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RESEARCH PAPER

Permeation of Piroxicam from the Poloxamer Gels

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ABSTRACT

Topical formulations of piroxicam were prepared using poloxamer 407 or poloxamer 188 by a cold method, and the permeation characteristics of piroxicam were evaluated. The permeation rate of piroxicam across the synthetic cellulose membrane and the rat skin decreased as the concentration of poloxamer increased. Though poloxamer gel exhibits reversed thermal behavior, the permeation rate of piroxicam increased with increasing temperature, indicating that the diffusional pathway of piroxicam is a water channel within the gel formulation. The pH of the gel did not affect the permeation rate of piroxicam significantly. As the concentration of piroxicam in the gel formulation increased, the permeation rate of piroxicam increased up to 1% and reached a plateau above 1%. Among various enhancers tested, polyoxyethylene-2-oleyl ether showed the highest enhancing effect, with an enhancement ratio of 2.84. Based on experimental results, the permeation rate of piroxicam can be controlled by changing the poloxamer concentration or drug concentration and by the addition of an appropriate enhancer.

INTRODUCTION

Piroxicam is one of the most potent nonsteroidal antiinflammatory agents that also have antipyretic activity. Piroxicam is well absorbed following oral administration; however, its use has been limited by a number of side effects, including bleeding and ulceration (1). Transdermal administration of piroxicam can overcome these side effects (2), and higher local concentration can be maintained at the target site, which is desirable for antiinflammatory agents. Transdermal drug delivery systems have the additional advantages of avoiding hepatic first-pass metabolism and providing the controlled delivery of the drug for an extended period (3,4). In the development

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of a transdermal drug delivery system, it is desirable to evaluate the skin permeation characteristics of drug in vitro before conducting in vivo studies in human volunteers. It is well known that a number of factors can affect the transdermal permeation of a drugs, including pH of the formulation, drug concentration, partition coefficient, source of the skin, and so on (3).

The objectives of this study were to develop the topical gel formulation of piroxicam using poloxamer as a gelling agent and to study its in vitro permeation characteristics. To optimize the piroxicam gel formulation, the effects of concentration of poloxamer, the concentration of the drug, the pH of the gel, and the addition of permeation enhancer on the permeation rate of piroxicam were evaluated.

MATERIALS AND METHODS

Materials

The piroxicam was a gift from Chodang Pharmaceutical Company (Seoul, Korea). Poloxamer 407 and poloxamer 188 were obtained from BASF Korea (Seoul, Korea). All other reagents were analytical grade and were used as received. The synthetic cellulose membrane was Spectra/Por membrane disks (MWCO 14,000) from Spectrum Medical Ind. (United States).

Preparation of Poloxamer Gel Formulations

The gel formulations containing a poloxamer were prepared using a cold technique (5). Poloxamer was added to water at about 5°C with gentle stirring, and the solution was left overnight in a refrigerator to complete polymer desolvation. Piroxicam dissolved in propylene glycol was added slowly with stirring to cold poloxamer solution prepared previously, and the content of propylene glycol was 40% in the final formulation. The formulation was stored in an oven at 37°C for at least 2 days. An enhancer can be added to the prepared gel formulation when needed. Various enhancers (5%) were added to poloxamer solutions, and then the solutions were left overnight in a refrigerator to complete the miscible solutions. The preparation was brought to final volume with the same concentration of cold poloxamer solution.

Solubility

The solubility of piroxicam was measured in a propylene glycol/phosphate buffer (pH = 7.4) mixture as a function of propylene glycol content. An excess amount of piroxicam was added to a mixture of various ratios of propylene glycol/phosphate buffer. The mixture was stirred with a magnetic bar for 48 hr at 37°C. The solubility was measured by ultraviolet (UV) spectrophotometer after the filtration.

Diffusion Study

The freshly excised full-thickness rat skin was mounted on the Franz diffusion cell with the stratum corneum side facing the donor compartment and the dermal side facing the receptor compartment. Two grams of poloxamer gel formulation were applied on the skin, and the top cell was clamped and covered with a parafilm. The sampling port was also sealed with a parafilm to prevent the evaporation of the receptor medium. The receptor medium was pH 7.4 Sörensen's phosphate buffer, which was maintained at constant temperature by a circulating water bath. The temperature was maintained at 37°C in all diffusion studies except for the temperature effect study. The samples were withdrawn from the receptor compartment at predetermined time intervals and replaced by an equal volume of fresh buffer solution. The samples were analyzed by a UV spectrophotometer. The same procedure was used when a synthetic cellulose membrane was used instead of the rat skin.

RESULTS AND DISCUSSION

Solubility of Piroxicam

Figure 1 shows the solubility of piroxicam in propylene glycol/phosphate buffer solution as a function of propylene glycol content. Piroxicam is sparingly soluble in water. Addition of propylene glycol greatly increased the solubility of piroxicam, which peaked at 40% propylene glycol. The solubility started to decrease when the propylene glycol content exceeded 40%. In the following diffusion study, 1% piroxicam gel formulation containing 40% propylene glycol was chosen based on the solubility study.

Effect of Poloxamer Concentration on the Permeation Rate of Piroxicam

The effect of poloxamer 407 concentrations on the permeation rate of piroxicam across a synthetic cellulose membrane and rat abdominal skin was studied at 37°C using various formulations containing 1% piroxicam and

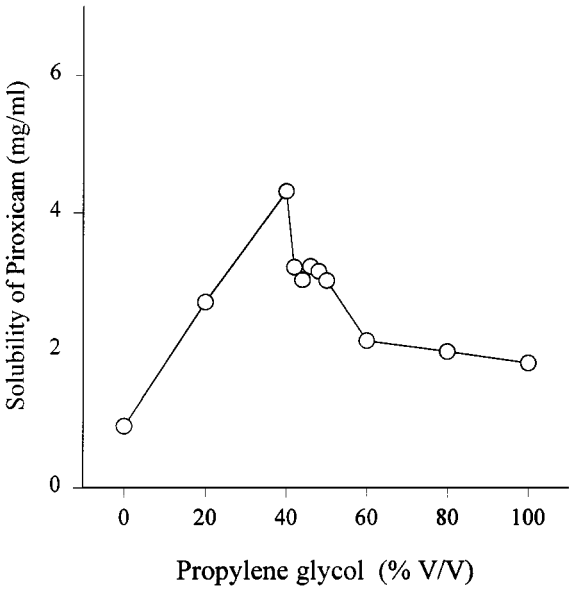

Figure 1. Solubility of piroxicam in propylene glycol/phosphate buffer mixture as a function of propylene glycol content.

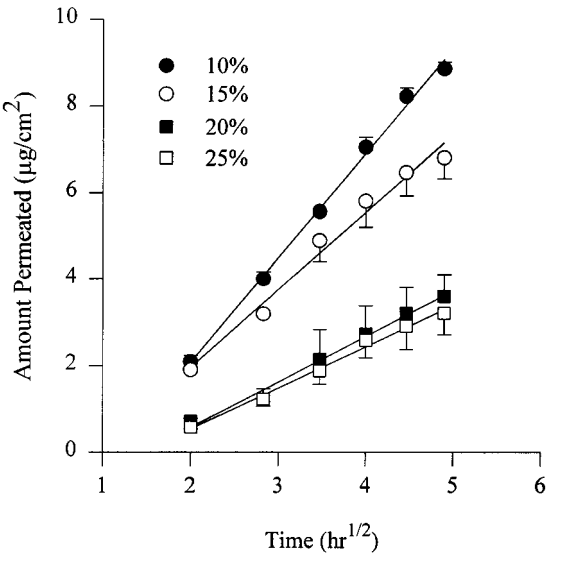

Figure 2. Effect of poloxamer 407 concentration on the permeation of piroxicam from various gel formulations across synthetic cellulose membrane. Each formulation contains 1% piroxicam, and the temperature was maintained at 37°C.

40% propylene glycol. The concentrations of poloxamer 407 tested were 10%, 15%, 20%, and 25%. The amount of piroxicam permeated across a synthetic cellulose membrane from various gel formulations as a function of the square root of time is shown in Fig. 2. The formulations showed fairly good linearity, resembling permeation of a drug from a suspension (6). The higher the concentration of poloxamer 407 was, the slower the drug permeation rate was, indicating that the higher concentration of poloxamer gel provide higher resistance to drug diffusion.

Other investigators, using photon correlation spectroscopy, have also reported a pronounced decrease in diffusion coefficient of a compound as the concentration of poloxamer 407 exceeded 10% (7–9). 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 was hypothesized that the drug is released by diffusion through the extramicellar water channels of the gel matrix, and the higher concentration of poloxamer causes the reduction in the size of water channels, the micellar growth, or greater tortuosity (10). As the concentration of poloxamer 407 exceeded 20%, its impact on the permeation rate of piroxicam became insignificant. A similar trend was observed when poloxamer 188 was used instead of poloxamer 407, even though the poloxamer 188 formulation did not form a gel.

The amount of piroxicam permeated across a rat abdominal skin from various gel formulations as a function of the square root of time is shown in Fig. 3. A similar trend was observed when the synthetic cellulose membrane was used except that the permeation rate was an order of magnitude smaller. It seems that the release rate of piroxicam from the gel formulation is a rate-determining step, and the membrane does not exhibit much resistance when the cellulose membrane is used; however, permeation across the rat skin becomes the rate-determining step, and the permeation rate retards significantly when the rat abdominal skin is used, even though the permeation profiles do not change significantly. These results indicate that a cellulose membrane can be used to predict, at least qualitatively, the permeation rate of piroxicam across the rat abdominal skin.

Effect of Temperature on the Drug Release

The poloxamer 407 can be used as a reservoir from which a drug is released when topically applied since it forms a soft gel at body temperature (11). The effect of temperature on the release of piroxicam across the cellulose membrane from a formulation containing 1% piroxi-

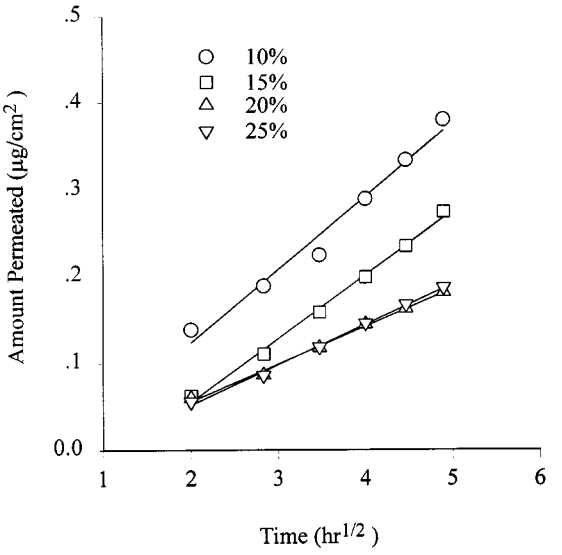

Figure 3. Effect of poloxamer 407 concentration on the permeation of piroxicam from various gel formulations across rat abdominal skin. Each formulation contains 1% piroxicam, and the temperature was maintained at 37°C.

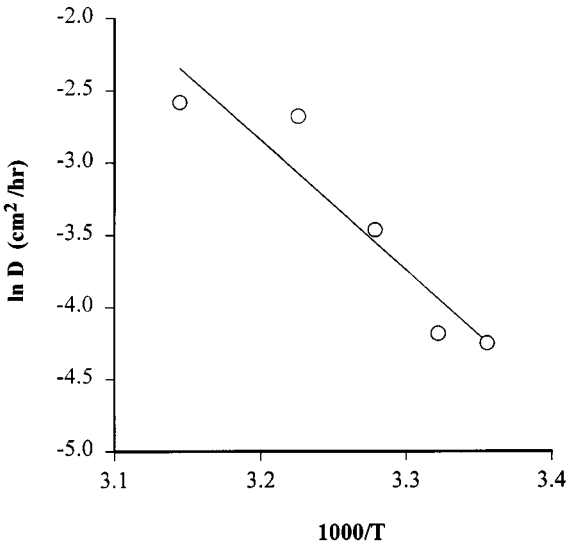

Figure 4. Effect of temperature on the apparent diffusion coefficient of piroxicam from 20% poloxamer 407 gel formulation across a synthetic cellulose membrane.

cam and 20% poloxamer 407 was evaluated at 25°C, 28°C, 32°C, 37°C, and 45°C. The apparent diffusion coefficient was calculated using the equation for the drug release from a suspension (6) and was increased with increasing temperature.

The relationship between the diffusion coefficient and the temperature is given by the following equation (12):

$$D = D_o e^{-Ea/RT}$$

When the logarithm of the diffusion coefficient was plotted as a function of the reciprocal of temperature, a linear relationship was observed with the correlation coefficient 0.943 (Fig. 4). The slope was used to calculate the activation energy for the drug diffusion of 17.9 Kcal/mol. Since poloxamer gel exhibits reverse thermal behavior, its viscosity increases as the temperature is increased. According to the Stokes-Einstein equation, it is expected that the apparent diffusion coefficient should decrease with increasing viscosity (12). However, the apparent diffusion coefficient of piroxicam was increased with increasing temperature. These results indicate that the diffusion of piroxicam from the poloxamer gel formulation is largely dependent on the microviscosity of the water channel rather than the macroviscosity of the gel (10).

The effect of temperature on the release of piroxicam from a formulation containing 1% piroxicam and 20% poloxamer 188 was also evaluated in a similar manner. It showed a similar trend except that the activation energy for the drug diffusion was 14.9 Kcal/mol.

Effect of pH on the Drug Permeation

The effect of pH of the gel containing 1% piroxicam, 20% poloxamer 407, and 40% propylene glycol on the permeation rate of piroxicam was studied with the pH varying from 3 to 7 (Fig. 5). Assuming that drug diffusion primarily occurs through the aqueous phase of the gel and only undissociated drug can permeate through the skin, a similar permeation rate is expected regardless of pH. From the results, it can be seen that the permeation rates of piroxicam were similar regardless of pH, with a tendency for a slightly higher permeation rate at a lower pH. Based on the results, the pH of the gel formulation can be modified without affecting the permeation rate of piroxicam.

Effect of Drug Concentration on the Permeation Rate

Figure 6 shows a plot of the permeated amount of piroxicam versus concentration of piroxicam in the gel formulation containing 20% poloxamer 407 and 40% propylene glycol. The permeation rate from a 0.5% formulation was about 30% higher than from a 0.2% formulation. However, the permeation rate from a 1.0% formulation was only about 10% higher than from the 0.5%

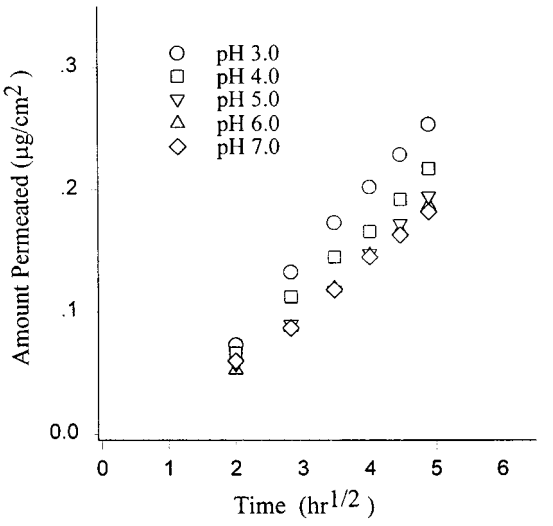

Figure 5. Effect of pH of the gel containing 1% piroxicam, 20% poloxamer 407, and 40% propylene glycol on the permeation rate of piroxicam across rat abdominal skin.

formulation, and there was no significant difference between 1.0% and 2.0% formulations. The solubility of piroxicam in 40% propylene glycol/phosphate buffer was 4 mg/ml, and adding poloxamer changed the solubility to some extent. Based on the visual observation of the gel formulation, 0.2% seemed to be below the saturation and 0.5% slightly over the saturation. Therefore, it can be expected that the permeation rate increases with increasing concentration of piroxicam in the formulation up to 0.5% since the permeability coefficient is constant for a given drug under the same experimental conditions. The extent of increase in the permeation rate when the amount of the drug exceeds saturation depends on the relative magnitude of diffusivity of the drug within the gel to the dissolution rate. When the diffusivity becomes the rate-limiting step, the permeation rate does not change significantly with increasing concentration, as was the case when the concentration of piroxicam exceeded 1.0%.

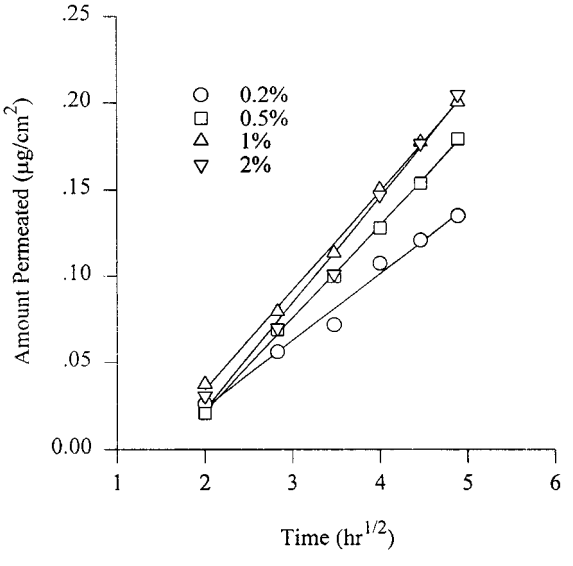

Figure 6. Effect of drug concentration of piroxicam on the permeation rate of piroxicam across rat abdominal skin.

Effect of Enhancer

The effect of various permeation enhancers on the permeation of piroxicam from poloxamer 407 gel formulations across rat skin was investigated. The enhancers tested included glycols, long-chain alcohols, fatty acids, bile salts, and nonionic surfactants. The effectiveness of permeation enhancers was determined by comparing piroxicam flux in the presence and the absence of each enhancer, and their ratio was defined as the enhancement factor. Table 1 shows the enhancement factor of each permeation enhancer tested. The glycols, such as diethylene glycol and tetraethylene glycol, increased the permeation rate of piroxicam only slightly. The long-chain alcohols showed a better enhancing effect than the glycols.

Table 1

Enhancement Factor of the Various Enhancers

Enhancer	EF
Control	1.00
Diethylene glycol	1.27
Tetraethylene glycol	1.14
Lauric acid	1.25
Linoleic acid	1.76
Capric acid	1.33
Oleic acid	1.65
Deoxycholic acid	1.44
Taurodeoxycholic acid	1.16
Taurocholic acid	1.62
1-Decanol	1.33
1-Octadecanol	1.77
Polyoxyethylene-23-lauryl ether	2.18
Polyoxyethylene-2-oleyl ether	2.84
Polyoxyethylene-2-stearyl ether	2.62

Among tested fatty acids, linoleic acid showed the greatest enhancing effect. Bile salts also showed some enhancing effect. Among all the permeation enhancers tested, polyoxyethylene-2-oleyl ether showed the best enhancing effect, with an enhancement ratio of 2.84.

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