[Chem. Pharm. Bull. 30(3) 985—991 (1982)]

Effects of Water-Soluble Polymers on the Crystalline Conversion of Prednisolone in Oil-in-Water Type Ointment Bases[1,2]

Fusao Kaiho,* Teruko Ishibashi, and Yuriko Kato

Faculty of Pharmaceutical Sciences, Sciences University of Tokyo, Ichigaya Funagawara-machi, Shinjuku-ku, Tokyo, 162, Japan

(Received July 29, 1981)

The effects of methylcellulose (MC) and hydroxypropylcellulose (HPC) on oil-in-water (o/w) type ointment bases and the crystalline conversion from the anhydrous form of prednisolone (A-PD) to its hydrated form (C-PD) in such o/w type ointment bases were studied.

The weight loss of the base, that is the volume of water released from the base, was measured in dry conditions and at a low temperature (5°C). The weight loss of the base without MC or HPC (No. 1 base) was about 7% in 10 d. On the other hand, the weight losses of the base containing MC (No. 3 base), and that containing HPC (No. 6 base) were about 1% and 4% under the same conditions, respectively.

The yield value of each of the bases Nos. 1, 3, and 6 was measured with a spreading meter. The yield value of No. 1 base was smaller than that of the other bases for 24 h after preparation at room temperature (25°C). The yield value of No. 3 base became lower and that of No. 6 base became slightly greater than that of 24 h for 7 d after preparation upon storage at room temperature and humidity (25°C). However, the yield value of No. 1 base increased after 7 d.

The crystalline conversion of A-PD in o/w type ointment base was measured by the use of an X-ray diffractometer. A-PD was entirely converted into C-PD in No. 1 base in only 1 d at 5°C. On the other hand, when MC or HPC was incorporated in the base, the conversion of A-PD to C-PD was retarded. The periods required for complete crystalline conversion from A-PD to C-PD in the bases (Nos. 2—4) containing MC and the bases (Nos. 5—7) containing HPC were about 20—30 d and 3—18 d, respectively.

Furthermore, *in vitro* release of PD from No. 1 base without MC and from No. 2 base containing MC were studied for 24 h after preparation at 5°C. Since A-PD was entirely converted into C-PD after 24 h at 5°C, the amount of PD released from No. 1 base was less than that of immediately after preparation, whereas the release pattern of PD from No. 2 base was the same as that from the base immediately after preparation since crystalline conversion did not occur in No.2 base. In addition, the release of PD from No.4 base was studied for 10 d after preparation at 5°C. The amount of PD released from No. 4 base after 10 d was the same as that of immediately after preparation, since crystalline conversion of PD did not occur in this base.

Water-soluble polymers such as MC and HPC act as protective colloids, and so the structure of the emulsion in the ointment base is stabilized. The structure of the emulsion in the base including water-soluble polymer is stabilized even at low temperature where the o/w type emulsion structure normally deteriorates.

It is suggested that water-soluble polymer is an effective additive to o/w type ointment bases.

Keywords——methylcellulose; hydroxypropylcellulose; oil-in-water type ointment base; weight loss; prednisolone; X-ray diffraction; crystalline conversion; *in vitro*; drug release

Many drugs containing corticosteroid hormones for external application have been developed and marketed for use in cases of dermatosis. If the conditions and methods of storage of these drugs from the time of preparation to use are not appropriate, the corticosteroid hormone in the ointment may decompose, and crystal growth and crystalline conversion in case having polymorphism may reduce the effectiveness of the drug. Thus, it is important to consider the storage conditions.

In a previous paper, we discussed the crystalline conversion from the anhydrous form

of prednisolone (A PD) to its hydrated form (C-PD) in oil-in-water (o/w) type ointment base, and found that the lower the storage temperature of the ointment bases containing A-PD, the more easily the conversion of PD from A-PD to C-PD occurred. Furthermore, it was found that this crystalline conversion of PD in o/w type ointment was due to deterioration of the o/w type emulsion in the ointment. Thus, since the conversion in the ointment was irreversible, it could be used as a measure of the stability of o/w type ointment containing A-PD.[3,4]

In the present study, we attempted to stabilize the emulsion in o/w type ointment and to retard the crystalline conversion of A-PD in the oitment.

Water-soluble polymers can act as protective colloids, and some kinds of polymer, *i.e.* methylcellulose (MC), hydroxypropylcellulose (HPC), hydroxyethylcellulose, sodium carboxymethylcellulose, soluble starch, carrageenan, and pectin, were tested for effect on the crystalline conversion of A-PD in the ointment at 5°C in preliminary examinations.

Consequently, it was found that MC and HPC could retard the crystalline conversion of A-PD in ointment. However, other polymers had little effect, and thus MC and HPC were further examined in the present study.

Experimental

Preparation of PD——The anhydrous PD (A-PD) used was recrystallized from acetone and sifted with a 100 mesh sieve.

Preparation of Ointment and its Storage——The o/w type ointment bases (Nos. 1—7) employed for this research were prepared according to the formulae in Table I.

Table I. Formulae of Oil-in-Water Type Ointment Bases

Composition[a]	Ointment No.						
	1	2	3	4	5	6	7
White petrolatum	25	25	25	25	25	25	25
Stearyl Alcohol	22	22	22	22	22	22	22
Sodium lauryl sulfate	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Propylene glycol	12	12	12	12	12	12	12
Methylcellulose	—	0.04	0.2	0.4	—	—	—
Hydroxypropylcellulose	—	—	—	—	0.04	0.2	0.4
Puirfied water, as required To make about	100	100	100	100	100	100	100

a) In grams.

MC (100 CPS, Nakarai Chemical Co. Ltd.) and HPC (150—200 CPS, Tokyo Kasei Kogyo Co, Ltd.) used as water-soluble polymers were prepared at various concentrations in aqueous solution in advance and were incorporated in the ointment bases (Nos. 2—7) in place of the same volume of water as in No. 1 base. A-PD was incorporated into the ointment bases (Nos. 1-7) up to 10% concentration, and the final products were packed into wellclosed containers and stored at the controlled temperature of 5°C.

X-Ray Diffraction——A Geigerflex model 2012 X-ray diffractometer (Ni-filter, Cu-$K\alpha$ radiation) manufactured by Rigaku Denki Co. Ltd. was used in this work to measure the X-ray diffraction pattern of the ointment base. The ointment was smeared on a glass holder for measurement.

Measurement of the Weight Loss of the Ointment Bases——Samples of Nos. 1, 3, and 6 bases without PD were packed (equal volumes corresponding to about 5 g) in open containers and placed in a desiccator containing about 200 g of silica gel as a drying agent. These samples were stored at the controlled temperature of 5°C, and were weight before and after storage. The loss in weight was taken as the loss of water from the base.

Measurement of the Yield Value——The yield values of Nos. 1, 3, and 6 bases were measured with a spreading meter manufactured by Rigosha Co. Ltd. A sample of each of the bases had previously been exposed to room temperature and humidity (25°C) for 24 h. In addition, after 1 week the yield values of the same samples were measured again.

The yield value of the samples was calculated as:

$$\sigma = \frac{11960\,GV}{\pi D} \qquad \text{Eq. 1}$$

where σ is the yield value (dyn/cm^2), G is the weight of glass plate (g), V is the volume of sample (cm^3) and D is the diameter of spreading of the sample under the glass plate (cm).[5]

***In Vitro* Release of PD from Ointment Base**——*In vitro* releases of PD from Nos. 1, 2, and 4 bases were measured according to the method described in a previous paper.[4]

The samples were prepared by incorporation 5% A-PD in the ointment bases (Nos. 1, 2, and 4), and *in vitro* release tests of Nos. 1 and 2 bases were carried out after storage for 24 h at 5°C, while No. 4 base was tested after storage for 10 d at 5°C.

Results and Discussion

Effects of Water-Soluble Polymers on o/w type Ointment Bases

Figure 1 shows the weight losses of Nos. 1,3, and 6 bases on aging at 5°C.

The weight loss of No. 1 base without the polymer was about 7% in 10 d at 5°C. On the other hand, those of No. 3 base containing MC and of No. 6 base containing HPC were about 1% and 4% respectively.

As may be seen from these results, the weight loss of a base was inhibited when a water-soluble polymer such as MC or HPC was incorporated in the base.

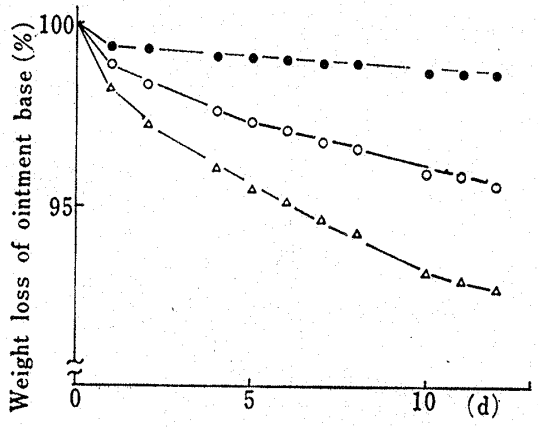

Fig. 1. Effects of Water-Soluble Polymer on the Weight Loss of the Ointment Bases at 5°C

Key: △, No. 1 ointment base; ●, No. 3 ointment base; ○, No. 6 ointment base.
Each value represents the mean of four experiments.

Table II. Yield Values of Oil-in-Water Type Ointment Bases stored for 1 d and 7 d at 25°C (dyn/cm^2)

Ointment No.	After 1 d	After 7 d
1	22347	30943
3	27377	22347
6	26181	26571

Each value represents the mean of two experiments.

Table II shows the yield values of Nos. 1, 3, and 6 bases that had been exposed to room temperature and humidity (at 25°C) in open containers for 24 h and 7 d. Since there was little difference in yield value measured with the spreading meter among the three bases stored at 5°C, these samples were exposed to room temperature (at 25°C) and measured.

The yield values of Nos. 3 and 6 bases containing a polymer were greater than that of No. 1 without polymer for 24 h after preparation. After 7 d, the yield value of No. 3 base was lower and that of No. 6 base was slightly greater than that at 24 h. On the other hand, No. 1 base showed an increase of yield value.

In an emulsified ointment base such as o/w type, evaporation occurs when the surface of the emulsion is exposed to the atmosphere, or when the product is stored for extensive periods of time.[6] Thus, the viscosity of emulsified bases increases in proportion to the water loss.

Generally, the lower the temperature of storage, the more readily the deterioration of the o/w type emulsion in the base occurs, and thus water is released readily from the emulsion in the base as the storage time increases.[7–9]

When the emulsified base is exposed to dry conditions at a low temperature (5°C), the water released from the emulsion readily evaporates off, and the weight of the ointment decreases. However, if it contains MC or HPC, the structure of the emulsion in the ointment base is stabilized, and the release of water from the emulsion is inhibited.[10]

Thus, the weight loss, *i.e.*, the loss of water from the base, of Nos. 3 and 6 bases was less than that from No. 1 base after storge for 10 d at 5°C.

As there are differences in water affinity and in protective colloid effect between MC and HPC, these may account for the difference in the water evaporation and the yield value between Nos. 3 and 6 bases. MC is obtained by partially replacing hydroxyl groups in the celluclose molecule with methoxyl groups, and as steric hindrance occurs within the MC molecule, water molecules easily approach that of the hydroxyl group.[10] As a result, the water affinity of MC is high. Thus, even on storage in dry conditions, the evaporation of water from No. 3 base was less than from other bases. Since the MC in the No. 3 base absorbed water from the atmosphere at room temperature, the yield value of its base exposed for 7 d was lower than that after 24 h.

Some polyols have been used as humectants to control the evaporation of water from an emulsified base, but their actions as humectant agents have not been found to be very effective.[6] Propylene glycol was employed as a humectant in this study and was incorporated in the bases. However, the volume of evaporated water from No. 1 base with addition of propylene glycol only was much more than from Nos. 3 or 6 base.

The emulsified bases seem to lose less water from the base and thus are better bases when a water-soluble polymer such as MC and a polyol are used together as humectants.

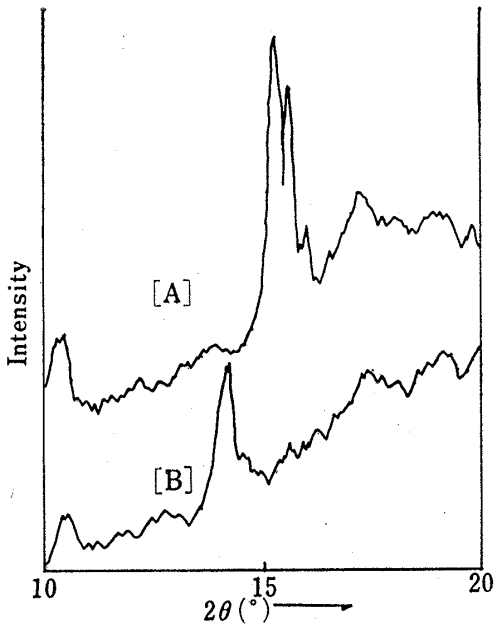

Fig. 2. Changes of X-Ray Diffraction Patterns of Prednisolone from Anhydrate (Form A) to Hydrate (Form C) in o/w Type Ointment Base (No. 1) stored at 5°C

[A]: immediately after preparation, [B]: stored for 1 d.

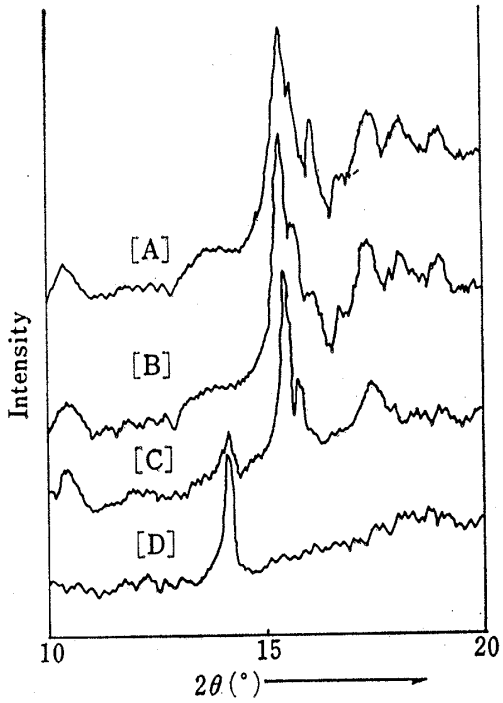

Fig. 3. Changes of X-Ray Diffraction Patterns of Prednisolone from Anhydrate (Form A) to Hydrate (Form C) in o/w Type Ointment Base (No. 3) stored at 5°C

[A]: immediately after preparation, [B]: stored for 3 d, [C]: stored for 7 d, [D]: stored for 28 d.

Crystalline Conversion of PD in Ointment Bases

The crystalline forms of A–PD and C–PD in the ointment bases can be identified by a reported X-ray diffraction method.[3]

Figure 2 shows the change in the X-ray diffraction patterns of A–PD in No. 1 base without water-soluble polymer at 5°C. A–PD in No. 1 base was entirely converted into C–PD in only one day at 5°C.

On the other hand, in No. 3 base, the peak due to C–PD in the X-ray diffraction patterns (2θ, 14.2°) began to appear after 7 d, whereas the A–PD peaks (2θ, 15.2° and 15.8°) began to diminish. All of the diffraction peaks of A–PD in No. 3 base were entirely changed into those of C–PD after about 28 d at 5°C, as shown in Fig. 3.

The crystalline conversion from A–PD to C–PD in ointment base is summarized in Fig. 4. The vertical axis of the left figure [A] shows the period of initial crystalline conversion of PD from A–PD to C–PD, and that of the right figure [B] shows the period required for the complete crystalline conversion of PD in ointment bases at 5°C. The horizontal axis in both figures shows the concentration of water-soluble polymers in purified water incorporated in the ointment bases.

The higher the concentration of water-soluble polymer in the ointment base, the slower was the crystalline conversion from A–PD to C–PD. For example, in No. 2 base, A–PD began

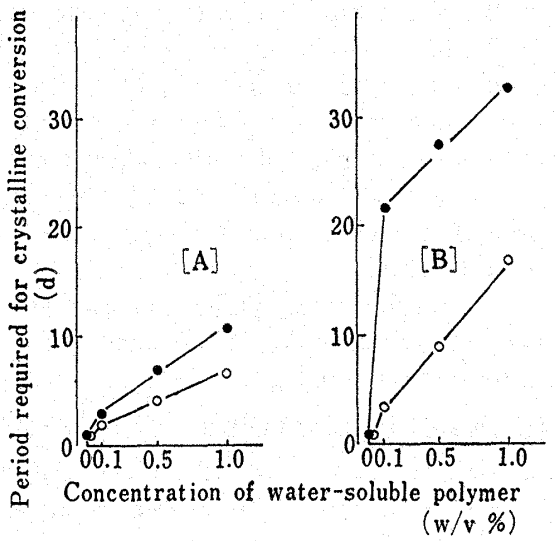

Fig. 4. Effects of the Concentration of Water-Soluble Polymer incorporated in Ointment Bases on Crystalline Conversion of Prednisolone from Anhydrate (Form A) to Hydrate (Form C)

Key: ●, methylcellulose; ○; hydroxypropylcellulose.
The vertical axis of the left figure [A] show the period of initial crystalline conversion of prednisolone from anhydrate to hydrate and that of the right figure [B] shows the period required for the complete crystalline conversion of anhydrate prednisolone. The horizontal axis of both figures shows the concentration of water-soluble polymers in purified water incorporated in the ointment bases.

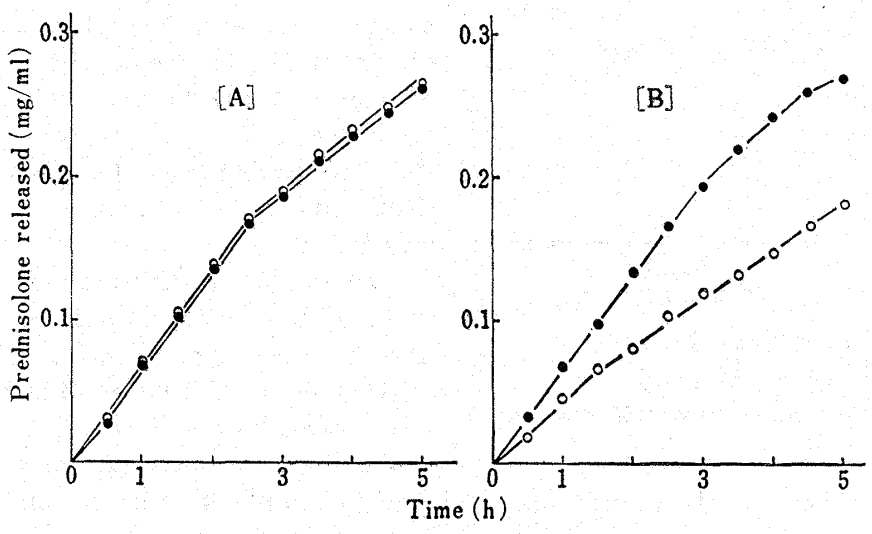

Fig. 5. Release of Prednisolone from o/w Type Ointment Bases

Key: ○, No. 1 ointment base; ●, No. 2 ointment base.
Left [A] and right [B] figures show the release patterns of prednisolone from o/w type ointment base immediately after preparation and after storage for 1 d at 5°C, respectively.

to change into C–PD after 3 d at 5°C, and was completely converted into C–PD after 22 d. On the other hand, in No. 3 base, A–PD began to change into C–PD after 10 d, and was completely converted into C–PD after about 33 d.

The crystalline conversion of PD from A–PD to C–PD in o/w type ointment base is due to the deterioration of the o/w type emulsion in the ointment base.[4] When the emulsion deteriorates, A–PD dissolves in water released from the emulsion, and accordingly C–PD is deposited in the ointment. This crystalline conversion of A–PD in the ointment bases is fast at a low storage temperature, since the lower the storage temperature, the more easily the deterioration of the emulsion occurs.

The emulsion structure in the ointment base was stabilizaed by MC and HPC, which act as protective colloids, and the crystalline conversion from A–PD to C–PD in the bases also seems to be retarded.

The difference of effect on the crystalline conversion from A–PD to C–PD between MC and HPC was due to the differences of the protective colloid action and water affinity between these two polymers.[10]

In Vitro Release of PD from Ointment Base

Figure 5-[A] shows the release properties of PD from Nos. 1 and 2 bases immediately after preparation. Similar release patterns of PD from the two bases were seen.

When the Nos. 1 and 2 bases containing A–PD were stored for 24 h at 5°C after preparation, the release pattern of PD from No. 2 base was the same as that seen immediately after preparation, and the amount of PD released from No. 1 bases decreased, as shown in Fig. 5-[B].

The decrement of release of PD from No. 1 base was due to the crystalline conversion from A–PD, which has a higher solubility in water than the hydrated form, to C–PD in the oinment base at 5°C.[4,11]

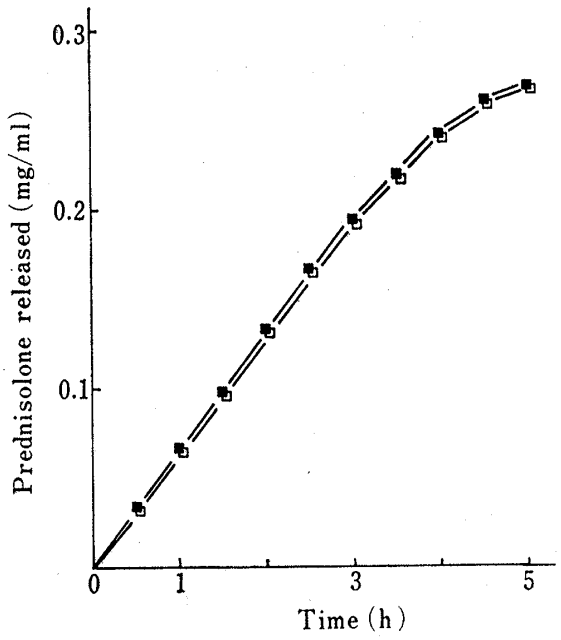

Fig. 6. Release of Prednisolone from No. 4 Ointment Base

Key: □, immediately after preparation; ■, after storage for 10 d at 5°C.

As the crystalline conversion of A–PD did not occur in No. 2 base after 24 h at 5°C, as shown in Fig. 4, the amount of released PD from this base was the same as that immediately after preparation.

Similarly, the amount of released PD from No. 4 base after storage for 10 d was the same as that immediately after preparation, as shown in Fig. 6, since the crystalline conversion of A–PD did not occur in No. 4 base after 10 d at 5°C. Furthermore, it was found that the amount of PD released from bases (Nos. 2 and 4) did not depend on the concentration of MC.

In order for the suspended drugs in the ointment base to be absorbed into the skin, they have to be soluble. Therefore, the crystalline conversion of a drug to another crystalline form possessing lower solubility will affect the availability. Thus, it appears that a water-soluble polymer such as MC or HPC can stabilize the emulsion structure in ointment bases and provide more effective bases for external therapeutics.

References and Notes

1) This paper forms Part III of "Studies of Crystalline Medicaments in Ointment." Preceding paper,

Part II: F. Kaiho, Y. Goto, and Y. Kato, *Chem. Pharm. Bull.*, **28**, 2240 (1980).
2) A part of this work was presented at 101st Annual Meeting of the Pharm. Society of Japan, Kumamoto, April 1981.
3) F. Kaiho, Y. Takigawa, A. Ando, and Y. Kato, *Yakugaku Zasshi*, **99**, 1068 (1978).
4) F. Kaiho, Y. Goto, and Y. Kato, *Chem. Pharm. Bull.*, **28**, 2240 (1980).
5) A. Voet and J.S. Brand, *Am. Ink Maker*, **28**, 28 (1950).
6) G.C. Henney, R.V. Evanson, and G.J. Sperandio, *J. Soc. Cosm. Chem.*, **9**, 329 (1958).
7) K. Shinoda and H. Saito, *J. Colloid and Interface Sci.*, **30**, 258 (1969).
8) K. Okamoto and H. Oishi, *Yakuzaigaku*, **37**, 52 (1977).
9) S. Fukushima, M. Yamaguchi, and F. Harusawa, *J. Colloid and Interface Sci.*, **59**, 159 (1977).
10) M. Nakamura (ed.), "Suiyosei Kobunshi," Kagaku Kogyo shya, TOKYO, 1973, p. 59, and 228.
11) D.E. Wurster and P.W. Taylor, *J. Pharm. Sci.*, **54**, 670 (1965).