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Release of Sodium Diclofenac from Vehicles Prepared with Hydrogenated Soya Lecithin and Methyl Palmitate

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The release of sodium diclofenac (DC) from vehicles prepared with hydrogenated soya lecithin (lecithin) and methyl palmitate was remarkably sustained, and was significantly influenced by each constituent in the vehicle. An increase of DC content as well as that of lecithin enhanced the release of DC. From these results, it is considered that the release of DC seems to be regulated by the infiltration rate of the dissolution medium. However, the release of DC during 24 h did not exceed 50% for all vehicles studied. This may be due to the poor solubility of lecithin in neutral water which is an important factor suppressing the infiltration of the medium into the matrix of the vehicle.

To improve the release of DC, mannitol was incorporated into the matrix. As the content of mannitol was increased, the rate of drug release increased without disintegration of the spherical mass. Thus, release of DC from the vehicle can be easily controlled by adjusting the amount of mannitol incorporated into the vehicle.

Keywords——controlled release; hydrogenated soya lecithin; methyl palmitate; sodium diclofenac; spherical waxy matrix; mannitol

Introduction

Sodium diclofenac (DC) is a widely used nonsteroidal anti-inflammatory drug. The plasma level of this drug increases rapidly following oral administration of commercially available preparations, but it decreases rapidly owing to the short half-life of DC in the living body. To avoid undesirable high plasma concentrations and the need for frequent repetitive dosing, sustained-release delivery devices are desirable for the administration of DC. Sustained release of many drugs has been extensively studied,[1–4] and hydrogenated soya lecithin (lecithin) was reported to be a potentially useful adjuvant for sustained-release delivery.[3,4]

Previously, Nishihata *et al.*[3,4] reported that the incorporation of lecithin into triglyceride base increased the solubility of DC in the base and sustained the release of DC. Thus, it may be considered that the mechanism of this sustained release is a decrease in the infiltration rate of rectal fluid into the suppository matrix owing to a reduced hydrophilicity of lecithin and DC, possibly as a result of complex formation between these compounds in the vehicle. The lecithin matrix may, therefore, also be available for oral delivery preparations.

In this report, we studied the availability of methyl palmitate as binder and mannitol as a water-infiltration enhancer for the sustained release of DC from the lecithin matrix.

TABLE I. Codes and Constituents of Vehicles

Code	Drug	Methyl palmitate	Lecithin	Mannitol	Weight of vehicle[a] (g)	Content of drug in vehicle[b] (mg/g vehicle)
	(g/g vehicle)					
1	0.010	0.285	0.705	0	0.471±0.032	9.9±0.4
2	0.020	0.285	0.695	0	0.469±0.025	22.4±1.4
3	0.050	0.285	0.665	0	0.475±0.020	50.2±1.7
4	0.075	0.285	0.640	0	0.473±0.021	73.7±1.6
5	0.100	0.285	0.615	0	0.476±0.036	102.0±4.1
6	0.150	0.285	0.565	0	0.481±0.041	147.2±3.7
7	0.050	0.125	0.825	0	0.472±0.032	51.6±2.4
8	0.050	0.165	0.785	0	0.479±0.016	50.2±0.9
9	0.050	0.380	0.570	0	0.459±0.031	53.8±1.6
10	0.050	0.950	0	0	0.472±0.024	50.9±2.7
11	0.050	0.165	0.585	0.200	0.609±0.014	53.1±2.1
12	0.050	0.165	0.485	0.300	0.600±0.010	50.2±0.5
13	0.050	0.165	0.185	0.600	0.611±0.013	54.1±2.2
3′	0.050	0.285	0.665	0	0.597±0.021	51.3±2.2
14	0.050	0.225	0.525	0.200	0.557±0.034	54.3±1.1
15	0.050	0.165	0.385	0.400	0.603±0.027	54.4±0.8
16	0.050	0.105	0.245	0.600	0.600±0.025	52.3±2.5

a) Each value represents the mean±S.D. ($n=12$). *b*) The values represent the mean±S.D. ($n=6$).

Experimental

Materials——Lecithin, which was kindly supplied by Nikko Chemicals Co., Ltd. (Tokyo, Japan), contains more than 98% phospholipid and about 30% phosphatidylcholine, and has an iodine value of about 6%. DC was supplied by Ciba Geigy Japan (Takarazuka, Japan). Methyl palmitate was purchased from Tokyo Kasei Kogyo Co., Ltd. (Tokyo, Japan). Other reagents were commercial products of analytical grade.

Preparation of Spherical Vehicle——The codes and constituents of vehicles used in this study are listed in Table I. Each constituent was passed through a 100-mesh sieve. Portions of the constituents were taken in a mortar, and mixed with a pestle at 80°C. After a gelatinous mixture was obtained, 0.5 or 0.6 g of this mixture was manually formed into a sphere of 9 mm (code-1 to code-10) or 10 mm (code-11 to code-16) diameter. After cooling, each bolus was stored at 4°C until use.

Release Study——A bolus, wrapped with two sheets of cotton gauze (JPX type I, 4×4 cm^2), was immersed in a beaker containing 100 ml of JPX dissolution medium (pH 6.8) at 37 or 18°C. The beaker was shaken at 90 cycles per minute, and 0.2 ml of the medium was collected through a Millipore filter (pore size of 0.45 μm) at designated time intervals. The assay of DC was carried out by using high-performance liquid chromatography (HPLC) as described by Yaginuma *et al.*[5]

Results and Discussion

Effect of DC Content in Vehicle on Release of DC

To investigate the effects of DC content in lecithin-methyl palmitate vehicle, formulations of code-1 to code-6 were examined (Table I). As shown in Fig. 1A, the increase of DC content resulted in an increase of DC amount released. When the amounts of DC released were plotted against the square root of time, a linear relationship was obtained for each formulation (Fig. 1B). From the present observations, a leaching-type drug release process as proposed by Higuchi[6] (Eq. 1) may be applied for the release of DC from the vehicles studied:

$$Q=[D\pi(2A-\pi C_s)C_s\cdot t/\tau]^{1/2} \quad (1)$$

where Q=the amount of drug released after time, t, per unit exposed area; D=the diffusitivity of the drug in the permeating fluid; τ=the tortuosity factor of the capillary system; A=the

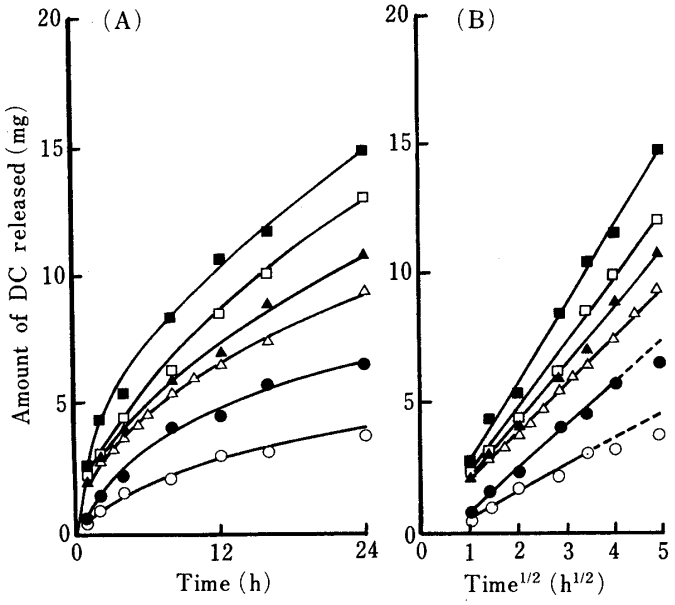

Fig. 1. Release Profiles of DC from Vehicles

(A) plots of the released amount of DC against time; (B) plots of the released amount of DC against the square root of time. (○), code-1; (●), code-2; (△), code-3; (▲), code-4; (□), code-5; (■), code-6.
Each value represents the mean ± S.D. ($n=4$ or 5).

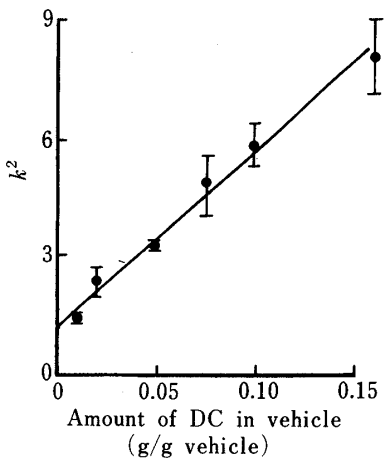

Fig. 2. Effect of DC Content on Diclofenac Release from Vehicles

The effect is represented as a plot of the release parameter k^2 against the content ratio of DC in the vehicle.
Each value represents the mean ± S.D. ($n=4$ or 5).

total amount of the drug present in the matrix per unit volume; C_s = the solubility of the drug in the permeating fluid; π = the porosity of the matrix.

By introducing an apparent surface area of vehicle effective for the release of DC, Eq. 1 can be modified as follows:

$$Q' = Q \cdot S_q = S_q \cdot [D\pi(2A - \pi C_s) \cdot C_s \cdot t/\tau]^{1/2} = k \cdot t^{1/2} \quad (2)$$

where Q' = the amount of the drug released after time, t, from the test vehicle; S_q = the total exposed area; k = the slope obtained from the straight line in Fig. 1B.

The value of k may be considered to be an apparent rate constant factor for the release of drug from vehicles, *i.e.*, a small value of k represents a slow release of drug from the vehicle (Table II). Higuchi[6] proposed that when the solubility of the drug is low, k in Eq. 2 can be written as follows:

$$k = S_q \cdot [2 \cdot A \cdot D \cdot C_s \cdot (\pi/\tau)]^{1/2} \quad (3)$$

In terms of ingredients, methyl palmitate is not soluble in the medium. From the linear relationship presented in Fig. 1B, lecithin may be considered to be poorly soluble at the neutral pH studied. Thus, the value of (π/τ) seems to be influenced predominantly by DC content. When the values of k^2 were plotted against the drug content per unit weight, a good straight line was obtained (Fig. 2). The plots in Fig. 2 are based on Eq. 4.

$$k^2 = [2 \cdot D \cdot C_s \cdot S_q^2(\pi/\tau)]A \quad (4)$$

Thus, the results in Fig. 2 may indicate that the value of (π/τ) is constant when the content of methyl palmitate is constant and that the capabilities of DC and lecithin to influence the value of (π/τ) are similar in degree. The intercept of the straight line in Fig. 2 may show the capability of lecithin to influence the value of (π/τ) of the vehicle.

From these results, it may be concluded that the vehicle containing lecithin and methyl palmitate sustains the release of DC in the neutral dissolution medium. However, the release

TABLE II. Apparent Constant Factor, k, for the Release of DC, Obtained from Eq. 2

Code	Temperature			
	37 °C		18 °C	
	k	% released with a 24 h	k	% released with a 24 h
1	1.15±0.04	74.2±5.1	No experiment	
2	1.51±0.13	60.7±6.7	No experiment	
3	1.74±0.19	39.6±2.7	1.42±0.09	27.9±3.0
4	2.21±0.19	30.3±2.1	No experiment	
5	2.41±0.11	25.4±1.9	No experiment	
6	2.83±0.17	19.9±2.7	No experiment	
7	2.11±0.18	44.1±3.2	1.57±0.11	33.7±2.4
8	1.97±0.19	42.7±1.6	1.54±0.07	29.6±1.9
9	1.70±0.11	33.1±3.9	1.33±0.11	22.4±1.2
10	—	100	—	6.9±2.1
11	3.21±0.21	47.6±3.0	No experiment	
12	3.52±0.42	51.6±3.6	No experiment	
13	6.69±0.44	80.8±3.1	No experiment	
3′	2.67±0.08	43.0±1.4	No experiment	
14	3.69±0.10	51.5±1.3	No experiment	
15	4.22±0.24	5.63±2.2	No experiment	
16	7.58±0.36	91.3±4.3	No experiment	

Each value represents the mean±S.D. (n=4 or 5).

of DC during 24 h decreased significantly with increase of the DC content (Table II).

Further, in spite of methyl palmitate having a melting point of 29 to 30°C, lecithin vehicles containing methyl palmitate (code-1 to code-6) did not change their spherical shape during the experimental period at 37°C suggesting that the gelling property of lecithin in methyl palmitate was sufficient to protect the matrix from disintegration.

Effect of Content Ratio of Methyl Palmitate and Lecithin on DC Release

To investigate the effect of lecithin content on the release of DC when the content of DC was fixed at 50 mg/g vehicle, preparations of code-3 and code-7 to cede-10 were examined.

The preparation of code-10 showed a rapid release of DC at 37 °C (Fig. 3A), because the vehicle without lecithin melted easily at 37 °C and fluidized rapidly at that temperature, resulting in a rapid exposure of DC particles to water. Gross observation revealed that other vehicles containing lecithin maintained a rigid state during the experimental period. Among the preparations of code-3, code-7, code-8 and code-9, the release rate of DC increased with increase of lecithin content at both temperatures studied (Fig. 3). Plots of the released amount of DC against the square root of time showed a linear relationship for each formulation, but that in the case of code-10 did not, suggesting the importance of the gell-forming property of lecithin.

The values of k and released amounts of DC during 24 h are summarized in Table II. These results indicate that the release of DC from lecithin-methyl palmitate vehicles progresses according to a leaching type mechanism. Compared with the case of lecithin-methyl palmitate vehicles, the release of DC from code-10 at 18°C was very small, suggesting that the permeation of water through the methyl palmitate matrix at low temperature was more difficult than that of lecithin (Fig. 3B). The initial release of DC from code-10 seems to be due to the dissolution of DC present at the surface of the vehicle. Thus, it is considered that lecithin in the vehicle may permit the infiltration of water into the gel matrix, probably by the hydration of lecithin.[7] Although DC particles disperse in the vehicle of code-10, the

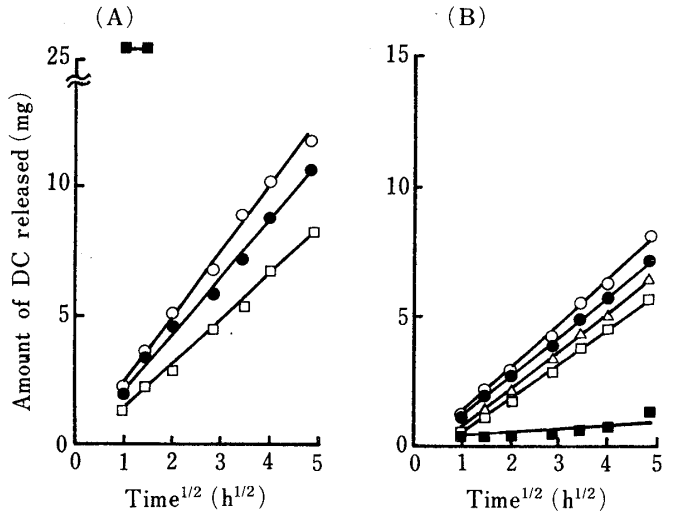

Fig. 3. Release Profiles of DC from Vehicle

The release study was carried out at the temperatures of 37 °C (A) and 18 °C (B). Plots of the released amount of DC against the square root of time. (△), code-3; (○), code-7; (●), code-8; (□), code-9; (■), code-10.

Each value represents the mean ± S.D. (n=4 or 5).

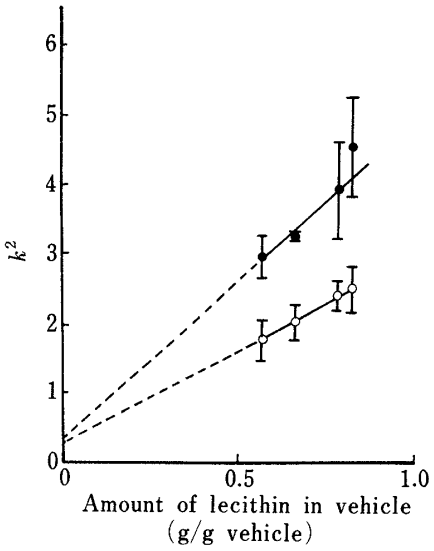

Fig. 4. Effect of Lecithin Content on Diclofenac Release from Vehicles

The effect is represented as a plot of the release parameter k^2 against the content ratio of lecithin in the vehicle. The release study was carried out at the temperatures of 37 °C (●) and 18 °C (○).

Each value represents the mean ± S.D. (n=4 or 5).

infiltration of water into the matrix was prevented at low temperature because of the low hydrophilicity of methyl palmitate.

In Eq. 3, the value of A is constant in the vehicles used in this section. Thus the factor in Eq. 3 that influences the value of k may be π/τ. When the values of k^2 were plotted against the content of lecithin in the vehicles, a linear relationship was observed at both temperature of 37 and 18 °C, except for code-5 at 37°C (Fig. 4). The difference of slopes at the two temperatures may be ascribed to the different solubility and diffusibility of DC under the two conditions. The value of k^2 for code-7 at 37 °C, which seems to be greater than that expected from the solid straight line in Fig. 4, may reflect a decrease of the physical stability of the vehicle as a result of the decrease of methyl palmitate as a binder, even though the vehicle retained its shape during the experimental period (by naked-eye observation). These observations indicate that the content of lecithin determines the value of π/τ. It is considered that lecithin is an important factor in producing a continuous route for solvent infiltration into the vehicle, based on the results at 18 °C.

Effect of Mannitol in the Vehicle on DC Release

As shown in Table II, when the vehicle contained 50 mg of DC per gram of vehicle, release of DC within 24 h was less than 50% for all preparations studied in the preceding experiments. This may be due to the poor solubility of lecithin in water, which is an important factor influencing the solvent infiltration. Thus, it was considered that addition of a hydrophilic ingredient to the lecithin vehicle may enhance the infiltration of water and accelerate the release of DC. Based on these considerations, mannitol was dispersed into the vehicles (Table I). Among the preparations, the vehicles of code-11 to code-13 were prepared with a fixed amount of methyl palmitate (165 mg/g vehicle) and those of code-15, and code-14 to code-16 were prepared to contain methyl palmitate and lecithin at the same ratio (3 : 7) as code-3′. Further, the content of DC was fixed at 50 mg/g vehicle. This amount of DC was selected for practical purposes.

From the results of code-11 to code-13 and code-15, an increase in the content of

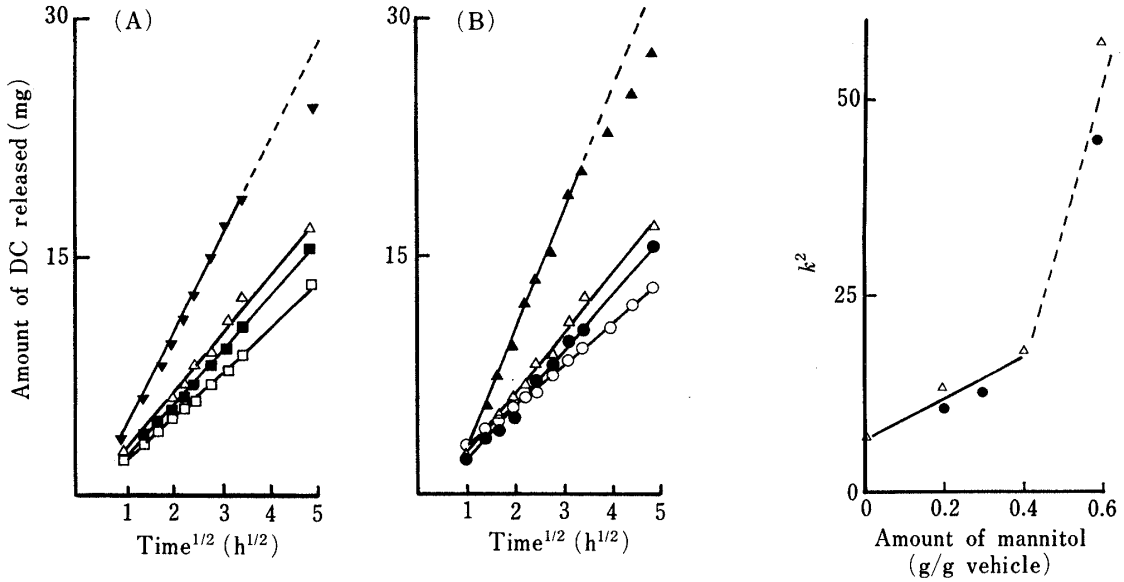

Fig. 5. Release Profiles of DC from Vehicles

The plots show the release of DC *versus* the square root of time.

(A) The vehicle contained a constant amount of methyl palmitate. (□), code-11; (■), code-12; (▼), code-13; (△), code-15.

(B) The ratio of methyl palmitate and lecithin in the vehicle was constant. (○), code-3′; (●), code-14; (△), code-15; (▲), code-16.

Each value represents the mean ± S.D. ($n=4$ or 5).

Fig. 6. Effect of Mannitol Content on Diclofenac Release from Vehicles

The effect is represented as a plot of the release parameter k^2 against the content ratio of mannitol in the vehicle.

(△), code-3′ to code-16; (●), code-11 to code-13.

Each value represents the mean ± S.D. ($n=4$ or 5).

mannitol increased the rate of release of DC (Fig. 5A). Among the vehicles studied, code-13 caused about 80% release within 24 h (Table II). As shown by straight lines in Fig. 5A, it is also suggested that the release of DC may occur according to a leaching-type mechanism even in the case of incorporation of mannitol.

Similarly the results for code-3′ and code-14 to code-16 revealed that an increase of mannitol also accelerated the release of DC (Fig. 5B) with about 90% release within 24 h for code-16 (Table II). The release of DC from each vehicle is also considered to occur by the leaching-type mechanism (Fig. 5B).

The increase of k value as a result of an increase of mannitol content in the vehicle seems to result from an increase in the porosity or number of channels in the vehicle owing to the dissolution of mannitol. When the values of k^2 were plotted against the content of mannitol, a straight line was observed for each preparation except for code-13 and code-16 (Fig. 6). This observation may indicate that the porosity in the vehicle can be easily controlled by the incorporation of water-soluble adjuvants such as mannitol.

In spite of the large values of k^2 for code-13 and code-16, the mode of release of DC from the two preparations is still considered to follow the leaching-type mechanism. From these observations, we suggest that the dissolution of mannitol in the infiltrated solvent and expulsion of dissolved mannitol from the vehicle influence the intrinsic porosity (π) and tortuosity (τ) in the vehicle. A large content of mannitol such as 0.6 g/g vehicle in comparison with a low content of mannitol may cause a significant decrease of τ value owing to rapid expulsion of mannitol, inducing a significant increase of the value of π/τ.

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