J Incl Phenom Macrocycl Chem (2009) 64:265–272
DOI 10.1007/s10847-009-9560-7

ORIGINAL ARTICLE

Thermo-reversible flurbiprofen liquid suppository with HP-β-CD as a solubility enhancer: improvement of rectal bioavailability

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Received: 13 January 2009 / Accepted: 1 March 2009 / Published online: 13 March 2009
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Abstract The purpose of this work was to develop a thermo-reversible flurbiprofen liquid suppository base composed of poloxamer and sodium alginate for the improvement of rectal bioavailability of flurbiprofen. Cyclodextrin derivatives such as α-, β-, γ-cyclodextrin and hydroxypropyl-β-cyclodextrin (HP-β-CD) were used to enhance the aqueous solubility of flurbiprofen. The effects of HP-β-CD and flurbiprofen on the physicochemical properties of liquid suppository were then investigated. Pharmacokinetic studies were performed after rectal administration of flurbiprofen liquid suppositories with and without HP-β-CD or after intravenous administration of commercial Lipfen® (flurbiprofen axetil-loaded emulsion) to rats, and their pharmcokinetic parameters were compared. HP-β-CD decreased the gelation temperature and reinforced the gel strength and bioadhesive force of liquid suppository, while flurbiprofen was opposed to HP-β-CD. Thermo-reversible flurbiprofen liquid suppository showed the physicochemical properties suitable for rectal administration. The flurbiprofen liquid suppository with HP-β-CD showed significantly higher plasma levels, AUC and C_{max} of flurbiprofen than those of the liquid suppository without HP-β-CD, indicating that flurbiprofen could be well absorbed due to the enhanced solubility by formation of inclusion complex. Moreover, the flurbiprofen liquid suppository with HP-β-CD showed an excellent bioavailability in that the AUC of flurbiprofen after its rectal administration was not significantly different from that after intravenous administration of commercial Lipfen®. It is concluded that HP-β-CD could be a preferable solubility enhancer for the development of liquid suppository containing poorly water-soluble drugs.

Keywords Flurbiprofen · Hydroxypropyl-β-cyclodextrin · Thermo-reversible liquid suppository · Poloxamer · Bioavailability

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Introduction

Flurbiprofen [2-(2-fluoro-4-biphenyl) propionic acid], a non-steroidal anti-inflammatory drug (NSAID), is widely used to treat gout [1], osteoarthritis [2] and rheumatoid arthritis [3]. Solubilization process influences on the absorption and oral bioavailability of flurbiprofen, since flurbiprofen is practically insoluble in water [4, 5]. Various oral formulations of flurbiprofen such as dry elixir [6], inclusion complex [7, 8], salt formation [9], solid dispersion [10] and microparticles [11], were developed to improve the solubility of flurbiprofen. However, orally administered flurbiprofen was associated with the upper gastrointestinal side effects like irritation and ulceration, and resulted in life-threatening mucosal damage within the small and large intestine [12].

Parenteral and transdermal preparations were developed as alternative dosage forms for oral flurbiprofen, but they showed some limitations to use. Parenteral preparations formulated in the form of microemulsion with flurbiprofen

itself [13] or flurbiprofen axetil [5, 14], even though they could enhance the solubility of flurbiprofen, were likely to cause various problems related to the dosage form such as physical and psychic pain, hypertrophy or atrophy of the subcutaneous fat at the injection site. Transdermal preparations formulated with permeability enhancers hardly improved the bioavailability of flurbiprofen [15, 16]. Hence, it is required to develop another alternative formulation for flurbiprofen with enhanced safety, patient compliance and bioavailability.

Thermo-reversible liquid suppository exists as a sol in vitro but a gel in vivo by modulating the gelation temperature of liquid suppository base. The thermo-reversible property, sol–gel transition, of liquid suppository can be achieved by controlling the ratio of poloxamers (P407 and P188), which are known to exhibit reverse thermal gelation [17]. Thermo-reversible liquid suppository was easy to administer to the anus, since it was in a liquid form at room temperature and turned into a gel instantly at physiological temperature and was also mucoadhesive to the rectal tissues without leakage after the dose. In addition, thermosensitive mucoadhesive gel formulations have been applied to vaginal administration for gynecological usage [18, 19] From previous studies, it was shown that thermo-reversible liquid suppository cloud enhance bioavailability of drug with good safety in rats and human subjects [20–22]. Furthermore, the rectal bioavailability was improved by enhancing the solubility of poorly water-soluble drug formulated in thermo-reversible liquid suppository [23].

Cyclodextrins are cyclic oligosaccharides obtained by the enzymatic degradation of starch. The special structure of cyclodextrins composed of a truncated cone with an apolar cavity and a hydrophilic external part conveys inclusion forming capability to natural and modified cyclodextrins. Hydrophobic molecules can be included in the apolar cavity. By the formation drug:CD complex, the physicochemical properties of the drug such as aqueous solubility, stability unwanted side effects, taste or odor [24, 25]. Cyclodextrins are also reported to convey controlled release properties to certain active ingredients. Natural cyclodextrin, β-cyclodextrin (β-CD) and its most frequently used derivative hydroxypropyl-β-cyclodextrin (HP-β-CD) are used to solubilize and stabilize active ingredients by the formation of drug:CD inclusion complexes [26].

Thus, in this study, it has been attempted to develop a thermo-reversible liquid suppository, which was a more convenient and effective rectal delivery system of flurbiprofen. The effects of cyclodextrin derivatives as solubility enhancers on the aqueous solubility of flurbiprofen were evaluated and the optimal ratio of flurbiprofen to a solubility enhancer was determined. The effects of a solubility enhancer, hydroxypropyl-β-cyclodextrin (HP-β-CD), and flurbiprofen on the physicochemical properties of liquid suppository base composed of P407, P188 and sodium alginate were investigated. Then, the pharmacokinetic studies were performed after rectal administration of flurbiprofen liquid suppository with and without HP-β-CD or after intravenous administration of commercial Lipfen® (flurbiprofen axetil-loaded emulsion) to rats, and their pharmcokinetic parameters were compared.

Materials and methods

Materials

Flurbiprofen, poloxamers (P407, P188) and sodium alginate were supplied from Samil Pharmaceutical (Seoul, Korea), BASF (Ludwigshafen, Germany) and BF Goodrich (Breesville, OH, USA), respectively. Cyclodextrin derivatives, α-, β-, γ-cyclodextrin and hydroxypropyl-β-cyclodextrin (HP-β-CD), were purchased from Sigma Chemical (St. Louis, MO, USA). All other chemicals were of reagent grade and used without further purification.

Effect of cyclodextrin derivatives on the aqueous solubility of flurbiprofen

To determine the optimal ratio of flurbiprofen to solubility enhancer, solubility test was performed with cyclodextrin derivatives. In brief, excess of flurbiprofen (300 mM) and various concentrations of cyclodextrin derivatives (4–30 mM) were added to 5 mL of distilled water, respectively. They were shaken at room temperature for 7 days, filtered through membrane filter (0.45 μm) and analyzed by UV/visible spectrophotometer (DU650, Beckman, USA) at 254 nm.

Characterization of flurbiprofen: HP-β-CD complex

Differential scanning calorimetry (DSC)

The formation of inclusion complex between flurbiprofen and HP-β-CD was confirmed by differential scanning calorimetry. To obtain a powder of inclusion complex, 0.5 g of flurbiprofen and 8.0 g of HP-β-CD (1:3, molar ratio) were dissolved in 100 mL of 5% ammonia solution, filtered through membrane filter (0.45 μm) and freeze-dried at −80 °C for 48 h. The powder was further dried at 40 °C for 24 h and thereafter at 60 °C for 24 h. DSC curves for flurbiprofen, HP-β-CD, physical mixture and inclusion complex were obtained by differential scanning calorimeter (DSC200, Netzsch, Germany) at a scan rate of 5 °C/min under nitrogen gas stream.

FT-IR spectrophotometry

FT-IR spectra of flurbiprofen, HP-β-CD, physical mixture and flurbiprofen: HP-β-CD inclusion complex were taken with a Jasco FT-IR (Model-300E, Jasco Ltd., Tokyo, Japan) using discs of each sample and previously prepared KBr containing 0.01 g sample in 0.1 g of potassium bromide between the wavenumber 400–4,000 cm^{-1}.

Preparation of liquid suppository

Flurbiprofen, sodium alginate and HP-β-CD were dissolved in distilled water at room temperature and cooled down to 4 °C. P407 and P188 were then slowly added to the solution with continuous agitation. The solution was kept at 4 °C until clear solution was obtained.

Physicochemical properties of liquid suppository

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 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.

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 (s) the apparatus took to sink 5 cm down through the liquid suppository. The device measuring the gel strength was used as previously developed by Choi et al. [17].

Determination of bioadhesive force

The bioadhesive force of liquid suppository was determined as previously described by Yun et al. [21]. 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 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) kept raised until two vials were detached. 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.

Pharmacokinetic study

Treatment groups

Male Sprague-Dawley rats weighing 250 ± 20 g were supplied from Experimental Animal Breeding Center of Seoul National University (Seoul, Korea). The protocol of this study was approved by the Animal Care and Use Committee of the College of Pharmacy, Seoul National University. The rats were fasted for 24–36 h prior to the experiments but allowed free access to water. Fifteen rats were divided into three groups. The rats in one group were intravenously administered with commercial product (Lipfen®, Green Cross, Japan). The rats in other groups were rectally administered with liquid suppository A [flurbiprofen/P407/P188/sodium alginate/HP-β-CD (1.25/14/13/0.6/22%)] and B [flurbiprofen/P407/P188/sodium alginate (1.25/14/13/0.6%)], respectively.

Administration and blood-collecting

Each rat, anesthetized in an diethylether-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. Lipfen® (equivalent to 12 mg/kg as free flurbiprofen) was intravenously administered. Liquid suppository A and B (equivalent to 12 mg/kg flurbiprofen) were administered into the rectum 4 cm above the anus through a stomach sonde needle fitted on a glass syringe. The entrance of anus was then blocked with a cyanoacrylate adhesive to prevent the suppositories from leaking out from the anus. Without cyanoacrylate adhesive, liquid suppository B was leaked out from the anus during the pharmacokinetic experiment, leading to obtaining inaccurate pharmacokinetic data. Each blood sample (500 μL) was collected from the right femoral artery at designated time intervals and centrifuged at 3000 rpm for 10 min to obtain plasma. Plasma was stored at −20 °C prior to HPLC analysis.

HPLC analysis

Plasma (100 μL) was mixed with 250 μL of acetonitrile solution containing naproxen (40 μg/mL), as an internal

standard. It was then centrifuged at 10,000 rpm for 10 min to precipitate the proteins. The supernatant (20 μL) was directly injected onto a μ-Bondapak C_{18} column (250 × 4.6 mm I.D., 10 μm, Waters, MA, USA). The HPLC system (Shimadzu, Japan) was equipped with a pump (LC-9A, Shimadzu), a system controller (SCL-6B, Shimadzu), a UV/visible detector (SPD-6A, Shimadzu) and an autosampler (TM717, Waters). The mobile phase, a mixture of acetonitrile, water and phosphoric acid (510/490/5, volume ratio), was eluted at a flow rate of 1.2 mL/min and the eluant was monitored with UV/visible detector at the wavelength of 254 nm.

Pharmacokinetic data analysis

The area under the drug concentration-time curve (AUC) was calculated using trapezoidal rule. The maximum blood concentration of drug (C_{max}) and time to reach maximum blood concentration (T_{max}) were directly obtained from plasma data. Levels of statistical significance ($p < 0.05$) were assessed using the Student-*t*-test between the two means for unpaired data. All results are expressed as mean ± standard deviation values.

Results and discussion

To determine the solubility enhancer for a poorly-water soluble flurbiprofen, cyclodextrin derivatives such as α-, β-, γ-cyclodextrin and HP-β-CD, were added, and then the solubility of flurbiprofen was compared. Cyclodextrin derivatives has been known to improve the solubility of flurbiprofen by forming non-covalent inclusion complexes [8, 27]. Among cyclodextrin derivatives, only HP-β-CD greatly improved the aqueous solubility of flurbiprofen proportional to the concentration of HP-β-CD (Fig. 1). Other cyclodextrin derivatives, α-, β- and γ-cyclodextrin, hardly improved the solubility of flurbiprofen. The enhanced solubility of flurbiprofen by addition of HP-β-CD can be attributed to not only the amorphous character and higher solubility of HP-β-CD but also the conformational change of β-cyclodextrin via hydroxypropylation. It was reported that the presence of alkyl or hydroxyalkyl groups in cyclodextrin derivatives increased the hydrophobic region of cyclodextrin by capping edge of the cavity and expanded the location of substrate binding [28]. In addition, the linear regression plot of the concentration of HP-β-CD versus phase solubility of flurbiprofen gave the slope of 0.336, indicating that more than 3-fold of HP-β-CD was needed for flurbiprofen to be completely soluble in water. From the results, the flurbiprofen/HP-β-CD ratio of 1/3 (molar ratio) was determined as optimal ratio and used in further studies.

The formation of inclusion complex between flurbiprofen and HP-β-CD was confirmed by DSC and FT-IR. The

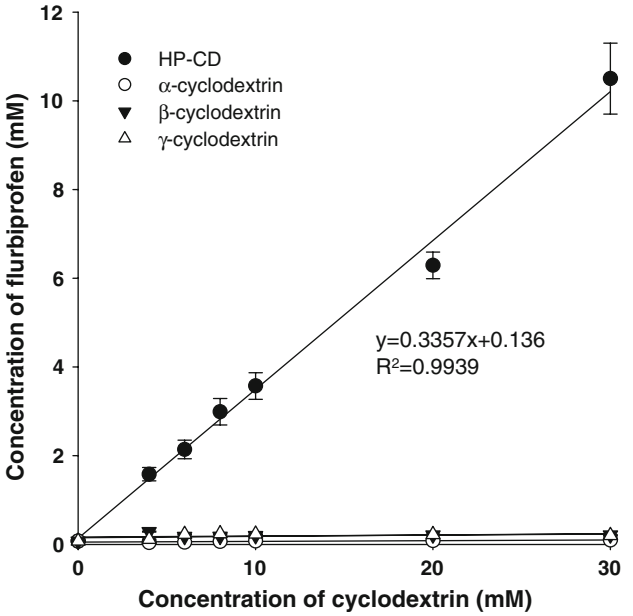

Fig. 1 Effects of cyclodextrin derivatives on the aqueous solubility of flurbiprofen. Each value represents the mean ± SD ($n = 5$)

endothermic peak of HP-β-CD was observed at 180 °C and also found in physical mixture and inclusion complex (Fig. 2). However, the distinctive peak of flurbiprofen at around 105 °C, which was observed in physical mixture, disappeared in the inclusion complex. The FT-IR indicated that the flurbiprofen carbonyl stretching band of carboxyl group at 1,700 cm^{-1} disappeared in the inclusion complex (Fig. 3), but it was not changed in the physical mixture. The disappearance in the inclusion complex may due to the dissociation of intermolecular hydrogen bonds of

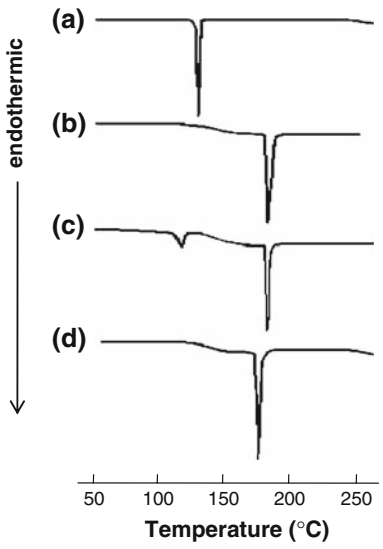

Fig. 2 DSC curves of (**a**) flurbiprofen, (**b**) HP-β-CD, (**c**) physical mixture of flurbiprofen and HP-β-CD (1:3, molar ratio) and (**d**) inclusion complex of flurbiprofen and HP-β-CD (1:3, molar ratio)

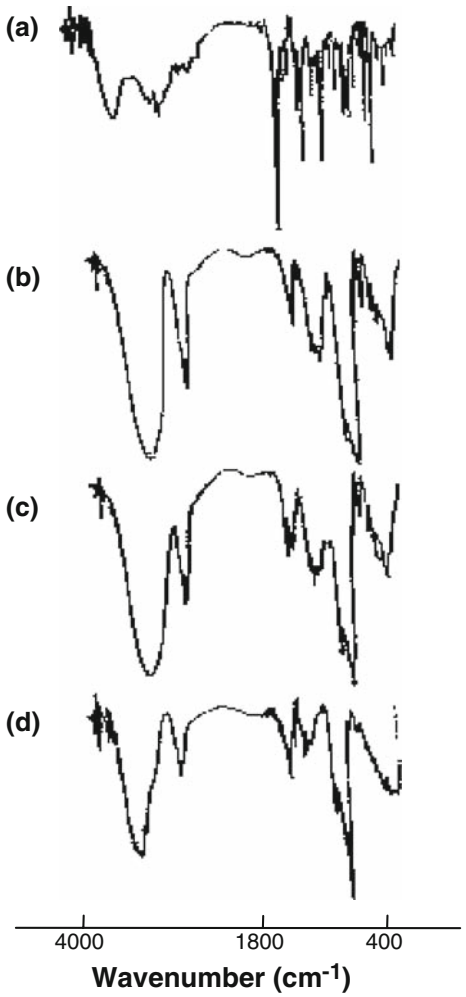

Fig. 3 FT-IR spectra of (**a**) flurbiprofen, (**b**) HP-β-CD, (**c**) physical mixture of flurbiprofen and HP-β-CD (1:3, molar ratio) and (**d**) inclusion complex of flurbiprofen and HP-β-CD (1:3, molar ratio)

flurbiprofen by distributions of molecular level through inclusion complex. These results indirectly proved that the inclusion complex between flurbiprofen and HP-β-CD was completely formed and the improved solubility of flurbiprofen was contributed by the formation of inclusion complex [29].

Table 1 Effect of HP-β-CD on the physicochemical properties of liquid suppository base

HP-β-CD (%)	Gelation temperature (°C)	Gel strength (s)	Bioadhesive force ($\times 10^2$ dyne/cm^2)
0	43.7 ± 0.5	10.8 ± 1.3	30.8 ± 3.4
20	32.6 ± 0.3	41.5 ± 0.5	42.8 ± 0.9
22	31.7 ± 0.6	49.2 ± 5.3	43.7 ± 4.5
25	27.3 ± 0.4	60.8 ± 9.8	46.3 ± 1.0

Liquid suppository base were prepared at the fixed ratio of [P407/P188/sodium alginate (14/13/0.6% (w/w))]. Each value represents the mean ± SD ($n = 5$)

Since characteristics of flurbiprofen liquid suppository should be suitable for rectal administration, the effects of HP-β-CD and flurbiprofen on physicochemical properties of liquid suppository base were investigated in terms of gelation temperature, gel strength and bioadhesive force, respectively. Various concentrations of HP-β-CD (20, 22, 25%) were added to the liquid suppository base composed of P407, P188 and sodium alginate (14/13/0.6%, w/w), and then the effects of HP-β-CD on the physicochemical properties were evaluated (Table 1). Our results indicated that the HP-β-CD decreased the gelation temperature and reinforced the gel strength and bioadhesive force of liquid suppository base. As a possible mechanism for the decrease of gelation temperature and increase of gel strength by addition of HP-β-CD, it is speculated that the hydrophilic hydroxyl group (OH) of the HP-β-CD interacted with water molecules and bound strongly with cross-linked reticular poloxamer gel via hydrogen bond. Hydrogen bonds among HP-β-CD, water molecules and poloxamer could reduce the quantity of free water molecules which prevent aggregation of poloxamer and increase the opportunities for poloxamer monomers to associate together strongly at lower temperature [23, 30]. However, our observations disagree with a previous study that the HP-β-CD shifts the gelation temperature by changing remarkably the microstructure of the gelled samples [31]. It is also supposed that HP-β-CD apolar cavity may interact with more hydrophobic portion of poloxamer especially when polymer begins the dehydration process, but the shift of gelation temperature can only be dependent on the interaction between the hydroxyl groups of HP-β-CD, in particular hydroxypropyl [31]. Furthermore, the increment of bioadhesive force at higher concentration of HP-β-CD appears to be contributed by the increased number of hydrogen bonds between the hydroxyl group of the HP-β-CD and the oligosaccharide chains of rectal mucous membranes [23].

Flurbiprofen (1.25%) was added to a liquid suppository base [P407/P188/sodium alginate/HP-β-CD (14/13/0.6/22%)], and then the physicochemical properties including gelation temperature, gel strength and bioadhesive force of liquid suppositories were also evaluated (Table 2). It can be observed from the results that flurbiprofen increased the gelation temperature (31.7 ± 0.6 vs. 34.7 ± 0.5 °C), while weakened the gel strength (49.2 ± 5.3 vs. 40.2 ± 3.3 s) and the bioadhesive force (43.7 ± 4.5 vs. 33.4 ± 3.5 × 10^2 dyne/cm^2) of liquid suppository base. Even though HP-β-CD was added enough to form inclusion complex completely, the physicochemical properties of liquid suppository were influenced by the addition of flurbiprofen. The presence of substituent in cyclodextrin derivatives reduced the stability of inclusion complex by steric interference [28]. It is assumed that the hydroxypropyl groups in HP-β-CD reduced the stability of inclusion complex, and therefore the

Table 2 Effect of flurbiprofen on the physicochemical properties of liquid suppository base

Formulation	Gelation temperature (°C)	Gel strength (s)	Bioadhesive force ($\times 10^2$ dyne/cm^2)
Flurbiprofen 0%	31.7 ± 0.6	49.2 ± 5.3	43.7 ± 4.5
Flurbiprofen 1.25%	34.7 ± 0.5	40.2 ± 3.3	33.4 ± 3.5

Liquid suppository base were prepared at the fixed ratio of [P407/P188/sodium alginate/HP-β-CD (14/13/0.6/22% (w/w))]. Each value represents the mean ± SD ($n = 5$)

hydrophobic flurbiprofen molecules were partially dissociated from the inclusion complex. As a possible mechanism by which flurbiprofen affected the gelation temperature and gel strength, it is also speculated that the free flurbiprofen could bind weakly with the cross-linked reticular poloxamer gel by placing flurbiprofen in the gel matrix [23]. Moreover, the decreased bioadhesive force appears to be contributed by weak binding of flurbiprofen with the oligosaccharide chains of rectal mucous membranes.

It was previously reported that the optimal liquid suppository should have the suitable range of gelation temperature (30–36 °C), gel strength (10–50 s) and bioadhesive force to administer easily to the anus and to remain at the administered site without leakage after the dose [20, 21]. From these results, the flurbiprofen liquid suppository [flurbiprofen/P407/P188/sodium alginate/HP-β-CD (1.25/14/13/0.6/22%)] had the gelation temperature (34.7 ± 0.5 °C), gel strength (40.2 ± 3.3 s) and bioadhesive force (33.4 ± 3.5 × 10^2 dyne/cm^2) suitable for liquid suppository.

The pharmacokinetic studies were performed after rectal administration of liquid suppository A [flurbiprofen/P407/P188/sodium alginate/HP-β-CD (1.25/14/13/0.6/22%)] and B [flurbiprofen/P407/P188/sodium alginate (1.25/14/13/0.6%)]. Average plasma concentration versus time curves of flurbiprofen after rectal and intravenous administration of flurbiprofen formulations to rats are shown in Fig. 4. The plasma concentration of flurbiprofen in rats increased to reach a maximum, 55 μg/mL at 1.5 h and 25 μg/mL at 1 h after rectal administration of liquid suppository A and B, respectively, followed by decreasing to ≤10 μg/mL by 11 h after the dose (Fig. 4a). The plasma concentrations of flurbiprofen in liquid suppository A were continuously higher compared with those of liquid suppository B. In particular, in liquid suppository A, from 0.75 h to 3 h, the plasma concentrations of flurbiprofen (25–55 μg/mL) were significantly higher than those of liquid suppository B (15–25 μg/mL). In case of intravenous administration of Lipfen®, flurbiprofen axetil, the prodrug of flurbiprofen, could not be detected in rat plasma sample. It might be due to the fast hydrolysis of flurbiprofen axetil to flurbiprofen in rat

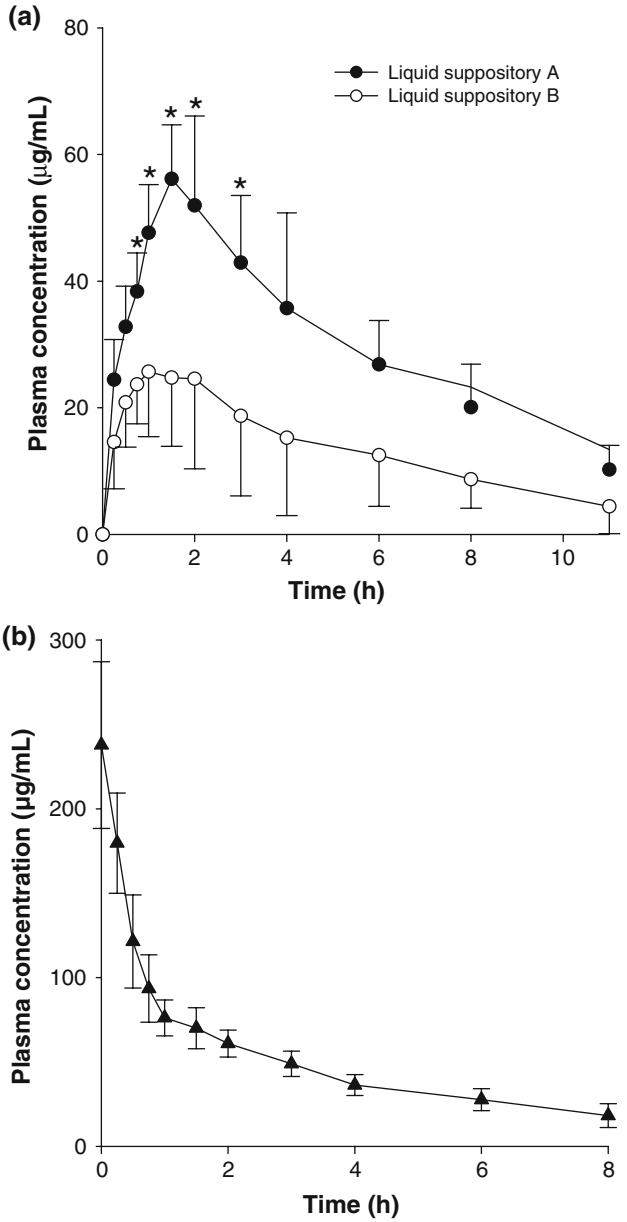

Fig. 4 Plasma concentration-time profiles of flurbiprofen after rectal administration of (**a**) liquid suppositories and (**b**) intravenous administration of commercial Lipfen® to rats. Liquid suppository A and B were composed of [flurbiprofen/P407/P188/sodium alginate/HP-β-CD (1.25/14/13/0.6/22%)] and [flurbiprofen/P407/P188/sodium alginate (1.25/14/13/0.6%)], respectively. Each value represents the mean ± S.D. ($n = 5$). *, $P < .05$ compared to liquid suppository B

plasma [32]. The plasma concentration of flurbiprofen after intravenous administration of commercial Lipfen® decreased to <10 μg/mL by 8 h after the dose (Fig. 4b).

The pharmacokinetic parameters are shown in Table 3. The T_{max} of flurbiprofen from liquid suppository A (1.5 ± 0.2 h) was not significantly different from that from liquid suppository B (1.0 ± 0.6 h). However, liquid suppository A gave significantly higher C_{max} of flurbiprofen

Table 3 Pharmacokinetic parameters of flurbiprofen after rectal administration of liquid suppositories and intravenous administration of commercial Lipfen® to rats

Parameter	Liquid suppository A	Liquid suppository B	Lipfen®
AUC (μg h/mL)	336.9 ± 102.7*	177.0 ± 101.6	379.8 ± 78.9*
T_{max} (h)	1.5 ± 0.2	1.0 ± 0.6	–
C_{max} (μg/mL)	56.1 ± 8.2*	25.7 ± 11.4	–

Each value represents the mean ± SD ($n = 5$)

* $P < 0.05$ compared to liquid suppository B

(56.1 ± 8.2 μg/mL) than did liquid suppository B (25.7 ± 11.4 μg/mL). The AUC of flurbiprofen from liquid suppository A (336.9 ± 102.7 μg h/mL) increased 1.9-fold compared with that from liquid suppository B (177.0 ± 101.6 μg h/mL). Furthermore, the AUC of flurbiprofen after rectal administration of liquid suppository A (336.9 ± 102.7 μg h/mL) was not significantly different from that after intravenous administration of commercial Lipfen® (379.8 ± 78.9 μg h/mL).

From these results, flurbiprofen from liquid suppository A was absorbed faster and higher than that from liquid suppository B. This fast and high absorption of flurbiprofen could be explained by the increased bioadhesive force of liquid suppository and the enhanced solubility of flurbiprofen in the presence of HP-β-CD. The increased bioadhesive force prolonged the retention of liquid suppository in rectal tissues and gave more opportunity for drug to permeate the rectal mucous membrane [33]. The solubility of poorly water-soluble drug in rectal fluid is also important factor in rectal absorption. The absorption of poorly water-soluble drug after rectal administration exhibited lower bioavailability than that after oral administration since the volume of rectal fluid available for dissolution is much smaller than that of gastrointestinal fluid [34]. It is speculated that the addition of HP-β-CD in liquid suppository enhanced the solubility of flurbiprofen in rectal fluid and resulted in the improved absorption of flurbiprofen in rectal tissue. Moreover, HP-β-CD could prevent mucous membrane from damaging by adverse effect of flurbiprofen since cyclodextrin derivatives reduced the irritation of rectal mucosa caused by NSAIDs [35].

Consequently, thermo-reversible flurbiprofen liquid suppository with HP-β-CD [flurbiprofen/P407/P188/sodium alginate/HP-β-CD (1.25/14/13/0.6/22%)] was the most suitable formulation for rectal delivery of poorly water-soluble drug, flurbiprofen.

Conclusion

Thermo-reversible flurbiprofen liquid suppository [flurbiprofen/P407/P188/sodium alginate/HP-β-CD (1.25/14/13/0.6/22%)] was prepared with the physicochemical properties suitable for rectal administration. Moreover, flurbiprofen liquid suppository with HP-β-CD showed higher rectal bioavailability than that without HP-β-CD, indicating that the rectal bioavailability of flurbiprofen was improved by the solubilizing effect of HP-β-CD. It is concluded that the thermo-reversible flurbiprofen liquid suppository with sol–gel transition property and mucoadhesiveness could have a potential to be developed as a more convenient and effective rectal delivery system and HP-β-CD could be a preferable solubility enhancer for the development of liquid suppository containing poorly water-soluble drugs.

Acknowledgements This work is financially supported by the Ministry of Education and Human Resources Development (MOE), the Ministry of Commerce, Industry and Energy (MOCIE) and the Ministry of Labor (MOLAB) through the fostering project of the Lab of Excellency.

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