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IN VITRO RELEASE OF LIDOCAINE FROM PLURONIC F-127 GELS

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SUMMARY

The release of lidocaine from aqueous, crystal clear and colorless gels of Pluronic F-127 (a polyoxyethylene–polyoxypropylene surface-active block polymer) has been studied in an in vitro release model which did not utilize a membrane. Pluronic F-127 forms micelles in aqueous systems and the gels are believed to be viscous isotropic liquid crystals. Due to their reverse thermal gelation behavior, good solubilization capacity, optical properties and low toxicity, they appear to have potential application as topical drug delivery systems. It has been found that the rate of lidocaine release was inversely proportional to its concentration, the concentration of Pluronic F-127 and electrolyte concentration (sodium chloride). Release of lidocaine was maximal at pH values close to its pK_a; however, release of the more water-soluble benzocaine (included for comparison purposes) was relatively pH-independent over the pH range studied. Since the apparent diffusion coefficient of lidocaine increased with increasing temperature, in spite of increasing macro-viscosity of the gel, it is apparent that drug is released by diffusion through the extramicellar aqueous channels of the gel matrix. Hence, the rate of drug release was determined by the micro-viscosity of the extramicellar fluid, the dimensions of the aqueous channels, and the equilibrium relationship of drug between the micelles and the external aqueous phase.

INTRODUCTION

Pluronic [1] F-127 is a non-toxic polyoxypropylene–polyoxyethylene surface-active block polymer with an average molecular weight of 11,500. The polymer consists by weight of approximately 70% ethylene oxide and 30% propylene oxide (Schmolka, 1972;

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[1] BASF-Wyandotte Corp.

BASF, OS-3012(765); BASF, 1973). Reverse thermal gelation is one of the characteristics of aqueous solutions of this compound, e.g. 20–30% Pluronic F-127 gels are fluid at refrigerator temperature (4–5°C), but are highly viscous gels at room temperature and body temperature. The gelation at elevated temperatures is reversible upon cooling. This reversible sol-gel property allows cool solutions to flow onto the skin or into wounds, where they can seek intimate surface contact before warming to form a non-occlusive gel (Schmolka, 1972; Nalbandian et al., 1972). Since the gelation is reversible, removal from the skin or wound is facilitated by immersion in, or irrigation with cool water. Recent work in our laboratory has confirmed that the gels consist of large populations of micelles, forming an apparent viscous isotropic liquid crystal (Chen-Chow and Frank, 1980a). Hence, these aqueous, crystal clear and colorless gels appear not only to be novel systems from a physical–chemical viewpoint, but also to have potential as topical drug delivery systems.

Pluronic F-127 gels containing silver nitrate or silver lactate have been reported to be useful in inhibiting bacterial infection in the treatment of rats with thermal burns (Schmolka, 1972; Nalbandian, 1972). Rigid gels have been also used as inserts for fallopian tube cauterization (Gregor et al., 1976). In addition to their other properties, Pluronic F-127 gels have a high solubilization capacity and are capable of forming gels in dilute hydroalcoholic vehicles. These properties have led to suggestions for their use in cosmetic and pharmaceutical applications (BASF, OS-3012(765); BASF, 1973).

Given the possible utilization of these gels for topical drug delivery, studies were undertaken to evaluate in vitro drug release from these systems. The drugs studied were two local anesthetics, lidocaine and benzocaine. The effects of temperature, pH, added salts, the concentration of drug and the concentration of Pluronic F-127 on drug release were evaluated.

MATERIALS AND METHODS

Materials

Lidocaine and ethylmethylglycinexylidide hydrochloride (gift from Astra Pharmaceutical Products), benzocaine (Aldrich Chemicals), Pluronic F-127 (gift from BASF Wyandotte), isopropyl myristate (Tridom Chemicals), benzene (Burdick and Jackson Laboratories), monopotassium phosphate and disodium phosphate (J.T. Baker Chemicals) were used as received.

Preparation of Pluronic F-127 gels

Pluronic F-127 (PF-127) gels, 20%, 25% and 30% (w/w), were prepared by the cold process (Schmolka, 1972; BASF, 0-513): an appropriate amount of Pluronic F-127 was slowly added to distilled-deionized water (5–10°C) under constant agitation, after which the dispersion was stored overnight in a refrigerator. With time, a clear, viscous solution formed. Appropriate amounts of lidocaine or benzocaine were then added to the cold solutions, and the systems incubated in the gel state at 30°C until clarity was restored. For studies of the effect of added electrolyte, sodium chloride was added simultaneously with lidocaine to cold solutions of PF-127. To study the effect of pH on drug release, appropriate concentrations of sodium hydroxide or hydrochloric acid (0.1 N, 0.5 N and

0.1 N solutions) were added in minimal quantities necessary to adjust pH. Adjustment of pH was initiated approximately one hour prior to the release experiments, while the systems were still in their sol state.

In vitro studies of drug release from Pluronic F-127 gels

These studies were conducted with an in vitro release model adapted from that of Poulsen et al. (1968) which did not utilize a membrane barrier. The release of benzocaine and lidocaine had initially been studied by an in vitro model utilizing a membrane to separate the gel from an aqueous sink. Because certain problems arose in the use of cellulosic membranes (osmotic back flux leading to changes in the composition of the vehicles) or dimethylpolysiloxane membranes (very high diffusional resistance), attention was directed to the development of a practical alternative model in which a membrane would not be used. The advantage of this latter system is that the gel is in direct contact with an organic sink (isopropyl myristate) and factors influencing drug diffusion which are inherent in the vehicle itself can be evaluated under perfect sink conditions.

For this model, an aqueous formulation was placed in a shallow dish (0.7 cm in height and either 1.75, 2.20 or 3.00 cm in diameter, depending upon experimental need), leveled to the top edge with a flat-bladed spatula, and the dish lowered into a thermostatted 200 ml jacketed beaker (diameter 6.2 cm, height 6.5 cm) which had been previously filled with an appropriate volume of isopropyl myristate and equilibrated at the experimental temperature (30°C, or as specified). A 4-bladed glass stirrer (45 mm diameter) attached to a dissolution apparatus stirring drive set at 90 rpm (Hanson Research, model 53), was positioned 0.8 cm above the formulation surface. Samples of the isopropyl myristate sink were periodically removed during the 6-h duration of the experiments, each sample being replaced by an equal volume of isopropyl myristate equilibrated at the experimental temperature.

Determination of lidocaine and benzocaine in isopropyl myristate

Lidocaine was determined by a GC method employing nitrogen–phosphorus detection, and benzocaine by ultraviolet spectrophotometry. Sample preparation for both compounds included a double extraction procedure. The instrumentation, operating conditions and assay procedures have been described previously (Chen-Chow and Frank, 1980b).

Data treatment

Drug release profiles were expressed in terms of the amount released as a function of time, and of the square-root of time. If an apparent linear relationship existed between the amount released and the square-root of time, the data was analyzed by linear regression and the slope used to calculate the apparent diffusion coefficient of the drug from the vehicle (Eqn. 1). Eqn. 1 describes release from one side of a layer of a semi-solid vehicle containing uniformly dissolved drug (Higuchi, 1962).

$$q = 2C_0\left(\frac{Dt}{\pi}\right)^{1/2} \quad (1)$$

where q = amount of drug released per unit area of application; C_0 = initial concentration of drug in vehicle; D = diffusion coefficient of drug in the vehicle; and t = time.

Solubility determination

The solubilities of lidocaine at 30°C in the semi-solid, transparent Pluronic F-127 gels were determined by visual observation of undissolved drug particles. A series of lidocaine concentrations at 0.1% (w/v) increments were prepared, equilibrated for two months, and examined side-by-side with a blank gel. A beam of light passing through the gel-containing tubes at right angles to the viewer, was used to detect the presence of drug particles as observed against a black background. The solubilities of lidocaine were determined to be the highest concentrations at which no suspended crystals were visible. For the 20%, 25% and 30% (w/w) gels, the solubilities were determined to be 2.4%, 2.7% and 3.2%, respectively.

RESULTS AND DISCUSSION

Effect of temperature on lidocaine release

Lidocaine release from 25% Pluronic F-127 gels was evaluated at 20°C, 30°C, 40°C and 50°C. Fig. 1 shows the temperature dependency of lidocaine release as a function of the square-root of time. Plotting the diffusion coefficients determined from the slopes in Fig. 1, as a function of temperature in the Arrhenius manner,

$$D = D_0 e^{-E/RT} \quad (2)$$

gives an excellent linear relationship between the logarithm of the diffusion coefficient, D, and the reciprocal of the absolute temperature, 1/T (Fig. 2). The energy for diffusion, E, has a value of 5.10 kcal/mole (S.D. = 0.107), and the pre-exponential term, D_0, is 6.68×10^{-3} cm^2/sec. The energy required for lidocaine release from the 25% Pluronic F-127 gel is close to the range of 4.5–5.0 kcal/mole for the diffusion of low-molecular weight non-electrolytes in liquids (Flynn et al., 1974). Since these gels exhibit reverse thermal behavior, their viscosity increased as temperature increased (see Table 1). How-

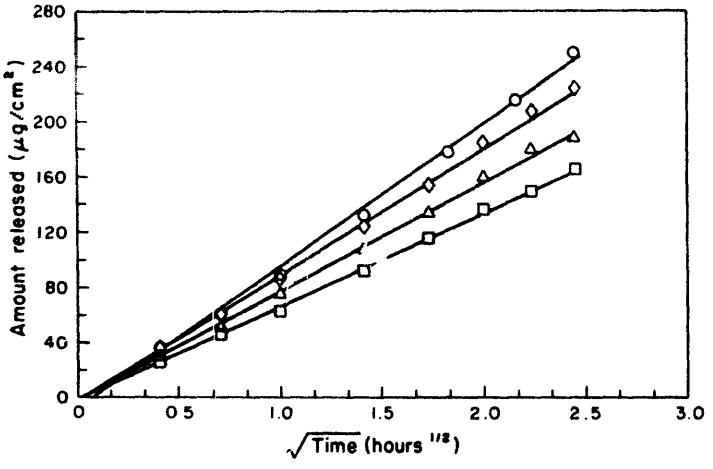

Fig. 1. Lidocaine release as a function of the square-root of time from 25% Pluronic F-127 gels at 20°C (□), 30°C (△), 40°C (◇) and 50°C (○) (concentration of lidocaine was 0.1% (w/v); and the initial pH of the formulation was 8.2).

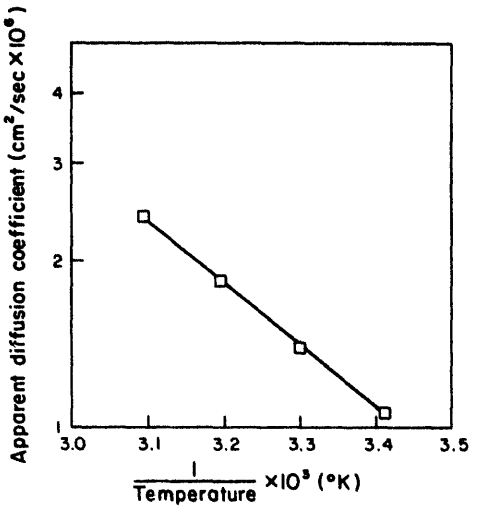

Fig. 2. Apparent diffusion coefficients for lidocaine release from 25% Pluronic F-127 gels as functions of the reciprocals of absolute temperature (concentration of lidocaine was 0.1% w/v).

ever, the apparent diffusion coefficient for lidocaine release increased also with increasing temperature, and the value of E was relatively low. Therefore, it may be suggested that the diffusion of lidocaine is largely dependent on the micro-viscosity of the fluid phase of the gel, rather than the macro-viscosity. Hence, the apparent diffusion coefficient, D, would be for lidocaine diffusing through water channels in the gel. The viscosity of water in these channels would be expected to closely resemble bulk water, and to decrease with increasing temperature. Since the Pluronic F-127 gels are isotropic liquid crystals consisting of micelles, the existence of such channels is highly probable.

Effect of Pluronic F-127 concentration on lidocaine release

In this study, both the initial concentration of lidocaine in the vehicle and temperature were held constant, while the concentration of Pluronic F-127 was varied (20%, 25% and 30% w/w). The relationships between the amount of lidocaine released and the square-root of time for each composition are shown in Fig. 3. A plot of the apparent diffusion coefficient as a function of vehicle composition was linear (Fig. 4). Since the rate of

TABLE 1

VISCOSITY [a] (cps X 10^{-6}) OF 25% PLURONIC F-127 GELS CONTAINING 0.1% (w/v) LIDOCAINE AS A FUNCTION OF TEMPERATURE

Revolutions per min	20°C	30°C	40°C	50°C
2	0.77	1.00	1.10	1.16
4	0.44	0.57	0.58	0.66

[a] Measured with a Brookfield Synchro-Lectric Viscometer (Model RVF) attached to a Brookfield Helipath Stand and fitted with size "F" T-bar spindle.

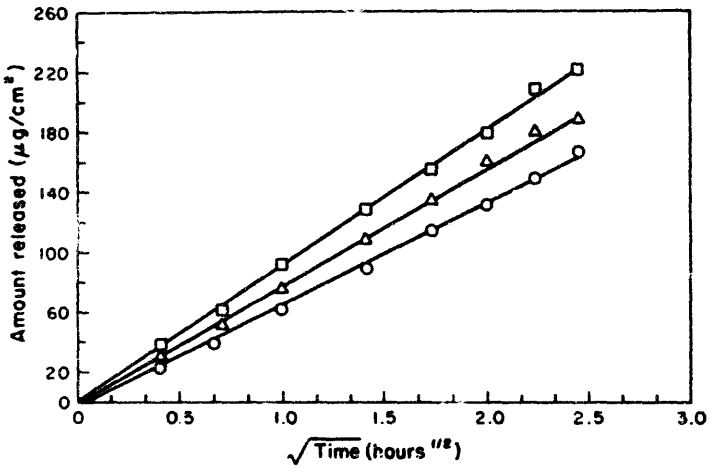

Fig. 3. Lidocaine release at 30°C as a function of the square-root of time from 20% (□), 25% (△) and 30% (○) (w/w) Pluronic F-127 gels (concentration of lidocaine was 0.1% w/v).

release decreased as the concentration of Pluronic F-127 in the vehicle increased, it is apparent that the structure of the gel functioned as an increasingly resistant barrier to drug diffusion as the concentration of Pluronic F-127 increased. The mechanism for such enhanced resistance may be due in part to reductions in the numbers and dimensions of water channels and to increased drug solubility, both due to the higher population of micelles.

Effect of pH on drug release

The release of lidocaine and benzocaine was studied at arbitrarily chosen pH values distributed around each respective pK_a. For lidocaine, the selected pH values were 3.1, 5.9, 6.9, 8.2, 9.2 and 11.9 ($pK_a \simeq 8.0$). Except for pH 3.1, the amounts of lidocaine released as a function of the square-root of time are shown in Fig. 5. At pH 3.1, a linear

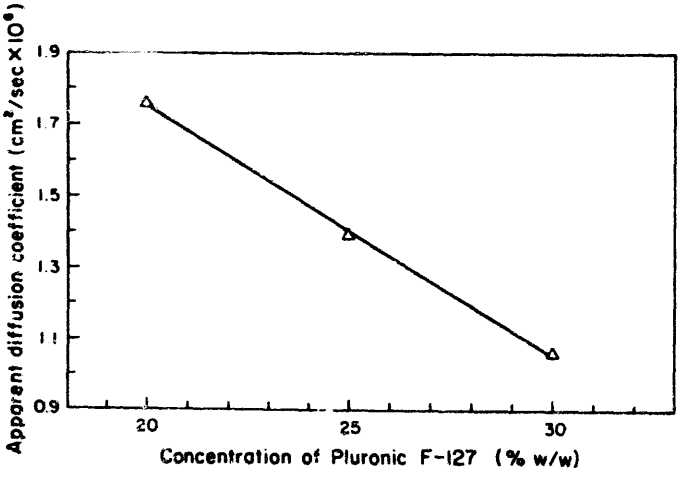

Fig. 4. The relationship of the apparent diffusion coefficients of lidocaine and the concentration of Pluronic F-127 at 30°C. Concentration of lidocaine was 0.1% (w/v).

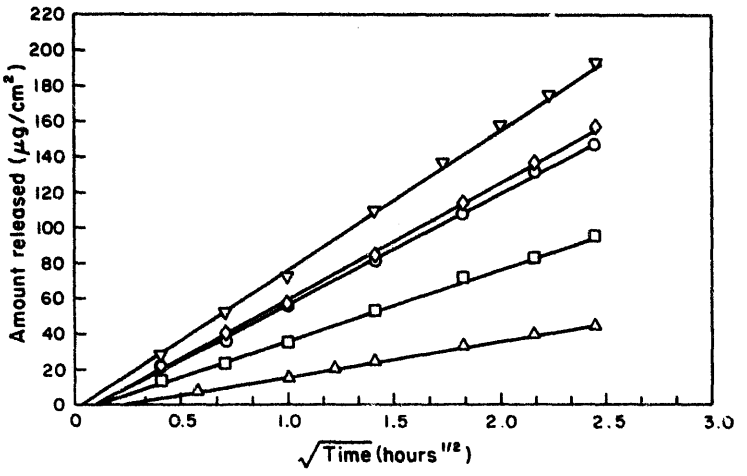

Fig. 5. Lidocaine release as a function of the square-root of time from 25% Pluronic F-127 gels at initial pH values of 5.9 (△), 6.9 (□), 11.9 (○), 9.2 (◇) and 8.2 (▽) at 30°C (concentration of lidocaine was 0.1% w/v).

relationship was found instead between the amount released and time (Fig. 6). The per cent release of lidocaine as a function of pH for each preparation is given in Fig. 7, where it can be seen that the release of lidocaine is maximal at the pH closest to its pK_a. By contrast, there was no appreciable difference between the release data for 3 formulations containing benzocaine, at pH 4.3, 5.9 (pK_a of benzocaine) and 7.3 (Table 2).

Since the Pluronic F-127 gels are believed to consist of a large population of micelles, the distribution of solute between the aqueous continuous phase and the micellar phase should depend on the nature of the solute and the properties of the aqueous phase (McBain and Hutchinson, 1955). When a Pluronic F-127 solution is saturated with the poorly soluble base, lidocaine, the solute can be expected to occur in several forms (Dyer, 1959; Kramer and Flynn, 1972):

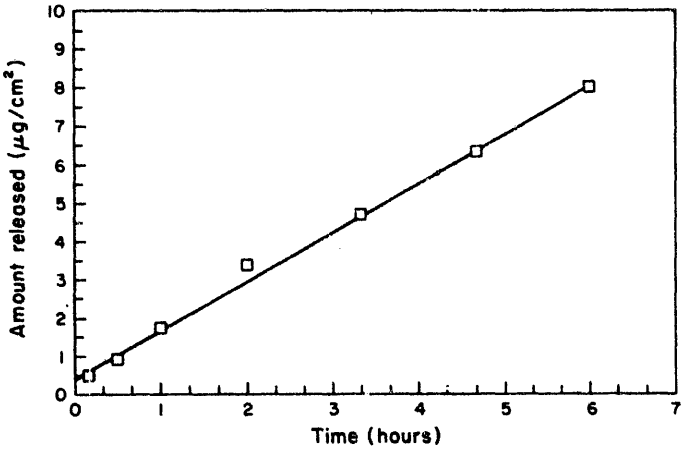

Fig. 6. Release of lidocaine at pH 3.14 as a function of time at 30°C from a 25% Pluronic F-127 gel containing 0.1% (w/v) lidocaine.

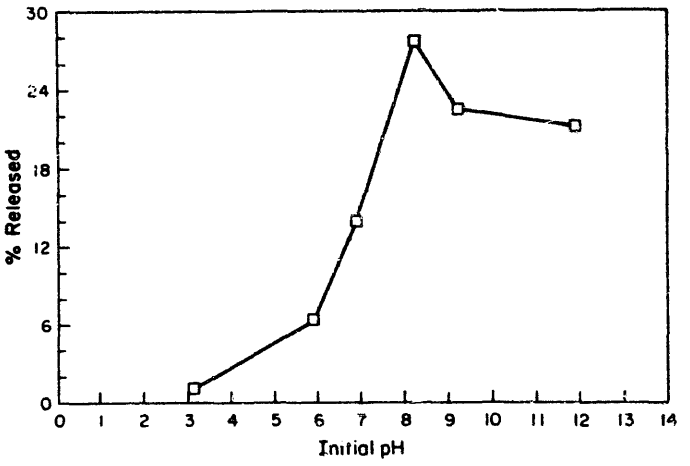

Fig. 7. Per cent of lidocaine released at 30°C from 25% Pluronic F-127 gels as a function of the initial pH of the gels. The concentration of lidocaine was 0.1% (w/v).

$$B_{excess} \rightleftharpoons B_{water} \rightleftharpoons BH^+ + OH^- \quad (3)$$
$$\Big\Downarrow\Big\Uparrow$$
$$B_{micelles}$$

If, B, indicates lidocaine, B_{water} will be the diffusible species detected by its accumulation in the isopropyl myristate sink. Since the release of lidocaine decreased at pH values both above and below the pK_a, it may be assumed in the former case that micellar solubilization accounted for the decrease in drug release, while in the latter case, the effective concentration of the diffusable form of lidocaine in the aqueous phase decreased. At the lowest pH 3.1, a zero-order dependency was observed, indicating that lidocaine release depended upon its solubility in the external aqueous phase, which in turn is limited by the equilibrium between lidocaine and lidocaine hydrochloride.

In contrast to the lidocaine systems, release of benzocaine from the Pluronic F-127 gels was not dependent on pH. Benzocaine is relatively more soluble than lidocaine (1 g in 2500 ml of water, compared to the relative water-insolubility of lidocaine), hence the

TABLE 2

EFFECT OF pH ON THE RELEASE OF BENZOCAINE FROM 25% PLURONIC F-127 GELS AT 30°C WITHIN 6 h (CONCENTRATION OF BENZOCAINE WAS 0.1% w/v)

pH	Percent released	Amount released, q ($\mu g/cm^2$)	Slope, $q/\sqrt{t}$ ($\mu g/cm^2, h^{1/2}$)	Diffusion coefficient ($cm^2/sec \times 10^7$)
4.3	20.84	145.9	59.84	7.81
5.9	19.93	139.5	56.64	7.00
7.3	20.54	143.8	60.61	8.02

The data are the average of 2 values.

equilibrium of benzocaine between the micellar phase and the external aqueous phase as a function of pH would be expected to be different from that of lidocaine, accounting in part for the absence of an observable pH-dependency.

Effect of initial lidocaine concentration on release

Lidocaine release as a function of the square-root of time for initial concentrations, C_0, of 0.05, 0.075, 0.1, 0.5, 1.0, 2.0 and 2.8% (w/v) are given in Fig. 8. Except at 2.8% (w/v), which exceeded the solubility of lidocaine in the gel (25% Pluronic F-127), Eqn. 1 could be used to calculate the apparent diffusion coefficients from the vehicle. The release profile for 0.075% lidocaine has been omitted from Fig. 8 to ensure clarity of the figure due to the close proximity of the 0.05% and 0.1% data.

A plot of the rates of lidocaine release as functions of initial lidocaine concentrations in the vehicle is given in Fig. 9. The apparent curvature of the plot, resulting in a negative deviation when C_0 reaches and is above 0.5%, is indicative of a concentration dependence of lidocaine release from the vehicle.

Higuchi has shown that a direct proportionality between drug release and the square-root of time holds regardless of whether the diffusion coefficient is dependent on or independent of C_0 (Koizumi and Higuchi, 1968). Theoretically, the diffusion coefficient should be independent of C_0 as long as C_0 is below the solubility of drug in the vehicle (Higuchi, 1962). Thus, it appears that other factors were influencing drug release in addition to the concentration of lidocaine in the gels. At lidocaine concentrations below 0.5%, the pH of the gel was stable at 8.1; however, at concentrations above 0.5%, pH gradually rose to values in excess of 9.0. Such changes in pH would be expected to reduce the effective concentration of drug in the external aqueous phase of the gel, resulting in a decreased rate of drug release. These conclusions are supported by the preceding study of the effect of pH on lidocaine release, where a reduced rate of release was attributed to a decreased effective concentration of lidocaine when the pH of the preparation exceeded

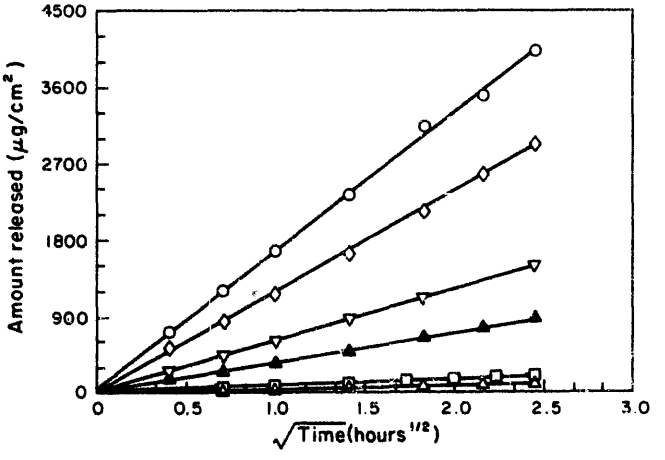

Fig. 8. Lidocaine release at 30°C as a function of the square-root of time from 25% Pluronic F-127 gels. Concentrations of lidocaine were 0.05% (△), 0.1% (□), 0.5% (▲), 1.0% (▽), 2.0% (◇) and 2.8% (○) (w/v).

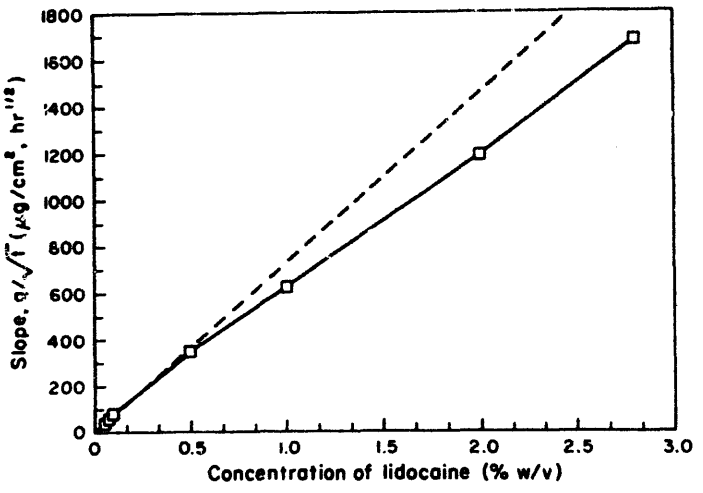

Fig. 9. Slopes of the amounts of drug released vs $\sqrt{t}$ at 30°C as functions of lidocaine concentration in 25% Pluronic F-127 gels.

8.2. The dependency of the apparent diffusion coefficient on initial concentration is not an uncommon phenomenon, and results from various physical–chemical changes, such as that of the partition coefficient of a drug at an elevated initial concentration (Bottari et al., 1979).

Effect of added salt on drug release

At sodium chloride concentrations of 0.02, 0.1, 0.2, 1.0, 5.0, 10.0 and 12.0% (w/v), linear relationships were found between the amount of drug released from each preparation and the square-root of time. From a statistical analysis of variance at sodium chloride concentrations of 5.0, 10.0 and 12.0% (w/v), the rate of drug release was significantly

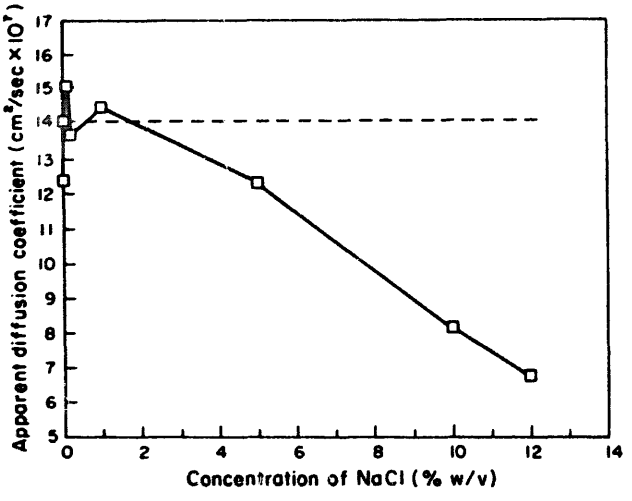

Fig. 10. Apparent diffusion coefficients for lidocaine released from 25% Pluronic F-127 gels at 30°C, as functions of sodium chloride concentration in the gels (concentration of lidocaine was 0.1% w/v).

slower than that in the absence of added salt. The apparent diffusion coefficients of lidocaine calculated from the rate of release from each gel are plotted in Fig. 10 as functions of the percentage of sodium chloride. It can be seen that at concentrations of sodium chloride above 4%, the apparent diffusion coefficient of lidocaine decreased significantly. Since the pH and macro-viscosity did not differ greatly among the various preparations, these factors are unlikely to be major influences in reducing release rates. At concentrations of sodium chloride below 2%, the effect of added salt on the micro-viscosity of the gel was apparently not sufficient to greatly alter drug release. However, as the concentration of sodium chloride increases, the expected decrease in the amount of free water and the increase in the micro-viscosity of the aqueous channels of the gel would be expected to account for the progressively decreasing rates of lidocaine release.

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