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In Vitro Release of Prednisolone from Oil-in-Water Type Ointment.[1,2] The Effect of Long-chain Alcohols on Drug Release

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The effects of two long-chain alcohols (stearyl alcohol, and cetyl alcohol) on prednisolone (PD) release *in vitro* from o/w type ointment bases were studied. When cetyl alcohol alone or mixtures of the two alcohols in various ratios were added to the o/w type ointment bases, the PD release rates were almost the same. On the other hand, when stearyl alcohol alone was added to the o/w type ointment base, the PD release rate was faster than those from the other ointment bases.

In order to confirm the above results, measurements of viscosity, and water penetration rate into the o/w type ointment base were carried out. It was found that the release rate of PD from o/w type ointment base was inversely proportional to its viscosity, and was proportional to the water penetration rate into the base.

Keywords——prednisolone; o/w type ointment base; *in vitro*; drug release; long-chain alcohol; viscosity; water penetration

In vitro drug release from various ointment bases may be difficult to correlate with *in vivo* results, but such studies may be useful for detecting interactions between drugs and bases which influence drug penetration. Thus, many attempts have been made to investigate drug release from ointment bases *in vitro*, and also to analyze the findings theoretically. In the previosu paper, we also examined the prednisolone (PD) release from o/w type ointment base, and found that the crystalline conversion of PD in the ointment base influenced the drug release.[3]

Several reports have been published on the influence of additives on *in vitro* drug release from ointment bases.[4,5] However, it appears that little or no attention has been paid to the effect on the drug release of the composition in the formulation, especially as regards long-chain alcohol, which acts as an adjuvant emulsifier in the emulsion-type ointment bases.

We have studied the effects of two long-chain alcohols (stearyl alcohol and cetyl alcohol) on the physical properties of o/w type ointment bases,[6] and we reported that the alcohols influenced the crystalline conversion of PD from the anhydrous form (A–PD) to the hydrated form (C–PD) in the o/w type ointment bases. We further observed that this crystalline conversion took place more easily when either stearyl alcohol (SOH) or cetyl alcohol (COH) was used alone in the formulation than when both alcohols were used simultaneously in an appropriate ratio. In addition, it was found that when both alcohols were used simultaneously in the o/w type ointment bases, the emulsions in the base were stabilized and the crystalline conversion of A–PD was retarded.

In order to examine the effects of composition in the formulation of ointment base on *in vitro* drug release from it, the present study was carried out to investigate the effects of two long-chain alcohols (SOH and COH) on the release of A–PD from the o/w type ointment bases. As the emulsions in the ointment base were stable under the experimental conditions, the crystalline conversion of A–PD was negligible.

Experimental

Materials——Prednisolone (PD) J.P. (Roussel Uclaf Co., Ltd.), white petrolatum J.P. (Kozakai Seiyaku Co., Ltd.), and sodium lauryl sulfate (Koso Chemical Co., Ltd.) were used. Stearyl alcohol (SOH), cetyl

alcohol (COH), and propylene glycol were of reagent grade from Tokyo Kasei Co., Ltd. Water was deionized and distilled.

Preparation of Ointment Bases——O/W type ointment bases were prepared according to the formulae in Table I. The white petrolatum and alcohol were heated at 70°C, then the water and other ingredients, previously heated to the same temperature, were added. The mixture was stirred until it congealed. A-PD recrystallized from acetone was passed through a 100 mesh sieve, and was incorporated mechanically (with a spatula) into the ointment base to give 5% concentration.

TABLE I. Formulae of Oil-in-water Type Ointments

Composition[a]	Ointments No.				
	1	2	3	4	5
White petrolatum	25	25	25	25	25
Stearyl alcohol (SOH)	22	17.6	11.0	4.4	0
Cetyl alcohol (COH)	0	4.4	11.0	17.6	22
Sodium lauryl sulfate	1.5	1.5	1.5	1.5	1.5
Propylene glycol	12	12	12	12	12
Purified water	40	40	40	40	40
SOH : COH	1:0	4:1	1:1	1:4	0:1

a) In grams.

Measurements of Viscosity of Ointment Bases——Rheological properties were measured at 30°C with a Rheomat 30 cone-and-plate viscometer (Contraves Co., Ltd.) under conditions which gave a maximum shear rate of 22.8 s^{-1} with a 15 s sweep time. Apparent viscosities were obtained from the shear stress at the maximum shear rate.

***In Vitro* Release of PD from the Ointment Bases**——*In vitro* release of PD from ointment bases was measured according to the method described in the previous paper.[3]

Water Penetration into the Ointment Bases——The Nos. 1—5 ointment bases containing PD (3 g each) were put into test tubes (1.0 cm i.d. × 7.0 cm) and packed tightly by centrifugation at 3000 rpm for 5 min. A 0.5 ml aliquot of 2% isonicotinohydrazide (INH) in 1 N HCl was then dropped onto the base in each tube, which was stoppered to prevent evaporation of the solvent. These tubes were allowed to stand in an incubator at 37°C.

The yellow color reaction of PD and INH solution takes place by the formation of hydrazones,[7] and this reaction can also be observed in the ointment base containing PD. The penetration distance (cm) of INH solution in the ointment base was determined by measuring the color change of ointment bases from white to yellow in the test tube.

Results and Discussion

In Vitro Release of PD from Ointment Bases

Higuchi[8] derived the following equation for the drug release from suspension-type ointments:

$$Q = \sqrt{Dt(2A - C_s)C_s} \quad (1)$$

where Q is the amount of drug released to the sink at time t per unit area; D is the diffusion coefficient of the drug in the ointment; A is the total drug concentration; and C_s is the solubility of the drug in the ointment. For the common case of $C_s \ll A$, this equation can be simplified to

$$Q = \sqrt{2ADC_s t} \quad (2)$$

As this equation predicts that plots of the amount of drug released against $\sqrt{t}$ will give a straight line, it can be simplified to

$$Q = K\sqrt{t} \quad (3)$$

where K is the release rate constant.

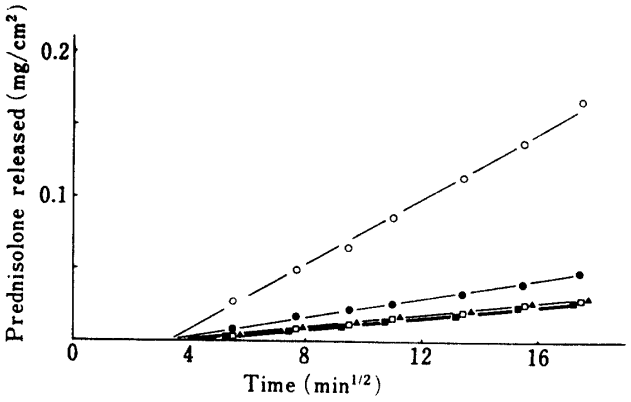

Fig. 1. Plots of the Amount of Prednisolone released from the O/W Type Ointment Bases *versus* the Square Root of Time

○: No. 1 ointment base, ▲: No. 2 ointment base, ■: No. 3 ointment base, □: No. 4 ointment base, ●: No. 5 ointment base.
Each value represents the mean of three experiments.

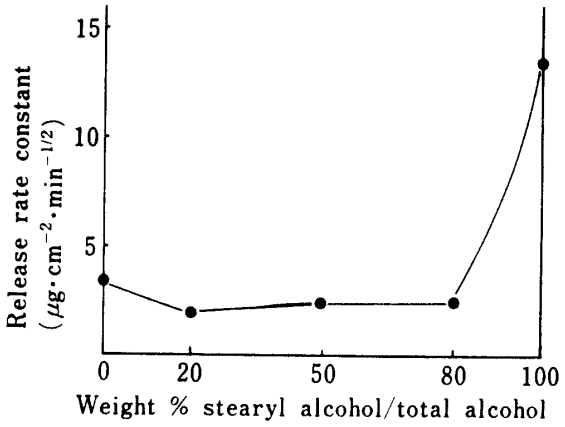

Fig. 2. Influence of the Ratio of Stearyl Alcohol to Total Alcohol in the Ointment Bases on the Release Rate Constant of Prednisolone

This model applies to the system used in this study, and the release patterns obtained from all the ointment bases are illustrated in Fig. 1. The figure shows plots of the amount of PD released from ointment bases *versus* the square root of time ($min^{1/2}$). As all the bases showed essentially linear plots over 8 h, PD release from the ointment bases was thought to be a diffusion-controlled process.

The release rate of PD from the ointment base (K) was estimated from the slope of the linear $Q-\sqrt{t}$ profile. The K values of Nos. 1,2,3,4, and 5 bases were 13.3, 2.50, 2.50, 2.0, and 3.3 $\mu g/cm^2/min^{1/2}$, respectively. In no case did the plots in Fig. 1 pass through the origin because of the lag time.

Fig. 2 shows the relationship between the K value and the percentage of SOH in the ointment bases (Nos. 1—5). The No. 1 base (SOH: 100%) gave the fastest drug release, but no significant differences could be seen among other bases. Thus, the ratio of SOH and COH in the ointment bases does influence the release rate of PD.

Effects of the Rheological Properties on *in Vitro* PD Release

The effects of rheological properties on the release of PD from the ointment bases were studied by the use of a rheometer. Fig. 3 shows the relationship between the apparent viscosity of ointment bases without PD and the percentage of SOH in the ointment bases. There was no significant difference in apparent viscosity among the Nos. 2, 3, and 4 bases, and the viscosities were 742, 750, and 801 P, respectively. That of No. 5 base was 600 P. The No. 1 base showed the lowest viscosity in this study, and its value was 389 P.

Barry[9] suggested that a lyotropic liquid crystal (LC) was formed from the ternary system (water-surfactant-alcohol) in the o/w type emulsion, and furthermore proposed that this LC participated in forming gel networks that gave consistency and stability to the system. Fukushima *et al.*[10] suggested that the stability of emulsion containing long-chain alcohols depended on the stability of LC formed in the system. They furthermore reported that if SOH and COH were used in the emulsion simultaneously in an appropriate ratio, the stability and consistency of the system were higher than in the cases when the alcohols were used individually. The results shown in Fig. 3 are similar to those reported by Fukushima *et al.*

Fig. 4 shows the relationship between the PD release rate and the reciprocal of the apparent viscosity. It appears from this figure that the relation is almost linear (coefficient of correlation: $r=0.980$), so that the PD release rate from the ointment base is inversely proportional

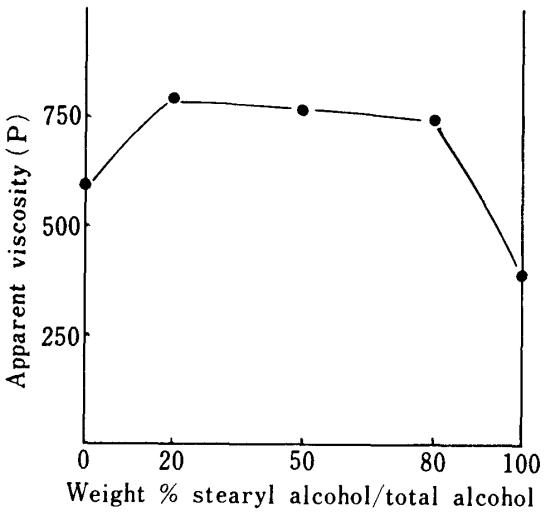

Fig. 3. Variation in Apparent Viscosity of O/W Type Ointment Bases as a Function of the Weight Ratio of Stearyl Alcohol to Total Alcohol

All apparent viscosities were determined at a shear rate of 22.8 s^{-1}. Each value represents the mean of three experiments.

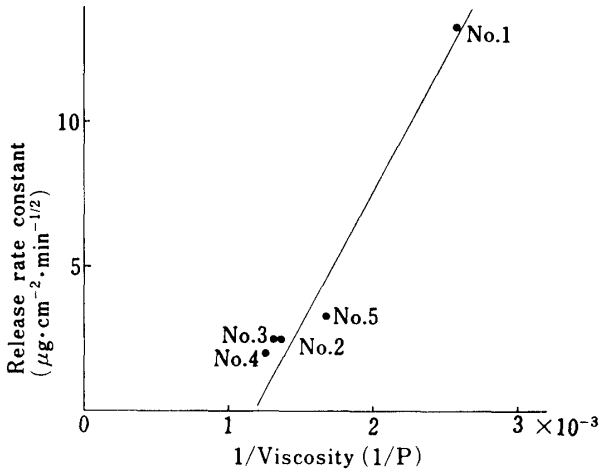

Fig. 4. Relationship between the Release Rate of Prednisolone from the O/W Type Ointment Bases and the Reciprocal of the Apparent Viscosity

to its viscosity.

Davis[11] has found that there was a more-or-less linear relationship between the release rate of salicyclic acid from plastibases and the reciprocal of the apparent viscosity, and this relationship was as would be expected from the Stokes–Einstein equation. This equation can be used if drug release from the base is a diffusion-controlled process.

Since the PD release from the ointment base is a diffusion-controlled process, as shown in Fig. 1, it is considered that the relationship between the release rate and the viscosity can be estimated from this equation.

Differences of Water Penetration among the Ointment Bases

Since cellophane membrane is freely permeable to water, a packaged water-compatible base, such as hydrophilic ointment base, can attract water, thus forming a solution and therefore allowing the drug to permeate from the aqueous solution rather than from the base.[12] Accordingly, it appears that the hydrophilicity of an ointment base plays an important role in drug release from it. The difference of hydrophilicity among the 5 bases used here was confirmed by a simple water penetration test, by observing the color reaction between PD and INH. Fig. 5 illustrates the penetration profile of INH solution into the ointment bases for 7 d. Here, the distance of water penetration is plotted as a function of time. The penetration rates of INH solution into Nos. 2—5 bases were similar, whereas that into No. 1 base was faster.

As is evident from Figs. 1 and 5, the differences of water penetration rate into the ointment base probably determine whether the process of drug release from the base is enhanced or retarded.

Nakano *et al.*[13] studied the permeation of salicylic acid from aqueous solution through hydrophilic ointment base, hydrophilic petrolatum, and polyethylene glycol ointment base, into another aqueous solution in a three-compartment diffusion cell, and found that the permeation profile of the drug resembled the release profile from the bases. In addition, they noted that the rates of permeation and of drug release would be affected by the partition coefficient of the drug between the ointment base and membrane. Whitworth *et al.*[14] investigated the effect of two different preparation techniques to incorporate a drug, that is, a mechanical

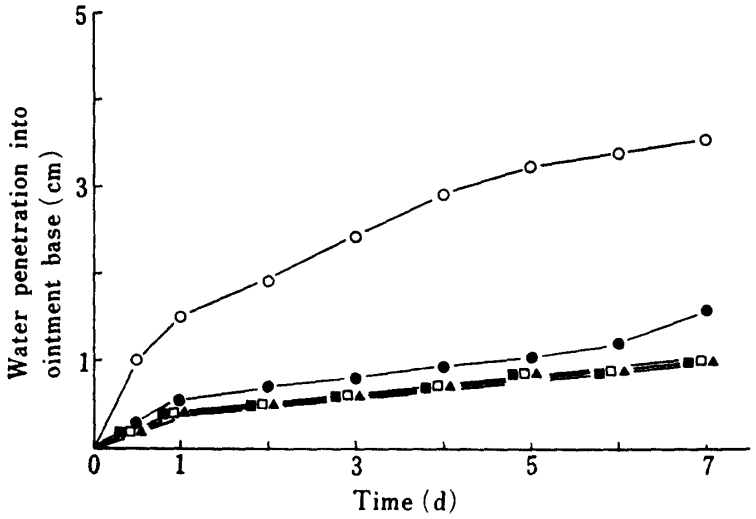

Fig. 5. Differences in Water Penetration among the Ointment Bases at 37°C

○: No. 1 ointment base, ▲: No. 2 ointment base, ■: No. 3 ointment base, □: No. 4 ointment base, ●: No. 5 ointment base. Each value represents the mean of four experiments.

method using a spatula, and a fusion method, on *in vitro* drug release from the ointment base. It was observed that the mechanical incorporation method gave a higher rate of drug release than the fusion method. This result was shown to be due to the differences in viscosity and in drug solubility between the two ointment bases prepared by the different techniques.

The results of the present study confirm that the physical properties of the ointment base, especially the viscosity, play an important role in *in vitro* drug release from the base.

References and Notes

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