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International Journal of Pharmaceutics 287 (2004) 73–78
international journal of pharmaceutics
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# Development of lidocaine gels for enhanced local anesthetic action

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Received 18 March 2004; received in revised form 12 August 2004; accepted 25 August 2004
Available online 12 October 2004

**Abstract**

In relieving local pains, lidocaine, one of ester type local anesthetics, has been used. To develop the lidocaine gels of enhanced local anesthetic effects, hydroxypropyl methylcellulose (HPMC) based bioadhesive polymer gel containing an enhancer was formulated. As the drug concentration in the gels increased up to 3%, the permeation rate of drug linearly increased, thereafter reaching a plateau. As the temperature of surrounding solutions increased, the permeation of drug increased. The activation energy of drug permeation was 3.29 kcal/mol for lidocaine. The permeation rate of drug through skin was studied using various enhancers, such as glycols, non-ionic surfactants, and bile salts. Among the enhancers studied, diethylene glycol showed the greatest enhancing effects on drug permeation through skin.

The analgesic activity was examined using a tail-flick analgesimeter. In the area under the efficacy curve (AUEC) of the rat-tail flick tests, lidocaine gel containing diethylene glycol showed about 3.89-fold increase in analgesic activity compared with the control. The addition of vasoconstrictor in the gels prolonged the analgesic effects. The result of this study supports that the bioadhesive gel with efficient anesthetic effect could be developed using HPMC with combination of enhancer and vasoconstrictor.
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*Keywords:* Local anesthetics; Lidocaine; Anesthetic action; Poloxamer; Permeation enhancer; Tail flick

## 1. Introduction

In relieving local pains, local anesthetics such as lidocaine, procaine, tetracaine, have been extensively used. Even though their analgesic activities have been well demonstrated, traditional methods of spinal anesthesia have problems in the outpatient setting (Ben-David et al., 2001). Moreover, since they have short half-lives after parenteral injection (Strichartz and Richie, 1987), an alternative route, to achieve the substantially sustained analgesic effects while avoiding any side effects, needs to be considered.

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doi:10.1016/j.ijpharm.2004.08.012

Of many drug delivery systems, the percutaneous drug delivery has been widely used as advanced drug delivery systems and has some advantages in the controlled and sustained delivery of various locally active drugs (Morganti et al., 2001). In their percutaneous or dental applications, the local anesthetics should remain in the skin surface as its uncharged, lipophilic form for a substantial period of time, so that it penetrates the stratum corneum and desensitize the underlying pain receptors within skin (Hou and Yu, 1994, 1997). It is difficult to predict the therapeutic effects of drug in ointments or creams delivered through percutaneous or dental applications, since wetting, movement and contacting easily remove them. Therefore, the need for the percutaneous delivery formulations that have suitable bioadhesion and enhanced analgesic efficacy is manifest.

The bioadhesive gels can be applied on skin, localized and removed easily. The use of penetration enhancers is a logical approach to increase the drug flux across the epithelium. It has been shown that dermal penetration can be improved by using compounds, which have been proven to be effective enhancers on other skin. The effect of various classes of transdermal penetration enhancers such as bile salts, surfactants, fatty acids and derivatives, and chelators has been studied (Angust and Rogers, 1989; Ishida et al., 1981; Shin et al., 1999, 2000, 2002; Evrard et al., 2001).

The present work was performed to determine the amounts of lidocaine released from the hydroxypropyl methylcellulose (HPMC)-poloxamer gels and to determine the feasibility of dermal delivery of lidocaine. The effects of temperature, drug concentration, and polymer composition on drug release were evaluated. The anesthetic effects of lidocaine gels were evaluated by tail-flick analgesic test. This study provides insight into the mechanism of skin permeability of locally applied anesthetics and lead to the development of bioadhesive gels, which has good analgesic activities.

## 2. Materials and methods

### 2.1. Materials

Lidocaine hydrochloride was a gift from Daihan Pharm. Co. Ltd. (South Korea). HPMC was obtained from Dow Chemical Co. (Midland, MI, USA) and Poloxamer 407 was from BASF Co. (Germany). Polyoxyethylene 2-stearyl ether, polyoxyethylene 2-oleyl ether, polyoxyethylene 23-lauryl ether, tetraethylene glycol (TEG), diethylene glycol (DEG), sodium taurodeoxycholate, and sodium deoxycholate were purchased from Sigma Chemical Co. (St. Louis, MO, USA). All reagents were of analytical grade were used without further purification.

### 2.2. Methods

#### 2.2.1. Preparation of HPMC-poloxamer 407 gels containing drug and enhancer

HPMC (0.2 g) and poloxamer 407 (2 g) were dissolved in water (about 5 ml) with gentle stirring. The solution was left in a refrigerator overnight to complete polymer dissolution. Three millilitres of 10% drug solution was added to the above polymer solution with vigorous stirring and water was added to it to make a final volume of 10 ml.

#### 2.2.2. In vitro drugs release

The HPMC-poloxamer gels (0.5 g) containing lidocaine were used for release test with 40% PPG/PBS in a modified Keshary–Chien diffusion cells. The diameter of the cell was 1.5 cm, providing 1.77 $cm^2$ effective constant area, and the volume of receptor chamber was 7 ml. The synthetic cellulose membrane (Spectra/Por) was mounted on top of receptor compartment of diffusion cells. The prepared gels were placed in intimate contact with cellulose membrane, the donor cap was covered with parafilm and clamped. The sampling port was sealed with a parafilm to prevent the evaporation of the receptor medium. The receptor compartment was filled with the receptor solution, which was stirred by a magnetic stirring bar and maintained at 37 °C by a circulating water bath. The donor compartment was maintained at ambient temperature of $25 \pm 1$ °C.

The samples were taken from the receptor side through the sampling port at predetermined intervals and analyzed by UV spectrophotomer at 263 nm for lidocaine. Each data point represents the average of five determinations. The effects of drug concentration on its release from the gels were studied according to drugs concentration of 1.5, 2, 2.5, 3, and 3.5% (w/w). The temperature effects on drug release were studied at 28, 32, 37 and 42 °C.

*2.2.3. Permeation studies*

A male mouse (ICR strain) was sacrificed by snapping the spinal cord at the neck. The abdominal hair was carefully removed with an electric clipper. A square section of the abdominal skin was excised. After incision, the adhering fats and other visceral debris in the skin were carefully removed from the under surface with tweezers, and the excised skin was used immediately. The prepared dermal tissue was mounted on the diffusion cell with a diffusion area of 1.33 $cm^2$. Five hundred milligrams of gels containing drug and enhancer, such as the glycols, the non-ionic surfactants, or the bile salts, were loaded on the diffusion cell. The diffusion studies were undertaken at $37 \pm 0.5\,^{\circ}C$ for 6 h. Samples were taken from the receptor side at a predetermined interval, refilled with the same amount of fresh buffer solution and subsequently analyzed using a UV spectrophotometer. Since various permeation enhancers could increase the permeation rate of drugs from the HPMC-poloxamer 407 gels, the effects of enhancers on the permeation of lidocaine through skin also were investigated using a similar method.

*2.2.4. Analysis of permeation data*

The effects of penetration enhancers on the permeation rate of lidocaine were determined by comparing the flux of drugs in the presence or the absence of enhancers. It was defined as the enhancement factor (EF).

EF = (drug flux from the gels containing enhancer)/(drug flux from the gels without enhancer)

*2.2.5. Tail-flick analgesic test*

The bioadhesive lidocaine gels containing tetrahydrozoline as a vasoconstrictor and diethylene glycol as a penetration enhancer was formulated, and the anesthetic effects of the lidocaine were evaluated by the tail-flick analgesic test. The rat was fixed on a tail-flick analgesimeter (tail-flick analgesimeter, Harvard, USA) with the portion of the tail, 10 cm from its tip, exposed to heat from a projector lamp. A single control switch simultaneously activated the light and a timer. The timer stops automatically when the exposed rat's tail flicks. The time interval between switching on the light and flick of the tail was recorded. A 30 s cut-off time was used to avoid thermal injury. Fifty milligrams of drug gels was applied on the root of the tail on midline. Tail-flick test started 5 min after a local application of gels, and the test was conducted every 5 min until duration time fell to blank.

## 3. Results and discussion

### *3.1. Effects of loading dose on drug release*

The high drug concentration induces better efficacy in general. However, when the drug reaches certain optimal concentration, there can be no differences in efficacy for certain drugs even treated with much higher concentration. Therefore, the optimal concentration should be decided to have good efficacy for each drug. For this, the effects of loading dose on drug release were studied from the prepared 2% HPMC gels at $37 \pm 0.5\,^{\circ}C$ (Table 1). The drug concentrations tested were 1.5, 2, 2.5, 3 and 3.5%, respectively. As the drug concentration in the gels increased to about 3%, the release rate of drug increased, thereafter slightly increased, but not significantly. The drug solubility in the gel might be saturated at about 3% and the driving force for the drug release might be is at its maximum. Therefore, we could formulate the drug concentration at 3%.

### *3.2. Effects of temperature on drug release*

The effects of temperature of surrounding solutions on drug release from the 3% drug gels was evaluated at temperatures of 28, 32, 37 and 42 °C (Fig. 1). The apparent permeation coefficient increased, as the temperature of system increased. The relationship between the permeation coefficient and the temperature is as follows:

Table 1
Effects of drug concentration on the flux of lidocaine from hydroxypropyl methylcellulose gels

| Lidocaine concentration (w/w%) | Lidocaine gels ($n = 5$) |
|---|---|
| | Flux ($\mu g/cm^2/h$) |
| 1.5 | 574 ± 27 |
| 2 | 758 ± 39 |
| 2.5 | 1066 ± 53 |
| 3 | 1210 ± 62 |
| 3.5 | 1298 ± 65 |

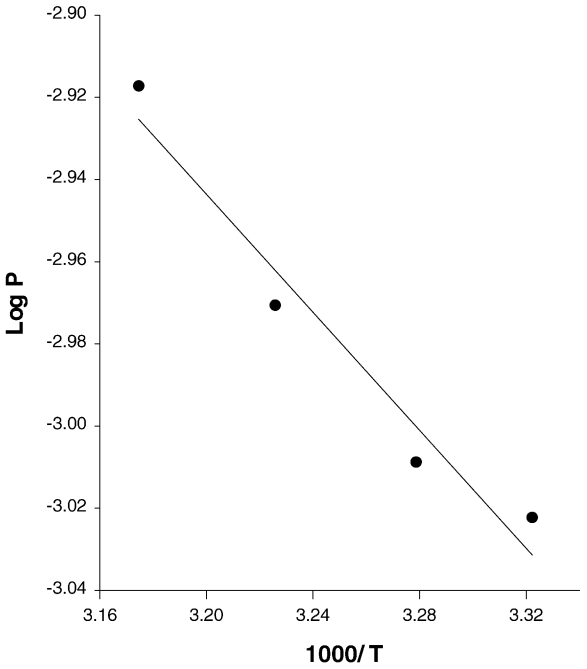


Fig. 1. Permeation coefficients of drugs as a function of temperature (*K*).

The relationship between the permeation coefficient and the temperature is as follows:

$$P = P_o e^{-E_a/RT} \quad (1)$$

$$\ln P = \ln P_o - \left(\frac{E_a}{1000\,R}\right)\left(\frac{1000}{T}\right) \quad (2)$$

The logarithm of permeation coefficient is plotted as a function of the reciprocal of temperature. As expected from Eq. (2), a plot of log *P* versus 1000/*T* yielded a straight line (Fig. 1). The slope calculated from the linear portion of plot (Eq. (2)) was used to calculate the activation energy. Activation energy for drug permeation was 3.29 kcal/mol for lidocaine.

The higher the temperature, the greater the drug release. The observation indicates clearly that the release of drug from the gels is an energy-linked process (Miyazaki et al., 1984). The increased release with increasing temperature suggests that release characteristics of drug from the gels would change over the body temperature range.

Table 2
Enhancement factor of various enhancers from lidocaine gels

| Enhancer | Lidocaine gels ($n = 5$) | |
|---|---|---|
| | Flux ($\mu g/cm^2/h$) | Enhancement factor |
| Control | 829 ± 78 | 1.00 |
| Sodium taurodeoxycholate | 903 ± 84 | 1.09 |
| Sodium deoxycholate | 1456 ± 123 | 1.76 |
| Polyoxyethylene 23-lauryl ether | 1723 ± 157 | 2.08 |
| Polyoxyethylene 2-stearyl ether | 1101 ± 101 | 1.33 |
| Polyoxyethylene 2-oleyl ether | 1338 ± 114 | 1.61 |
| Tetraethylene glycol | 1180 ± 99 | 1.42 |
| Diethylene glycol | 1945 ± 172 | 2.35 |

### *3.3. Effects of permeation enhancers on drug permeation through skin*

The effects of various permeation enhancers on drug permeation through skin were investigated. The enhancers such as bile salts, glycols, and non-ionic surfactants were used at a concentration of 5%. The effects of various enhancers on the percutaneous permeation of lidocaine are shown in Table 2. The enhancers, such as bile salts, glycols, and non-ionic surfactants, have been very effective on enhancement of drug permeation through skin. Since local anesthetics have short half-lives after parenteral injection, such as 7–30 min for lidocaine, the sustained and enhanced delivery for analgesic drugs is needed. Among the permeation enhancers tested, diethylene glycol showed the greatest enhancing effects.

### *3.4. Tail-flick analgesic test of drugs gels containing enhancer*

Lidocaine gels containing diethylene glycol, which showed the greatest enhancing effects in percutaneous permeation studies, were used in the rat tail-flick analgesic test. In the tail-flick test, it appears that the first 5 min, there was acclimation of the animals and the flick response time was shortened from the control gels group. During fixing the rats using the rat restrainer for evaluating the anesthetic effects by tail-flick analgesimeter, the rats might be somewhat stressed. Nociception could be modulated by external factors through alterations in intrinsic pain pathways. Among these factors, exposure to acute stress is known to produce analgesia (Gamaro et al., 1998).

When we applied the gels on the root of rat-tail on midline, the flick response time of rat tail to the heat from a projector lamp from the lidocaine gels group were all sustained than the control gels group. The value of area under the efficacy curve ($AUEC_{0\rightarrow 50\,min}$) of lidocaine gel containing diethylene glycol was $270.75 \pm 69.94$ s min, while it was $69.53 \pm 22.52$ s min in the absence of enhancers. The efficacy of lidocaine gel containing diethylene glycol was about 3.89-fold greater than that without diethylene glycol.

From the rat-tail flick test, the greatest analgesic effects were shown at 15 min for the lidocaine gels containing diethylene glycol. In evaluating the effects of a vasoconstrictor (i.e., tetrahydrozoline) added in the gels on the analgesic effects, the lidocaine gels containing diethylene glycol showed similar efficacy to those containing both diethylene glycol and tetrahydrozoline, but the latter showed more prolonged analgesic effects than the former (Fig. 2). This indicates that the addition of a vasoconstrictor may further enhance the efficacy of the local anesthetics.

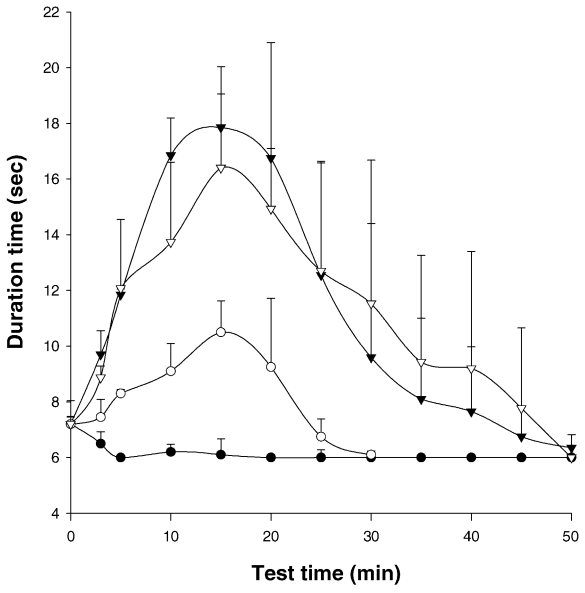


Fig. 2. Tail-flick test of 3% lidocaine gels; key: (●), control gels without lidocaine and additives; (◯), lidocaine gels without additives; (▼) lidocaine gels containing diethylene glycol; (▽) lidocaine gels containing diethylene glycol and tetrahydrozoline.

## 4. Conclusion

In this study, HPMC-based bioadhesive polymer gels of lidocaine was formulated and its permeation studies were carried out. Among the enhancers used, diethylene glycol showed the greatest enhancing effects on drug permeation through skin. In a tail-flick test, the AUEC was increased by the addition of vasoconstrictors in the system. The result of this study supports that the bioadhesive gel with efficient anesthetic effect could be developed using HPMC with combination of enhancer and vasoconstrictor.

## Acknowledgement

This work was supported by Korea Research Foundation Grant (KRF-2002-041-E00300).

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