Transfer of Diclofenac Sodium across Excised Guinea Pig Skin on High-Frequency Pulse Iontophoresis. I. Equivalent Circuit Model

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High frequency pulse iontophoresis of diclofenac sodium across excised guinea-pig skin was carried out in vitro. An equivalent circuit model was constructed to simulate the time courses of voltage drop across the donor solution and the skin. Parameter values obtained by the least-squares adaptation of the model to observed data were consistent with expectation and validated the proposed model.

Keywords iontophoresis; pulse iontophoresis; diclofenac sodium; voltage drop; equivalent circuit; skin; drug transport; guinea pig

Enhanced transdermal delivery of drugs by means of the technique of iontophoresis has been reported by many authors. This method involves the migration of charged substances into the skin or tissues under a gradient of electrical potential.

Taking the electrical nature of skin reported by Yamamoto and Yamamoto into account, Okabe et al. developed a pulse-generating device for iontophoresis and applied it to transdermal administration of metoprolol. We have determined the transport rates of diclofenac sodium across excised guinea-pig skin under electric pulse driving. Time courses of voltage drop across the donor solution, the excised skin and the acceptor solution were recorded, as well as the cumulative amount of the drug transported through the skin.

The aim of this part of the study was to construct an equivalent circuit model for in vitro high-frequency pulse iontophoresis and to evaluate the model parameters.

Theory

General Description of the Equivalent Circuit Model

The model circuit is shown in Fig. 1. Simplifying the circuit proposed by Yamamoto et al., the electrical features of skin are simulated by a parallel connection of a resistance $R_s$ and a capacitor $C_s$. Those of the donor or acceptor solution are represented by series connection of a resistance ($R_d$ or $R_a$) and a cell ($E_d$ or $E_a$).

Electric cells $E_d$ and $E_a$ represent, among others, charged species which are unable to follow to a quick alternation of the electrical field, due to their moment of inertia. The power source provides an applied voltage, $E_0$ (1 - 10 V) for $t_1$ (7.5 μs) followed by a depolarizing period $t_2$ (17.5 μs).

Mathematical representation of the model is provided by the following set of equations.

\[ e_d = R_d(i + j) + E_a \]  \hspace{1cm} (1)

\[ e_a = R_d(i + j) + E_a \]  \hspace{1cm} (2)

\[ e_s = R_s \cdot i \]  \hspace{1cm} (3)

\[ \frac{di}{dt} + \frac{E_0}{C_s} = e_d + e_a \]  \hspace{1cm} (4)

\[ E_0 = e_d + e_a + e_s \]  \hspace{1cm} (5)

\[ 0 = e_d + e_a + e_s \]  \hspace{1cm} (6)

where $e$'s are the electrical potential difference of the respective sites denoted by the subscript, and $i$ and $j$ are electrical current specified in Fig. 1.

Inserting equations Eq. 1 through Eq. 4 into Eq. 5, and rearranging, we obtain Eq. 7.

\[ (R_d + R_s) \cdot \frac{di}{dt} + (R_d + R_s + R_a)j = E_0 - E_a - E_s \]  \hspace{1cm} (7)

Solving Eq. 7 for $i$, and using Eq. 3, the expression for $e_s^+$, $e_s^-$ of the charging period, is obtained (Eq. 8).

\[ e_s^+ = \frac{R_s(E_0 - E_a - E_s)}{(R_d + R_a + R_s)} + A \exp \left( -t \cdot \frac{1}{C_s \cdot R_s + R_a + R_s} \right) \]  \hspace{1cm} (0 < t < t_1)  \hspace{1cm} (8)

where $A$ is an integration constant.

Likewise, $e_s^-$ of the depolarizing period, $e_s^-$, is obtained by using Eq. 6, as Eq. 9.

\[ e_s^- = \frac{-R_s(E_a + E_s)}{(R_a + R_s + R_s)} + B \exp \left( -t \cdot \frac{1}{C_s \cdot R_s + R_a + R_s} \right) \]  \hspace{1cm} (t_1 < t < t_1 + t_2)  \hspace{1cm} (9)

where $B$ is an integration constant.

Since the end of the charging period is the beginning of the depolarizing period and the end of the depolarizing period is the beginning of the charging period, Eqs. 10 and 11 are obtained.

\[ \frac{R_s(E_0 - E_a - E_s)}{(R_d + R_a + R_s)} + A \cdot e^{-\lambda t} = \frac{R_s(E_a + E_s)}{(R_d + R_a + R_s)} + B \]  \hspace{1cm} (10)

\[ \frac{R_s(E_0 - E_a - E_s)}{(R_d + R_a + R_s)} + A \cdot e^{-\lambda t} = \frac{-R_s(E_a + E_s)}{(R_a + R_s + R_s)} + B \]  \hspace{1cm} (11)

where

\[ \lambda = \frac{1}{C_s \cdot R_s + R_a + R_s} \]

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Solving these equations for $A$ and $B$, and substituting Eqs. 8 and 9, final expressions for $e_x^+$ and $e_x^-$ are obtained as Eq. 12 and Eq. 13, respectively.

$$e_x^+ = \frac{R_x}{(R_d + R_x + R_s)} \left[ (E_0 - E_x - E_d) - E_0 \left( \frac{1 - e^{-\lambda t}}{1 - e^{-\lambda t + \gamma t}} \right) e^{-\lambda t} \right]$$

(12)

$$e_x^- = \frac{R_s}{(R_d + R_x + R_s)} \left[ (E_0 - E_x - E_d) + E_0 \left( \frac{1 - e^{-\lambda t}}{1 - e^{-\lambda t + \gamma t}} \right) e^{-\lambda t} \right]$$

(13)

The following expressions for $e_x^+$, $e_x^-$, $e_x^+$ and $e_x^-$ were derived through similar manipulation.

$$e_x^+ = \frac{R_d}{R_d + R_x + R_s} \left[ (E_0 - E_x - E_d) + R_x \left( \frac{1 - e^{-\lambda t}}{1 - e^{-\lambda t + \gamma t}} \right) E_0 e^{-\lambda t} \right]$$

(14)

$$e_x^- = \frac{R_x}{R_d + R_x + R_s} \left[ (E_0 - E_x - E_d) - R_x \left( \frac{1 - e^{-\lambda t}}{1 - e^{-\lambda t + \gamma t}} \right) E_0 e^{-\lambda t} \right]$$

(15)

$$e_x^+ = \frac{R_s}{R_d + R_x + R_s} \left[ (E_0 - E_x - E_d) + R_s \left( \frac{1 - e^{-\lambda t}}{1 - e^{-\lambda t + \gamma t}} \right) E_0 e^{-\lambda t} \right]$$

(16)

$$e_x^- = \frac{R_s}{R_d + R_x + R_s} \left[ (E_0 - E_x - E_d) - R_s \left( \frac{1 - e^{-\lambda t}}{1 - e^{-\lambda t + \gamma t}} \right) E_0 e^{-\lambda t} \right]$$

(17)

**Results**

**Model Adaptation** The proposed model was fitted to the observed data. The observed time courses of voltage drop across the donor solution and the excised skin are shown in Figs. 3 and 4 with the model estimates. Coincidence of the values with the model estimates verifies the applicability of the proposed model. Estimated parameters are listed in Tables I and II.

**Effect of Applied Potential $E_o$** Table I shows model parameters obtained in drug transport experiments with different applied potentials, in which the drug concentration of the donor solution was kept constant (5.0 mg/ml, Fig. 3). It is clear from Table I that $E_x^+ + E_x^-$ are $E_o$-dependent but $R_d/R_x$, $R_d/R_s$, and $R_s/C_s$ are independent of $E_o$.

**Effect of Donor Concentration** Table II shows model parameters obtained in drug transport experiments with different drug concentrations of the donor solution, and with the applied potential kept constant (5 V, Fig. 4). Although $R_d/R_x$, $R_d/R_s$, and $E_x^+$ were independent of the donor concentration, $R_d/R_s$, $R_d/R_s$, and $E_x^-$ showed a trend of drug-concentration dependency.

![Fig. 2. Schematic Diagram of Diffusion Cell](image)

![Fig. 3. Time Courses of Voltage Drop across the Skin with Various Applied Voltages](image)
Fig. 4. Time Courses of Voltage Drop across the Skin and the Donor Solution with Various Donor Concentrations

Table I. Parameters Obtained by Model Adaptation (1)

<table>
<thead>
<tr>
<th>$E_0$ (V)</th>
<th>$E_a + E_0$ (V)</th>
<th>$R_d/R_s + R_a/R_s$</th>
<th>$R_s$, $C_s$ (µs)</th>
<th>Conc. (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.0</td>
<td>0.890</td>
<td>1.589</td>
<td>7.417</td>
<td>5.0</td>
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<tr>
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<td>1.418</td>
<td>1.134</td>
<td>9.730</td>
<td>5.0</td>
</tr>
<tr>
<td>7.0</td>
<td>1.780</td>
<td>1.205</td>
<td>8.956</td>
<td>5.0</td>
</tr>
<tr>
<td>10.0</td>
<td>1.989</td>
<td>1.084</td>
<td>9.506</td>
<td>5.0</td>
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Table II. Parameters Obtained by Model Adaptation (2)

<table>
<thead>
<tr>
<th>$E_0$ (V)</th>
<th>$E_a$ (V)</th>
<th>$E_n$ (V)</th>
<th>$R_d/R_s$</th>
<th>$R_a/R_s$</th>
<th>$R_s$, $C_s$ (µs)</th>
<th>Conc. (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.0</td>
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<td>3.918</td>
<td>0.7113</td>
<td>6.64</td>
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<td>0.2168</td>
<td>1.214</td>
<td>0.683</td>
<td>0.3549</td>
<td>10.39</td>
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<td>5.0</td>
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<td>1.335</td>
<td>0.769</td>
<td>0.4417</td>
<td>9.11</td>
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</tr>
<tr>
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<td>1.321</td>
<td>0.565</td>
<td>0.2926</td>
<td>8.66</td>
<td>10.0</td>
</tr>
</tbody>
</table>

should depend both on applied potential and on drug concentration. However, compared with the donor solution, the drug concentration is negligibly small in the acceptor solution, and this explains the ambiguity of observed dependency of $E_a$'s on drug concentration.

Consequently, the proposed equivalent-circuit model is considered to be suitable for evaluations of experimental conditions and environments.

References