermoreversibility of PF-127. According to the Stokes-Einstein equation: $D = \kappa T/6\pi a\eta$ where D is the diffusion coefficient of the solute; $\kappa$, the Boltzmann constant; T, the absolute temperature; a, the molecular collision radius of the solute; and $\eta$ is the viscosity, the diffusion coefficient is inversely proportional to the medium viscosity. The expected reduction in naproxen diffusion with increased gel viscosity was not observed, suggesting that the bulk viscosity was not the dominant factor that determined the release of naproxen. Instead, the diffusion of naproxen in the PF-127 gel was probably controlled by the microviscosity of the gel which represents the viscosity of the entrapped aqueous phase within the polymer channels. It is known that the diffusion of solutes in the polymer gels normally occurs through the water-filled channels. The larger D found at the increased bulk viscosity due to the higher temperature supports the role of the microviscosity in the diffusion of naproxen in PF-127 gels.

Fig. 6 shows a linear relationship ($r > 0.997$) between the diffusion coefficient and 1/T according to the Arrhenius equation: $D = Do \times \exp(-Ea/RT)$

where Do is the hypothetical diffusivity at infinite temperature and Ea is the activation energy for the diffusion of naproxen in the gel which was found to be 7.45 Kcal/mole. Since the activation energies for the diffusion of low molecular weight nonelectrolytes in dilute solutions are usually in the range of 4.5 - 5.0 Kcal/mole (Flynn et al., 1974), the activation energy of 7.45 Kcal/mole for the diffusion of naproxen in the PF-127 gel suggested that the microviscosity of the PF-127 gel was probably higher than that of the dilute aqueous solution.

## 4. Conclusions

The solubility of naproxen was significantly increased in the presence of PF-127. The micellar solubilization was an energetically favored, spontaneous process resulting in a lower thermodynamic orderliness. Micelles served as a reservoir for the release of naproxen at pH 2. The release of naproxen from PF-127 gels was dependent upon the formulation factors. Higher release was observed at lower drug loading and lower PF-127 concentration. The medium pH significantly affected the release of naproxen due to its effect on the extent of micellar entrapment of naproxen. The greatest release was observed at pH 6.3. A linear relationship was found between the diffusion coefficient and temperature. The results suggest that PF-127 is a useful vehicle for controlling the release of naproxen from various aqueous formulations.

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