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International Journal of Pharmaceutics 301 (2005) 54–61
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

Physicochemical characterization and in vivo evaluation of poloxamer-based solid suppository containing diclofenac sodium in rats

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Received 20 August 2004; received in revised form 3 May 2005; accepted 10 May 2005
Available online 15 July 2005

Abstract

To develop a poloxamer-based solid suppository with poloxamer mixtures, the melting point of various formulations composed of poloxamer 124 (P 124) and poloxamer 188 (P 188) were investigated. The dissolution and pharmacokinetic study of diclofenac sodium delivered by the poloxamer-based suppository were performed. Furthermore, the identification test in the rectum and morphology test of rectal tissues were carried out after its rectal administration in rats. The poloxamer mixtures composed of P 124 and P 188 were homogeneous phases. Very small amounts of P 188 affected the melting point of poloxamer mixtures. In particular, the poloxamer mixture [P 124/P 188 (97/3%)] with the melting point of about 32 °C was a solid form at room temperature and instantly melted at physiological temperature. Very small amounts of P 188 hardly affected the dissolution rates of diclofenac sodium from the suppository. Dissolution mechanism analysis showed the dissolution of diclofenac sodium was proportional to the time. The poloxamer-based suppository gave significantly higher initial plasma concentrations and faster T_{max} of diclofenac sodium than did conventional PEG-based suppository, indicating that the drug from poloxamer-based suppository could be absorbed faster than that from PEG-based one in rats. It retained in the rectum for at least 4 h and could not irritate or damage the rectal tissues of rats. Thus, the poloxamer-based solid suppository with P 124 and P 188 was a mucoadhesive, safe and effective rectal dosage form for diclofenac sodium.

Keywords: Diclofenac sodium; Poloxamer 124; Poloxamer 188; Mucoadhesive; Poloxamer-based solid suppository; Pharmacokinetics

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doi:10.1016/j.ijpharm.2005.05.037

1. Introduction

Conventional suppository, a polyethylene glycol (PEG)-based suppository, which may softens or melts lately in the rectum due to its relatively high melting point, can not be rapidly absorbed in the rectal mucous membranes (Burstein et al., 2000; Eboka et al., 1997; Huang et al., 1987; Nagatomi et al., 1997). Furthermore, such a PEG-based suppository, which may reach the end of the colon, has a loss of drug at colonic level and may also allow the carried drugs to undergo the first-pass effect (Choi et al., 1998; Huang et al., 1987; Kim et al., 1998). To solve the problems of conventional solid suppository, it would be desirable to develop a novel solid suppository, which was a solid phase at room temperature and instantly melted at physiological temperature, and was mucoadhesive to the rectal mucous membranes not to reach the end of the colon. Such a suppository must have the suppository base with the suitable melting points (30–36 °C) and mucoadhesive property.

In this study, as a base of novel poloxamer-based suppository, a mixture of poloxamer 124 (P 124) and poloxamer 188 (P 188) with the melting point of about 15 and 55 °C, respectively, has been selected (Abhaham, 1994; Choi et al., 1998; Kim et al., 1998). In addition, P 124 and P 188 are known to have suitable mucoadhesive force (Choi et al., 1998; Kim et al., 1998), low toxicity (Yun et al., 1999), less skin irritation (Choi et al., 1998), good drug release characteristics (Choi et al., 1998; Miyazaki et al., 1987) and compatibility with other chemicals.

Thus, in this study, to develop a novel poloxamer-based mucoadhesive solid suppository system using P 124 and P 188, the melting point of various formulations composed of P 124 and P 188 were investigated. The dissolution and pharmacokinetic study of diclofenac sodium delivered by the poloxamer-based suppository were performed. Furthermore, the identification test in the rectum and morphology test of rectal tissues were carried out after its rectal administration in rats. Diclofenac sodium was selected here as a model drug, since it was applied to rectal suppository form due to its rapid absorption in the rectum (Nakanishi et al., 1994; Schneeweis and Muller-Goymann, 1997).

2. Materials and methods

2.1. Materials

Diclofenac sodium and poloxamers (P 188, P 124) were supplied from SK chemical (Suwon, South Korea) and BF Goodrich (Breesville, OH, USA), respectively. Semipermeable membrane tube (Spectra membrane tubing No.1) was from Spectrum Medical Industries Inc. (Los Angeles, CA, USA). Acetonitrile and methanol were from Aldrich Chemical Co. (Milwaukee, WI, USA). All other chemicals were of reagent grade and used without further purification.

2.2. Preparation of poloxamer-based suppository

Various poloxamers such as P 124 and P 188 were mixed and heated up to 55 °C. Diclofenac sodium was then slowly added to the solution with continuous agitation. The resulting solution was moving to the suppository mould and cooled down to 25 °C. The melting point of suppository was determined using DSC (Netzsch, Model 200) at the raising temperature condition of 10 K/min (Burstein et al., 2000; Choi et al., 2001).

2.3. Dissolution test

Poloxamer-based suppository [diclofenac sodium/poloxamer mixture (2.5/97.5%)] (5 g) and conventional PEG-based suppository [diclofenac sodium/PEG 4000 (2.5/97.5%)] (5 g) containing 125 mg diclofenac sodium were inserted into a semipermeable membrane tube, respectively. The poloxamer mixture of poloxamer-based suppository were composed of [P 124/P 188 (100/0%)], [(99/1%)], [(98/2%)], [(97/3%)] and [(0/100%)], respectively. 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 (DST-600, Fine Chemical, 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 1 h interval, 5 ml of the medium was sampled and filtered. The filtrate was analyzed by UV–vis variable wavelength detector (Philips, Model PU8730) at 277 nm (Iwata et al., 1999).

2.4. Pharmacokinetic study

2.4.1. 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. Ten rats were divided into two groups. The rats in each group were administered with conventional PEG-based suppository [diclofenac sodium/PEG 4000 (2.5/97.5%)] and poloxamer-based suppository, respectively. Poloxamer-based suppository was composed of 2.5% diclofenac sodium and 97.5% poloxamer mixture [P 124/P 188 (97/3%)].

2.4.2. 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. PEG-based or poloxamer-based suppository was administered with a dose of 1.5 g/kg (equivalent to diclofenac sodium 37.5 mg/kg) into the rectum 4 cm above the anus (Choi et al., 1998). The entrance of the anus was then blocked with a cyanoacrylate adhesive, since the suppositories 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) (Nakanishi et al., 1994; Schneeweis and Muller-Goymann, 1997).

2.4.3. Blood sample analysis

Plasma (0.1 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 ethanol. 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 6.8) (4:6, v/v). The eluent was monitored at 280 nm with a flow rate of 1.0 ml/min (Garcia et al., 1998; Idkaidek et al., 1998; Pinto Pereira et al., 1999).

2.5. Identification of poloxamer-based suppository localization in vivo

Male Sprague–Dawley rats weighing 250 ± 20 g were fasted for 24–36 h prior to the experiments but allowed free access to water. Poloxamer-based suppository with 0.1% blue lake was administered at 1.5 g/kg into the rectum 4 cm above the anus using a stomach sondle needle. At 4 h after administration, the rectum was sectioned and the localization of poloxamer-based suppository in the rectum was identified by the blue color (Kim et al., 1998).

2.6. Morphology test of rectal tissues

Male Sprague–Dawley rats weighing 250 ± 20 g were fasted for 24–36 h prior to the experiments but allowed free access to water. Poloxamer-based suppository was administered at 1.5 g/kg into the rectum 4 cm above the anus through the stomach sondle needle. At 4 h after administration, the rectum was isolated, rinsed with a saline solution, fixed in 10% neutral carbonate-buffered formaldehyde, embedded in paraffin using an embedding center and cut into slices. The slices were stained with hematoxylin-eosin and observed under a light microscope (Leitz; Laborlux 12 Pols, Germany) (Miyazaki et al., 1987; Watanabe et al., 1993).

3. Results and discussion

3.1. Melting point of poloxamer mixtures

The poloxamer mixtures were easily prepared by mixing and heating P 124 and P 188 (100/0%, w/w), (99/1%), (98/2%), (97/3%) and (0/100%), respectively. DSC curve showed that the wide peak at around 15 °C, which was observed for [P 124/P 188 (100/0%)] (A), shifted to high temperature and changed to relatively sharper peak in the poloxamer mixtures B [P 124/P 188 (99/1%)], C [(98/2%)] and D [(97/3%)] (Fig. 1). Furthermore, their DSC curves had no peaks of P 124 and P 188, indicating that the poloxamer mixtures composed of P 124 and P 188 were not heterogeneous but homogeneous phases (Choi et al., 2001). The poloxamer mixtures A [P 124/P 188 (100/0%)], B [(99/1%)], C [(98/2%)], D [(97/3%)] and E [(0/100%)] had the melting point of about 15, 20, 27, 32 and 55 °C, respectively

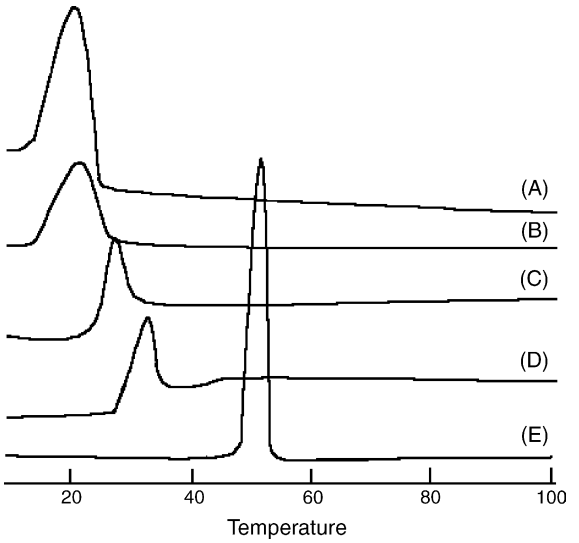

Fig. 1. DSC curves: (A) P 124/P 188 (100/0%); (B) (99/1%); (C) (98/2%); (D) (97/3%); (E) (0/100%).

(Abhaham, 1994). Our results suggested that very small amounts of P 188 affected the melting point of poloxamer mixtures. The poloxamer mixture D [P 124/P 188 (97/3%)] was selected as a suppository base, since it was a solid form at room temperature and instantly melted at physiological temperature.

3.2. Dissolution of diclofenac sodium from poloxamer-based suppository

To test whether the ratio of P 124/P 188 affected the dissolution rates of diclofenac sodium from the poloxamer-based suppositories, we performed the dissolution studies on the five formulations composed of 2.5% diclofenac sodium and 97.5% poloxamer mixtures. The poloxamer mixtures was composed of [P 124/P 188 (100/0%)], [(99/1%)], [(98/2%)], [(97/3%)] and [(0/100%)], respectively. Additionally, the dissolution test of PEG-based suppository [diclofenac sodium/PEG 4000 (2.5/97.5%)] was carried out.

Among the poloxamer-based suppositories tested, the suppository with only P 188 had significantly lowest dissolution rates of diclofenac sodium. There were no significant differences among the dissolution rates of diclofenac sodium from any other poloxamer-based suppositories (Fig. 2). Our results suggested that very small amounts of P 188 hardly affected the dissolution rates of diclofenac sodium from poloxamer-based suppository. As a possible mechanism by which the dissolution rates of diclofenac sodium retarded from poloxamer-based suppository with only P 188, it is speculated that it remained in a solid phase and could not turned into a gel in the dissolution medium due to relatively high melting point of P 188 (Choi et al., 1998; Iwata et al., 1999). Furthermore, the PEG-based suss-pository had significantly higher dissolution rates of diclofenac sodium than any poloxamer-based suppositories. These results suggested that PEG was soluble in the dissolution medium, while poloxamer was not soluble but gelled (Choi et al., 1998).

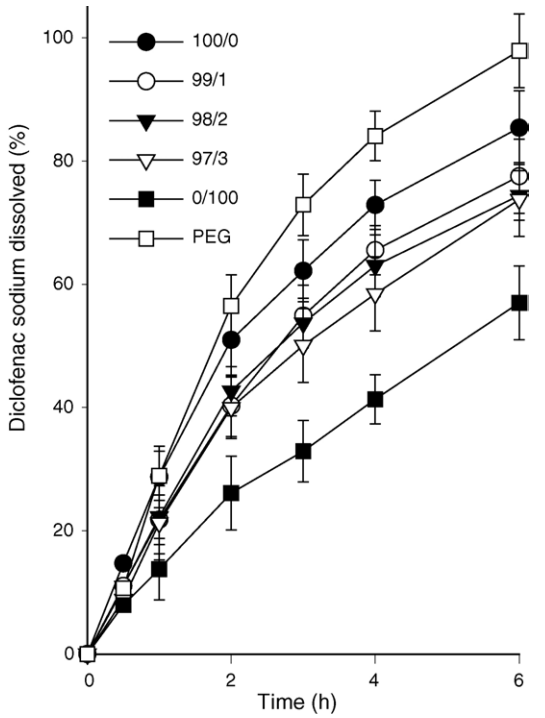

Fig. 2. Effect of poloxamer on the dissolution of diclofenac sodium from poloxamer-based suppositories. Poloxamer-based suppositories [diclofenac sodium/poloxamer mixture (2.5/97.5%)] (5 g) and PEG-based suppository [diclofenac sodium/PEG 4000 (2.5/97.5%)] (5 g) containing 125 mg of diclofenac sodium were used as dissolution samples. The poloxamer mixtures of poloxamer-based suppositories were composed of [P 124/P 188 (100/0%)], [(99/1%)], [(98/2%)], [(97/3%)] and [(0/100%)], respectively. Each value represents the mean ± S.E. ($n = 6$).

To understand the dissolution mechanisms of diclofenac sodium, we described the dissolution rate

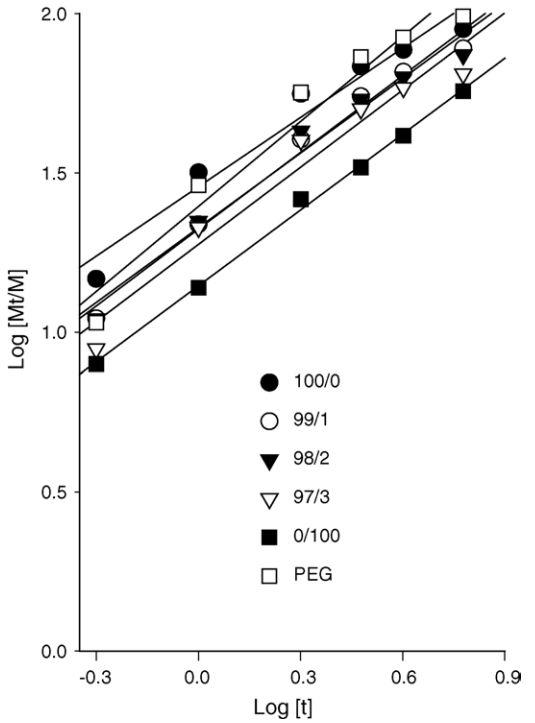

Fig. 3. Dissolution kinetics of diclofenac sodium. Logarithm of dissolved fractions of diclofenac sodium was plotted against logarithm of time.

using the following equations.

$$\frac{Mt}{M} = kt^n \quad (1)$$

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

where Mt/M is the fraction of dissolved drug at time t, k a characteristic constant of the poloxamer-based suppository 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 dissolution kinetics, $0.5 < n < 1$ means a non-Fickian dissolution model and $n = 0.5$ indicates Fickian diffusion (Higuchi model) (Peppas, 1985; Choi et al., 2000). From the plot of $\log(Mt/M)$ versus $\log(t)$ (Fig. 3), kinetic parameters, n and k, were calculated. Table 1 showed that most of n values were close to 1, suggesting that the dissolution rate of diclofenac sodium from poloxamer-based suppositories was independent of the time (Choi et al., 1998). The relatively parallel slopes of the plots indicated that the content of P 124 and P 188 might not affect the dissolution mechanisms (Choi et al., 2000).

Table 1
Dissolution kinetic parameters

	Release exponent, n	Kinetic constant, k (%/h^n)	Correlation coefficient, r
P 124/P 188 (100/0%)	0.985	1.457	0.961
P 124/P 188 (99/1%)	1.003	1.328	0.985
P 124/P 188 (98/2%)	0.980	1.326	0.975
P 124/P 188 (97/3%)	1.007	1.276	0.956
P 124/P 188 (0/100%)	0.993	1.145	0.987
Polyethylene glycol	1.089	1.395	0.951

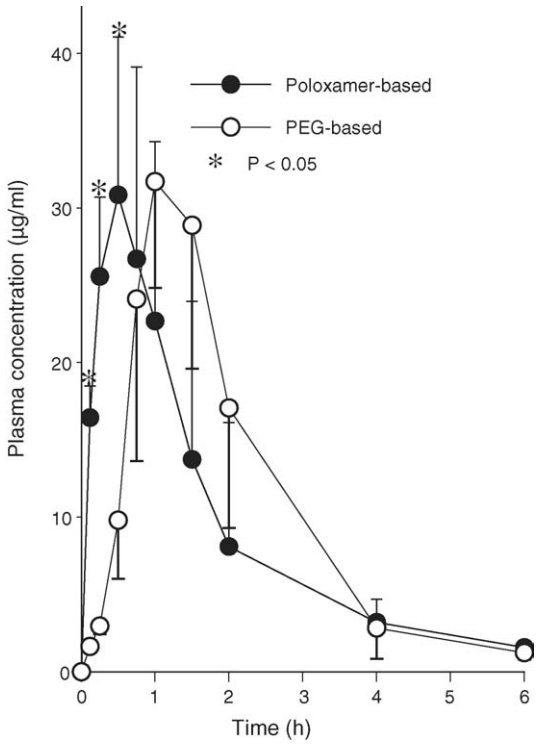

Fig. 4. Plasma concentration-time profiles of diclofenac sodium after rectal administration of poloxamer-based and PEG-based suppository to rats. Poloxamer-based and PEG-based suppository were composed of [diclofenac sodium/poloxamer mixture (2.5/97.5%)] and [diclofenac sodium/PEG 4000 (2.5/97.5%)], respectively. Poloxamer mixture was composed of [P 124/P 188 (97/3%)]. Each value represents the mean ± S.D; ($n = 5$). $^*P < 0.05$ compared to PEG-based suppository.

3.3. In vivo experiments

The pharmacokinetic parameters of diclofenac sodium were determined after rectal administration of poloxamer-based and PEG-based suppository in rats. The poloxamer-based suppository was composed of 2.5% diclofenac sodium and 97.5% poloxamer mixture [P 124/P 188 (97/3%)]. The PEG-based suppository was composed of 2.5% diclofenac sodium and 97.5% PEG 4000.

Fig. 4 shows the change of mean plasma concentration of diclofenac sodium after rectal administration of suppositories in rats. The initial plasma concentrations of diclofenac sodium in poloxamer-based suppository were higher compared with those in PEG-based suppository. In particular, in poloxamer-based suppository, from 7 to 30 min, the plasma concentrations of diclofenac sodium (16–31 μg/ml) at the same time interval were significantly higher than those in PEG-based suppository (1–10 μg/ml) ($P < 0.05$), respectively. Our results indicated that the drug from poloxamer-based suppository could be absorbed faster than that from PEG-based one in rats. The reason for this fast absorption might be dependent upon the fast melting of poloxamer-based suppsotory and mucoadhesive property of poloxamer (Garcia et al., 1998; Idkaidek et al., 1998; Pinto Pereira et al., 1999; Ramakrishna et al., 1996). PEG-based suppository was not mucoadhesive, and gradually dissolved by physiological fluid. On contrast, poloxamer-based mucoadhesive suppository was dissolved speedily at physiological temeprature, gelled and attached on the rectal mucous membranes due to its relatively low melting point (32 °C versus 69 °C) (Yong et al., 2001). However, from 45 min after the dose, the plasma concentrations of diclofenac sodium in poloxamer-based suppository, were not significantly different from those in the PEG-based suppository.

The pharmacokinetic parameters are shown in Table 2. Poloxamer-based suppository gave significantly faster T_{max} of diclofenac sodium (0.60 ± 0.15 h) than did PEG-based suppository (0.94 ± 0.13 h) ($P < 0.05$). However, the AUC, C_{max}, K_{el} and $t_{1/2}$ values of diclofenac sodium from poloxamer-based suppository were not significantly different from those from PEG-based suppository. Therefore, the

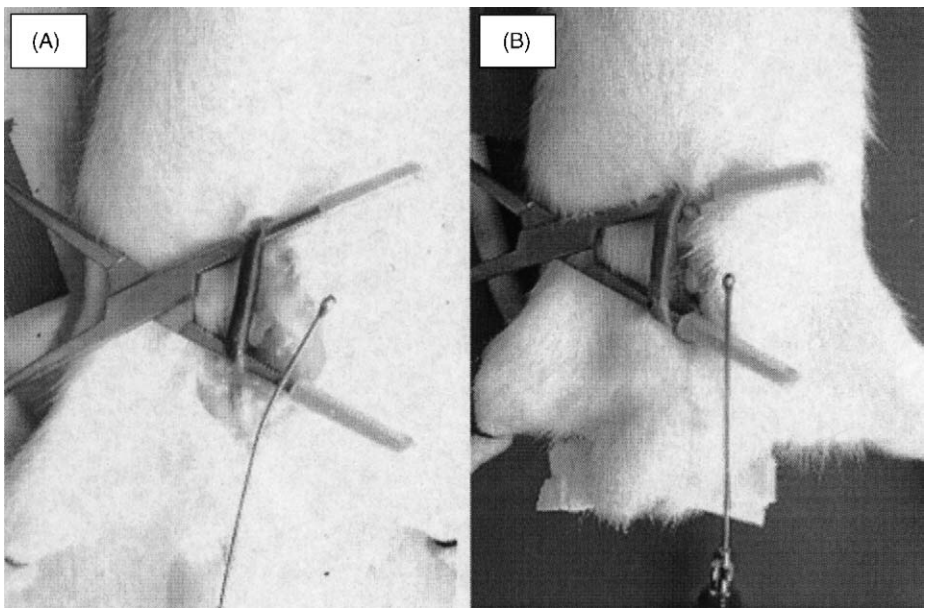

Fig. 5. In vivo localization of poloxamer-based suppository in the rectum of a rat. Poloxamer-based suppository composed of [diclofenac sodium/poloxamer mixture (2.5/97.5%)] was added with 0.1% blue lake and was administered into the rectum of a rat. At 5 min (A) and 4 h (B) after administration, the rectum was sectioned. The suppository is shown in blue. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Table 2
Pharmacokinetic parameters of diclofenac sodium delivered by PEG-based or poloxamer-based suppositories

Parameters	PEG-based suppository	Poloxamer-based suppository
AUC (h μg/ml)	63.78 ± 20.08	55.76 ± 25.21
MRT (h)	1.76 ± 0.61	1.54 ± 0.57
T_{max} (h)	0.94 ± 0.13	0.60 ± 0.15*
C_{max} (μg/ml)	31.70 ± 7.33	30.84 ± 11.22
K_{el} (h^{-1})	0.73 ± 0.24	0.47 ± 0.19
$t_{1/2}$ (h)	0.99 ± 0.32	1.49 ± 0.36

Each value represents the mean ± S.E. ($n = 5$).
* $P < 0.05$ compared with PEG-based suppository.

poloxamer-based suppository could not give the improved biavailability of diclofenac sodium. However, it gave only the faster absorption of drug due to its relatively fast melting and mucoadhesive property of poloxamer. Diclofenac sodium, an NSAIDs was needed to be relatively fast absorbed, even if the poloxamer-based suppository hardly improved the biavailability of drug compared to PEG-based suppository (Yong et al., 2001). Our results suggested that the poloxamer-based suppository would be useful to deliver diclofenac sodium in a pattern that allows fast absorption in the initial phase.

Poloxamer-based suppository with 0.1% blue lake was administered into rats, and the retention in the rectum was observed (Kim et al., 1998). At 5 min after administration, the blue color of the poloxamer-based suppository was clearly shown in the rectum. At 4 h after administration, the blue color of the suppository in the rectum was faded. However, the position of suppository in the rectum did not significantly change with time (Fig. 5). Our results suggested that the poloxamer-based suppository remained in the rectum for at least 4 h due to the mucoadhesive property of poloxamer (Choi et al., 1998; Yong et al., 2001).

The safety test of poloxamer-based suppository composed of 2.5% diclofenac sodium and 97.5% poloxamer mixture [P 124/P 188 (97/3%)] was performed by observing any irritation of poloxamer-based suppository on the rectal tissues (Miyazaki et al., 1987; Watanabe et al., 1993). The morphology of rectal tissues indicated that the poloxamer-based suppository could not irritate or damage the rectal tissues (Fig. 6). Previously, poloxamers, the non-ionic surfactants were reported to be inert, giving no damage to mucous membranes (Dumortier et al., 1991).

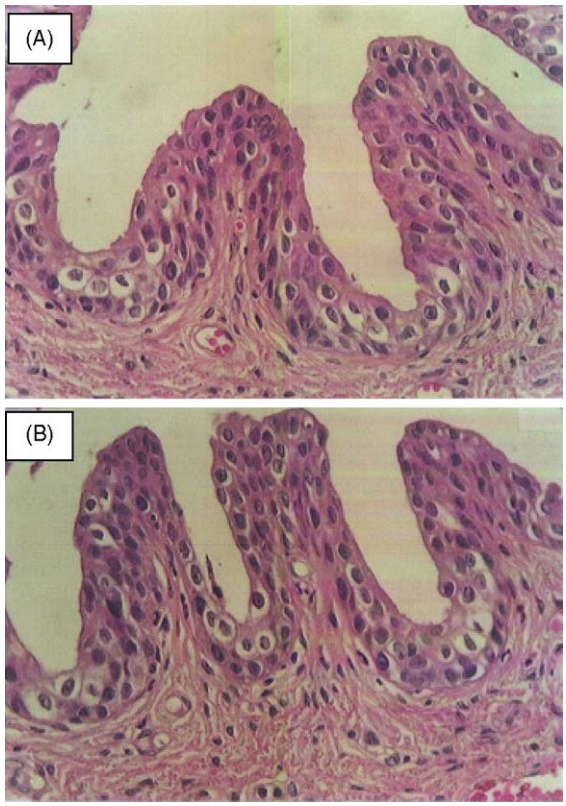

Fig. 6. Morphology of rectal mucosa of rats after rectal administration of poloxamer-based suppository (×250): (A) before administration and (B) 4 h after administration.

4. Conclusion

Taken together, it is concluded that the poloxamer-based solid suppository composed of 97% P 124 and 3% P 188, which was a solid form at room temperature and instantly melted at physiological temperature, retained in the rectum for at least 4 h and could not irritate or damage the rectal tissues of rats. Furthermore, the poloxamer-based suppository gave significantly higher initial plasma concentrations and faster T_{max} of diclofenac sodium than did conventional PEG-based suppository, indicating that the drug from poloxamer-based suppository could be absorbed faster than that

from PEG-based one in rats. Thus, the poloxamer-based solid suppository with P 124 and P 188 was a mucoadhesive, safe and effective rectal dosage form for diclofenac sodium.

Acknowledgements

This research was supported by grant No. RTI04-01-04 from the Regional Technology Innovation Program of the Ministry of Commerce, Industry and Energy (MOCIE) and by a grant from the Ministry of Science and Technology, South Korea.

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