Chem. Pharm. Bull. 28(7)2240—2243(1980)

In Vitro Release of Prednisolone from Oil-in-Water Type Ointment.[1] The Effect of Crystalline Conversion on Drug Release

Fusao Kaiho, Yoshiaki Goto, and Yuriko Kato

Faculty of Pharmaceutical Sciences, Science University of Tokyo[2]

(Received February 5, 1980)

The effects of crystalline conversion from the anhydrous form of prednisolone (A-PD) to its hydrated form (C-PD) on prednisolone (PD) release from o/w type ointment was studied *in vitro* at 37° and 5°, by using a diffusion cell and X-ray diffractometer.

The conversion of A-PD in the ointment (A-PD ointment) into C-PD started on incubation for 4 days at 37° and the A-PD was entirely converted into C-PD after about 18 days. The longer the time of storage of the A-PD ointment at 37°, the less the release of PD from the ointment.

On the other hand, A-PD was entirely converted into C-PD in the ointment in only one day at 5°; the amount of PD released from the ointment was not dependent upon the time of storage and showed a constant release pattern.

The crystalline conversion from A-PD to C-PD in the ointment is apparently due to the deterioration of the o/w type emulsion (in the ointment) with the passage of time. When the emulsion deteriorates, the A-PD dissolves in water released from the emulsion, and accordingly hydrated prednisolone (C-PD) is deposited in the ointment to an increasing extent.

The reduction of PD release from the ointment stored at 37° is apparently due to the different solubilities of A-PD and C-PD in water.

It is suggested that emulsion type ointment should be stored under suitable conditions.

Keywords——prednisolone; o/w type ointment; X-ray diffraction; crystalline conversion; *in vitro*; drug release; diffusion cell; HPLC

Many attempts have been made to investigate drug release from ointments *in vitro*, and also to examine the findings theoretically.[3]

Furthermore, the physicochemical properties of the ointment base and the drug also influence drug release from the ointment, and in particular, phase conversion and growth of drug crystals in the ointment seem to reduce the amount of drug released from the ointment.[4]

However, it appears that little detailed attention has been paid to the effect of different crystal forms arising from phase conversion on the drug release from the ointment.

This paper describes the relation between the phase conversion and the release of prednisolone when it is mixed by kneading into o/w type ointment.

Experimental

Preparation of Ointment and Its Storage——Modified hydrophilic ointment base was prepared according to the formula in Table I.

1) This paper forms part II of "Studies of Crystalline Medicamens in Ointment." Preceding paper, Part I: F. Kaiho, Y. Takigawa, A. Ando, and Y. Kato, *Yakugaku Zasshi*, **99**, 1068 (1979).
2) Location: *Ichigaya Funagawara-machi, Shinjuku-ku, Tokyo, 162, Japan.*
3) F.M. Plakogiannis and M. Yaakob, *Pharm. Acta Helv.*, **52**, 236 (1977); M. Nakano and N.K. Patel, *J. Pharm. Sci.*, **59**, 985 (1970); D.E. Loveday, *J. Soc. Cosm. Chem.*, **12**, 224 (1961); T. Higuchi, *J. Soc. Cosm. Chem.*, **11**, 85 (1960); T. Higuchi, *J. Pharm. Sci.*, **50**, 874 (1961); K. Kakemi, H. Kameda, M. Kakemi, M. Ueda, and T. Koizumi, *Chem. Pharm. Bull.*, **23**, 2109 (1975); H. Shinkai, *Yakugaku Zasshi*, **89**, 365 (1969); *etc.*
4) J. Haleblian and W. McCrone, *J. Pharm. Sci.*, **58**, 911 (1969); Y. Kato and Y. Watanabe, The 93rd Annual Meeting of the Pharm. Society of Japan, Tokyo, April, 1973.

Table I. Formula for o/w Type Ointment

Composition[a]	
White Petrolatum	25.0
Stearyl alcohol	22.0
Sodium lauryl sulfate	1.5
Propylene glycol	12.0
Purified water	39.5

a) In grams.

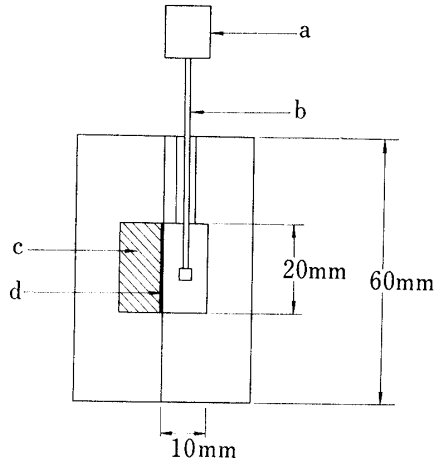

Fig. 1. Diagramatic Section of the Apparatus Used to Study Drug Release from Ointment

a: motor, b: stirrer, c: ointment, d: cellophane membrane.

The anhydrous form of prednisolone (A-PD) recrystallized from acetone was sifted with a 100 mesh sieve, and was incorporated mechanically into the hydrophilic ointment base up to 10% concentration.

The final product was packed into a well-closed container and stored in a temperature controlled-reservoir at 5° or 37°.

Release from the Ointment——The release of prednisolone from the ointment was determined by using diffusion cells as shown in Fig. 1.

One side of the cells was filled with A-PD ointment; this side was separated by a cellophane membrane from the other side, which was filled with saline solution. The cells was immersed in a constant-temperature bath (37°). The saline solution was preheated before pouring into the compartment.

Five μl aliquots of saline solution were taken from the compartment at suitable times and the concentration of prednisolone (PD) was determined by high performance liquid chromatography.

X-Ray Diffraction——A Gigerflex model 2012 X-ray diffractometer (Ni-filter, Cu-Kα radiation) manufactured by Rigakudenki Co. Ltd. was used in this work to measure the X-ray diffraction of the ointment. The ointment was smeared on a glass holder for measurement.

High Performance Liquid Chromatography (HPLC)——A Hitachi 635A HPLC machine was used under the following conditions; column, Hitachi Gel 3010, 3 mm i.d. × 50 cm; column temperature, room temperature; mobile phase, methanol; flow rate, 0.5 ml/min; detector, UV (245 nm); and range, 0.32 A.U.F.S. Five μl aliquots of sample solution taken with a micro-syringe was immediately injected into the machine.

Results and Discussion

Conversion of Prednisolone Crystals from the Anhydrous Form to the Hydrated Form in the Ointment

The crystalline forms of prednisolone, A (anhydrate) and C (hydrate), can be recognized from the different X-ray diffraction patterns (Fig. 2). These crystalline forms in the ointment can also be identified by a reported X-ray diffraction method.[5]

Fig. 3 shows the change in the X-ray diffraction patterns in the ointment against the time of storage of the A–PD ointment at 37°. The peak due to the hydrated form of prednisolone (C–PD) in the X-ray diffraction pattern (2θ, 14.2°) began to appear after 4 days, whereas the A–PD peaks (2θ, 15.2° and 15.8°) began to diminish. All of the diffraction peaks of A–PD in the ointment were entirely changed into those of C–PD after about 18 days.

On the other hand, A–PD was entirely converted into C–PD in the ointment in only one day at 5°, as shown in Fig. 4.

5) F. Kaiho, Y. Takigawa, A. Ando, and Y. Kato, *Yakugaku Zasshi*, **99**, 1068 (1979).

The above results are due to deterioration of the o/w type emulsion in the ointment with the passage of time.[6] When the emulsion deteriorates, the A–PD dissolves in water released from the emulsion, and accordingly C–PD is deposited in the ointment.[5] From Fig. 4, it can be seen that the lower the storage temperature, the more easily the deterioration of the emulsion occurs.

As this crystalline conversion from A–PD to C–PD in the ointment seems to be irreversible, it can be used as a measure of the stability of the o/w type ointment containing A–PD.

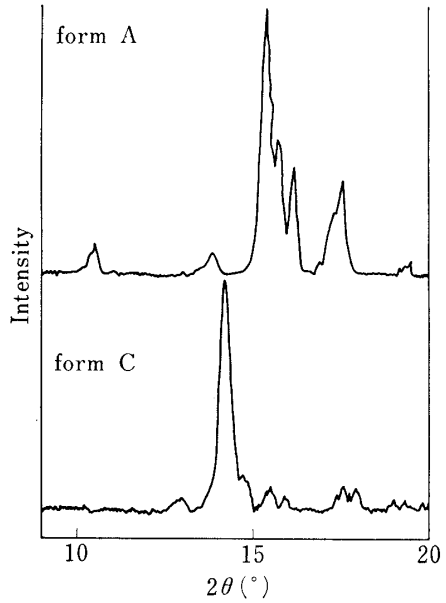

Fig. 2. X-Ray Diffraction Patterns of Prednisolone, Forms A and C

Release of Prednisolone from the Ointment

The release properties of PD from the ointment for 8 hr are illustrated in Figs. 5 and 6.

The longer the time of storage of the A–PD ointment at 37°, the less was the release of PD from the ointment (Fig. 5). On the other hand, it was observed that the amount of PD released from the ointment was not dependent upon the time of storage at 5°, and a constant release pattern was seen.

These results might be due to crystalline conversion from A–PD to C–PD in the ointment, as shown in Figs. 3 and 4. Generally, anhydrous forms of crystalline drugs possess higher solubility in water than hydrous forms.[7] It appears that the different solubilities in water of the two crystalline forms affect the release of PD from the ointment.

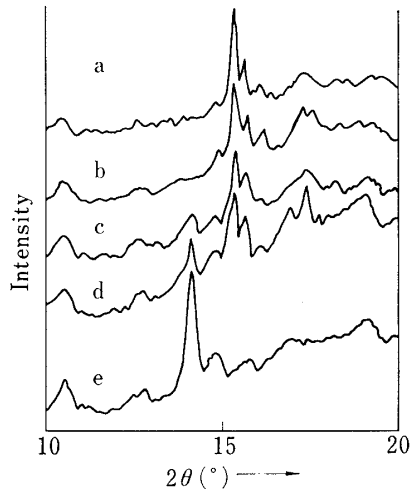

Fig. 3. Changes of X-Ray Diffraction Patterns of Prednisolone from Anhydrate (Form A) to Hydrate (Form C) in o/w Type Ointment stored at 73°

a: immediately after preparation,
b: stored for 2 days,
c: stored for 4 days,
d: stored for 8 days,
e: stored for 18 days.

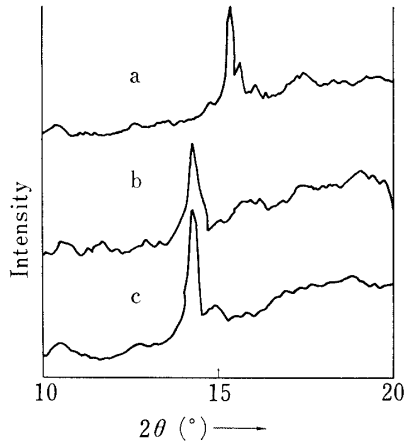

Fig. 4. Changes of X-Ray Diffraction Patterns of Prednisolone from Anhydrate (Form A) to Hydrate (Form C) in o/w Type Ointment stored at 5°

a: immediately afte preparation,
b: stored for 1 day,
c: stored for 18 days.

6) S. Fukushima, M. Takahashi, and M. Yamaguchi, *J. Colloid and Interface Sci.*, **57**, 201 (1976); S. Fukushima, M. Yamaguchi, and F. Harusawa, *J. Colloid and Interface Sci.*, **59**, 159 (1977).
7) D.E. Wurster and P.W. Taylor, *J. Pharm. Sci.*, **54**, 670 (1965).

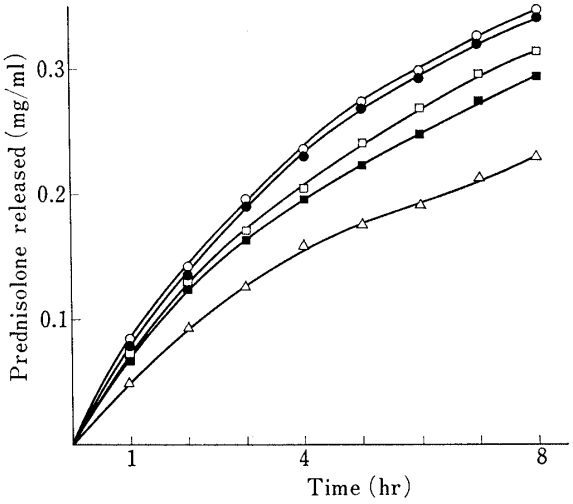

Fig. 5. Release of Prednisolone from o/w Type Ointment stored at 37°

Key: ○, stored for 1 day; ●, stored for 2 days; □, stored for 4 days; ■, stored for 8 days; △, stored for 18 days.

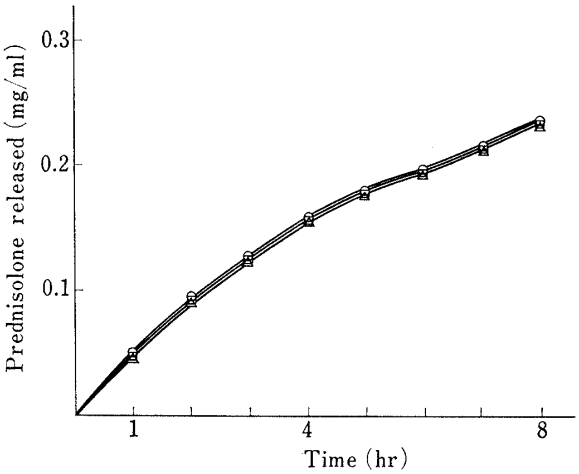

Fig. 6. Release of Prednisolone from o/w Type Ointment stored at 5°

Key: ○, stored for 1 day; □, stored for 4 days; △, stored for 18 days.

When the A–PD ointment was stored at 37°, A–PD was converted gradually into C–PD in the ointment as shown in Fig. 3. This crystalline conversion from A–PD to C–PD in the ointment corresponded well to the reduction of PD release (Fig. 5). However, as A–PD was converted into C–PD in a day at 5° (Fig. 4), the amount of PD released from the ointment was observed to be independent of the time of storage, though the release pattern of PD from ointment stored for 18 days at 37° was the same as that from ointment stored at 5°.

Since drug solubility is necessary for skin absorption, conversion of the drug to another crystalline form having lower solubility (A–PD to C–PD) will clearly affect the bioavailability. Thus, care is required in selecting suitable storage conditions for emulsion-type ointments.