The Solubility-Modulated Osmotic Pump: *In Vitro/in Vivo* Release of Diltiazem Hydrochloride

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Received March 15, 1990; accepted June 18, 1990

A generalized method was investigated for conversion of controlled-porosity osmotic pump release profiles from first-order to zero-order kinetics using diltiazem · HCl as a model drug. Diltiazem · HCl has an aqueous solubility >590 mg/ml (37°C) and was released from controlled-porosity osmotic pump devices with first-order kinetics. This high solubility was markedly reduced (155 mg/ml; 37°C) in the presence of NaCl (1 *M*). Based on theory for osmotically actuated drug release, this reduced solubility would be expected to result in a zero-order release profile of >80% of an initial diltiazem · HCl load. Devices were prepared with cores that contained diltiazem · HCl and sufficient NaCl granules coated with a microporous cellulose acetate butyrate 381-20 film to maintain a 1 *M* NaCl concentration within the drug compartment over a 16-hr period. This resulted in release of ~75% of the initial diltiazem · HCl load with zero-order kinetics over a 14- to 16-hr period. The *in vivo* performance of these devices in beagle dogs was analyzed. The *in vivo* percentage diltiazem absorbed profiles were superimposable with the *in vitro* release profile. These results suggest that diltiazem release and absorption from the solubility modulated osmotic pump occur throughout the GI tract in a fashion predictable from *in vitro* dissolution data.

KEY WORDS: osmotic pump; microporous coat; solubility modulation; diltiazem hydrochloride.

INTRODUCTION

Significant advances have been made in the development of drug delivery devices that control the amount of drug released in a defined period. Among these are devices that utilize osmotic pressure as the driving force. To gain the advantages of pH- and agitation-independent release performance leading to similar *in vitro/in vivo* delivery, osmotically actuated drug delivery has been extensively investigated (1–3). Candidate drugs for osmotic delivery have water solubilities of 50 to 300 mg/ml. Configurations based on core tablets coated with semipermeable polymeric films that are impermeable to the drug, and films of controlled porosity that are freely permeable to the drug, have been described in the literature and shown to be "osmotic pumps" (2,3). An approach for extension of osmotic pump technology to drugs of inappropriate solubility has been reported (4). The present study details the design and evaluation of a solubility-modulated controlled-porosity osmotic pump for delivery of the highly water-soluble drug diltiazem hydrochloride.

The kinetics of osmotic drug release are directly related to the solubility of the drug in the intended release medium (usually aqueous). Assuming a tablet core of pure drug, the fraction of the core released with zero-order kinetics is given by Eq. (1) (2).

$$F(z) = 1 - (S/\rho) \quad (1)$$

where $F(z)$ is the fraction released zero-order, S is the drug solubility (g/cm^3), and ρ is the density (g/cm^3) of the core tablet. Agents whose water solubility is $\geq$0.3 g/cm^3 will be delivered with $\leq$70% zero-order kinetics (assuming a core density of 1 g/cm^3). The drug release rate from an osmotic pump device during the zero-order portion is described by Eq. (2) (2).

$$(dM/dt)_{zo} = (A/h)\, L_p \sigma \pi_s S \quad (2)$$

where $(dM/dt)_{zo}$ is the zero-order release rate, A is the surface area of the film coat, h is the film thickness, L_p is the hydraulic permeability of the film, σ is the reflection coefficient, π_s is the osmotic pressure difference across the film at saturation, and S is the drug solubility. Drugs with a solubility of $\leq$0.05 g/cm^3 would be released with $\geq$95% zero-order kinetics according to Eq. (1). However, the zero-order release rate would be slow according to Eq. (2) due to the small osmotic pressure gradient. Conversely, highly water-soluble drugs would demonstrate a high release rate that would be zero-order for release of a small percentage of the initial drug load. Thus, the intrinsic water solubility of many drugs might preclude them from incorporation into an osmotic pump. By modulating the solubility of these drugs within the core, effective release patterns may be obtained with drugs which might otherwise have been poor candidates. This approach permits the conversion of release profiles from substantially first-order to substantially zero-order kinetics without altering the chemical structure of the drug. This was accomplished in the present study through incorporation of coated sodium chloride crystals (i.e., microosmotic pumps) into the core tablet formulation of a diltiazem hydrochloride controlled porosity osmotic pump. This pump-in-a-pump design was necessary to prevent the rapid depletion, and large attendant concentration variation, of the solubility modulating agent (sodium chloride) within the diltiazem hydrochloride core tablet environment. Thus, the release of the solubility modulator was controllable and, in the instant case, was designed to provide modulation of the drug solubility for a prolonged period.

MATERIALS AND METHODS

Diltiazem hydrochloride (Davos Chemical Corporation, Fort Lee, New Jersey), citric acid (Fisher Scientific Company, Fairlawn, New Jersey), adipic acid (Eastman Kodak Company, Rochester, New York), sodium chloride (Mallinckrodt Incorporated, Paris, Kentucky, and Morton Thiokol, Hutchinson, Kansas), and polyvinylpyrrolidone 29-32K (GAF Corporation, Wayne, New Jersey) were used as

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0724-8741/91/0100-0088$06.50/0

received to manufacture the core tablets. Cellulose acetate 398-30 (CA-398-30) and cellulose acetate butyrate 381-20 (CAB-381-20) (Eastman Chemical Products, Kingsport, Tennessee), sorbitol (Aldrich Chemical Company, Milwaukee, Wisconsin), and polyethylene glycol 400 (Sigma Chemical Company, St. Louis, Missouri) were used to form the various controlled porosity coatings.

Assays for diltiazem hydrochloride in device residuals, solubility determinations, and *in vitro* dissolution/release studies were performed by HPLC (Shimadzu Corp., Kyoto, Japan). An acidified (0.75 ml of 70% perchloric acid per liter of mobile phase) acetonitrile:water (1:1, by volume) mobile phase pumped at a flow rate of 2.5 ml/min through a C_8 column (Brownlee 13-cm RP-8 Spheri-5) (Brownlee Labs Inc., Santa Clara, California) was used with UV detection and quantitation at 238 nm. A linear detector response ($r^2 > 0.99$) was observed over the concentration range of interest (1–450 mg/liter). Plasma diltiazem and metabolite concentrations were analyzed as previously reported (5).

Core tablets were prepared from a wet (ethanol) granulation of diltiazem hydrochloride, controlled-release sodium chloride (CR NaCl), rapid-release sodium chloride (RR NaCl), citric acid, adipic acid, and polyvinylpyrrolidone. The granulation was sized through a No. 18 U.S. Standard Sieve and dried for 18 hr at 45°C. The dried granules were lubricated with stearic acid followed by compression to produce tablets of >20-kg hardness. For comparison cores containing no NaCl were also prepared. The core compositions have been summarized in Table I.

A controlled-porosity wall was applied to these tablet cores by fluidized-bed (Uni-Glatt, Glatt Air Techniques Inc., Ramsey, New Jersey) spray coating techniques. CA-398-30 (72 g), sorbitol (54 g), and polyethylene glycol 400 (7.2 g) were dissolved in a water:methanol:methylene chloride (1:10:15, by parts) solvent blend.

Diltiazem hydrochloride release from these devices into 900-ml volumes of HCl buffer (pH 1.2) and phosphate buffer (pH 8.0; 0.07 *M* phosphate), both made isoosmotic with NaCl, was monitored using USP paddle dissolution Method 2 (50-rpm paddle speed/37°C; VanKel Industries, Edison, New Jersey). Volume losses from sample withdrawals and evaporation were replaced with buffer. Diltiazem hydrochloride release from the devices was assayed by HPLC.

The solubility of diltiazem hydrochloride was analyzed by adding excess diltiazem · HCl to solutions of various sodium chloride concentration. These solutions were equilibrated in a 37°C water bath with mild agitation. Samples were withdrawn periodically, diluted with pH 4.5 phosphate buffer (9 g KH_2PO_4/liter), and assayed by HPLC. This procedure was repeated until the analyzed solubility value was constant (typically within 8 hr).

CR NaCl was prepared from sieved sodium chloride crystals (minus No. 20, plus No. 30) that were spray coated with a microporous wall designed to meter NaCl into the core tablet environment over a prolonged period. The spray solution was 100 g CAB-381-20 containing 20 g sorbitol as a pore-forming agent dissolved in water:methanol:methylene chloride blended (1:12:14, by volume). This coat was applied by standard spray coating techniques in a lab scale fluidized-bed apparatus (Uni-Glatt, Glatt Air Techniques Incorporated, Ramsey, New Jersey). The release kinetics of sodium chloride from the CR NaCl source into deionized water (37°C) were monitored conductiometrically (Jenway PCM3, Felsted, Gt. Dunmow, Essex, U.K.). The conductiometric response was linear ($r^2 > 0.99$) over the NaCl concentration range of interest (0–500 mg/liter).

The release of sodium chloride from the CR NaCl source in the core of the devices was also analyzed. Devices were equilibrated in deionized water (900 ml; 37°C) in a USP paddle dissolution method 2 apparatus. At various times devices were removed, the coating cut with a scalpel, and the residual core contents briefly rinsed with deionized water on a No. 80 mesh sieve to expose the CR NaCl granules. The CR NaCl granules were transferred into a glass mortar, crushed, and diluted with deionized water (200 ml). The residual sodium chloride in the granules was analyzed conductiometrically and the amount released calculated by difference. To confirm that the coats of CR NaCl granules remained intact once compressed into the core tablets, uncoated cores were rinsed briefly (~5 min) to dissolve everything except the CR NaCl granules. These isolated CR NaCl granules were then placed into deionized water and the NaCl release profile analyzed conductiometrically. The extent and rate of NaCl release were identical to that obtained with ungranulated/uncompressed CR NaCl granules. This experiment confirmed that the coated granules were not compromised during either the wet granulation or tablet compression fabrication steps.

The *in vivo* evaluation of the Core I diltiazem · HCl dosage form was part of a four-way study which examined the *in vivo* release performance of osmotic diltiazem extended-release dosage forms and the attendant diltiazem pharmacokinetics in beagle dogs (5). In that study each dog was fed ~50 g of a standard dog chow mix before device administration and every hour thereafter.

Table I. Osmotic Pump Cores (mg/Tablet)

Component	Core I	Core II	Core III
Diltiazem · HCl	360	72	360
Adipic acid	85	25	85
Citric acid	70	19	70
CR NaCl	50	45	—
RR NaCl	50	45	—
PVP 29-32K	35	5	30
Stearic acid	7	3	5

Extended-Release Tablet Administration

Each of six dogs was administered one Core I osmotic tablet containing 360 mg diltiazem · HCl. Blood samples (3 ml) were taken immediately prior to dosing and 2, 4, 6, 8, 10, 12, 14, 16, 20, 24, and 30 hr postadministration, centrifuged for the isolation of plasma, and stored at −20°C until assayed. Plasma diltiazem concentrations were analyzed as previously reported (5). Devices were also retrieved from the feces and analyzed for residual drug content.

Area under the concentration versus time curve (AUC) estimates following Core I device administration were cal-

Table II. Diltiazem Hydrochloride Solubility in Various Sodium Chloride Solutions (37°C)

Solubility of diltiazem · HCl (mg/ml)	Sodium chloride concentration (*M*)	Theoretical release profile[a] (% zero-order)
>590	0	<51
545 ± 12	0.25	55
395 ± 29	0.50	67
278 ± 10	0.75	77
155 ± 20	1.00	87
40 ± 5	1.20	99

[a] Based on diltiazem · HCl density = 1.2 g/cm^3.

culated by the trapezoidal method. The AUC from the last plasma diltiazem concentration to infinity ($AUC_{last-\infty}$) was calculated by Eq. (3):

$$AUC_{last-\infty} = C(last)/\beta \quad (3)$$

where C(last) is the plasma diltiazem concentration at 30 hr and β is the terminal disposition rate constant for the individual dog following iv administration (5).

The individual plasma diltiazem concentrations following administration of the Core I dosage form were numerically deconvoluted [using the point-area method (6)] with plasma diltiazem concentrations determined following administration of an oral solution (5). The apparent *in vivo* release rates were estimated by linear regression of the initial slope of percentage absorbed versus time curves.

Comparisons were made with ANOVA, and differences (least significant difference or Student–Newman–Kuel) were considered significant at $P < 0.05$ (7). All data are presented as mean ± standard deviation.

RESULTS AND DISCUSSION

Diltiazem hydrochloride, a calcium channel blocker, has a water solubility >590 mg/ml at 37°C. At this solubility diltiazem · HCl would rapidly dissolve inside an osmotic pump core and show predominantly first-order rather than the desired zero-order release kinetics. The solubility of diltiazem hydrochloride was sensitive to the level of sodium chloride in the aqueous environment.

The solubility of diltiazem · HCl (37°C) in various sodium chloride solutions was analyzed and the results summarized in Table II. It should be noted that the final sodium chloride concentrations listed in Table II are approximate and were not corrected for volume changes associated with the diltiazem hydrochloride additions. A >10-fold decrease in diltiazem · HCl solubility was readily achieved over a 1.2 *M* sodium chloride concentration range. The theoretically expected zero-order release characteristic that would ac-

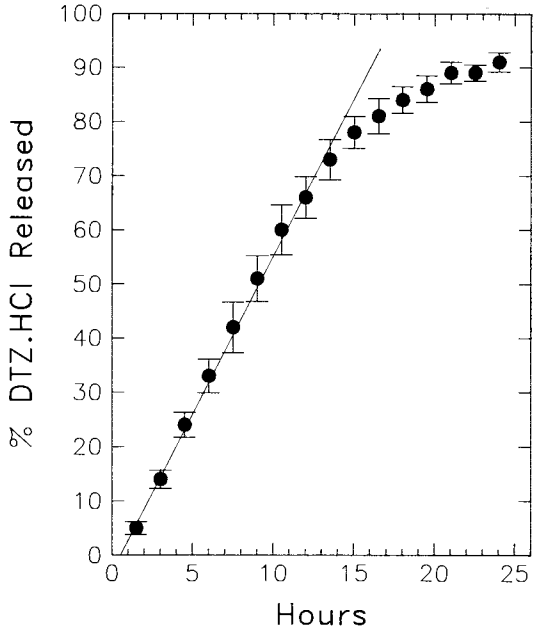

Fig. 2. *In vitro* release of diltiazem · HCl from Core I devices at pH 1.2 and 8.0 (superimposable). $n = 6$ at each pH.

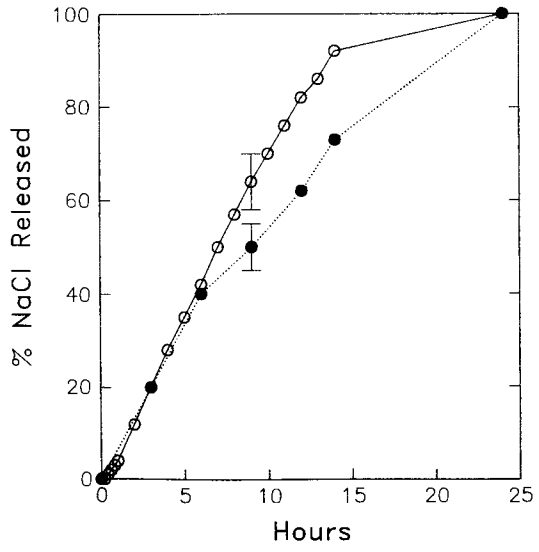

Fig. 1. Release of sodium chloride from the CR NaCl source into deionized water (○) and the Core I environment (●). $n = 6$.

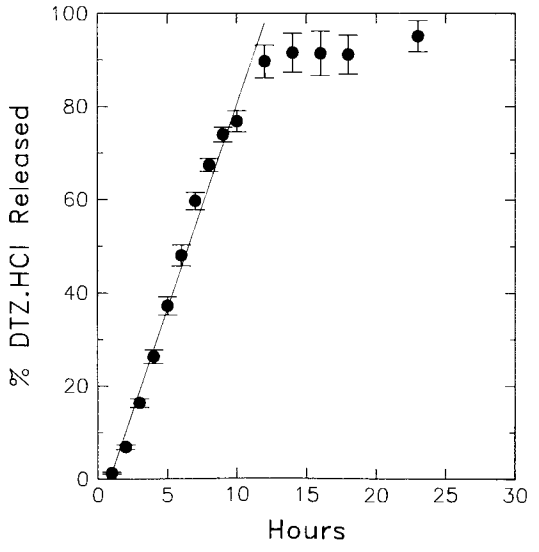

Fig. 3. *In vitro* release of diltiazem · HCl from Core II devices at pH 1.2 and 8.0 (superimposable). $n = 6$ at each pH.

Table III. *In Vitro* Release

Device core	% zero-order		Rate (mg/hr)	
	pH 1.2	pH 8.0	pH 1.2	pH 8.0
I	70–75	70–75	24.0	22.5
II	85	85	6.4	6.4

company the various sodium chloride-modulated drug solubilities were calculated. Concentrations of sodium chloride maintained at ≥0.75 *M* were anticipated to result in release profiles with >75% zero-order character. The osmotic pump devices were fabricated to capitalize on this solubility dependence.

Controlled-release (CR) NaCl combined with RR NaCl was incorporated into the core compartment of an osmotic pump device to decrease and maintain the solubility of diltiazem hydrochloride. A CR NaCl source was designed which gave 12 hr of zero-order sodium chloride release, followed by 4–6 hr of first-order release, in water at 37°C (Fig. 1). Also included in Fig. 1 is the NaCl release profile of the CR NaCl source in the core solution environment of a functioning device. Compared to the profile in deionized water, the sodium chloride release in the core solution has been retarded, presumably as a result of the lower osmotic differential. When included as a component of an osmotic pump drug delivery device, the CR NaCl source would act to maintain the sodium chloride concentration for a prolonged period which could be readily adjusted. Two osmotic cores were prepared utilizing the CR NaCl element as outlined in Table I.

The *in vitro* diltiazem · HCl release profiles from Cores I and II are shown in Figs. 2 and 3, respectively. In both cases pH-independent release of diltiazem · HCl in a substantially zero-order fashion was achieved. The steady-state rates and percentages released zero-order were calculated and are summarized in Table III. The devices containing the highest ratio of NaCl:diltiazem · HCl (Core II) showed an increased zero-order performance as would be predicted from the data in Table II. The performance of Core I devices was 70–75% zero-order, which from Table II would require

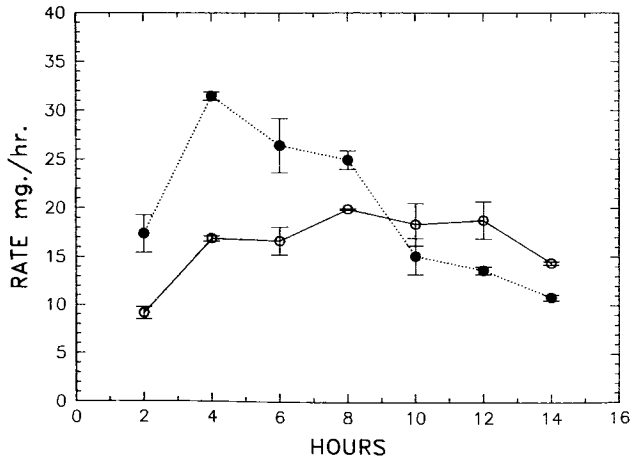

Fig. 4. *In vitro* release rates of solubility modulated (○; Core I) and unmodulated (●; Core III) devices at pH 8.0. $n = 6$ for each device.

Table IV. Selected Pharmacokinetic Parameters Following Oral Administration of Diltiazem · HCl as an Oral Solution or Core I Formulation

	Oral solution[a]	Core I formulation
Dose (mg)	60	360
AUC (ng · hr/ml)	839 ± 354	3920 ± 942
F (%)[b]	48.9 ± 17.5	32.3 ± 7.8
C_{max} (ng/ml)	329 ± 115	276 ± 80
T_{max} (hr)	0.67 ± 0.25	7.3 ± 3.0
k_0, *in vivo* (%/hr)[c]	—	5.5 ± 0.7
k_0, *in vitro* (%/hr)[d]	—	5.5

[a] From Ref. 5.
[b] Relative to intravenous administration (5).
[c] Estimated by deconvolution; see text.
[d] $n = 6$.

a diltiazem · HCl solubility of ~275 mg/ml. This diltiazem · HCl solubility is associated with a 0.75 *M* NaCl concentration. During the diltiazem · HCl zero-order release period the CR NaCl source (Fig. 1) releases at ~2.7 mg NaCl/hr. Thus the CR NaCl source would maintain the core fluid sodium chloride concentration at the required ~0.7 *M* for the 12-hr period of zero-order release.

The effect of sodium chloride on diltiazem · HCl release profiles was investigated further in a head-to-head comparison of the diltiazem · HCl release performance from equivalently coated Core I (contain NaCl) and Core III (no NaCl) devices (see Table I). The diltiazem · HCl rate vs time data are summarized in Fig. 4. Solubility modulation resulted in a significant change in the release performance with a predominantly first-order release profile (unmodulated case) converted into a zero-order release profile (modulated case).

In Vivo Performance

The performance of the Core I devices *in vivo* was examined in dogs. Table IV summarizes pharmacokinetic parameters following the peroral administration of a solution

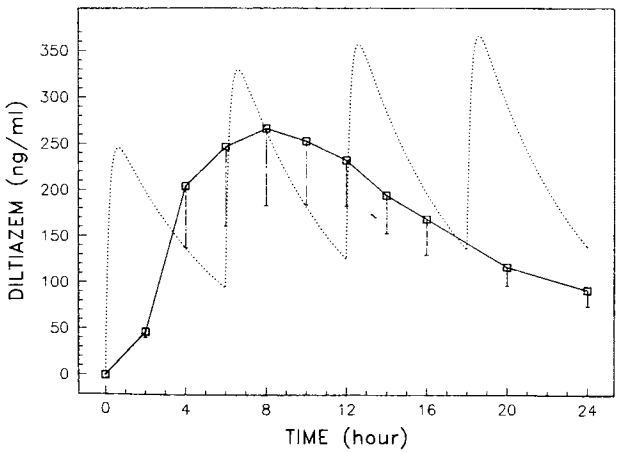

Fig. 5. Plasma diltiazem concentrations following peroral administration of 360 mg diltiazem HCl as a Core I device formulation (□). The stippled line is a simulation of 90 mg diltiazem HCl orally administered as a solution, every 6 hr. Mean ± SD are shown ($n = 6$).

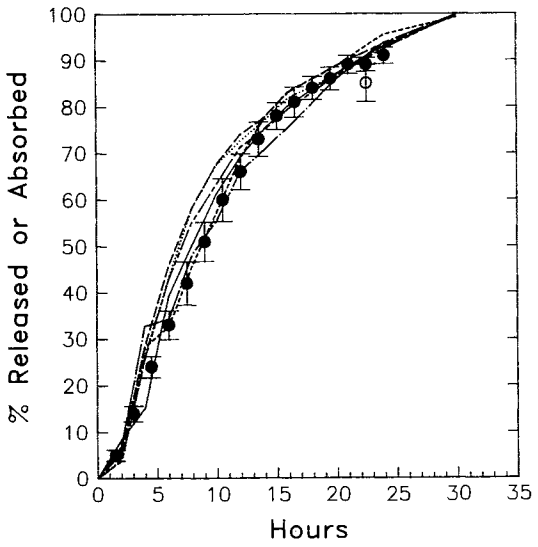

Fig. 6. Individual percentage absorbed versus time plots following administration of Core I devices. For comparison purposes the *in vitro* release profile (●; $n = 6$) and fecal recovery data (○; $n = 3$) are included.

and the Core I formulation. The bioavailability (F) of the Core I formulation was 32.3 ± 7.8%. This value was similar to both that reported (29 ± 10%) previously (5) and the orally administered solution. The maximum plasma diltiazem concentration (C_{max}) was similar for both the Core I devices and the solution. However, compared to the solution, the time to reach C_{max} (T_{max}) was significantly ($P < 0.05$) extended with the Core I formulation.

The mean diltiazem plasma concentration profile following Core I device administration is shown in Fig. 5. For comparison purposes, included in the figure is the simulated concentration profile for peroral administration of 90 mg diltiazem HCl as a solution every 6 hr. This simulation was constructed with iv and peroral solution diltiazem pharmacokinetic parameters (5) in a simple biexponential model.

The AUC of the major active metabolite (8) *N*-desmethyl diltiazem (N) following Core I device administration was calculated for each dog by the trapezoidal method. Following the oral solution (4) and Core I device administration, the $AUC_{0-\infty,N}$ (scaled to the solution dose and corrected for diltiazem bioavailability) was 820 ± 225 and 985 ± 340 ng · ml/hr, respectively. Thus, the Core I device formulation did not alter the formation of N or the cumulative of N plus diltiazem.

The individual percentage diltiazem absorbed profiles following Core I device administration are shown in Figure 6. These profiles were obtained by numerically deconvoluting individual Core I data with the orally administered solution data collected from the same dog (5). The percentage diltiazem absorbed vs time data from 2 to 10 hr were individually analyzed by linear regression to provide estimates of apparent *in vivo* release rates. As summarized in Table IV and graphically shown in Fig. 6, the *in vivo* percentage diltiazem absorbed profiles are superimposable with the *in vitro* release profile. The *in vivo/in vitro* correlation was excellent (r^2, 0.99 ± 0.01) with a slope of 1.02 ± 0.02 and intercept of 0.08 ± 1.82. Additionally, the diltiazem · HCl levels in fecally recovered devices also agreed with the *in vitro* data (Fig. 6). These results suggest that drug release and absorption from the Core I formulation occurs throughout the gastrointestinal tract in a fashion that appears to correlate with *in vitro* dissolution data.

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