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Drug release from Pluronic F-127 gels

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Summary

Low toxicity, reverse thermal gelation and high drug loading capabilities, suggest that PF-127 gels have great potential as a drug delivery system. The release of benzoic acid and related compounds from Pluronic F-127 (PF-127) gels has been studied in an in vitro release model. Release of the model drugs has been shown to decrease with increasing poloxamer concentration which is probably due to an increase in size and number of micelles and a subsequent decrease in size and number of aqueous channels. The diffusion coefficients of benzoic acid and *p*-hydroxybenzoic acid have been shown to decrease in an apparent exponential manner with respect to PF-127 concentration. The influence of drug lipophilicity on drug release has been studied by use of a series of *p*-hydroxybenzoate esters at three different temperatures. An increase in lipophilicity causes a decrease in release rate of the esters due to a greater partitioning into the micellar region within the gel structure. The energies of activation for diffusion of the *p*-hydroxybenzoate esters were estimated from their temperature dependence and were shown to increase with an increase in lipophilicity.

Introduction

Pluronic F-127 (PF-127 or Poloxamer 407) is one in the series of poloxamer ABA block copolymers, the members of which share the chemical formula shown below.

$$H(O-CH_2-CH_2)_a(O-\underset{\displaystyle CH_3}{\underset{|}{CH}}-CH_2)_b(O-CH_2-CH_2)_aOH$$

The polymers are produced by condensation of ethylene oxide and propylene oxide. PF-127 has a molecular weight of 11,500, 70–79% of which is accounted for by the hydrophilic ethylene oxide portion. It is more soluble in cold water than hot due to increased solvation and hydrogen bonding at lower temperatures. Aqueous solutions of between 20 and 30% w/ẇ PF-127 have the interesting characteristic of reverse thermal gelation, that is they are liquid at refrigerated temperatures (4–5°C) but gel upon warming to ambient levels (Schmolka, 1972). The gelation is reversible upon cooling.

It is thought that the gel is micellar in nature, being constructed from a cubic orientation of micellar subunits (Chen-Chow, 1980). By use of ultrasonic velocity and light-scattering measurements (Rassing and Attwood, 1983) a micellar

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mode of association has since been indicated for PF-127 over the temperature range 10–40°C. Gelation of PF-127 is thought to occur due to the dehydration of the polymer leading to an increased chain friction and entanglement, producing a hydrophobic association (Rassing et al., 1984; Vadnere et al., 1984).

Reverse thermal gelation and low toxicity have been the basis of research into the use of PF-127 as a possible drug delivery system in man. It has been considered for topical delivery of lidocaine (Chen-Chow and Frank, 1981), and anti-cancer agents (Miyazaki, 1984), and for the covering of burn wounds (Nalbandian, 1972). Investigations into ophthalmic use have been carried out using pilocarpine as the model drug and PF-127 as the vehicle (Miller and Donovan, 1982). Finally, PF-127 has been studied for possible use as a vehicle for injectables by both the intramuscular and subcutaneous routes (Hadgraft and Howard, 1982; Collett et al., 1985).

We have characterized in vitro solute release from PF-127 gels by investigating the effect of poloxamer concentrations in the vehicle and also the effect that the solutes own physicochemical properties have on its release. A series of benzoic acid derivatives were chosen as model compounds as they provide a series of structurally related compounds covering a wide range of physicochemical properties.

Materials and Methods

Materials

Benzoic acid, *p*-hydroxybenzoic acid and ethyl *p*-hydroxybenzoate (British Drug Houses), methyl and propyl *p*-hydroxy benzoate (Thornton and Ross), butyl *p*-hydroxybenzoate (Sigma Chemicals), isopropyl myristate (Croda Chemicals), Pluronic F-127 (a gift from Atochem), and Celgard 2500 microporous engineering film (a gift from Celanese fibres), were used as received.

PF-127 gel preparation

Gels containing the solutes were prepared by use of the "cold" method described by Schmolka (1972). A weighed amount of PF-127 was slowly added to a cold solution of buffer over a period of 2–3 min with gentle mixing. The PF-127 was then allowed to hydrate and disperse overnight at 4°C. Upon complete dissolution of the PF-127 the required amount of solute was added to the cold PF-127 solution with gentle mixing. The mixture was then incubated at 30°C overnight to facilitate complete dissolution of the solute.

The concentration of incorporated solute was 0.2% w/v and the aqueous phase of the gel was McIlvane's buffer (pH 3). This pH ensured that at least 93% of the solute was in the unionized form.

Method

Solute release from the gels was measured by use of a diffusion cell based on the design of that developed by Billups and Patel (1970).

Cold PF-127 solution (10 ml) containing the test solute was introduced into the inner compartment. The solution was separated from the receptor phase by an isopropyl myristate (IPM) impregnated Celgard 2500 membrane. The membrane was then sealed with a rubber gasket, screw-cap, and Nescofilm. The inner compartment was then inverted in to the receptor compartment. The whole assembly was placed in a water bath, preset at the required temperature, and left for half-an-hour to enable the gel to form and the system to equilibrate. Pre-thermostated receptor phase (100 ml, pH 7.4 phosphate buffer) was then introduced to the outer compartment and the time this occurred was designated as the start of the diffusion experiment. The receptor phase was stirred with a magnetic stirring bar and sampled at preset intervals during a 5-h test period. The solute concentrations were measured spectrophotometrically.

Treatment of results

Solute release from PF-127 gels can be treated in the same way as from other pharmaceutical semi-solids like ointments and creams. Higuchi (1962) described the following relationship between drug diffusion and release of drug from semi-solids by the following equation:

$$Q = 2C\left(\frac{D_{app} \cdot t}{\pi}\right)^{1/2} \quad (1)$$

where Q = amount of drug released to the sink per unit area; D_{app} = apparent diffusion coefficient of the drug in the vehicle; t = time; C = the initial concentration of drug in the vehicle.

Thus a plot of Q vs $t^{1/2}$ should produce a straight line, the gradient of which is related to the release rate of the drug out of the gel, and can be used to calculate the apparent diffusion coefficient D_{app}.

Results

Effect of PF-127 concentration on solute release

Benzoic acid release from PF-127 gels of concentrations between 22% and 30% w/w were evaluated at 37°C. The initial concentration of the benzoic acid in the vehicle was kept constant at 0.2% w/v. At this concentration the benzoic acid was well below its solubility limit. Concentrations of less than 22% w/w PF-127 were found not to gel satisfactorily. Fig. 1 shows a plot of apparent diffusion coefficient (D_{app}) of benzoic acid versus concentration of PF-127.

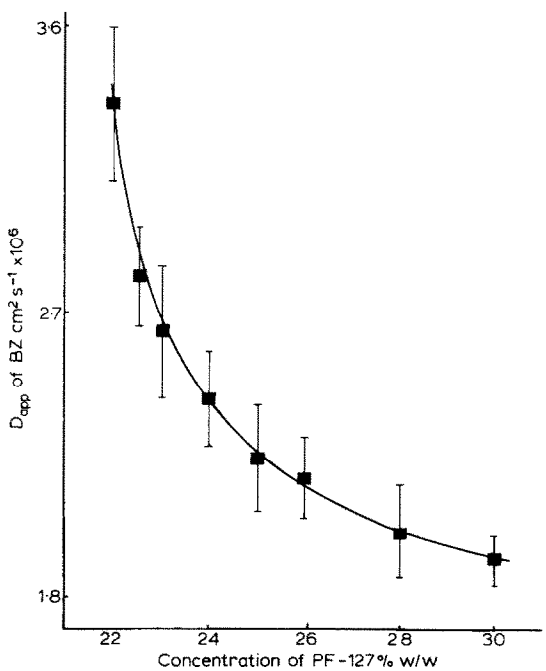

Fig. 1. The relationship between the apparent diffusion coefficient of benzoic acid and the concentration of Pluronic F-127 at 37°C. Concentration of benzoic acid was 0.2% w/v.

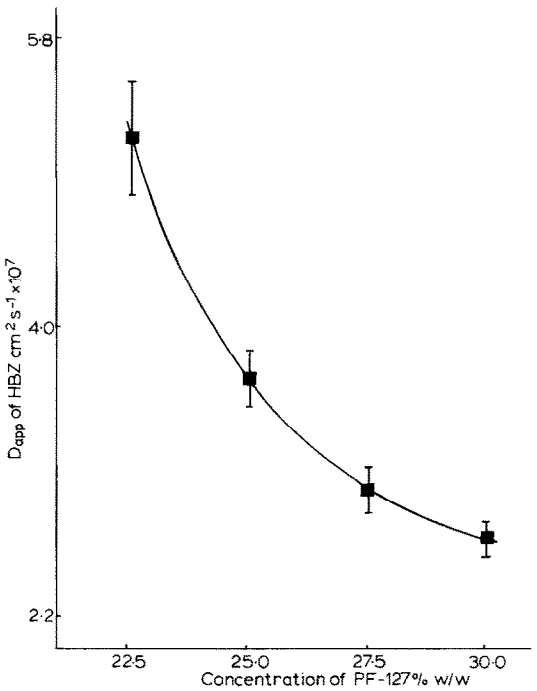

Fig. 2. The relationship between the apparent diffusion coefficient of *p*-hydroxybenzoic acid and the concentration of Pluronic F-127 at 37°C. Concentration of *p*-hydroxybenzoic acid was 0.2% w/v.

p-Hydroxybenzoic acid, and methyl and ethyl *p*-hydroxybenzoate were studied at concentrations of PF-127 between 22% and 30% w/w, the initial concentration of drug and temperature being kept constant as with the benzoic acid. The results are plotted in Figs. 2 and 3.

Effect of solute lipophilicity on its release from PF-127 gels

The release of a series of esters (the *p*-hydroxybenzoates) was investigated at three temperatures: 30°C, 37°C and 50°C. The concentration of the PF-127 gel was 25% w/w in all cases and the initial drug concentration 0.2% w/v. The drugs studied were the methyl, ethyl, propyl and butyl esters. Fig. 4 shows the apparent diffusion coefficients for each of the solutes at each temperature. They are plotted as a function of the number of CH_2 groups in the ester chain. The apparent

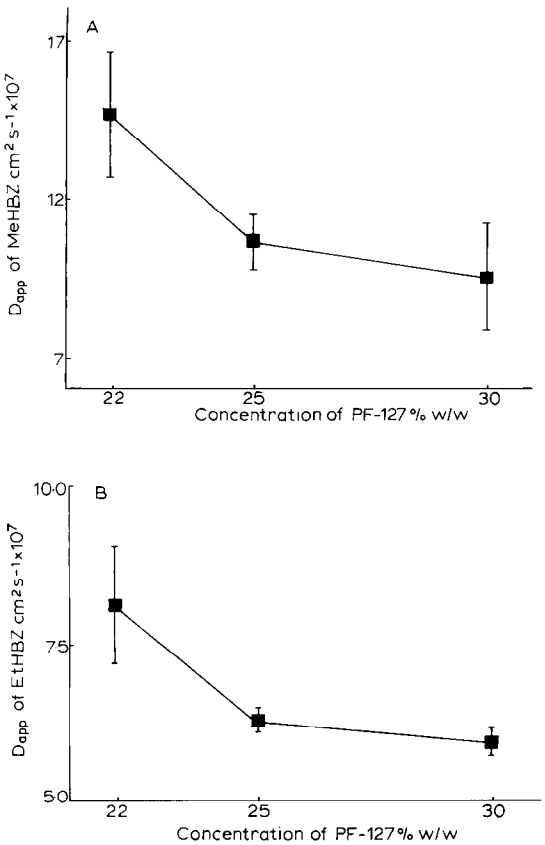

Fig. 3. a: the relationship between the apparent diffusion coefficient of methyl *p*-hydroxybenzoate and the concentration of Pluronic F-127 at 37°C. Concentration of methyl *p*-hydroxybenzoate was 0.2% w/v. b: the relationship between the apparent diffusion coefficient of ethyl *p*-hydroxybenzoate and the concentration of Pluronic F-127 at 37°C. Concentration of ethyl *p*-hydroxybenzoate was 0.2% w/v.

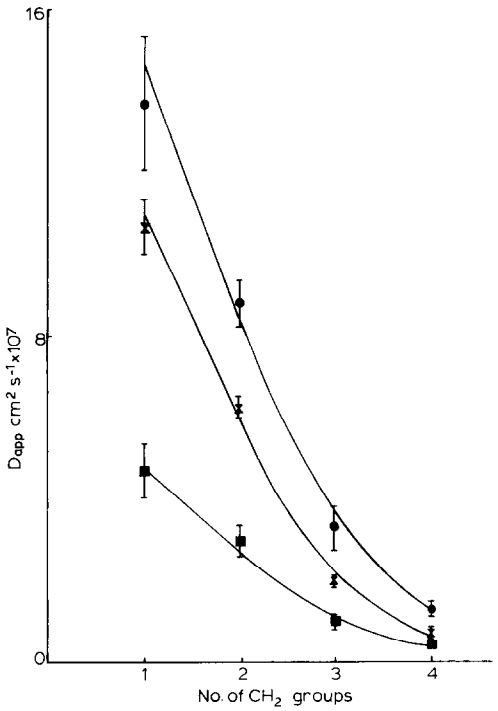

Fig. 4. The relationship between the apparent diffusion coefficients of *p*-hydroxybenzoate esters from 25% Pluronic F-127 gels as a function of ester chain length at 30°C (■), 37°C (×), and 50°C (●). The concentration of the solutes was 0.2% w/v.

TABLE 1

THE CALCULATED ENERGIES OF DIFFUSION (kJ/mol) OF THE *p*-HYDROXYBENZOATES IN 25% PLURONIC F-127 GELS.

Solute concentration was 0.2% w/v.

p-Hydroxybenzoate ester	Energy of diffusion (kJ/mol)
Methyl	40.3
Ethyl	41.0
Propyl	45.9
Butyl	48.1

diffusion coefficients (D_{app}) for the four esters were also plotted as a function of absolute temperature (1/T) in the Arrhenius manner (2):

$$D_{app} = D_o \cdot e^{-E/RT} \quad (2)$$

so that the energy of diffusion (E) could be calculated from the slopes of the lines. The results are shown in Table 1.

Discussion

It can be seen from the results obtained for all the solutes examined that, as the concentration of PF-127 is increased, the diffusion coefficient of the solute decreases. The results from the studies using benzoic acid suggest that the relationship between the concentration of PF-127 and the apparent diffusion coefficient of drug is not linear,

which does not agree with the findings of earlier workers (Chen-Chow and Frank, 1981). Regression analysis showed that the data were best fitted by an exponential equation

$$y = 7213 \exp(-0.39\ x) + 1.84 \quad (r = 0.984).$$

Similarly, the results for *p*-hydroxy benzoic acid were not linear and the data could be described by an exponential equation

$$y = 2605 \exp(-0.31\ x) + 2.41 \quad (r = 0.999).$$

Methyl and ethyl *p*-hydroxybenzoate were studied and were also found to support the previous results. Thus the data presented clearly indicate that there is not a linear relationship between concentration of PF-127 and apparent diffusion coefficient, but that it can be described by an exponential for the solutes studied.

Solutions of below 22% w/w PF-127 did not gel. We would suggest therefore that slight changes in poloxamer concentration around this point would greatly affect the release characteristics of the gel. It appears that at a certain poloxamer concentration ($\simeq$ 25% w/w) substantial chain interactions occur and further increase in polymer concentration will only slightly alter the ability of the gel to hinder the diffusion of the drug molecule. If the region between 25% and 30% w/w PF-127 is considered alone then one might possibly assume linearity. As the earlier workers cited have used PF-127 synthesized by a different manufacturer we would suggest that this could be one reason for differences in the results obtained. In their studies, Chen-Chow and Frank examined gels only in the region of strong polymer chain interactions, where the relationship between vehicle concentration and drug release could be said to be linear. However, as shown, at concentrations of PF-127 below this region a linear relationship is not obtained suggesting that, overall, there is an apparent exponential relationship. The reason for the decrease in diffusion coefficient as PF-127 concentration is increased is probably related to the increase in the number and size of micelles within the gel structure. This produces a subsequent decrease in number and size of water channels, thereby causing an increased path of diffusion and hence decreasing diffusion coefficient.

It can be seen that as the lipophilicity of the solute is increased from the methyl *p*-hydroxybenzoate ester through to the butyl ester the apparent diffusion coefficient, hence release rate is decreased. The effect reaches an asymptote with increasing lipophilicity. These results would be expected when the structure of the gel is considered in conjunction with the physicochemical properties of the solutes investigated. PF-127 gels have been considered to consist of micelles and aqueous channels, the latter being the region from which the incorporated solute is directly available for release. The more lipophilic the drug the more it will partition into the micelles and the less will exist in the aqueous channels. Also there is an increase in molecular size in the transition from the methyl to the butyl ester and there will be an increasing resistance to diffusion. This explains why the more lipophilic esters are released at a slower rate. The same relationship can be seen at all three temperatures examined and, as seen by others (Chen-Chow and Frank, 1981; Hadgraft and Howard, 1982), an increase in temperature increases the release rate despite an increase in bulk viscosity. It should be noted that the effect of temperature decreases and the calculated energies of diffusion increase as the solutes become more lipophilic. The more lipophilic the ester the more their diffusion is hindered. However, the values for all the esters are similar and are between 40–50 kJ/mol which is of the same order, although slightly higher, as that indicated by previous authors for lignocaine and barbiturates (Chen-Chow and Frank, 1981; Hadgraft and Howard, 1982). In the case of lignocaine and the barbiturates, a substantial fraction of the dissolved drug will be in the ionized form. The regions of the gel structure through which these solutes will diffuse are therefore the aqueous channels. This is reflected in the activation energies. For the *p*-hydroxybenzoates, which are more lipophilic in nature, the region of diffusion is probably associated with the micellar polymer chains. Thus the activation energies are higher for this group of molecules than for the previously studied solutes.

From the data presented it would seem that the most important factor in controlling the release of a solute from PF-127 gels is the physicochemical properties of the solute or permeant. The concentration of PF-127 and temperature influence the physical properties of the gel and thus the solute release, but these effects are small when compared with those of lipophilicity and molecular size of the said solute.

Acknowledgement

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