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In situ gelling and mucoadhesive liquid suppository containing acetaminophen: enhanced bioavailability

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Abstract

Solutions of poloxamers and bioadhesive polymers were previously reported to undergo a phase transition to bioadhesive gels at body temperature. For the development of a convenient acetaminophen-loaded liquid suppository which gels in situ after rectal administration, we studied the release and pharmacokinetics of acetaminophen delivered by the liquid suppository systems composed of poloxamer P 188, P 407 and a bioadhesive polymer, polycarbophil. The release of acetaminophen was differently affected by the components of liquid suppository such as P 188 and polycarbophil. P 188 showed little effect on the release rates of acetaminophen from liquid suppositories. However, polycarbophil significantly delayed the release kinetics of acetaminophen from a certain concentration due to strong gel strength and bioadhesive force. The release rates of acetaminophen did not significantly differ between no polycarbophil and 0.2% polycarbophil-loaded suppositories, while they began to decrease as the concentrations of polycarbophil increased higher than 0.4%. The analysis of release mechanism showed that the release of acetaminophen was proportional to the square root of time, indicating that acetaminophen might be released from the suppositories by Fickian diffusion. Liquid suppository A [P 407/P 188/polycarbophil/acetaminophen (15:19:0.8:2.5%)], which was strongly gelled and mucoadhesive in the rectum, showed more sustained acetaminophen release profile than did other suppositories and gave the most prolonged plasma levels of acetaminophen in vivo. Liquid suppository A also showed higher bioavailibility of acetaminophen than did the conventional formulation. Moreover, liquid suppository A did not cause any morphological damage to the rectal tissues and remained stable for at least 6 month during storage. These results suggest that mucoadhesive and in situ gelling liquid suppository could be a more effective and convenient rectal delivery system of acetaminophen.

Keywords: Liquid suppository; Dissolution; Pharmacokinetics; Acetaminophen; Poloxamer; Bioadhesive polymer; Polycarbophil

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1. Introduction

Suppositories have been favorable dosage forms for infants, children and unconscious patients. Ideal suppository should be easy to administer without any pain during insertion and remain at the administered sites to avoid the first pass effect in the liver and the gastrointestinal tracts. However, conventional suppositories are solid dosage forms which melt or soften in the rectum. Such solid form suppositories can give a feeling of alien, discomfort and refusal to the patients, possibly lowering patient compliance. Furthermore, solid type suppository which might reach the end of the colon, may also allow the carried drugs to undergo the first-pass effect (Huang et al., 1987).

To solve the problems of conventional solid suppositories, there have been several attempts to develop suppositories which exist as liquid in vitro but gel in vivo, by modulating the gelation temperatures of poloxamer solutions (Schmolka, 1973; Holsman et al., 1984; Blackman and Ralske, 1989). Recent report showed that mucoadhesive liquid suppositories composed of poloxamers and bioadhesive polymers could not only gel at 30–36°C, but also remain in the rectum without leakage after administration (Choi et al., 1998). However, the previous studies focused on modulating the physicochemical properties of liquid suppositories and there has been lack of information on the release and absorption of drugs from the suppositories. Thus, in this study, we investigated the release and pharmacokinetic profiles of acetaminophen from the liquid suppositories. Furthermore, we evaluated the rectal tissue irritation of the liquid suppository and the stability of acetaminophen in the suppository during storage. Our results indicate that the poloxamer-based mucoadhesive liquid suppository can improve the bioavailability of acetaminophen with good safety and stability.

2. Materials and methods

2.1. Materials

Poloxamers (P 407, P 188) were purchased from BASF (Ludwigshafen, Germany). Polycarbophil was from BF Goodrich (Brecksville, OH). Acetaminophen was of USP grade. Tetrabutylammonium dihydrogen phosphate, phosphoric acid and potassium dihydrogen phosphate were supplied from Junsei Chemical Co (Tokyo, Japan). Acetonitrile and methanol were from Aldrich Chemical Co (Milwaukee, WI). Semipermeable membrane tube (Spectra membrane tubing No. 1) was from Spectrum Medical Industries Inc. (Los Angeles, CA).

2.2. Preparation of liquid suppository

The liquid suppository was prepared as previously described by Choi et al. (1998). In brief, various components such as acetaminophen and polycarbophil were solubilized in distilled water and the solution was 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. The stability of liquid suppository A and B by the physical appearance and the contents of acetaminophen was evaluated over 6 months at 4, 25 and 45°C. No noticeable changes were observed during the period.

2.3. Release test

The liquid suppository (5 g) or a conventional suppository (5 g) containing 125 mg of acetaminophen was inserted into a semipermeable membrane tube. Both sides of the tube were tied up with a thread to prevent leakage. The semipermeable membrane tube was then placed in a dissolution tester (DST-600, Fine Chemical, Korea). Drug release test was performed at 36.5°C using the paddle method at 100 rpm with 500 ml phosphate buffer (pH 6.8) as a dissolution medium. At 1 h intervals, 5 ml of the medium was sampled and filtered. The filtrate was analyzed by UV/visible variable wavelength detector (Philips, Model PU8730) at 250 nm (Chen-chow and Frank, 1981).

2.4. Pharmacokinetic study

2.4.1. In vivo experiments

Male Sprague-Dawley rats weighing 250 ± 20 g were fasted for 24–36 h prior to the experiments

Table 1
Release kinetic parameters

P 407/P 188	Polycarbophil (%)	Release exponent (n)	Kinetic constant (k, %/h^n)	Correlation coefficient (r)
15:15%	0	0.3992	48.1392	0.9538
	0.2	0.3998	48.1385	0.9612
	0.4	0.4339	42.4815	0.9917
	0.8	0.5586	32.7039	0.9944
15:17%	0	0.4464	39.3913	0.9840
	0.2	0.4476	39.4000	0.9745
	0.4	0.4582	36.1743	0.9932
	0.8	0.5260	29.7167	0.9964
15:18%	0	0.4929	38.9852	0.9680
	0.2	0.4944	38.9903	0.9543
	0.4	0.5247	34.4747	0.9914
	0.8	0.5975	29.0001	0.9952
15:19%	0	0.5139	37.0339	0.9692
	0.2	0.5156	37.0373	0.9690
	0.4	0.4893	36.1493	0.9927
	0.8	0.5975	26.1879	0.9947
15:20%	0	0.5997	31.1387	0.9769
	0.2	0.5918	31.1365	0.9762
	0.4	0.5534	30.4439	0.9913
	0.8	0.5654	25.9776	0.9986
Conventional form		0.6510	37.9640	0.9543

but allowed free access to water. Eighteen rats were divided into three groups. The rats in each group were administered with acetaminophen conventional suppository [polyethyleneglycol 6000/acetaminophen (97.5:2.5%)], acetaminophen liquid suppository A [P 407/P 188/polycarbophil/acetaminophen (15:19:0.8:2.5%)], or with liquid suppository B [P 407/P 188/polycarbophil/acetaminophen (15:18:0.2:2.5%)], respectively.

2.4.2. Administration and blood-collecting

Each rat, anesthetized in an ether-saturated chamber, was secured on a surgical board in the supine position with a thread. A polyethylene tube was inserted into the right femoral artery of the rat. Liquid suppository A or B (1.5 g/kg equivalent to acetaminophen 37.5 mg/kg) was administered into the rectum 4 cm above the anus through a stomach sonde needle fitted on a glass syringe. Acetaminophen conventional suppository was administered with a dose of 0.4 g/kg (equivalent to acetaminophen 37.5 mg/kg) into the rectum 4 cm above the anus (Miyazaki et al., 1987). The entrance of the anus was then blocked with a cyanoacrylate adhesive to prevent the suppositories from leaking out from the anus. Without cyanoacrylate adhesive, conventional suppository and liquid suppository B were leaked out from the anus during the pharmacokinetic experiment, leading to not obtaining accurate pharmacokinetic data. Half milliliter of blood was collected from the right femoral artery at various intervals and centrifuged at 3000 rpm for 10 min using a centrifuge 5415C (Eppendorf, USA).

2.4.3. Blood sample analysis

Plasma (0.2 ml) was mixed with 0.2 ml of acetonitrile solution containing theophylline (200 μg/ml) as an internal standard. It was then centrifuged at 3000 rpm for 10 min to precipitate the proteins. The supernatant was then analyzed by HPLC (Waters TM 717 plus Autosampler with sic chomatorecorder 12) with following assay condi-

tions (Korduba and Petruzzi, 1984; Sood and Green, 1987). In brief, mobile phase was prepared as follows; methanol, water and tetrabutylammonium dihydrogen phosphate solution in water (1.0 M) were mixed in the ratio of 120:880:20. One gram of potassium dihydrogen phosphate was then added to the solution and the pH was adjusted to 2.4 with phosporic acid. The mobile phase was run at a flow rate of 1.5 ml/min. Then, 10 μl of the supernatant was injected into the column (Lichosorb RP-18 (0.5 μm), 0.46 × 25 cm) and the column effluent was monitored by UV detection at 250 nm.

2.5. Morphology test of rectal tissues

Male Sprague-Dawley rats weighing 250 ± 20 g were fasted for 24–36 h prior to the experiments but allowed free access to water. Liquid suppository A was administered at 1.5 g/kg into the rectum 4 cm above the anus through the stomach sonde needle. At 6 h after administration, the rectum was isolated, rinsed with a saline solution, fixed in 10% neutral carbonate-buffered formaldehyde, embedded in paraffin using an embedding center and cut into slices. The slices were stained with hematoxylin-eosin (Miyazaki et al., 1987; Watanabe et al., 1993) and observed under a light microscope (Leitz; Laborlux 12 Pols, Germany).

3. Results and discussion

3.1. Release of acetaminophen from liquid suppository

To test whether P 188 or polycarbophil affects the release rates of acetaminophen from the liquid suppositories, we performed the release test with the formulations composed of constant amount of P 407 (15%) and variable amounts of P 188 (15–20%) and polycarbophil (0–0.8%) as shown in Table 1. It was reported that the liquid suppositories composed of P 407/P 188 (15:15%–15:20%) had the gelation temperatures (30–36°C) suitable for acetaminophen liquid suppository (Choi et al., 1998). Also, it was observed that bioadhesive polymers such as carbopol or polycarbophil must be added to reinforce the gel strength and bioadhesive force which were significantly reduced by acetaminophen (Choi et al., 1998).

The release of acetaminophen was variously affected by the components of liquid suppository such as P 188 and the bioadhesive polymer, polycarbophil. Poloxamer P 188 showed little effect on the release rates of acetaminophen from liquid suppositories. Regardless of the contents of P 188, 50% of acetaminophen was released out within 2 h and about 90% of the drug was released at 6 h in all formulations (Fig. 1). Polycarbophil delayed the release rates of acetaminophen from a certain concentration. Although the release rates of acetaminophen did not significantly differ between no polycarbophil and 0.2% polycarbophil-loaded suppositories, the release rates of acetaminophen tended to decrease as the concentrations of polycarbophil increased higher than 0.4% (Fig. 2). Polycarbophil consistently decreased the release of acetaminophen in various liquid suppositories with different contents of poloxamer P 188 (Fig. 2A–C). Among various suppositories containing different amounts of P 188 and polycarbophil, the slowest release of acetaminophen was shown in

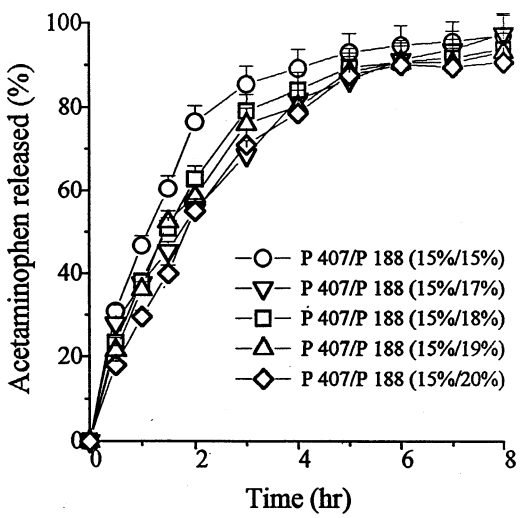

Fig. 1. Effect of poloxamer P 188 on the release of acetaminophen. Liquid suppositories were composed of 15–20% of poloxamer P 188, 15% poloxamer P 407 and 2.5% acetaminophen. Release test was performed using the paddle method in phosphate buffer (pH 6.8).

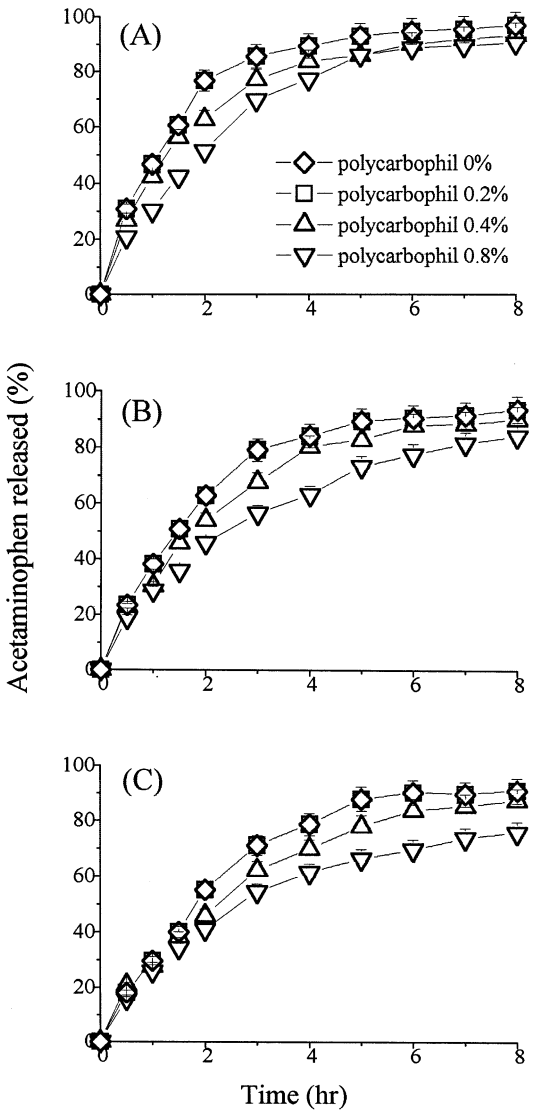

Fig. 2. Effect of polycarbophil on the release of acetaminophen. Liquid suppositories were composed of 0–0.8% polycarbophil, various amounts of P 188, 15% P 407 and 2.5% acetaminophen. The contents of P 188 were 15% (A), 18% (B) and 20% (C). Release test was performed using the paddle method in phosphate buffer (pH 6.8).

the suppository with 0.8% polycarbophil and 20% P 188 (Fig. 2C). Such a slow release of acetaminophen appears to be contributed by the higher gel strength of the formulation with 20% P 188 and 0.8% polycarbophil than other formulations.

3.2. Analysis of release mechanism

To understand the release mechanisms of acetaminophen from suppositories, we described the release rate using the following equations:

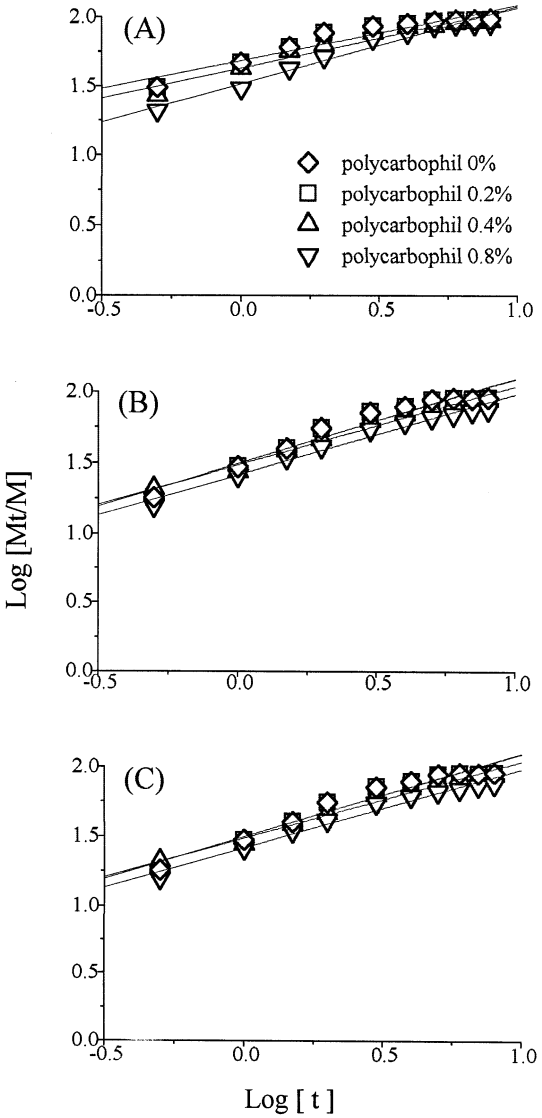

Fig. 3. Release kinetics of acetaminophen. Liquid suppositories were composed of 0–0.8% polycarbophil, various amounts of P 188, 15% P 407 and 2.5% acetaminophen. The contents of P 188 were 15% (A), 18% (B) and 20% (C). Logarithm of released fractions of acetaminophen was plotted against logarithm of time.

Table 2
Physicochemical properties of liquid suppositories

Liquid suppository	Gelation temperature (°C)	Gel strength (s)	Bioadhesive force (dyne/cm$^2 \times 10^2$)
A	30.0 ± 0.2	34.22 ± 2.34	91.3 ± 11.0
B	33.7 ± 0.5	9.26 ± 0.14	32.4 ± 3.4

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

$$Mt/M = kt^n \quad (1)$$

$$\log (Mt/M) = \log k + n \log (t) \quad (2)$$

where Mt/M is the fraction of released drug at time t, k is a characteristic constant of the liquid suppository and n is an indicative of release mechanism. As the k value becomes higher, the drug is released faster. The n value of 1 corresponds to zero-order release kinetics, $0.5 < n < 1$ means a non-Fickian release model and $n = 0.5$ indicates Fickian diffusion (Higuchi model) (Peppas, 1985). From the plot of $\log (Mt/M)$ versus $\log (t)$ (Fig. 3), kinetic parameters, n and k, were calculated. Table 1 shows that most of n values are close to 0.5, suggesting that acetaminophen might be released from the suppositories by Fickian diffusion through extramicellar aqueous channels of the gel matrix which means the outer layer of poloxamer cross-linking system (poloxamer micelle). The relatively parallel slopes of the plots (Fig. 3) indicate that the content of polycarbophil and P 188 might not affect the release mechanisms. However, the k values indicate that acetaminophen released more slowly from liquid suppositories with higher concentration of P 188 and polycarbophil. P 188 and polycarbophil seem to affect the release rates by influencing the physicochemical property of gel matrix. The physicochemical characteristics of liquid suppository A and B such as gelation temperature, gel strength and bioadhesive force were measured as described previously (Choi et al.,

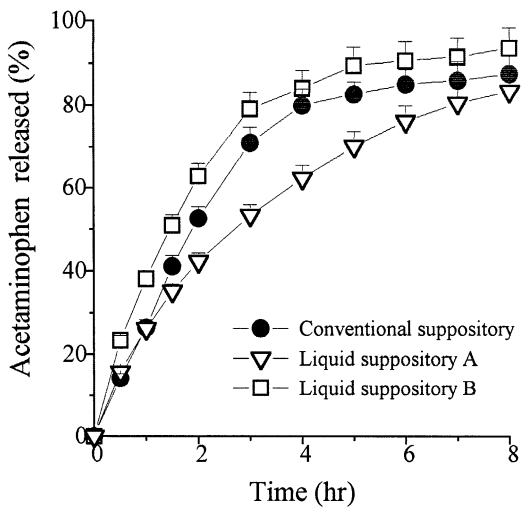

Fig. 4. Release of acetaminophen from liquid suppositories A, B and a conventional suppository. Liquid suppository A [P 407/P 188/polycarbophil/acetaminophen (15:19:0.8:2.5%)], suppository B [P 407/P 188/polycarbophil/acetaminophen (15:18:0.2:2.5%)] and a conventional suppository [polyethylene glycol/acetaminophen (97.5:2.5%)] were placed in a dissolution tester.

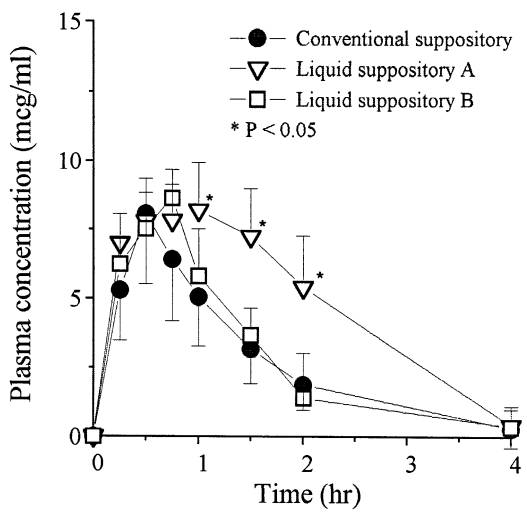

Fig. 5. Plasma concentration–time profiles of acetaminophen after the rectal administration of acetaminophen liquid suppository A, B and conventional suppository to rats. Liquid suppositories were composed of P 407, P 188, polycarbophil and acetaminophen. Each point represents the average of three separate experiments ($n = 6$).

Table 3
Pharmacokinetic parameters of acetaminophen delivered by the conventional or liquid suppositories

Parameters	Conventional suppository	Liquid suppository A	Liquid Suppository B
AUC ($h \cdot \mu g/ml$)	10.86 ± 4.13	17.91 ± 4.36	11.68 ± 3.42
MRT (h)	1.28 ± 0.18	1.47 ± 0.40	1.24 ± 0.36
T_{max} (h)	0.46 ± 0.09	0.96 ± 0.09	0.71 ± 0.09
C_{max} ($\mu g/ml$)	8.07 ± 2.44	8.18 ± 1.75	8.63 ± 1.20
K_{el} (h^{-1})	0.94 ± 0.34	1.06 ± 0.26	1.08 ± 0.40
$t_{1/2}$ (h)	0.74 ± 0.43	0.65 ± 0.58	0.64 ± 0.32

Each value represents the mean $\pm$ S.E. ($n = 6$).

1998) and listed in Table 2. Polycarbophil, which enhances gel strength and decreases gelation temperature (Choi et al., 1998) could distort or squeeze the diffusion channels, delaying the release process. Liquid suppository A with highest gel strength has the smallest k value, whereas liquid suppository B with lowest gel strength has the largest k value among liquid suppositories prepared with polycarbophil in the range of 0.2–0.8%, which had the different gelation temperature, gel strength and bioadhesive force. The release profiles of acetaminophen in liquid suppository A, B and the conventional one are illustrated in Fig. 4. As compared with the conventional suppository, liquid suppository A showed slower release, while liquid suppository B showed faster release of acetaminophen.

3.3. Pharmacokinetic study

In order to test any correlation between the release kinetics in vitro and bioavailability in vivo, two formulations were selected: liquid suppository A [P 407/P188/polycarbophil/acetaminophen (15:19:0.8:2.5%)] and liquid suppository B [P 407/P 188/polycarbophil/acetaminophen (15:18:0.2:2.5%)]. Among conventional and liquid suppositories, liquid suppository A showed the highest absorption of acetaminophen in rats (Fig. 5). Over 4 h after the dose, the conventional suppository and liquid suppository B which did not differ significantly in the release kinetics (Fig. 4) showed similar plasma levels of acetaminophen. In liquid suppository A, until 45 min after the dose, the plasma concentrations of acetaminophen were not significantly different from those in the conventional suppository. However, from 1 h after the dose, liquid suppository A, which showed more sustained acetaminophen release profile than did other suppositories, significantly increased the plasma levels of acetaminophen compared with other suppositories. It appears that the physicochemical characteristics of suppository bases besides the release rates of acetaminophen should be considered.

Pharmacokinetic parameters are shown in Table 3. The AUC of acetaminophen from conventional suppository (polyethylene glycol base) was not greater than that from liquid suppository A and B. The reason for this difference might be dependent upon the dispersability (fluidity) and bioadhesive force. Solid type conventional suppository was not bioadhesive, and slowly dissolved and dispersed in the rectum. In contrast, bioadhesive liquid suppositories were dispersed rapidly in the rectum, gelled and attached on the rectal mucous membranes, since bioadhesive liquid suppositories were a fluid initially. As shown in Table 3, liquid suppository B and the conventional suppository which did not significantly differ in the release kinetics (Fig. 4) showed similar AUC of acetaminophen. On the other hand, liquid suppository A gave significantly higher AUC of acetaminophen than did two other suppositories. The AUC of acetaminophen from liquid suppository A was 1.6-fold higher than that from other suppositories, indicating that liquid suppository A can enhance the bioavailability of acetaminophen. This phenomena might be dependent on the gel strength and bioadhesive force of liquid suppositories. Without cyanoacrylate adhesive, liquid suppository B as well as

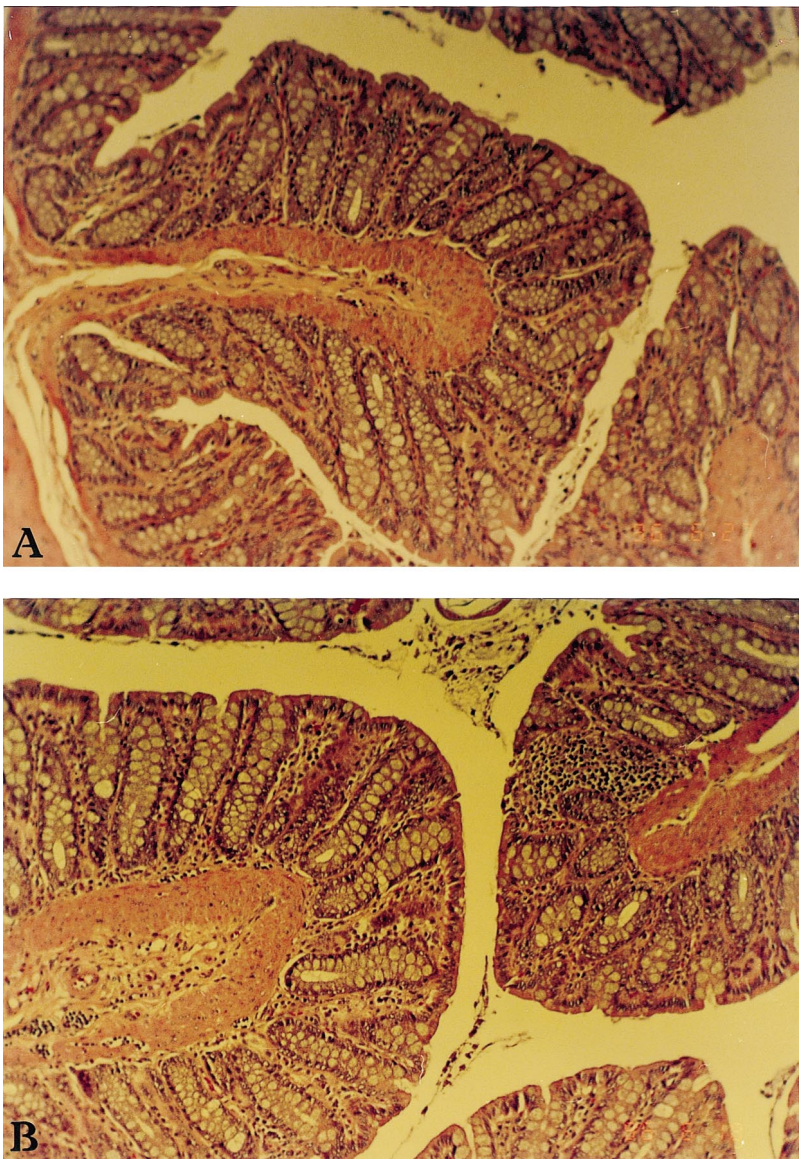

Fig. 6. Morphology of rectal mucosa of rats after rectal administration of acetaminophen liquid suppository A (× 250): (A) before the dose and (B) 6 h after the dose.

conventional suppository was leaked out from the anus during the pharmacokinetic experiment. It means that the gel strength and mucoadhesive force of liquid suppository B were not strong to hold the weakly gelled suppository in the rectum. Since liquid suppositories B was weakly gelled and mucoadhesive in the rectum (Choi et al., 1998), it might reach the end of the colon and had a possible loss of drug at colonic level through first-pass effect as like as conventional suppository which was not bioadhesive. However, liquid suppository A was strongly gelled and mucoadhesive in the rectum, therefore, it could be remained at the administered sites without leakage after the dose. The drug could be absorbed continuously at the rectal sites without first-pass effect. Although

the release rate of acetaminophen from liquid suppository A was more retarded by polycarbophil, the AUC of acetaminophen increased compared with liquid suppository B and conventional one. Therefore, liquid suppository A which release the acetaminophen in more sustained rate than did other formulations gave the most prolonged plasma levels of acetaminophen with enhanced bioavailability.

From these findings, liquid suppository A would be useful to deliver acetaminophen in a pattern that allows fast absorption in the initial phase followed by the sustained blood level.

3.4. Safety

Since pharmacokinetic study showed that liquid suppository A gave the highest AUC of acetaminophen, the safety of liquid suppository A was tested. Safety test was performed by observing any irritation of liquid suppository on the rectal tissues. The morphology of rectal tissues indicates that liquid suppository A did not irritate or damage the rectal tissues (Fig. 6). Previously, poloxamers, the non-ionic surfactants, were reported to be inert, giving no damage to mucous membranes (Lenaerts et al., 1987; Dumortier et al., 1991), whereas polycarbophil was shown to be able to irritate mucous membranes due to their bioadhesive properties (Robert et al., 1988; Leung and Robinson, 1990). No irritation of liquid suppository A containing polycarbophil might be explained by that the content (0.8%) of polycarbophil which was lower than tissue-damaging threshold level.

4. Conclusion

Taken together, it is concluded that liquid suppository A, [P 407/P 188/polycarbophil/acetaminophen (15:19:0.8:2.5%)], which remained at the administered sites due to strong gel strength and mucoadhesive force, could enhance the bioavailability of acetaminophen without first-pass effect and without damaging the rectum. Furthermore, the desirable physicochemical properties such as in situ gelling property, suitable gel strength and bioadhesive force of the liquid type suppository, could alleviate the patients a feeling of alienation, discomfort and refusal during application, increasing patient compliance.

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