Preparation of Controlled-Release Granules of Sodium Diclofenac

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The release of sodium diclofenac from granules prepared with hydrogenated soya lecithin (lecithin) alone occurred slightly more slowly than that from a commercial tablet. The addition of cholesterol to the granules caused a significantly slower release as the cholesterol content in the granules was increased. The release of sodium diclofenac from granules containing cholesterol seems to occur by the leaching mechanism proposed by Higuchi.

Keywords—controlled release; granule; sodium diclofenac; lecithin; cholesterol; in vitro study

Although the intensity of a pharmacological effect is related to the drug concentration at the site of action, which is in turn generally related to the plasma drug concentration, an ideal situation is obtained when the concentration in the body is continuously maintained between the minimal effective and the maximal safe values. However, when the drug has a relatively short elimination half life, it is impossible to maintain the concentration within the therapeutic range without frequent dosing or the use of sustained-release formulations.

Among non-steroidal anti-inflammatory drugs, oral administration of sodium diclofenac in a commercial tablet caused a transient rapid increase of plasma diclofenac concentration, followed by relatively rapid elimination from the plasma in humans.1) Recently we have reported2,3) that addition of lecithin in a triglyceride suppository base gave sustained release of sodium diclofenac from the suppository, and that the administration of the suppository avoided a transient high plasma diclofenac concentration and gave a well maintained plasma diclofenac concentration in dogs and humans. Since lecithin is known to be hydrated4) in spite of its poor solubility in water, it was suggested that lecithin in the suppository base regulated the infiltration of rectal fluid.5) Thus, it is expected that a vehicle matrix prepared with lecithin can control the release of drugs contained in the matrix.

In the present study, we prepared granules of sodium diclofenac with hydrogenated soya lecithin, and investigated the release of sodium diclofenac from them.

Experimental

Materials—Sodium diclofenac was supplied by Ciba Geigy Japan (Takarazuka, Japan). Hydrogenated soya lecithin (lecithin), more than 95%, hydrogenated, was supplied by Nikko Chemical (Tokyo, Japan). Cholesterol was obtained from Sigma Inc. (St. Louis, U.S.A.). Other reagents used were of analytical grade.

Preparation of Granules—Granules of sodium diclofenac were prepared as follows; the constituents are listed in Table I. Sodium diclofenac, lecithin and cholesterol (total amount, 1 g) were dissolved in 20 ml of chloroform–ethanol (50%: 50%), with warming if necessary. After complete dissolution, the solvents were evaporated off at 50 °C under reduced pressure for 5 h, followed by drying of the solid at room temperature for 24 h under reduced pressure. The solid was pulverized with a mortar and pestle, and then granules in the size range of 74 to 149 μm were collected.
Granules prepared are listed in Table I. Release Study—Release of sodium dichlofenac was examined by the rotating basket method in JP X at 100 rpm or at 150 rpm. One gram of granules was employed for each study and 500 ml of JP X 2nd fluid (pH 6.8; 0.2 M KH₂PO₄—NaOH buffer) was used as the medium at 37°C. The basket was covered with cotton gauze. After starting the experiment, 1 ml aliquots were collected through a Millipore filter (pore size of 0.45 μm) at designated time intervals for 24 h. The concentration of sodium diclofenac in each sample solution was measured by spectrophotometric method at the wavelength of 275 nm, or by high-performance liquid chromatography. Statistical Analysis—Statistical analyses were performed by using Student’s t-test.

Results and Discussion

Granules of code-1 to code-4 with the same content of sodium diclofenac (50 mg/g) were examined, together with a commercial tablet containing 25 mg of sodium diclofenac. As shown in Fig. 1, release of diclofenac from granules of code-1 was only slightly slower than that from the commercial tablet. A greater content of cholesterol in the granules caused a slower release of diclofenac. Thus, it is considered that cholesterol delays the degradation of granules, or decreases the volume of medium infiltration into the matrix or the rate of its infiltration.

Release of a drug from granules often occurs as a result of degradation of the granules, as suggested by Hixson and Crowell. In this case, drug release may be represented by Eq. 1 (the Hixson—Crowell equation):

\[
1 - (W/W_0)^{1/3} = k_1 t
\]

where \( W_0 \) represents the total amount of drug in the granules, \( W_t \) represents the remaining amount of drug in the granules after time \( t \) (remaining amount was calculated from the measurement of the released amount in the present study), and \( k_1 \) is a constant for each type of granules. As shown in Fig. 2A, data analyzed according to Eq. 1 did not give a good straight line, especially at the early stage, except for code-1. Thus, release of diclofenac seems to occur through the mechanism of granule degradation only from granules of code-1. Since degradation of granules of code-2, code-3 and code-4 was not apparent to the naked eye at least up to 8 h, another mechanism may be involved in the release of diclofenac from these granules. Further, it was observed that the initial release of diclofenac was greater than expected. This initial burst of release of diclofenac may reflect rapid dissolution of diclofenac which was adsorbed on the granule surface (see below).

A possible mechanism of the drug release from granules of code-2 to -4 may be leaching, as proposed by Higuchi. This is described by Eq. 2:

### Table I. Codes and Constituents of Granules of Sodium Diclofenac

<table>
<thead>
<tr>
<th>Code</th>
<th>Sodium diclofenac (mg)</th>
<th>Lecithin (mg)</th>
<th>Cholesterol (mg)</th>
<th>Recovery of sodium diclofenac (mg/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50</td>
<td>950</td>
<td>0</td>
<td>49.5 ± 3.1</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>855</td>
<td>95</td>
<td>50.5 ± 3.4</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>760</td>
<td>190</td>
<td>49.3 ± 5.2</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
<td>475</td>
<td>475</td>
<td>48.6 ± 4.8</td>
</tr>
<tr>
<td>5</td>
<td>200</td>
<td>640</td>
<td>160</td>
<td>47.5 ± 3.5</td>
</tr>
<tr>
<td>6</td>
<td>100</td>
<td>720</td>
<td>180</td>
<td>52.2 ± 4.4</td>
</tr>
<tr>
<td>7</td>
<td>25</td>
<td>780</td>
<td>195</td>
<td>49.6 ± 5.0</td>
</tr>
</tbody>
</table>

*Recovery of sodium diclofenac was measured by the dissolution of granules in 1 N NaOH solution. Each value represents the mean ± S.D. (n=3).*
where $Q$ represents the amount of drug released from unit surface area, $D$ represents the diffusivity of the drug in the infiltration solvent, $\varepsilon$ represents the porosity of granules, $\tau$ represents the tortuosity factor of granules, $A$ represents the total amount of drug in unit volume and $C_s$ is the solubility of the drug in the infiltration medium ($C_s$ of sodium diclofenac in the solvent was 18 mm at 37°C). The fraction, $F$, of diclofenac released from test granules can be represented by Eq. 3:

$$\frac{Q'}{Q} = \frac{Q'}{Q} = S\left[D\varepsilon(2A-\varepsilon C_s)/\tau\right]^{1/2}/AV_0$$

Fig. 1. Release of Sodium Diclofenac from Various Granules as a Function of Time

Release of sodium diclofenac is represented as the fraction of sodium diclofenac released, $F$. Granules used are symbolized as follows: ○, code-1; ●, code-2; △, code-3; and ▲, code-4. The symbol ■ represents the release of sodium diclofenac from a commercial tablet containing 25 mg of sodium diclofenac. Rotation speed was 100 rpm. Data in this figure were obtained with one example of each formulation.

As shown in Fig. 2B, a plot of $F$ against the square root of time (h) gave a good straight line for each of the granules. These results suggest that release of diclofenac from granules occurs by leaching. The slope, $k_2$, of the line is represented by Eq. 4

$$k_2 = S\left[D\varepsilon(2A-\varepsilon C_s)/\tau\right]^{1/2}/AV_0$$

Since the solubility of sodium diclofenac is low, it may be estimated that $2A$ is greater
than $\varepsilon C_s$. Equation 5 was obtained from Eq. 4

$$k_2 = \frac{[S(2ADC_s)^{1/2}/AV_0]}{\varepsilon/t}$$

(5)

In Eq. 5, the change of $k_2$ is related to the value of $\varepsilon/t$. Thus, the decrease of $k_2$ value with the increase of cholesterol content in the granules may indicate that cholesterol decreases the value of $\varepsilon/t$ in Eq. 5. When the $k_2$ values for granules of code-2 to -4 were plotted (closed circles in Fig. 3) against the square root of the content ratio of cholesterol, a good straight line was obtained. This result suggests that cholesterol in granules decreases the porosity of the granules and/or increases the tortuosity of the granules. Thus, release of sodium diclofenac from granules prepared with lecithin can be controlled easily by adjusting the cholesterol content.

Since sodium diclofenac dissolves in the infiltration medium, decrease of the content of sodium diclofenac may decrease the value of $\varepsilon/t$ in Eq. 5. To investigate the effect of content of sodium diclofenac, code-3, code-5, code-6 and code-7 granules were used. As shown in Table II, a smaller content of sodium diclofenac in granules resulted in a smaller $k_2$ value. However, since increase of the content of sodium diclofenac in the granules prepared in this study was accompanied with a decrease of cholesterol content, the $k_2$ value was also plotted against the square root of the content ratio of cholesterol. In this case, the value of slope obtained from

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**TABLE II. Comparison of $k_2$ Values as a Parameter of Release from Various Granules, and the Effect of Rotation Speed**

<table>
<thead>
<tr>
<th>Code</th>
<th>$k_2$ at 100 rpm</th>
<th>$r^{b)}$</th>
<th>$k_2$ at 150 rpm</th>
<th>$r^{b)}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1$^{a)}$</td>
<td>$24.2 \pm 4.2$</td>
<td>$&gt; 0.994$</td>
<td>$34.7 \pm 3.9^{a)}$</td>
<td>$&gt; 0.989$</td>
</tr>
<tr>
<td>2</td>
<td>$13.9 \pm 0.8$</td>
<td>$&gt; 0.994$</td>
<td>$14.6 \pm 2.1$</td>
<td>$&gt; 0.991$</td>
</tr>
<tr>
<td>3</td>
<td>$10.4 \pm 0.5$</td>
<td>$&gt; 0.990$</td>
<td>$11.2 \pm 1.7$</td>
<td>$&gt; 0.992$</td>
</tr>
<tr>
<td>4</td>
<td>$5.1 \pm 0.8$</td>
<td>$&gt; 0.991$</td>
<td>$5.7 \pm 0.4$</td>
<td>$&gt; 0.994$</td>
</tr>
<tr>
<td>5</td>
<td>$12.5 \pm 1.2$</td>
<td>$&gt; 0.997$</td>
<td>Not determined</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>$10.8 \pm 1.1$</td>
<td>$&gt; 0.991$</td>
<td>Not determined</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>$8.1 \pm 0.8$</td>
<td>$&gt; 0.993$</td>
<td>Not determined</td>
<td></td>
</tr>
</tbody>
</table>

* $^{a)}$ The $k_2$ values were obtained from the slope of the straight line obtained when the fraction of sodium diclofenac released was plotted against the square root of time.  
  $^{b)}$ Correlation coefficient of the straight line to obtain $k_2$ value.  
  $^{c)}$ A straight line was obtained up to 1 h.  
  $^{d)} p < 0.05$ versus value at 100 rpm.  
  Each value represents the mean ± S.D. ($n = 3$).
the apparent straight line (closed circles in Fig. 3) was significantly greater than that obtained from the open circle in Fig. 3. Thus, the content of sodium diclofenac seems to affect the value of $\varepsilon/\tau$ in Eq. 5.

When the speed of the rotating basket was changed, the release of diclofenac from granules of code-2 to code-4 remained unchanged between 100 and 150 rpm (Table II). However, the release from code-1 granules at 150 rpm was greater than that at 100 rpm (Table II). Thus, although the release from code-1 granules may occur predominantly by degradation of the granules, the release from code-2, -3 and -4 granules occurs predominantly by the leaching mechanism rather than by degradation.

As can be seen in Fig. 2B, each regression line gave an intercept with a positive value at zero time. In plots based on Higuchi’s equation, the intercept often gives a negative value at zero time because there should be a lag time before the infiltration of solvent into the granules. Thus, the granules in the present study might have adsorbed more sodium diclofenac than expected on their surface during the process of granule preparation. Some sodium diclofenac dissolved in the organic solvent may have been adsorbed on the surface of solids which precipitated before the complete evaporation of the solvent.

References and Notes