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Enhanced Oral Bioavailability of Ibuprofen in Rats by Poloxamer Gel Using Poloxamer 188 and Menthol

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ABSTRACT To improve the oral bioavailability of poorly water-soluble ibuprofen 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 ibuprofen-loaded preparations 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 an 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. The simultaneous addition of menthol and poloxamer 188 significantly improved the dissolution rates of ibuprofen from aqueous solution due to the ibuprofen solubility-improving effect of menthol in the presence of poloxamer. Furthermore, the ibuprofen-loaded preparation with menthol and poloxamer 188 gave significantly higher initial plasma concentrations, Cmax, and AUC of ibuprofen than did the preparation without menthol and poloxamer 188, indicating that the simultaneous addition of menthol and poloxamer 188 could improve the oral bioavailability of ibuprofen in rats. In modern pain management it is always desirable for the ibuprofen-loaded preparation with poloxamer 188 and menthol to show a rapid onset of action with a minimal phase of lag time to feel the decreased pain. From an industry point of view, it is more desirable for a formulation to be fast acting, easy to use, and cost effective. Thus, the ibuprofen-loaded preparation with poloxamer 188 and menthol was a more effective oral dosage form for poorly water-soluble ibuprofen.

KEYWORDS Ibuprofen, Menthol, Poloxamer 188, Solubility, Oral absorption, Pharmacokinetics

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INTRODUCTION

Ibuprofen [2-(4-isobutylphenyl)propionic acid], a nonsteroidal anti-inflammatory agent, is widely used in treatment of mild to moderated pain and fever. Since it is practically insoluble in water, the bioavailability of ibuprofen after oral administration is relatively low (Ghorab & Adeyeye, 2001; Glowka, 2000). Various oral formulations of ibuprofen such as prodrug (Bansal et al., 1994; Murtha & Ando, 1994), inclusion complex (Charoenchaitrakool et al., 2002; Ghorab & Adeyeye, 2001), microencapsulation (Adeyeye & Price, 1994; Bodmeier & Wang, 1993; Kachrimanis et al., 2000), and solid dispersion (Bodmeier et al., 1992; Geisslinger et al., 1989; Khan & Jiabi, 1998) were developed to improve the solubility of ibuprofen. Because ibuprofen causes gastrointestinal disturbances in patients, there have been attempts to develop an alternative dosage form—the rectal preparation—for ibuprofen (Greenhalgh et al., 1999; Kokot & Zmidzinska, 2001). Solid oral dosage forms such as tablets and capsules were useful in improving the solubility of ibuprofen. However, in the liquid oral formulation, after preparation of prodrug and microencapsulation, these ibuprofen-improved materials were dissolved in water (Adeyeye & Price, 1994; Bansal et al., 1994; Bodmeier & Wang, 1993; Kachrimanis et al., 2000; Murtha & Ando, 1994), a tedious process that increase of the formulation time and cost. Furthermore, inclusion complex and solid dispersion did not greatly improve the solubility of ibuprofen (Bodmeier et al., 1992; Geisslinger et al., 1989; Khan & Jiabi, 1998). Thus, there is a great need for an efficient, easy, quick, and cost-effective method to improve the solubility and bioavailability of ibuprofen.

Because no research has been done to increase the solubility of ibuprofen by applying the principle of eutectic mixtures, in this study, it has been attempted to develop an efficient oral liquid formulation of ibuprofen with significantly improved solubility and bioavailability, only by mixing various additives so as to make the process easier and fast. The eutectic mixture was reported to be more soluble in the aqueous solution than the drug itself due to its lower melting point (Miguel, 1994; Wagner et al., 1994; Yong et al., 2004). Menthol and poloxamer were selected here as solubilizing agents, since they formed the eutectic mixture with ibuprofen (Greenhalgh et al., 1999; Kokot & Zmidzinska, 2001; Stott et al., 1998).

To improve the oral bioavailability of poorly water-soluble ibuprofen, 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 ibuprofen-loaded preparations composed of poloxamer 188 and menthol were then performed.

Although there exist many methods to improve the solubility of ibuprofen, enhanced solubility by eutectic mixture is the most advantageous of all because it is simple, less time-consuming, and can be directly applied to liquid dosage form. In addition, the results obtained are more reproducible, and this method significantly increased the solubility and bioavailability of ibuprofen. As this method is more economical in terms of the materials, time, and manpower used in the formulation process, it would have great potential in the pharmaceutical industry in the near future.

Our results suggest that an ibuprofen-loaded preparation with menthol and poloxamer would be useful to deliver ibuprofen in a pattern that allows fast absorption in the initial phase, leading to better absorption. These results are particularly important in pain management because faster absorption would definitely show the earlier onset of action of ibuprofen from our formulation.

MATERIALS AND METHODS

Materials

Ibuprofen and menthol were supplied by Dongwha Pharm. Co. Ltd. (Anyang, South Korea). Poloxamer 188 was supplied from BF Goodrich (Breesville, OH). All other chemicals were of reagent grade and used without further purification. Semipermeable membrane tubing (Spectra membrane tubing No.1; cut-off 6,000–8,000) was purchased from Spectrum Medical Industries Inc. (Los Angeles, CA).

Aqueous Solubility of Ibuprofen

Various homogeneous mixtures with various ratios of ibuprofen and menthol (0:10–10:0) were prepared by triturating in a mortar and pestle for 1 min. Excessive eutectic mixtures (100 mg) were added in

10 mL water or 2.5–30% poloxamer gels, respectively, and shaken at room temperature for 7 days, filtered through membrane filter (0.45 μm), appropriately diluted with ethanol, and analyzed by UV/visible variable wavelength detector at 220 nm (Choi et al., 2001; de Villiers et al., 1999; Ghosh et al., 1998) (Philips, Model PU8730) at 220 nm (Ghosh et al., 1998; Hussain et al., 1999).

Melting Point of Eutectic Mixture of Ibuprofen with Menthol

The eutectic mixture of ibuprofen with menthol was prepared by triturating menthol (400 mg) and ibuprofen (600 mg) in a mortar and pestle for 1 min. The melting point of ibuprofen powder, menthol powder, and the above eutectic mixture was evaluated using DSC (Netzsch, Model 200) with the condition of 10°K/min.

Preparation of Ibuprofen-Loaded Preparations

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 ibuprofen-loaded preparation was left at 4°C until a clear solution was obtained (Choi et al., 1998).

Dissolution Test

Each ibuprofen-loaded preparation (5 g) containing 125 mg of ibuprofen was placed 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 test apparatus (Shinseang Instrument Co., South Korea). Dissolution test was performed at 36.5°C, as per USP XXII, paddle method at 100 rpm with 500 mL phosphate buffer (pH 6.8) as a dissolution medium. At predetermined interval, 5 mL aliquots of the medium were sampled and filtered. The filtrates were appropriately diluted and analyzed by UV/visible variable wavelength detector (Philips, Model PU8730) at 220 nm (Ghosh et al., 1998; Hussain et al., 1999).

Pharmacokinetic Study

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. Sixteen rats were divided into four groups. The rats in each group were orally administered through a stomach sondle needle fitted on a glass syringe with ibuprofen-loaded preparation A [ibuprofen/1% povidone solution (2.5/97.5%)] as a control sample, B [ibuprofen/poloxamer 188 (2.5/15%)], C [ibuprofen/menthol (2.5/0.25%)], D [ibuprofen/poloxamer 188/menthol (2.5/15/0.25%)], respectively. All animal care and procedures were conducted according to the Guiding Principles in the Use of Animals in Toxicology, as adopted by the Society of Toxicology (USP) in 1989.

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. Four ibuprofen-loaded preparations (1.2 g/kg equivalent to ibuprofen 30 mg/kg) were orally administered through a stomach sondle needle fitted on a glass syringe, respectively. A half milliliter of blood was collected from the right femoral artery at various intervals and centrifuged at 3000 g for 10 min using a centrifuge 5415°C (Eppendorf, USA) (Geisslinger et al., 1989; Theis et al., 1994).

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 g 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 acetonitrile 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).

Pharmacokinetic Data Analysis

The noncompartmental pharmacokinetic parameters, including area under the plasma concentration-time curve (AUC), were calculated using the RSTRIP II program (Salt Lake City, UT). The maximal plasma concentration of drug (C_{max}) and time to reach maximum plasma concentration (T_{max}) were also obtained from plasma data. The data from different formulations were compared for statistical significance by one-way analysis of variance (ANOVA). The statistical significance of means among different formulations was then compared by multiple range method of least significant difference. All results were expressed as means±standard deviation (S.D.) (Gibaldi & Perrier, 1982).

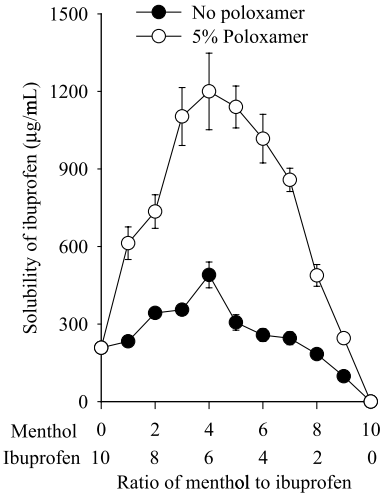

FIGURE 1 **Effects of Menthol and Poloxamer 188 on the Aqueous Solubility of Ibuprofen. Each Value Represents the Mean±S.E. (n=5).**

RESULTS AND DISCUSSION

To improve the aqueous solubility of 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).

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 ibuprofen alone. Our results suggest that four parts menthol formed a 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). The DSC curve shows 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, a new peak at around 20°C, a eutectic point of ibuprofen with menthol, 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 4:6 formed nearly a complete eutectic mixture, resulting in its lower melting point, around 20°C. Moreover, these results suggest that the improved solubility of ibuprofen might be caused by the formation of a eutectic mixture of ibuprofen with menthol in aqueous solution (Miguel, 1994; Wagner et al., 1994).

On the other hand, 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. 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 a ratio of 4:6 showed more than a 2.5-fold increase in the solubility of ibuprofen compared with that without additives. Furthermore, this solution showed more than a 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 additions of menthol and poloxamer 188, which formed eutectic mixtures 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

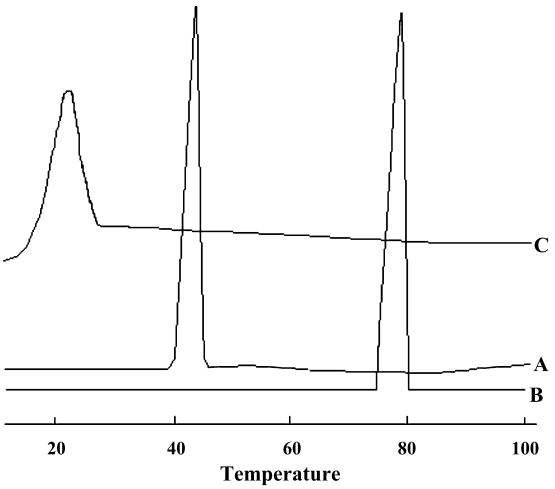

FIGURE 2 DSC Curves: (A) Menthol, (B) Ibuprofen, (C) Menthol/Ibuprofen Eutectic Mixture (4:6).

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%, respectively, followed by no change in the solubility of ibuprofen, 1.2 mg/mL above the concentration of 15% and 5%, respectively. The higher concentrations of poloxamer were needed in the aqueous solution with lower menthol/ibuprofen ratios to have the maximum solubility of ibuprofen.

To develop an ibuprofen-loaded preparation for oral dosage form, a small amount of menthol must be

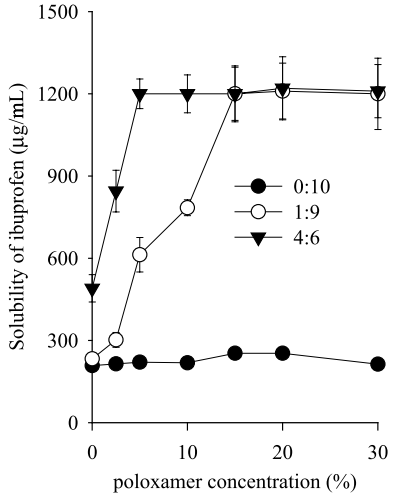

FIGURE 3 Effects of Poloxamer 188 Concentration on the Aqueous Solubility of Ibuprofen in Various Ratios of Menthol to Ibuprofen. Each Value Represents the Mean ± S.E. (n = 5).

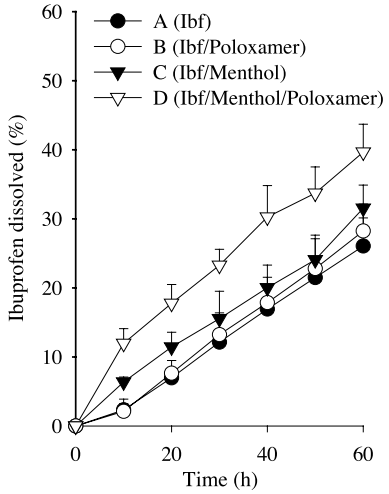

FIGURE 4 Effect of Menthol on the Dissolution of Ibuprofen from Four Ibuprofen-Loaded Preparations. Ibuprofen-Loaded Preparations A, B, C, and D were Composed of [Ibuprofen/1% Povidone Solution (2.5/97.5%)], [Ibuprofen/Poloxamer 188 (2.5/15%)], [Ibuprofen/Menthol (2.5/0.25%)], [Ibuprofen/Poloxamer 188/Menthol (2.5/15/0.25%)], Respectively. Each Value Represents the Mean ± S.E. (n = 6).

added in the poloxamer gel, since menthol was reported to irritate the mucous membranes (Li et al., 2001; Obata et al., 2000); in addition, menthol gives a cooling sensation that may aid to mask the bitter test of ibuprofen. Figure 3 indicates that the poloxamer gel with a menthol/ibuprofen ratio of 1:9 and higher than 15% poloxamer 188 had the maximum solubility of ibuprofen, 1.2 mg/mL.

To evaluate whether menthol and poloxamer affect the dissolution rates of drug from the ibuprofen-loaded preparations, we performed the dissolution studies on four ibuprofen-loaded preparations such as preparation A [ibuprofen/1% povidone solution (2.5/97.5%)], B [ibuprofen/poloxamer 188 (2.5/15%)], C [ibuprofen/menthol (2.5/0.25%)], and D [ibuprofen/poloxamer 188/menthol (2.5/15/0.25%)]. Preparation A, which was prepared by dispersing ibuprofen in 1% povidone-water solution as a suspending agent, was used as a control sample. Furthermore, to simplify the formulation of ibuprofen-loaded preparations, instead of menthol/ibuprofen ratio of 1:9, preparation D, poloxamer gel with menthol/ibuprofen ratio of 1:10 and 15% poloxamer 188 was selected as the ibuprofen-loaded preparation because it had the maximum solubility of ibuprofen, 1.2 mg/mL.

Menthol and poloxamer 188 alone improved the dissolution rates of ibuprofen from aqueous solution (Fig. 4). However, menthol was more efficient than

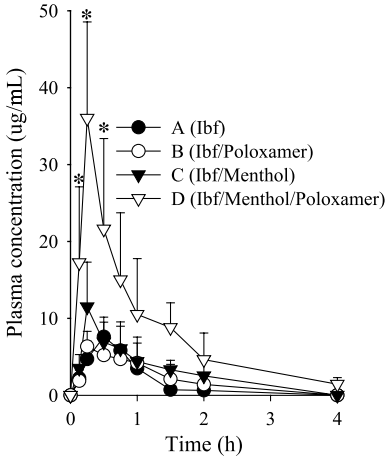

FIGURE 5 **Plasma Concentration-Time Profiles of Ibuprofen After Oral Administration of Four Ibuprofen-Loaded Preparations to Rats. Ibuprofen-Loaded Preparations A, B, C, and D were Composed of [Ibuprofen/1% Povidone Solution (2.5/97.5%)], [Ibuprofen/Poloxamer 188 (2.5/15%)], [Ibuprofen/Menthol (2.5/0.25%)], [Ibuprofen/Poloxamer 188/Menthol (2.5/15/0.25%)], Respectively. Each Value Represents the Mean±S.E. (n=4). (*), P<0.05 Compared to Other Preparations.**

poloxamer as the dissolution rates of samples containg only menthol were higher than that of samples containing poloxamer 188 alone.

However, the dissolution rates of ibuprofen in preparation A were not significantly different from those in preparations B and C. Furthermore, the simultaneous addition of menthol and poloxamer 188 as in preparation D significantly improved the dissolution rates of ibuprofen in aqueous solution. The reason for this improved dissolution of ibuprofen was due to the ibuprofen solubility-improving effect of menthol in the presence of poloxamer 188 (Miguel, 1994; Stott et al., 1998).

The pharmacokinetic parameters of ibuprofen were determined after oral administration of four preparations. Figure 5 shows the change of mean plasma concentration of ibuprofen after oral administration of preparations in rats.

The initial plasma concentrations of ibuprofen in preparation B with menthol alone, until 15 min, were higher compared with those in preparation A without menthol. However, there were no significant differences between those initial plasma concentrations of ibuprofen. From 30 min after the dose, the plasma concentrations of ibuprofen in preparation B were not significantly different from those in preparation A. These results indicate that menthol improved the oral absorption of ibuprofen from the preparation due to its solubility-improving effects, but did so only slightly (Yong et al., 2004).

The plasma concentrations of ibuprofen in preparation D with menthol and poloxamer 188 were higher compared with those in other preparations. In particular, in preparation D, from 8 min to 30 min, the plasma concentrations of ibuprofen (11–36 μg/mL) were significantly higher than those in other preparations ($P<0.05$). However, from 45 min after the dose, the plasma concentration of ibuprofen in preparation D was not significantly different from those in other preparations (Canaparo et al., 2000; Gillespie et al., 1982; Haikala et al., 1991). Our results indicate that the drug from preparation D with menthol and poloxamer 188 could be orally absorbed faster than that from other preparations in rats. The reason for this faster absorption might be dependent upon the more solubility-improving effect of menthol in the presence of poloxamer (Kaka & Tekle, 1992; Passerini et al., 2002; Yong et al., 2004).

The pharmacokinetic parameters are shown in Table 1. Preparation D with menthol and poloxamer 188 gave significantly higher AUC and C_{max} of ibuprofen than did other preparations ($P<0.05$). In particular, the AUC of ibuprofen from preparation D was about three-fold higher than that from preparations A-C, indicating that the simultaneous addition of menthol and poloxamer 188 could improve the oral bioavailability of ibuprofen in rats. However, the T_{max},

TABLE 1 **Pharmacokinetic Parameters of Ibuprofen Delivered by Four Preparations**

Parameters	A	B	C	D
AUC (h·μg/mL)	6.99±3.02	9.36±5.01	12.31±4.87	33.58±17.08[a]
T_{max} (h)	0.50±0.20	0.25±0.16	0.25±0.16	0.25±0.16
C_{max} (μg/mL)	7.61±3.73	6.35±4.10	11.50±4.77	36.02±16.38[a]
K_{el} (h^{-1})	1.19±0.27	0.78±0.19	1.27±0.31	0.88±0.37
$t_{1/2}$ (h)	0.58±0.38	0.89±0.24	0.59±0.28	0.79±0.21

[a]$P<0.05$ compared with other preparations.
Each value represents the mean±S.E. (n=4).

K_{el}, and $t_{1/2}$ values of ibuprofen from preparation D were not significantly different from those of other preparations. Our results suggest that ibuprofen-loaded preparations with menthol and poloxamer would be useful to deliver ibuprofen in a pattern that allows fast absorption in the initial phase, leading to better absorption.

These results are particularly important in pain management because faster absorption would definitely show the earlier onset of action of ibuprofen from our formulation.

CONCLUSION

It is concluded that the ibuprofen-loaded preparation developed using a eutectic mixture of menthol and poloxamer 188 gave significantly higher initial plasma concentrations, C_{max}, and AUC of ibuprofen than did that without menthol and poloxamer 188, indicating that the drug from preparation could be more orally absorbed in rats. Thus, the preparation with poloxamer 188 and menthol was a more effective oral dosage form for poorly water-soluble ibuprofen. Further studies on the oral bioavailability in human subjects of ibuprofen-loaded preparations will be performed to develop a commercial ibuprofen product.

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