Controlled Release of Tetracycline II: Development of an *In Vivo* Flow-Limited Pharmacokinetic Model

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Abstract □ Controlled delivery of pharmaceuticals at zero-order rates from a polymer implant vehicle offers a valuable means by which constant drug levels may be maintained in the plasma over prolonged periods. A 2-hydroxyethyl methacrylate–methyl methacrylate copolymer was applied in the fabrication of a membrane-controlled tetracycline delivery device with previously demonstrated *in vitro* zero-order release rates. The trilaminate tetracycline-releasing disks were evaluated *in vivo* by implantation in the peritoneal cavities of female Sprague–Dawley rats. The implanted disks were coated with copolymer membranes of either 2:98 or 22:78 2-hydroxyethyl methacrylate–methyl methacrylate composition. *In vivo* release rates of tetracycline were constant with time, as measured by the cumulative drug release from disks recovered over different implantation periods. Steady-state tetracycline release rates from the trilaminate devices—158 μg/day for the 22:78 2-hydroxyethyl methacrylate–methyl methacrylate copolymer-coated disks and 123 μg/day for the 2:98 2-hydroxyethyl methacrylate–methyl methacrylate-coated disks—were in excellent correlation with the steady-state total daily excretion of the drug (153 and 110 μg/day for the two systems, respectively) by the rats. Plasma tetracycline concentrations reached steady-state levels within 2–3 days of trilaminate disk implantation and remained constant over the 14-day implantation period. Steady-state tissue tetracycline concentrations averaged 10–12 μg/g in the bone; 3–4 μg/g in the liver, kidney, and GI tract; 2–3 μg/g in the muscle; and <1 μg/g in the fat tissue. A flow-limited pharmacokinetic model was constructed to simulate *in vivo* tetracycline delivery from the trilaminate disks and the subsequent drug distribution. Model predictions of tissue and plasma tetracycline concentrations based on the experimentally determined zero-order drug release rates were in good agreement with experimental measurements.

Keyphrases □ Tetracycline—controlled-release dosage form, pharmacokinetics, hydroxyethyl methacrylate—methyl methacrylate copolymer implant, rats, *in vivo* □ Antibacterial agents—tetracycline, controlled-release dosage form, pharmacokinetics, hydroxyethyl methacrylate–methyl methacrylate copolymer implant, rats, *in vivo* □ Models, pharmacokinetic—tetracycline controlled-release dosage form, rats, *in vivo* □ Dosage forms, controlled release—tetracycline, hydroxyethyl methacrylate–methyl methacrylate copolymer implant, rats, *in vivo*

Numerous studies (1–6) attempted to measure plasma and tissue tetracycline levels in animals following oral or parenteral administration of the antibiotic. These early reports dealt with short-term drug studies and failed to determine steady-state tetracycline disposition in the animal. Such information is necessary to understand the correlation of serum tetracycline levels with the drug's therapeutic efficacy and potential toxicities. To achieve true steady-state drug kinetics, a constant-rate drug delivery system such as a long-term infusion pump apparatus is necessary, and the difficulty of performing such experiments with small animals is readily appreciated. Multiple oral administrations fall far short of meeting steady-state drug delivery requirements, producing a typical sawtooth pattern of serum drug concentrations with time.

A practical alternative to this problem is controlled drug release with an implantable system that delivers the pharmaceutical at a constant rate. Steroid delivery polymer devices based on a matrix-controlled diffusional process have been developed and investigated *in vivo* (7–9). Matrix devices with a characteristic release profile that is initially high and decreases with time fail to deliver the drug at a constant rate. Winkler *et al.* (10) developed a matrix-controlled progesterone-releasing intravaginal matrix device which, due to the unequal lag times of the device's inner and outer surfaces, produced a pseudo-zero-order release profile *in vivo*.

Chien *et al.* (11) recently reported a zero-order rate device for deoxycorticosterone acetate delivery from subcutaneous implants in rats. This device, named the microsealed drug delivery system, provided constant drug release for studying the production of metacorticoid hypertension in rats.

A previous publication (12) detailed the development in this laboratory of a membrane-controlled drug delivery system designed to release tetracycline at a constant rate with time. *In vitro* testing demonstrated the zero-order release characteristics of the trilaminate device in which the release rate was adjustable by either varying the copolymer coating membrane composition or altering the coating membrane thickness and/or the device geometry.

The present report details the *in vivo* release characteristics of the trilaminate tetracycline device implanted intraperitoneally in rats. A flow-limited pharmacokinetic modeling approach, as previously reported (13), was used to correlate *in vivo* zero-order tetracycline release rates from the implanted trilaminate device with the subsequent steady-state drug distribution in the plasma and tissues. The flow-limited model is based on measurable anatomical and physiological parameters and is designed to provide a conceptual representation of the mass transfer and elimination of drugs and their metabolites between real organ compartments. This modeling approach was chosen to define steady-state tetracycline disposition and to confirm the zero-order release characteristics of the trilaminate device.

EXPERIMENTAL

Tetracycline–Copolymer Device Fabrication—Disk-shaped trilaminate tetracycline-releasing devices were prepared by a procedure outlined previously (12). In brief, [^{3}H]tetracycline is mixed with a 63:37 2-hydroxyethyl methacrylate–methyl methacrylate copolymer to form the core of the device (20% drug by weight loading). The core is enclosed by a uniform membrane layer constructed of either a 2:98 or a 22:78 2-hydroxyethyl methacrylate–methyl methacrylate copolymer which, by its reduced tetracycline permeability (relative to the core material), maintains a constant drug concentration gradient within the enclosure, providing for a constant steady-state tetracycline release rate. The implanted disks were 15 mm in diameter and had an average coating thickness of 0.055 mm.

Animals—All animals were virgin female Sprague–Dawley rats weighing 180–220 g. For the pharmacokinetic studies, the rats were housed individually in standard metabolic cages, permitting the collection

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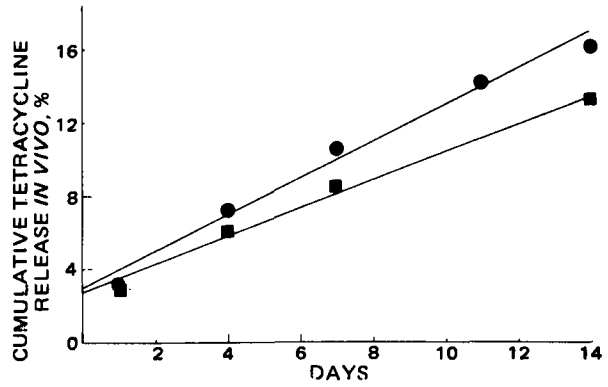

Figure 1—*Steady-state tetracycline release from trilaminate disks in 200-g rats. Percent release was determined by analysis of drug remaining in recovered disks. Key:* ■, *2:98 2-hydroxyethyl methacrylate–methyl methacrylate-coated trilaminate disks; and* ●, *22:78 2-hydroxyethyl methacrylate–methyl methacrylate-coated trilaminate disks.*

and quantitation of separate daily urine and fecal samples. The rats were fed[1] and provided with unrestricted water.

Biocompatibility Studies—Copolymer trilaminates (either containing tetracycline or with drug-free cores) were implanted subcutaneously in a pocket constructed by blunt dissection beneath the dorsal fascia layers and directly superficial to the spinotrapezius muscle. The incision was closed superficially with wound clips. Five rats received implants containing 1% tetracycline by weight in the cores, and an additional five rats received drug-free implants constructed in an otherwise identical manner to the tetracycline-containing implants. Before implantation, the trilaminate disks were washed in a small volume of sterile saline solution to remove surface contaminants.

At 1, 2, 4, 6, and 9 weeks following implantation, one rat from each group was sacrificed and the implant was removed carefully along with its surrounding tissue capsule. The tissue block containing the implant was fixed in formaldehyde for 24–48 hr. Paraffin sections were prepared and stained with hematoxylin and eosin and with trichrome dyes for histological investigation.

This procedure was repeated for a series of 10 intraperitoneal implants. The animals were laparotomized, and the saline-washed trilaminate disks were placed within the lower portion of the peritoneal cavity; the peritoneum and skin incisions then were closed separately with interrupted sutures. Recovered implants and tissue capsules were sectioned and stained as described previously.

Pharmacokinetic Studies—Trilaminate devices in the pharmacokinetic studies were implanted intraperitoneally, according to the outlined procedure, to minimize variations in implant drug release rates due to site-specific tissue capsule formation and associated inflammatory response. Ten rats received tetracycline–copolymer implants coated with a 22:78 2-hydroxyethyl methacrylate–methyl methacrylate copolymer membrane, and 10 rats received implants coated with a 2:98 2-hydroxyethyl methacrylate–methyl methacrylate copolymer membrane. Immediately prior to implantation, the trilaminate disks were washed with a saline solution and the saline wash solutions were analyzed for [^{3}H]-tetracycline. In all cases, the tetracycline loss into the saline wash was insignificant (always <0.01% of the original drug loading).

One day prior to surgery, a control blood sample was taken and the animals were placed in the metabolic cages to collect control fecal and urine samples. Blood was obtained from the jugular vein by puncture with a 1-ml tuberculin syringe fitted with a 26-gauge intradermal tip needle. Blood was drawn once a day from each rat up to and including the day the animal was sacrificed. Daily urine and feces from each animal were weighed and collected for [^{3}H]tetracycline analysis.

The urine sample was centrifuged to remove solids, and 0.2 ml was added with 0.5 ml of distilled water, to prevent salting out, to 10 ml of fluor[2] in a glass counting vial. A 100–150-mg sample of the daily fecal collection was prepared according to a modified oxidative procedure described in the literature (14). The dissolved fecal sample, to which 10 ml of fluor[3] was added, was allowed to equilibrate overnight before counting. Whole blood samples were centrifuged, 0.2 ml of plasma was

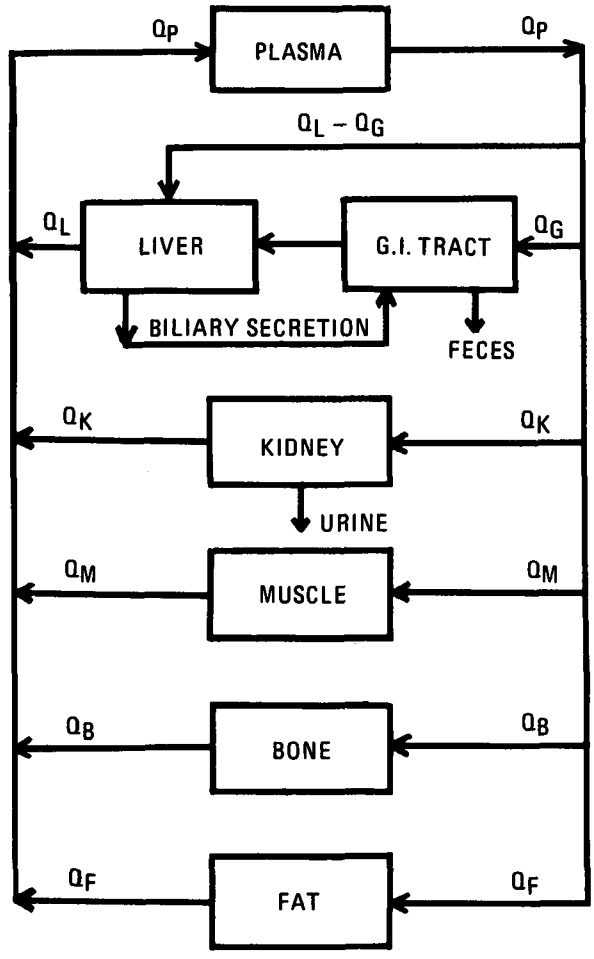

Figure 2—*Flow scheme and organ compartmental diagram utilized in pharmacokinetic model; Q represents plasma flow rate to indicated organs. Model parameter values are listed in Table I.*

added to a glass vial containing 10 ml of fluor[2], and concentrations were determined in a liquid scintillation counter[4].

Animal Sacrifice and Tissue Recovery—Rats were sacrificed (two from each series) on Days 1, 4, 7, 10, and 14 of implantation by cervical-spinal dislocation. Tissues and organs were removed carefully to prevent excess bleeding and blotted gently. Gut tissue was obtained from the upper small intestine. The kidneys were clamped at the renal arteries and removed *in toto*. A section of the liver from the upper right lobe was recovered. The tibia was dissected clean of muscle and connective tissue and crushed, and a muscle sample was removed from the lower thigh.

Sections of soft tissue (100–150 mg) were prepared by a tissue digestion technique (15). Minced tissue was weighed into glass vials to which 1.0 ml of a tissue solubilizer[5] was added. The vials were capped tightly and incubated at 55° for 16–24 hr until digestion was complete. Hydrogen peroxide (0.1 ml/sample) was added to decolorize the samples, the vials were cooled, and 10 ml of fluor[6] was added to each vial. Samples were allowed to equilibrate overnight before counting. Unlabeled tissue samples were processed in an identical manner to correct for background radiation and quenching effects.

Bone samples were prepared by a modified tetracycline extraction procedure (16). Clean bone samples fractured into small fragments were weighed and added to glass vials (~100–150 mg) containing 3 ml of 0.25 *N* HCl. The vials were sealed tightly and stored at 4° with daily shakings. After 1 week, the extract was removed; bone contents were washed with distilled water and transferred to new vials to repeat the procedure (a total of three times). The extract was centrifuged, and 1 ml of the supernate was assayed for [^{3}H]tetracycline by counting in 10 ml of fluor[2].

[1] Purina Rat Chow, Ralston Purina Co., St. Louis, Mo.
[2] Scintosol, Isolabs, Akron, Ohio.
[3] Biofluor, New England Nuclear, Boston, Mass.
[4] Isocap, Searle Analytic, Des Plaines, Ill.
[5] Protosol, New England Nuclear, Boston, Mass.
[6] Econofluor, New England Nuclear, Boston, Mass.

Table I—Physiological Parameters for Tetracycline Pharmacokinetic Model

Tissue[a]	Volume[b], V, ml	Plasma Flow[c], Q, ml/hr	Partition Coefficient, R_i	Literature Values for Tissue–Plasma Concentration Ratio
Plasma	9.0	1416.0	—	—
Liver	8.3	585.0	5.3	4.1[d]
Kidneys	2.0	487.0	4.8	3.3[d]
Bone	10.0[e]	40.0	12.5	8.95[f]
Muscle	100.0	292.0	2.9	1.2[d]
Fat	14.0[g]	19.2[g]	0.7	0[h], 1.5[d]
GI tract	16.0	463.0	4.4	3.1[i]

[a] Values given are for 200-g female rat. [b] Reference 18. [c] Reference 19. [d] Reference 1. [e] Calculated as 2.5 times bone marrow volume reported. [f] Reference 2; concentration was measured in mouse femur. [g] Reference 20; values were scaled down from those reported for a 250-g rat. [h] Reference 6. [i] Reference 14.

Implants recovered at sacrifice were blotted dry of surface fluid and weighed. Sections of the recovered implants and the original trilaminate film were dried to constant weight in a vacuum oven (2.1 kg/cm^2, 40°) and allowed to dissolve in 10 ml of dioxane over 2–3 weeks at 50–60°. Measured aliquots of the dioxane solution were analyzed on the liquid scintillation counter for [^{3}H]tetracycline. Tetracycline remaining in the recovered implant was calculated and expressed as a percentage of the original weight of drug loaded in the trilaminate film (Fig. 1).

Blood Volume Measurements—Organ blood volumes in five rats were measured by a standard ^{51}Cr-red blood cell labeling procedure (17). One milliliter of whole blood, obtained by jugular puncture from the animal to be tested, was added to 1.0 ml of citrate–dextrose solution, Strumia type, containing chromate 51 salt. After 20–30 min of incubation at room temperature, the whole blood solution was centrifuged at 2000×g for 10 min, the supernate was discarded, and 1.0 ml of fresh saline–plasma (5:1) solution was mixed with the suspended cells, after which the sample was recentrifuged. This procedure was repeated four to eight times until extracellular radionuclide levels were <0.1%.

After the final wash, 0.5 ml of the fresh saline–plasma solution was mixed with the suspended cells, and the total volume was injected by cardiac puncture into the rat. Heparinized whole blood samples were taken by jugular vein puncture at 10 and 20 min postinjection; the animal was then sacrificed by cervical-spinal dislocation. Tissues were removed exactly as already described in an effort to measure organ residual blood volumes best reflecting the tissue recovery techniques employed in the kinetic studies. In all cases, radionuclide levels in the whole blood were similar, to within 5%, at the 10- and 20-min sampling periods. Whole blood, saline wash solutions, and minced tissue samples were analyzed using an automatic gamma counter[7].

Pharmacokinetic Model—The pharmacokinetics of zero-order tetracycline delivery from controlled-release implants and tissue drug distribution were described by a mathematical model based on the blood flow-limited concept of drug transport. The relevant compartments and general blood flow scheme are depicted in Fig. 2. This model employs true physiological and anatomical parameters to generate a series of mass balance equations for seven organ compartments. An example of such a mass balance equation is presented for the hypothetical compartment i:

$$V_i \frac{dC_i}{dt} = Q_i C_P - Q_i \frac{C_i}{R_i} - K_i \frac{C_i}{R_i} \qquad \text{(Eq. 1)}$$

where C_i is the tissue drug concentration, V_i is the tissue volume, R_i is the equilibrium partition coefficient (tissue–plasma), K_i is the rate of drug elimination or clearance by the tissue, C_P is the plasma drug concentration, Q_P is the plasma flow rate, and t is time.

Organ volumes, blood plasma flow rates, and drug partition coefficients (determined by best fit analysis of the data) are listed in Table I. Total drug clearance was estimated from the total daily excretion rates and the steady-state plasma concentrations. Approximately 30% of the drug was excreted in the urine, while 70% of the drug was accounted for by fecal elimination. The biliary clearance was estimated from available literature data (21). For simplicity, the gut tissue and gut contents were combined as one compartment. Fecal tetracycline clearance calculations were adjusted by a factor equal to the approximate steady-state ratio of tetracycline concentration in the gut tissue and gut contents.

Tetracycline delivery was modeled as a zero-order input term into the plasma compartment. The magnitude of this input term was set equal to the zero-order release rate determined from the implant recovery analysis. The balance equation for the plasma is:

$$V_P \frac{dC_P}{dt} = K_0 + Q_L \frac{C_L}{R_L} + Q_G \frac{C_G}{R_G} + Q_K \frac{C_K}{R_K} + Q_M \frac{C_M}{R_M} + Q_B \frac{C_B}{R_B} + Q_F \frac{C_F}{R_F} - Q_P C_P \qquad \text{(Eq. 2)}$$

where subscripts L, K, M, B, F, P, and G denote liver, kidney, muscle, bone, fat, plasma, and GI tract, respectively; and K_0 is the zero-order input term.

Burst effects corresponding to experimentally measured values are incorporated into the K_0 term and into the clearance terms for the first 24 hr of implantation.

RESULTS AND DISCUSSION

Biocompatibility—Subcutaneous implant studies revealed no differences in fibrous capsule formation or general tissue response between the tetracycline-loaded trilaminate disks and the control trilaminate disks containing no drug in the core. Capsule thickness was maximal by 4–6 weeks implantation time, followed by further organization of the surrounding fibrous tissue. Early implant capsules (1–2 weeks) demonstrated mild inflammation with some surrounding tissue edema and loose granulation tissue with onset of fibrous capsule formation. There was little evidence of any chronic inflammatory processes in the long-term implants (4–9 weeks), the surrounding capsules consisting of well-organized, dense collagen fibrils with little cellular infiltration. These results agree with previous observations (22) concerning the tissue biocompatibility of methyl methacrylate polymers, indicating that the coating copolymer surface (containing 2% 2-hydroxyethyl methacrylate and 98% methyl methacrylate) was the controlling factor in the response of the surrounding tissue to the implanted device.

By comparison, fibrous capsule formation was essentially absent for both drug-loaded and control disks implanted in the peritoneal cavities of rats. Only a thin membrane formed over the intraperitoneal implants, and this membrane was easily disrupted upon implant recovery. In most cases, the implant lodged in the intraperitoneal fat near the site of the original laparotomy. In three cases, the implant migrated to the upper peritoneum, resting on either the dome of the lower left lobe of the liver or the omentum.

***In Vivo* Implant Hydration**—Equilibrium swelling was achieved for samples of both the 2:98 and 22:78 implant series retrieved on the 4th day of implantation. For these implant series, the equilibrium swelling values were 44.5 ± 2.6 and 44.8 ± 1.6%, respectively (mean ± SE taken over the entire implantation period). These similar values indicate that equilibrium hydration of the device is best represented by the swelling of the core component (63:37 copolymer) that makes up the bulk of the trilaminate disk.

The *in vivo* swelling measurement of 44–45% is higher than the equilibrium hydration value of 26.5% previously reported for blank 63:37 copolymer membranes measured *in vitro* (12). The observed difference in swelling values between the *in vivo* disks and the blank 63:37 membrane tested *in vitro* was likely due to the osmotic action of the drug contained in the core (20% drug, w/w) of the implanted device.

Cumulative Release and Excretion Data—Tetracycline release from the implanted trilaminate disks (Fig. 1) appeared constant with time and exhibited a zero-order release profile similar to that reported in the *in vitro* trials. The release rates of the 2:98 (123 μg/day) and the 22:78 (158 μg/day) copolymer coated disks differed significantly. The fact that both series demonstrated a nonzero intercept indicates an initial burst effect of 2–3% over the first 24 hr of release.

To confirm the observation of *in vivo* zero-order release from the implanted trilaminate disks, tetracycline levels were measured in fecal and urine samples. Total daily fecal and urine volumes were recorded over the implantation period. These values were employed to quantitate total daily tetracycline elimination in the excretion products. This method provides a reliable estimate of total physiological drug elimination since tetracycline is not metabolized by the rat (23). Over the steady-state drug release period (Days 2–14), the mean cumulative daily physiological elimination of tetracycline (Table II, measured as the sum of the total daily drug excretion in the steady-state fecal and urine outputs) was 110

[7] Model 1185, Searle Analytic, Des Plaines, Ill.

Table II—Comparison of Steady-State Cumulative Tetracycline Release and Elimination Rates

Coating Composition of Membrane Device	Zero-Order Release Rate[a], μg/day	Total Elimination by Rat[b], μg/day, Mean ± *SD*
2:98 series	123	110 ± 32
22:78 series	158	153 ± 42

[a] Determined from slope of cumulative release curve (Fig. 1). [b] Sum of urine and fecal tetracycline excretion per day over steady-state period (12 days).

μg/day for the 2:98 copolymer-coated implant series and 153 μg/day for the 22:78 copolymer-coated implant series.

These elimination rate values agree remarkably well with the steady-state, *in vivo* release rates. The initial drug release burst of 2–3% from the implants also was evident in the initial high drug elimination levels recorded over the first 1 or 2 days of implantation (~480 μg total for the first 2 days in the 22:78 implant series and 435 μg total for Days 1–3 in the 2:98 series, corresponding to 2.7–3.0% the initial drug loading in the disks). For both implant series, daily tetracycline elimination was ~31% in the urine and ~69% by the fecal route.

Without further data, it would be inappropriate to correlate *in vivo* release rates with the physiological drug elimination rate. However, given the evidence of near-constant plasma and tissue tetracycline levels over the same steady-state period (Figs. 3 and 4), a true mass balance is possible for the *in vivo* system. The analysis of drug release from recovered disks, daily tetracycline elimination rates, and steady-state drug levels in the blood and tissues provides indisputable experimental evidence that the implants are releasing tetracycline at a constant rate over the steady-state portion of the implantation period. This finding confirms the earlier *in vitro* observations on the zero-order release rate character of the copolymer trilaminate device.

Experimental Drug Levels in Blood and Tissue—Plasma tetracycline achieved near-constant levels within 2–4 days following implantation and remained stable during the experiment (Fig. 3). Experimental tissue tetracycline concentration values were corrected for residual blood content. Experimental values for residual blood volumes in individual organs were determined by a ^{51}Cr-red blood cell labeling technique (17). These results are compared to literature values given in Table III.

Minimum organ blood volumes reported by Sharpe *et al.* (24) were determined by a radiolabeled cell method in which the rats were anesthetized with ether and bled maximally from the abdominal aorta or inferior vena cava before the organs were recovered and analyzed for radiolabeled blood cell content. Organ blood volume values reported by Everett *et al.* (25) (Table III) were determined by achieving maximal recovery of residual blood in the respective tissues. In this method, the rats were injected with radiolabeled red blood cells or ^{135}I-serum albumin; after a suitable circulatory mixing period (3–15 min), the rats were sacrificed quickly by freezing in liquid nitrogen. Quick freezing of the animal's body fluids and tissues produced a rapid stasis of the blood, permitting dissection of the organs for radioassay without blood loss.

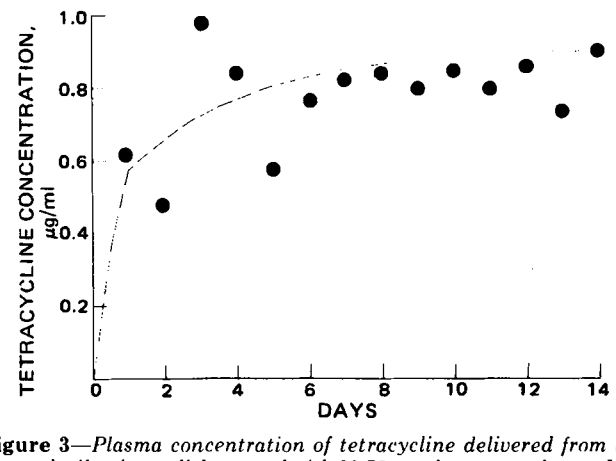

Figure 3—*Plasma concentration of tetracycline delivered from implanted trilaminate disks coated with 22:78 copolymer membrane. Key: ●, experimentally determined plasma tetracycline concentrations; and ---, model simulation results.*

Table III—Tissue Residual Blood Volumes (Milliliter of Whole Blood per Gram of Wet Tissue)

Tissue	Experimental Results[a], Mean ± *SD*	Reference Values: Minimum Volume[b]	Reference Values: Total Volume[c]
Liver	0.060 ± 0.012	0.047	0.265
Kidney	0.087 ± 0.027	0.049	0.154
Muscle	0.008 ± 0.002	0.004	0.023
Fat	0.006 ± 0.001	—	—
Gut	0.016 ± 0.004	—	0.035
Bone	0.028 ± 0.009	—	0.033

[a] As determined from five experiments employing ^{51}Cr-labeled red blood cells. [b] Data from Ref. 24. [c] Data from Ref. 25.

Residual blood volumes calculated in the present experiment are the result of a procedure designed to reflect the organ blood volumes remaining in the various tissues after the experimental dissection of the organs for analysis of drug content. As expected, these experimental values fall within the range of results presented by the more radical techniques. Previous investigations of differential tissue drug levels failed to correct for residual blood drug content. Depending on actual blood–tissue drug partitioning effects, the method of sacrifice, and the organ recovery techniques employed, failure to correct for the residual blood volume can lead to significant errors in experimental drug content analysis. The need for accurate tissue drug level determinations is critical when attempts are made to fit experimental data to pharmacokinetic models; false experimental values produce erroneous estimates of model transport and kinetic parameters.

The highest tissue tetracycline concentrations were recorded in the whole bone samples (Fig. 4). This result is in agreement with previous observations (26) on the deposition of high tetracycline levels in growing bone tissue. High tetracycline levels in the kidney and liver (Fig. 4) reflect the roles of these organs in tetracycline elimination through the urine and bile, respectively. The lowest tetracycline concentrations were measured in the fat tissue, which failed to concentrate the antibiotic above levels measurable in the plasma. Steady-state plasma and tissue levels were not significantly different in the two tetracycline delivery series. The difference in recorded release rates apparently contributed only to the observed differences in tetracycline elimination rates since the tissues reached similar equilibrium saturation levels early in the experiment for the observed range of drug delivery rates from the two implant series.

Pharmacokinetic Model—There was good general agreement between predictions based on the flow-limited pharmacokinetic model (Fig. 2) and the actual experimental measurements of the organ disposition of tetracycline and of tetracycline elimination. Experimental tetracycline concentrations in the plasma (Fig. 3) and individual tissues (Fig. 4) demonstrated levels consistent with model predictions based on the zero-order rate diffusional input determined from the slopes of the cumulative release curves (Fig. 1). The tissue–plasma equilibrium partition

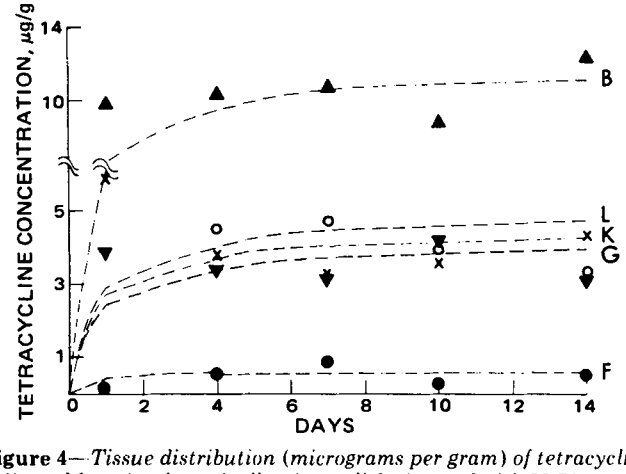

Figure 4—*Tissue distribution (micrograms per gram) of tetracycline delivered from implanted trilaminate disks (coated with 22:78 copolymer membranes). Key (experimentally determined values): ●, fat tissue; ▼, GI tissue; ×, kidney; ○, liver; and ▲, bone. The dashed lines (labeled at right) represent model simulation results for these tissues: F, fat tissue; G, GI tissues; K, kidney; L, liver; and B, bone.*

coefficients (Table I) were estimated initially from the results of earlier intravenous bolus studies with tetracycline (1, 2, 4, 6) and later were adjusted by trial and error to best fit the model predictions to the experimental tissue concentrations.

The ability of trilaminate controlled-release disks fabricated from 2-hydroxyethyl methacrylate–methyl methacrylate copolymers to deliver tetracycline at a constant release rate when implanted in rats has been demonstrated. A full range of *in vivo* zero-order release kinetics is attainable through variations in the copolymer composition of the diffusion-controlling coating membrane of the trilaminate disk. The ability of such a device to deliver a pharmaceutical at a desired constant release rate over a long period is extremely valuable both as a therapeutic and an investigational tool. This system may be extended to the study of other drugs where long-term constant delivery rates are desired.

A flow-limited pharmacokinetic model is presented that utilizes the ability of the trilaminate controlled-release device to deliver tetracycline at constant rates over a prolonged implantation period. Predictions based on this model are consistent with tissue tetracycline concentrations measured in experiments with these implant devices. The physiological pharmacokinetic model can be utilized to provide reliable predictions of tissue drug levels and is useful in studies of differential organ toxicities due to effects caused by the parent drug or its metabolites (27). The model also contributes information valuable for the design of proper drug dosing regimens and for the fabrication and placement of controlled drug delivery systems designed to deliver drugs to selected physiological target sites.

The coupling of the principles of controlled release from a zero-order rate device and long-term physiological pharmacokinetic modeling is a unique research concept and will be used in investigational systems where such drug delivery characteristics help elucidate physiological rate mechanisms.

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