Design and Evaluation of an Osmotic Pump Tablet (OPT) for Prednisolone, a Poorly Water Soluble Drug, 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) for poorly water soluble drugs using a sulfobutyl ether-β-cyclodextrin, $(SBE)_{7m}$-β-CD or Captisol™, which acted as both a solubilizer and as an osmotic agent.

Methods. Prednisolone (PDL) was chosen as a model drug for this study. The release of PDL from osmotic pump devices and tablets was studied. *In vivo* absorption of PDL from OPT was evaluated in male beagle dogs.

Results. PDL release from the osmotic pump tablet with $(SBE)_{7m}$-β-CD was complete. Another cyclodextrin, hydroxypropyl-β-cyclodextrin (HP-β-CD), and a sugar mixture of lactose and fructose resulted in incomplete release. Although PDL release from the OPT with $(SBE)_{7m}$-β-CD and the sugar formulation displayed mainly zero-order release characteristics, the tablet utilizing HP-β-CD showed apparent first-order release characteristics. An *in vivo* absorption study in dogs correlated very well with the *in vitro* release profiles using the Japanese Pharmacopoeia dissolution method.

Conclusions. The present results confirm that $(SBE)_{7m}$-β-CD can serve as both the solubilizer and the osmotic agent for OPT of PDL, and modify the input rate of PDL without compromising oral bioavailability.

KEY WORDS: osmotic pump; controlled-porosity osmotic pump tablet; $(SBE)_{7m}$-β-CD; cyclodextrins, HP-β-CD; poorly water soluble drug; prednisolone.

INTRODUCTION

Sulfobutyl ether-β-cyclodextrin, $(SBE)_{7m}$-β-CD as a sodium salt, is a β-cyclodextrin derivative which is variably substituted by an average of seven sulfobutyl ether groups on the 2-, 3- and the 6- positions of the glucose unit of β-cyclodextrin. Recently, the properties of $(SBE)_{7m}$-β-CD and $(SBE)_{4m}$-β-CD (substituted with average of four sulfobutyl groups) have been reported. The properties include an improved toxicity profile (1–6), increased solubilization of poorly soluble drugs, and enhanced oral, parenteral and ophthalmic delivery of poorly water-soluble drugs (7–11). A manuscript on the development of a porosity-controlled osmotic pump tablet using $(SBE)_{7m}$-β-CD has been accepted for publication (12).

A porosity-controlled osmotic pump tablet is one coated by a semipermeable membrane containing leachable materials. The idea was first formally developed by Zentner et al. (13–17). In this system, drug, after dissolution, is released from the OPT by hydrostatic pressure through pores created by the dissolution of pore formers incorporated into the membrane. The hydrostatic pressure is created by an osmotic agent, the drug itself or a tablet component, after water is imbibed across the semipermeable membrane. This system is generally applicable for only highly water soluble drugs. Because poorly water-soluble drugs dissolve slowly, it is not possible to completely deliver drugs with poor solubility properties from such devices. This problem can be overcome by adding $(SBE)_{7m}$-β-CD which can act as both a solubilizer and as an osmotic agent.

The release rate of drugs from the osmotic pump device can be accounted for by purely osmotic effects by Equation 1 (18).

$$dm/dt = (AS/h)L_p\sigma\Delta\pi \quad (1)$$

In Equation 1, dm/dt is the release rate, A is the surface area of the film coated membrane, h is the membrane thickness, $L_p\sigma$ is the fluid permeability of the membrane, $\Delta\pi$ is the osmotic pressure difference across the membrane at saturation, and S is the drug solubility. In our previous study, the solubility of testosterone in the device, S, was improved by a factor of 2,000 with $(SBE)_{7m}$ -β-CD over that seen in water, and the osmotic pressure difference was five times higher with $(SBE)_{7m}$-β-CD compared to hydroxypropyl-β-cyclodextrin, a neutral uncharged cyclodextrin (12).

Also, in our earlier testosterone study, drug release was monitored from a die with only one exposed surface (12). In the present study, an actual controlled porosity osmotic pump tablet of prednisolone, a poorly water soluble drug, was prepared and the drug release characteristics utilizing $(SBE)_{7m}$-β-CD, HP-β-CD and sugars as excipients 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 (1). HP-β-CD (Encapsin™; mw 1338; degree of substitution, 4.2; molar substitution, 0.6) was supplied by American Maize Products Co. (Hammond, IN, USA). Prednisolone (PDL), lactose, fructose, sorbitol and polyethylene glycol were purchased from Wako Pure Chemical Company. (Osaka, Japan). Cellulose acetate (CA-398-10) was purchased from Eastman Chemical Company (Kingsport, TN, USA) while methylcellulose was purchased from Shinetu Chemical Co. (Nigata, Japan).

Phase-Solubility Study

The binding constants between PDL and $(SBE)_{7m}$-β-CD and HP-β-CD were determined using the phase solubility method (19). An excess of PDL was added to 0 to 0.05M β-

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CD derivative-water solutions, and agitated at 25°C for 72 hours. Equilibrium solubility was confirmed by preliminary studies. After centrifuging at 10,000 rpm, the isolated supernatant was diluted with a mobile phase and analyzed by an HPLC assay. PDL was fractionated on a Hypersil ODS column with detection at 250 nm using a mobile phase of 60% acetonitrile-water. The binding constants for PDL with the two β-CD derivatives were calculated using least squares regression analysis (Delta Graph®; Delta Point Inc., CA, USA) based on an equation reported by Higuchi and Connors (19).

Preparation of Core Tablets

The core tablets for the osmotic pump tablet were prepared by using an eccentric tableting machine (Okada Seikou Company) using a 9 mmϕ punch with kneaded powder of PDL and the respective osmotic pump agents, $(SBE)_{7m}$-β-CD, HP-β-CD or a sugar mixture (lactose:fructose at a 1:1 weight ratio). The kneaded powder was prepared by vacuum drying for 12 hours at 40°C after mixing the composition with minimal water using a mortar and pestle. The components of the kneaded powder were as follows; PDL:$(SBE)_{7m}$-β-CD at a 1:1 and 1:2 molar ratio; PDL:HP-β-CD at a 1:2 molar ratio; the PDL:sugar mixture at a weight ratio equivalent to the PDL:$(SBE)_{7m}$-β-CD at the 1:2 molar ratio.

Preparation of the Osmotic Pump Tablets (OPT)

The OPT were prepared using a modification of the method of Zentner et al (13) in which a suspension composed of micronized lactose/cellulose acetate (CA-398-10)/triethyl citrate in a weight ratio of 2/2/1 in ethanol/dichloromethane in a weight ratio of 10.5/31.5 was film-coated onto the core tablets. A Flow Coater Mini® (Floint Company) was used for the film-coating.

Release Studies

The release of PDL from uncoated cores or OPT (containing the equivalent to 20 mg PDL) utilized the Japanese Pharmacopoeia (JP) XIII dissolution test (50 rpm, 37°C), paddle method. The dissolution solvent volume was 900 ml of distilled water. The released PDL was quantitated with 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 its absorbance measured at 250 nm.

Absorption Studies

This research adhered to the "Principles of Laboratory Animal Care" (NIH publication #85-23, revised 1985). The preparations were administered with 30 ml of water to three male dogs (10–11 kg weight) under both fasted and fed conditions with one week washout interval between studies. Formulations containing the equivalent of 20 mg PDL from a polyethylene glycol solution, a suspension in 0.5% w/v methylcellulose, an uncoated core tablet and an OPT with $(SBE)_{7m}$-β-CD were compared. One milliliter of PDL solution with 0.1 M SBE7-β-CD (equivalent to 10 mg PDL) was prepared for an 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 drug dosing. The plasma concentration of PDL was determined according to the HPLC-assay method reported by Sugawara et al. (20)

RESULTS AND DISCUSSION

Phase Solubility of PDL with β-CD Derivatives

The intrinsic solubility of PDL, a poorly water-soluble drug, is 0.2 mg/ml at 37°C in water (21). The solubility of PDL linearly increased with increasing concentration through 0.05M for both $(SBE)_{7m}$-β-CD (slope = 165.3, intercept = 0.26, r^2 = 0.999) and HP-β-CD CD (slope = 128.0, intercept = 0.18, r^2 = 0.999), suggesting 1:1 complexation in this concentration range. Binding constants calculated by the method reported by

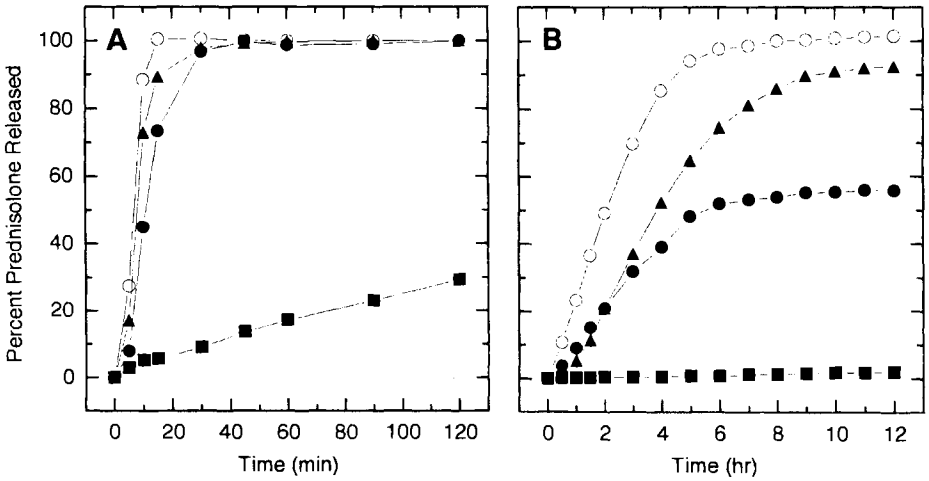

Fig. 1. Release profiles of PDL from core tablets (n = 1) (uncoated), A, or OPTs, B. PDL:$(SBE)_{7m}$-β-CD at a 1:1 (molar ratio), ●; PDL:$(SBE)_{7m}$-β-CD at a 1:2 (molar ratio), ○; PDL:HP-β-CD at a 1:2 (molar ratio), ▲; PDL:sugar, ■.

Higuchi and Connors (19) were 1,513 M^{-1} for $(SBE)_{7m}$-β-CD compared to 960 M^{-1} for HP-β-CD.

Choice of Core Tablet Components

Figure 1 shows the release behaviors of PDL from the core tablets (uncoated, Figure 1A) and the OPTs (Figure 1B). These tablets were prepared with $(SBE)_{7m}$-β-CD, HP-β-CD or the sugar mixture (lactose and fructose with a weight ratio of 1:1). Also, to investigate the appropriate amount of excipient to be used for an OPT, the molar ratio of $(SBE)_{7m}$-β-CD to PDL was varied. The release rate of PDL from the core which had twice the molar ratio of $(SBE)_{7m}$-β-CD to PDL was the fastest from the core tablets. The release rate of PDL from the sugar mixture was significantly slower, consistent with the non-solubilizing effect of the sugar mixtures compared to the β-CD derivatives. The order of the release rate of PDL from the core tablets was $(SBE)_{7m}$-β-CD (1:2) > HP-β-CD (1:2) > $(SBE)_{7m}$-β-CD (1:1) >> the sugar mixture. The release rates of PDL from the OPT coated with 0.35 mm membranes displayed similar rank order behavior to the core tablets except that PDL from OPT with HP-β-CD (1:2), $(SBE)_{7m}$-β-CD (1:1) and sugar mixture were incomplete over 12 hours. This suggested that the appropriate amount of $(SBE)_{7m}$-β-CD necessary to ensure complete release must be at least twice the molar amount of PDL. Therefore, in this study, to fairly compare the ability of $(SBE)_{7m}$-β-CD, the added amount of PDL to HP-β-CD was set at the same molar ratio (1:2), and that of the sugar mixture was set at the same weight ratio as for the $(SBE)_{7m}$-β-CD.

In Vitro Release from OPT

Figure 2 shows the release profiles into water of PDL from OPT with $(SBE)_{7m}$-β-CD, HP-β-CD and the sugar mixture through membranes of varying thickness. Both the order of release (apparent zero order versus apparent first order) and the rate and extent of release were used to characterize the various materials. From the percent released data, PDL from an OPT with $(SBE)_{7m}$-β-CD resulted in complete release, however, with both HP-β-CD and the sugar mixture, release was incomplete with 80–90% release of PDL from the OPT with HP-β-CD, and less than 10% release from the sugar mixture. This is consistent with the relative ability of the HP-β-CD to solubilize PDL compared to $(SBE)_{7m}$-β-CD as reflected by the phase-solubility data. The sugar mixture had no effect on the equilibrium solubility of PDL. The $(SBE)_{7m}$-β-CD/OPT showed apparent zero-order release of PDL up to 90% of the nominal contents. For the HP-β-CD/OPT formulation, zero-order release was only observed up to 50% of the nominal contents. These observations can be explained by considering different possible contributions from osmotic pressure effects versus a diffusional component to the release rate as expressed by Equation 2 (13,18).

$$dm/dt = (AS/h)L_p\sigma\Delta\pi + PAS \text{ where } P = DK/h \quad (2)$$

In Equation 2, P is the permeability coefficient of the drug through the membrane, D is the diffusivity and K is the membrane/water partition coefficient. The first term represents the contribution from osmotic pumping component and the second term is that from simple Fickian diffusion. It was shown

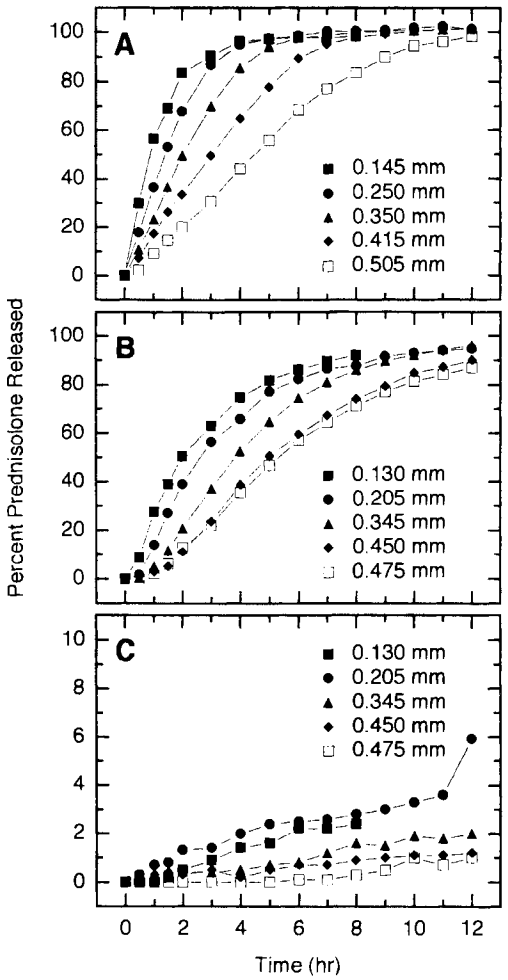

Fig. 2. Effect of membrane thickness on release of PDL in water at 37°C from OPTs. (n = 1). A, $(SBE)_{7m}$-β-CD; B, HP-β-CD; and C, sugar mixture.

in the testosterone study that in the presence of $(SBE)_{7m}$-β-CD, release is mainly governed by the contribution from the osmotic pressure differences while the contribution of diffusion with HP-β-CD was probably more significant (12). This resulted from the difference in the induced osmotic pressure in the devices because the osmotic pressure from a saturated solution of $(SBE)_{7m}$-β-CD was significantly larger than that from a saturated solution of HP-β-CD (12). Therefore, it is proposed that $(SBE)_{7m}$-β-CD and the sugar mixture, which both produce high osmotic pressures, mainly produce the zero-order release, which is consistent osmotic pump preparations.

Figure 3 is a plot of the release rates calculated from zero-order release portions of the release profiles from Figure 2 versus the inverse thickness of the membrane. Each relationship, by linear regression, was linear ($r^2 > 0.99$) following from Equation 2 (or Equation 1). However, for the OPT with $(SBE)_{7m}$-β-CD, which acts as both a solubilizer and as an osmotic agent, the release is faster than HP-β-CD and the sugar.

In Vivo Absorption from OPT

Generally a decrease in oral bioavailability (BA) has been experienced when controlled or sustained release preparations

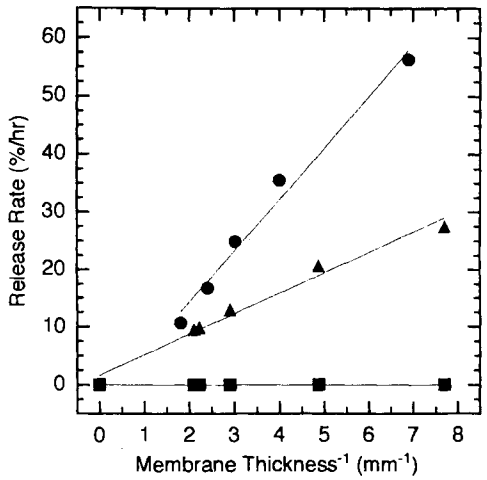

Fig. 3. Relationship between the release rate of PDL from OPTs with $(SBE)_{7m}$-β-CD (●) HP-β-CD (▲) or sugar (■) and the inverse of membrane thickness.

of poorly water soluble drugs are administered to animals or humans (22–24). For example, a decrease in BA for PDL was reported by Sugawara et al. (20). In that case, the alginate gel beads of PDL did not completely release PDL *in vitro* and showed decreased BA when administered to beagle dogs compared to PDL powder.

Figure 4 shows the mean plasma concentration-time profiles in fasted and fed beagle dogs after intravenous administration of PDL dissolved in 0.1M $(SBE)_{7m}$-β-CD (equivalent to 10 mg PDL). These profiles were fit to a two-compartment open model by non-linear least squares regression analysis, and the calculated pharmacokinetic parameters are listed in Table I. No changes in pharmacokinetic parameters were observed between the fasted and fed dogs.

The mean plasma concentration-time profiles in the fasted and fed beagle after oral administration of each oral preparation are shown in Figure 5 with the appropriate pharmacokinetic parameters summarized in Table II. A PDL solution with polyethylene glycol (PEG), a suspension with 0.5% methylcellulose, the core tablet (no coating) with $(SBE)_{7m}$-β-CD and OPTs with $(SBE)_{7m}$-β-CD of two different release rates (OPT-1; 20%/hr

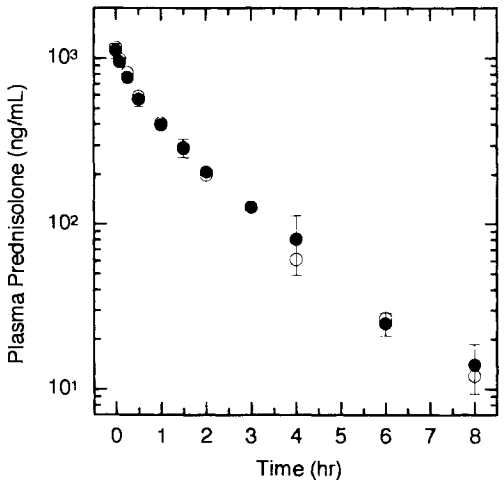

Fig. 4. Plasma profiles of PDL after intravenous administration of PDL from 0.1M $(SBE)_{7m}$-β-CD solution (equivalent to 10 mg PDL) to three beagle dogs under fasted or fed conditions. Fasted, ●; Fed, ○.

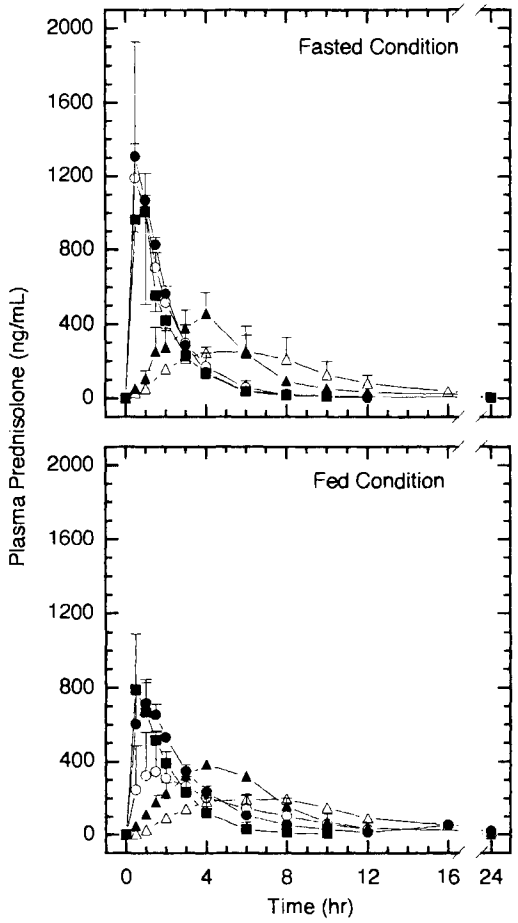

Fig. 5. Plasma profiles of PDL after oral administration of preparations (equivalent to 20 mg PDL) to three beagle dogs under fasted and fed conditions. PEG solution, ○; core tablet, ●; suspension, ■; OPT-1, ▲; and OPT-2, Δ.

Table I. Pharmacokinetic Parameters of PDL After Intravenous Administration of a PDL Solution Made with 0.1M SBE7-β-CD (Equivalent to 10 mg PDL) in Fasted and Fed Dogs (n = 3)

Feed condition	AUC_{0-8} (ng/ml·hr)	C_0 (ng/ml)	$T_{1/2}\alpha$ (hr)	$T_{1/2}\beta$ (hr)	Vp (L/kg)	CL_{tot} (ml/kg/min)
Fasted	1374 ± 260	1156 ± 80	0.18 ± 0.05	1.05 ± 0.08	0.87 ± 0.03	12.7 ± 1.2
Fed	1393 ± 99	1059 ± 66	0.16 ± 0.01	1.26 ± 0.03	0.95 ± 0.06	12.4 ± 0.6

Note: Values are mean ± SD.

Table II. Pharmacokinetic Parameters[a] of PDL After Oral Administration of Its Preparations (Equivalent to 20 mg) in Fasted and Fed Dogs (n = 3)

Sample	Feed condition	Tmax (hr)	Cmax (ng/ml)	AUC_{0-24} (ng/ml•hr)	MRT (hr)	BA[b]
PEG solution	Fasted	0.5 ± 0	1188 ± 186	2563 ± 523	2.0 ± 1.2	93
Suspension	Fasted	0.7 ± 0.3	1152 ± 379	2175 ± 307	2.2 ± 0.4	79
Core tablet	Fasted	0.8 ± 0.3	1333 ± 598	2667 ± 469	1.9 ± 0.2	97
OPT-1	Fasted	3.7 ± 0.6[c]	501 ± 39	2532 ± 326	5.6 ± 0.4[c]	92
OPT-2	Fasted	5.3 ± 1.2[c]	295 ± 81	2471 ± 834.3	7.4 ± 0.5[c]	90
PEG solution	Fed	2.2 ± 1.6	370 ± 198	2076 ± 114	4.7 ± 2.3	75
Suspension	Fed	0.7 ± 0.6	800 ± 284[d]	1796 ± 165[e]	2.0 ± 0.8	65
Core tablet	Fed	1.2 ± 0.3	728 ± 113	2465 ± 48[c]	2.8 ± 0.3	89
OPT-1	Fed	4.0 ± 0[d]	382 ± 27	2570 ± 161[d]	5.6 ± 0.8	92
OPT-2	Fed	7.3 ± 1.2[c]	205 ± 19	2269 ± 123	9.0 ± 0.3[d]	82

[a] Values are mean ± SD.
[b] Absolute bioavailability.
[c] $P < 0.01$ vs. PEG solution of each feed condition.
[d] $P < 0.05$ vs. PEG solution of each feed condition.
[e] $P < 0.01$ vs. core of each condition.

and OPT-2; 10%/hr) which were controlled by modulating the membrane thickness were administered.

The plasma profiles from the OPTs were slower from the OPT formulations confirming the expected decreased release rate compared to the non-controlled formulations. T_{max} and MRT of both OPTs were significantly longer compared to the PEG solution and the core tablet and this effect was independent of the feeding condition. Also, although a significantly longer MRT value with the PEG solution was observed under the fed condition compared to the fasted condition, other formulations did not show this effect.

With respect to the extent of absorption there were no statistically significant differences in absolute bioavailability (BA) between the preparations in the fasted animals. In the fed state, however, the BA of the PEG solution and the suspension were significantly decreased compared with the core and OPT-1. Also, the BA of OPT-2 was apparently slightly decreased compared with the other $(SBE)_{7m}$-β-CD preparations, however, the results were not statistically significant. From these results, therefore, it was concluded that the addition of $(SBE)_{7m}$-β-CD resulted not only in better BA performance compared to the PEG solution under the fasted condition, but also prevented

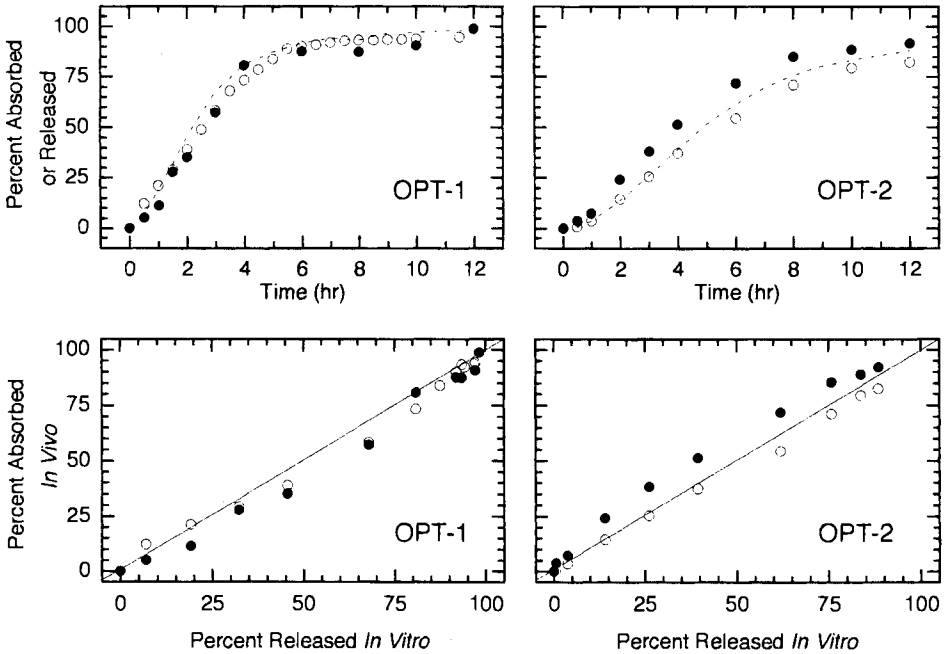

Fig. 6. *In vitro/In vivo* correlations for OPT-1 and OPT-2. *In vivo* absorbed (fasted, ●); *in vivo* absorbed (fed, ○), dotted line; *in vitro* released.

any decrease in BA due to food intake. Moreover, in spite of the extended plasma profiles, OPT containing $(SBE)_{7m}$-β-CD as a solubilizing and osmotic pump agent resulted in significantly higher BA and did not appear to be compromised by GI transit time differences between fed and fasted state animals.

In Vitro/In Vivo Correlation

Recently, 1:1 correlations between *in vitro* and *in vivo* release have been investigated (25–27). Skelly et al. proposed various correlation levels (A to C) as a measure of the degree of correlation (28). Therefore, an attempt was made to correlate the *observed in vitro* release with *in vivo* absorption for the current tablets.

Figure 6 shows the *in vitro/in vivo* correlation for the OPT-1 and OPT-2 formulations displayed by two different approaches. The *in vivo* absorption of PDL were calculated from the data in Figure 5 by the Loo-Riegelman method (29) using the pharmacokinetic parameters from the intravenous data. The *in vitro* release profiles of PDL from OPTs were measured according to the JP XIII methodology using the paddle method (speed; 50 rpm) in 900 ml of water at 37°C. Generally, the release rates of drug from OPT with $(SBE)_{7m}$-β-CD were unaffected by stirring speed (13,18), and since PDL is a neutral compound and the ionization of $(SBE)_{7m}$-β-CD is pH independent, the release rate is pH independent. For the first correlation, the *in vitro* percent released versus time profiles of both OPTs were almost superimposable upon the *in vivo* percent absorption versus time profiles under both feed and fasted conditions, suggesting a 1:1 correlation of level A (top figures). In the second correlation (bottom figures), the plots of the *in vivo* percent absorption versus the *in vitro* percent released displayed excellent point-to-point relationships ($r^2 = 0.99$) with a slope of 0.99. Therefore, it was concluded that the *in vivo* absorption of PDL from the OPT 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.

In conclusion, the present results suggest that $(SBE)_{7m}$-β-CD can serve as both a solubilizer and as an osmotic agent for an OPT of PDL, and that the absorption rate and BA of a poorly water-soluble drug from an OPT is unaffected (in this case) by fed conditions in the dog. Furthermore, the *in vivo* absorption profiles of PDL from OPT with $(SBE)_{7m}$-β-CD in dogs correlated well with the *in vitro* release profiles using a standard dissolution apparatus and conditions. Some future studies will examine how the release rates of ionizable drugs perform in this system and an in-depth study to dissect the mechanism/s operative in these OPTs.

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