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Effect of sodium chloride on the gelation temperature, gel strength and bioadhesive force of poloxamer gels containing diclofenac sodium

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Abstract

Liquid suppository systems composed of poloxamers and bioadhesive polymers were easy to administer to the anus and mucoadhesive to the rectal tissues without leakage after the dose. However, a liquid suppository system containing diclofenac sodium could not be developed using bioadhesive polymers, since the drug was precipitated in this preparation. To develop a liquid suppository 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. The mixtures of P 407 (15%) and P 188 (15–20%) existed as a liquid at room temperature, but gelled at physiological temperature. Diclofenac sodium significantly increased the gelation temperature and weakened the gel strength and bioadhesive force, while sodium chloride did the opposite. Furthermore, the poloxamer gels with less than 1.0% of sodium chloride, in which the drug was not precipitated, were inserted into the rectum of rabbits without difficulty and leakage, and retained in the rectum of rats for at least 6 h. Our results suggested that a thermosensitive liquid suppository system with sodium chloride and poloxamers was a more physically stable and convenient rectal dosage form for diclofenac sodium.

Keywords: Diclofenac sodium; Sodium chloride; Poloxamer gel; Thermosensitive

1. Introduction

Ideal suppository would be easy to administer with good patient compliance and remain at the

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administered sites avoiding the first pass effect in the liver and gastrointestinal tracts. Conventional suppository is a solid dosage form that melts or softens in the rectum. Such a solid suppository can give a feeling of alien, discomfort and refusal to the patients, possibly lowering patient compliance. Furthermore, a solid 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).

In order to solve these problems, an attempt was recently made to develop a rectal dosage form termed 'thermosensitive liquid suppository' which existed as a liquid in vitro but a gel in vivo. As a base of liquid suppository, poloxamer, a copolymer of poly(oxyethylene)–poly(oxypropylene)–poly(oxyethylene), was used. Poloxamer solutions are known to exhibit the phenomenon of reverse thermal gelation, remaining as solutions at low temperatures and gelling upon increasing the temperature (Dumortier et al., 1991; Lenarets et al., 1987). Furthermore, the bioadhesive polymers such as carbopol, polycarbophil and sodium alginate were used to control the gel strength and bioadhesive force of liquid suppository (Choi et al., 1998; Yun et al., 1999). The thermosensitive liquid suppository was easy to administer to the anus, since it was a liquid at room temperature and turned into a gel at physiological temperature, and was also mucoadhesive to the rectal tissues without leakage after the dose (Choi et al., 1998; Yun et al., 1999). It showed the enhanced bioavailability of drugs such as acetaminophen (Choi et al., 1998) and insulin (Yun et al., 1999) with good safety in rats. However, in the development of liquid suppository 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 (Yun et al., 1999).

Thus, in this study, to develop a thermosensitive liquid suppository 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. Diclofenac sodium was selected here as a model drug, since it was poorly water-soluble and solubilized in aqueous medium by poloxamers (Anderson and Conradi, 1985; Iwata et al., 1999; Schneeweis and Muller-Goymann, 1997). Diclofenac sodium was precipitated in the liquid suppository systems composed of poloxamers and bioadhesive polymers. Moreover, it was applied to rectal suppository form due to its rapid absorption in the rectum (Nakanishi et al., 1994; Ramakrishna et al., 1996). Sodium chloride, a very water-soluble material, has been used to control the gel strength and bioadhesive force of diclofenac liquid suppository.

2. Materials and methods

2.1. 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.

2.2. Preparation of poloxamer gel containing diclofenac sodium

Various components such as sodium chloride and diclofenac sodium were dispersed or dissolved in distilled water at room temperature and the solution was cooled down to 4 °C. Poloxamer P 407 and P 188 were 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; Schmolka, 1972).

2.3. Measurement of gelation temperature

A 20 ml transparent vial containing a magnetic bar and 10 g of poloxamer gel was placed in a low-temperature thermostat water bath (Heto, Scandinavia). A digital thermosensor (Ika Labortechnik, RET digi-visc) connected to a ther-

mistor 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 (Choi et al., 1998; Miyazaki et al., 1991).

2.4. 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 apparatus for measuring gel strength (weight: 35 g) was then placed onto the poloxamer gel (Fig. 1). The gel strength, which means the viscosity of poloxamer gel at physiological temperature, was determined by the time (s) the apparatus took to sink 5 cm down through the poloxamer gel. In cases that it took more than 300 s to drop the apparatus into the gel, various weights were placed on the top of the apparatus, and the gel strength was described by the minimal weights that pushed the apparatus 5 cm down through the gel (Choi et al., 1998).

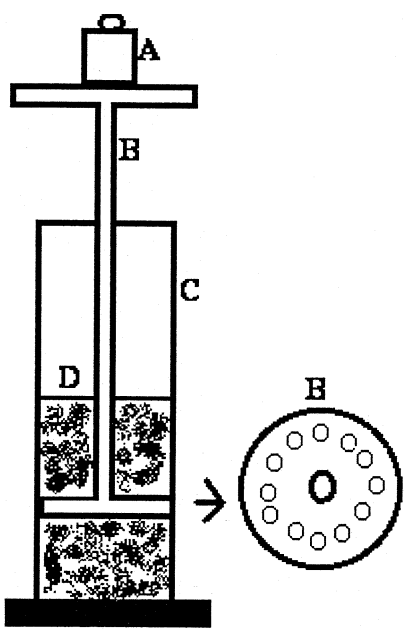

Fig. 1. Gel strength-measuring device, (A) weights; (B) device; (C) mess cylinder; (D) poloxamer gel.

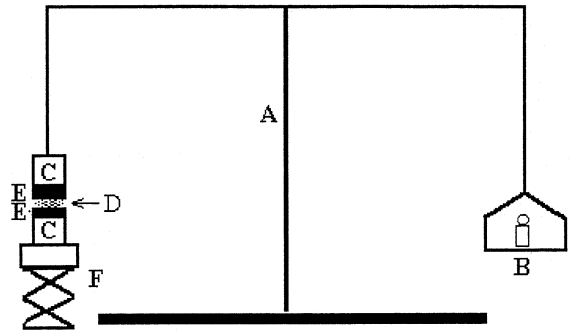

Fig. 2. Bioadhesive force-measuring device, (A) modified balance; (B) weights; (C) glass vial; (D) poloxamer gel; (E) rectal tissue; (F) height-adjustable pan.

2.5. Determination of bioadhesive force

The bioadhesive force of poloxamer gel was determined by using measuring device in Fig. 2. 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) 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 (Choi et al., 1998; Miyazaki et al., 1987, 1998).

2.6. Measurement of gel strength threshold in vivo

To measure the threshold of gel strength, poloxamer gel was administered at a dose of 1.5 g/kg into the rectum of a New Zealand white rabbit, which was captured in the frame and raised with 45° slope, through a stomach sondle needle fitted on a glass syringe without anesthetization. Each poloxamer gel was then evalu-

ated 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 during 30 min after administration. Thus, poloxamer gels with the gel strength between two thresholds were easily inserted into the anus and not leaked out after insertion (Choi et al., 1998).

2.7. Identification of poloxamer gel 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 gel 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 6 h after administration, the rectum was sectioned and the localization of poloxamer gel in the rectum was identified by the blue color (Choi et al., 1998).

3. Results and discussion

3.1. Gelation temperatures of poloxamer solutions

Gelation temperature is the temperature at which liquid phase makes transition to gel. Gelation temperature range suitable for liquid suppository would be 30–36 °C. If the gelation temperature of liquid suppository is lower than 30 °C, gelation occurs at room temperature leading to difficulty in administering. If the gelation temperature is higher than 36 °C, the suppository still stays as a liquid form at physiological temperature, resulting in leakage from the anus. Thus, liquid suppository must have the suitable gelation temperature, 30–36 °C, to be a liquid form at room temperature and to form a gel phase in the rectum (Choi et al., 1998; Miyazaki et al., 1998).

As bases of liquid suppository with the suitable gelation temperatures (30–36 °C), poloxamer P 407 and/or P 188 were selected due to their thermosensitive gelling properties (Miyazaki et al., 1987; Schmolka, 1985). Various mixtures of P 407 and P 188 gelled at the suitable gelation temperatures while solutions of each poloxamer alone did not gel at the desirable range (Table 1). Solutions of single poloxamer containing less than 16% of P 407 or less than 25% of P 188 did not form a gel over the temperature ranges tested. The gelation temperature of poloxamer solutions containing 18–25% of P 407 alone or 30% of P 188 was 13–25 °C and 48 °C, respectively. Our results indicated that P 407 or P 188 alone could not provide the suitable gelation temperature. In the cases of P 407 and P 188 mixtures, several formulations gelled at the physiological temperature. As the concentration of P 407 increased, the mixtures needed smaller amounts of P 188 to gel at the desirable gelation temperature. The w/w percentage ratios of P 407/P 188 with gelation tempera-

Table 1
Gelation temperatures of poloxamer solutions

Poloxamer	Concentration (%, w/w)	Gelation temperature (°C)
P 407	10	>50
	16	>50
	18	24.5 ± 0.1
	20	21.7 ± 0.2
	25	17.3 ± 0.3
	30	13.4 ± 0.5
P 188	20	>50
	25	>50
	30	48.1 ± 0.2
P 407/P 188	9/3	>50
	9/15	>50
	9/20	43.3 ± 0.2
	9/25	33.6 ± 0.1
	12/3	>50
	12/8	>50
	12/10	46.5 ± 0.5
	12/15	41.1 ± 0.4
	12/20	35.8 ± 0.5
	12/25	28.8 ± 0.2
	15/3	45.5 ± 0.2
	15/10	41.6 ± 0.3
	15/15	35.7 ± 0.3
	15/20	29.2 ± 0.5
	15/25	23.9 ± 0.5

Each value represents the mean $\pm$ S.E. ($n = 5$).

Table 2
Effect of diclofenac sodium on the physicochemical properties of poloxamer gels

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 (s)	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

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

ture in the range of 30–36 °C were 9/25%, 12/20% and 15/15–15/20%. Among these compositions, five formulations of P 407/P 188 mixtures (15/15–15/20%) were selected as the systems of choice for the liquid suppository, since they might give flexibility in formulation with other components.

The temperature-dependent gelation of poloxamer solutions could be explained by configuration change (Kramaric et al., 1992). 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.

3.2. Effect of diclofenac sodium and sodium chloride on the physicochemical properties of poloxamer gels

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. Diclofenac sodium was precipitated in the liquid suppository systems composed of 2.5% diclofenac sodium and more than 0.2% bioadhesive polymers such as carbopol, polycarbophil and sodium alginate (Choi et al., 1998). In this study, sodium chloride, instead of bioadhesive polymers, was used to prepare the diclofenac liquid suppository (Choi et al., 1999). Since sodium chloride was very water-soluble, the poloxamer gels containing diclofenac sodium were easier to prepare and the drug was not precipitated in the poloxamer gels.

3.2.1. 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), respectively, and then the physicochemical properties such as gelation temperature, gel strength and bioadhesive force of poloxamer gels were evaluated (Table 2). Diclofenac sodium markedly increased the gelation temperature of poloxamer solutions. In the presence of diclofenac sodium, the gelation temperature of 15/15 markedly increased from 35.7 to 46.0 °C. Similarly, the gelation temperature of 15/20 increased from 29.2 to 37.5 °C. Such a gelation temperature enhancing effect of diclofenac sodium was consistently observed as the content of P 188 changed from 15 to 20% in the P 407/P 188 mixtures (Fig. 3).

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. 4). Sodium chloride decreased the gelation temperatures in the absence of diclofenac sodium, whereas in the presence of diclofenac sodium, such impacts were increased. 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, 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. Given that the gelation temperature range for liquid suppository with a liquid form at room temperature and a gel phase in the rectum was 30–36 °C (Fig. 4), it appeared to be possible to prepare the diclofenac liquid suppository with suitable gelation temperature by adjusting the contents of sodium chloride from 0.2 to 1.0% (Choi et al., 1999).

To select the optimal formulations suitable for diclofenac liquid suppository system, 0.2–1.0% sodium chloride were added to the five poloxamer gels [diclofenac sodium/P 407/P 188 (2.5/15/15%)], [(2.5/15/17%)], [(2.5/15/18%)], [(2.5/15/19%)] and [(2.5/15/20%)], respectively. Then, the physicochemical properties such as gelation temperature, gel strength and bioadhesive force of poloxamer gels were evaluated.

The gelation temperatures of poloxamer gels were also affected by the compositions of poloxamers and the concentrations of sodium chloride (Fig. 5). In the poloxamer gels, sodium chloride abruptly decreased the gelation temperature as the concentration increased from 0 to 1.0%. The more

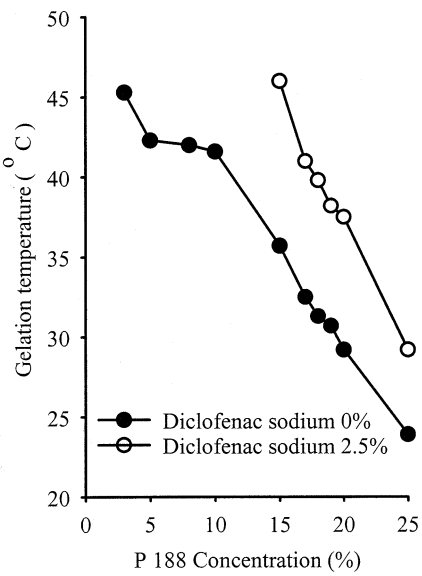

Fig. 3. Gelation temperatures of P 407 and P 188 mixtures. In all mixtures, the concentration of P 407 was fixed as 15% and the concentrations of P 188 varied from 2.5 to 25%. Diclofenac sodium was added to the mixtures of poloxamer composed of P 188 (15–25%) and P 407 (15%). Each value represents the mean ± S.E. ($n = 5$).

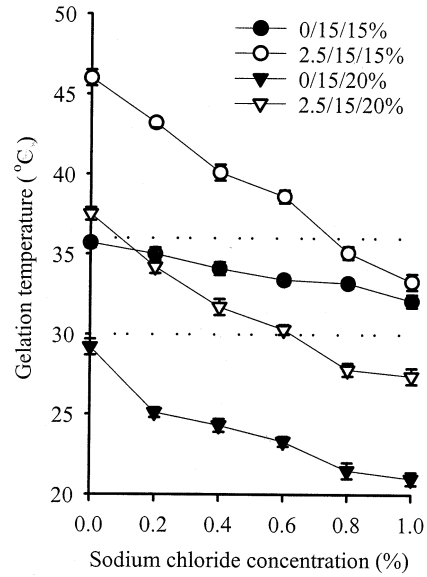

Fig. 4. Effect of diclofenac sodium and sodium chloride on the gelation temperature of poloxamer mixtures. Diclofenac sodium (2.5%) and 0.2–1.0% of sodium chloride were added to the poloxamer mixtures composed of P 407/P 188 (15/15%) and (15/20%), respectively. Each value represents the mean ± S.E. ($n = 5$).

increased the concentration of P 188, the lower the gelation temperature of poloxamer gels. Fig. 5 and Table 3 illustrated that among the poloxamer gels tested, thirteen formulations including [diclofenac sodium/P 407/P 188/sodium chloride (2.5/15/17/0.8%)] had the suitable gelation temperature, 30–36 °C.

3.2.2. Gel strength

In the development of liquid suppository, the gel strength is important in finding the condition, which allows the easy insertion of the suppository and no leakage from the anus. Thus, the ranges of gel strength suitable for liquid suppository system were investigated by inserting poloxamer gels into the anus of a rabbit and observing any leakage after insertion. 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 poloxamer gels with sodium chloride, the range was 10–50 s (Choi et al., 1998).

Diclofenac sodium reduced the gel strength of poloxamer gels (Table 2, Fig. 6). 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. 6). Sodium chloride increased the gel strength in the absence of diclofenac sodium, whereas in the presence of diclofenac sodium, such impacts were increased. Similar phenomena were observed in 15/15 and 15/20. With the addition of 1.0% sodium chloride, the gel strength of 15/15 increased from 4 to 271 s in the absence of diclofenac sodium, while the gel strength increased from 3 to 11 s in the presence of diclofenac sodium. In 15/20 poloxamer mixture, the gel strength increased from 58 to 275 s (650 g) with the addition of 1.0% sodium chloride, whereas it increased from 14 to 264 s in the presence of diclofenac sodium. Given that the gel strength thresholds for liquid suppository with easy insertion and no leakage was 10-50 s, it appeared to be possible to prepare diclofenac liquid suppository with suitable gel strength by adjusting the contents of sodium chloride from 0.2 to 1.0% (Choi et al., 1999).

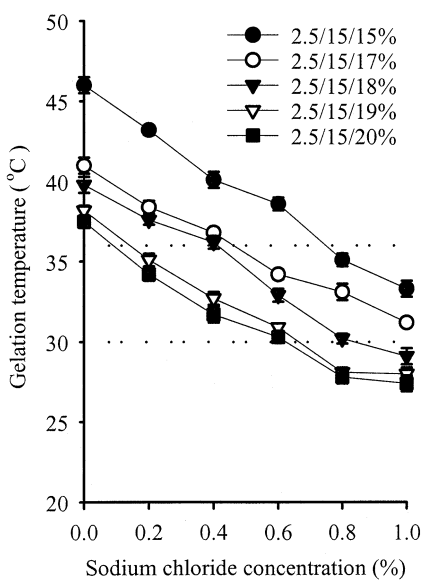

Fig. 5. Effect of sodium chloride contents on the gelation temperature of poloxamer gels. Sodium chloride (0.2–1.0%) were added to the poloxamer gels composed of diclofenac sodium/P 407/P 188 (2.5/15/15%), (2.5/15/17%), (2.5/15/18%), (2.5/15/19%) and (2.5/15/20%), respectively. Each value represents the mean ± S.E. ($n = 5$).

The gel strength of poloxamer gels was also affected by the compositions of poloxamers and the concentrations of sodium chloride (Fig. 7). In the poloxamer gels [diclofenac sodium/P 407/P 188 (2.5/15/17%)], [(2.5/15/18%)], [(2.5/15/19%)] and [(2.5/15/20%)], sodium chloride abruptly increased the gel strength as the concentration increased from 0 to 1.0%. However, in the poloxamer gel [diclofenac sodium/P 407/P 188 (2.5/15/15%)], sodium chloride gently increased the gel strength as the concentration increased. The more increased the concentration of P 188, the greater the gel strength of poloxamer gels. Fig. 7 and Table 3 illustrated that among the poloxamer gels tested, 12 formulations including [diclofenac sodium/P 407/P 188/sodium chloride (2.5/15/17/0.8%)] had the suitable gel strength, 10–50 s.

3.2.3. Bioadhesive force

Bioadhesive force means the force with which liquid suppository 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 (Choi and Kim, 2000). The stronger the bioadhesive force is, the more it can prevent the gelled suppository 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 (Choi et al., 2000; Robert et al., 1988). Therefore, liquid suppository must have the balanced bioadhesive force.

Diclofenac sodium decreased the bioadhesive force of poloxamer gels. In the presence of diclofenac sodium, the bioadhesive force of 15/15 and 15/20 was reduced from 6.8 to 3.2×10^2 dyne/cm^2 and from 97.3 to 38.8×10^2 dyne/cm^2, respectively (Table 2). Diclofenac sodium also significantly decreased the bioadhesive force of poloxamer gels containing sodium chloride.

Table 3
Physicochemical properties of poloxamer gels containing diclofenac sodium

P 407/P 188	Sodium chloride	Gelation temperature	Gel strength	Bioadhesive force
15/15	0	No[a]	No[c]	No[e]
	0.2	No	No	Yes[f]
	0.4	No[b]	No	Yes
	0.6	No	No	Yes
	0.8	Yes[b]	No	Yes
	1.0	Yes	Yes[d]	Yes
15/17	0	No	No	No
	0.2	No	No	Yes
	0.4	No	Yes	Yes
	0.6	Yes	Yes	Yes
	0.8	Yes	Yes	Yes
	1.0	No	Yes	Yes
15/18	0	No	No	No
	0.2	No	Yes	Yes
	0.4	No	Yes	Yes
	0.6	Yes	Yes	Yes
	0.8	Yes	No	Yes
	1.0	Yes	No	Yes
15/19	0	No	Yes	No
	0.2	Yes	Yes	Yes
	0.4	Yes	Yes	Yes
	0.6	Yes	Yes	Yes
	0.8	No	No	Yes
	1.0	No	No	Yes
15/20	0	No	Yes	No
	0.2	Yes	Yes	Yes
	0.4	Yes	Yes	Yes
	0.6	Yes	Yes	Yes
	0.8	No	No	Yes
	1.0	No	No	Yes

[a] The gelation temperature of poloxamer gel was less than 30 °C or more than 36 °C.
[b] The gelation temperature of poloxamer gel was 30–36 °C.
[c] The gel strength of poloxamer gel was less than 10 s or more than 50 s.
[d] The gel strength of poloxamer gel was 10–50 s.
[e] The bioadhesive force of poloxamer gel without sodium chloride.
[f] The bioadhesive force of poloxamer gel was more than that of poloxamer gel without 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 bioadhesive force of 6.8 and 97.3×102 dyne/cm^2, respectively. Our results suggested that the poloxamers with hydrophilic oxide group could bind to oligosaccharide chains, resulting in moderate bioadhesive forces (Choi et al., 1998).

Sodium chloride, which enhanced gel strength, efficiently increased the bioadhesive force (Fig. 8). 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 increased 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. 8). 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 the gradual decrease of bioadhesive forces with increasing concentrations of sodium chloride. Similar phenomena were observed in 15/20.

The bioadhesive forces of poloxamer gels were affected by the compositions of poloxamers and the concentrations of sodium chloride (Fig. 9). In all poloxamer gels, sodium chloride abruptly increased the bioadhesive forces as the concentration increased from 0 to 1.0%. The more increased the concentration of P 188, the greater the bioadhesive forces of poloxamer gels. Fig. 9 illustrated that the diclofenac liquid suppositories with sodium chloride had the stronger bioadhesive forces than did those without sodium chloride (Table 3).

From these findings, among the poloxamer gels tested, 10 formulations including [diclofenac sodium/P 407/P 188/sodium chloride (2.5/15/17/0.8%)] had the gelation temperature, gel strength and bioadhesive force suitable for liquid suppository system (Table 3).

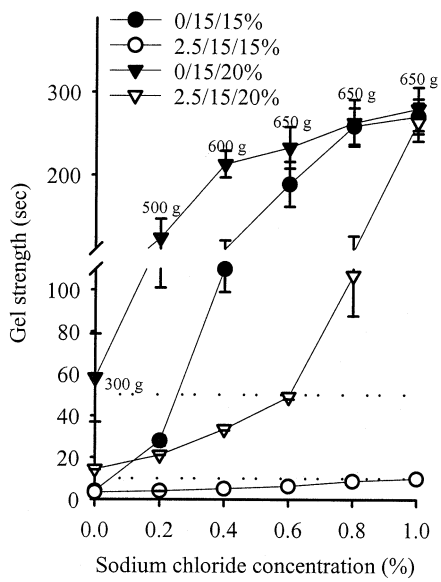

Fig. 6. Effect of diclofenac sodium and sodium chloride on the gel strength of poloxamer mixtures. Diclofenac sodium (2.5%) and 0.2–1.0% of sodium chloride were added to the poloxamer mixtures composed of P 407/P 188 (15/15%) and (15/20%), respectively. Each value represents the mean ± S.E. ($n = 5$). *Gels composed of 15/20 without diclofenac sodium were so strong that the apparatus could not move down within 300 s.

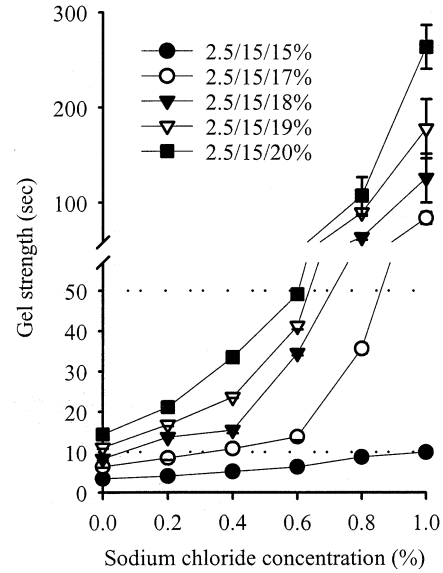

Fig. 7. Effect of sodium chloride contents on the gel strength of poloxamer gels. Sodium chloride (0.2–1.0%) were added to the poloxamer gels composed of diclofenac sodium/P 407/P 188 (2.5/15/15%), (2.5/15/17%), (2.5/15/18%), (2.5/15/19%) and (2.5/15/20%), respectively. Each value represents the mean ± S.E. ($n = 5$).

3.3. In vivo retention of poloxamer gel in the rectum

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 (Yun et al., 1999). At 6 h 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. The 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 h.

Our results indicated that diclofenac sodium increased the gelation temperature of poloxamer

solutions, while decreasing the gel strength of poloxamer gels. 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 inserting diclofenac sodium in the poloxamer gel (Choi et al., 1998, 1999). 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 (Choi et al., 1999).

Additionally, diclofenac sodium weakened the bioadhesive force of poloxamer gels, while sodium chloride reinforced. Poloxamer gels composed of only P 407 and P 188 had the moderate bioadhesive forces, since the poloxamer with hydrophilic oxide group could bind to oligosaccharide chains (Choi et al., 1998). However, sodium chloride and diclofenac sodium had no capacity of binding to them. The bioadhesive force-weakening effect of diclofenac sodium seemed to be due to its gel strength-weakening effect of poloxamer gel, resulting in the weaker binding of poloxamer gels with the oligosaccharide chains of rectal mucous membranes. Similarly, sodium chloride could reinforce the gel strength of cross-linked reticular poloxamer gel, resulting in the more increased binding of poloxamer gels with them (Choi et al., 1998; Yun et al., 1999). It indicated that the gel strength of poloxamer gel seemed to play a role in affecting the bioadhesive force of poloxamer-based liquid suppository.

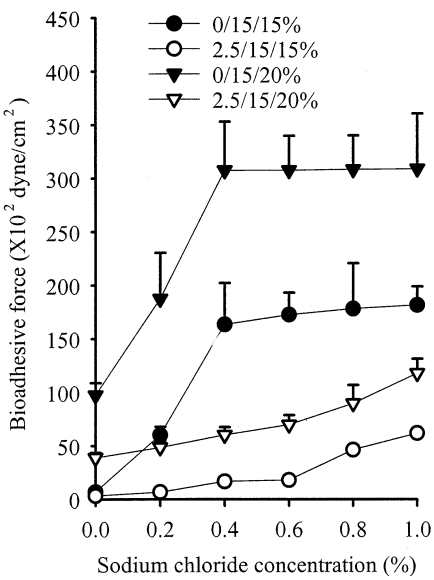

Fig. 8. Effect of diclofenac sodium and sodium chloride on the bioadhesive force of poloxamer mixtures. Diclofenac sodium (2.5%) and 0.2–1.0% of sodium chloride were added to the poloxamer mixtures composed of P 407/P 188 (15/15%) and (15/20%), respectively. Each value represents the mean ± S.E. ($n = 5$).

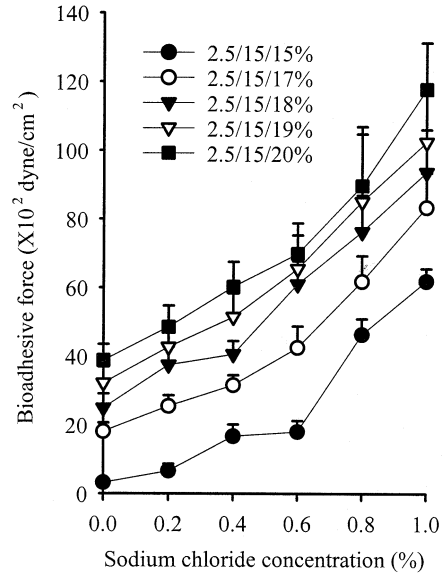

Fig. 9. Effect of sodium chloride contents on the bioadhesive force of poloxamer gels. Sodium chloride (0.2–1.0%) were added to the poloxamer gels composed of diclofenac sodium/P 407/P 188 (2.5/15/15%), (2.5/15/17%), (2.5/15/18%), (2.5/15/19%) and (2.5/15/20%), respectively. Each value represents the mean ± S.E. ($n = 5$).

4. Conclusion

Taken together, it is concluded that the mixtures of P 407/P 188 (15/15–15/20%) were the optimal systems which had the gelation temperature suitable for liquid suppository system. The diclofenac liquid suppository with less than 1.0% of sodium chloride, in which the drug was not

precipitated, were inserted into the rectum of rabbit without difficulty and leakage and retained in the rectum of rats for at least 6 h. Thus, the thermosensitive liquid suppository system with sodium chloride and poloxamer was a more physically stable and convenient rectal dosage form for diclofenac sodium. The further study on the dissolution, phamacokinetics and morphology of diclofenac sodium-containing poloxamer gel in rats will be performed.

Acknowledgements

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