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Physicochemical Characterization and *In Vivo* Evaluation of Thermosensitive Diclofenac Liquid Suppository

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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 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. Furthermore, the pharmacokinetic study of diclofenac sodium delivered by the liquid suppository was performed. Diclofenac sodium significantly increased the gelation temperature and weakened the gel strength and bioadhesive force, while sodium chloride did the opposite. The liquid suppositories with less than 1.0% of sodium chloride, in which the drug was not precipitated, were inserted into the rectum without difficulty and leakage. Furthermore, liquid suppository gave significantly higher initial plasma concentrations and faster Tmax of diclofenac sodium than did solid suppository, indicating that drug from liquid suppository could be absorbed faster than that from solid one in rats. Our results suggested that a thermosensitive liquid suppository system with sodium chloride and poloxamers was a more physically stable, convenient and effective rectal dosage form for diclofenac sodium.

Key words: Diclofenac sodium, Sodium chloride, Liquid suppository, Thermosensitive, Pharmacokinetics

INTRODUCTION

Ideal suppository would be easy to administer with good patient compliance and remain at the 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.*, 1998b; 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 exists as a liquid *in vitro* but a gel *in vivo* (Choi *et al.*, 1999; Dumortier *et al.*, 1991; Yun *et al.*, 1999). 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 temperature and gelling upon increasing the temperature. Moreover, the bioadhesive polymers such as carbopol, polycarbophil and sodium alginate were used to control the gel strength and bioadhesive force of liquid suppository (Dumortier *et al.*, 1991; Yun *et al.*, 1999). The thermosensitive liquid suppository was easy to administer to the anus, since it was a liquid form at room temperature and turned into a gel instantly

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at physiological temperature, and was also mucoadhesive to the rectal tissues without leakage after the dose. It showed the enhanced bioavailability of drugs such as acetaminophen (Dumortier *et al.,* 1991) 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. Furthermore, the pharmacokinetic study of diclofenac sodium delivered by the liquid suppository in rats was performed. Diclofenac sodium was selected here as a model drug, since it was poorly water-soluble and solubilized in aqueous medium by poloxamers (Anderson and Conradi 1985; Iwata *et al.,* 1999; Schneeweis and Muller-Goymann, 1999). 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.

MATERIALS AND METHODS

Materials

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

Preparation of liquid suppository

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 liquid suppository was left at 4°C until a clear solution was obtained (Choi *et al.,* 1999).

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. Liquid suppository 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.,* 1999; Miyazaki *et al.,* 1991).

Measurement of gel strength

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 liquid suppository at physiological temperature, was determined by the time (sec) the apparatus took to sink 5 cm down through the liquid suppository. In cases that it took more than 300 sec to drop the apparatus into the gel, various weights were placed on the top of the apparatus and gel strength was described by the minimal weights that pushed the apparatus 5 cm down through the gel (Choi *et al.,* 1999).

Determination of bioadhesive force

A section of tissue was cut from the fundus of rabbit rectum and instantly secured with mucosal side out onto 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 with a section of tissue was connected to the balance and the other vial was placed on a height-adjustable pan. Liquid suppository 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 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.,* 1999; Miyazaki *et al.,* 1987; Miyazaki *et al.,* 1998).

Measurement of gel strength threshold *in vivo*

To measure the threshold of gel strength, the liquid suppository was administered at a dose of 1.5 g/kg into the rectum of a New Zealand white rabbit raised with 45° slope through a stomach sonde needle fitted on a glass syringe. Each liquid suppository was then evaluated by the difficulty of insertion into the anus and the leakage of gel from the anus during 30 min after administration. The upper threshold of gel strength was defined as the maximum gel strength at which liquid suppository 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 liquid suppository was not leaked out from the anus during 30 min after administration. Thus, liquid suppository with the gel strength between two thresholds was easily inserted into the anus and not leaked out after insertion (Choi *et al.*, 1999).

Pharmacokinetic study

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

Administration and blood-collecting : Each rat, anesthetized in an ether-saturated chamber, was secured on a surgical board in the supine position with a thread. A polyethylene tube was inserted into the right femoral artery of the rat. Liquid suppository (1.5 g/kg equivalent to diclofenac sodium 37.5 mg/kg) was administered into the rectum 4 cm above the anus through a stomach sondle needle fitted on a glass syringe. Solid suppository was administered with a dose of 1.5 g/kg (equivalent to diclofenac sodium 37.5 mg/kg) into the rectum 4 cm above the anus (Miyazaki *et al.*, 1998). 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 liquid suppository was 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) (Choi *et al.*, 1999; Nakanishi *et al.*, 1994; Ramakrishna *et al.*, 1996).

Blood sample analysis : Plasma (0.1 mL) was mixed with 0.4 mL of acetonitrile solution containing flufenamic acid (0.5 μg/mL), as an internal standard. It was then centrifuged at 3000 rpm for 10 min to precipitate the proteins. The supernatant layer (0.4 mL) was evaporated under N_2 (g). The residue was reconstituted in 50 μL of ethanol. Then, the resulting solution was analyzed by HPLC (Hitachi, Model L-7100) equipped with an Inertsil ODS-3 C_{18} column (GL science, 0.5 μm, 15 cm×0.46 cm i.d.) and UV detector (Model L-7450). The mobile phase consisted of acetoniltrile and phosphate buffer (pH 6.8) (4:6, volume ratio). The eluent was monitored at 280 nm with a flow rate of 1.0 mL/min (Garcia *et al.*, 1998; Idkaidek *et al.*, 1998; Pinto Pereira *et al.*, 1999).

RESULTS AND DISCUSSION

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 liquid suppositories were evaluated (Table I). Diclofenac sodium markedly increased the gelation temperature of liquid suppositories. Sodium chloride decreased the gelation temperatures in the absence of diclofenac sodium, whereas in the presence of diclofenac sodium, such impacts were increased. 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. 1), 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.*, 1998).

In the development of liquid suppository, the gel strength

Table I. Effect of diclofenac sodium on the physicochemical properties of liquid suppository

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

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

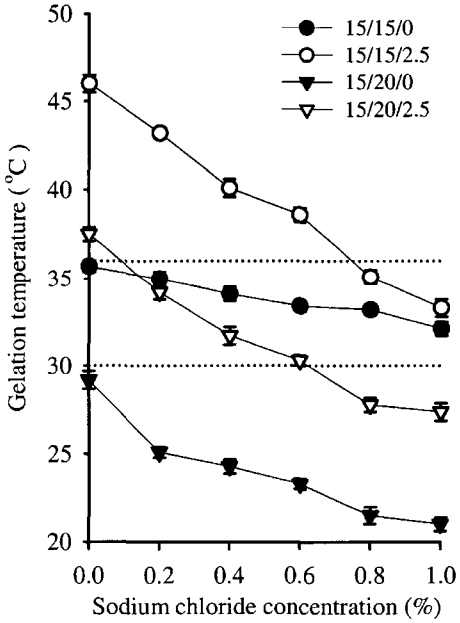

Fig. 1. Effect of diclofenac sodium and sodium chloride on the gelation temperature of liquid suppositories. Each value represents the mean ± S.E. (n = 5).

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 liquid suppository system were investigated by inserting liquid suppositories 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 liquid suppositories. Under the lower limits, the liquid suppositories leaked out from the anus. In the gels with sodium chloride, the range was 10-50 sec (Choi *et al.*, 1998a).

Diclofenac sodium reduced the gel strength of liquid suppositories (Table I, Fig. 2). Sodium chloride increased the gel strength in the absence of diclofenac sodium, whereas in the presence of diclofenac sodium, such impacts were not eased. Given that the gel strength thresholds for liquid suppository with easy insertion and no leakage was 10-50 sec, 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.*, 1998b).

Diclofenac sodium decreased the bioadhesive force of gelled poloxamers. Sodium chloride, which enhanced gel strength efficiently increased the bioadhesive force (Fig. 3).

Diclofenac sodium increased the gelation temperature of liquid suppositories, while decreasing the gel strength of liquid suppositories. The temperature-dependent gelation of poloxamer solutions could be explained by configuration change (Choi *et al.*, 1998a; Kramic *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. 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 liquid suppository by placing diclofenac sodium in the poloxamer gel (Choi *et al.*, 1998a; b). However, sodium chloride exerted highly opposite effects on the gelation temperature and gel strength of liquid suppositories, resulting from that sodium chloride could bind strongly with the cross-linked reticular liquid suppository by the strong cross-linking bonding of sodium salt with poloxamer (Garcia *et al.*, 1998).

Additionally, diclofenac sodium weakened the bioadhesive force of liquid suppositories, while sodium chloride reinforced (Fig. 3). Liquid suppositories composed of only P 407 and P 188 showed the moderate bioadhesive forces, since the poloxamer with hydrophilic oxide group could bind to oligosaccharide chains (Choi *et al.*, 1999). However, sodium chloride and diclofenac sodium had no capacity of binding to them. The bioadhesive force-weakening effect of diclofenac sodium seemed to be contributed by its gel strength-weakening effect of poloxamer, resulting in the weaker binding of liquid suppositories with the oligosaccharide chains of rectal mucous membranes. Similarly, the high bioadhesive force-reinforcing effect of sodium chloride was due to that sodium chloride could reinforce the gel strength of cross-linked reticular liquid suppository, resulting in the more increased binding of liquid suppositories with

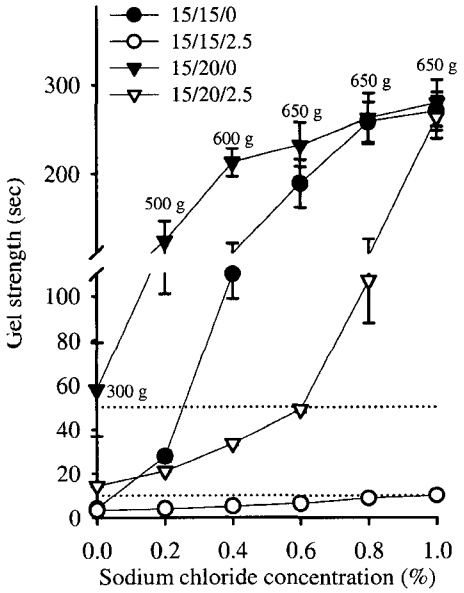

Fig. 2. Effect of diclofenac sodium and sodium chloride on the gel strength of liquid suppositories. Each value represents the mean ±S.E. (n = 5) *Gels composed of 15/20 without diclofenac sodium were so strong that the apparatus could not move down within 300 sec.

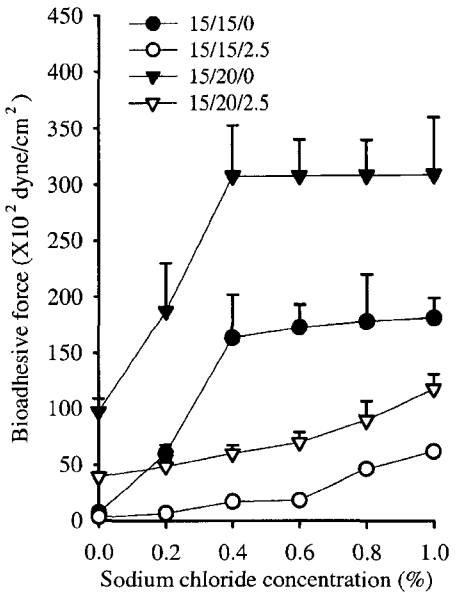

Fig. 3. Effect of diclofenac sodium and sodium chloride on the bioadhesive force of liquid suppositories. Each value represents the mean ± S.E. (n = 5).

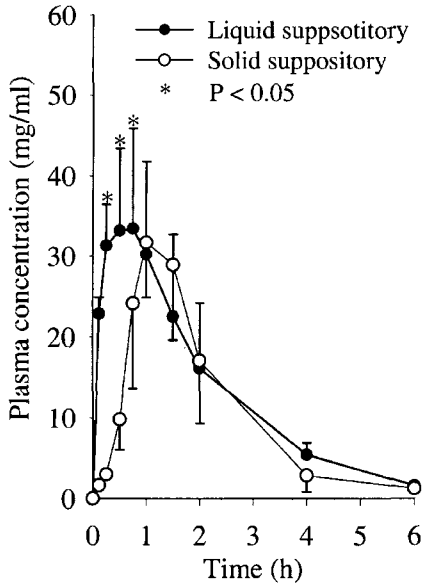

Fig. 4. Plasma concentration-time profiles of diclofenac sodium after rectal administration of liquid and solid suppository to rats. Each value represents the mean ± S.E. (n = 5). (*) P<0.05 compared to solid suppository.

them (Yun *et al.*, 1999). It indicated that the gel strength of liquid suppository seemed to play a role in affecting the bioadhesive force of poloxamer-based liquid suppository.

The pharmacokinetic parameters of diclofenac sodium were determined after rectal administration of liquid suppository [P 407/P 188/sodium chloride/diclofenac sodium (15%/17%/0.8%/2.5%)] and solid one [polyethylene glycol/diclofenac sodium (97.5%/2.5%)] (Choi *et al.*, 1998b).

Fig. 4 shows the change of mean plasma concentration of diclofenac sodium after rectal administration of suppositories in rats. The initial plasma concentrations of diclofenac sodium in liquid suppository were higher compared with those in solid suppository. In particular, in liquid suppository, from 7 min to 30 min, the plasma concentrations of diclofenac sodium (22-34 μg/mL) were significantly higher than those in solid suppository (1-10 μg/mL). However, from 1 h after the dose, the plasma concentrations of diclofenac sodium in liquid suppository, were not significantly different from those in the solid suppository (Nakanishi *et al.*, 1994; Ramakrishna *et al.*, 1996; Schneeweis and Muller-Goymann, 1997). Our results indicated that the diclofenac sodium from liquid suppository could be absorbed faster than that from solid one in rats. The reason for this fast absorption might be dependent upon the dispensability (fluiduty) and bioadhesive force (Choi *et al.*, 1998 b). Solid suppository was not bioadhesive, and gradually dissolved and dispersed. On contrast, liquid suppository was spread easily in the rectum, gelled and attached on the rectal mucous membranes, since bioadhesive liquid suppository was a fluid initially (Choi *et al.*, 1998 b; Yun *et al.*, 1999).

Table II. Pharmacokinetic parameters of diclofenac sodium delivered by suppositories

Parameters	Solid suppository	Liquid suppository
AUC (h· μg/mL)	63.78 ± 20.08	80.55 ± 25.03
Tmax (h)	0.94 ± 0.13	0.50 ± 0.22*
Cmax (μg/ml)	31.70 ± 7.33	33.42 ± 9.90
K_{el} (h^{-1})	0.73 ± 0.24	0.59 ± 0.13
$t_{1/2}$ (h)	0.95 ± 0.32	1.18 ± 0.38

* P<0.05 compared with solid suppository.
** Each value represents the mean ± S.E. (n = 6).

The pharmacokinetic parameters are shown in Table II. Liquid suppository gave significantly faster Tmax of diclofenac sodium (0.50 ± 0.22 h) than did solid suppository (0.94 ± 0.13 h) (P<0.05). However, the AUC, Cmax, K_{el} and $t_{1/2}$ values of diclofenac sodium from liquid suppository were not significantly different from those from solid suppository (80.55 ± 25.03 vs. 63.78 ± 25.03 h μg/mL; 33.42 ± 9.90 vs. 31.70 ± 7.33 μg/mL; 0.59 ± 0.13 vs. 0.73 ± 0.24 h^{-1}; 1.18 ± 0.38 vs. 0.99 ± 0.32 h). Our results suggested that liquid suppository with sodium chloride would be useful to deliver diclofenac sodium in a pattern that allows fast absorption in the initial phase.

CONCLUSION

Taken together, it is concluded that the liquid suppositories with less than 1.0% of sodium chloride, in which the drug was not precipitated, were inserted into the rectum without difficulty and leakage. Furthermore, liquid suppository gave significantly higher initial plasma concentrations and faster Tmax of diclofenac sodium than did solid suppository, indicating that drug from liquid suppository could be absorbed faster than that from solid one in rats. Thus, the thermosensitive liquid suppository with sodium chloride and poloxamer was a more physically stable, convenient and effective rectal dosage form for diclofenac sodium.

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