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# In vitro release of nicotinic acid alkyl esters from poloxamer vehicles

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## Summary

Poloxamers are poly(oxyethylene)poly(oxypropylene) block copolymers. Aqueous solutions of these polyols show reverse thermal gelation, low toxicity and good solubilization capacity. As such, they appear to be useful as components of topical drug delivery systems. The objectives of this study were to systematically investigate the effects of (1) poloxamer lipophilicity, (2) poloxamer concentration and (3) temperature on the in vitro release rate of drug from formulations containing hexyl nicotinate. Studies were conducted in a membrane-less model using isopropylmyristate as the receptor phase; for some studies, a series of *n*-alkyl nicotinates (methyl, ethyl, butyl and hexyl) were used as model compounds. Results indicated that the diffusion coefficients decreased with increasing poloxamer concentration and increased with increasing temperature. Results with different poloxamers indicated that the release rate increased with increasing poloxamer hydrophilic-lipophilic balance (HLB). The order of release rate for alkyl nicotinates was methyl > ethyl > butyl >> hexyl. The markedly lower release rate for hexyl nicotinate was explained by a stronger interaction between drug and poloxamer.

## Introduction

Poloxamer copolymer have the following general formula:

$$OH(CH_2CH_2O)_a(CH[CH_3]CH_2O)_b(CH_2CH_2O)_cH$$

where, *a* and *c* are statistically equivalent (BASF Wyandotte, OS-3012(765)). A rather unique property of aqueous-based poloxamer solutions is that they undergo thermal gelation (Schmolka, 1972); concentrated solutions of some poloxamers are fluid at refrigerator temperature but are viscous gels at body temperature. This suggests that, when applied to the skin, these preparations will intimately contact the skin surface and may subsequently gel. These semi-solids can ultimately be easily removed with cool water. It has further been reported that aqueous poloxamer gels may exist as isotropic liquid crystals (Chen-Chow, 1979). Theoretically, it may be possible to utilize this tortuous structure to control the physicochemical vehicle properties in order to regulate the delivery rate of drugs. While there have been some promising results reported in the area of poloxamer drug delivery systems (Chen-Chow and Frank, 1981; Miller and Donovan, 1982; Miyazaki et al., 1984), a systematic investigation of the in vitro

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drug release characteristics of poloxamers has not been undertaken.

Generally, to control drug release from polymers, researchers can either modify the drug properties or the polymer properties to obtain the required release rate of the active species. Different poloxamers offer a wide range of various physicochemical properties, thus, it may be possible to control the release rate from these systems by judicious poloxamer selection. Furthermore, interactions between the drug and poloxamer may also affect the release rate. A systematical investigation of the effects of solute and vehicle properties on the release rate may permit a better understanding of the mechanism(s) of drug release from these systems and provide information on which to base predictions for related systems.

## Materials and Methods

### *Materials*

Poloxamers 188, 238, 288, 333, 334, 335, 338, and 407 were a gift from BASF Wyandotte Corp. Methyl nicotinate, ethyl nicotinate, hexyl nicotinate and sodium phosphate dibasic (anhydrous, reagent grade) were obtained from Sigma. Butyl nicotinate was obtained from Pfaltz & Bauer. Methanol (HPLC grade) and sodium phosphate monobasic (monohydrate, AR grade) were obtained from J.T. Baker. Deionized water was used in all formulations.

### *Methods*

*Preparation of aqueous-based poloxamer gels*

The cold technique was used for all formulations; an appropriate amount of poloxamer was slowly added to cold water (5–10°C) with gentle agitation via a magnetic stirrer (Schmolka, 1972). The solution was left overnight in a refrigerator to effect complete polymer dissolution. Four alkyl nicotinates were chosen as model compounds; these were methyl nicotinate (MN), ethyl nicotinate (EN), butyl nicotinate (BN) and hexyl nicotinate (HN). The alkyl nicotinate was added slowly with stirring to 20 ml of a cold poloxamer solution of specific concentration contained in a 25 ml volumetric flask. The solution was then stored in a thermostatted oven at 30°C for at least 40 h to ensure complete dissolution of the drug. The preparation was then brought to final volume with the same concentration of cold poloxamer solution.

*Preparation of phosphate buffer*

A phosphate buffer solution (pH 7.0, 0.067 M) was prepared by mixing 40 ml of a stock solution of monobasic sodium phosphate (9.2 g of $NaH_2PO_4$ monohydrate, per l) with 60 ml stock solution of dibasic sodium phosphate (9.47 g $Na_2HPO_4$, anhydrous, per l).

*In vitro release studies*

A 250 ml jacketed beaker (o.d. 8.5 cm, height 10 cm) was filled with 75 ml of isopropyl myristate (IPM) and equilibrated to the experimental temperature before starting the release studies. A shallow dish with surface area 19.635 $cm^2$, 2.5 cm radius and 0.6 cm height was filled with 10 ml of poloxamer gel containing the drug. The dish was placed in the bottom of the beaker. A glass stirrer shaft (o.d. 5 mm, length 31 cm) with a teflon blade of 40 mm diameter was attached to an over-head motor; the stirring rate was constant at 150 rpm. Water circulated through the jacketed beaker from a constant temperature circulator thermostatted to the appropriate temperature.

Time zero was taken to be the time at which the dish was placed in the beaker and stirring was initiated. At various times over the duration of experiments (2.5 h for MN, EN; 6 h for BN, HN), a fixed volume of the IPM solution (0.5 ml for MN, EN; 2 ml for BN, HN) was removed from the receptor phase. An equal volume of fresh IPM (which had been equilibrated at the experimental temperature) was added to the receptor phase after sampling. Collected samples were then diluted with methanol to a final volume up to 10 ml and assayed as described below.

*Assay methods*

A series of standard solutions of the alkyl nicotinates in IPM and methanol were freshly prepared. For MN and EN standards, the solvent was 5% v/v IPM in methanol. For BN and HN standards, the

solvent was 20% v/v IPM in methanol. Solutions of alkyl nicotinates in methanol or ethanol produce an absorption peak at 263 nm (Hadgraft et al., 1962). Absorbances of the standard solutions were determined by ultraviolet spectrophotometry (UV) at 263 nm. The standard curves for each of the four alkyl nicotinates were linear over the experimental concentration range of 4–40 mg/l. The absorbances of samples were similarly determined; drug concentrations were determined from the linear regression equations of the standard curves.

*Data analysis*

Data were obtained as a function of time; the data treatment was based on the following simplified equation which described release from one side of a layer of vehicle containing uniformly dissolved drug (Higuchi, 1962):

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

where, $Q$ denotes the amount of drug released per unit area of application, $q$ is the amount of drug released, $A$ represents the area of application, $C_0$ is the initial concentration of drug in the vehicle, $D$ denotes the diffusion coefficient of drug in the vehicle, and $t$ is the time after application.

*Drug-polymer interaction studies*

The effects of drug lipophilicity on solubilization were conducted using a homologous series of *n*-alkyl nicotinates. An appropriate amount of poloxamer 407 was added to phosphate buffer to obtain solutions of varying concentration (0.1, 0.3, 0.5% w/v) of poloxamer 407. Excess quantities of the alkyl nicotinates (EN, BN or HN) were added to 25 ml Erlenmeyer flasks; to these, 10 ml of poloxamer 407 solution was added. The flasks were shaken in a constant temperature water bath at 37°C for 24 hours which apparent equilibrium solubility was achieved. Samples were centrifuged at 37°C for 45 min in an ultracentrifuge at 60800 × *g* in polycarbonate tubes. Aliquot portions of the supernatant liquid were removed and diluted appropriately with phosphate buffer. The diluted samples were assayed for alkyl nicotinate by ultraviolet absorption spectrophotometry at 263 nm. The presence of poloxamer did not interfere with the assay.

The effect of poloxamer properties on solubilization were conducted using structurally related poloxamers (poloxamer 188, 238, 288, 333, 334, 335, 338, 407). Some of the physicochemical characteristics of these poloxamers are summarized in Table 1. An appropriate amount of each poloxamer was added to phosphate buffer (pH 7.0, 0.067 M) to obtain $4 \times 10^{-4}$ M poloxamer solutions. Excess quantities of hexyl nicotinate were added to the different poloxamer solutions. These were then equilibrated at 37°C for 24 h, ultracentrifuged and assayed as described above.

Table 1

*Physicochemical characteristics of selected poloxamers and effect of poloxamer properties on the release of 1% w/v hexyl nicotinate from 30% poloxamer at 37°C*

| Poloxamer | Trade name | Physical characteristics | | | | Diffusion coefficient ($10 \times 10^7$ cm$^2$/s) |
|---|---|---|---|---|---|---|
| | | Molecular weight | POE/kg | POP/kg | HLB at 25°C | |
| 188 | F-68 | 8350 | 17.96 | 3.59 | 29.0 | – |
| 238 | F-88 | 10800 | 17.96 | 3.61 | 28.0 | 1.62 |
| 288 | F-98 | 13000 | 18.77 | 3.62 | 27.5 | 1.57 |
| 333 | P-103 | 4950 | 8.08 | 10.91 | 9.0 | – |
| 334 | P-104 | 5850 | 10.60 | 9.23 | 13.0 | 0.99 |
| 335 | P-105 | 6500 | 11.69 | 8.31 | 15.0 | 1.03 |
| 338 | F-108 | 14000 | 18.29 | 3.86 | 27.0 | 1.50 |
| 407 | F-127 | 12500 | 15.68 | 5.36 | 22.0 | 1.16 |

## Results and Discussion

*Effect of poloxamer concentration on drug release*

The effect of poloxamer 407 concentration on the rate of drug release was studied in formulations containing hexyl nicotinate and different concentrations of poloxamer 407 (20, 25, 30% w/w). Both the initial concentration of hexyl nicotinate in the vehicle (1% w/v) and the temperature (37°C) were held constant.

For each vehicle composition, the cumulative amount of hexyl nicotinate released per unit area to the IPM sink followed Eqn 1. Data obtained are listed in Table 2. Regression analysis of the apparent diffusion coefficients and poloxamer 407 concentration gave a negative correlation with a slope of $-3.07 \times 10^{-9}$ cm$^2$/s (w/w %) and an intercept of $2.07 \times 10^{-7}$ cm$^2$/s ($p<0.01$). The higher the poloxamer 407 concentration, the slower was the drug release rate. This indicated that poloxamer gels of higher concentration have higher resistance to drug diffusion than the lower poloxamer concentration gels. The effect of poloxamer 407 concentration (20, 25, 30% w/w) on the release of lidocaine (Chen-Chow and Frank, 1981), 5-FU and adriamycin (Miyazaki et al., 1984) was studied at 30°C. Data from both studies showed the same trend as observed in this study. That is, the release rate decreased with increasing poloxamer 407 concentration. Other investigators (Al-saden et al., 1979; Attwood et al., 1985; Collett et al., 1985) have reported a pronounced apparent decrease in diffusion coefficient as the poloxamer 407 concentration exceeded 10 g/dl using photon correlation spectroscopy. It was interpreted that these changes in diffusion coefficient were due to a marked increase of mean micellar size and the polydispersity of the micelles. Since poloxamer 407 gels are viscous isotropic liquid crystals consisting of micelles, it may be hypothesized that the drug is released by diffusion through the extramicellar water channels of the gel matrix. The lower apparent diffusion coefficient for higher poloxamer concentration gels might, in part, be due to the reduction in the size of water channels, the increase of drug solubility, micellar growth or greater tortuosity.

TABLE 2

*Effect of poloxamer 407 concentration on the release of 1% w/v hexyl nicotinate from poloxamer 407 at 37°C*

| Poloxamer concentration (% w/w) | Trial | Diffusivity (cm$^2$/s $\times 10^7$) |
|---|---|---|
| 20 | 1 | 1.39 |
| | 2 | 1.55 |
| | 3 | 1.61 |
| | 4 | 1.34 |
| | Average | 1.47 |
| | S.E. | 0.06 |
| 25 | 1 | 1.42 |
| | 2 | 1.14 |
| | 3 | 1.17 |
| | Average | 1.24 |
| | S.E. | 0.09 |
| 30 | 1 | 1.03 |
| | 2 | 1.05 |
| | 3 | 1.13 |
| | 4 | 1.48 |
| | 5 | 1.12 |
| | 6 | 1.14 |
| | Average | 1.16 |
| | S.E. | 0.07 |

*Effect of temperature on the drug release*

The effect of temperature on the release of hexyl nicotinate from poloxamer 407 was evaluated at 24, 30, 37, 44, and 50°C. Both the initial concentration of hexyl nicotinate in the vehicle (1% w/w) and the poloxamer 407 concentration (30% w/w) were held constant. All experiments were carried out at least in triplicate. The temperature dependency of the release of hexyl nicotinate to the IPM sink as a function of the square root of time is illustrated in Fig. 1. The data showed that the apparent diffusion coefficient increased with increasing temperature. The relationship between the diffusion coefficient and the temperature is as follows (Flynn et al., 1974):

$$D = D_0 \, e^{-E_a/RT} \qquad (3)$$

A linear relationship was observed between the natural logarithm (ln) of apparent diffusivity ($D$) and the reciprocal of temperature ($T$) as shown in Fig. 2; error bars denote standard error of means. The slope was used to calculate the activation energy for drug diffusion ($E_a$ = 11 kcal/mol); the in-

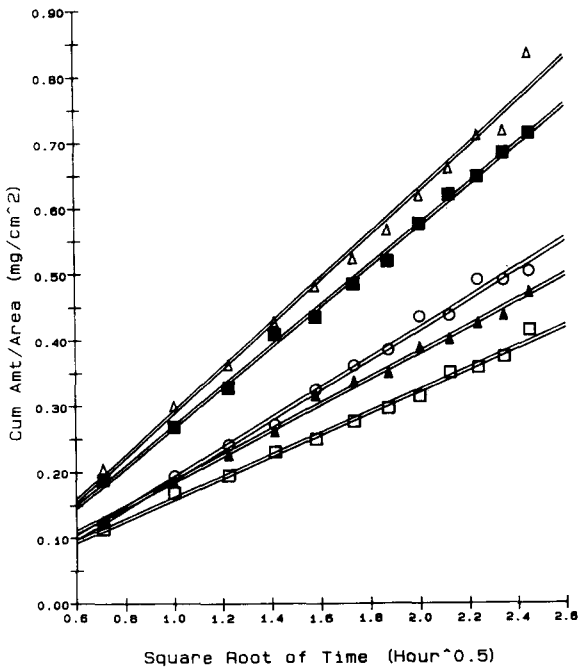


Fig. 1. Release of 1% w/v HN as a function of square root of time from 30% w/w poloxamer 407 gels at 24°C (□), 30°C (▲), 37°C (○), 44°C (■) and 50°C (△).

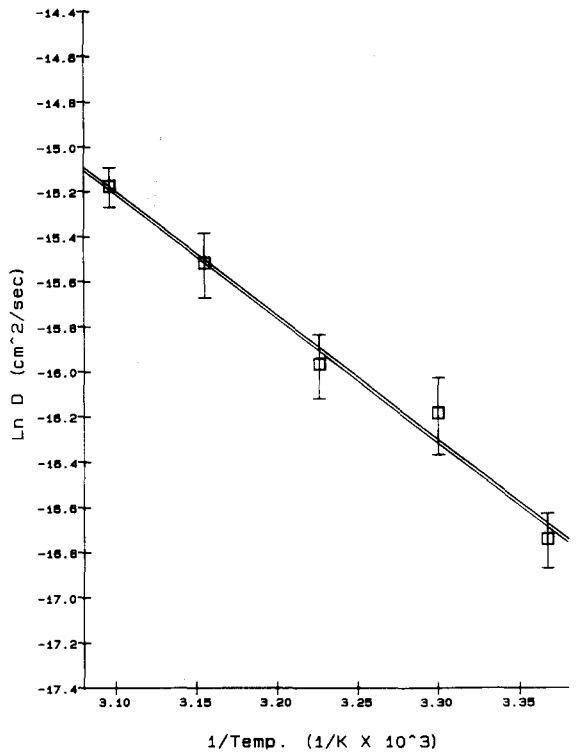


Fig. 2. Effect of temperature on apparent diffusivity of HN from 30% w/w poloxamer 407 gels.

tercept was used to calculate the pre-exponential term ($D_0$ = 4.1 cm$^2$/s). Since poloxamer gels exhibit reverse thermal behavior, their viscosities increase as temperature is increased. According to the Stokes-Einstein equation (Flynn et al., 1974), it is expected that apparent diffusion coefficients should decrease with increasing viscosity. However, the apparent diffusion coefficient of HN increased with increasing temperature. These results suggest that the diffusion of HN is largely dependent on the microviscosity of the water channel of the gel rather than the macroviscosity of the gel.

The apparent diffusivities of HN in the gels ($D_g$) and in water ($D_w$; theoretically calculated according to Wike and Chang, 1955) were correlated with water viscosities at different temperatures. A log-log plot of $D_g/T$ or $D_w/T$ vs water viscosity at 24, 30, 37, 44, and 50°C is shown in Fig. 3. Fitting either curve via linear regression (equal weighting) showed good correlation between diffusivity and water viscosity (correlation coefficient; $r$=0.99 for $D_g$ plot, $r$=1.0 for $D_w$ plot). It appears that the diffusivity of HN in the gels or in water is directly related to the water viscosity at the temperatures studied. However, the slopes of two regression lines were statistically different ($\alpha$ = 0.05). This implies that the water viscosity may not be the only factor contributing to the observed diffusivities at different temperatures. Changes of water structure by solvents and polymers have been reported (Ueberreiter, 1982). Thus, water structuring in poloxamer gels may be different from that in pure water. In addition, the apparent diffusivity of HN in gels at different temperatures might also be influenced by dehydration of micelles, micellar size changes and/or different degrees of interaction over the temperature range studied.

*Effect of drug lipophilicity on drug release*

The effects of drug lipophilicity on the release of drugs from poloxamer 407 were determined. A homologous series of alkyl nicotinates (methyl,

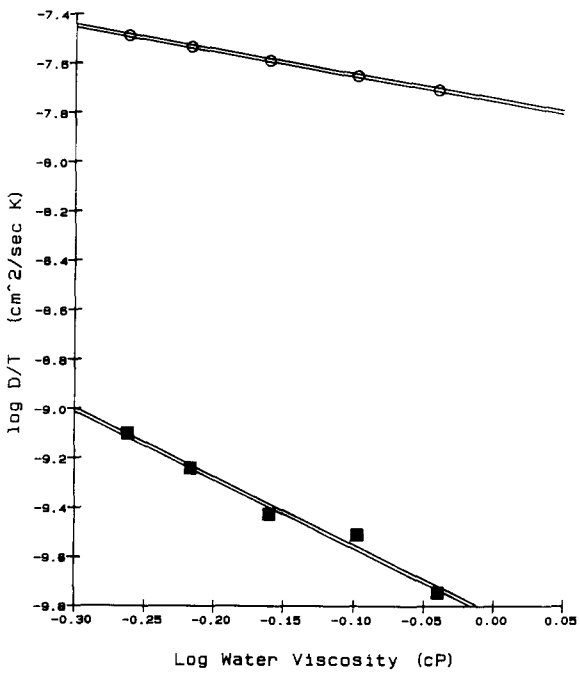


Fig. 3. Effect of water viscosity on apparent diffusivity of 1% w/v HN in water (○) or in poloxamer 407 gel (■).

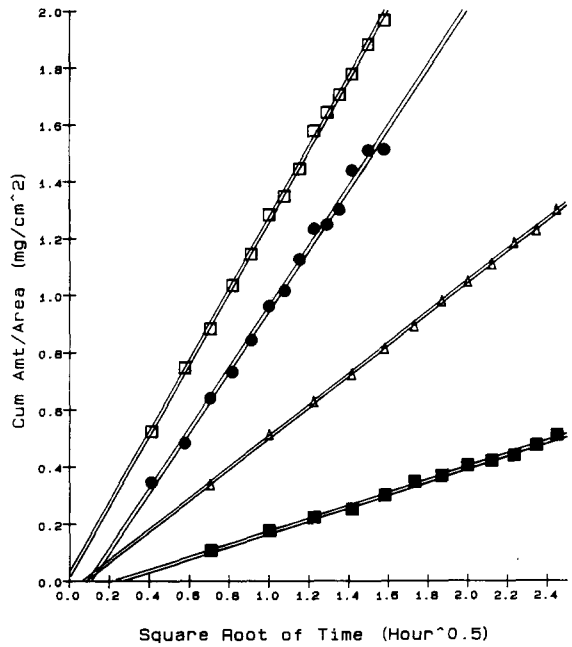


Fig. 4. Release of 1 % w/v alkyl nicotinates (MN, □; EN, ●; BN, △; HN, ■) as a function of square root of time from 30% w/w poloxamer 407 gels at 37°C.

ethyl, butyl and hexyl nicotinate) were chosen to cover a range of lipophilicity. The initial concentration of nicotinate in the vehicle (1% w/w), poloxamer 407 concentration (30% w/w) and temperature (37°C) were held constant. Typical release profiles, which illustrate the relationship between the cumulative amount of the four alkyl nicotinates (MN, EN, BN, HN) released per unit area to the IPM sink and the square root of time were obtained (Fig. 4). The order of release rate for the homologous series of alkyl nicotinates was MN > EN > BN >> HN. Analysis of variance and multiple comparison of means testing by the method of Scheffe indicated that the release of all four nicotinates were significantly different from each other.

*Effect of drug lipophilicity on solubilization*

The solubility ratio ($S/S_0$) is expressed as the ratio of alkyl nicotinate solubility in poloxamer solution ($S$) to its solubility in phosphate buffer ($S_0$). Due to its high solubility in water, MN was not evaluated. A plot of solubility ratio as a function of poloxamer concentration for three alkyl nicotinate is shown in Fig. 5. For butyl nicotinate, determinations were made in duplicate with error bar on symbol denoting standard deviation. Generally, the solubility ratio of each alkyl nicotinate in poloxamer increased linearly with increasing concentration of poloxamer. The data indicated that the higher the poloxamer 407 concentration, the higher the solubilizing capacity. At each concentration of poloxamer 407, the higher solubilizing capacity of poloxamer 407 for more lipophilic alkyl nicotinates may contribute to their lower observed diffusion coefficients.

*Effect of poloxamer properties on drug release*

A series of different poloxamers (Table 1), which covered a wide range of hydrophile-lipophile balance (HLB) and molecular weight, were chosen to investigate how poloxamer properties affect the drug release. In these studies, the initial concentration of hexyl nicotinate in the vehicle (1% w/w), poloxamer concentration (30% w/w) and temperature (37°C) were held constant. All experiments were carried out at least in quintu-

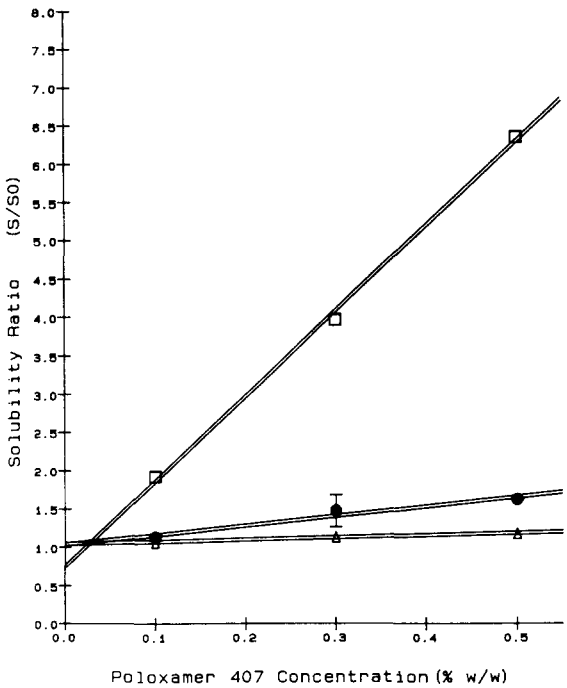


Fig. 5. Effect of drug lipophilicity on solubilization at 37°C (HN, □; BN, ●; EN, △).

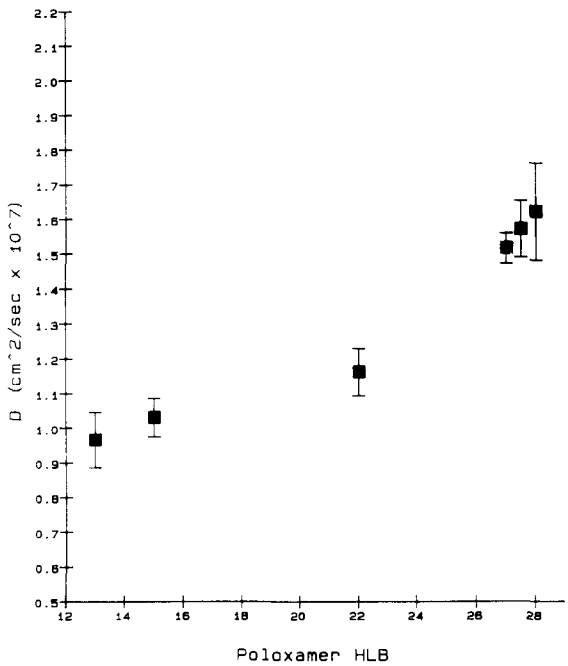


Fig. 6. Effect of poloxamer HLB on the apparent diffusivity of 1% hexyl nicotinate (■) in 30% w/w poloxamer at 37°C.

plicate. A plot of the apparent diffusion coefficient of HN as a function of poloxamer HLB is shown in Fig. 6, error bars denote standard error of means. Anova indicated that there was a significant difference between groups ($P<0.001$). Multiple comparison of means testing by the method of Scheffe that poloxamers of range 13–22 HLB or 27–28 HLB were not significantly different from each other. However, in all cases, each pair-wise comparison between groups was significantly different. Generally, apparent diffusivities increased with increasing poloxamer HLB. Because HN could be located in both the hydrophobic interior and the hydrophilic exterior of nonionic micelles, it might be suggested that both the polyoxypropylene group (POP) and the polyoxyethylene groups (POE) in poloxamers affected the release rates of hexyl nicotinate. Different poloxamers were normalized by their molecular weight in order to make comparisons among them. The results in Table 1 showed that the higher the number POP units per kg of poloxamer, the lower the diffusion coefficient of hexyl nicotinate. On the other hand, the diffusion coefficient of hexyl nicotinate tended to increase with increasing the number of POE units. It might be explained that the stronger interaction between hexyl nicotinate and poloxamer occurs mostly with the POP group which accounts for the lower release rate of HN from poloxamers containing more POP units. However, poloxamer hydration, due to the interaction of water with POE units, may also play a role in protecting the drug from interacting with POP group. Therefore, the ratio of POP and POE units may play an important role in optimizing the release rate of HN. The apparent diffusivity profile as a function of HLB (Fig. 6) suggested that the dominant factor affecting release might differ between less hydrophilic poloxamers (poloxamer 334, 335) and hydrophilic poloxamers (poloxamer 338, 288, 238). Poloxamer 407 having a high hydrophobe molecular weight and highly hydrophilic properties appeared to be at a transition point between these two groups. Additional studies are required before this can be confirmed. A similar comparison of the apparent diffusion coefficient of methyl nicotinate as function of poloxamer HLB was made

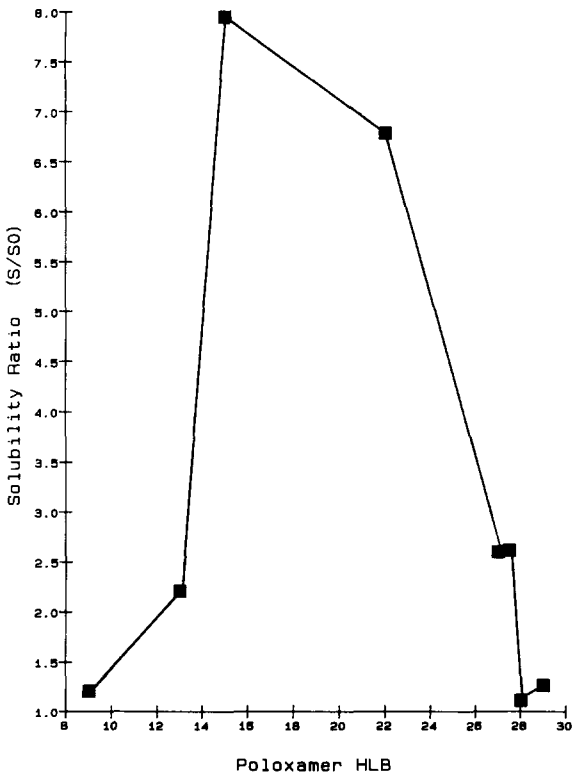


Fig. 7. Effect of poloxamer HLB on solubilization of HN (37°C).

and found to be statistically insignificant. That is, compared to the hexyl nicotinate profile, methyl nicotinate was less sensitive to poloxamer HLB changes. This suggested that, due to the hydrophilicity of methyl nicotinate, a lower interaction tendency with poloxamers accounted for the similar release rates of methyl nicotinate from different poloxamers.

*Effect of poloxamer properties on solubilization*

A plot of the solubility ratio ($S/S_0$) as a function of poloxamer HLB (Fig. 7) showed that initially the solubilizing capacity increased with increasing HLB, reached a maxima, then dropped. This implied that the ratio of POE to POP was an important factor relating to the solubilizing capacity. In addition to the interaction between the drug and poloxamer, different degree of hydration, aggregation size, conformation and porosity among different poloxamer gels might account for the observed solubilization data and the release data.

In conclusion, the results in the study of the temperature and poloxamer concentration effects on the drug release suggest that the drug is released by diffusion through the water channels of the gel matrix. Hence, the release rate of drug from these systems is related to the size and viscosity of water channels. Systematically investigating the effect of solute and vehicle properties on the release rate demonstrate that the stronger drug-poloxamer interaction may account for the lower release rate. Therefore, it is possible to control the drug release rate from these systems by modifying the lipophilicity of drug or poloxamer.

## Acknowledgement

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