MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY®
Vol. 29, No. 5, pp. 545–553, 2003

RESEARCH PAPER

Physicochemical Characterization of Diclofenac Sodium-Loaded Poloxamer Gel as a Rectal Delivery System with Fast Absorption

Chul Soon Yong,[1] Hongkee Sah,[2] Yurngdong Jahng,[1] Hyeun Wook Chang,[1] Jong-Keun Son,[1] Seung Ho Lee,[1] Tae Cheon Jeong,[1] Jong-Dal Rhee,[1] Suk Hwan Baek,[3] Chong-Kook Kim,[4] and Han-Gon Choi[1,*]

[1]College of Pharmacy, Yeungnam University, Dae-Dong, Gyongsan, Korea
[2]College of Pharmacy, Catholic University of Daegu, Gyongsan, South Korea
[3]College of Medicine, Yeungnam University, Taegu, Korea
[4]College of Pharmacy, Seoul National University, Shinlim-Dong, Kwanak-Ku, Seoul, Korea

ABSTRACT

Rectal poloxamer gel systems composed of poloxamers and bioadhesive polymers were easy to administer to the anus and were mucoadhesive to the rectal tissues without leakage after the dose. However, a poloxamer gel containing diclofenac sodium could not be developed using bioadhesive polymers, since the drug was precipitated in this preparation. To develop a poloxamer gel using sodium chloride instead of bioadhesive polymers, the physicochemical properties such as gelation temperature, gel strength, and bioadhesive force of various formulations composed of diclofenac sodium, poloxamers, and sodium chloride were investigated. Furthermore, the pharmacokinetic study of diclofenac sodium delivered by the poloxamer gel was performed. Diclofenac sodium significantly increased the gelation temperature and weakened the gel strength and bioadhesive force, while sodium chloride did the opposite. The poloxamer gels with less than 1.0% sodium chloride, in which the drug was not precipitated, were inserted into the rectum without difficulty and leakage, and were retained in the rectum of rats for at least 6 hr. Furthermore, poloxamer gel gave significantly higher initial plasma concentrations and faster T_{max} of diclofenac sodium than did solid suppository, indicating that drug from poloxamer gel could be absorbed faster than that from the solid one in rats. Our results suggested that a rectal poloxamer gel system with sodium chloride and poloxamers was a more physically stable, convenient, and effective rectal dosage form for diclofenac sodium.

*Correspondence: Prof. Han-Gon Choi, College of Pharmacy, Yeungnam University, 214-1, Dae-Dong, Gyongsan 712-749, Korea; Fax: +82-53-811-3871; E-mail: hangon@yu.ac.kr.

DOI: 10.1081/DDC-120018643
0363-9045 (Print); 1520-5762 (Online)

www.dekker.com

Key Words: Diclofenac sodium; Sodium chloride; Poloxamer gel; Pharmacokinetics.

INTRODUCTION

Ideal suppository would be easy to administer with good patient compliance and would remain at the administered sites avoiding the first-pass effect in the liver and gastrointestinal tract. Conventional suppository is a solid dosage form that melts or softens in the rectum. Such a solid suppository can give in uncomfortable feeling and may be a factor in patient noncompliance. Furthermore, a solid suppository, which may reach the end of the colon, has a loss of drug at the colonic level and may also allow the carried drugs to undergo the first-pass effect.[1,2]

In order to solve the problems of solid suppository, an attempt was recently made to develop a rectal dosage form, thermosensitive poloxamer gel which exists as a liquid in vitro but a gel in vivo.[3–5] Poloxamer solution has been known to exhibit the phenomenon of reverse thermal gelation, remaining as solution at low temperature and gelling upon increasing the temperature. Moreover, the bioadhesive polymers such as carbopol, polycarbophil, and sodium alginate were used to control the gel strength and bioadhesive force of poloxamer gel.[3,4] The poloxamer gel was easy to administer to the anus, since it was a liquid form at room temperature and turned into a gel instantly at physiological temperature, and was also mucoadhesive to the rectal tissues without leakage after the dose. However, in the development of poloxamer gel containing a drug that was poorly water-soluble and solubilized in aqueous medium by poloxamers, the bioadhesive polymers such as carbopol, polycarbophil, and sodium alginate could not be used, since the drug was precipitated in this preparation.[5]

Thus, in this study, to develop a poloxamer gel system using sodium chloride instead of bioadhesive polymers, the physicochemical properties such as gelation temperature, gel strength, and bioadhesive force of various formulations composed of diclofenac sodium, poloxamers, and sodium chloride were investigated. Furthermore, the pharmacokinetic study of diclofenac sodium delivered by the poloxamer gel in rats was performed. Diclofenac sodium was selected here as a model drug, since it was poorly water-soluble and solubilized in aqueous medium by poloxamers.[6–8] Diclofenac sodium was precipitated in the poloxamer gel systems composed of poloxamers and bioadhesive polymers. Moreover, it was applied to rectal suppository form due to its rapid absorption in the rectum.[9,10] Sodium chloride, a very water-soluble material, has been used to control the gel strength and bioadhesive force of diclofenac poloxamer gel.

MATERIALS AND METHODS

Materials

Diclofenac sodium and poloxamers (P 407, P 188) were supplied from SK chemical (Suwon, South Korea) and BF Goodrich (Breesville, OH, USA), respectively. Sodium chloride was of USP grade. All other chemicals were of reagent grade and used without further purification.

Preparation of Diclofenac Sodium-Loaded Poloxamer Gel

Various components such as sodium chloride (0–1.0 g) and diclofenac sodium (2.5 g) were dispersed or dissolved in distilled water at room temperature and the solution was cooled down to 4°C. Poloxamer P 407 (15 g) and P 188 (15–20 g) were then slowly added to the solution with continuous agitation (Young-Ji Instruments Co. Ltd., Seoul, Korea). The poloxamer gel was left at 4°C until a clear solution was obtained.[3]

Measurement of Gelation Temperature

A 20-mL transparent vial containing a magnetic bar and 10 g poloxamer gel was placed in a low-temperature thermostat water bath (Heto, Scandinavia). A digital thermosensor (Ika Labortechnik, RET digi-visc) connected to a thermistor was immersed in the poloxamer gel. Poloxamer gel was heated at the rate of 1°C/min with the continuous stirring of 30 rpm. When the magnetic bar stopped moving due to gelation, the temperature displayed on the thermistor was determined as a gelation temperature.[11]

Measurement of Gel Strength

Poloxamer gel (50 g) was put in a 100-mL graduated cylinder and gelled in a thermostat at 36.5°C. The homemade apparatus for measuring gel strength

(weight: 35 g) was then placed onto the poloxamer gel. The gel strength, which means the viscosity of poloxamer gel at physiological temperature, was determined by the time (sec) the apparatus took to sink 5 cm down through the poloxamer gel. In case it took more than 300 sec to drop the apparatus into the gel, various weights were placed on the top of the apparatus and gel strength was described by the minimal weights that pushed the apparatus 5 cm down through the gel.[4]

Determination of Bioadhesive Force

The bioadhesive force of poloxamer gel was determined by using the measuring device in Fig. 1. In brief, a section of tissue was cut from the fundus of rabbit rectum and instantly secured with mucosal side out onto each glass vial (C) using a rubber band and an aluminum cap. The vials with the rectal tissues were stored at 36.5°C for 10 min. Next, one vial with a section of tissue (E) was connected to the balance (A) and the other vial was placed on a height-adjustable pan (F). Poloxamer gel (D) was added onto the rectal tissue on the other vial. Then, the height of the vial was adjusted so that the poloxamer gel could be placed between the mucosal tissues of both vials. The weights (B) were kept raised until two vials were attached. Bioadhesive force, the detachment stress (dyne/cm^2), was determined from the minimal weights that detached two vials. The rectal tissue pieces were changed for each measurement.[4,12,13]

Measurement of Gel Strength Threshold In Vivo

To measure the threshold of gel strength, the poloxamer gel was administered at a dose of 1.5 g/kg into the rectum of a New Zealand white rabbit raised with 45° slope through a stomach sonde needle fitted on a glass syringe. The separation between stomach sonde needle and glass syringe during administration was investigated. Furthermore, it was investigated whether poloxamer gel was not leaked out from the anus during 30 min after administration. Each poloxa mer gel was then evaluated by the difficulty of insertion into the anus and the leakage of gel from the anus during 30 min after administration. The upper threshold of gel strength was defined as the maximum gel strength at which poloxamer gel could be inserted into the anus of rabbits without difficulty. The lower threshold of gel strength was defined as the minimum gel strength at which poloxamer gel was not leaked out from the anus 30 min after administration. Thus, poloxamer gel with the gel strength between two thresholds was easily inserted into the anus and did not leak out after insertion.[1]

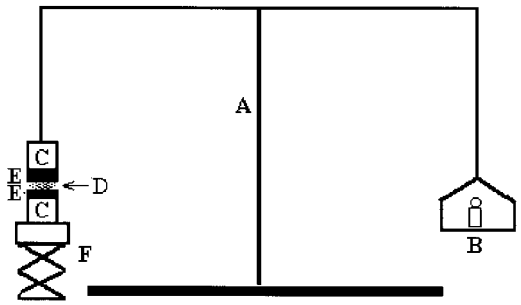

Figure 1. Bioadhesive force-measuring device: A, modified balance; B, weights; C, glass vial; D, poloxamer gel; E, rectal tissue; F, height-adjustable pan.

Identification of Poloxamer Gel Localization In Vivo

Male Sprague-Dawley rats weighing 250 ± 20 g were fasted for 24–36 hr prior to the experiments but allowed free access to water. The poloxamer gel [P 407/P 188/sodium chloride/diclofenac sodium (15/17/0.8/2.5)] with 0.1% blue lake was administered at 1.5 g/kg into the rectum 4 cm above the anus using a stomach sonde needle. At 6 hr after administration, the rectum was sectioned and the localization of poloxamer gel in the rectum was identified by the blue color.[5]

Pharmacokinetic Study

In Vivo Experiments

Male Sprague-Dawley rats weighing 250 ± 20 g were fasted for 24–36 hr prior to the experiments but allowed free access to water. Twelve rats were divided into two groups. The rats in each group were administered the solid suppository [polyethylene glycol/diclofenac sodium (97.5/2.5)] and rectal poloxamer gel [P 407/P 188/sodium chloride/diclofenac sodium (15/17/0.8/2.5)], respectively.

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 (1.5 g/kg equivalent to diclofenac sodium 37.5 mg/kg) was administered into the rectum 4 cm above the anus through a stomach sonde needle fitted on a glass syringe. Solid 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.[12] The entrance of the anus was then blocked with a cyanoacrylate adhesive, since the preparations might leak out from the anus during the pharmacokinetic experiment, leading to inaccurate pharmacokinetic data. A half milliliter of blood was collected from the right femoral artery at various time intervals and centrifuged at 3000 rpm for 10 min using a centrifuge 5415C (Eppendorf, USA).[9,10]

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 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 acetoniltrile and phosphate buffer (pH 6.8) (4:6, volume ratio). The eluent was monitored at 280 nm with a flow rate of 1.0 mL/min.[14–16]

RESULTS AND DISCUSSION

Since diclofenac sodium is an active material and sodium chloride is added to the poloxamer gels in order to reinforce their gel strength and bioadhesive force, their effects on the physicochemical properties of poloxamer gel should be studied. Throughout the experiments, the concentration of diclofenac sodium was fixed as 2.5%, the usual content of diclofenac sodium in rectal dosage forms. In the previous studies, we found that diclofenac sodium was precipitated in the poloxamer gel system composed of 2.5% diclofenac sodium and more than 0.2% of bioadhesive polymers such as carbophil, polycarbophil, and sodium alginate.[5] Thus, in this study, sodium chloride, instead of bioadhesive polymers, has been used to prepare the diclofenac poloxamer gel. Since sodium chloride was freely water-soluble, the poloxamer gels containing diclofenac sodium were easier to prepare and the drug was not precipitated.

Gelation Temperature

Firstly, 2.5% of diclofenac sodium was added to P 407/P 188 (15%/15%) (abbreviated as 15/15) and (15%/20%) (abbreviated as 15/20), and then the physicochemical properties such as gelation temperature, gel strength, and bioadhesive force of poloxamer gels were evaluated (Table 1). It was previously reported that the poloxamer gels 15/15 and 15/20 existed as liquid at room temperature but gelled at physiological temperatures.[1,5] Diclofenac sodium markedly increased the gelation temperature of poloxamer gels 15/15 and 15/20.

The impact of sodium chloride on the gelation temperatures depended on the concentration of sodium chloride and on the presence of diclofenac sodium in the formulations (Fig. 2). The effect of sodium chloride decreasing the gelation temperature was significantly lower in the presence of diclofenac sodium. Similar phenomena were observed in 15/15 and 15/20. With the addition of 1.0% sodium chloride, the gelation temperature of 15/15 decreased 3°C in the absence of diclofenac sodium, while the gelation temperature decreased 13°C in the presence of diclofenac sodium. In 15/20 poloxamer mixture,

Table 1. Effect of diclofenac sodium on the physicochemical properties of poloxamer gel.

P 407/P 188	15/15		15/20	
Diclofenac sodium	0%	2.5%	0%	2.5%
Gelation temperature (°C)	35.7 ± 0.3	46.0 ± 0.5	29.2 ± 0.5	37.5 ± 0.4
Gel strength (sec)	4.03 ± 0.2	3.40 ± 0.1	> 300	14.4 ± 0.25
Bioadhesive force ($\times 10^2$ dyne/cm^2)	6.8 ± 2.4	3.2 ± 1.3	97.3 ± 11.4	38.8 ± 4.7

Note: Each value represents the mean ± S.E. ($n = 5$).

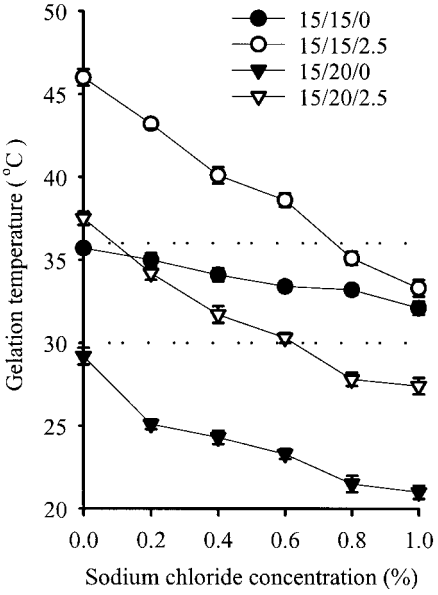

Figure 2. Effect of diclofenac sodium and sodium chloride on the gelation temperature of poloxamer gels. Sodium chloride (0.2–1.0%) was added to the poloxamer mixtures (P 407/P 188/diclofenac sodium). Each value represents the mean ± S.E. ($n = 5$).

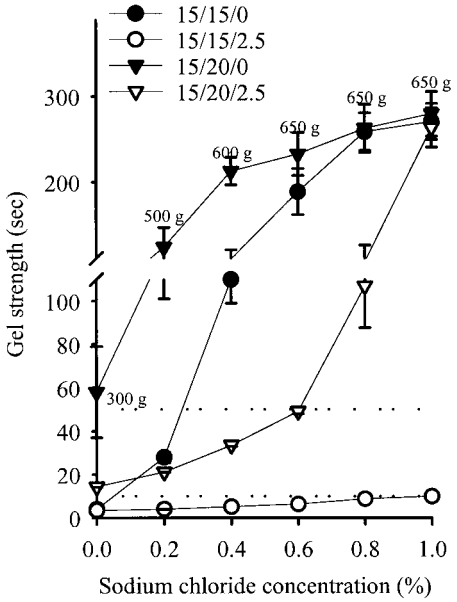

Figure 3. Effect of diclofenac sodium and sodium chloride on the gel strength of poloxamer gels. Sodium chloride (0.2–1.0%) was added to the poloxamer mixtures (P 407/P 188/diclofenac sodium). Each value represents the mean ± S.E. ($n = 5$). Gels composed of 15/20 without diclofenac sodium were so strong that the apparatus could not move down within 300 sec.

the gelation temperature decreased 8°C with the addition of 1.0% sodium chloride, whereas it decreased 10°C in the presence of diclofenac sodium. It appeared that the larger impact of sodium chloride on the gelation temperature in the presence of diclofenac sodium was due to the gelation temperature-enhancing effects of diclofenac sodium.[4] Given that the gelation temperature range for poloxamer gel with a liquid form at room temperature and a gel phase in the rectum was 30–36°C (Fig. 2), it appeared to be possible to prepare the diclofenac poloxamer gel with suitable gelation temperature by adjusting the contents of sodium chloride from 0.2 to 1.0%.

Gel Strength

In the development of poloxamer gel, the gel strength is important in finding the condition which allows the easy insertion of the suppositories and no leakage from the anus. Thus, the ranges of gel strength suitable for poloxamer gel system were investigated by inserting poloxamer gels into the anus of a rabbit and observing any leakage after insertion.[1] We observed two thresholds in gel strength; the upper and the lower limit. Above the upper threshold of gel strength, it was difficult to insert the poloxamer gels. Under the lower limits, the poloxamer gels leaked out from the anus. In the gels with sodium chloride, the range was 10–50 sec.

Diclofenac sodium reduced the gel strength of poloxamer gels (Table 1, Fig. 3). Diclofenac sodium also affected the gel strength of poloxamer gels containing sodium chloride. The gel strength-reducing effect of diclofenac sodium depended on the concentration of sodium chloride and the composition of poloxamer gels (Fig. 3). The effect of sodium chloride increasing the gel strength was significantly lower in the presence of diclofenac sodium. Similar phenomena were observed in 15/15 and 15/20. In particular, with the addition of 1.0% sodium chloride, the gel strength of 15/15 increased from 4 to 271 sec in the absence of diclofenac sodium, while the gel strength increased from 3 to 11 sec in the presence of diclofenac sodium. In 15/20 poloxamer mixture, the gel strength increased from 58 sec (300 g) to 275 sec (650 g) with the addition of 1.0% sodium chloride, whereas it increased from 14 to 264 sec in the presence of diclofenac sodium. Given that the gel strength thresholds for poloxamer gel with easy insertion and no leakage was 10–50 sec, it appeared to be possible to prepare diclofenac poloxamer gel with

suitable gel strength by adjusting the contents of sodium chloride from 0.2 to 1.0%.

Bioadhesive Force

Bioadhesive force means the force with which poloxamer gel binds to rectal mucous membranes at 36.5°C. Since the rectal mucous membranes consist of oligosaccharide chains with asialic acid, the polymers with hydrophilic groups such as carboxyl, oxide, and hydroxyl group can bind strongly to oligosaccharide chains, resulting in strong bioadhesive force.[17] The stronger the bioadhesive force is, the more it can prevent the gelled suppositories from reaching the end of the colon, the pathway for the first-pass effect. But if the bioadhesive force is too excessive, the gel can damage the rectal mucous membranes.[17,18] Therefore, poloxamer gels must have the balanced bioadhesive force.

Diclofenac sodium decreased the bioadhesive force of gelled poloxamers (Table 1). Diclofenac sodium also significantly decreased the bioadhesive force of poloxamer gels containing sodium chloride. Moreover, it was noteworthy that the poloxamer gels composed of only P 407 and P 188, 15/15 and 15/20, had the moderate bioadhesive force, suggesting that the poloxamers with hydrophilic oxide group could bind to oligosaccharide chains.[19,20]

Sodium chloride, which enhanced gel strength efficiently increased the bioadhesive force (Fig. 4). In the absence of diclofenac sodium, 1.0% sodium chloride strengthened the bioadhesive forces of 15/15 and 15/20 as much as 26.7- and 3.2-fold, respectively. However, the impact of sodium chloride on the bioadhesive force was significantly lessened by diclofenac sodium. In the presence of diclofenac sodium, 1.0% sodium chloride strengthened the bioadhesive forces of 15/15 and 15/20 as much as 10.0- and 3.0-fold, respectively. The bioadhesive forces of poloxamer solutions were affected by the concentrations of sodium chloride (Fig. 4). In the absence of diclofenac sodium, sodium chloride abruptly increased the bioadhesive forces of 15/15 as the concentration increased to 0.4%, while they did not significantly affect the bioadhesive forces at the higher concentrations (0.6–1.0%). However, in the presence of diclofenac sodium, 15/15 showed gradual increase of bioadhesive forces with increasing concentrations of sodium chloride. Similar phenomena were observed for 15/20.

The results indicated that diclofenac sodium increased the gelation temperature of poloxamer gels,

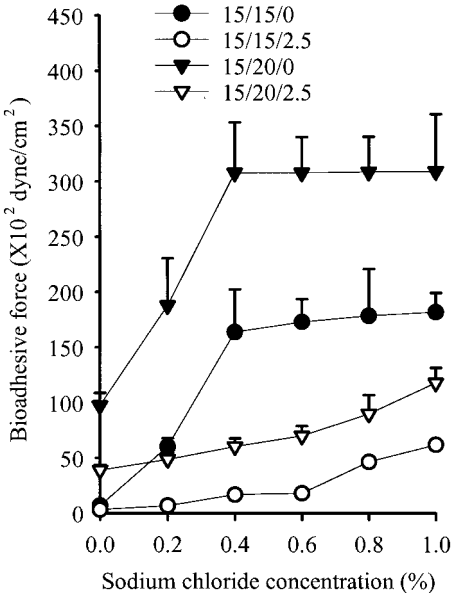

Figure 4. Effect of diclofenac sodium and sodium chloride on the bioadhesive force of poloxamer gels. Sodium chloride (0.2–1.0%) was added to the poloxamer mixtures (P 407/P 188/diclofenac sodium). Each value represents the mean ± S.E. ($n = 5$).

while decreasing the gel strength of poloxamer gels. The temperature-dependent gelation of poloxamer solutions could be explained by configuration change.[21] Poloxamer molecules exhibit a well-arranged zigzag configuration. With increasing temperature, the zigzag configuration of poloxamer may be transformed into a close-packed meander configuration, forming a more close-packed and more viscous gel. Thus, the formulation with higher P 188 content had lower gelation temperature and higher gel strength compared to that with lower P 188 content. Furthermore, as a possible mechanism by which diclofenac sodium affected the gelation temperature and gel strength, it is conceivable that hydrophobic diclofenac sodium could bind weakly with the cross-linked reticular poloxamer gel by placing diclofenac sodium in the poloxamer gel.[1] However, sodium chloride exerted highly opposite effects on the gelation temperature and gel strength of poloxamer gels, resulting from that sodium chloride could bind strongly with the cross-linked reticular poloxamer gel by the strong cross-linking bonding of sodium salt with poloxamer.[14]

Additionally, diclofenac sodium weakened the bioadhesive force of poloxamer gels, while sodium chloride reinforced. Poloxamer gels composed of only P 407 and P 188 showed the moderate

bioadhesive forces, since the poloxamer with hydrophilic oxide group could bind to oligosaccharide chains.[17,18] The formulation with higher P 188 content had higher bioadhesive force compared to that with lower P 188 content. However, sodium chloride and diclofenac sodium had no capacity of binding to them. The bioadhesive force-weakening effect of diclofenac sodium seemed to be contributed by its gel strength-weakening effect of poloxamer, resulting in the weaker binding of poloxamer gels with the oligosaccharide chains of rectal mucous membranes. Similarly, the high bioadhesive force-reinforcing effect of sodium chloride was due to sodium chloride reinforcing the gel strength of cross-linked reticular poloxamer gel, resulting in the more increased binding of poloxamer gels with them.[5] It indicated that the gel strength of poloxamer gel seemed to play a role in affecting the bioadhesive force of poloxamer-based poloxamer gel.

In Vivo Retention of Poloxamer Gel in the Rectum

The poloxamer gel [diclofenac sodium/P 407/P 188/sodium chloride (2.5/15/17/0.8)] with 0.1% blue lake was administered into rats, and the retention in the rectum was observed. This gel with the suitable gelation temperature ($33.1 \pm 0.5^{\circ}C$), gel strength (35.66 ± 1.23 sec) and bioadhesive force ($61.8 \pm 7.5 \times 10^2$ dyne/cm^2) was easy to administer to the anus and mucoadhesive to the rectal tissues without leakage after the dose.[1] At 6 hr after administration, the blue color of the poloxamer gel was clear in the rectum 4 cm above the anus and not observed in colon, indicating that the position of poloxamer gel in the rectum did not significantly change with time. Our results suggested that the bioadhesive force of poloxamer gel composed of diclofenac sodium, poloxamer and sodium chloride was strong enough to hold the poloxamer gel in the rectum for at least 6 hr.

Pharmacokinetic Study

The pharmacokinetic parameters of diclofenac sodium were determined after rectal administration of rectal poloxamer gel [P 407/P 188/sodium chloride/diclofenac sodium (15/17/0.8/2.5)] and solid suppository [polyethylene glycol/diclofenac sodium (97.5/2.5)]. Figure 5 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 gel were higher compared with those in solid suppository. In particular, in poloxamer gel, from 7 to 30 min, the plasma concentrations of diclofenac sodium (22–34 μg/mL) were significantly higher than those in solid suppository (1–10 μg/mL). However, from 1 hr after the dose, the plasma concentrations of diclofenac sodium in poloxamer gel were not significantly different from those in the solid suppository. Our results indicated that the diclofenac sodium from poloxamer gel 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.[1] Solid suppository was not bioadhesive, and gradually dissolved and dispersed. On contrast, poloxamer gel was spread easily in the rectum and gelled and attached on the rectal mucous membranes, since bioadhesive poloxamer gel was a fluid initially.[1,5]

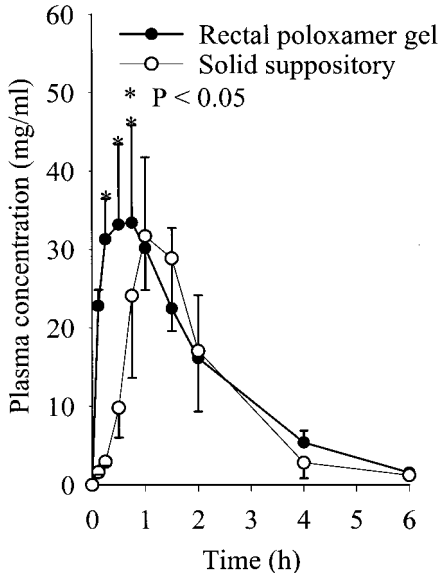

Figure 5. Plasma concentration–time profiles of diclofenac sodium after rectal administration of rectal poloxamer gel and solid suppository to rats. The rectal poloxamer gel and solid suppository were composed of [P 407/P 188/sodium chloride/diclofenac sodium (15/17/0.8/2.5)] and [polyethylene glycol/diclofenac sodium (97.5/2.5)], respectively. Each value represents the mean ± S.E. ($n = 6$). (*), $P < 0.05$ compared to solid suppository.

The pharmacokinetic parameters are shown in Table 2. Poloxamer gel gave significantly faster T_{max} of diclofenac sodium (0.50 ± 0.22 hr) than did solid suppository (0.94 ± 0.13 hr) ($P < 0.05$). However, the AUC, C_{max}, K_{el}, and $t_{1/2}$ values of diclofenac

Table 2. Pharmacokinetic parameters of diclofenac sodium following rectal administration of solid suppositories and 15/17/0.8/2.5 poloxamer gels to rats.

Parameters	Solid suppository	Rectal poloxamer gel
AUC (hr μg/mL)	63.78 ± 20.08	80.55 ± 25.03
MRT (hr)	1.76 ± 0.61	1.66 ± 0.53
T_{max} (hr)	0.94 ± 0.13	0.50 ± 0.22[a]
C_{max} (μg/mL)	31.70 ± 7.33	33.42 ± 9.90
K_{el} (hr^{-1})	0.73 ± 0.24	0.59 ± 0.13
$t_{1/2}$ (hr)	0.95 ± 0.32	1.18 ± 0.38

Note: Each value represents the mean ± S.E. ($n = 6$).
[a] $P < 0.05$ compared with solid suppository.

sodium from poloxamer gel were not significantly different from those of solid suppository. Our results suggested that poloxamer gel with sodium chloride would be useful to deliver diclofenac sodium in a pattern that allows fast absorption in the initial phase.

CONCLUSION

It is concluded that the poloxamer gels with less than 1.0% sodium chloride, in which the drug was not precipitated, were inserted into the rectum without difficulty and leakage, and were retained in the rectum of rats for at least 6 hr. Furthermore, poloxamer gel gave significantly higher initial plasma concentrations and faster T_{max} of diclofenac sodium than did solid suppository, indicating that drug from poloxamer gel could be absorbed faster than that from solid one in rats. Thus, the thermosensitive poloxamer gel with sodium chloride and poloxamer was a more physically stable, convenient, and effective rectal dosage form for diclofenac sodium.

ACKNOWLEDGMENT

This work was supported by Korea Research Foundation Grant (KRF-2002-E00018).

REFERENCES

1. Choi, H.G.; Jung, J.H.; Ryu, J.M.; Yoon, S.J.; Oh, Y.K.; Kim, C.K. Development of in-situ gelling and mucoadhesive acetaminophen liquid suppository. Int. J. Pharm. **1998**, *165*, 33–44.
2. Huang, C.H.; Tokumura, T.; Machida, Y.; Nagai, T. Formulation of double-layered suppository for prolonged stay in lower rectum. Yakuzaigaku **1987**, *47*, 42–48.
3. Dumortier, G.; Zumer, M.; Courarraze, G.; Chaumeil, J.C.; Grossiord, J.L. Rheological study of a thermoreversible morphine gel. Drug Dev. Ind. Pharm. **1991**, *17*, 1255–1265.
4. Choi, H.G.; Kim, M.H.; Lee, M.K.; Kim, C.K. Effect of additives on the physicochemical properties of liquid suppository. Int. J. Pharm. **1999**, *190*, 13–19.
5. Yun, M.O.; Choi, H.G.; Jung, J.H.; Kim, C.K. Development of thermoreversible insulin liquid suppository with sodium salicylate. Int. J. Pharm. **1999**, *189*, 137–145.
6. Anderson, B.D.; Conradi, R.A. Predictive relationships in the water solubility of salts of a nonsteroidal anti-inflammatory drug. J. Pharm. Sci. **1985**, *74*, 815–820.
7. Iwata, M.; Takayama, K.; Takahashi, Y.; Obata, Y.; Machida, Y.; Nagai, T.; Shirotake, S. Effect of temperature on drug release and drug absorption in mixed type diclofenac sodium suppositories. Yakugaku Zasshi (Japan) **1999**, *119*, 170–177.
8. Schneeweis, A.; Muller-Goymann, C.C. In vivo and in vitro diclofenac sodium evaluation after rectal application of soft gelatine capsules enabling application induced transformation (AIT) into a semisolid system of liquid crystals (SSLC) for controlled release. Pharm. Res. **1997**, *14*, 1726–1729.
9. Nakanishi, K.; Masukawa, T.; Masada, M.; Nadai, T. Improvement of the rectal bioavailability of latamoxef sodium by adjuvants following administration of a suppository. Biol. Pharm. Bull. **1994**, *17*, 1496–1500.
10. Ramakrishna, S.; Fadnavis, N.W.; Diwan, P.V. Comparative pharmacokinetic evaluation of

compressed suppositories of diclofenac sodium in humans. Arzneimittelforschung **1996**, *46*, 175–177.
11. Miyazaki, S.; Nakamura, T.; Takada, M. Thermo-sensitive sol–gel transition of Pluronic F-127. Yakuzaigaku **1991**, *51*, 36–43.
12. Miyazaki, S.; Nakamura, T.; Yokouchi, C.; Tanaka, M. Effect of pluronic gels on the rectal absoption of indomethacin in rabbits. Chem. Pharm. Bull. **1987**, *35*, 1243–1248.
13. Miyazaki, S.; Suisha, F.; Kawasaki, N.; Shirakawa, M.; Yamatoya, K.; Attwood, D. Thermally reversible xyloglucan gels as vehicles for rectal drug delivery. J. Control. Rel. **1998**, *56*, 75–83.
14. Garcia, M.S.; Albero, M.I.; Sanchez-Pedreno, C.; Molina, J. Flow-injection spectrophotometric determination of diclofenac sodium in pharmaceuticals and urine samples. J. Pharm. Biomed. Anal. **1998**, *17* (2), 267–273.
15. Idkaidek, N.M.; Amidon, G.L.; Smith, D.E.; Najib, N.M.; Hassan, M.M. Determination of the population pharmacokinetic parameters of sustained-release and enteric-coated oral formulations, and the suppository formulation of diclofenac sodium by simultaneous data fitting using NONMEM. Biopharm. Drug Dispos. **1998**, *19* (3), 169–174.
16. Pinto Pereira, L.M.; Chen, D.; Clement, Y.; Simeon, D. Analgesic effects of diclofenac suppository and injection after preoperative administration. Int. J. Clin. Pharmacol. Res. **1999**, *19* (2), 47–51.
17. Choi, H.G.; Jung, J.H.; Yong, C.S.; Rhee, J.D.; Lee, M.K.; Han, J.H.; Park, K.M.; Kim, C.K. Formulation and in vivo evaluation of omeprazole buccal adhesive tablet. J. Control. Rel. **2000**, *68*, 405–412.
18. Choi, H.G.; Kim, C.K. Development of omeprazole buccal adhesive tablets with stability enhancement in human saliva. J. Control. Rel. **2000**, *68*, 397–404.
19. Robinson, S.S.; Robinson, J.R. Polymer structure features contributing to mucoadhesion. II. J. Control. Rel. **1990**, *12*, 187–194.
20. Robert, C.R.; Buri, P.A.; Peppas, N.A. Experimental method for bioadhesive testing of various polymers. Acta Pharm. Technol. **1988**, *34*, 95–98.
21. Kramaric, A.; Resman, A.; Kofler, B.; Zmitek, J. Thermoreversible Gel as a Liquid Pharmaceutical Carrier for a Galenic Formulation. European Patent 0551 626 (A1), 1992.