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Salt effects on the diffusion and release rate of propranolol from poloxamer 407 gels

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Abstract

In this report we show that salts commonly included in the formulation of poloxamer 407 (P407) gels can dramatically change the release rate of a drug from the gel. We used a model drug, propranolol, and measured its diffusion from a 21% P407 gel into an aqueous medium at 37°C through a cellulose membrane. The data followed the Higuchi square root law during the first hour of release. The release rate and diffusion coefficient of propranolol were significantly reduced when NaCl, Na_2SO_4, NaH_2PO_4, $MgSO_4$ and $CaCl_2$ were added to the gels. The magnitude of the effect on release rate depends on the nature and concentration of the salt. Since propranolol is expected to be located outside the micelles in the gel, we attribute these salt effects to an increase in microviscosity of the aqueous regions of the gel, rather than to a change in micellization behavior. This is analogous to the change in the aggregation and phase behavior of aqueous solutions of non-ionic surfactants in the presence of salts.

Keywords: Salt effects; Propranolol; Poloxamer 407 gels; Pluronic F127 gels

1. Introduction

Poloxamers are non-ionic, polyoxyethylene-polyoxypropylene-polyoxyethylene triblock copolymers that have many pharmaceutical applications. Poloxamer 407 (P407), which has a nominal molecular weight of 12500 and a PEO/PPO ratio of 2:1 by weight, has been the most widely used of these copolymers. P407 solutions at concentration of 20% or above show thermoreversible gelation behavior (Schmolka, 1972). This has made them attractive in formulating thermoreversible gels for transdermal, injectable and controlled delivery of many drugs. The release profiles of a few drugs from P407 gels have been reported (Gilbert et al., 1986; Chi and Jun, 1991; Miyazaki et al., 1984; Bhardwaj and Blanchard,

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1996; Suh and Jun, 1996). In general, these studies show that release into both aqueous and non-aqueous media follows the Higuchi square root law (Higuchi, 1962). These studies also show that diffusion coefficients of drug in the gel decrease with increasing P407 content, which is consistent with a consequent increase in bulk viscosity. Interestingly, although bulk viscosity of the gels has also been shown to increase with temperature, release rates also increase with temperature (Chi and Jun, 1991; Suh and Jun, 1996). This has led the authors to propose that drug release is controlled by the microviscosity of the gel, rather than by bulk viscosity.

Most pharmaceutical P407 gels are formulated with buffer salts (Gilbert et al., 1986; Wang and Johnston, 1995; Allen, 1993; Suh and Jun, 1996), and may contain the salt form of a drug. We have shown in earlier studies (Pandit and Kisaka, 1996) that salts dramatically alter the gel formation and gel melting transition temperatures of P407 gels; in some cases, gels do not form at all. A study on the rheology of poloxamer vehicles at 5°C showed that the addition of 1% NaCl to a 25% P407 solution had little effect, while 5% NaCl dramatically increased the bulk viscosity of the solution (Miller and Drabik, 1984). These reports suggest that salts might have a significant influence on drug release from P407 gels at body temperature.

The effect of ionic additives on drug release from P407 gels has not been studied systematically. Chen-Chow and Frank (1981) investigated the release of lidocaine from 25% P407 gels into isopropyl myristate, and found that drug release was significantly slower when the gel contained NaCl. They attributed this to an increase in the microviscosity of the aqueous channels of the gel. Others have shown the influence of pH on release rates, but have ascribed this solely to changes in the ionization state of the drug molecule (Chi and Jun, 1991; Suh and Jun, 1996). Although ionic additives at various concentrations continue to be used in P407 gels, no subsequent work has examined their influence on release.

We report here the effect of several salts on the release of a model drug, propranolol HCl, from 21% P407 gels. We have examined release across a cellulose membrane into an aqueous receptor phase in order to simulate injectable delivery. Other researchers have used isopropyl myristate, a lipophilic medium, as the receptor phase to model transdermal use. A change in the microviscosity of the gel is expected to alter diffusion from the gel regardless of the receptor phase, although the magnitude of effect may be different in the two cases.

Propranolol (PNL) was selected as the model drug for several reasons. It is a weak base with a pK_a of 9.45 and should be completely ionized under the conditions of our experiments (the pH of our systems ranged between 4.8 and 6.2). Since charged molecules are not expected to enter the hydrophobic interior of micelles, we believe that PNL in our gels is predominantly located in the outer aqueous region and PEO chain network rather than inside the P407 micelles. Thus, a change in PNL diffusion is expected to reflect a change in the microviscosity of the region outside the micelles rather than a change in micellar size, number, or polarity, although these latter properties may also change in the presence of salts. Many of the drugs used previously in release rate studies have been either lipophilic or partially unionized under the experimental conditions. As a result, they may have been located both inside and outside the micelles, complicating the analysis of factors responsible for release rate changes.

2. Materials and methods

2.1. Materials

Propranolol HCl (ICN Biomedicals, Costa Mesa, CA) and P407 (Sigma, St. Louis, MO) were used as received. The regenerated cellulose membrane (MWCO 6000) was purchased from Fisher Scientific (Pittsburgh, PA). The salts (NaCl, Na_2SO_4, NaH_2PO_4, $CaCl_2$, $MgSO_4$), all analytical grade, were obtained from Mallinckrodt (Phillipsburg, NJ).

2.2. Preparation of gel solution

The gel was made on a weight basis using the 'cold method' (Schmolka, 1972). P407 was first

mixed with water and refrigerated at 4–5°C until a homogenous solution was obtained. The PNL and salts were then added and the mixture refrigerated again until homogenous. All our studies were carried out with 21% w/w P407 and, unless otherwise specified, 1.25% w/w PNL (corresponding to a concentration of 0.043 molal).

2.3. Measurement of pH

One of the objectives of using PNL as the model drug was because it is expected to be completely ionized in our gel systems. We wanted to confirm that the pH of our systems were sufficiently below the pK_a to make this possible; however, pH measurements of viscous gels are difficult and often give erratic results. P407, being non-ionic, is not expected to change aqueous pH. We checked the pH of P407 solutions up to a concentration of 10% w/w and found that all had a pH value of 5.8–6.2. We also checked the pH values of salt solutions containing propranolol hydrochloride, at salt and PNL concentrations used in our gels. The pH values ranged between 4.8 and 6.2, with the NaH_2PO_4 solution having the lowest value of 4.8. Since the pK_a of PNL is 9.45, it is expected to be $>99.9\%$ ionized in our experimental systems. The pH measurements were made using a Corning model 350 pH meter with a combination electrode.

2.4. Release studies

A Lucite diffusion cell was constructed for our experiments. The cylindrical gel compartment had a diameter of 2.22 cm and a depth of 1.11 cm. The volume of the gel compartment was 4.29 cm^3, and the surface area of exposed gel was 3.88 cm^2.

The cold P407-PNL solution was placed in the diffusion cell, and the meniscus brought to the top of the compartment. This system was placed in a 37°C oven until the solution gelled and equilibrated. Excess gel was removed with the edge of a clean glass slide. The cellulose membrane, previously soaked in water, was placed over the compartment and clamped into position. The exterior of the cell was washed with water, checked for leaks and re-equilibrated at 37°C. It was then placed in a 600-ml covered, jacketed beaker maintained at 37°C. Four hundred milliliters of water at 37°C was carefully added to the beaker. A mechanical paddle-type stirrer (Stir-Pak, Cole Parmer Instruments, Vernon Hills, IL) was immersed so that it was 3 cm above the cell, and the medium stirred at 110 rpm. The stirring speed was checked using a phototachometer (Extech Instruments, Waltham, MA). Periodically, 3-ml samples were withdrawn, and the PNL concentration measured spectrophotometrically (8452A Photodiode Array Spectrophotometer; Hewlett Packard, Palo Alto, CA) at 290 nm. The samples were returned to the beaker after each measurement.

2.5. Data treatment

Our system represents drug release from one side of a semisolid slab, where the drug is completely dissolved in a vehicle. Such systems follow the Higuchi square root law (Higuchi, 1962);

$$Q = 2C_0(Dt/\pi)^{1/2} \quad (1)$$

where Q is the amount of drug released per unit area, C_0 is the initial drug concentration, D is the diffusion coefficient of the drug and t is time. If drug release obeys this law, the amount of drug released is a linear function of $t^{1/2}$, and D can be calculated from the slope. The assumptions in this treatment are that the drug is the only component diffusing out of the vehicle, sink conditions are maintained in the receptor phase, and D is constant with respect to time and position in the vehicle. The cellulose membrane in our study had a MWCO of 6000, and hence P407 could not diffuse out. Sink conditions were maintained in our experiments, in that the concentration of PNL at the end of the experiments was less than 0.1% of the solubility of PNL in the medium, and less than 10% of the PNL in the gel was released during the experiment. We were thus able to use Eq. (1) to treat the data. Values for D were reproducible; replicate measurements of D gave a standard error of the mean between 1 and 2%.

3. Results

The main purpose of our studies was to examine the effects of salts on PNL release from P407 gels. Hence, buffer salts were not used to adjust pH in either the gel or the receptor medium. Water with no additives was used as our receptor phase. We did have some concerns that the osmotic pressure difference between the gel and the receptor phase would result in dilution of the gel, causing a gradual increase of release rate. Our preliminary results showed that the release of PNL from a P407 gel followed Eq. (1) well, showing no evidence of any such problems over 3 h of release. However, in gels containing salts, the release rate begins increasing slowly after about 60 min; both these effects are illustrated in Fig. 1 for gels with and without Na_2SO_4. We believe the increase may be due to the salt diffusing out of the gel, leaving behind a gel with lower salt concentration. We, therefore, used the linear region from 15 to 60 min to calculate and compare diffusion coefficients.

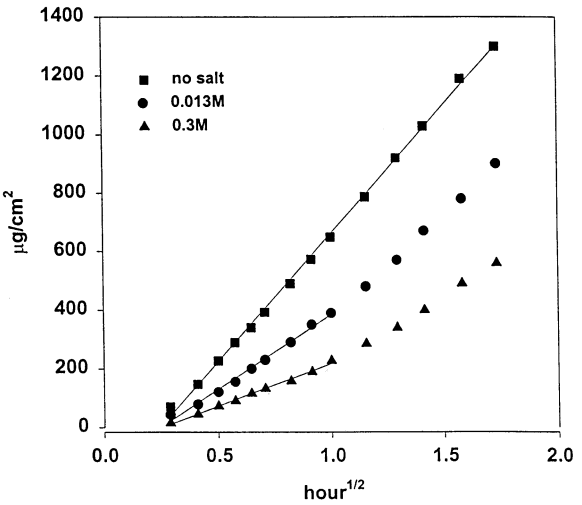

Fig. 1. Effect of Na_2SO_4 on release rate of PNL from a 21% P407 gel at 37°C. Linear regression lines are plotted through the initial linear region. The release rate gradually increases after 1.5 h.

Table 1
Effect of P407, and initial PNL concentration (C_0) on the diffusion coefficient (D) of PNL at 37°C

Formulation	C_0 (% w/w)	D (cm^2/s)
Water	0.58	$9.2\times10-6$
Water	1.25	$8.0\times10-6$
21% P407 gel	0.58	$1.6\times10-6$
21% P407 gel	1.25	$1.4\times10-6$

The standard error of the mean (S.E.M.) for D was less than 2% in all cases.

3.1. Effect of P407 and PNL concentration on diffusion

To see how much the P407 gel slowed down the diffusion of PNL, we carried out an experiment using an aqueous solution of PNL in the diffusion cell. This was done at two PNL concentrations, 0.58% and 1.25%. The study was repeated with the same concentrations of PNL in a 21% P407 gel. The results followed Eq. (1), and the diffusion coefficients calculated are shown in Table 1. As expected, D is lower in the gel as compared to water. The release rate of PNL from the gel also increases with initial PNL concentration, C_0, as predicted from Eq. (1). If the equation were obeyed exactly, the PNL diffusion coefficient, D, for each formulation should be independent of C_0; however, D decreases slightly as C_0 increases. We believe this is due the slightly higher ionic strength as the PNL concentration is increased, since we used the hydrochloride salt form of the drug. As will be seen from our subsequent results, the addition of salts decreases the release rate and diffusion coefficient of PNL from P407 gels.

3.2. Effect of salts on PNL release rate

Fig. 2 shows a typical release rate plot for the diffusion of PNL from a gel containing salts; this particular figure is for gels containing various concentrations of NaH_2PO_4. All the systems obey Eq. (1) and the presence of NaH_2PO_4 dramatically reduces the release rate. Similar results were obtained for all the salts studied. Fig. 3 shows a comparison of release rates of PNL from gels containing 0.1 M of various salts, compared to a gel with no salt.

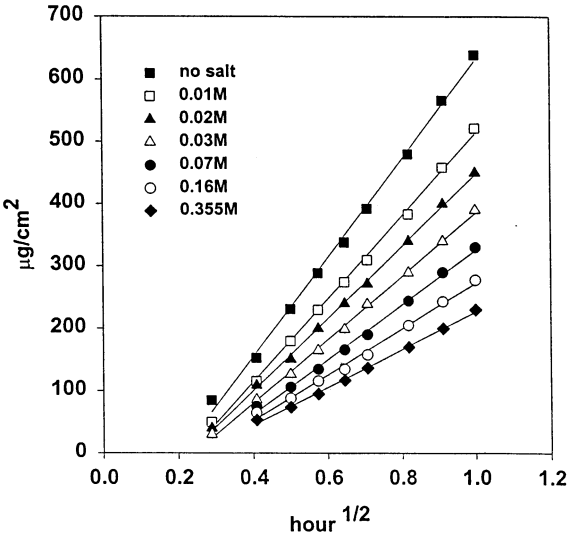

Fig. 2. Effect of NaH_2PO_4 concentration on release rate of PNL from a 21% P407 gel at 37°C. Linear regression lines are fitted to the data.

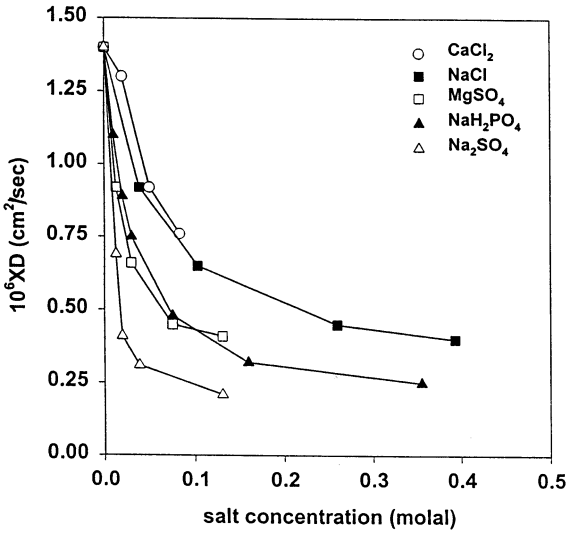

Fig. 4. Effect of salts on the diffusion coefficient, D, of PNL from 21% P407 gels at 37°C.

3.3. Effect of salts on PNL diffusion coefficients

Diffusion coefficients for PNL were calculated from the linear portions of the release rate graphs, and plotted versus added salt concentration (Fig. 4). It is apparent that the diffusion coefficient drops significantly with only a small amount of added salt, and then levels off as salt concentration is increased further. The effect is not merely due to non-specific ionic strength effects, but appears to include contributions due to the specific interaction of each ion with P407 or with water.

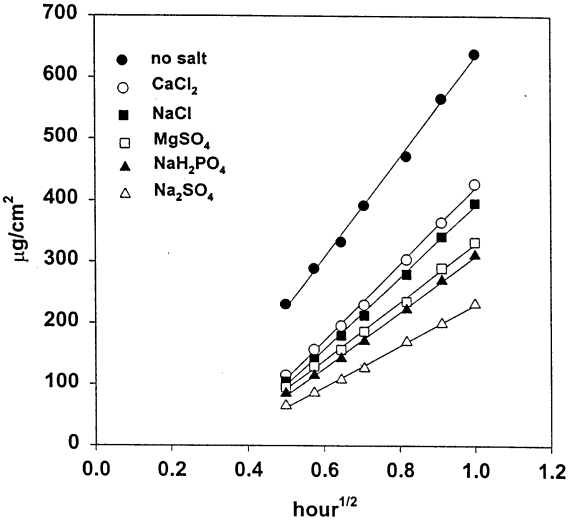

Fig. 3. Effect of 0.1 molal concentration of various salts on release rate of PNL from a 21% P407 gel at 37°C. Linear regression lines are fitted to the data.

4. Discussion and conclusions

It is well known that the presence of salts changes the cmc of non-ionic surfactants and can alter micellar size and number (Schott and Han, 1975, 1976; Attwood and Florence, 1983; Meguro et al., 1987). However, in our case, these effects should not alter release rate significantly because PNL is expected to be located outside the micelles. Thus, the decrease in PNL diffusion coefficient when salts are present most likely represents an increase in the microviscosity in the aqueous region of the gel. This region is composed of a network of entangled PEO chains, which presumably become tighter when salts are added. This is analogous to the behavior of aqueous solutions of PEO and PEO-containing surfactants in the presence and absence of salts; a brief discussion of this behavior follows.

Aqueous solutions of PEO surfactants exhibit a cloud point (CP) at higher temperatures which has been attributed to a decrease in hydrogen bonding between PEO chains and water as temperature increases (Bailey and Koleske, 1987). Addition of salts can change this CP. The CP is lowered due to salting-out effects by anions such as Cl^-, $SO_4^{2}{}_-$, PO_4^{-3}, and by alkali metal cations such as Na^+ and K^+. The CP is increased by anions such as SCN^-, which are known to break water structure. Cations such as Ca^{2+} and Mg^{2+} also cause an increase in CP because of their ability to complex the ether groups of PEO (Schott and Han, 1976; Schott and Royce, 1984; Schott et al., 1984; Schott, 1997). Thus, the net effect of a salt on the behavior of PEO in aqueous solution depends on the contributions of both the anion and the cation.

We believe that the PEO chains forming the P407 gel network are also similarly affected by various ions. The salts used in our study reduced the diffusion of PNL, implying that the PEO chain network became tighter. This tightening of PEO chains of P407 in the presence of salts also manifests itself as lowered gel formation and gel melting temperatures, as we have shown earlier (Pandit and Kisaka, 1996). A report on the rheology of poloxamer vehicles (Miller and Drabik, 1984), also showed that the bulk viscosity of a 25% poloxamer solution increased from 67 cps to 700 cps at 5°C in the presence of 5% NaCl. However, no other salts were studied.

Using Fig. 4, we can examine the magnitude of effect of each individual salt on the release rate. Comparing NaCl and $CaCl_2$, we find that their net effect on D is the about same. Although, at a given molal concentration, twice as many Cl^- ions are present in $CaCl_2$ solutions compared to NaCl, and Ca^{2+} ions can complex with PEO chains and loosen the network, thus modifying the effect. For similar reasons, $MgSO_4$ has a less pronounced effect on D than Na_2SO_4 at the same molal concentration.

The leveling off of the diffusion coefficient at higher concentrations of salts is interesting, and we present our current thinking on this. As discussed before, low concentrations of salts promote water structure, and increase PEO-PEO interactions. This initially results in a tighter PEO network between P407 micelles, and a resultant higher gel microviscosity. However, as salt concentration is increased, the P407 micelle shape and/or size may change, resulting in a decrease in PEO chain interactions among micelles. The result is that the PEO chain network begins to collapse, and gel microviscosity does not increase any further. One would expect that the microviscosity would actually begin to decrease at even higher salt concentrations. We found this indirectly, in that the gel begins to melt at higher salt concentrations, i.e. the gel melting temperature is close to 37°C when high salt concentrations are present. This limited the usable concentration range of each salt. Phase diagrams of P407 gels with various salts can be found in our earlier work (Pandit and Kisaka, 1996).

Our results have important implications for formulation of injectable P407 gels. We have demonstrated that ionic additives such as buffers can change release rates, and that small quantities of salts have dramatic effects on release. Typical buffers added to P407 gels have been 0.2 M HCl, phthalate and phosphate buffers (Suh and Jun, 1996) and McIlvane's buffer (Gilbert et al., 1986). Other studies (Chi and Jun, 1991) used a variety of buffers to change the pH of the gel, but did not specify buffer ingredients or concentrations. Our work clearly shows the importance of these seemingly innocuous additives. Changing the anion or cation of the salt, or the pH of a buffered gel (because pH affects the concentrations of the ions in a buffer), can affect release rates significantly. This can be either an unexpected complication, or a deliberate formulation approach.

Although we have used an aqueous release medium to simulate injectable delivery, our results have implications for other applications of F127 gels, such as transdermal delivery. Indications from early studies (Chen-Chow and Frank, 1981) suggest that inclusion of NaCl reduced the release rate of lidocaine from 25% P407 gels into isopropyl myristate. The influence of gel pH on release rates of ketoprofen (Chi and Jun, 1991), and naproxen (Suh and Jun, 1996) into isopropyl myristate was ascribed solely to changes in the ionization state of the drug. Our results suggest

that this is at least partially due to the ionic effect of the various buffers in the gels.

Another factor to consider when adding salts to P407 gels is the lowering of the gel melting temperature by salts. Although a system might be a gel at room temperature when formulated, its melting temperature may have been reduced sufficiently by the salt, so that it is a liquid under in vivo conditions (37°C) (Pandit and Kisaka, 1996).

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