Drug Targeting Efficacy to Underlying Muscle Following Topical Application. I. Evaluation Based on a Physiological Pharmacokinetic Model

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A physiological pharmacokinetic model describing the absorption and disposition of topically applied drugs was proposed, and the effect of various pharmacokinetic and physiological parameters on the drug delivery into the targeted muscle was simulated. The proposed model consists of vehicle, and stratum corneum, viable epidermis and muscle below the application and reference sites, and plasma, each joined with transfer clearance and plasma flow. Indomethacin concentrations in tissues and plasma after topical application to rats could be explained by the model. Most indomethacin delivered into the underlying muscle was via direct penetration. The model simulation showed that the increase in plasma clearance and clearance between viable skin and muscle, and the decrease in application area and plasma flow rate into viable skin and muscle would promote the targeting efficacy of topically applied drugs to the underlying muscle.

Key words drug targeting; topical application; physiological pharmacokinetic model; indomethacin; nonsteroidal antiinflammatory drug; site-specific delivery

A number of rate-controlled transdermal therapeutic systems containing systemically active drugs have been developed and commercialized over the last few decades. Pharmaceutical knowledge on percutaneous absorption has accumulated throughout this period. The skin was originally recognized as a port of drug administration to achieve local therapeutic effects. Even now, there are many topical formulations of nonsteroidal inflammatory drugs (NSAIDs) to relieve pain and inflammation in various subjacent structures such as muscle and synovium. It is interesting to reevaluate the concept of using the transdermal route to target the underlying sites based on present pharmaceutical knowledge.

From the viewpoint of drug targeting, NSAIDs are most desirably delivered into the targeted sites via direct penetration from the topical formulations rather than via systemic absorption and recirculation. Some examples where topical administration of a drug resulted in a high drug concentration in the underlying muscle can be found in the literature. However, the contribution of direct penetration is not always high, e.g., biphenylacetic acid and diclofenac seem to distribute to the knee joint and synovial fluid below the application site mainly via the systemic blood supply. Recent publications have further pointed out that cutaneous blood flow and tissue binding play important roles in determining the disposition of a drug after topical application. What factors determine or influence the extent to which topically applied drugs can be targeted locally to the subcutaneous structures should be systematically investigated.

A great deal of effort has been devoted to the pharmacokinetic evaluation of site-specific or targeted drug delivery systems such as microspheres, drug-conjugates and liposomes. These studies afforded some quantifiable measure of drug targeting efficacy of these systems and their physicochemical, pharmacokinetic and physiological factors. Physiological and compartmental pharmacokinetic models have been proposed to describe the dermal pharmacokinetics. Unfortunately, the models are unsuitable to assess quantitatively the targeting efficacy of topically applied drugs, because of removal of the stratum corneum, the principal barrier to the percutaneous absorption of many drugs.

In the present study, we developed a physiological pharmacokinetic model for topically applied drugs. Indomethacin concentrations in various tissues and plasma were measured following topical application to rats, and the data were analyzed based on the model to test its validity. Equations for calculating the indexes for drug targeting to the underlying muscle were also derived from the model, and the effect of various pharmacokinetic and physiological parameters on the indexes were simulated.

MATERIALS AND METHODS

Materials Indomethacin and [14C]-indomethacin were purchased from Nacalai Tesque (Kyoto, Japan) and New England Nuclear (Boston, MA, U.S.A.). Liquid scintillation cocktail, Atomlight and tissue solubilizer, NCS II were obtained from Packard Instruments (Meriden, CT, U.S.A.) and Amersham International (Buckinghamshire, England). All other chemicals and solvents were at least reagent grade and were obtained commercially.

Animals Male Wistar rats (Japan SLC, Hamamatsu, Japan) aged 9 weeks were used throughout the studies and were allowed free access to water and laboratory chow prior to the experiments. For the intravenous infusion study, the rats were cannulated in the femoral vein the previous day.

Topical Application Study Indomethacin was topically administered to the restrained rats as a 40% (v/v) ethanolic aqueous solution containing 7.5 mg/ml indomethacin and 10 μCi/ml radiolabelled indomethacin. The abdominal hair was removed by electric clippers and a shaver, taking care not to injure the skin surface, and 10 or 90 μl of drug solution was applied onto a 1 or 9 cm2 area of the shaven ab-
domen. At predetermined times after dosing, a blood sample was taken from the jugular vein into a heparinized syringe and then the rat was sacrificed. Immediately, the applied area on the skin was wiped with ethanol to completely remove the drug solution, and the underlying skin and muscle were dissected. Similar tissues were also taken from the contralateral side as non-dosed reference tissues. The blood sample was centrifuged at 12000 rpm for 3 min to separate plasma. The tissue samples below the application and reference sites were rinsed with normal saline, blotted on filter paper and weighed. After the stratum corneum was stripped with adhesive tape twenty times, the skin (viable skin) samples were reweighed. The tissue and plasma samples were stored at −20°C until analyzed.

Indomethacin content in the tissue and plasma samples was determined from the radioactivity after tissue digestion. Each sample was incubated with 1 to 2 ml of tissue solubilizer at 50°C for 5 h. After cooling the digested tissue to room temperature, 10 ml of liquid scintillation cocktail was added. The sample was counted for 3 min on an Aloka LSC-5100 liquid scintillation counter (Aloka, Tokyo, Japan). The strips of adhesive tape used to remove the stratum corneum from skin were directly immersed in 10 ml of liquid scintillation cocktail and the radioactivity was considered to be the indomethacin content in stratum corneum.

**Intravenous Infusion Study** An intravenous infusion study was carried out to determine the unbound fraction of indomethacin in stratum corneum, viable skin and plasma. The rat was applied with a 40% (v/v) ethanolic aqueous solution containing only non-labelled indomethacin on a 1 cm² area of the abdomen as in the topical application study. Non-labelled and radiolabelled indomethacin were immediately administered as a bolus dose of 10 µg/kg (125 µCi/kg) and continuously infused at 1.0 µg/h/kg (12.5 µCi/h/kg) via a femoral vein cannula. At 4 h after indomethacin dosing, the tissue and plasma samples were taken and assayed in the same way as after topical application, and the tissue/plasma partition coefficients were calculated. A part of the plasma sample was ultrafiltrated in Ultrafree MC (Millipore, Bedford, MA) at 2000×g for 30 min and the ultrafiltrate was also counted. The unbound fraction of indomethacin in plasma was determined as the concentration ratio of ultrafiltrate to plasma, and that in stratum corneum and viable skin was calculated by dividing the plasma unbound fraction by the corresponding partition coefficient.

**Pharmacokinetic Analysis** Figure 1 shows the physiological pharmacokinetic model used in the present study. The model consists of topical formulation (vehicle), and stratum corneum, viable skin and muscle underlying the application and reference sites, and plasma, each joined with transfer clearance (CL = PS) and plasma volume flow (Q = Q/V) where P, S, Q’, and V are the permeation constant, application area, plasma flow per tissue volume and tissue volume. Common parameters were assumed for both application and reference sites except for the unbound fraction in the stratum corneum, which cannot be expected to show the same value between the two sites due to the different treatment of skin surface. Assumptions were also made that each tissue is well-stirred and that a pseudo equilibrium exists between a tissue and the perfusing plasma. The principle of mass balance can be expressed as follows:

\[ V_i \frac{dC_i}{dt} = \left( P_{v \rightarrow s} S(f_{u_c}, C_{or} - C_i) \right) \]

\[ V_{or} \frac{dC_{or}}{dt} = \left( P_{or \rightarrow s} S(f_{u_c}, C_{or} - f_{u_c}, C_{or}) + P_{or \rightarrow s} S(f_{u_c} - f_{u_c}, C_{or}) \right) \]

\[ V_{or} \frac{dC_{or}}{dt} = \left( P_{or \rightarrow s} S(f_{u_c}, C_{or} - f_{u_c}, C_{or}) \right) + Q_{or} V_{or} f_{p} C_{or} - f_{u_c} C_{or} + P_{or \rightarrow s} S(f_{u_c} - f_{u_c}, C_{or}) \]

\[ V_{or} \frac{dC_{or}}{dt} = \left( P_{or \rightarrow s} S(f_{u_c}, C_{or} - f_{u_c}, C_{or}) \right) + Q_{or} V_{or} f_{p} C_{or} - f_{u_c} C_{or} + P_{or \rightarrow s} S(f_{u_c} - f_{u_c}, C_{or}) \]

\[ V_{or} \frac{dC_{or}}{dt} = \left( P_{or \rightarrow s} S(f_{u_c}, C_{or} - f_{u_c}, C_{or}) \right) + Q_{or} V_{or} f_{p} C_{or} - f_{u_c} C_{or} + P_{or \rightarrow s} S(f_{u_c} - f_{u_c}, C_{or}) \]

\[ V_{or} \frac{dC_{or}}{dt} = \left( P_{or \rightarrow s} S(f_{u_c}, C_{or} - f_{u_c}, C_{or}) \right) + Q_{or} V_{or} f_{p} C_{or} - f_{u_c} C_{or} + P_{or \rightarrow s} S(f_{u_c} - f_{u_c}, C_{or}) \]

where the C and f terms denote the concentrations at time t and unbound fractions of drug, the first subscripts v, sc, vs, m and p refer to vehicle, stratum corneum, viable skin, muscle and plasma, and the second subscripts a and r correspond to application and reference sites.

Drug targeting to the underlying muscle following topical application was quantitatively assessed by two indexes using the area under the concentration–time curve (AUC). The first
is \(1 - \frac{AUC_{m,t}}{AUC_{m}}\) where \(AUC_{m,t}/AUC_{m}\) is the ratio of \(AUC\) in muscle below the reference site to that below the application site, and the second is the \(AUC\) ratio of underlying muscle to plasma (\(AUC_{m,t}/AUC_p\)). Based on the model described above, the indexes can be related with various pharmacokinetic and physiological parameters. Considering that the tissue volumes were proportional to the application area (\(V = Sh\)), the following equations are obtained:

\[
1 - \frac{AUC_{m,t}}{AUC_m} = \frac{SA(A+B)}{(SA+D)(A+B+C)+SAAC}
\]

(9)

\[
\frac{AUC_{m,t}}{AUC_p} = \frac{f_m(SA+D)(A+B+C)+SAAC}{f_mS(A+B)(A+B+C)}
\]

(10)

where

\[
A = P_{v,red}Q_nh_n + Q_nh_n + Q_nQ_nh_nh_n
\]

\[
B = P_{v,red}Q_nh_n
\]

\[
C = P_{r,red}P_n
\]

\[
D = P_{v,red}C_p
\]

Model adaptation and simulation were carried out on a personal computer (PC-9801DA, NEC, Tokyo) using FORTRAN programs. In the model adaptation, Eqs. 1—8 were numerically integrated and all concentration data for indomethacin were simultaneously fitted to the equations based on the least squares method using the algorithm of Berman et al.\(^\text{11}\) to obtain the permeation constants and muscle unbound fraction. The volume of vehicle and tissues, and unbound fraction of indomethacin in plasma and tissues except for muscle are fixed to the values obtained experimentally. The plasma flow rate into tissues was taken from the literature.\(^\text{15}\)

The steady state volume of distribution and total body clearance of indomethacin were calculated from the plasma concentration profile after intravenous bolus injection in rats\(^\text{19}\) and regarded as the plasma volume and product of plasma clearance by plasma unbound fraction in the model adaptation. Effects of several pharmacokinetic and physiological parameters on the targeting efficacy of topically applied drugs were simulated with Eqs. 9 and 10 using the parameter values for 1 cm² application of indomethacin in the model adaptation except for an independent variable. The parameter values used in the model adaptation and simulation, other than those shown as the experimental and analytical results, are listed in Table 1.

**RESULTS**

Figure 2 shows the concentration of indomethacin in various tissues and plasma after the application to a 1 cm² area of abdominal skin of rats. The concentration was highest in the underlying stratum corneum, followed by viable skin, muscle and plasma, and was below the detection limit in tissues below the reference site. Each of the obtained concentration profiles was biphasic. The increase of the first phase was slower for the deeper tissues and slower for plasma. In the second phase, the tissue concentrations decreased with almost the same slope. A nine-fold higher dosing was also attempted to obtain the data for tissues below the reference site, but it failed due to the detection limit. The indomethacin concentrations in tissues underlying the application site and plasma at 4 h after the higher dosing are shown in Fig. 2.

Tissue/plasma partition coefficients and unbound fractions of indomethacin determined in the intravenous infusion study are listed in Table 2. The partition coefficients were less than 1 for all tissues tested. The stratum corneum/plasma partition coefficient below the application site was significantly lower than that below the reference site and thus the unbound fraction was separately calculated for each site. The binding levels of indomethacin in stratum corneum, viable skin and plasma were very high.

The tissue and plasma concentration data following topical application of indomethacin in Fig. 2 were simultaneously analyzed based on the physiological pharmacokinetic model in Fig. 1 using the parameter values in Tables 1 and 2. The estimated muscle unbound fraction and permeation constants are listed in Tables 2 and 3, and the best-fit curves are shown in Fig. 2. The tissue and plasma concentration profiles were fully described by the proposed model. The estimated muscle unbound fraction was higher than that in other tissues and plasma. Higher permeation constants were obtained for deeper tissues.

Based on the results of model adaptation, two indexes of targeting efficacy to the underlying muscle after topical application of indomethacin to a 1 cm² area were calculated using Eqs. 9 and 10. The index values were nearly 1 for \(1 - \frac{AUC_{m,t}}{AUC_{m,t}}\) and 8.99 for \(AUC_{m,t}/AUC_p\), indicating high

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**Table 1. Parameter Values Used in Model Adaptation and Simulation**

<table>
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<tr>
<th>Parameter</th>
<th>Value (cm²)</th>
<th>Value (ml)</th>
<th>Value (g)</th>
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<th>Value (g)</th>
<th>Value (ml)</th>
<th>Value (ml/min)</th>
<th>Value (ml/min)</th>
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<tr>
<td>S</td>
<td>1.00</td>
<td>9.00</td>
<td>1.00 × 10⁻²</td>
<td>9.00 × 10⁻²</td>
<td>5.32 × 10⁻²</td>
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<td>Cₚ</td>
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<td>Qₚₚ</td>
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<td>Qₚₚ</td>
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<td>Qₚₚ</td>
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**Fig. 2. Indomethacin Concentration in Underlying Tissues and Plasma Following Topical Application to Rats**

Each point represents the mean ± S.E. of 3 or 4 rats. Closed circles, triangles, squares and diamonds represent the concentrations in underlying stratum corneum, viable skin, muscle and plasma after 1 cm² application, and the open symbols are those after 9 cm² application. Solid and dotted curves are nonlinear least-squares fit of data after 1 and 9 cm² application, respectively, to the physiological pharmacokinetic model shown in Fig. 1.
Table 2. Tissue/Plasma Partition Coefficient and Unbound Fraction of Indomethacin

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Partition coefficient</th>
<th>Unbound fraction</th>
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<tbody>
<tr>
<td></td>
<td>Reference site</td>
<td>Application site</td>
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<tr>
<td>Stratum corneum</td>
<td>$1.07 \times 10^{-1}\pm 0.34 \times 10^{-1}$</td>
<td>$3.98 \times 10^{-2}\pm 0.60 \times 10^{-2}$</td>
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<td>Viable skin</td>
<td>$2.53 \times 10^{-1}\pm 0.34 \times 10^{-1}$</td>
<td>$2.08 \times 10^{-2}\pm 0.20 \times 10^{-1}$</td>
</tr>
<tr>
<td>Muscle</td>
<td>$8.78 \times 10^{-2}\pm 1.46 \times 10^{-2}$</td>
<td>$1.13 \times 10^{-1}\pm 0.16 \times 10^{-1}$</td>
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<tr>
<td>Plasma</td>
<td>-</td>
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</table>

Each value represents the mean±S.D. of 3 experiments. * The value represents the mean±computer-calculated S.D. in model adaptation. ** Significantly different from reference site at p<0.05 (unpaired t-test).

The drug targeting index (DTI), which refers to the ratio of drug delivered to the desired target site and toxicity site when the targeting system is used, to that when the free drug is administered systemically, is the most accepted measure. [10] Two indexes, $1 = \frac{AUC_{m,a}}{AUC_{m,a}}$ and $\frac{AUC_{m,a}}{AUC_{p}}$, were selected here. Although the indexes give no information about the advantage over systemic administration, they clarify the extent to which topically applied drugs can be targeted locally to the underlying muscle. Furthermore, the former indicates the relative contribution of direct penetration from the topical formulation to drug delivery into the targeted muscle, and the latter was a classical index to compare the targeting to systemic drug exposure [11] and to calculate the DTI together with the corresponding value after systemic administration [10].

To check the validity of the developed model, indomethacin concentrations in various tissues and plasma were measured after topical application to rats. Indomethacin is one of the most popular NSAIDs and is frequently administered in various topical formulations such as solutions, ointments and cataplasm. The concentration of indomethacin decreased in deeper tissues below the application site, and these concentrations were remarkably higher than those in reference tissues and plasma (Fig. 2), indicating a high targeting efficacy. One order higher concentration in muscle of treated paw than in muscle of nontreated paw and plasma has been found at 2 h after the application of 1% indomethacin gel to rats. [12] In contrast, the indomethacin level in underlying muscle was less than that in plasma when the drug solution was applied to anesthetized rat dermis. [22] It has been reported that the rat epidermis is about 20 μm thick and is thinner than the human epidermis. [23] If the rat epidermis were removed by an electrodermatom set at a thickness of 80 μm as in the dermal application study, the dermis would be injured. The data obtained under such conditions may overestimate the contribution of blood supply to indomethacin delivery into the targeted muscle due to the direct transfer of drug from solution to blood.

The unbound fraction of indomethacin in stratum corneum, viable skin and plasma was determined from the concentration data at 4 h after intravenous infusion. In the preliminary infusion study, it was confirmed that a steady state was obtained at this time and the plasma concentration corresponded to that after topical application (data not shown). Indomethacin was extensively bound to tissue and plasma protein (Table 2). High plasma protein binding has also been reported for human and dog (90—98%), [19] although the tissue and plasma binding data are not available for rat. The stratum corneum/plasma partition coefficient and unbound fraction of indomethacin were significantly different between application and reference sites. This may reflect different sur-

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Each value represents the mean±computer-calculated S.D.

**DISCUSSION**

We developed a physiological pharmacokinetic model to quantitatively evaluate the advantages and major determinants of drug targeting into subjacent muscle by topical application (Fig. 1). Such a physiological model has been employed in the theoretical prediction of benefits derived from site-specific targeting, [10,12—14] and in the model analysis of experimental data following intraarterial and regional drug administrations. [20,21] Theoretical and experimental studies have provided useful information, which can be directly utilized to optimize the targeting systems, compared with studies based on the compartmental models. The strategy was then adapted to topical application study.

The model developed here is essentially equivalent to that by Singh and Roberts. [15] However, the epidermis was excluded from their model, and thus the pharmacokinetics was described only for the remaining tissues. The removal of epidermis from skin may make the detection of drug in the deeper or reference tissues easy and produce more precise analysis of dermal pharmacokinetics. Unfortunately, this is far from a clinical situation, however, where the epidermis functions as the main barrier to the percutaneous absorption of many drugs.

A number of indexes have been proposed as a means of measuring quantitative gain associated with targeting. [10—14] Targeting efficacy. The same parameter values were used in the model simulation for the effects of pharmacokinetic and physiological parameters on the indexes. As shown in Fig. 3, an increase in application area and plasma flow rates caused a decrease in the two indexes, whereas an increase in plasma clearance and permeation constant between viable skin and muscle enhanced the drug targeting. Muscle permeation constant showed a contrary effect on the two indexes: it affected $1 = \frac{AUC_{m,a}}{AUC_{m,a}}$ positively and $\frac{AUC_{m,a}}{AUC_{p}}$ negatively. Although $1 = \frac{AUC_{m,a}}{AUC_{m,a}}$ was definitely independent of unbound fractions, $\frac{AUC_{m,a}}{AUC_{p}}$ decreased and increased with rise in muscle and plasma unbound fractions, respectively.
Fig. 3. Effect of Pharmacokinetic and Physiological Parameters on Drug Targeting Efficacy

(a) Application area; (b) plasma clearance; (c) muscle permeation constant; (d) permeation constant between viable skin and muscle; (e) plasma flow rate into viable skin; (f) plasma flow rate into muscle; (g) unbound fraction in muscle; (h) unbound fraction in plasma. Solid and dotted curves represent the simulation results of $1 - \frac{AUC_m}{AUC_{ea}}$ and $AUC_m/AUC_{ea}$ with Eqs. 9 and 10 using parameter values in Tables 1—3. Each arrow represents the value of indomethacin.

face conditions of the stratum corneum, on which the vehicle exists only for the application site.

The concentration data following topical application of indomethacin to rats were analyzed based on the proposed physiological pharmacokinetic model (Fig. 2). Although the fitting values of plasma concentrations after 1 cm² application were slightly higher than the observed data, other results including plasma concentrations after 9 cm² application indicated that the model adequately described the disposition of indomethacin after topical application. The discrepancy may be due to low plasma concentrations close to the detection limit. The estimated muscle unbound fraction was higher than the value calculated by dividing the plasma unbound fraction by the muscle/plasma partition coefficient in Table 2, suggesting that the contribution of muscle clearance to the partition coefficient cannot be ignored. The higher clearance values for deeper tissues may reflect the higher drug diffusivities resulting from the looser structures. From these results, the proposed physiological pharmacokinetic model was judged to be valid as a model describing the absorption and disposition of a topically applied drug.

Next, the targeting efficacy of topically applied drugs to the subjacent muscle was simulated to know how the pharmacokinetic and physiological parameters affect the drug targeting. Equations 9 and 10, which were derived from the proposed model to quantitatively evaluate the drug targeting,
seem very complex. The parameters used in these equations are, however, limited to the application area, clearances (permeation constants) below viable skin, plasma flow rates, and unbound fraction in muscle and plasma. In other words, the targeting efficacy is independent of clearances from vehicle to viable skin and unbound fraction in stratum corneum and viable skin.

The simulation results shown in Figs. 3(a), (e) and (f) show that low application area and plasma flow rate into viable skin and muscle result in high drug targeting. The high targeting efficacy with small application area are intuitively understood, because the drug cannot be targeted to a specific site by application to the entire skin surface, the maximum application area. This can also be confirmed by comparing the data between 1 and 9 cm$^2$ applications (Fig. 2). The application area should be restricted to the skin surface just overlying the inflammatory site for drug targeting. The decrease in plasma flow rates lowers the removal of drug from tissues into plasma thus resulting in high drug targeting. Coadministration with a vasoconstrictor is an effective method to get high targeting efficacy of an objective drug, as reported previously.\(^4,3\) In contrast to the parameters mentioned above, an increase in plasma clearance and permeation constant between viable skin and muscle enhance the drug targeting (Figs. 3(b) and (d)). The effects may be understood by a term of drug accumulation in muscle relative to plasma. Drugs having high total body clearance are favorable for targeting with topical application; drugs having small molecular weight are also favorable because the permeation constant between viable skin and muscle intrinsically depends on the drug size. There is a possibility that the permeation constant is raised by the convective flow (solvent flow), which effect was found for some combinations of drug and vehicle.\(^7,27\) Effect of muscle permeation constant is different between two targeting indexes (Fig. 3(c)). An increase in the parameter directly decreases the drug concentration in muscle, and indirectly that in plasma to a lesser extent (decrease in $1 - \frac{AUC_{ms}/AUC_{m}}{AUC_{mp}/AUC_{p}}$) and thus the influx from plasma to muscle compared with direct penetration (increase in $AUC_{ms}/AUC_{p}$). The contribution of direct penetration to drug delivery into the targeted muscle is not essentially affected by unbound fraction in muscle or plasma, although $\frac{AUC_{ms}/AUC_{p}}{AUC_{mp}/AUC_{m}}$ changes dependent on the parameters (Figs. 3(g) and (h)). It seems difficult to control the targeting efficacy by muscle permeation constant and unbound fractions. It is unclear at the present time which factors are responsible for the high targeting efficacy of indomethacin. Further experiments using other drugs and formulations are required.

In conclusion, a physiological pharmacokinetic model for topically applied drugs was proposed, and the effect of various pharmacokinetic and physiological parameters on drug targeting to the subjacent muscle was simulated based on the model. The proposed model could well explain the concentration profiles in tissues and plasma after topical application of indomethacin. The model simulation suggests that a high drug targeting the underlying muscle can be obtained when a drug having high total body clearance and small molecular weight is applied to a small area of skin together with compounds having the capability to increase the clearance between viable skin and muscle and to constrict the blood vessels. These results would provide instructive information for the design of topical formulations with high drug targeting.

REFERENCES