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Local Drug Delivery Systems for the Treatment of Periodontal Disease

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Filmy local drug delivery systems (LDDSs) were administered to periodontal pockets in beagles with induced periodontitis, and the *in vivo–in vitro* correlation of drug release from the LDDS and changes in the clindamycin (CLDM) concentration in the periodontal pocket fluid were studied.

The *in vitro* drug release rate from the LDDS was determined by the dissolution study, without agitation, using phosphate buffer as the dissolution medium at 37 °C, and the *in vivo* drug release rate was determined according to the decrease in the drug load remaining in the LDDS after administration in periodontal pockets. The *in vivo* drug release rate from LDDSs was lower than the *in vitro* rate determined by the dissolution study, but the two rates showed a correlation in LDDSs that released drugs by diffusion. Therefore, the *in vivo* drug release rate was considered to be estimated from the results of the *in vitro* dissolution study.

Changes in the drug concentration in the periodontal pocket fluid after administration of LDDS were dependent on the drug release properties of the LDDS. Also, when CLDM was administered as an aqueous solution in periodontal pockets, its concentration in the periodontal pocket fluid decreased according to a pseudo first-order equation. Therefore, the concentration in the periodontal pocket fluid after administration of a LDDS is considered to be simulated by the one compartment model based on a pseudo first-order elimination process.

Keywords — periodontal disease; pharmacokinetics; clindamycin; local drug delivery system

Introduction

Periodontal disease has been shown to be caused and aggravated by pathogenic bacteria living in plaque, especially anaerobic gram-negative bacteria.[1-3] This fact has encouraged the use of antibiotics for the treatment of the disease, and the bacteriological and clinical efficacy of oral antibiotic therapy has been established.[4,5] However, long-term administration of antibiotics is required for the treatment of chronic periodontal disease, and prolonged oral administration is associated with the risk of developing resistant bacteria and superinfection, as well as with side effects such as gastrointestinal disorders. Therefore, oral antibiotic therapy has not been accepted as a treatment for chronic periodontal disease from the viewpoint of safety.

In this context, local administration of antibiotics and synthetic antimicrobial drugs has attracted the attention of many investigators, but treatments based on conventional methods such as irrigation and mouth rinses have been reported to be insufficiently effective.[6,7] With recent advancements in the studies of drug delivery systems, treatment of periodontal disease using local drug delivery systems (LDDSs) has emerged as a matter of interest, and the bacteriological and clinical usefulness of this treatment has been evaluated.[8-12] However, there have been few pharmacokinetic studies of changes in the drug concentration in the periodontal pocket fluid after administration of LDDSs.

In this study, *in vitro* drug release from LDDSs and *in vivo* release in periodontal pockets of beagles were examined, and the drug concentration in the periodontal pocket fluid was analyzed pharmacokinetically on the basis of the *in vitro–in vivo* correlation of drug release.

Materials and Methods

Materials — Clindamycin HCl (CLDM, Sigma Chemical Co., U.S.A.), a weakly alkaline drug with potent antibacterial activities against

TABLE I. Compositions of LDDSs

	LDDS A(%)	LDDS B(%)	LDDS C (%)	LDDS D(%)	LDDS E(%)
Methylene blue	1	—	—	—	—
Clindamycin HCl	—	—	2	5	5
Acid red	—	2	—	—	—
Eudragit® RL	79	78	78	—	—
Eudragit® L	—	—	—	75	—
Eudragit® S	—	—	—	—	75
Plasticizers	20	20	20	20	20

pathogens of periodontal disease and a high chemical stability, was used for the study.[13,14] The monosodium salt of 9-(2′-sulfonium-4′-sulfophenyl)-6-diethylamino-3-(*N,N*-diethylimino)-3-isoxanthene (acid red, San-ei Chemicals Industrials Ltd., Japan), an acidic water-soluble dye, and methylene blue (Sumitomo Chemicals Co., Ltd., Japan), an alkaline water-soluble dye, were alos employed as acidic and alkaline drugs, respectively.

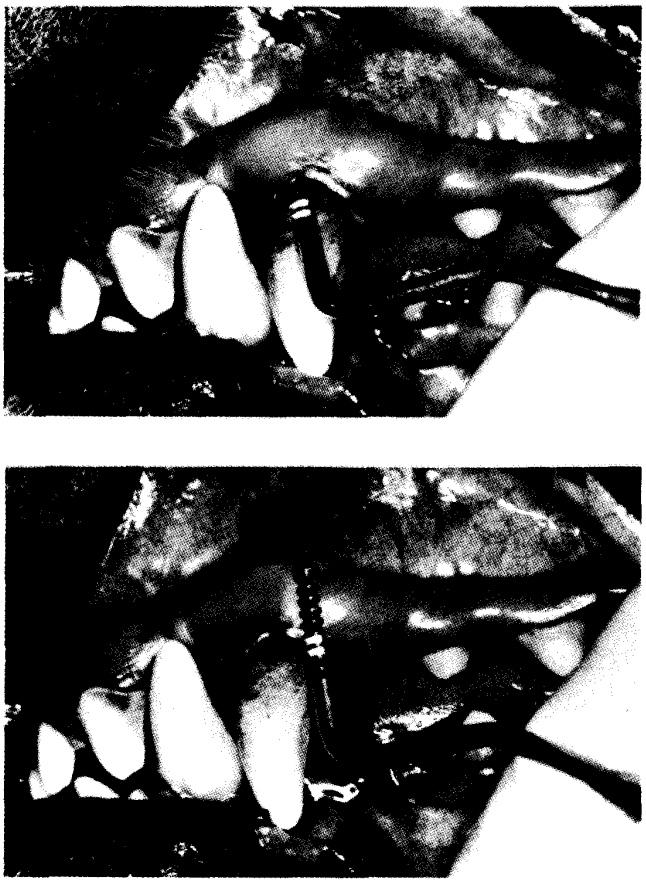

Fig. 1. Observation of Beagles with Experimental Periodontal Disease

One scale unit of the probe is 1 mm. A periodontal pocket 5 mm in depth was observed.

Two polymers with different monomer compositions, which dissolve in alkaline medium, methacrylic acid/methylmethacrylate copolymers (Eudragit® L and Eudragit® S, Rhöm Pharma, West Germany), and a non-water soluble polymer, ethyl methacrylate/chlorotrimethylammonium methyl methacrylate copolymer (Eudragit® RL, Rhöm Pharma, West Germany), were used as matrices for the filmy LDDS. Triacetin (Wako Pure Chemicals Ind., Japan), polyethylene glycol 400, and 6000 (Wako Pure Chemicals Ind., Japan) were used alone or in combination, as plasticizers.

Preparation of Filmy LDDSs — Five filmy LDDSs, namely Eudragit® RL matrices containing methylene blue (LDDS A), acid red (LDDS B), and CLDM (LDDS C); a Eudragit® L matrix containing CLDM (LDDS D); and a Eudragit® S matrix containing CLDM (LDDS E), were prepared (Table I).

The drug, the matrix polymer, and the plasticizer were dissolved in a mixture of ethanol and water (95:5, w/w), and a film about 200 μm in thickness was produced by the casting method. The film was cut into 2.5 × 2.5 mm and 10 × 10 mm sheets and was used for the *in vivo* release study and the *in vitro* dissolution study respectively.

Preparation of Beagles with Induced Periodontitis — Periodontal disease was induced in 2 male beagles (9 months old) by the method of Yamashita *et al.*[15] Silk thread was tied around the upper and lower 4th teeth (4 teeth in all) in order to promote the deposit of dental plaque, and periodontitis was produced by feeding the animals for 3 months with a solid animal food

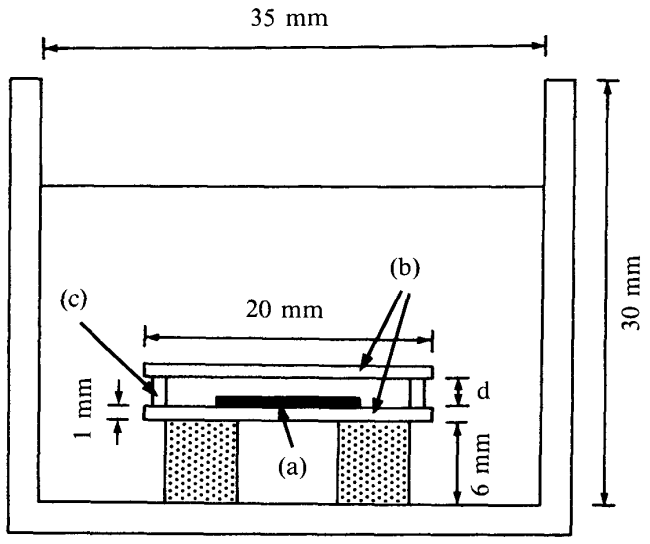

Fig. 2. Apparatus Used for *in Vitro* Dissolution Study with LDDS Placed between Glass Plates
(a) LDDS, (b) glass plate, (c) spacer, d, distance of glass plates.

(CD-5, CLEA Japan Inc., Japan) softened into paste. Periodontal pockets 5—7 mm in depth were selected as the administration sites (Fig. 1).

Evaluation of *in Vitro* Release — A piece of the LDDS (10 × 10 mm) was placed in a sinker (JP XI), and the drug was eluted in 20 ml of 50 mM phosphate buffers (pH 6.5, 7.2, and 7.6) at 37 °C without agitation.

Then, (1) the viscosity of the periodontal pocket fluid and (2) the space in the periodontal pocket (distance between the internal walls) were selected as representative elution conditions in the periodontal pocket, and the following two elution studies were carried out to evaluate the effects of these factors on the drug release. (a) A piece of the LDDS (10 × 10 mm) was placed in a sinker, and the drug was eluted in 20 ml of 50 mM phosphate buffer (pH 7.2) containing 1% (w/w) hydroxypropyl cellulose (HPC-H, Nippon Soda Co., Ltd., Japan) at 37 °C without agitation. (b) A piece of the LDDS (10 × 10 mm) was placed between two glass plates (20 × 20 × 1 mm) (Fig. 2) separated at various distances, and the drug was eluted in 20 ml of 50 mM phosphate buffer (pH 7.2) at 37 °C without agitation, and the effect of the distance between the glass plates on the drug release profile was studied.

Evaluation of *in Vivo* Release — A piece of LDDS (2.5 × 2.5 mm) was inserted into each periodontal pocket. The LDDSs were recovered after predetermined intervals, and each pocket was washed with physiological saline using a microsyringe. The drug load remaining in the LDDS was measured, and the cumulative drug release until the predetermined time was calculated from the residual drug load. This procedure was repeated, and the *in vivo* release of CLDM was determined sequentially.

Evaluation of CLDM Concentration in the Periodontal Pocket Fluid after LDDS Administration — A piece of LDDS (2.5 × 2.5 mm) was inserted into each periodontal pocket. The LDDSs were removed after predetermined intervals, the periodontal pocket fluid was collected immediately, and the pocket was washed with physiological saline using a microsyringe to remove the residual drug completely. This procedure was repeated, and sequential changes in the CLDM concentration in the periodontal pocket fluid were studied.

Changes in the CLDM Concentration in the Periodontal Pocket Fluid after Administration of CLDM Aqueous Solution — CLDM was dissolved in purified water at 1.0 mg/ml. Fifty μl of CLDM aqueous solution was poured into the bottom of the periodontal pockets of beagles using a microsyringe, the solution that overflowed from the pocket was removed immediately with cotton, and the periodontal fluid was collected at predetermined intervals. After each collection of the periodontal fluid, the pocket was washed thoroughly with physiological saline using a microsyringe. Sequential changes in the CLDM concentration in the periodontal pocket fluid were studied by repeating this procedure.

Collection of Periodontal Pocket Fluid — Periodontal pocket fluid was collected by using filter paper strips (3 × 15 mm, No.4A, Toyo Roshi Co., Japan).[16] After absorption of the periodontal fluid, the paper strips were dried and stored in microtubes at a low temperature until analysis. The volume of the periodontal pocket fluid collected was estimated from a calibration curve prepared from the equilibrium wet areas noted in paper strips after absorption of known amounts of distilled water.

Assay of the Drug in LDDS and *in Vitro* Dissolution Medium — LDDSs C, D, and E, which contained CLDM, were dissolved in ethanol. CLDM in these test solutions was assayed by high performance liquid chromatography (HPLC) (Shimadzu LC-6A system, Shimadzu Seisakusho Ltd., Japan), using a stainless steel column (4 mmi.d. × 30 mm) packed with Nucreosil $_{10}C_{18}$ (M. Nagel Co., West Germany). The mobile phase, which was a mixture of 10 mM phosphate buffer (pH 7.2) containing 5 mM sodium pentasulfonate and methanol (25/75, v/v), was applied at a flow rate of 1.2 ml/min. The CLDM level was determined by ultraviolet (UV) absorption (214 nm).

LDDSs A and B were dissolved in a mixture of acetone and water (95/5, v/v), and acid red and methylene blue contained in these test solutions were assayed with a UV spectrophotometer (Shimadzu UV-260 Shimadzu Seisakusho Ltd., Japan) at optical density 565 and 663 nm, respectively.

CLDM, acid red, and methylene blue in the dissolution medium were also assayed by HPLC, as above, or by spectrophotometry.

Assay of CLDM in Periodontal Fluid — CLDM in the periodontal fluid was measured by bioassay using *Streptococcus mutans* OMZ 176 as the test organism. The paper strips that absorbed the periodonta fluid were placed on BHI agar plate (DIFCO Lab., U.S.A.) containing pre-cultivated *St. mutans* OMZ 176, and were incubated overnight at 37 °C. The area of the growth inhibition circles was measured, and the amount of the drug contained was determined from the calibration curve of the area of the inhibition circle *versus* the amount of drug.

Results

In Vitro Release Profiles

Figure 3 shows the *in vitro* drug release profiles of LDDSs A, B, C, D, and E when they were treated in a sinker with 50 mM phosphate buffers, pH 6.5, 7.2, and 7.6, as dissolution media.

Within the first 70% of the total released drug, the amount of drug released was proportional to $t^{1/2}$ in LDDSs A, B, and C (Fickian diffusional release[17]). At pH 7.2, the drug release rates ($\%/t^{1/2}$) from LDDSs A, B, and C decreased in the following order: LDDS A, C, and B. The drug release profile of LDDS C was studied in a dissolution medium with different

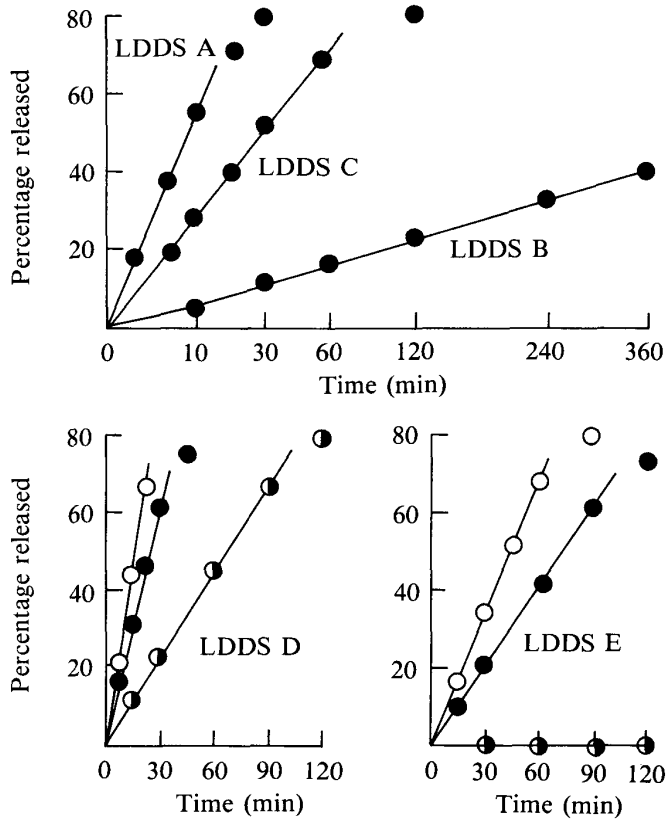

Fig. 3. *In Vitro* Drug Release Profiles of LDDSs A, B, C, D, and E

Each point represents the mean ($n=3$). ◑, pH 6.5; ●, pH 7.2; ○, pH 7.6.

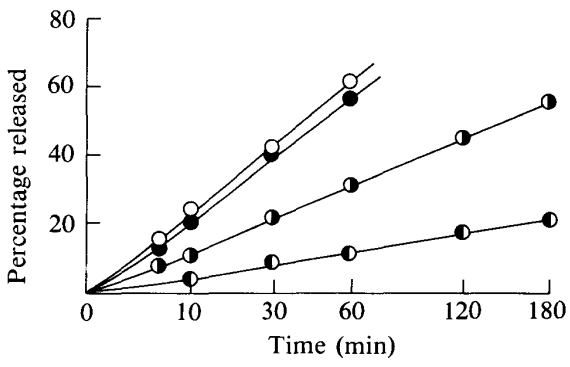

Fig. 4. Effects of the Distance of Glass Plates (d) on the *in Vitro* Drug Release Profile of LDDS A

Each point represents the mean ($n=3$). ○, $d=2.0$ mm; ●, $d=0.7$ mm; ◑, $d=0.40$ mm; ◐, $d=0.25$ mm.

pH values, but the release rate of CLDM was not affected by the pH of the dissolution medium.

The release profile of methylene blue from LDDS A in phosphate buffer containing 1% (w/w) HPC-H was different from that in phosphate buffer not containing HPC-H in that a time lag was observed in the former, but there was little difference in the drug release rate once the release started.

Figure 4 shows the *in vitro* drug release profiles of methylene blue from LDDS A placed between glass plates. The release of methylene blue was increased in all conditions in proportion to $t^{1/2}$, but the drug release rate decreased with the distance of the glass plates when the distance was 0.7 mm or less.

LDDSs D and E showed zero-order release, but drug release was not observed from LDDS E at pH 6.5. The drug release rate of both LDDSs increased with increasing pH. The drug release from LDDS E was slower than that from LDDS D at all pHs tested.

From these findings, the 5 LDDSs were categorized into 2 types according to their drug release profiles. LDDSs A, B, and C, prepared from a cationic non-water soluble matrix, were classified as Fickian diffusional release types, and LDDSs D and E prepared from soluble matrices in alkaline aqueous media, were classified as zero-order release types.

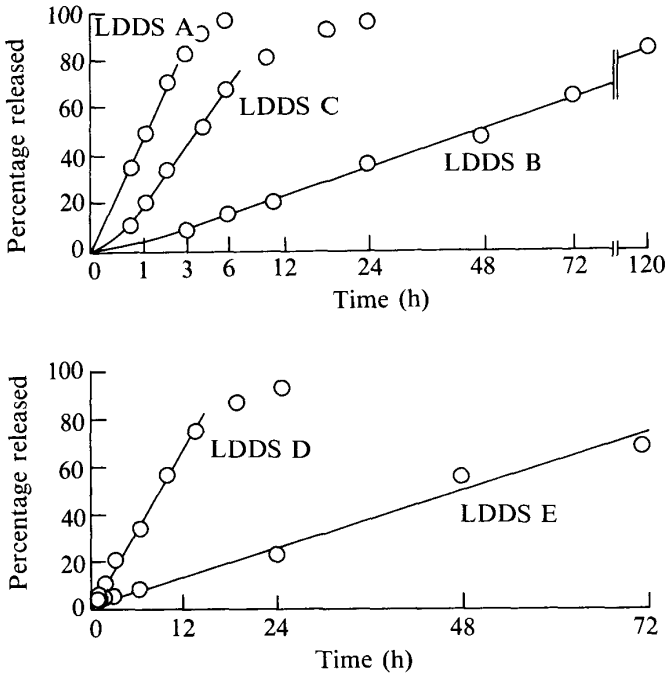

Fig. 5. *In Vivo* Drug Release Profiles of LDDSs A, B, C, D, and E
Each point represents the mean ($n=4$).

TABLE II. *In Vitro* and *in Vivo* Drug Release Rates of LDDS A, B and C

	Drug release rate	
	In vitro (pH 7.2)	*In vivo*
LDDS A	16.90[a]	6.90[a] (9.14)[b]
LDDS B	2.11[a]	1.05[a] (2.78)[b]
LDDS C	9.66[a]	4.35[a] (8.11)[b]

Each value represents the mean ($n=3$—4). *a)* %/min$^{1/2}$, *b)* μg/h$^{1/2}$/LDDS.

In Vivo Release Profiles

Figure 5 shows the *in vivo* drug release profiles of LDDSs A, B, C, D, and E.

In vivo, LDDSs A, B, and C also showed Fickian diffusional release, as they did *in vitro*, within the first 70% of the total released drug. The *in vivo* drug release rate (%/$t^{1/2}$) decreased in the following order: LDDS A, C, and B, as did the *in vitro* release rate (Table II). *In vivo–in vitro* correlations were observed in the drug release rates of LDDSs A, B, and C (Fig. 6).

LDDSs D and E also showed zero-order release *in vivo*, as they did *in vitro*. The *in vivo* release of CLDM from LDDS E was slower than that from LDDS D. Table III shows the ratios of the *in vivo* and *in vitro* drug release rates from LDDSs D and E.

CLDM Concentration in Periodontal Pockets after Administration of LDDS

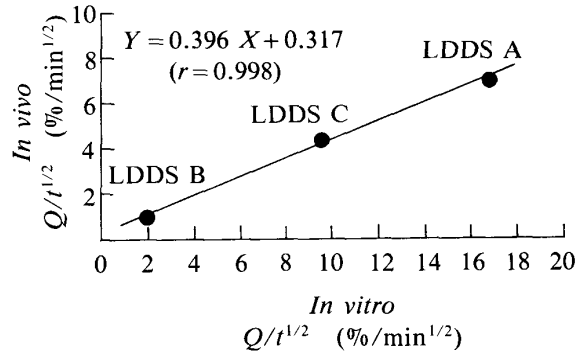

Fig. 6. *In Vitro–in Vivo* Correlations for the Drug Release Rates of LDDSs A, B, and C

TABLE III. *In Vitro* and *in Vivo* Drug Release Rates of LDDS D and E

		LDDS D		LDDS E	
		Release rate	Ratio ($\frac{In\ vivo}{In\ vitro}$)	Release rate	Ratio ($\frac{In\ vivo}{In\ vitro}$)
In vitro	pH 6.5	0.73[a]	0.129	—	—
	pH 7.2	2.03[a]	0.046	0.67[a]	0.025
	pH 7.6	2.93[a]	0.032	1.13[a]	0.015
In vivo		0.094[a]		0.017[a]	
		(3.05)[b]		(0.757)[b]	

Each value represents the mean ($n=3$—4). *a*) %/min, *b*) μg/h/LDDS.

Figure 7 shows time profiles of CLDM concentration in periodontal pockets after administration of LDDSs C, D, and E. The mean CLDM loads of LDDSs C, D, and E were 24, 57 and 73 μg, respectively, per preparation.

After administration of LDDS C, CLDM concentration in the periodontal pocket fluid increased rapidly to about 700 μg/ml in 0.5 h, but decreased sharply thereafter to about 5 μg/ml or less after 24 h.

After administration of LDDS D, CLDM concentration in the periodontal pocket fluid increased gradually and remained at a constant level of about 550 μg/ml until about 12 h after administration. Thereafter, the level of CLDM decreased gradually, but remained at abut 300 μg/ml even after 24 h.

After administration of LDDS E, CLDM concentration in the periodontal pocket fluid increased gradually and remained at a constant level of about 150 μg/ml. This constant level,

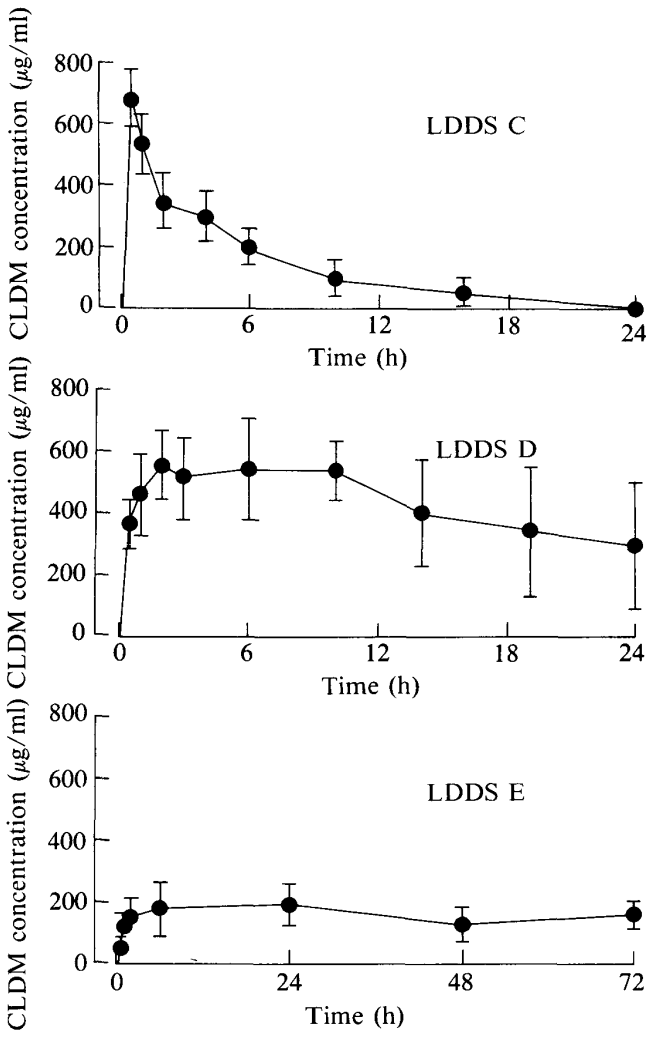

Fig. 7. Changes in CLDM Concentration in the Periodontal Pocket Fluid after Administration of LDDSs C, D, and E
Each point represents the mean ± S.D. ($n=4$).

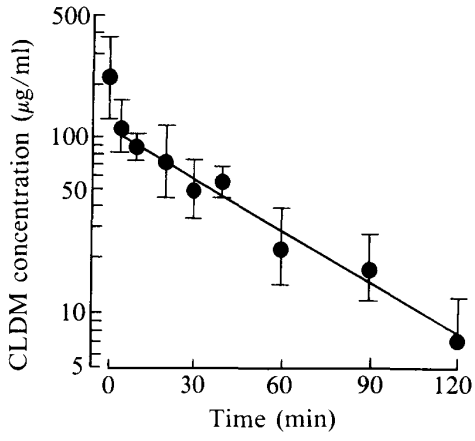

Fig. 8. Changes in CLDM Concentration in the Periodontal Pocket Fluid after Irrigation with CLDM Aqueous Solution
Each point represents the mean ± S.D. ($n=4$).

though it was lower than that of LDDS D, was maintained until 72 h after administration.

These results suggest that the pattern of changes in CLDM concentration in the periodontal pocket fluid differs between the Fickian diffusional release LDDS (LDDS C) and the zero-order release LDDSs (LDDS D and E) and that the drug concentration maintained in the periodontal pocket fluid after administration of zero-order release LDDSs is dependent on the drug release rate.

CLDM Concentration in Periodontal Pocket Fluid after Local Administration of CLDM Aqueous Solution

As shown in Fig. 8, CLDM in periodontal pocket fluid disappeared very rapidly, and its concentration decreased to about 7 μg/ml at 2 h after administration. Changes in CLDM concentration were approximated by a pseudo first-order equation, in which the disappearance rate constant, calculated from the decreased in the concentration from 15 min to 2 h after administration, was 1.36 h^{-1}.

Discussion

In the treatment of periodontal disease, it is important to eliminate the bacteria, deposited in periodontal pockets, which cause the development and progression of this disease.[18] In the antibiotic therapy of periodontal disease, maintaining an effective drug concentration in the periodontal pocket fluid for a sufficient period is considered to be more important than increasing drug concentration in periodontal tissues such as the gingiva. For this reason, administration of antibiotics, using LDDSs which enable controlled release directly into periodontal pockets, is expected to be a very effective therapeutic measure for periodontal disease.

Recently, the use of LDDSs for the treatment of periodontal disease has been evaluated by a number of investigators, but approaches from the biopharmaceutical viewpoint have not been sufficient.

In this study, in order to clarify the *in vitro–in vivo* drug release relationship, drug release profiles of LDDSs were examined *in vitro* and *in vivo* in periodontal pockets in beagles, and the drug concentration in periodontal pockets was studied according to this relationship.

First, the *in vitro–in vivo* correlation of drug release was studied in insoluble LDDSs that release drugs by diffusion and in soluble LDDSs that release drugs by dissolution. *In vitro* release was evaluated in a sinker without agitation. Since the periodontal pocket fluid was considered to be a mixture of saliva and gingival crevicular fluid effusing from periodontal tissues, phosphate buffers ranging in pH from 6.5 to 7.6 were used as dissolution media.

LDDSs A, B and C, which release drugs by a diffusion mechanism, were all confirmed to show Fickian diffusional release, both *in vitro* and *in vivo*. The drug release rate of these preparations decreased in the following order: LDDS A, C, and B; this difference is considered to be based on the strength of electric interactions between the drug and the polymer matrix.[19] Regarding the *in vitro–in vivo* relationship of drug release rates, drug release was slower *in vivo* than *in vitro* in all preparations, and a correlation (Fig. 6) was observed between *in vivo* and *in vitro* drug release rates. These results suggest that, in LDDSs which release drugs by diffusion, *in vivo* drug release can be estimated from the results of *in vitro* dissolution study.

Next, in order to evaluate the phenomenon that the *in vivo* drug release rate was lower by a fixed percentage than the *in vitro* drug release rate, the presence or absence of diffusional resistance factors[20] *in vivo* was examined. Since the viscosity of the periodontal pocket fluid was considered to be a factor in the *in vivo* diffusional resistance, a dissolution study was carried out using a diffusion medium containing HPC-H. However, no reduction in the drug release rate was observed, and the viscosity of the periodontal pocket fluid was excluded as a major factor in the low *in vivo* drug release rate.

A periodontal pocket is a small space formed between the tooth and the epithelial lining (interior wall) of the pocket (Fig. 1). When a filmy LDDS is administered in a periodontal pocket, one side of the preparation comes into contact with the epithelial lining of the pocket and the other side comes into contact with the dental surface. If the distance between the preparation and

the body surface becomes less than the thickness of the diffusional boundary layer which is formed on the surface of the preparation in the drug release process, the drug concentration gradient in the diffusional layer decreases, producing a non-sink condition in some areas of the surface of the preparation. This decreases the effective area of drug release, resulting in a reduction in the release rate. Therefore, in order to evaluate the effects of the unique microenvironment of periodontal pockets on drug release, we placed LDDS A between two glass plates, and studied the effect of the distance between the glass plates on drug release. Although there was no change in drug release type, when the distance of the glass plates was reduced to less than about 0.7 mm, the drug release rate decreased (Fig. 4). From these results, we ascribed the reduction in the observed *in vivo* drug release rates to a reduction in the effective area of drug release, caused by the close contact of the preparation with the body surface.

In LDDSs D and E, which release the drug by dissolution of the polymer matrix, these were all confirmed to show a zero-order release, both *in vitro* and *in vivo*. However, the ratios of the *in vitro* and *in vivo* drug release rates were different in LDDS D and E, as indicated by Table III. *In vivo* release rates, as compared with *in vitro* release rates, were inclined to be reduced more notably than those in the preparations which release drugs by diffusion. Dissolution of weakly anionic polymers such as methacrylic acid/methylmethacrylate copolymers is generally known to be affected by the pH or by the kinds and the strength of ionic content in the aqueous medium.[21,22] The greater decrease in the *in vivo* release rate from these soluble LDDSs may be explained by differences in the dissolution rates of the polymer in the *in vitro* and *in vivo* media, as well as by other features of the periodontal pocket as an environment for drug release.

Next, we attempted a pharmacokinetic analysis of the drug concentration in the periodontal pocket fluid after administration of the LDDS. From the results of the *in vitro* and *in vivo* dissolution tests, it was found that the amount of drug released in a unit time decreased with time in LDDS C and was constant in LDDSs D and E. These results suggest that the drug concentration in the periodontal pocket was dependent on the drug release from the LDDS, as indicated by Fig. 7. The drug in the periodontal pocket is considered to be eliminated by absorption from the mucosal epithelium of the pocket, dilution by the gingival crevicular fluid effusing from periodontal tissues, and outflow from the pocket. To clarify the process whereby the drug was eliminated from the periodontal pocket, an aqueous solution of CLDM, in which the effect of drug release could be excluded, was administered into the periodontal pocket, and the decrease in the drug concentration in the periodontal pocket was examined sequentially. The elimination process of the drug from the pocket was found to be closely approximated by a pseudo first-order equation, and the elimination rate (rate constant for total elimination, E_T) was calculated to be 1.36 h^{-1}, although the relative importance of individual factors could not be determined.

Thus, we developed a one compartment model based on a pseudo first-order drug elimination process (Fig. 9). According to this model, changes in the drug concentration in the periodontal pocket (C, μg/ml) are considered to be simulated by Eq. 1 for LDDSs of the zero-order release type, and by Eq. 2 for those of the Fickian diffusional release type.

In zero-order release type LDDSs,

$$C = \frac{k}{E_T \cdot V}(1 - \exp(-E_T \cdot t)) \quad (1)$$

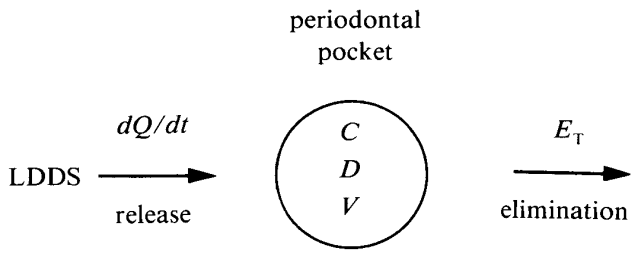

Fig. 9. Compartment Model

D, Amount of drug in periodontal pocket (μg); E_T, total drug elimination rate constant from the periodontal pocket (h^{-1}); V, volume of periodontal pocket (ml); t, Time after administration of LDDSs (h); dQ/dt, drug release rate constant of LDDS; C, drug concentration in the periodontal pocket fluid (μg/ml).

where k is the *in vivo* drug release rate constant (μg/h/LDDS), t is the time after administration (h), V is the volume of periodontal pocket fluid (ml), and E_T is the drug elimination rate constant in the periodontal pocket (h^{-1}).

In Fickian diffusional release type LDDSs,

$$C = \frac{K\sqrt{t}}{V}\left(\sum_{n=1}^{\infty} \frac{(E_T \cdot t)^n}{n!\,(2n+1)} + 1\right) \exp(-E_T \cdot t) \qquad (2)$$

where K is the *in vivo* drug release rate constant ($\mu g/h^{1/2}$/LDDS).

Using these pharmacokinetic equations, simulation of changes in the CLDM concentration in the periodontal pocket fluid after administration of LDDSs C, D, and E was attempted. In this analysis, the drug release rates of LDDSs C, D, and E were determined at 8.11 $\mu g/h^{1/2}$/LDDS, 3.05 μg/h/LDDS, and 0.757 μg/h/LDDS, respectively, on the basis of the results of the *in vivo* release study. The drug elimination rate for all LDDSs was set at 1.36 h^{-1}, which was the value obtained by administration of the aqueous solution of CLDM. The volume of the periodontal pocket fluid was regarded as a variable and was determined as an apparent volume.

The results of this simulation are shown in Fig. 10. The apparent volumes of periodontal pocket fluid after administration of LDDSs C, D, and E were 7, 4, and 3 μl, respectively. The simulation curve was in close agreement with the measured values of the concentrations for all three preparations with their different modes and rates of drug release, indicating the validity of this analysis. From these observations, we considered that the pharmacokinetics in the periodontal pocket were simulated by a one compartment model based on a pseudo first-order drug elimination process.

This study demonstrated an *in vivo–in vitro* correlation of the drug release from LDDSs and suggested that the drug release from LDDSs in periodontal pockets can be estimated from the results of *in vitro* dissolution studies. Moreover, the changes which occurred in drug concentrations in periodontal pockets after administration of LDDSs were shown to be dependent on the drug release pattern of the LDDS and to be simulated by a one compartment model based on a pseudo first-order elimination process. These fundamental observations, which allow estimation of the pharmacokinetics of drugs in the periodontal pocket after administration of LDDS from the results of *in vitro* elution studies, are considered to be useful information for the future development of LDDSs to be used in the treatment of periodontal disease.

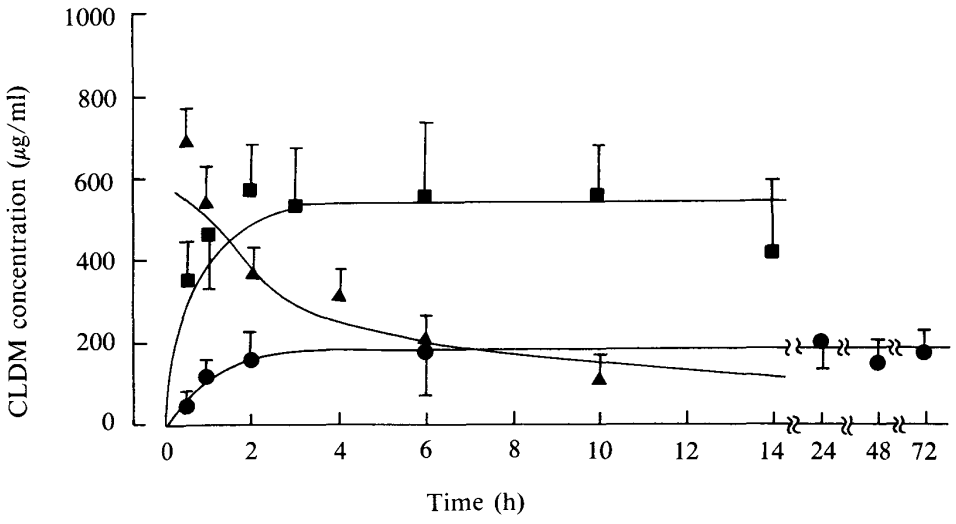

Fig. 10. Results of Simulation of Changes in the CLDM Concentration in the Periodontal Pocket Fluid after Administration of LDDSs C, D, and E

Each point represents the measured values with LDDS C (▲), D (■), and E (●), respectively. The lines are the simulation curves obtained with Eq.1 and Eq.2.

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