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RESEARCH PAPER

# Sustained Release of Diclofenac from Polymer-Containing Suppository and the Mechanism Involved

Y. Azechi,[1] K. Ishikawa,[2] N. Mizuno,[3] and K. Takahashi,[3,*]

[1]*Formulation Development Laboratory, Eli Lilly Japan K. K., 4-3-3 Takatsukadai Nishi-ku, Kobe, Hyogo 651-2271, Japan*
[2]*Pharmaceutical Laboratory, Tsumura and Company, Japan, 12-7 Niban-cho, Chiyoda-ku, Tokyo 102, Japan*
[3]*School of Pharmaceutical Sciences, Mukogawa Women's University, 11-68 Koshien Kyuban-cho, Nishinomiya, Hyogo 663-8179, Japan*

**ABSTRACT**

*Sustained release of diclofenac sodium (DcNa) from suppositories composed of triglycerides and polymer was investigated by dissolution testing through an artificial membrane. DcNa was slowly released from a suppository containing carboxyvinyl polymer (CVP), and the extent of the release decreased with the amount of CVP added. Little effect was noted with the addition of other water-soluble polymers, such as hydroxyethylcellulose (HEC), xanthan gum, and polyvinylalcohol (PVA). When sodium benzoate was used instead of DcNa, a similar result was obtained with the addition of CVP. The result of release rate analysis together with the viscosity and pH in these cases showed that the reduction of solubility and diffusion due to sodium exchange between DcNa and CVP played an important role in the sustained release from the suppository. Also, in comparison with the results when CVP was not used, the plasma concentration profile of diclofenac after the administration of CVP suppository displayed a twofold longer half-life time.*
***Key Words:*** *Diclofenac; Suppository; Sustained release; Water-soluble polymer.*

* To whom correspondence should be addressed. Telephone: +81 798 45 9943. Fax: +81 798 41 2792. E-mail: koichi@mwu.mukogawa-u.ac.jp

## INTRODUCTION

Rectal administration of a drug offers many advantages, such as avoidance of the first-pass effect by the liver (1), decrease of gastrointestinal side effects (2), and avoidance of unfavorable effects of meals on drug absorption. In spite of these advantages, there are restrictions in using suppositories, including trouble with repeated and daily used.

To reduce the frequency of suppository administration, many investigators have recently reported that addition of some water-soluble polymers and other additives into the suppository base made possible sustained release of the drug from the suppository and could prolong the absorption rate of the drug from the rectum (3–5). In the case of diclofenac sodium (DcNa), additives studied have included lecithin (6), adipic acid (7,8), fumaric acid (8), light silicic anhydride (9), and carboxyvinyl polymer (CVP) (10). Iwamoto et al. (10) reported that a suppository composed of DcNa and CVP showed a slightly sustained release of diclofenac.

In this study, DcNa suppositories containing several water-soluble polymers were examined by a membrane diffusion method (11,12) to search for additives that enable much slower release. We also present a detailed slow-release mechanism of the CVP-containing suppository based on examination of release rates, viscosities, and pH values of the suppositories. The plasma concentration profiles of diclofenac after rectal administration of the suppositories were also investigated using rats.

## EXPERIMENTAL

### Materials

DcNa was obtained from Junsei Kagaku Company, Limited (Tokyo, Japan). Suppository base (Hard Fat™) was purchased from Nippon Oil and Fats Company, Limited (Tokyo, Japan). CVP (Carbopol™ resin, BF-Goodrich Co., USA), hydroxyethylcellulose (HEC) (SE900), xanthan gum (Kerthorol™), and polyvinylalcohol (PVA) were obtained from Chugai Trade Company, Limited (Tokyo, Japan), Daicel Chemical Industries, Limited (Osaka, Japan), Dainippon Pharmaceutical Company, Limited (Osaka, Japan), and Nippon Synthetic Chemical Industry Company, Limited (Tokyo, Japan), respectively. Free acid of diclofenac (Dc) was prepared by precipitation with a pH-lowering agent; DcNa was dissolved in 1 N hydrochloric acid aqueous solution, and the resulting precipitation was dried under vacuum before use. Other reagents were analytical or special reagent grade and were used without further purification.

### Preparation of Suppository

Triglyceride (suppository base), drug, and additives were melted and mixed at 40°C with a Polytron homomixer PT-10 (Kinematica AG, Switzerland) and then cooled at 35°C. The resulting mixture was kept at 35°C, poured into 2.25-ml plastic molds (Nichii Packing Co., Ltd., Osaka, Japan), placed in a refrigerator (4°C) for rapid solidification, and kept there until use. Table 1 shows the formulas of the suppositories prepared.

### In Vitro Release from Suppository

The release test of the suppositories was carried out with a modified membrane diffusion method using a suitable dissolution tester (model NTR-VS6P, Toyama Industries Co., Ltd., Toyama, Japan). The testing medium was phosphate buffered saline (pH 7.4, 1/3 M, 900 ml). A 1.0-g sample of suppository soaked in 3 ml of the medium was placed in a cellophane Visking tube (50 mm long, 16 mm diameter; the tube can exclude materials with a molecular weight more than 12,000). The outer medium in the dissolution vessel was stirred at a speed of 150 rpm and kept at 38°C. At predetermined times, an aliquot (3 ml) of the outer medium was removed from the vessel with an autosampler and subjected to ultraviolet (UV) measurement at 244 nm.

### Viscosity and pH Measurement

A 2.0-g suppository was weighed and melted in 10 ml of hot water (80°C) with stirring. After cooling it below 40°C, the pH and viscosity at 38°C were measured with a pH meter (model B-212, Horiba Ltd., Kyoto, Japan) and an EHD-viscometer (Toki Sangyo Co., Ltd., Tokyo, Japan), respectively. The apparent viscosity coefficient $\mu$ at 38°C was calculated from the curve of the shear stress (data from 0.5 to 100 rpm with 3° cone).

### Absorption Study in Rats

Male Sprague-Dawley (SD) rats with body weights ranging from 200 g to 250 g were fasted for 36 hr before the experiment with free access to water. A 200-mg suppository (3.5 $\times$ 6 mm) was administered to the rats, and then the anus was closed with adhesive (Alon-Alfa A, Sankyo Co., Ltd., Tokyo, Japan) soaked in cotton.

***Table 1***

*Formulas*

| Code | Hard Fat (mg) | Polymer | mg | Na-Diclofenac (mg) | Diclofenac (mg) | Na-Benzoate (mg) |
|---|---|---|---|---|---|---|
| 1 | 962.5 | — | 0.0 | 37.5 | 0.0 | 0.0 |
| 2 | 862.5 | HEC | 100.0 | 37.5 | 0.0 | 0.0 |
| 3 | 862.5 | Xanthan gum | 100.0 | 37.5 | 0.0 | 0.0 |
| 4 | 862.5 | PVA | 100.0 | 37.5 | 0.0 | 0.0 |
| 5 | 862.5 | CVP | 100.0 | 37.5 | 0.0 | 0.0 |
| 6 | 895.0 | CVP | 100.0 | 5.0 | 0.0 | 0.0 |
| 7 | 887.5 | CVP | 100.0 | 12.5 | 0.0 | 0.0 |
| 8 | 875.0 | CVP | 100.0 | 25.0 | 0.0 | 0.0 |
| 9 | 850.0 | CVP | 100.0 | 50.0 | 0.0 | 0.0 |
| 10 | 952.5 | CVP | 10.0 | 37.5 | 0.0 | 0.0 |
| 11 | 937.5 | CVP | 25.0 | 37.5 | 0.0 | 0.0 |
| 12 | 912.5 | CVP | 50.0 | 37.5 | 0.0 | 0.0 |
| 13 | 812.5 | CVP | 150.0 | 37.5 | 0.0 | 0.0 |
| 14 | 900.0 | CVP | 100.0 | 0.0 | 37.5 | 0.0 |
| 15 | 962.5 | — | 0.0 | 0.0 | 0.0 | 37.5 |
| 16 | 862.5 | HEC | 100.0 | 0.0 | 0.0 | 37.5 |
| 17 | 862.5 | Xanthan gum | 100.0 | 0.0 | 0.0 | 37.5 |
| 18 | 862.5 | PVA | 100.0 | 0.0 | 0.0 | 37.5 |
| 19 | 862.5 | CVP | 100.0 | 0.0 | 0.0 | 37.5 |

Blood samples (0.6 ml) were collected from the jugular vein at 30 min and 1, 1.5, 2, 4, 7, 12, and 24 hr after administration. The plasma samples were obtained by centrifugation of heparinized blood samples and frozen until the assay. The plasma concentration of Dc was measured by the following procedure.

An aliquot (0.3 ml) of plasma was collected in a test tube containing a fixed amount of internal standard (4′-methoxy diclofenac), and pH 2.0 buffer solution was added to the tube. After mixing in the tube, the sample was poured into a preliminarily treated Bond-Elute packed column (200 mg C18, GL-Science, Tokyo, Japan), and the column was washed successively with 6 ml of pH 2.0 buffer and 24 ml of deionized water. From this column, Dc was eluted with 3 ml of methanol. The eluted solution including Dc and internal standard was dried under nitrogen stream at 40°C.

To the residue was added 0.3 ml of a high-performance liquid chromatography (HPLC) mobile phase solution, and 80 μl of the resultant solution was injected onto an HPLC column. The HPLC system was equipped with a pump (880-PU, Jasco, Tokyo, Japan), a UV detector (875-UV, Jasco), a column (4.6 × 150 mm) packed with ODS-2 C18 (GL-Science, Tokyo, Japan), and an integrator (CR3A, Shimadzu, Kyoto, Japan). The mobile phase was pH 7.0 phosphate buffer containing 0.05% of *t*-butyl ammonium chloride, methanol, and acetonitrile at a ratio of 45:30:25. The pump flow rate was 1.0 ml/min, and the column temperature was kept at 40°C.

### Data Analysis

The area under the plasma concentration-time curve $AUC_{0\text{-}\infty}$ was calculated according to the trapezoidal rule with extrapolation to infinity. The mean residence time (MRT) of the drug was calculated by the method of Yamaoka et al. (13).

## RESULTS AND DISCUSSION

### Release of Diclofenac from Suppositories Containing Various Polymers

Figure 1 shows the release profiles of Dc from suppositories containing 10% polymer. The release of Dc from these suppositories was suppressed compared with the control (code 1). Among these suppositories, the one containing CVP (code 5) showed the slowest release profile (Fig. 1A). By plotting the percentage of Dc released against the square root of time, a linear relationship was obtained in the early stage of the dissolution with each formulation, indicating that the Fickian diffusion model

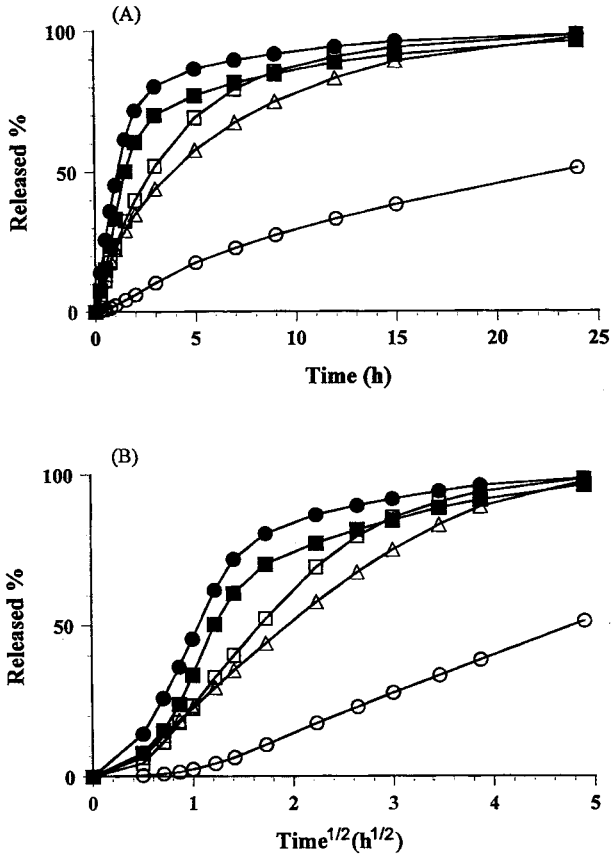


**Figure 1.** Release profiles of Dc from suppositories: (A) plots of the released percentage of Dc against time; (B) plots of the released percentage of Dc against the square root of time. ●, code 1; △, code 2; □, code 3; ■, code 4; ○, code 5. Each value represents the mean ($n$ = 4 or 5).

(Higuchi model) (14) can be applied for the release of Dc from the suppositories (Fig. 1B). The slope $k$, which is one measure of an apparent rate (diffusion) constant of drug release, is listed in Table 2. These $k$ values showed that the suppository containing CVP (code 5) displayed the slowest release of Dc, and the $k$ value was 15 times lower than that of the control. The other suppositories (codes 2, 3, and 4) also showed slower release than the control, and the $k$ value was about two times lower than that of the control. Thus, the suppository containing CVP is the most appropriate for sustained release of Dc.

### Effect of Diclofenac Sodium and Carboxyvinyl Polymer Content in Suppository on Diclofenac Release

Since DcNa is a water-soluble drug, the concentration (amount) of DcNa can be expected to affect the release rate of Dc from the suppository. To examine for such an effect at a constant CVP concentration, preparations of code 1 and those of codes 5 through 9 were studied. As shown in Fig. 2, the release rate of Dc decreased with increasing DcNa content. On the other hand, the DcNa content did not affect the release of Dc in suppositories without CVP (data not shown). Figure 3 shows the effect of CVP content on the release of Dc at a constant DcNa

***Table 2***

*Suppository Dissolution Parameters*

| Code | $k$ | pH | Viscosity (mPa · s) |
|---|---|---|---|
| 1 | 39.5 | 8.2 | 1 |
| 2 | 20.4 | 8 | 205 |
| 3 | 19.6 | 7.5 | 75 |
| 4 | 27.8 | 7.6 | 36 |
| 5 | 2.3 | 3.7 | 258 |
| 6 | 6.8 | 2.8 | 146 |
| 7 | 4.7 | 3.3 | 206 |
| 8 | 3.1 | 3.6 | 235 |
| 9 | 2.3 | 3.5 | 286 |
| 10 | 13.6 | 6.8 | 28 |
| 11 | 8.9 | 5.2 | 162 |
| 12 | 4 | 4.2 | 197 |
| 13 | 1.4 | 3.5 | 279 |
| 14 | 1.8 | 2.6 | 66 |

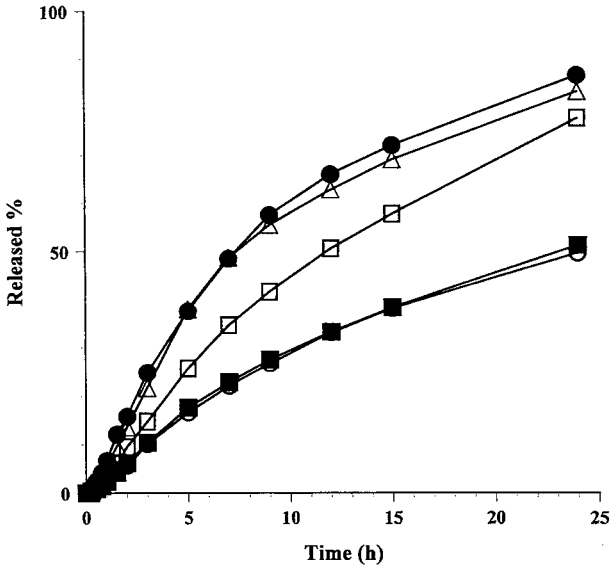


**Figure 2.** Effect of DcNa content on the release of Dc from suppositories. ●, code 6; △, code 7; □, code 8; ■, code 5; ○, code 9. Each value represents the mean ($n$ = 4 or 5).

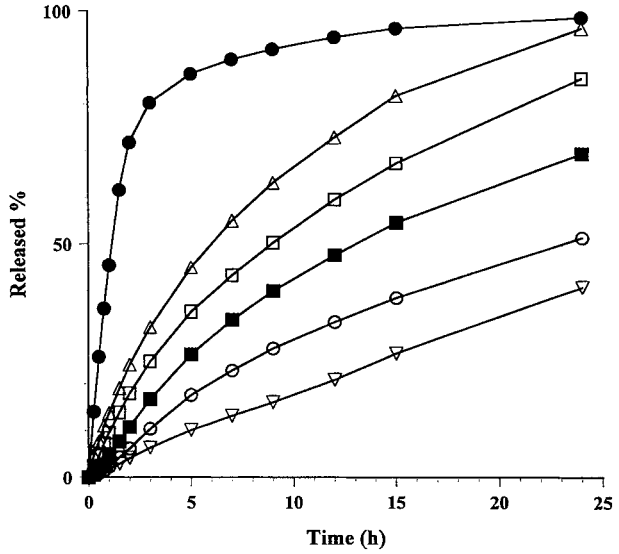


**Figure 3.** Effect of CVP content on the release of Dc from suppositories. ●, code 1; △, code 10; □, code 11; ■, code 12; ○, code 5; ▽, code 13. Each value represents the mean ($n$ = 4 or 5).

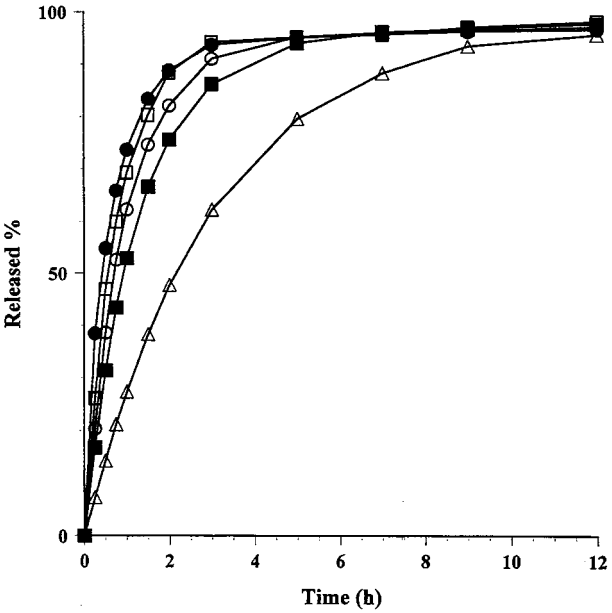


**Figure 5.** Effect of polymer addition on benzoate release from suppositories. ●, code 15; △, code 19; □, code 16; ■, code 17; ○, code 18. Each value represents the mean ($n$ = 4 or 5).

concentration. The release rate of Dc decreased with increasing CVP content. These results indicate that the release rate of Dc is affected by the amount of DcNa or CVP; thus, there are some interactions that occur between DcNa and CVP that induce slow release of Dc from a suppository.

Iwamoto et al. (10) suggested that the sustained release of DcNa from CVP suppository was caused by enhanced viscosity in the suppository. As shown in Table 2, the viscosity of the suppository increased with the con-

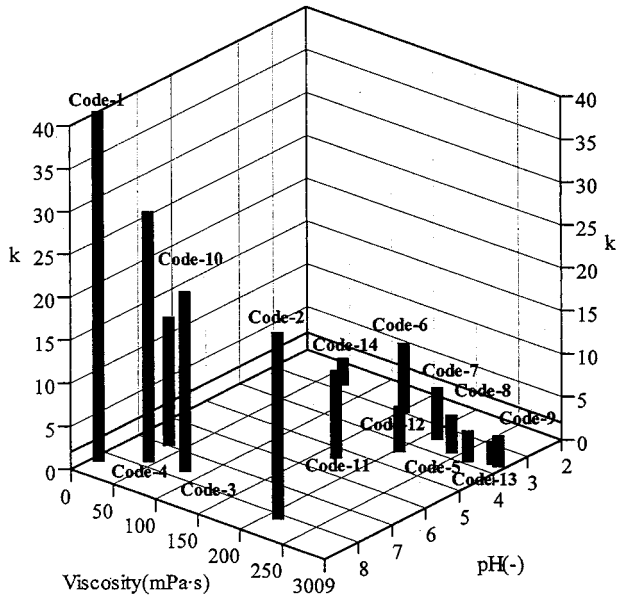


**Figure 4.** Correlation between base viscosity and pH on Dc release from suppositories.

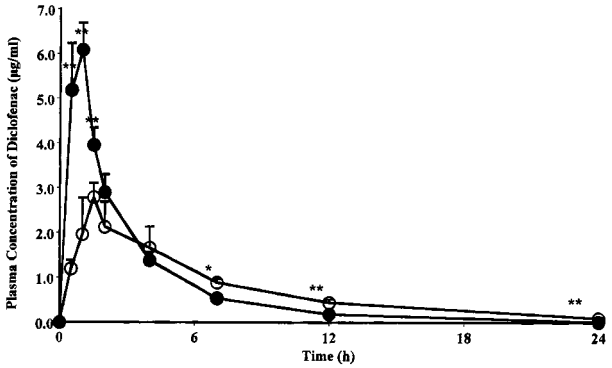


**Figure 6.** Plasma Dc concentration in rats after rectal administration of suppository. ○, code 1; ●, code 5. Each point represents mean ± SE ($n$ = 4 to 8). *$p < .05$; **$p < .01$.

***Table 3***

*Pharmacokinetic Parameters of DcNa Suppositories in Rats*

| Code | Dose (mg/kg) | $C_{max}$ (μg/ml) | $T_{max}$ (hr) | MRT (hr) | AUC (μg · hr/ml) | rBA (%) |
|---|---|---|---|---|---|---|
| 1 | 10.0 | 6.1 ± 0.6 | 0.83 ± 0.11 | 3.46 ± 0.38 | 18.6 ± 1.1 | 100 |
| 5 | 10.0 | 2.8[a] ± 0.4 | 1.58[a] ± 0.17 | 6.07[b] ± 0.79 | 17.7 ± 2.7 | 95.6 |

Each value represents mean ± SE ($n$ = 4 to 9).
[a] $p < .01$ vs. code 1.
[b] $p < .05$ vs. code 1.

tent of CVP (code 5, codes 10 to 13), and the *k* value decreased with increasing viscosity. However, the *k* value of the HEC suppository (code 2) was 8.7 times higher than that of the CVP suppository (code 5), although the viscosity was almost the same. The results suggest that other factors might affect the sustained-release properties of Dc from suppositories.

The sodium ion reacts with carboxy groups of CVP, and the molecular structure of CVP undergoes transformation from a helix (low viscosity) to a straight type (high viscosity). Accompanying this change are increases in the viscosity and pH of aqueous solutions of CVP. When the aqueous solution of CVP is acidic, DcNa may exist mostly as a free acid form in this solution. Sodium ion exchange between DcNa and CVP may occur, resulting in increased viscosity. The solubility of Dc in water is lower than that of DcNa. The value of *k* in code 14, which is the suppository containing Dc instead of DcNa, was similar to that in code 5, although the viscosity value in code 14 was lower than that in code 5 (Table 2).

To investigate further the interaction between DcNa and CVP, the relationship among the viscosity, pH, and the values of *k* in the suppository were compared. As presented in Table 2 and Fig. 4, increasing viscosity and decreasing pH value lead to prolongation of Dc release, and the effect of viscosity on the *k* value is smaller than that of pH. These results strongly suggested that the mechanism for the sustained release by CVP could be additive to the increased viscosity and the lower solubility of the drug.

### Release of Sodium Benzoate from the Suppository Containing Polymer

To investigate the effect of the interaction between DcNa and CVP, another sodium salt of the drug was used. The sodium benzoate used was released faster than DcNa because of the low molecular weight and high solubility in water (Fig. 5). However, the prolongation effect with CVP was observed, also indicating that a water-soluble polymer such as HEC, xanthan gum, and PVA had little or no effect on the slow release.

### Absorption Study on Suppositories Containing Carboxyvinyl Polymer

The data shown in Fig. 6 represent the mean with the standard error (mean ± SE). Statistical analysis of the data was carried out using the Student *t* test. Figure 6 shows the plasma concentration of Dc after rectal administration of suppositories with or without CVP to rats. Rectal administration of the DcNa suppository without CVP (code 1) caused an early peak in the plasma level of Dc and a high maximum concentration. Dc was eliminated rapidly from the plasma. On the other hand, the Dc concentrations after rectal administration of the suppository containing CVP (code 5) were relatively low at an early stage and then showed a sustained level. The pharmacokinetic parameters are summarized in Table 3. In code 5, both values of $T_{max}$ and MRT (mean residence time) were larger than those in code 1 without decrease of bioavailability.

## CONCLUSION

The results of this study indicate that suppositories containing a mixture of DcNa and CVP in a triglyceride base prolonged the release in both in vitro and in vivo studies, and that the mechanism of this prolonged release may be the additive effects of the increased viscosity and lowering of drug solubility. Furthermore, wider application of this interaction may enable prolonged rectal absorption of other sodium salts of drugs.

## REFERENCES


1. A. G. de Boer, Clin. Pharmacol. Ther., 26, 701–709 (1979).
2. V. Cioli, B. Silvestrini, and F. Dordoni, Exp. Mol. Pathol., 6, 68–83 (1967).
3. S. Miyazaki, F. Suisha, N. Kawasaki, M. Shirakawa, K. Yamatoya, and D. Attwood, J. Controlled Release, 56, 75–83 (1998).
4. Y. Matsumoto, I. Yamamoto, Y. Watanabe, and M. Matsumoto, Biol. Pharm. Bull., 18, 1744–1749 (1995).
5. K. Uekama, T. Kondo, K. Nakamura, T. Irie, K. Arakawa, M. Shibuya, and J. Tanaka, J. Pharm. Sci., 84, 15–20 (1995).
6. T. Nishihata, H. Wada, and A. Kamada, Int. J. Pharm., 27, 245–253 (1985).
7. A. Iwasa, M. Murata, S. Kasai, K. Imamori, and T. Nagai, Yakuzaigaku, 51, 199–203 (1991).
8. A. Iwasa, M. Murata, H. Kishi, S. Kasai, and T. Nagai, Yakuzaigaku, 51, 192–198 (1991).
9. H. Tabata, Y. Iwamoto, K. Morimoto, and K. Morisaka, Yakuzaigaku, 47, 141–146 (1987).
10. Y. Iwamoto, H. Tabata, K. Morimoto, and K. Morisaka, Yakuzaigaku, 47, 244–247 (1987).
11. H. Yoshino, M. Kobayashi, and M. Samejima, Yakuzaigaku, 41, 102–112 (1981).
12. W. H. Thomas and R. McCormack, J. Pharm. Pharmacol., 23, 490–494 (1971).
13. K. Yamaoka, T. Nakagawa, and T. Uno, J. Pharm. Pharmacol., 35, 19–22 (1983).
14. T. Higuchi, J. Pharm. Sci., 52, 1145–1149 (1963).