# Design and Evaluation of an Osmotic Pump Tablet (OPT) for Chlorpromazine Using $(SBE)_{7m}$-β-CD

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***Purpose.*** The purpose of this study was to develop a controlled-porosity osmotic pump tablet (OPT) which exhibits pH-independent release profiles for a basic drug using a sulfobutyl ether-β-cyclodextrin, $(SBE)_{7m}$-β-CD, which acts as both a solubilizer and as an osmotic agent.
***Methods.*** Chlorpromazine free base (CLP) was chosen as a model drug for this study. The release of CLP from osmotic pump tablets was studied *in vitro*. *In vivo* absorption of CLP from the OPT was evaluated in male beagle dogs.
***Results.*** The CLP release profile from an OPT prepared from a core tablet composed of a 1:10 molar ratio of CLP to $(SBE)_{7m}$-β-CD was pH-independent, and was controlled by modulating the membrane thickness of the OPT. Another cyclodextrin, hydroxypropyl-β-cyclodextrin (HP-β-CD), and a sugar mixture of lactose and fructose resulted in pH-dependent release at the same molar ratio. An *in vivo* absorption study in dogs with an OPT containing $(SBE)_{7m}$-β-CD correlated very well with the *in vitro* release profiles using the Japanese Pharmacopoeia dissolution method.
***Conclusions.*** In addition to serving as a solubilizer and osmotic agent, $(SBE)_{7m}$-β-CD can also serve as the controlling agent for pH independent release of CLP from OPTs. This system successfully modified the *in vivo* input rate of CLP without compromising oral bioavailability.

**KEY WORDS:** osmotic pump; controlled-porosity osmotic pump tablet; $(SBE)_{7m}$-β-CD; cyclodextrins; HP-β-CD.

## INTRODUCTION

Oral controlled-release preparations have historically been used to gain therapeutic advantages for specific drugs (1–4). Among oral controlled-release devices, osmotic pumping systems including tablets with a micro-orifice drilled through a semipermeable membrane (5,6,11–13) and controlled-porosity membrane tablets (7–10) have demonstrated predictable and reproducible release properties. These properties include exhibition of zero-order release kinetics (5–15), good *in vitro-in vivo* correlation (6,10–13), amelioration of pH-dependent release (14,15), and application to poorly water soluble drugs (9–11,16). However, a single osmotic pumping system in which all of the above properties are addressed has not been reported.

Sulfobutyl ether-β-cyclodextrin, $(SBE)_{7m}$-β-CD as the sodium salt, is a β-cyclodextrin derivative which is variably substituted by an average of seven sulfobutyl ether groups on the 2-, 3-, and 6- positions of the glucose unit of β-cyclodextrin (17). Because of its high osmotic pressure (9) and high solubilizing potential (9,10,18,19), $(SBE)_{7m}$-β-CD has been used in the development of a porosity-controlled osmotic pump tablet (OPT), primarily for poorly water soluble and neutral drugs like prednisolone. Release of these drugs from the OPT were complete and showed zero-order kinetics. Moreover, an *in vivo* absorption study using an OPT containing $(SBE)_{7m}$-β-CD correlated very well with the *in vitro* release profiles using the Japanese Pharmacopoeia dissolution method (10). Except for improving pH-dependent release, an OPT with $(SBE)_{7m}$-β-CD has addressed the properties described above.

Zentner *et al.* (14) reported obtaining pH-independent release of diltiazem hydrochloride from an OPT by modulating the solubility of the drug using sodium chloride or the positively charged anion-exchange resin, poly(4-vinyl pyridine). Also, Bodmeier *et al.* (15) reported the release profile of theophylline, a weakly basic drug which is slightly soluble in water, from an OPT coated with a membrane including a charged pore former, diabasic calcium phosphate, was pH-independent. However, it was assumed these approaches could not be applied to a poorly water soluble, charged drug like CLP without utilizing a solubilizer in the system. In the present study, OPTs of CLP were prepared with an increasing ratio of $(SBE)_{7m}$-β-CD to CLP in the core tablet, and the pH-dependency of the drug release utilizing $(SBE)_{7m}$-β-CD, HP-β-CD, and sugars as osmotic pump agents were compared. A bioavailability study in dogs allowed for *in vitro/in vivo* correlations to be made.

## MATERIALS AND METHODS

### Materials

The synthesis and characterization of $(SBE)_{7m}$-β-CD have been described previously (17). HP-β-CD (Encapsin™; mw 1338; degree of molar substitution, 0.6) was supplied by American Maize Products Co. (Hammond, Indiana, USA). Chlorpromazine hydrochloride, lactose, and fructose were purchased from Wako Pure Chemical Company (Osaka, Japan). Chlorpromazine free base (CLP) was obtained by converting salts to the free base using aqueous sodium bicarbonate. Cellulose acetate (CA-398-10) was purchased from Eastman Chemical Company (Kingsport, Tennessee, USA). Micronized lactose was purchased from DMV (The Netherlands).

### Phase Solubility Study

The stability constants between CLP and $(SBE)_{7m}$-β-CD or HP-β-CD were determined using the phase solubility method (18,20). An excess of CLP was added to 0 to 0.05 M β-CD derivatives in phosphate or bicarbonate buffered solutions of pH 8–11. The samples were agitated at 25°C for 72 hours. Equilibrium solubility was confirmed by preliminary studies. After centrifuging at 10,000 rpm, the isolated supernatant was

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diluted with mobile phase and analyzed by HPLC. CLP was fractionated on a Hypersil ODS column with detection at 254 nm using a mobile phase of 60% acetonitrile-pH 4 0.1 M acetate buffer. The $pK_a$ values and intrinsic solubilities of each agent were calculated from the solubility of each agent in the absence of added cyclodextrin using least squares regression analysis (Scientist; MicroMath, Salt Lake City, Utah). The stability constants of CLP with β-CD derivatives, $K_1$ for the neutral CLP with the cyclodextrin, and $K_2$ for the positive charged CLP, were calculated using non-linear least squares regression analysis (Scientist; MicroMath, Salt Lake City, Utah) based on an equation reported by Okimoto *et al.* (18).

### Preparation of Core Tablets

The core tablets for the osmotic pump tablet were prepared by using an eccentric tabletting machine (Okada Seikou Company) using a 7 to 10 mm round punch with kneaded powder of CLP with the osmotic pump agents, $(SBE)_{7m}$-β-CD, HP-β-CD, or a sugar mixture (lactose:fructose = 1:1 as the weight ratio). The kneaded powder was prepared by vacuum drying for 12 hours at 40°C after mixing the composed materials with a 20% (v/v) ethanol-water solution using a mortar and pestle. The components of the kneaded powder were as follows; CLP:β-CD derivatives = 1:1, 1:2.5, 1:5, 1:7.5, 1:10, and 1:15 as the molar ratio; and the sugar:CLP = quantitatively the same components as those of CLP:β-CD derivatives.

### Preparation of the Osmotic Pump Tablets (OPT)

The OPTs were prepared using a modification of the Zentner *et al.* method (7) in which a suspension composed of micronized lactose/cellulose acetate (CA-398-10)/triethyl citrate with a weight ratio of 2/2/1 in ethanol/dichloromethane with a weight ratio of 10.5/31.5 was film-coated onto the core tablets using a Flow Coater Mini® (Floint Company).

### Release Studies

The release of CLP from the cores or OPTs (equivalent to 10 mg CLP) was examined according to the paddle method of the Japanese Pharmacopoeia (JP) XIII dissolution test (50 rpm, 37°C). The dissolution media (900 ml) were the JP first fluid (pH 1.2) and the JP second fluid (pH 6.8). Released CLP was monitored by an automatic dissolution tester (Hewlett 8451A Diode Array Spectrophotometer), in which the test medium was sampled through a metal filter (porosity 10–20 μm) and measured at 254 nm.

### Absorption Studies

This research adhered to the "Principles of Laboratories Animal Care" (NIH publication #85–23, revised 1985). The preparations were administered with 30 ml of water to three male dogs under both fasted and fed conditions with a one week washout interval between the studies. The dogs used at each feeding condition were different and weighed as follows: 9.0, 11.8, and 13.6 kg in the fasted condition; 12.9, 13.9, and 15.0 kg in the fed condition. For the oral preparations of CLP (equivalent to 30 mg CLP), CLP as a hydrochloride solution prepared by dissolving chlorpromazine hydrochloride in water, three core tablets (10 mg CLP/core tablet), and three OPTs with $(SBE)_{7m}$-β-CD (10 mg CLP/OPT) were used. Two milliliters of CLP solution with 0.1 M $(SBE)_{7m}$-β-CD (equivalent to 10 mg CLP) was prepared for the intravenous control experiment. The fasted dogs received no food, but had free access to water for 24 hours prior to drug administration. The fed dogs received 100 g of dog food (DS-5®, Oriental Koubo Company) 30 min before receiving a dose of the preparations.

Blood samples were pulled at various time intervals and plasma was isolated by centrifugation. A half milliliter of plasma was mixed with 50 μl methanol, 0.5 ml of 0.1 N sodium hydroxide, 6 ml of dichlormethane, and 50 μl of imipramine (10 μg/ml). The sample was vortex mixed for 10 min followed by centrifugation at 3000 rpm for 10 min. Four milliliters of the dichlormethane phase was evaporated and the residue was redissolved in 100 μl of mobile phase, 40 μl of which was injected for the determination of CLP. The HPLC conditions were as follows: UV detector, SPD-10A (Shimadzu CO., Kyoto, Japan); pump, Model 510 (Waters Associates, Mississippi, USA); column, Inertsil ODS-S (5 mm, 4.6-mm i.d. × 150 mm; GL Science Inc., Tokyo); mobile phase, acetonitrile/0.1 M acetate buffer (65/35); flow rate, 1 mL/min; detection, 254 nm; and column temperature, 40°C.

## RESULTS AND DISCUSSION

### Phase Solubility of PDL with β-CD Derivatives

The intrinsic solubility of CLP, a basic dug, was $2.74 \times 10^{-6}$ mol/L and its pKa was 9.3 at 37°C. In the phase solubility studies the solubility of CLP in various pH solutions increased almost linearly with increasing concentration of both β-CD derivatives up to 0.05 M, suggesting 1:1 complexation. Stability constants, ($K_1$) of neutral CLP with β-CD derivatives and ($K_2$) of positively charged CLP with β-CD derivatives, calculated by the method reported by Okimoto *et al.* (18) were as follows; $K_1 = 73{,}100\ M^{-1}$, $K_2 = 32{,}100\ M^{-1}$ for $(SBE)_{7m}$-β-CD, and $K_1 = 44{,}600\ M^{-1}$, $K_2 = 7{,}010\ M^{-1}$ for HP-β-CD. These results are consistent with previous studies which showed $(SBE)_{7m}$-β-CD to bind more effectively to positively charged drugs than HP-β-CD, which might be due to charge interactions.

### Design of OPT Showing pH-Independent Release

In the previous study, poorly water soluble drugs like testosterone and prednisolone in the presence of β-CD derivatives were released from OPTs as a complex rather than a free drug (9,10). Figure 1 shows the release behaviors of CLP from core tablets (uncoated, Fig. 1A) and OPTs prepared from the core tablets (Fig. 1B). Since CLP was suggested to form a 1:1 inclusion complex with $(SBE)_{7m}$-β-CD, the core tablet was prepared with a 1:1 molar ratio of CLP to $(SBE)_{7m}$-β-CD. Also, to evaluate the pH-dependency of CLP release, the JP dissolution-paddle method was used with the JP first fluid (pH 1.2) and the JP second fluid (pH 6.8). The release rate of CLP from the core tablet was pH-independent, and the release was complete in both mediums within 30 minutes. However, the release profiles of CLP from the OPT coated with 0.25 mm membrane displayed pH-dependency. The CLP release rate at pH 6.8 was much slower than that observed at pH 1.2, and the release at pH 6.8 was incomplete over 12 hours. This suggested a larger amount of $(SBE)_{7m}$-β-CD was necessary to ameliorate the pH-dependency of CLP release from the OPT.

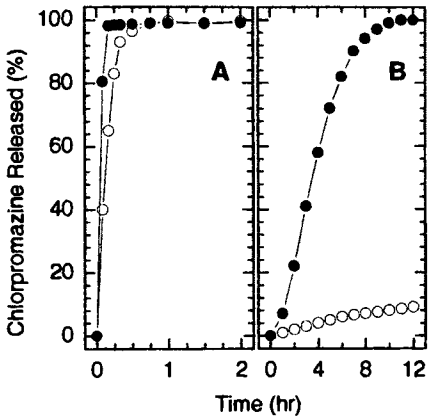


**Fig. 1.** Release profiles of CLP from uncoated core tablets (A) or OPTs (B) composed of CLP:$(SBE)_{7m}$-β-CD at a 1:1 molar ratio in the different pH media. pH 1.2 (•); pH 6.8 (○).

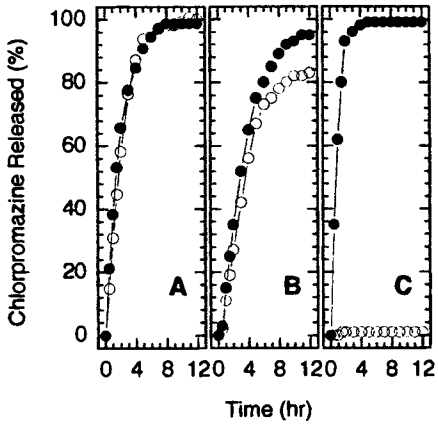


**Fig. 3.** Comparison of CLP release rate from OPT prepared using a core tablet composed of CLP:$(SBE)_{7m}$-β-CD (A), CLP:HP-β-CD (B), or a CLP:sugar mixture (C) at a molar ratio of 1:10 in the different pH media. pH 1.2 (•); pH 6.8 (○).

Figure 2 illustrates the release profiles in different pH mediums of CLP from OPTs in which the molar ratio of $(SBE)_{7m}$-β-CD to CLP was varied. The release rates of CLP from OPTs were almost the same in pH 1.2 medium regardless of the amount of $(SBE)_{7m}$-β-CD (Fig. 2A). In comparison, the release rates in pH 6.8 medium (Fig. 2B) increased with an increasing molar ratio of $(SBE)_{7m}$-β-CD to CLP, and the release was complete at ratios over 1:10 (CLP:$(SBE)_{7m}$-β-CD).

In addition, CLP release from OPTs containing $(SBE)_{7m}$-β-CD was compared to the release characteristics of CLP from OPTs in which $(SBE)_{7m}$-β-CD is replaced by HP-β-CD, which does not exhibit high osmotic properties, or a sugar mixture, which acts as a general osmotic pump agent without possessing solubilizing ability. Figure 3 shows the release profiles of CLP from OPTs with $(SBE)_{7m}$-β-CD, HP-β-CD and the sugar mixture through membranes of 0.25 mm thickness in pH mediums of pH 1.2 and pH 6.8. To fairly compare the ability of $(SBE)_{7m}$-β-CD, the added amount of CLP to HP-β-CD was set at the same molar ratio (1:10) and the added amount of the sugar mixture was set at the same weight ratio as for the $(SBE)_{7m}$-β-CD. The pH-dependency of CLP release rate from OPTs with $(SBE)_{7m}$-β-CD was not observed, however, OPTs with the other excipients still exhibited the pH-dependency. The release rate of CLP with the sugar mixture in pH 6.8 medium was significantly slower, which is consistent with the non-solubilizing effect of the sugar mixtures compared to the β-CD derivatives. Also, the CLP percent release with the HP-β-CD was incomplete at about 80%. This is consistent with the relative ability of the HP-β-CD to solubilize CLP compared to $(SBE)_{7m}$-β-CD as shown in the phase solubility studies. From these results, it is concluded that $(SBE)_{7m}$-β-CD is effective in ameliorating pH-dependent release of drugs from OPTs. The appropriate amount of $(SBE)_{7m}$-β-CD necessary to ensure pH-independent release must be at lease ten-fold the molar amount of CLP, but may vary for other basic drugs depending on their physical and chemical properties.

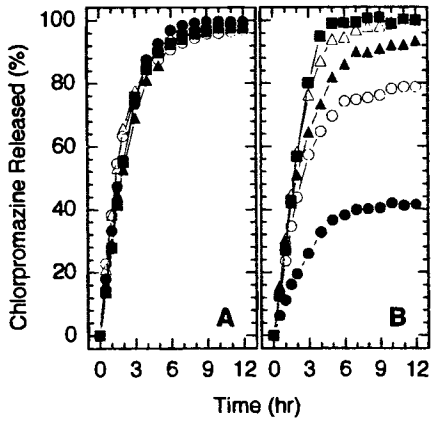


**Fig. 2.** Effect of CLP:$(SBE)_{7m}$-β-CD ratio in core tablets on the pH-dependency of the CLP release rate from OPTs in pH 1.2 medium (A) and in pH 6.8 medium (B). CLP:$(SBE)_{7m}$-β-CD = 1:2.5 (•); 1:5 (○); 1:7.5 (▲); 1:10 (△); 1:15 (■).

### Effect of Membrane Thickness on Release of CLP from OPT

Figure 4A shows the release profiles of CLP through membranes of varying thickness from OPTs with $(SBE)_{7m}$-β-CD at pH 1.2 and pH 6.8. Figure 4B is a plot of the release rates calculated from the zero-order release portions of the release profiles versus the inverse thickness of the membrane. The relationship is linear ($r^2 > 0.99$) demonstrating the release rates from the OPTs were controlled by modulating the thickness of the membrane and that the CLP was approximately released in a pH-independent manner.

The release rate of a drug from the controlled-porosity osmotic pump can be represented by Eq. 1.

$$\frac{dm}{dt} = \frac{A \cdot S \cdot Lp\sigma \cdot \Delta\pi}{h} \quad (1)$$

In Eq. 1, dm/dt is the release rate, A is the surface area of the film coated membrane, h is the membrane thickness, Lpσ is the fluid permeability of the membrane, Δπ is the osmotic pressure difference across the membrane at saturation, and S is the drug solubility. Both relationships in Fig. 4B are linear ($r^2 > 0.99$), and the slopes are almost the identical, following the release rate equation for osmotic pumping. Therefore, it is concluded the pH-independent release rate of CLP

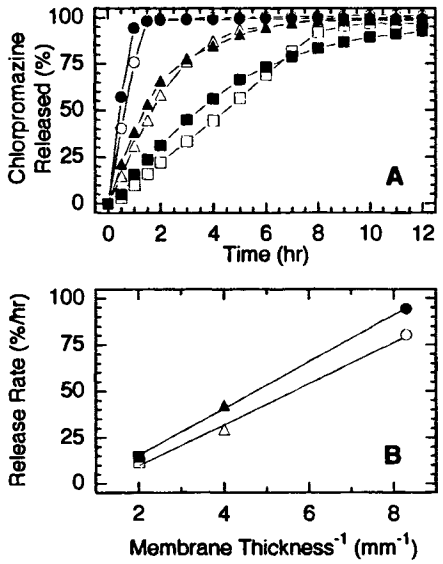


**Fig. 4.** Effect of membrane thickness on release of CLP from OPTs in different pH media (A) and relationship between the release rate of CLP and the inverse of membrane thickness (B). 0.12 mm (●, ○); 0.25 mm (▲, △); 0.5 mm (■, □) in pH 1.2 (closed symbols) and pH 6.8 media (open symbols).

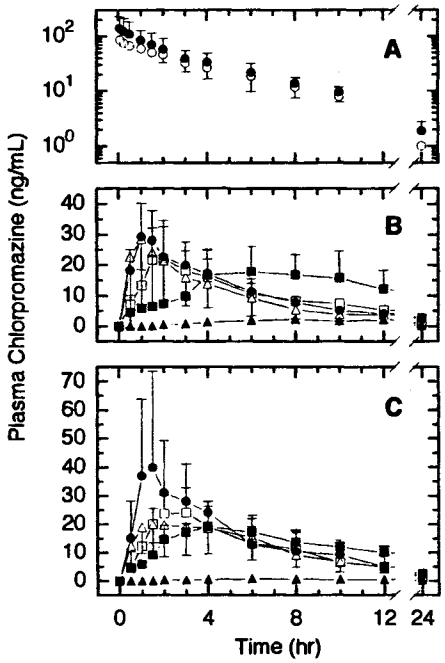


**Fig. 5.** Average plasma concentrations of CLP (n = 3) after intravenous administration (A) or oral administration of CLP in the fed (B) or fasted state (C). Intravenous doses (A) were from a 0.1M $(SBE)_{7m}$-β-CD solution (equivalent to 10 mg CLP) under fasted (●) and fed conditions (○). Oral dosages (equivalent to 30 mg CLP) under fed (◧) and fasted conditions (C) were as follows: hydrochloride solution (◐); core tablet (CLP:$(SBE)_{7m}$-β-CD = 1:1) (△); core tablet (CLP:$(SBE)_{7m}$-β-CD = 1:10) (□); OPT-1 (▲); OPT-2 (■).

from the OPT can be simply controlled by modulating the membrane thickness.

### *In Vivo* Absorption of OPT

Historically, several commercial controlled or sustained release preparations for pH-dependent solubility drugs exhibited variations in oral bioavailability when administered to animals or humans (21–23). Figure 5A shows the mean plasma concentration-time profiles in fasted and fed beagle dogs after intravenous administration of CLP dissolved in 0.1 M $(SBE)_{7m}$-β-CD (equivalent to 10 mg CLP). These profiles were fit to a two-compartment open model by nonlinear least squares regression analysis. The pharmacokinetic parameters were calculated and tabulated in Table I. The difference in the pharmacokinetic parameters between the fasted and the fed conditions is consistent with the weight variation of the dogs used.

The mean plasma concentration-time profiles in the beagle dogs in fed and fasted conditions, respectively, after oral administration of each preparation are shown in Figs. 5B and 5C with the important pharmacokinetic parameters summarized in Table II. A solution of chlorpromazine hydrochloride dissolved in water, core tablet (no coating) with $(SBE)_{7m}$-β-CD of two different molar ratios to CLP (CLP:$(SBE)_{7m}$-β-CD = 1:1 and 1:10), and two different OPTs (OPT-1 and OPT-2, respectively) prepared from the two different core tablets with 0.42 mm membrane thickness were administered. The CLP release rate from OPT-1 prepared from the core tablet with a 1:1 molar ratio was 12%/hr in pH 1.2 medium and 0.8%/hr in pH 6.8 medium. In comparison, the CLP release rates from OPT-2 prepared from the core tablet with a 1:10 molar ratio were the same, 13% ± 1.5%, in both mediums.

Markedly higher plasma level profiles from OPT-2 were found compared to OPT-1 in both fed and fasted conditions, suggesting pH-independent release. Also, the plasma profiles from OPT-2 were extended compared to the non-controlled preparations. With regard to absorption rate, there was significant difference in $T_{max}$ and MRT between OPT-2 and the hydrochloride solution, and this result was independent of the feeding condition. Also, although a significant difference in $T_{max}$ and MRT between OPT-1 and the hydrochloride solution were observed under the fed condition, differences under the fasted condition were not observed. Moreover, there was no statistically significant difference between the hydrochloride solution and the core tablets under both feeding conditions. Additionally, there were no statistically significant differences in absolute bioavailability between the preparations except for OPT-1. The bioavailability of OPT-1 was significantly decreased compared with the hydrochloride solution and the other preparations under both feeding conditions. From these results it can be concluded that the OPT-2, which shows a pH-independent release profile, resulted in much better bioavailability performance and extended plasma profile compared to OPT-1, which shows pH-dependent release. Moreover, in spite of the extended plasma profiles, the OPT-2 did not appear to be compromised by pH differences in the GI tract and GI transit time differences between fasted and fed state animals.

### *In Vitro/In Vivo* Correlation

Recently, Skelly et al. proposed various correlation levels (A to C) as a measure of the degree of *in vitro/in vivo* correlation

**Table I.** Pharmacokinetic Parameters of CLP After Intervenous Administration of a CLP Solution Made with 0.1 M $(SBE)_{7m}$-β-CD (Equivalent to 10 mg CLP) in Fasted and Fed Dogs (n = 3)

| Feed condition | $AUC_{0-24}$ (ng/ml hr) | $C_0$ (ng/ml) | $T_{1/2\ \alpha}$ (hr) | $T_{1/2\ \beta}$ (hr) | $V_p$ (L/kg) | $CL_{tot}$ (ml/kg/min) |
|---|---|---|---|---|---|---|
| Fasted | 459.3 ±207.4 | 134.1 ±47.1 | 1.12 ±0.21 | 4.95 ±1.12 | 7.13 ±3.48 | 31.9 ±7.7 |
| Fed | 346.5 ±78.2 | 84.2 ±6.0 | 1.58 ±0.25 | 4.62 ±1.21 | 9.41 ±1.82 | 38.7 ±8.1 |

*Note*: Values are mean ± SD.

**Table II.** Pharmacokinetic Parameters[a] of CLP After Oral Administration of Its Preparation (Equivalent to 30 mg) in Fasted and Fed Dogs (n = 3)

| Sample | Feed condition | $T_{max}$ (hr) | $C_{max}$ (ng/ml) | $AUC_{0-24}$ (ng/ml·hr) | MRT (hr) | BA[b] (%) |
|---|---|---|---|---|---|---|
| Hydrochloride solution | Fasted | 2.5 ± 3.0 | 41.8 ± 16.5 | 298.0 ± 126.2 | 6.3 ± 0.4 | 21.8 |
| Core tablet for OPT-1 | Fasted | 1.5 ± 0.5 | 21.7 ± 11.6 | 195.0 ± 91.9 | 7.1 ± 1.2 | 14.2 |
| Core tablet for OPT-2 | Fasted | 3.3 ± 0.6 | 25.2 ± 8.4 | 229.4 ± 89.2 | 7.4 ± 0.8 | 16.7 |
| OPT-1 | Fasted | 5.3 ± 3.1 | 0.8 ± 0.1* | 10.7 ± 3.9* | 3.9 ± 0.5 | 0.8* |
| OPT-2 | Fasted | 5.3 ± 1.2* | 19.6 ± 6.8 | 234.7 ± 47.6 | 8.7 ± 0.9* | 17.1 |
| Hydrochloride solution | Fed | 1.2 ± 0.3 | 30.2 ± 11.1 | 193.7 ± 60.5 | 7.0 ± 0.7 | 18.6 |
| Core tablet for OPT-1 | Fed | 1.3 ± 0.6 | 28.8 ± 21.0 | 158.8 ± 108.5 | 5.6 ± 0.6 | 15.3 |
| Core tablet for OPT-2 | Fed | 2.5 ± 1.3 | 23.3 ± 11.7 | 176.3 ± 28.4 | 7.1 ± 1.5 | 17.0 |
| OPT-1 | Fed | 9.3 ± 2.3* | 2.4 ± 0.3* | 30.7 ± 2.6* | 10.3 ± 1.1* | 3.0* |
| OPT-2 | Fed | 6.7 ± 1.2** | 17.8 ± 8.2 | 250.1 ± 101.6 | 9.4 ± 0.16* | 24.0 |

[a] Values are mean ± SD.
[b] Absolute bioavailability.
* $P < 0.05$ vs. hydrochloride solution of each feed condition.
** $P < 0.01$ vs. hydrochloride solution of each feed condition.

(24). Therefore, an attempt was made to correlate the observed *in vitro* release with *in vivo* absorption for the current tablet.

Figure 6 shows the *in vitro*/*in-vivo* correlation of OPT-2 displayed by two different approaches. The *in vivo* absorption of CLP was calculated from the data presented in Figure 5 by the Loo-Riegelman method (25) using the pharmacokinetic parameters from the intravenous data. The *in vitro* release profiles of CLP from OPT-2 were measured according to the JP XIII methodology using only the paddle method (speed; 50 rpm) in 900 ml of JP first fluid (pH 1.2) and JP second fluid (pH 6.8) at 37°C. For the first correlation, the *in vitro* percent released versus time profiles of OPT-2 in pH 1.2 or pH 6.8 medium were almost superimposeable upon the percent *in vivo* absorption versus time profiles under both feeding conditions, suggesting a 1:1 correlation of level A (Figure 6A). In the second correlation (Figure 6B), the plots of the percent *in vivo* absoprtion versus the *in vitro* percent released in pH 1.2 or pH 6.8 medium displayed a good point-to-point relationship ($r^2 > 0.95$) with a slope of 0.90 to 1.07 as the mean values. Therefore, it was concluded that the *in vivo* absorption of CLP from the OPT-2 occurred throughout the gastrointestinal tract in dogs and that a level A correlation existed between *in vivo* performance and release under the JP dissolution-paddle method using both pH 1.2 and pH 6.8 mediums. This correlation suggests $(SBE)_{7m}$-β-CD is effective at ameliorating the pH-dependent absorption of CLP *in vivo* and interbatch *in vivo* performance may be predicted by *in vitro* release studies.

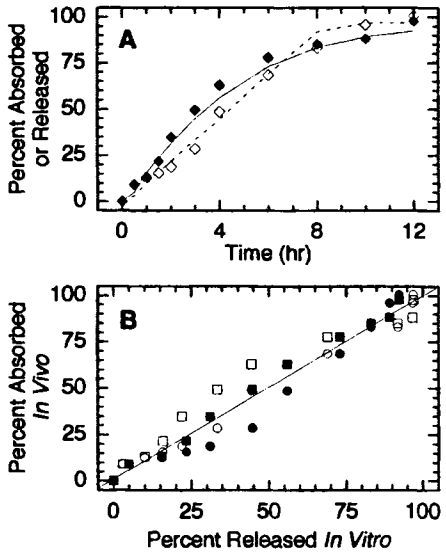


**Fig. 6.** *In vitro*/*in vivo* correlations for OPT-2. (A) *In vivo* absorbed fasted state (◆); *in vivo* absorbed fed state (◇), solid line is *in vitro* released in pH 1.2 medium and dotted line is *in vitro* released in pH 6.8 medium. (B) pH 6.8 fasted (□); pH 1.2 fasted (■); pH 6.8 fed (○); and pH 1.2 fed (●).

## CONCLUSIONS

The present results suggest $(SBE)_{7m}$-β-CD can serve not only as both a solubilizer and an osmotic agent, also an ameliorating agent of pH-dependency on a release profile from OPT

for CLP. Furthermore, the absorption rate and bioavailability of CLP from an OPT is unaffected in this case by feeding conditions in the dog, and the *in vivo* absorption profiles of CLP from OPT with $(SBE)_{7m}$-β-CD in dogs correlated well with the *in vitro* release profiles using a standard dissolution apparatus and conditions.

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