Use of Hydrogenated Soya Phospholipids as a Diluent: Preparation of Sustained-Release Tablets of Theophylline and Sodium Diclofenac

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Sustained-release tablets (SR-tablet), prepared with hydrogenated soya phospholipids, gave slow release of theophylline and sodium diclofenac into a solvent at pH 6.8, in an in vitro study. The release profile of theophylline from the SR-tablet remained unchanged at pH values between 2.0 and 6.8. However, the release of diclofenac from the SR-tablet into a solvent at pH 2.0 was very slight, due to the low solubility at pH 2.0. The release of both drugs seems to occur predominantly by a leaching mechanism, as proposed by Higuchi. The oral administration of SR-tablets to dogs avoided a transient peak of drug concentration in the plasma and maintained plasma drug concentrations at higher levels for a longer period, in comparison with the oral administration of theophylline in suspension form or a commercial tablet of sodium diclofenac.

Keywords—tablet; theophylline; sodium diclofenac; hydrogenated soya phospholipid; in vitro release study; acidic pH; neutral pH; dog; oral administration; plasma concentration

Although the intensity of pharmacological effect is related to the drug concentration at the site of action, which in turn is often also related to the drug plasma concentration, it is desirable to maintain the drug concentration in the body continuously between the minimal effective and the maximal safe levels. Drugs, such as theophylline, sodium diclofenac and indomethacin, may require the use of a sustained-release formulation to avoid a transient peak of drug concentration in plasma and to maintain an effective plasma drug concentration for a long period.

As sustained-release formulations of oral administration, osmotic pump systems of indomethacin, theophylline and antipyrine are available,2-4 but are rather complicated to produce, so that a simple sustained-release tablet (SR-tablet) would be preferable from a commercial point of view.

Recently, we have reported5 that addition of hydrogenated soya phospholipids (H-phospholipids) to a triglyceride base controlled the release of sodium diclofenac from a suppository. We have also reported that sustained-release granules of sodium diclofenac, which were prepared with phospholipids.6 In the granules, the release rate of sodium diclofenac was regulated by the addition of cholesterol to the granules. Since phospholipids are hydrated, in spite of their poor solubility,7 the mechanism might be dependent on the permeation rate of solvent through the suppository matrix containing phospholipids.

In the present study, we investigated the release of theophylline and sodium diclofenac from SR-tablets as a single-unit dosage form, prepared with phospholipids alone as a diluent. Further, we examined plasma drug concentrations after oral administration of the tablets to dogs.

Experimental

Materials—H-Phospholipids, supplied by Nikko Chemicals Co., Ltd. (Tokyo, Japan), contains more than
98% phospholipids (about 70% phosphatidylcholine), and had an iodine value of about 6%. Sodium diclofenac and theophylline were supplied by Ciba-Geigy Japan (Takarazuka, Japan) and Shiratori Pharmaceutical Industry (Chiba, Japan), respectively. The particle size of these substances was less than 75 \( \mu m \). Commercial tablets of sodium diclofenac were obtained from a public hospital. Other reagents used were of analytical grade.

**Preparation of SR-Tablet** — Two grams of theophylline or sodium diclofenac was mixed well with 18 g of H-phospholipids. Ethanol was then added to the mixture to obtain a paste by thorough mixing after gradual addition of 5 ml portions of ethanol. After drying of the paste under reduced pressure, the solid mass was pulverized with a mortar and a pestle. Granules with a size of 150 to 350 \( \mu m \) were compressed at 250.7 ± 3.2 mg (\( n = 60 \)) and the content of sodium diclofenac was 26.2 ± 1.4 mg (\( n = 20 \)). Tablets of theophylline, with 8 mm diameter and 3 mm thickness, weighed 247.1 ± 4.6 mg (\( n = 60 \)) and the content of theophylline was 24.9 ± 1.1 mg (\( n = 20 \)).

**An in Vitro Release Study** — A tablet wrapped with gauze was immersed in a beaker containing 200 ml of solvent at 37°C. The beaker was shaken at 40 cycle/min or at 100 cycle/min and 100 \( \mu l \) aliquots were collected at designated time intervals, passed through a Millipore filter (pore size: 0.45 \( \mu m \)), and assayed to determine the release of theophylline or sodium diclofenac. As a solvent, 0.01 \( \text{N HCl} \) saline solution (pH 2.0) and 0.1 \( \text{M} \) sodium phosphate buffer (pH 6.8) was used. For comparison, commercial tablets of sodium diclofenac and theophylline powder were examined. The powder was immersed directly in solvent. The solubility of each drug in the solvent at pH 2.0 and at pH 6.8 was determined after incubation of 1 g of drug in 5 ml of solvent at 37°C for 48 h (Table I).

When 1 \( \mu m \) drug solution was incubated at 37°C for 48 h, recovery of each drug was more than 98% for theophylline, 99.2 ± 1.7% (\( n = 4 \)) at pH 2.0 and 99.7 ± 1.9 (\( n = 4 \)) at pH 6.8; for sodium diclofenac, 98.1 ± 1.1% (\( n = 4 \)) at pH 2.0 and 99.1 ± 1.2% at pH 6.8; thus, degradation of each drug in the solvent during the experimental period was ignored.

**Data Analyses of Drug Release in the in Vitro Study** — Release of drugs from an SR-tablet can be described in terms of the fraction of drug released (\( F \)) by Eq. 1.

\[
F = \frac{\text{initial amount of drug in SR-tablet}}{\text{amount of drug released from SR-tablet at time } t}
\]  

(1)

When a linear relationship is observed between \( F \) and the square root of time (as shown in Figs. 1 and 2), the release of drugs from SR-tablet seems to occur by the leaching mechanism proposed by Higuchi,\(^8\) according to Eq. 2.

\[
Q = \left[ D(2A - \varepsilon Cs)Cs \cdot t / \tau \right]^{1/2}
\]  

(2)

Where \( Q = \) the amount of drug released after time \( t \) per unit exposed area; \( D = \) the diffusivity of the drug in the permeating fluid; \( \tau = \) the tortuosity factor of the capillary system; \( A = \) the total amount of drug present in the matrix per unit volume; \( Cs = \) the solubility of drug in the permeating fluid; and \( \varepsilon = \) the porosity of the matrix.

Thus, the amount of drug released from an SR-tablet after time \( t \) can be represented by Eq. 3.

\[
Q = Q' \cdot Sq
\]  

(3)

Where \( Sq = \) the total exposed area of an SR-tablet. When the total volume of an SR-tablet is presented by \( V_o \), \( F \) in Eq. 1 is given by Eq. 4.

\[
F = \frac{Q'}{(AV_o)} = \frac{(Q' \cdot Sq)}{(AV_o)}
\]  

(4)

Thus, Eq. 5 is obtained from Eqs. 2 and 4.

\[
F = \frac{(Q' \cdot Sq)}{(AV_o)} \left[ D(2A - \varepsilon Cs)Cs \cdot t / \tau \right]^{1/2} = k t^{1/2}
\]  

(5)

In Eq. 5, \( k \) represents the slope of the straight line obtained when the \( F \) values are plotted against the square root of time, and it may represent an apparent overall control factor for the release of drug from an SR-tablet; i.e., a small value of \( k \) implies slow release of drug from the tablet.

**TABLE I. Solubility of Theophylline and Sodium Diclofenac in Solvent at pH 6.8 and at pH 2.0, at 37°C**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Solubility ( a ) (mm)</th>
<th>pH 6.8</th>
<th>pH 2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Theophylline</td>
<td>58.4 ± 2.2</td>
<td>62.6 ± 3.4</td>
<td></td>
</tr>
<tr>
<td>Sodium diclofenac</td>
<td>18.2 ± 1.2</td>
<td>0.011 ± 0.002</td>
<td></td>
</tr>
</tbody>
</table>

\( a \) Each value represents the mean ± S.D. (\( n = 4 \)).
An in Vivo Absorption Study in Dogs—Three male beagle dogs, weighing 9.0 to 9.8 kg, were fasted (but water was given freely) for 16 h prior to experiments and used in a cross-over study. Dogs were walked for 30 min prior to the oral administration of drug and were used in a conscious state. After oral administration of tablet followed by administration of 20 ml of water via a gastric catheter, blood was collected from the femoral vein at designated time intervals for 30 h. Theophylline powder was administered in suspension form with 2 ml of distilled water through a gastric catheter. During the experimentation, water was given freely. After centrifugation of the blood, plasma was collected to assay drug concentrations. The area under the curve of drug concentrations in plasma for 30 h was determined by trapezoidal integration after the oral administration.

Assays—Assays of diclofenac\(^9\) and theophylline\(^{10}\) were performed by high-performance liquid chromatography as described previously. The detection limits were 0.04 \(\mu\)g/ml for diclofenac and 0.10 \(\mu\)g/ml for theophylline.

Statistical Analyses—Statistical analyses were performed by using Student’s \(t\)-test.

Results and Discussion

An in Vitro Release Study

Complete dissolution of theophylline in the powder form was observed both at pH 2.0 and at pH 6.8 within 0.5 h (Fig. 1).

In terms of the release of theophylline from an SR-tablet, which occurred slowly, there were only slight differences between the patterns at pH 2.0 and 6.8, and those at 40 and 100 cycle/min, up to 8 h (Fig. 1). A linear relationship was also observed between the fraction of theophylline released (\(F\) in Eqs. 1 and 5) and the square root of time (immersion time) up to 8 h, in both solvent (Fig. 1); the \(k\) value (slope of the line) are given in Table II. These results may indicate that release of theophylline from an SR-tablet occurs by the leaching mechanism, proposed by Higuchi.\(^8\) The fact that the \(k\) value for theophylline release is independent of the pH of the solvent (Table II) may be related to the fact that the solubility of theophylline is similar at pH 2.0 and 6.8 (Table I).

Further, no significant disintegration of SR-tablet was observed, but swelling occurred at pH 2.0 during the experimental period (naked eye observation). At pH 6.8, swelling was also observed during the experimental period at 40 cycle/min, but a gradual disintegration of the SR-tablet occurred at 100 cycle/min after 8 h. Thus, the disintegration of the SR-tablet may result in a surge of theophylline release after 8 h at pH 6.8 and at 100 cycle/min, in comparison

![Fig. 1.](image-url)
with the release expected on the basis of a leaching mechanism (shown in a dashed line in Fig. 1).

When an SR-tablet of theophylline was immersed in a solvent at pH 6.8 after 1 h in a solvent at pH 2.0, the $k$ value was not changed in comparison with that in pH 6.8 alone (Fig. 1 and Table II).

Release of about 75% of diclofenac from the commercial tablet along with disintegration was observed within 2 h in a solvent at pH 6.8, but only slight release of diclofenac was observed in a solvent at pH 2.0 (Fig. 2). The apparently poor release of diclofenac at pH 2.0 is due to its poor solubility at pH 2.0 (Table I).

Slight release of diclofenac an SR-tablet at pH 2.0 was also observed (Fig. 2A). For the release of diclofenac at pH 6.8, a linear relationship (the value of slope, $k$, are summarized in

![Fig. 2. Fraction of Diclofenac Released versus Square Root of Shaking Time](image)

The release profile of diclofenac from a conventional tablet (triangles) and from an SR-tablet (circles) at pH 2.0 (A), at pH 6.8 (B), and at pH 6.8 after immersion for 1 h at pH 2.0. Open symbols and closed symbols represent the results when tablets were shaken at 40 cycle/min and at 100 cycle/min, respectively. Each value represents the mean ± S.D. ($n=4$).

|$a$) $p<0.05$ versus at 40 cycle/min.

<table>
<thead>
<tr>
<th>Drug</th>
<th>pH 2.0</th>
<th>pH 6.8</th>
<th>pH 6.8$^{b)}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Theophylline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>at 40 cycle/min</td>
<td>0.312 ± 0.029</td>
<td>0.309 ± 0.031</td>
<td>0.304 ± 0.027</td>
</tr>
<tr>
<td>($r = 0.093 ± 0.002,$</td>
<td>($r = 0.990 ± 0.005,$</td>
<td>($r = 0.986 ± 0.002,$</td>
<td></td>
</tr>
<tr>
<td>$p &lt; 0.05$)</td>
<td>$p &lt; 0.05$</td>
<td>$p &lt; 0.05$</td>
<td></td>
</tr>
<tr>
<td>at 100 cycle/min</td>
<td>0.341 ± 0.074</td>
<td>0.336 ± 0.057</td>
<td>0.351 ± 0.042</td>
</tr>
<tr>
<td>($r = 0.982 ± 0.011,$</td>
<td>($r = 0.990 ± 0.006,$</td>
<td>($r = 0.971 ± 0.012,$</td>
<td></td>
</tr>
<tr>
<td>$p &lt; 0.1$)</td>
<td>$p &lt; 0.05$</td>
<td>$p &lt; 0.05$</td>
<td></td>
</tr>
<tr>
<td>Sodium diclofenac</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>at 40 cycle/min</td>
<td>0.148 ± 0.012</td>
<td>0.162 ± 0.036</td>
<td></td>
</tr>
<tr>
<td>($r = 0.994 ± 0.004,$</td>
<td>($r = 0.990 ± 0.006,$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$p &lt; 0.05$)</td>
<td>$p &lt; 0.05$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>at 100 cycle/min</td>
<td>0.174 ± 0.042</td>
<td>0.182 ± 0.039</td>
<td></td>
</tr>
<tr>
<td>($r = 0.982 ± 0.009,$</td>
<td>($r = 0.977 ± 0.014,$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$p &lt; 0.1$)</td>
<td>$p &lt; 0.1$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$a$) Value obtained from the slope of the solid straight line in Figs. 1 and 2.  
$b$) The $k$ value was obtained after changing the solvent to pH 6.8, following immersion of the tablet in the solvent to pH 2.0 for 1 h. Each value represents the mean ± S.D. ($n=4$).
Table II) was observed between the fraction of diclofenac released ($F$ in Eqs. 1 and 5) and the square root of immersion time up to 24 h, when the tablet was shaken at 40 cycle/min (Fig. 2B). It is considered that the release of diclofenac from an SR-tablet may also occur by the leaching mechanism. The release of diclofenac under the above conditions was about 60% at 24 h, though complete release of theophylline was observed (Fig. 2). This slow release of diclofenac is due to the low solubility of diclofenac, since the release of the drug from the formulation in the leaching system according the Eq.5 is dependent on the drug solubility. When the tablet was shaken at pH 6.8 and at 100 cycle/min, a linear relationship was obtained between the fraction of diclofenac released and the square root of time up to 8 h. However, after 8 h, the release of diclofenac from the tablet under these conditions was greater than that expected from a leaching system, as observed with theophylline. This unexpectedly large release of diclofenac also seemed to be due to the disintegration of SR-tablets by vigorous shaking.

When an SR-tablet was immersed in the solvent at pH 6.8 after incubation for 1 h in the solvent at pH 2.0, the release profile of diclofenac similar to that in the solvent of pH 6.8 alone after a lag time (Fig. 2C). The observation of a lag time on changing the solvent from pH 2.0 to 6.8 may be due to a period of displacement of the initial solvent of pH 2.0 by the solvent of pH 6.8

An in Vivo Absorption Study in Dogs

After an oral administration of theophylline in suspension form at a dose of 25 mg to a dog, a transient high theophylline concentration in the plasma was observed with a maximum level of more than 30 μg/ml at 4 h (Fig. 3). However, administration of theophylline in an SR-tablet avoided the transient high theophylline concentration, and a maximum plasma theophylline concentration of about 10 μg/ml was observed at about 6 h. Further, the concentration of theophylline at 30 h was about 3 μg/ml in the case of the SR-tablet but less
than 0.5 μg/ml with the suspension. These observations also indicate that the administration of an SR-tablet maintained the plasma theophylline concentration for a long period. The relative bioavailability (area under the blood concentration curve (AUC) up to 30 h) was greater in the suspension than in the test tablet (Table III). The low bioavailability of theophylline after the administration of an SR-tablet may be due to incomplete release of theophylline in vivo, in spite of the observation that almost complete release of theophylline from an SR-tablet occurred within 24 h in the in vitro study (Fig. 1).

Similar results were obtained for diclofenac (Fig. 4). Oral administration of a commercial tablet resulted in a high transient diclofenac concentration in plasma, followed by rapid elimination. However, the administration of the SR-tablet did not give such a transient peak and the plasma diclofenac concentration was maintained for a long period. After 30 h, the plasma diclofenac concentration was about 0.35 μg/ml in the case of the SR-tablet, but was less than 0.1 μg/ml with the commercial tablet. The relative bioavailability of diclofenac (AUC up to 30 h) was greater from the commercial tablet than from the SR-tablet (Table III).

In spite of the rapid release of theophylline from an SR-tablet in comparison with the release of sodium diclofenac in the in vitro study, the T_max for the sodium diclofenac was faster than that for theophylline (Figs. 3 and 4, and Table III). Although we did not investigate the pharmacokinetic behavior of the drugs, this discrepancy may be due to differences of the absorption and elimination rates of the two drugs.

In the present study, it can be concluded that the SR-tablets of theophylline and sodium diclofenac, prepared with H-phospholipids, avoided a transient peak of drug concentration in plasma and maintained high plasma drug concentrations in dogs after oral administration, owing to the slow release of the drug from the SR-tablet.

### References and Notes

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### Table III. AUC<sub>a)</sub> of Plasma Drug Concentration up to 30 h, C<sub>max</sub> and T<sub>max</sub> after Oral Administration

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation</th>
<th>AUC (μg·h/ml)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (μg/ml)</th>
<th>T&lt;sub&gt;max&lt;/sub&gt; (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Theophylline</td>
<td>Suspension</td>
<td>430 ± 102</td>
<td>39.4 ± 8.6</td>
<td>2.3 ± 0.58</td>
</tr>
<tr>
<td></td>
<td>SR-tablet</td>
<td>222 ± 62&lt;sup&gt;b)&lt;/sup&gt;</td>
<td>10.9 ± 1.1&lt;sup&gt;b)&lt;/sup&gt;</td>
<td>8.0 ± 2.0&lt;sup&gt;b)&lt;/sup&gt;</td>
</tr>
<tr>
<td>Sodium diclofenac</td>
<td>Commercial tablet</td>
<td>51.9 ± 12.2</td>
<td>11.7 ± 4.1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>SR-tablet</td>
<td>25.4 ± 7.9&lt;sup&gt;b)&lt;/sup&gt;</td>
<td>2.8 ± 0.9&lt;sup&gt;b)&lt;/sup&gt;</td>
<td>2.9 ± 1.1&lt;sup&gt;b)&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a)</sup> AUC was obtained from the plasma drug concentration in Figs. 3 and 4. Each value represents the mean ± S.D. (n = 3).  
<sup>b)</sup> p < 0.05 versus suspension for theophylline and versus commercial tablet for sodium diclofenac.