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Enhanced rectal bioavailability of ibuprofen in rats by poloxamer 188 and menthol

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Abstract

To improve the bioavailability of poorly water-soluble ibuprofen in the rectum with poloxamer and menthol, the effects of menthol and poloxamer 188 on the aqueous solubility of ibuprofen were investigated. The dissolution and pharmacokinetic study of ibuprofen delivered by the poloxamer gels composed of poloxamer 188 and menthol were then performed. In the absence of poloxamer, the solubility of ibuprofen increased until the ratio of menthol to ibuprofen increased from 0:10 to 4:6 followed by an abrupt decrease in solubility above the ratio of 4:6, indicating that four parts menthol formed eutectic mixture with six parts ibuprofen. In the presence of poloxamer, the solutions with the same ratio of menthol to ibuprofen showed abrupt increase in the solubility of ibuprofen. The poloxamer gel with menthol/ibuprofen ratio of 1:9 and higher than 15% poloxamer 188 showed the maximum solubility of ibuprofen, 1.2 mg/ml. Menthol improved the dissolution rates of ibuprofen from poloxamer gels. Release mechanism showed that the release rate of ibuprofen from the poloxamer gels without menthol was independent of the time but the drug might be released from the poloxamer gels with menthol by Fickian diffusion. Furthermore, the poloxamer gel with menthol (poloxamer/menthol/ibuprofen (15%/0.25%/2.5%)) gave significantly higher initial plasma concentrations, C_{max} and AUC of ibuprofen than did solid suppository, indicating that the drug from poloxamer gel could be more absorbed than that from solid one in rats. Thus, the poloxamer gel with poloxamer 188 and menthol was a more effective rectal dosage form for ibuprofen.

Keywords: Ibuprofen; Menthol; Poloxamer 188; Solubility; Pharmacokinetics

1. Introduction

Ibuprofen [2-(4-isobutylphenyl)propionic acid], a non-steroidal anti-inflammatory agent, is widely used in treatment of mild to moderated pain and fever. However, the bioavailability of ibuprofen is relatively

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low after oral administration, since it was practically insoluble in water (Ghorab and Adeyeye, 2001; Glowka, 2000). Various oral formulations of ibuprofen such as prodrug (Bansal et al., 1994; Murtha and Ando, 1994), inclusion complex (Charoenchaitrakool et al., 2002; Ghorab and Adeyeye, 2001), microencapsulation (Adeyeye and Price, 1994; Bodmeier et al., 1992; Kachrimanis et al., 2000) and solid dispersion (Bodmeier and Wang, 1993; Greenhalgh et al., 1999; Khan and Jiabi, 1998) were developed to improve the solubility of ibuprofen. Furthermore, it was attempted to develop the alternative dosage form, rectal preparation, since ibuprofen gave the gastro-intestinal disturbances to patients (Hermann et al., 1993; Glowka, 2000; Kaka and Tekle, 1992).

In this study, to improve the bioavailability of poorly water-soluble ibuprofen in the rectum with poloxamer and menthol, the effects of menthol and poloxamer 188 on the aqueous solubility of ibuprofen were investigated. Then, the dissolution and pharmacokinetic study of ibuprofen delivered by poloxamer gel composed of poloxamer 188 and menthol was performed. Menthol was selected here as a solubilizing agent, since it formed the eutectic mixture with ibuprofen (Greenhalgh et al., 1999; Kokot and Zmidzinska, 2001; Stott et al., 1998). The eutectic mixture was reported to be more soluble in the aqueous solution than the drug itself due to its lower melting point (Wagner et al., 1994; Miguel, 1994). Furthermore, among poloxamer series, poloxamer 188 was selected as a base of poloxamer gel because it has been reported to have a permeation enhancing effect on ibuprofen to the mucous membranes (Iervolino et al., 2001; Park et al., 2000).

2. Materials and methods

2.1. Materials

Ibuprofen and menthol were supplied from Dongwha Pharm. Co. Ltd. (Anyang, South Korea). Poloxamer 188 was supplied from BF Goodrich (Breesville, OH, USA). All other chemicals were of reagent grade and used without further purification. Semipermeable membrane tube (Spectra membrane tubing No.1) was from Spectrum Medical Industries Inc. (Los Angeles, CA, USA).

2.2. Aqueous solubility of ibuprofen

Homogeneous eutectic mixtures with various ratios of ibuprofen and menthol (0:10–10:0) were prepared using pestle and mortar. Excessive eutectic mixtures (100 mg) were added in 10 ml of water or 2.5–30% poloxamer gels, respectively. They were shaken at room temperature for 7 days, filtered through membrane filter (0.45 μm) and analyzed by UV/visible variable wavelength detector (Philips, Model PU8730) at 220 nm (Choi et al., 2001; de Villiers et al., 1999; Ghosh et al., 1998).

2.3. Preparation of poloxamer gel

Various components such as menthol and ibuprofen were dispersed or dissolved in water at room temperature and the solution was cooled down to 4 °C. Poloxamer 188 was then slowly added to the solution with continuous agitation. The poloxamer gel was left at 4 °C until a clear solution was obtained (Choi et al., 1998).

2.4. Dissolution test

Each poloxamer gel (5 g) containing 125 mg of ibuprofen was inserted into a semipermeable membrane tube. Both sides of the tube were tied up with a thread to prevent leakage. The semipermeable membrane tube was then placed in a dissolution tester (Shinseang Instrument Co., South Korea). Dissolution test was performed at 36.5 °C using the paddle method at 100 rpm with 500 ml phosphate buffer (pH 6.8) as a dissolution medium. At predetermined interval, 5 ml of the medium was sampled and filtered. The filtrate was analyzed by UV/visible variable wavelength detector at 220 nm (Ghosh et al., 1998; Hussain et al., 1999).

2.5. Pharmacokinetic study

2.5.1. In vivo experiments

Male Sprague–Dawley rats weighing 250 ± 20 g were fasted for 24–36 h prior to the experiments but allowed free access to water. Fifteen rats were divided into three groups. The rats in each group were administered with poloxamer gel A (poloxamer 188/ibuprofen (15%/2.5%)), B (poloxamer 188/menthol/ibuprofen

(15%/0.25%/2.5%)), or solid suppository (polyethylene glycol/ibuprofen (97.5%/2.5%)), respectively.

2.5.2. Administration and blood-collecting

Each rat, anesthetized in an ether-saturated chamber, was secured on a surgical board in the supine position with a thread. A polyethylene tube was inserted into the right femoral artery of the rat. Poloxamer gel (1.2 g/kg equivalent to ibuprofen 30 mg/kg) was administered into the rectum 4 cm above the anus through a stomach sondle needle fitted on a glass syringe. Solid suppository was administered with a dose of 1.2 g/kg (equivalent to ibuprofen 30 mg/kg) into the rectum 4 cm above the anus. The entrance of the anus was then blocked with a cyanoacrylate adhesive, since these preparations might be leaked out from the anus during the pharmacokinetic experiment, leading to not obtaining accurate pharmacokinetic data. Half milliliter of blood was collected from the right femoral artery at various intervals and centrifuged at 3000 rpm for 10 min using a centrifuge 5415C (Eppendorf, USA) (Geisslinger et al., 1989; Theis et al., 1994).

2.5.3. Blood sample analysis

Plasma (0.05 ml) was mixed with 0.4 ml of acetonitrile solution containing flufenamic acid (0.5 μg/ml), as an internal standard. It was then centrifuged at 3000 rpm for 10 min to precipitate the proteins. The supernatant layer (0.4 ml) was evaporated under N_2 (g). The residue was reconstituted in 50 μl of mobile phase. Then, the resulting solution was analyzed by HPLC (Hitachi, Model L-7100) equipped with an Inertsil ODS-3 C_{18} column (GL science, 0.5 μm, 15 cm × 0.46 cm i.d.) and UV detector (Model L-7450). The mobile phase consisted of acetoniltrile and phosphate buffer (pH 3.5; 4:6, volume ratio). The eluent was monitored at 220 nm with a flow rate of 1.2 ml/min (Canaparo et al., 2000; Gillespie et al., 1982; Haikala et al., 1991).

3. Results and discussion

3.1. Aqueous solubility of ibuprofen

To improve the aqueous solubility of a poorly water-soluble ibuprofen, various ratios of ibuprofen and menthol (0:10–10:0) were added in water and 5% poloxamer 188, respectively, and then the solubility of ibuprofen in the aqueous solutions was evaluated (Fig. 1).

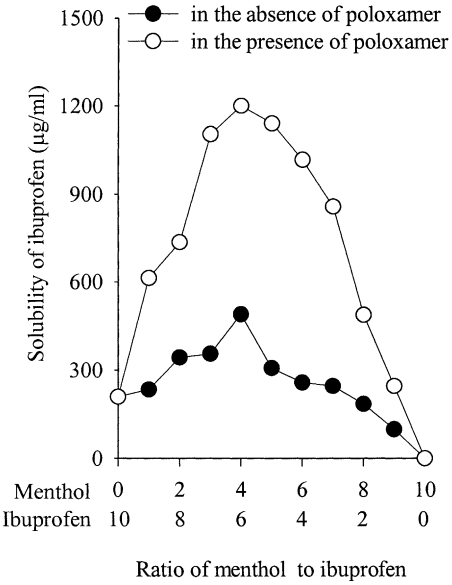

Fig. 1. Effects of menthol and poloxamer 188 on the aqueous solubility of ibuprofen.

In the absence of poloxamer, as the ratio of menthol to ibuprofen increased from 0:10 to 4:6, the solubility of ibuprofen in water increased. However, as the ratio of menthol to ibuprofen increased from 4:6 to 10:0, the solubility of ibuprofen decreased. In particular, the solution with ratio of 4:6, which had the highest solubility of ibuprofen, about 0.5 mg/ml, showed more than 2.5-fold increase in the solubility of ibuprofen compared with that with only ibuprofen. Our results suggested that that four parts menthol formed eutectic mixture with six parts ibuprofen (Choi et al., 2001).

The eutectic mixture of ibuprofen with menthol was prepared by mixing and grinding 400 mg of menthol and 600 mg of ibuprofen (4:6, weight ratio). DSC curve showed that the peak at around 40 and 80 °C, which was observed for menthol and ibuprofen, respectively, disappeared in the eutectic mixture (Fig. 2). However, new peak at around 20 °C, which was not observed for ibuprofen and menthol, appeared in the eutectic mixture (Stott et al., 1998). Our results proved indirectly that the menthol/ibuprofen ratio of

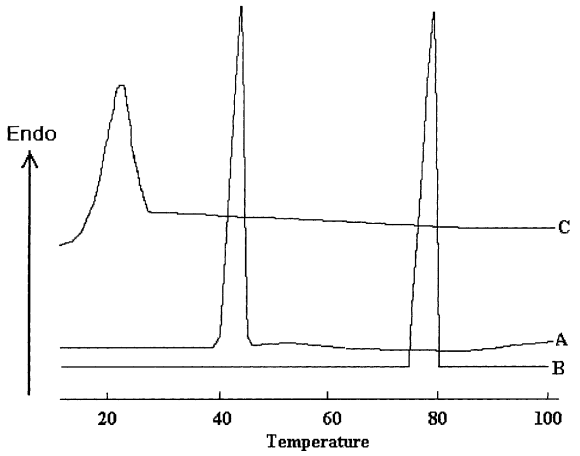

Fig. 2. DSC curves: (A) menthol; (B) ibuprofen; (C) menthol/ibuprofen eutectic mixture (4:6).

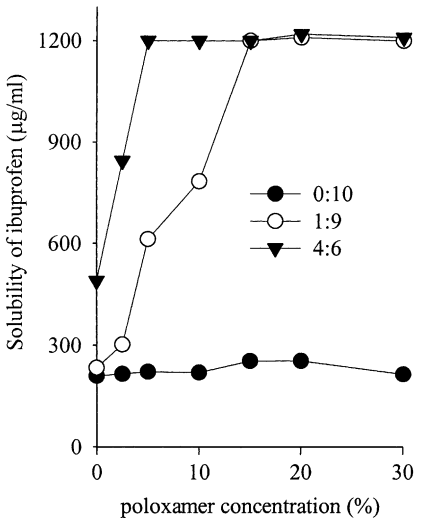

Fig. 3. Effects of poloxamer 188 concentration on the aqueous solubility of ibuprofen in various ratio of menthol to ibuprofen.

4:6 formed nearly complete eutectic mixture, resulting in its lower melting point, around 20 °C. Moreover, these results suggested that the improved solubility of ibuprofen might be contributed by the formation of eutectic mixture of ibuprofen with menthol in aqueous solution (Wagner et al., 1994; Miguel, 1994).

On the other hand, in the presence of poloxamer, the solubility of ibuprofen also increased until the ratio of menthol to ibuprofen increased from 0:10 to 4:6 followed by an abrupt decrease in solubility above the ratio of 4:6. In the presence of poloxamer, the solutions with the same ratio of menthol to ibuprofen showed abrupt increase in the solubility of ibuprofen. In particular, in the presence of poloxamer, the solution with ratio of 4:6 showed more than 2.5-fold increase in the solubility of ibuprofen compared with that without additives. Furthermore, this solution showed more than six-fold increase in the solubility of ibuprofen compared with that without menthol. However, the solution with ratio of 0:10 (only ibuprofen) in the presence of poloxamer showed no increase in the solubility of ibuprofen compared with that with only ibuprofen in the absence of poloxamer. Thus, the simultaneous addition of menthol and poloxamer 188, which formed eutectic mixture with ibuprofen, respectively, in aqueous solution greatly improved the aqueous solubility of ibuprofen (Greenhalgh et al., 1999; Passerini et al., 2002).

To investigate the effect of poloxamer 188 on the solubility of ibuprofen in the aqueous solution, various ratios of ibuprofen and menthol were added in 2.5–30% poloxamer 188, respectively, and then the aqueous solubility of ibuprofen was evaluated (Fig. 3). In the menthol/ibuprofen ratio of 0:10, poloxamer hardly affected the solubility of ibuprofen in the aqueous solution. However, in the ratio of 1:9 and 4:6, the solubility of ibuprofen increased until the poloxamer concentration increased to 15 and 5% followed by no changeable solubility of ibuprofen, 1.2 mg/ml above the concentration of 15 and 5%, respectively. The more increased poloxamer concentrations were needed in the aqueous solution with lower menthol/ibuprofen ratios to have the maximum solubility of ibuprofen.

To develop an ibuprofen-loaded poloxamer gel for transdermal and rectal dosage form, a small amount of menthol must be added in the poloxamer gel, since menthol was reported to irritate the mucous membranes (Li et al., 2001; Obata et al., 2000). Fig. 3 indicated that the poloxamer gel with menthol/ibuprofen ratio of 1:9 and higher than 15% poloxamer 188 had the maximum solubility of ibuprofen, 1.2 mg/ml. Thus, in this study, the formulation (poloxamer 188/menthol/ibuprofen (15%/0.25%/2.5%)) with the maximum solubility of ibuprofen and lower menthol content was selected as a base of ibuprofen-loaded poloxamer gel.

3.2. Dissolution of ibuprofen from poloxamer gel

To test whether ibuprofen or menthol affect the dissolution rates of drug from the poloxamer gels, we performed the dissolution studies on the formulations composed of constant amount of poloxamer 188 (15%), ibuprofen (2.5%) and variable amounts of menthol (0.15–0.35%). Additionally, the dissolution test of solid suppository (poloxamer/ibuprofen (15%/2.5%)) was carried out.

Menthol improved the dissolution rates of ibuprofen from poloxamer gels (Fig. 4). The reason for this improved dissolution of ibuprofen from poloxamer gels was dependent upon the ibuprofen solubility-improving effect of menthol (Wagner et al., 1994; Miguel, 1994). The poloxamer gels with menthol had higher dissolution rates than those without menthol. Furthermore, the solid suppository had significantly lower dissolution rates of ibuprofen than any poloxamer gels. These results suggested that solid suppository was slowly soluble in the dissolution medium, while poloxamer gel was gelled (Choi et al., 1998).

To understand the dissolution mechanisms of ibuprofen, we described the dissolution rate using the following equations.

$$\frac{Mt}{M} = kt^n \tag{1}$$

$$\log\left(\frac{Mt}{M}\right) = \log k + n\log(t) \tag{2}$$

where Mt/M is the fraction of dissolved drug at time t, k is a characteristic constant of poloxamer gel and n is an indicative of dissolution mechanism. As the k value becomes higher, the dissolution occurs faster. The n value of 1 corresponds to zero-order release kinetics, $0.5 < n < 1$ means a non-Fickian dissolution model and $n = 0.5$ indicates Fickian diffusion (Higuchi model) (Peppas, 1985). From the plot of log (Mt/M) versus log(t) (Fig. 5), kinetic parameters, n and k, were calculated. Table 1 shows that the values of poloxamer gels without menthol are close to 1, suggesting that the dissolution rate of ibuprofen was independent of the time. However, the poloxamer gels with menthol showed the n values of 0.5, indicating that the drug might be dissolved from gels by Fickian

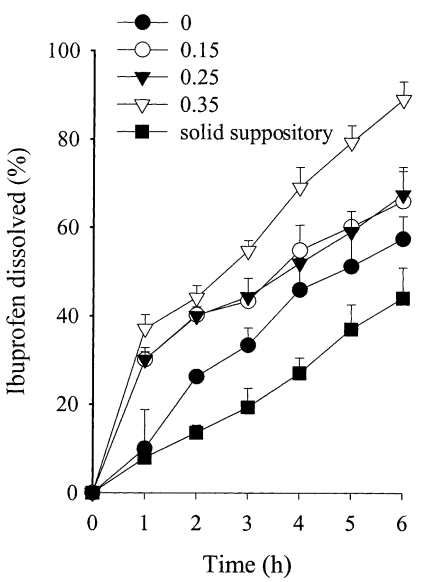

Fig. 4. Effect of menthol on the dissolution of ibuprofen from poloxamer gels. Various amounts of menthol (0.15–0.35%) were added to the poloxamer gel composed of 2.5% ibuprofen and 15% poloxamer 188, respectively. Each value represents the mean±S.E. ($n = 6$).

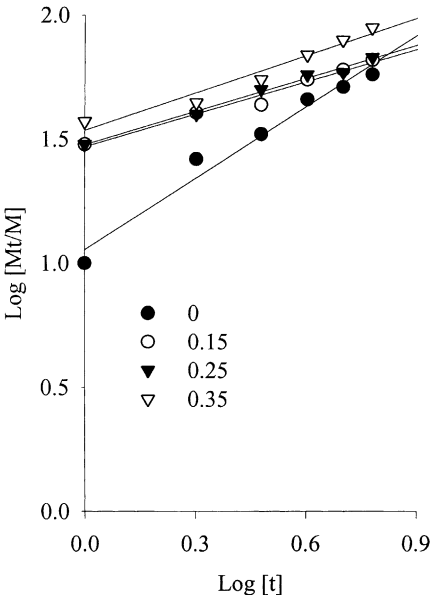

Fig. 5. Dissolution kinetics of ibuprofen. Various amounts of menthol (0.15–0.35%) were added to the poloxamer gel composed of 2.5% ibuprofen and 15% poloxamer 188, respectively. Logarithm of dissolved fractions of ibuprofen was plotted against logarithm of time.

Table 1
Dissolution kinetic parameters

Poloxamer 188/menthol/ ibuprofen (%)	Release exponent, n	Kinetic constant, k	Correlation coefficient, r
Solid suppository	0.970	7.345	0.987
15/0/2.5	0.961	11.324	0.970
15/0.15/2.5	0.437	29.444	0.977
15/0.25/2.5	0.447	29.992	0.989
15/0.35/2.5	0.505	34.198	0.956

diffusion (Choi et al., 1998). As a possible mechanism by which menthol-containing poloxamer gels showed the first-order dissolution kinetics, it might be considered that ibuprofen was easily dissolved with the menthol from the gels due to its forming eutectic mixture, leading to initial high dissolution rates of drugs. The relatively parallel slopes of the plots in Fig. 5 indicated that the concentration of ibuprofen and menthol might not affect the dissolution mechanisms. The k values indicated that ibuprofen was more slowly dissolved from poloxamer gels with higher concentration of menthol.

3.3. Pharmacokinetic study

The pharmacokinetic parameters of ibuprofen were determined after rectal administration of poloxamer gel A (poloxamer 188/ibuprofen (15%/2.5%)), B (poloxamer 188/menthol/ibuprofen (15%/0.25%/2.5%)) or solid suppository (polyethylene glycol/ibuprofen (97.5%/2.5%)), respectively.

Fig. 6 shows the change of mean plasma concentration of ibuprofen after rectal administration of preparations in rats. The initial plasma concentrations of ibuprofen in poloxamer gels, until 1 h 30 min, were higher compared with those in solid suppository. In particular, in poloxamer gel B, from 45 min to 1 h, the plasma concentrations of ibuprofen (70–85 μg/ml) were significantly higher than those in solid one (40–50 μg/ml). However, from 2 h after the dose, the plasma concentrations of ibuprofen in poloxamer gels were not significantly different from those in the solid suppository. Our results indicated that the drug from poloxamer gels could be absorbed faster than that from solid one in rats. The reason for this fast absorption might be dependent upon the dispensability (fluidity) and bioadhesive force of poloxamer gels. Solid suppository was not bioadhesive, and gradually dissolved and dispersed. On contrast, poloxamer gel was spread easily in the rectum, gelled, and attached on the rectal mucous membranes, since bioadhesive poloxamer gel was a fluid initially (Choi et al., 1998).

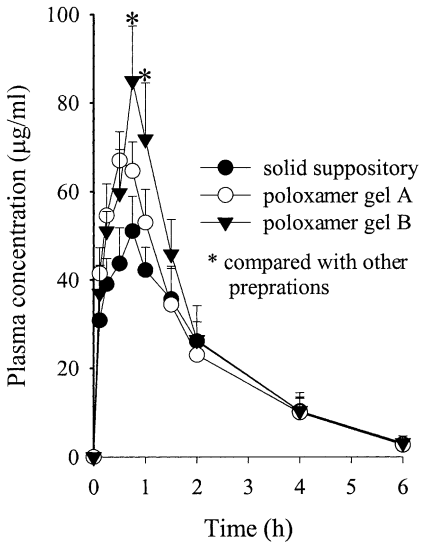

Fig. 6. Plasma concentration-time profiles of ibuprofen after rectal administration of poloxamer gels and solid suppository to rats. Poloxamer gel A, B and solid suppository were composed of poloxamer/ibuprofen (15%/2.5%), poloxamer/menthol/ibuprofen (15%/0.25%/2.5%), and polyethylene glycol/ibuprofen (97.5%/2.5%), respectively. Each value represents the mean ± S.E. ($n = 5$). $^{*}P < 0.05$ compared to poloxamer gel A and solid suppository.

The initial plasma concentrations of ibuprofen in poloxamer gel A, until 30 min were higher compared with those in poloxamer gel B. However, there were no significant differences between those initial plasma concentrations of ibuprofen. However, in poloxamer gel B, from 45 min to 1 h, the plasma concentrations of ibuprofen (70–85 μg/ml) were significantly higher than those in solid one (50–60 μg/ml). From 1 h 30 min after the dose, the plasma concentrations of ibuprofen in poloxamer gel B, were not significantly different from those in poloxamer gel A (Canaparo et al., 2000; Gillespie et al., 1982; Haikala et al., 1991). These results indicated that the drug from poloxamer gel with menthol could be more absorbed than that from that without menthol in rats. The reason for this better absorption might

Table 2
Pharmacokinetic parameters of ibuprofen delivered by three preparations

Parameters	Solid suppository	Poloxamer gel A	Poloxamer gel B
AUC (h μg/ml)	124.70 ± 10.08	137.12 ± 14.03	157.28 ± 13.01*
T_{max} (h)	0.75 ± 0.13	0.50 ± 0.22	0.75 ± 0.22
C_{max} (μg/ml)	51.08 ± 7.33	67.03 ± 8.23	85.03 ± 9.90*
K_{el} (h^{-1})	0.45 ± 0.24	0.53 ± 0.11	0.51 ± 0.13
$t_{1/2}$ (h)	1.53 ± 0.32	1.32 ± 0.35	1.37 ± 0.38

Each value represents the mean ± S.E. ($n = 5$).
* $P < 0.05$ compared with solid suppository and poloxamer gel A.

be contributed by the solubility-improving (Miguel, 1994; Wagner et al., 1994) and permeation-enhancing effect of menthol (Li et al., 2001; Obata et al., 2000).

The pharmacokinetic parameters are shown in Table 2. Poloxamer gel B with menthol gave significantly higher AUC and C_{max} of ibuprofen than did poloxamer gel A without menthol and solid suppository ($P < 0.05$). However, the T_{max}, K_{el}, and $t_{1/2}$ values of ibuprofen from poloxamer gel B were not significantly different from those from poloxamer gel A without menthol and solid suppository. Our results suggested that poloxamer gel with menthol would be useful to deliver ibuprofen in a pattern that allows fast absorption in the initial phase, leading to better absorption.

4. Conclusion

It is concluded that the ibuprofen-loaded poloxamer gel developed using eutectic mixture with menthol gave significantly higher initial plasma concentrations, C_{max} and AUC of ibuprofen than did solid suppository, indicating that the drug from poloxamer gel could be more absorbed than that from solid one in rats. Thus, the poloxamer gel with poloxamer 188 and menthol was a more effective rectal dosage form for ibuprofen. The further study on the safety in rats and rectal bioavailability in human subjects of ibuprofen-loaded poloxamer gel will be performed.

Acknowledgements

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