ELSEVIER

International Journal of Pharmaceutics 165 (1998) 33–44

international journal of pharmaceutics

Development of in situ-gelling and mucoadhesive acetaminophen liquid suppository

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Received 17 April 1997; received in revised form 13 November 1997; accepted 17 November 1997

Abstract

Conventional suppositories are solid forms which often cause discomfort during insertion. The leakage of suppositories from the rectum also gives uncomfortable feelings to the patients. In addition, when the solid suppositories without mucoadhesivity reach the end of the colon, the drugs can undergo the first-pass effect. To solve these problems, we developed a novel in situ-gelling and mucoadhesive acetaminophen liquid suppository with gelation temperature at 30–36°C and suitable gel strength and bioadhesive force. Poloxamer 407 (P407) or/and poloxamer 188 (P188) were used to confer the temperature-sensitive gelation property. The mixtures of P407 (15%) and P188 (15–20%) existed as a liquid at room temperature, but gelled at 30–36°C. Acetaminophen, the active ingredient of the suppositories, slightly increased gelation temperature, but significantly decreased gel strength and bioadhesive force. To modulate the gel strength and the bioadhesive force of acetaminophen liquid suppositories, bioadhesive polymers such as polyvinylpyrrolidone (PVP), hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), carbopol and polycarbophil were studied. The bioadhesive polymers exerted various impacts on the physicochemical properties of liquid suppositories. The gelation temperature was not significantly affected by PVP, HPMC and HPC, but decreased by carbopol and polycarbophil. Of bioadhesive polymers, carbopol and polycarbophil most significantly enhanced both gel strength and bioadhesive force. The liquid suppositories with carbopol or polycarbophil were inserted into the rectum of rats without difficulty and leakage and retained in the rectum for at least 6 h. These results suggest that in situ-gelling and mucoadhesive liquid suppository for humans can be further developed as a more convenient and effective rectal dosage form.

Keywords: Liquid suppository; In situ-gelling; Mucoadhesive; Poloxamer; Acetaminophen

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0378-5173/98/$19.00
PII S0378-5173(97)00386-4

1. Introduction

A conventional suppository is a medicated solid dosage form which melts or softens at body temperature. It is a favorable dosage form for infants, children and unconscious patients. One major advantage of suppositories over other oral dosage forms is that the drugs given by suppositories do not undergo the first pass effect in the gastrointestinal tracts and the liver. Moreover, the suppositories are less painful and more acceptable than injection forms. Due to these merits, suppositories have been widely applied to anti-inflammatory analgesics, anti-hemorrhoids and analgesics. However, the conventional solid type suppositories often give the patients a feeling of alien, discomfort and refusal. Furthermore, if the solid suppositories without mucoadhesivity reach the end of colon, the drugs delivered by the suppositories might undergo the first-pass effect (Huang et al., 1987). From an industrial viewpoint, solid suppositories are inconvenient to manufacture and handle since a heating process is required for melting the suppositories and filling them in a vessel. The vessel needs to be packaged together to maintain the shape of suppositories until administration.

To solve the problems of conventional solid suppositories, it would be desirable to develop a liquid suppository which: (1) forms a gel at body temperature; (2) has a suitable gel strength not to be leaked out from the anus after administration; and (3) has a suitable bioadhesive force so as not to reach the end of the colon. As a base of liquid suppositories, poloxamer as a surfactant, copolymer of poly(oxyethylene)-poly(oxypropylene)-poly(oxyethylene), has been studied. Poloxamer solutions are known to exhibit the phenomenon of reverse thermal gelation; remaining as solutions at low temperature and gelling when temperature increases. Furthermore, poloxamers were reported not to cause any damage on mucosal membranes (Lenaerts et al., 1987; Dumortier et al., 1991). There have been several attempts to modulate the gelation temperature of poloxamer-based liquids. The gelation temperature of poloxamer solutions was adjusted by modifying cross-linking agents and monomers (Schmolka, 1973; Holsman et al., 1984; Blackman and Ralske, 1989), by mixing the different series of poloxamers (Abhaham, 1994), by changing the weight of poloxamers (Schmolka, 1985), or by changing the pH and the ionic strength (Gilbert et al., 1987). However, most previous studies have been focused on modulating only the gelation temperatures of poloxamer solutions. There has been a lack of knowledge on the strength and the bioadhesive force of gelled poloxamers, although these two factors are crucial in designing desirable liquid suppositories which do not leak out from the anus and do not reach the end of the colon after administration.

In this study, we developed not only temperature-sensitive but also mucoadhesive liquid suppositories containing acetaminophen using poloxamers and bioadhesive polymers. Acetaminophen was selected here as a model drug, since it has been applied to many conventional suppository forms due to its rapid absorption in the rectum (Lowenthal et al., 1970; Sidman et al., 1980). To develop poloxamer-based liquid suppositories which gel at the physiological temperature without leakage after administration and remain mucoadhesive to the rectal mucous lining, gelation temperature, gel strength and bioadhesive forces of various formulations composed of poloxamers and bioadhesive polymers were investigated.

2. Materials and methods

2.1. Materials

Poloxamers (Pluronic series) and polyvinylpyrrolidone (PVP, K-25) were purchased from BASF (Ludwigshafen, Germany). Carbopol (934P) and polycarbophil were supplied from BF Goodrich (Breesville, OH). Hydroxypropylcellulose (HPC, H-20) and hydroxypropylmethylcellulose (HPMC, 2208, 4000 cps) were from Shinetsu (Tokyo, Japan). Acetaminophen was of USP grade.

2.2. Preparation of liquid suppository

Various amounts of excipients except poloxamer were completely dispersed in distilled water with continuous agitation at room temperature

and cooled down to 4°C. Poloxamer was then slowly added to the solution with continuous agitation. The liquid suppository was left at 4°C until a clear solution was obtained.

2.3. Measurement of gelation temperature

A 20-ml transparent vial containing a magnetic bar and 10 g of poloxamer solution 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 solution. Poloxamer solution was heated at a constant rate with constant stirring. When the magnetic bar stopped moving due to gelation, the temperature displayed on the thermistor was determined as a gelation temperature (Miyazaki et al., 1991).

2.4. Measurement of gel strength

Poloxamer solution (50 g) was put in a 100 ml-mass cylinder and gelled in a thermostat at 36.5°C. The apparatus for measuring gel strength (weight: 35 g) was then placed onto the gelled poloxamer. The gel strength was determined by the time(s) it took to move the apparatus 5 cm down through the poloxamer gel (Schmolka, 1972). In cases that took more than 10 min to drop the apparatus into the gel, various weights were placed on top of the apparatus and gel strength was described by the minimal weights that pushed the apparatus 5 cm down through the gel.

2.5. Determination of bioadhesive force

A section of tissue was cut from the fundus of the rabbit rectum and secured with mucosal side out on to each glass vial 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 was connected to the balance and the other vial was placed on a height-adjustable pan (Fig. 1). Poloxamer gels were added onto the rectal tissue on the other vial. Then, the heights of the other vial was adjusted so that the gel could be placed between the mucosal tissues of both vials. The weights of the apparatus were kept raised until two vials became separated. Bioadhesive force, the detachment stress (dyne/cm^2), was determined from the minimal weights that detached two vials (Ch'ng et al., 1985; Lehr et al., 1990). The rectal tissue pieces were changed for each tensile measurement.

2.6. Measurement of gel strength threshold in vivo

To measure the threshold of gel strength, gelled poloxamer was administered at a dose of 1.5 g/kg into the rectum of a New Zealand white rabbit raised at a 45° slope through a stomach sonde needle fitted on a glass syringe. Each poloxamer gel formulation was then evaluated by the difficulty of insertion into 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

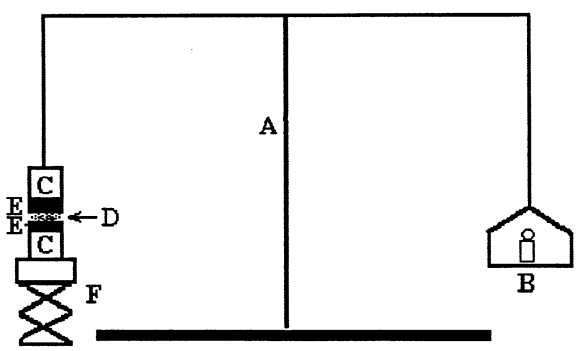

Fig. 1. Bioadhesive force-measuring device: (A) modified balance; (B) weights; (C) glass vial; (D) poloxamer gel; (E) rectal tissue; (F) height-adjustable pan. A section of rabbit rectal tissue was placed onto each glass vial using a rubber band and an aluminum cap. One glass vial with a section of tissue (E) was connected to the balance and the other vial was placed on a height-adjustable pan and added with 0.15 g of gelled poloxamer. The height of the other vial was adjusted so that the gel could adhere to the tissue of the upper glass vial. The weights (B) kept raised until two vials were separated. Bioadhesive force, detachment stress (dyne/cm^2), was determined from the minimal weights that separated the two vials.

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 did not leak out after insertion.

2.7. Identification of liquid suppository localization in vivo

Male, Sprague-Dawley rats weighing 250 ± 20 g, were fasted for 24–36 h prior to the experiments but were allowed free access to water. Liquid suppository with 0.1% blue lake was administered at a dose of 1.5 g/kg into the rectum 4 cm above the anus using a stomach sonde needle. At 5 min and 6 h after administration, the rectum was sectioned and the localization of liquid suppository in the rectum was identified by the blue color.

3. Results and discussion

3.1. Gelation temperatures of poloxamer solutions

Gelation temperature is the temperature at which the liquid phase makes a transition to gel. A 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 manufacturing, handling and administering. If the gelation temperature is higher than 36°C, the suppository still stays as a liquid at body temperature, resulting in leakage from the anus. Therefore, 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 instantly in the rectum.

As bases of liquid suppository with the suitable gelation temperatures (30–36°C), poloxamer 407 (P407) and/or poloxamer 188 (P188) were selected due to their thermo-sensitive gelling properties. In addition, P407 and P188 are known to have low toxicity, less skin irritation, excellent water-solubility, high solubilizing capacity for acetaminophen, good drug release characteristics and compatibility with other chemicals.

Table 1
Gelation temperatures of poloxamer solutions

Poloxamer	Concentration (%, w/w)	Gelation temperature (°C)[a]
P407	10	>50
	16	>50
	18	24.5 ± 0.1
	20	21.7 ± 0.2
	25	17.3 ± 0.3
	30	13.4 ± 0.5
P188	20	>50
	25	>50
	30	48.1 ± 0.2
P407/P188	9/3	>50
	9/10	>50
	9/15	>50
	9/20	43.3 ± 0.2
	9/25	33.6 ± 0.1
	12/3	>50
	12/5	>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
	15/5	42.3 ± 0.3
	15/8	42.0 ± 0.4
	15/10	41.6 ± 0.3
	15/15	35.7 ± 0.3
	15/20	29.2 ± 0.5
	15/25	23.9 ± 0.5

[a] Each value represents the mean $\pm$ S.E. of five experiments.

Various mixtures of poloxamers P407 and P188 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 P407 or less than 25% of P188 did not form a gel over the temperature ranges tested. The gelation temperatures of poloxamer solutions containing 18–25% of P407 alone or 30% of P188 were 13–25°C and 48°C, respectively. This indicates that P407 or P188 alone could not provide the suitable gelation temperature. In cases of P407 and P188 mixtures, several formulations gelled at the body temperature. As the concentration of P407 increased, the mixtures needed smaller amounts of P188 to gel at the desirable gelation temperature. The w/w per-

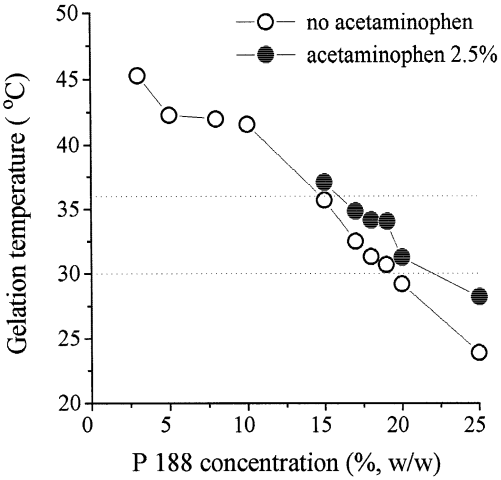

Fig. 2. Gelation temperatures of P407 and P188 mixtures. In all mixtures, the concentration of P407 was fixed as 15% and the concentrations of P188 varied from 3.0 to 25%. Acetaminophen was added to the mixtures of poloxamer composed of P188 (15–25%) and P407 (15%). Each point represents the average of three separate experiments.

centage ratios of P407/P188 with a gelation temperature in the range of 30–36°C were 9/25, 12/20 and 15/15–15/20. Among these compositions, five formulations of P407/P188 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 (Schick, 1966; 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 acetaminophen and bioadhesive polymers on the physicochemical properties of liquid suppository

Since acetaminophen is the active material of the poloxamer-based suppository, the effect of acetaminophen on the physicochemical characteristics of the liquid suppositories should be studied. Throughout the experiments, the concentration of acetaminophen was fixed as 2.5%, the usual content of acetaminophen in rectal dosage forms.

To reinforce the gel strength and bioadhesive force of the liquid suppositories, the poloxamer solutions was added with bioadhesive polymers. PVP, HPMC, HPC, carbopol and polycarbophil were selected as the bioadhesive polymers. These bioadhesive polymers are water-soluble or swellable, but different in their nature and charges. PVP is cationic and soluble in water. HPC, a cellulose derivative, is neutral and soluble in water. HPMC, cellulose derivatives, is neutral and swelling in water. Carbopol 934P, a polyacrylic acid derivative polymerized without cross-linking agent, is anionic and water-swellable. Polycarbophil, a polyacrylic acid derivative polymerized with a cross-linking agent, is also anionic and swelling in water. Polycarbophil and carbopol are known to be excellent bioadhesive polymers (Robinson and Robinson, 1990). For the selection of bioadhesive polymer suitable for liquid suppository, we studied the effect of each bioadhesive polymer on the physicochemical characteristics of the liquid suppositories with or without acetaminophen.

Table 2
Effect of acetaminophen on the physicochemical properties of poloxamer system[a]

P407/P188	15/15		15/20	
	Acetaminophen (0%)	Acetaminophen (2.5%)	Acetaminophen (0%)	Acetaminophen (2.5%)
Gelation temperature (°C)	35.7 ± 0.3	37.0 ± 0.3	29.2 ± 0.5	31.2 ± 0.3
Gel strength (s)	4.03 ± 0.2	2.72 ± 0.2	>300	11.1 ± 0.7
Bioadhesive force (dyne/cm^2 × x10^2)	6.8 ± 2.4	3.2 ± 1.3	97.3 ± 11.4	11.1 ± 1.5

[a] Each value represents the mean ± S.E. of five experiments.

3.2.1. Gelation temperature

Acetaminophen slightly increased the gelation temperature of poloxamer solutions (Fig. 2, Table 2). In the presence of acetaminophen, the gelation temperature of P407/P188 (15/15%) (abbreviated as 15/15) slightly increased from 35.7 to 37.0°C. Similarly, the gelation temperature of P407/P188 (15/20%) (abbreviated as 15/20) increased from 29.2 to 31.2°C. Such a gelation temperature-enhancing effect of acetaminophen was consistently observed as the content of P188 changed from 15 to 20% in the P407/P188 mixtures (Fig. 2).

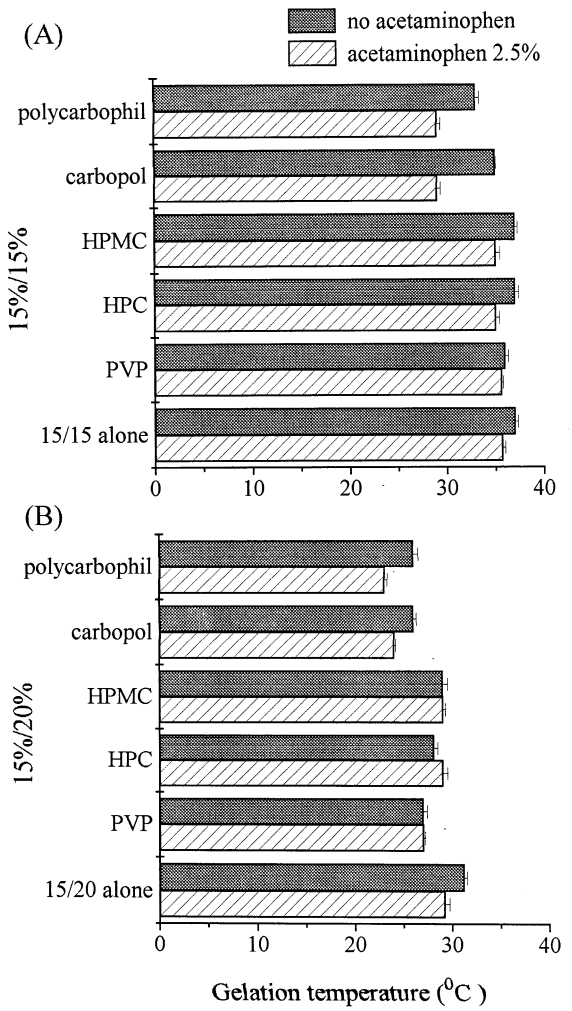

Fig. 3. Effect of acetaminophen and bioadhesive polymers on the gelation temperature of poloxamer mixtures. Acetaminophen (2.5%) was added to the mixtures of P407/P188; 15/15 (A) and 15/20 (B). The concentration of bioadhesive polymers was 1%. Each bar represents the average of more than three separate experiments.

The impact of bioadhesive polymers on the gelation temperatures depended on the nature of bioadhesive polymers and on the presence of acetaminophen in the formulations (Fig. 3). Of bioadhesive polymers, PVP, HPMC and HPC did not significantly affect the gelation temperature regardless of acetaminophen. However, carbopol and polycarbophil decreased the gelation temperatures in the absence of acetaminophen, whereas, in the presence of acetaminophen, such impacts were diminished. Similar phenomena were observed in 15/15 and 15/20. With the addition of 1% of carbopol or polycarbophil, the gelation temperature of 15/15 decreased by 7°C in the absence of acetaminophen, while the gelation temperature decreased by 2–4°C in the presence of acetaminophen. In 15/20 poloxamer mixture, the gelation temperature decreased by 5–6°C with the addition of 1% of carbopol or polycarbophil, whereas, it decreased by 3°C in the presence of acetaminophen. It appears that the smaller impact of carbopol and polycarbophil on the gelation temperature in the presence of acetaminophen is contributed by the gelation temperature-enhancing effect of acetaminophen.

The gelation temperatures of poloxamer solutions were also affected by the compositions of poloxamers and the concentrations of the bioadhesive polymers (Fig. 4). In 15/15 poloxamer mixtures, carbopol and polycarbophil did not significantly affect the gelation temperature at the lower concentrations (0.2–0.6%), while they abruptly decreased the gelation temperature as the concentration increased from 0.6 to 0.8%. Unlike 15/15, 15/20 showed gradual decrease of gelation temperature with increasing concentrations of carbopol and polycarbophil.

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 suppositories and no leakage from the anus. Thus, the ranges of gel strength suitable for poloxamer gel were investigated by inserting poloxamer gels into

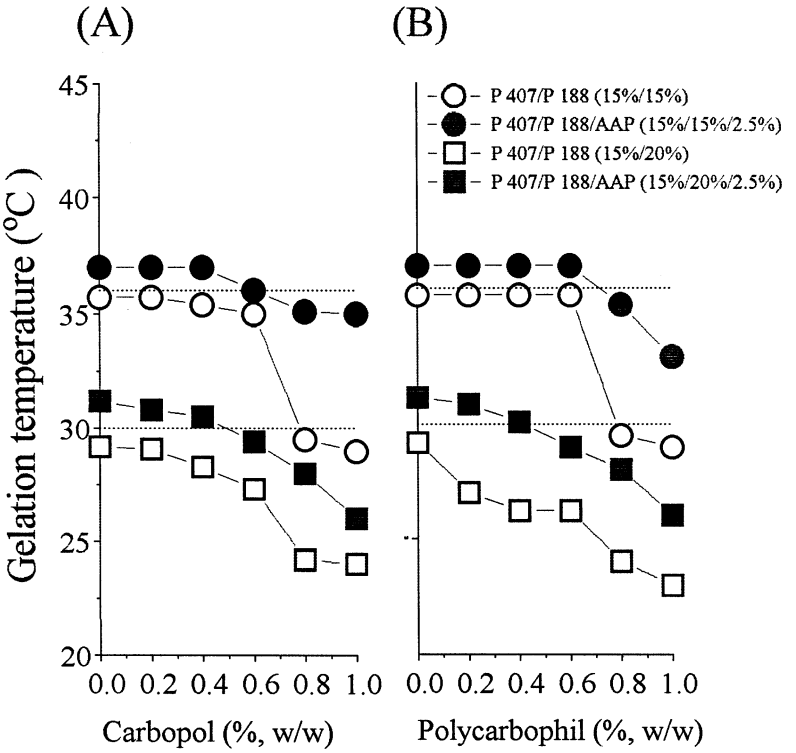

Fig. 4. Effect of carbopol and polycarbophil contents on the gelation temperature. The gelation temperature of poloxamer was measured in various concentrations of carbopol (A) and polycarbophil (B). Poloxamer compositions of P407/P188 were 15/15 and 15/20. The concentration of acetaminophen (AAP) was 2.5%. Each point represents the average of three separate experiments.

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 the gel strength, it was difficult to insert the suppositories. Under the lower limits, the suppositories leaked out from the anus. The threshold ranges differed between gels containing various bioadhesive polymers. In the gels with PVP, HPMC or HPC, the threshold range was 15–50 s, while in the gels with carbopol or polycarbophil, the range was 10–50 s. The broader threshold range of liquid suppositories containing carbopol or polycarbophil (10–50 s) than those with PVP, HPMC or HPC (15–50 s) appears to be due to the stronger bioadhesive force of carbopol and polycarbophil than the other polymers.

Acetaminophen reduced the strength of the poloxamer gels (Table 2) and also affected the strength of the poloxamer gels containing various bioadhesive polymers. The gel strength-reducing effect of acetaminophen depended on the nature of bioadhesive polymers and the composition of poloxamer gels. In 15/15 poloxamer mixtures, acetaminophen did not alter the strength of the gels with PVP, HPC or HPMC, but greatly reduced the strength of gels containing carbopol or polycarbophil (Fig. 5A). In the presence of acetaminophen, the gel strength of 15/15 with carbopol or polycarbophil diminished from 120 to 20 s and 130 to 27 s, respectively. In 15/20 poloxamer mixtures, acetaminophen reduced the strength of all the gels regardless of bioadhesive polymers (Fig. 5B). Gel strengths of 15/20 gels without acetaminophen were higher than 300 s. When acetaminophen was added to 15/20 gels, the strengths of gels significantly decreased.

Carbopol and polycarbophil enhanced the gel strength much higher than other bioadhesive polymers. Either in 15/15 or in 15/20, gels containing carbopol or polycarbophil showed higher

strengths than did those with PVP, HPC or HPMC (Fig. 5). It needs to be noted that carbopol and polycarbophil enhanced the gel strength to a similar extent in 15/15, but carbopol increased the gel strength about 1.8-fold higher than that of polycarbophil in 15/20 gel with acetaminophen.

Carbopol and polycarbophil reinforced the gel strength in proportion to their concentrations although their impacts on the gel strength became smaller in acetaminophen-containing gels. In the presence of carbopol and acetaminophen, the gel strengths of 15/15 and 15/20 ranged from 3.9 to 14 s and 10 to 240 s, respectively (Fig. 6A). In polycarbophil-containing acetaminophen gels, the gel strength ranges from 15/15 and 15/20 were 3.0–28 s and 10–110 s, respectively (Fig. 6B). Given that the gel strength thresholds for liquid suppository with easy insertion and no leakage was 10–50 s, it appears to be possible to prepare acetaminophen liquid suppository with suitable gel strength by adjusting the contents of carbopol or polycarbophil.

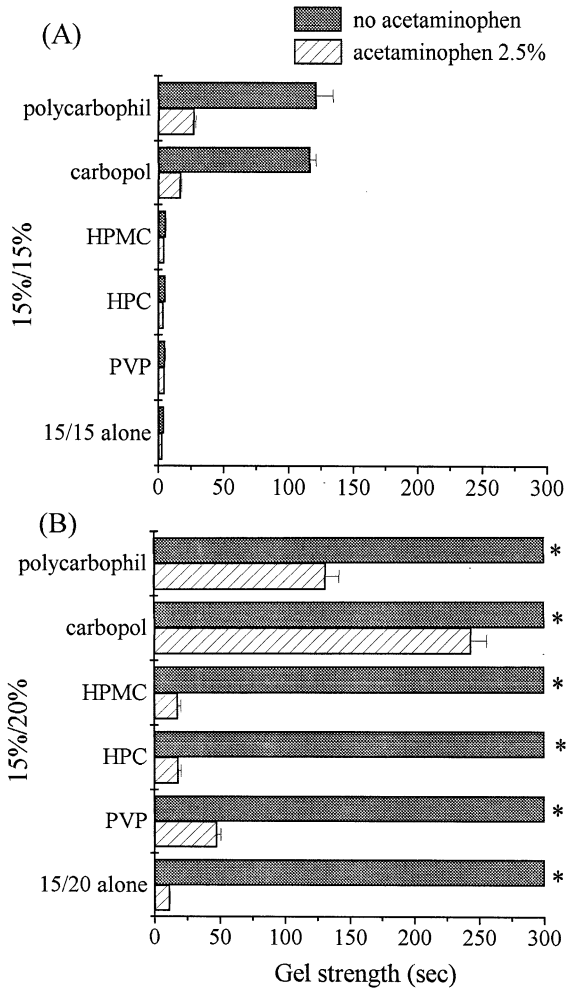

Fig. 5. Effect of acetaminophen and bioadhesive polymers on the gel strength of poloxamer mixtures. Acetaminophen (2.5%) was added to the mixtures of P407/P188; 15/15 (A) and 15/20 (B). The concentration of bioadhesive polymers was 1%. Each bar represents the average of more than three separate experiments. Gels composed of 15/20 without acetaminophen were so strong that the apparatus could not move down within 300 s.

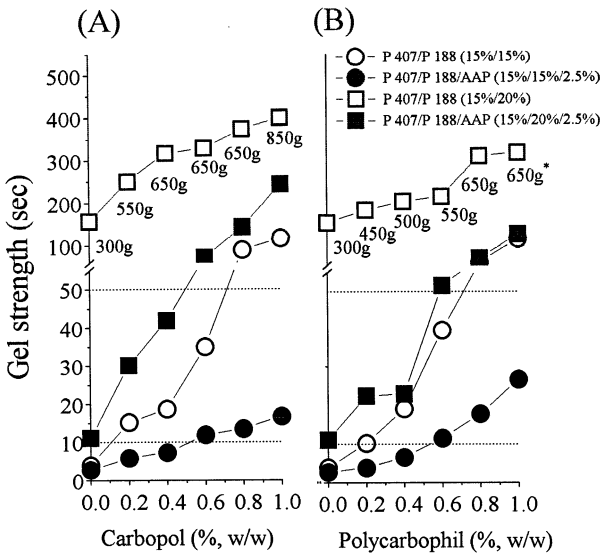

Fig. 6. Effect of carbopol and polycarbophil contents on the gel strength. The strength of gelled poloxamer was measured in varying concentrations of carbopol (A) and polycarbophil (B). Poloxamer compositions of P407/P188 were 15/15 and 15/20. The concentration of acetaminophen was 2.5%. Gel strength was measured by the time that the apparatus itself (35 g) without any weights move down the gel. Each point represents the average of three separate experiments. Gel strength of 15/20 without acetaminophen was described as time and the weights that pushed the apparatus 5 cm down.

3.2.3. Bioadhesive force

Bioadhesive force means the force with which liquid suppositories bind to rectal mucous lining at 36.5°C. Since rectal mucous lining consists of

oligosaccharide chains with sialic acid, the polymers with hydrophilic groups such as the carboxyl and hydroxyl groups can bind strongly to oligosaccharide chains, resulting in strong bioadhesive force. The bioadhesive force is known to be dependent on the nature and the concentration of bioadhesive polymers. 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 membrane (Robert et al., 1988; Leung and Robinson, 1990). Therefore, liquid suppositories must have the suitable bioadhesive force.

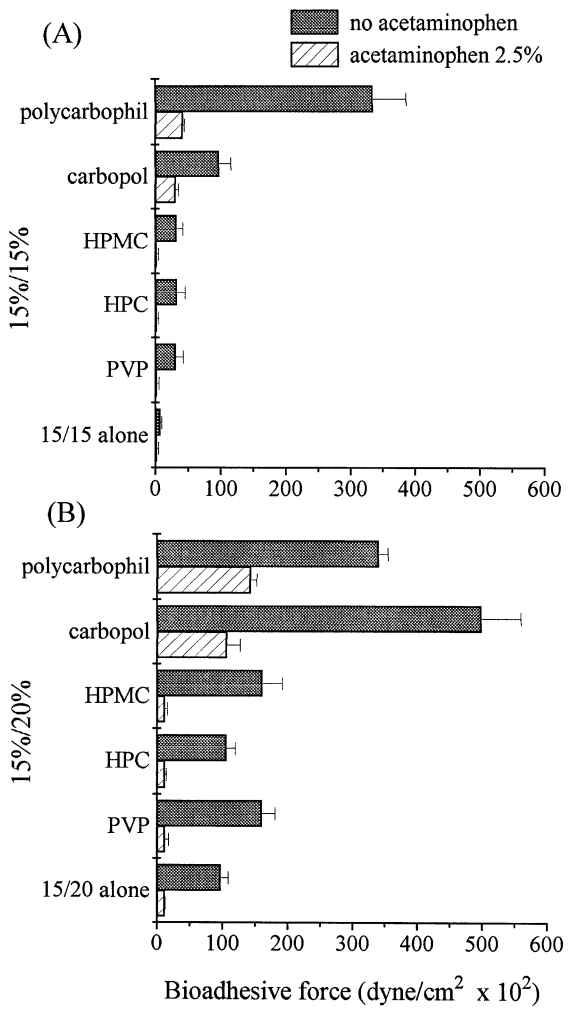

Fig. 7. Effect of acetaminophen and bioadhesive polymers on the bioadhesive force of poloxamer mixtures. Acetaminophen (2.5%) was added to the mixtures of P407/P188; 15/15 (A) and 15/20 (B). The concentration of various bioadhesive polymers was 1%. Each bar represents the average of more than three separate experiments.

Acetaminophen decreased the bioadhesive force of gelled poloxamers. In the presence of acetaminophen, the bioadhesive force of 15/15 and 15/20 was reduced from 6.8 to 3.2 and from 97.3 to 11.1 dyne/cm^2 $\times$ 10^2, respectively (Table 2, Fig. 7). Acetaminophen also significantly decreased the bioadhesive force of other gels containing various bioadhesive polymers.

Among bioadhesive polymers, carbopol and polycarbophil—which enhanced gel strength most efficiently (Fig. 5)—also increased bioadhesive force higher than that of the other bioadhesive polymers. In the absence of acetaminophen, PVP and HPMC reinforced the bioadhesive forces 4.7-fold compared to 15/15 alone and 1.7-fold compared to 15/20 alone, whereas, in the presence of acetaminophen, they did not show significant effect on the bioadhesive force (Fig. 7). In the absence of acetaminophen, carbopol and polycarbophil strengthened the bioadhesive forces of 15/15 as much as 14.3- and 49-fold, respectively. In 15/20 gels, carbopol and polycarbophil enhanced the bioadhesive forces 5.1- and 3.5-fold, respectively. However, the impact of carbopol and polycarbophil on the bioadhesive force was significantly lessened by acetaminophen. It is noteworthy that carbopol and polycarbophil, which exerted different impacts on the bioadhesive force in the absence of acetaminophen, showed a similar extent of bioadhesive force-strengthening effects in the presence of acetaminophen.

The bioadhesive forces of 15/15 and 15/20 increased with the concentrations of carbopol and polycarbophil (Fig. 8). The increase of bioadhesive forces over bioadhesive concentrations showed relatively good linearity for 15/15 with acetaminophen. However, in 15/20 without acetaminophen, there was a substantial increase of bioadhesive force as carbopol concentration increased from 0.8 to 1.0%.

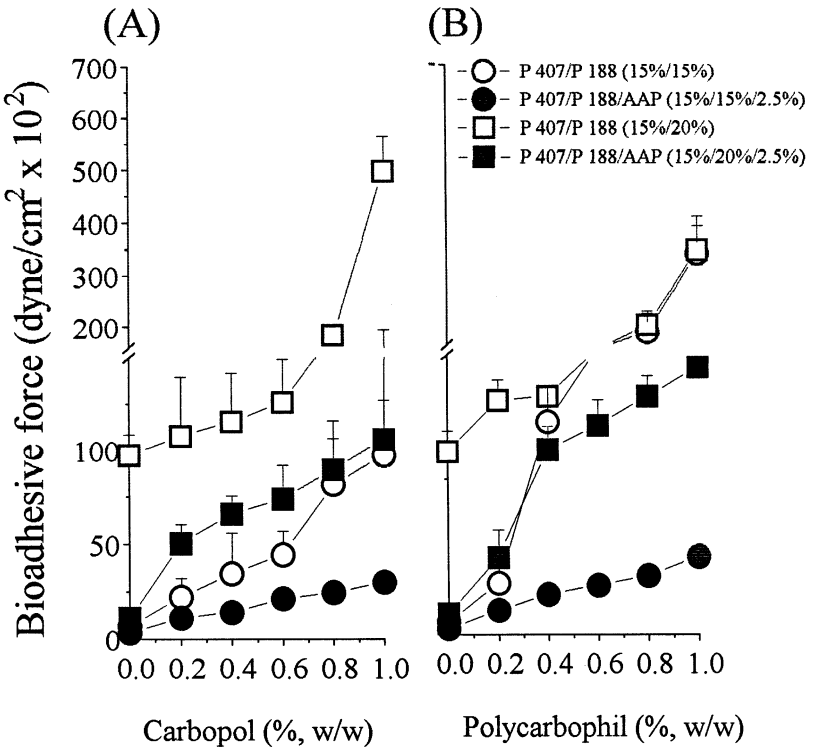

Fig. 8. Effect of carbopol and polycarbophil contents on the bioadhesive force. The bioadhesive force of poloxamers was measured in various concentrations of carbopol (A) and polycarbophil (B). Poloxamer compositions of P407/P188 were 15/15 and 15/20. The concentration of acetaminophen (AAP) was 2.5%. Each point represents the average of three separate experiments.

3.3. In vivo retention of liquid suppository in the rectum

Liquid suppository composed of P407/P188/polycarbophil/acetaminophen (15%/19%/0.8%/2.5%) was administered into rats and its retention in the rectum was observed. Then 5 min after administration (Fig. 9A), the blue color of the suppository was clearly shown in the rectum. Then 6 h after administration (Fig. 9B), 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. It indicates that the bioadhesive force of liquid suppository is strong enough to hold the gelled suppository in the rectum of rats for at least 6 h.

Our results indicate that acetaminophen increased the gelation temperature of poloxamer solutions, while decreasing the strength and the bioadhesive force of poloxamer gels. As a possible mechanism by which acetaminophen affected the physicochemical properties of gel, it is speculated that the binding force (hydrogen bonding) of cross-linked reticular poloxamer gel became weaker by placing acetaminophen in the gel matrix.

PVP, HPMC and HPC showed little effect on the gelation temperature and gel strength, but increased bioadhesive force significantly in the absence of acetaminophen. Such effects on the bioadhesive force might be due to the binding of these polymers with the oligosaccharide chains of rectal mucous lining. Given that PVP has positive charges and that HPMC and HPC have neutral charges, the charges of bioadhesive polymers seem not to play a major role in affecting the physicochemical properties of poloxamer-based liquid suppository. Compared to PVP, HPMC and

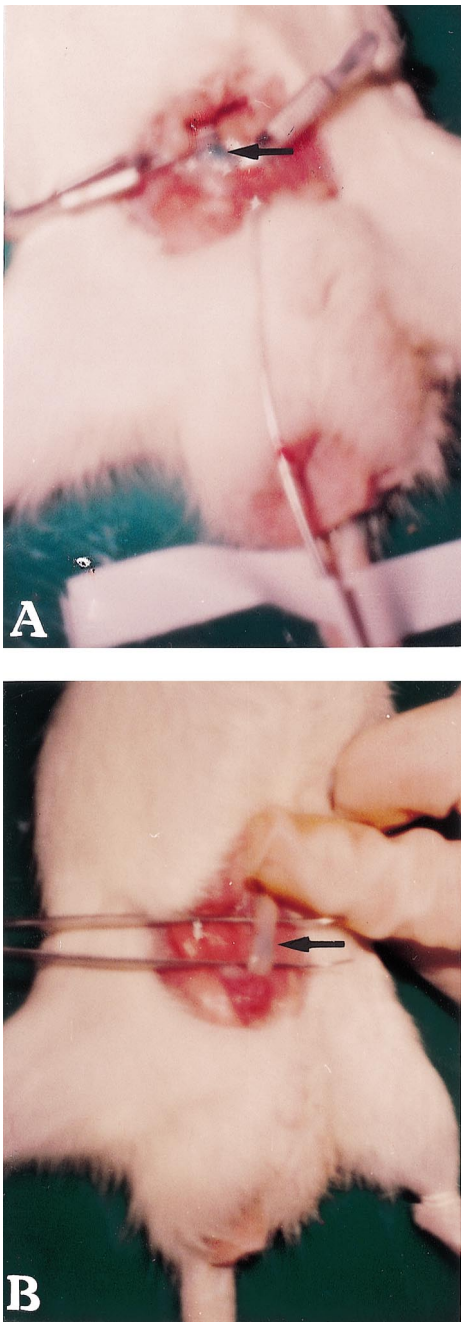

Fig. 9. In vivo localization of liquid suppository in the rectum. Liquid suppository composed of P407/P188/polycarbophil/acetaminophen (15/19/0.8/2.5) with 0.1% blue lake was administered into the rectum of a rat. At 5 min (A) and 6 h (B) after administration, the rectum was sectioned. The liquid suppository is shown in blue.

HPC, carbopol and polycarbophil exerted higher effects on the gelation temperature, gel strength and bioadhesive force of both 15/15 and 15/20. The stronger effects of carbopol and polycarbophil on the physicochemical properties seem to be due to their carboxyl groups which could bind strongly with the cross-linked reticular poloxamer gel by putting their molecules in between the gel. Furthermore, their bioadhesive force-strengthening effects appear to be contributed by their strong binding with the oligosaccharide chains of rectal mucous lining (Khosla and Davis, 1987; Lehr et al., 1990; Robinson and Robinson, 1990).

From these findings, it is suggested that the mixtures of P407/P188 (15/15–15/20) are the optimal systems which have the gelation temperature suitable for acetaminophen liquid suppository. Furthermore, less than 1.0% of carbopol or polycarbophil must be added to prevent the leakage of suppositories from the anus and retain the gelled suppositories in the rectum. This system might be applicable for the development of in situ-gelling and mucoadhesive liquid suppository for humans as a more convenient and effective rectal dosage form.

Acknowledgements

This research is partly supported by the grant from KOSEF-RCNDD and the Research Institute of Pharmaceutical Sciences in College of Pharmacy, Seoul National University.

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