ELSEVIER

International Journal of Pharmaceutics 174 (1998) 201–207

international journal of pharmaceutics

Trials of in situ-gelling and mucoadhesive acetaminophen liquid suppository in human subjects

Chong-Kook Kim *, Sa-Won Lee, Han-Gon Choi, Mi-Kyung Lee, Zhong-Gao Gao, In-Sook Kim, Kyung-Mi Park

College of Pharmacy, Seoul National University, San 56-1, Shinlim-Dong, Kwanak-Ku, Seoul, 151-742, South Korea

Received 12 May 1998; received in revised form 8 July 1998; accepted 30 July 1998

Abstract

For the development of in-situ gelling and mucoadhesive acetaminophen liquid suppository prepared with poloxamers (P 407, P 188) and sodium alginate, the physicochemical characteristics of liquid suppositories [acetaminophen/P 407/P 188/sodium alginate (5/15/19/0–1.0%)] were evaluated. Furthermore, a pharmacokinetic study of acetaminophen from liquid and conventional solid suppositories in human subjects was carried out. The results showed that acetaminophen liquid suppository [acetaminophen/P 407/P 188/sodium alginate (5/15/19/0.6%)] with optimal gelation temperature, gel strength and bioadhesive force had a similar release pattern to conventional suppository. The area under the drug concentration–time curve (AUC), mean residence time (MRT), biological half-life ($t_{1/2}$) and apparent elimination rate constant (K_{el}) of acetaminophen from liquid suppository were not significantly different from those from conventional suppository. However, liquid suppository gave significantly faster the time to reach the maximum plasma concentration (T_{max}) and higher the maximum plasma concentration of drug (C_{max}) of acetaminophen than conventional suppository ($p < 0.05$). It is concluded that in situ gelling and mucoadhesive acetaminophen liquid suppository, which was easy to administer to the anus and showed faster absorption of acetaminophen in human subjects than conventional suppository, was more comfortable for the patients and therefore, is thought to be a favorable anti-pyretic and analgesic dosage form for infants and children.

Keywords: Liquid suppository; Acetaminophen; Poloxamer; Sodium alginate; Pharmacokinetics

1. Introduction

Acetaminophen suppository is commonly used as an anti-pyretic and analgesic drug for infants and children. However, the conventional supposi-

* Corresponding author. Tel.: + 82 2 8807867; fax: + 82 2 8737482.

0378-5173/98/$ - see front matter
PII S0378-5173(98)00258-0

tory is in a solid form which melts or softens in the rectum. Such a solid suppository can be uncomfortable for patients and can lead to patient refusal, lowering patient compliance. Furthermore, a solid type suppository might reach the end of colon allowing the carried drugs to undergo the first-pass effect (Huang et al., 1987). The ideal suppository would be easy to administer without any pain during insertion and would remain at the administered site avoiding the first-pass effect in the liver and the gastrointestinal tract.

To improve patient compliance of conventional acetaminophen suppository, in-situ gelling and mucoadhesive liquid suppository was developed, composed of acetaminophen, poloxamers and polycarbophil, which exists as a liquid in vitro but a gel in vivo, by modulating the gelation temperature of poloxamer solution (Choi et al., 1998b,c). It was gelled at physiological temperature and was mucoadhesive to the rectal tissues in rats. Furthermore, it exhibited similar or improved acetaminophen bioavailability compared to conventional solid suppository, with good safety in rats (Choi et al., 1998a). However, there is no information on the pharmacokinetics of acetaminophen from liquid suppository in human subjects. Thus, in this study, we developed in-situ gelling and mucoadhesive acetaminophen liquid suppository with sodium alginate, and investigated the pharmacokinetics of acetaminophen from liquid suppository in human subjects.

2. Materials and method

2.1. Materials

Poloxamers (P 407, P 188) were purchased from BASF (Ludwigshafen, Germany). Acetaminophen was of USP grade. Sodium alginate (300-400 cP) and phosphoric acid were supplied from Wako Chemical (Osaka, Japan) and Junsei Chemical (Tokyo, Japan), respectively. Acetonitrile and ethanol were from Aldrich (Milwaukee, WI, USA). Semipermeable membrane tube (Spectra membrane tubing No. 1) was from Spectrum Medical Industries (Los Angeles, CA, USA).

2.2. Preparation of liquid suppository

The liquid suppository was prepared as previously described by Choi et al. (Choi et al., 1998a,b,c). In brief, various components such as acetaminophen and sodium alginate were dispersed in distilled water and the solution was cooled down to 4°C. Poloxamers were then slowly added to the solution with continuous agitation. The liquid suppository was kept at 4°C.

2.3. Measurement of gelation temperature

A 20-ml transparent vial containing a magnetic bar and 10 g of liquid suppository 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 liquid suppository. The liquid suppository 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 the gelation temperature.

2.4. Measurement of gel strength

The liquid suppository (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 liquid suppository. The gel strength, which means the viscosity of the liquid suppository at physiological temperature, was determined by the time (s) the apparatus took to sink 5 cm down through the liquid suppository (Choi et al., 1998b).

2.5. Determination of bioadhesive force

The bioadhesive force of the liquid suppository was determined by using the measuring device shown in Fig. 1. In brief, a section of tissue was cut from the fundus of rabbit rectum and 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

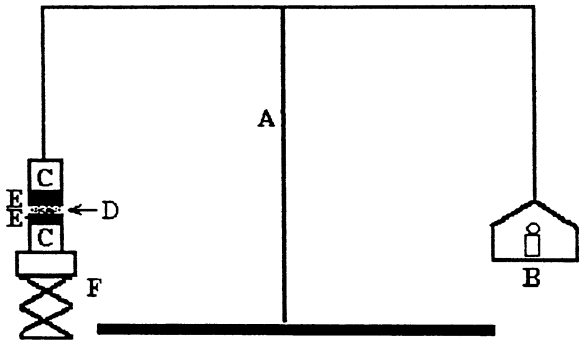

Fig. 1. Bioadhesive force-measuring device: (A) modified balance; (B) weights; (C) glass vial; (D) liquid suppository; (E) rectal tissue; (F) height-adjustable pan.

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). Liquid suppository (D) was added onto the rectal tissue on the other vial. Then, the height of the vial was adjusted so that the liquid suppository could be placed between the mucosal tissues of both vials. The weights (B) were kept raised until the two vials were attached. Bioadhesive force, the detachment stress (dyn/cm^2), was determined from the minimal weights that detached the two vials. The rectal tissue pieces were changed for each measurement.

2.6. Release test

The conventional solid suppository [acetaminophen/PEG 4000 (5/95%)] (2.5 g) and liquid suppositories [acetaminophen/P 407/P 188/sodium alginate (5/15/19/0–1.0%)] (2.5 g) containing 125 mg of acetaminophen were inserted into the semipermeable membrane tubes. Both sides of the tube were tied with a thread to prevent leakage. The semipermeable membrane tubes were then placed in a dissolution tester (DST-600, Fine Chemical, Korea). Dissolution test was performed at 36.5°C using the paddle method at 100 rpm with 500 ml phosphate buffer (pH 6.8) as a dissolution medium. At 1-h interval, 5 ml of the medium was sampled and filtered. The filtrate was analyzed by UV/visible variable wavelength detector (Philips, Model PU8730) at 250 nm.

2.7. Pharmacokinetic study

2.7.1. In vivo experiments

A total of 18 healthy male human subjects, weighing 56–72 kg and 22–27 years old, fasted for 12 h prior to drug administration and were divided into two groups: one group for the four conventional solid suppositories and the other group for the four liquid suppositories. At designated time intervals 2 ml of blood were taken and centrifuged at $1000 \times g$ for 10 min.

2.7.2. Blood sample analysis

To 0.3 ml of plasma in a conical tube, 0.1 ml of ethanol solution containing theophylline (20 μg/ml) as an internal standard was added, mixed, and extracted with 0.8 ml of chloroform-acetonitrile mixed solution (60:40, v/v, %) by vortexing for 1 min. It was then centrifuged at $1000 \times g$ for 10 min. Then, 0.7 ml of organic layer was transferred to another conical tube and evaporated to dryness under nitrogen gas at 40°C. The residue was reconstituted with 0.2 ml of mobile phase and then analyzed by HPLC (Waters TM 717 plus Autosampler with chromatorecorder 12). In brief, mobile phase was prepared as follows; methanol, water and acetonitrile were mixed in the ratio of 92:5:3, and the pH was adjusted to 2.5 with phosphoric acid. The mobile phase was run at a flow rate of 1.0 ml/min and aliquots of 10 μl were 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.

3. Results and discussion

3.1. Physicochemical properties of liquid suppository

To develop the acetaminophen liquid suppository, 0.2–1.0% of sodium alginate were added to a liquid suppository composed of 5% acetaminophen, 15% P 407 and 19% P 188, and then the physicochemical properties including gelation temperature, gel strength and bioadhesive force of liquid suppositories were evaluated. Table 1 shows that the liquid suppository without sodium

Table 1
Effect of sodium alginate contents on the physicochemical properties of liquid suppositories [acetaminophen/P 407/P 188/sodium alginate (5/15/19/0–1.0%)]

Sodium alginate (%)	Gelation temperature (°C)	Gel strength (s)	Bioadhesive force ($\times 10^2$ dyn/cm^2)
0	34.4 ± 0.5	16.51 ± 1.88	3.2 ± 0.1
0.2	33.4 ± 0.5	18.24 ± 2.04	3.2 ± 0.1
0.4	33.1 ± 0.4	27.95 ± 1.69	11.0 ± 1.4
0.6	32.0 ± 0.3	45.18 ± 3.77	58.0 ± 7.2
0.8	30.7 ± 0.4	76.23 ± 18.56	105.1 ± 11.1
1.0	28.2 ± 0.2	96.41 ± 12.14	120.7 ± 14.3

Each value represents the mean $\pm$ S.D.

alginate becomes a gel at 34.4°C. This means that the formula is liquid at room temperature and turns into a gel instantly at physiological temperature. Sodium alginate decreased the gelation temperature and reinforced the gel strength and bioadhesive force of liquid suppository. It was previously reported that the optimal liquid suppository must have a suitable gelation temperature (30–36°C), gel strength (10–50 s) and bioadhesive force so as to be administered easily and to be mucoadhesive to the rectal tissues without leakage after the dose (Choi et al., 1998a,b,c). Therefore, liquid suppositories containing less than 0.6% sodium alginate had the gelation temperature (32.0–34.4°C), gel strength (16.51–45.18 s) and bioadhesive force ($3.2–58.0 \times 10^2$ dyn/cm^2) suitable for acetaminophen liquid suppository.

As a possible mechanism by which sodium alginate affected the gelation temperature and gel strength, it is speculated that sodium alginate with hydroxyl groups could bind strongly with the cross-linked reticular poloxamer gel (liquid suppository) by placing sodium alginate in the gel matrix (Lenaerts et al., 1987; Kramaric et al., 1992; Choi et al., 1998a). Furthermore, their bioadhesive force-strengthening effects appear to be enhanced by their strong binding with the oligosaccharide chains of rectal mucous membranes (Robert et al., 1988; Leur et al., 1990; Robinson and Robinson, 1990).

3.2. Release of acetaminophen from liquid suppository

As shown in Fig. 2, sodium alginate slowed the release rates of acetaminophen as well as polycarbophil and carbopol (Choi et al., 1998a). Although the release rates of acetaminophen from the suppositories which contained less than 0.2% sodium alginate were not significantly changed, the release rates of acetaminophen tended to decrease as the concentrations of sodium alginate increased more than 0.4%.

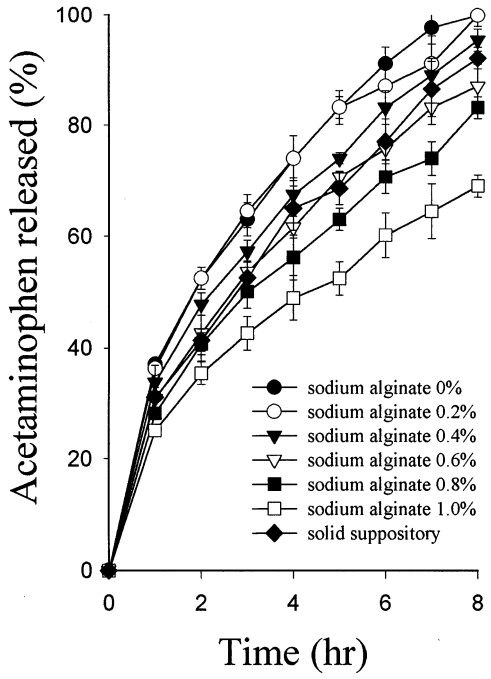

Fig. 2. Release of acetaminophen from liquid suppositories and conventional solid suppository. Liquid suppositories were composed of [acetaminophen/P 407/P 188/sodium alginate (5/15/19/0–1.0%)]. Conventional solid suppository was composed of [acetaminophen/PEG 4000 (5/95%)].

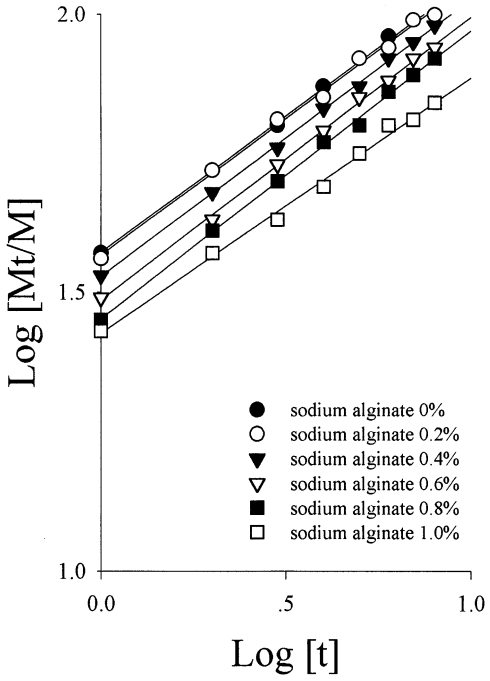

Fig. 3. Log-log plots of released fractions of acetaminophen versus time. Liquid suppositories were composed of [acetaminophen/P 407/P 188/sodium alginate (5/15/19/0–1.0%)].

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

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

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

where M_t/M is the fraction of released drug at time t, k is a characteristic constant of the liquid suppository and n is an indication 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 $\log(M_t/M)$ versus $\log(t)$ (Fig. 3), kinetic parameters, n and k, were calculated. Table 2 shows that most of the n values are close to 0.5, suggesting that acetaminophen is released from the liquid 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 in Fig. 3 indicate that the amount sodium alginate might not affect the release mechanisms. However, the k values indicate that acetaminophen was released more slowly from liquid suppositories with higher concentrations of sodium alginate. Such a slow release of acetaminophen appears to be partly caused by the higher gel strength of the liquid suppository.

As shown in Fig. 2 and Tables 1 and 2, the liquid suppository with 0.6% sodium alginate and with the optimal gelation temperature (32.0 ± 0.3°C), gel strength (45.18 ± 3.77 s) and bioadhesive force ($58.0 \pm 7.2 \times 10^2$ dyn/cm^2), showed a similar release pattern and k value compared to conventional suppository (30.03 vs 30.61%/h$^{1/2}$). Thus, the liquid suppository, [acetaminophen/P 407/P 188/sodium alginate (5/15/19/0.6%)] was selected as a test sample for pharmacokinetic study in human subjects.

3.3. Pharmacokinetic study

Plasma concentration-time profiles and pharmacokinetic parameters are shown in Table 3 and Fig. 4. Using liquid suppository, for the first 2 h after the dose, the plasma concentrations of acetaminophen (1.59–3.45 μg/ml) were significantly higher than those using conventional suppository (0.70–2.27 μg/ml), followed by similar plasma concentrations over the next 2.5 h (Fig. 3). The area under the drug concentration–time active curve (AUC), mean residence time (MRT), biological half-life ($t_{1/2}$) and apparent elimination rate constant (K_{el}) of acetaminophen from liquid suppository (28.74 ± 9.78 h μg/ml, 7.15 ± 0.93 h, 5.00 ± 0.68 h and 0.14 ± 0.03 h^{-1}, respectively) were not significantly different from those from conventional suppository (26.07 ± 6.90 h μg/ml, 8.63 ± 2.37 h, 5.09 ± 2.26 h and 0.14 ± 0.04 h^{-1}, respectively). However, liquid suppository gave significantly faster the time to reach the maximum plasma concentration (T_{max}) and higher the maximum plasma concentrations of drug (C_{max}) of acetaminophen (2.39 ± 0.55 h, 3.97 ± 1.27 μg/ml) than conventional suppository (3.50 ± 0.68 h, 2.89 ± 0.66 μg/ml) indicating that in human sub-

Table 2
Release kinetic parameters of acetaminophen from conventional solid suppository and liquid suppositories

	Release exponent (n)	Kinetic constant (k, %/h^n)	Correlation coefficient (r)
Solid suppository	0.532	30.033	0.9963
Liquid suppository			
Sodium alginate (%)			
0	0.51	36.88	0.9996
0.2	0.50	36.58	0.9983
0.4	0.50	33.96	0.9999
0.6	0.51	30.61	0.9993
0.8	0.51	28.35	0.9989
1.0	0.49	24.97	0.9975

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

Parameter	Liquid suppository	Solid suppository
AUC (h·μg/ml)	28.74 ± 9.78	26.07 ± 6.90
T_{max} (h)*	2.39 ± 0.55	3.50 ± 0.68
C_{max} (μg/ml)*	3.97 ± 1.27	2.89 ± 0.66
MRT (h)	7.15 ± 0.93	8.63 ± 2.37
K_{el} (h^{-1})	0.14 ± 0.03	0.14 ± 0.04
$t_{1/2}$ (h)	5.00 ± 0.68	5.09 ± 2.26

Each value represents the mean $\pm$ S.D. ($n = 9$).
* $p < 0.05$.

jects acetaminophen from liquid suppository can be absorbed faster initially than that from conventional suppository. The reason for this difference might be the dispersability (fluidity) and bioadhesive force. The solid type conventional suppository was not bioadhesive, and slowly dissolved and dispersed in the rectum. In contrast, the bioadhesive liquid suppository was dispersed rapidly in the rectum (since it was initially a fluid), gelled and attached to the rectal mucous membranes.

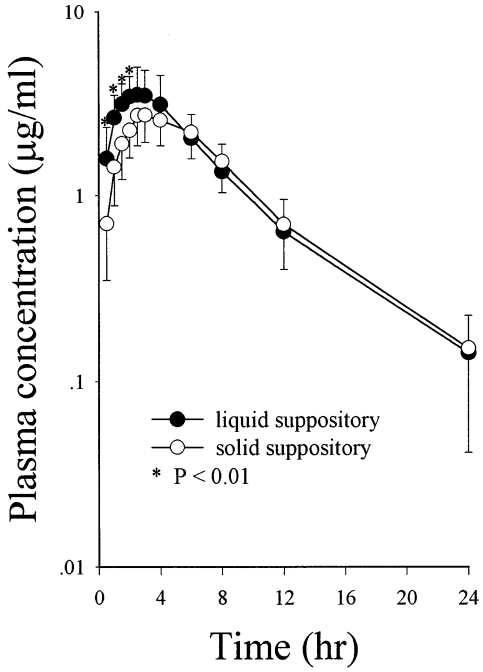

Fig. 4. Plasma concentration-time profiles of acetaminophen after the rectal administration of liquid and conventional solid suppositories to human subjects. Liquid suppository was composed of [acetaminophen/P 407/P 188/sodium alginate (5/15/19/0.6%)]. Conventional solid suppository was composed of acetaminophen/PEG 4000 (5/95%).

4. Conclusion

Taken together, it is concluded that acetaminophen liquid suppository, which allowed faster absorption of acetaminophen in human subjects than did conventional suppository, would be more comfortable during application, increasing patient compliance. Therefore, the in-situ gelling and mucoadhesive acetaminophen liquid suppository is thought to be a favorable antipyretic and analgesic dosage form for infants and children.

Acknowledgements

This work was supported in part by the Research Institute of Pharmaceutical Sciences and the Korea Science and Engineering Foundation through the Research Center for New Drug Development at College of Pharmacy, Seoul National University.

References

Choi, H.K., Oh, Y.K., Kim, C.K., 1998a. In-situ gelling and mucoadhesive liquid suppository containing acetaminophen: enhanced bioavailability. Int. J. Pharm. 165, 23–32.

Choi, H.K., Jung, J.H., Ryu, J.M., Yoon, S.J., Oh, Y.K., Kim, C.K., 1998b. Development of in-situ gelling and mucoadhesive acetaminophen liquid suppository. Int. J. Pharm. 165, 33–44.

Choi, H.K., Jung, J.H., Ryu, J.M., Lee, M.-K., Kim, I.-S., Lee, B.-J., Kim, C.K., 1998c. Effect of additives on the physicochemical properties of acetaminophen liquid suppository. Yakhak Hoeji 42 (3), 290–295.

Huang, C.H., Tokumura, T., Machida, Y., Nagai, T., 1987. Formulation of double-layered suppository for prolonged stay in lower rectum. Yakuzaigaku 47, 42–48.

Kramaric, A., Resman, A., Kofler, B., Zmitek, J., 1992. Thermoreversible gel as a liquid pharmaceutical carrier for a galenic formulation. European Patent, 0551 626 (A1).

Lenaerts, V., Triqueneaux, C., Quarton, M., Falson, F.R., Couvreur, P., 1987. Temperature-dependent rheological behavior of pluronic F-127 aqueous solutions. Int. J. Pharm. 31, 121–127.

Leur, C.M., Bouwstra, J.A., Tukker, J.J., Junginger, H.E., 1990. Intestinal transit of bioadhesive microspheres in an in situ loop in the rat: a comparative study with copolymers and blends based on poly(acrylic acid). J. Control. Release 13, 51–62.

Peppas, N.A., 1985. Analysis of Fickian and non-Fickian drug release polymers. Pharm. Acta Helv. 60, 110–111.

Robert, C.R., Buri, P.A., Peppas, N.A., 1988. Experimental method for bioadhesive testing of various polymers. Acta Pharm. Technol. 34, 95–98.

Robinson, S.S., Robinson, J.R., 1990. Polymer structure features contributing to mucoadhesion. II. J. Control. Release 12, 187–194.