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## Ointment-type Oral Mucosal Dosage Form of Carbopol containing Prednisolone for Treatment of Aphtha<sup>1,2)</sup>

MASAMI ISHIDA,\* NAOKI NAMBU, and TSUNEJI NAGAI

Faculty of Pharmaceutical Sciences, Hoshi University,<sup>3)</sup> Ebara 2-4-41,  
Shinagawa-ku, Tokyo 142, Japan

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The aim of this study was to investigate the availability of an oral ointment base which contains Carbopol-934 (CP) and sticks to the oral mucosa for the treatment of aphtha. The ointment base (CP ointment) was prepared by mixing 0, 10, 20 or 30% (w/w) CP with the following three kinds of ointment bases: white petrolatum (WP), hydrophilic petrolatum (HP), and absorptive ointment (AO). Finally, prednisolone was added to each base as a model drug.

The *in vitro* pharmaceutical properties of CP ointments were evaluated by penetrating, shearing stickiness and drug release tests. An *in vivo* absorption test using hamster cheek pouch was carried out by periodic measurement of the amount of drug remaining in the ointment applied.

In each ointment, the consistency, the shearing stickiness and % of prednisolone released increased with increase in the content of CP. In the *in vivo* absorption test, no absorption of prednisolone was detected from the ointments of HP and AO, while absorption occurred from the CP ointment with WP base.

**Keywords**—oral mucosal dosage form; Carbopol-934; prednisolone; aphtha; hamster cheek pouch; shearing stickiness

A drug in a dosage form applied to the oral mucosa is dissolved in the saliva first and then absorbed.<sup>4)</sup> The swallowing of dissolved drug thus cannot be ignored. Accordingly, in this route of administration, it is important to ensure that the drug is absorbed from the part of the dosage form in contact with the oral mucosa.

The authors reported previously on the absorption of insulin<sup>5)</sup> and lidocaine<sup>6)</sup> from a mucosal dosage form consisting of a core base and peripheral base, formed from hydroxypropyl cellulose-H and Carbopol-934 (CP). However, this dosage form seemed to have the following disadvantages: (1) A large amount of drug is not absorbed because the absorption area in contact with the oral mucosa is very small. (2) There was mechanical difficulty in preparing the device because the core base, which contains drugs, is so small. (3) Prolonged action is difficult to obtain when cacao butter is used as the core base. With the aim of overcoming these disadvantages, an ointment-type dosage form containing CP was prepared in the present work. It was considered that the area in contact with the oral mucosa in the ointment-type dosage form would be greater than that in the case of the solid dosage form, and it should be relatively easy to prepare the dosage form.

Therefore, in this study, the local activity of this ointment for aphtha was investigated using prednisolone as a model drug. At present, various commercial products are available such as Kenalog® and Aftach® which stick to the oral mucosa. However, there is no ointment-type oral mucosal dosage form using CP, though some use has been made of CP as a dermatological base.<sup>7-9)</sup>

### Experimental

**Materials**—CP and white petrolatum were commercial products. Lauromacrogol was supplied by Nikko Chemicals Co., Ltd., and prednisolone was supplied by Tokyo Kasei Co., Ltd.

**Preparation of the Oral Ointment using CP**—White petrolatum (WP), hydrophilic petrolatum (HP) and absorptive ointment (AO) were used as the original bases. Each base was prepared according to J.P.X.

CP was mixed completely with each base to give 0, 10, 20 or 30% CP. Then, prednisolone was added to each CP ointment at a concentration of 1%. These ointments containing CP are abbreviated as WP-CP, HP-CP and AO-CP ointments, respectively. CP and prednisolone that passed through a 200 mesh sieve were used for the investigation. Prednisolone was confirmed to have a drug content in the range of 95 to 105%.

**Penetration Test of CP Ointment**—The consistency of CP ointment was investigated by changing the content of CP in WP, HP and AO. A Yoshida penetrometer with a needle angle of  $60^\circ$  and needle weight of 51.94 g was used at  $25^\circ\text{C}$ . The depth of the needle was measured after 5 s.

**Shearing Stickiness Test of CP Ointment**—The shearing stickiness was investigated by changing the content of CP in the bases at  $25^\circ\text{C}$ . The apparatus used for the shearing stickiness test is shown in Fig. 1. The thickness of ointment between two glass plates was 0.3–0.4 mm. A string was wound by means of a motor at a constant speed of 140 cm/min and the value of shearing stickiness was represented by the reading on the spring balance when the two glasses separated. In this test, two cases were examined for each ointment: (1) without water and (2) containing 10% water.

**Release Test of Prednisolone from CP Ointment**—

About 0.5 g of each CP ointment was inserted into a cellulose tube through a 1 ml syringe, 5 ml of saline was added, and both sides of the tube were tied with a fishline. This tube was put into a Nessler test tube containing 30 ml of saline and shaken in an incubator at  $37 \pm 0.5^\circ\text{C}$ . Samples (2 ml) were taken at 2, 4, 6, 12, 24, 48 and 72 h. Each sample was filtered through a  $0.45\ \mu\text{m}$  membrane filter and the concentration of prednisolone was determined by high performance liquid chromatography (HPLC).

**In Vivo Absorption Test of Prednisolone using Hamster Cheek Pouch**—A male golden hamster weighing 80–100 g was anesthetized with Nembutal®, and the inside of the cheek pouch was cleaned with a tampon. About 0.5 g of a CP ointment was administered through a 1 ml syringe so as to reach the inside tip of the cheek pouch. Then, 0.5 ml of saline was added to it. To prevent the ointment being swallowed, the cheek pouch was sutured. Food and water were given freely for the period of the experiment.

The residual ointment in the cheek pouch was removed and put into a flask containing 100 ml of ethanol at  $70^\circ\text{C}$ , and the flask was shaken sufficiently. After cooling, the solution was made up to 200 ml with ethanol. The extract was filtered through a  $0.45\ \mu\text{m}$  membrane filter and prednisolone was determined by HPLC.

**Determination of Prednisolone in Release and Absorption Tests**—Prednisolone was determined by the use of a Shimadzu LC-3A high performance liquid chromatograph at a wavelength of 254 nm, using a  $250\ \text{mm} \times 4\ \text{mm}$  i.d. stainless-steel column packed with Lichrosorb RP-18. The solvent for the mobile phase was methanol/water = 80/20.

## Results and Discussion

### Selection of the Original Base

In general, it is believed that an oleaginous base is better than a water-soluble one for an oral ointment, since the saliva is aqueous. In the case of macrogol ointment or hydrophilic ointment as the original base, CP ointment containing 10% CP could not be prepared, while CP ointments containing less than 10% CP were easily dissolved by saliva and did not stick tightly to the oral mucosa. For these reasons, WP as an oleaginous base, HP and AO as a w/o type emulsion base were used as the original bases in this study.

### Consistency and Sticking Properties of the Three CP Ointments

Fig. 2 shows the effect of the content of CP on the consistency of each ointment in the penetrating test. In the case of 0% CP, the consistency of each ointment was in the order  $\text{HP} > \text{WP} > \text{AO}$ . When CP was added, the consistency increased with increase of CP in all CP

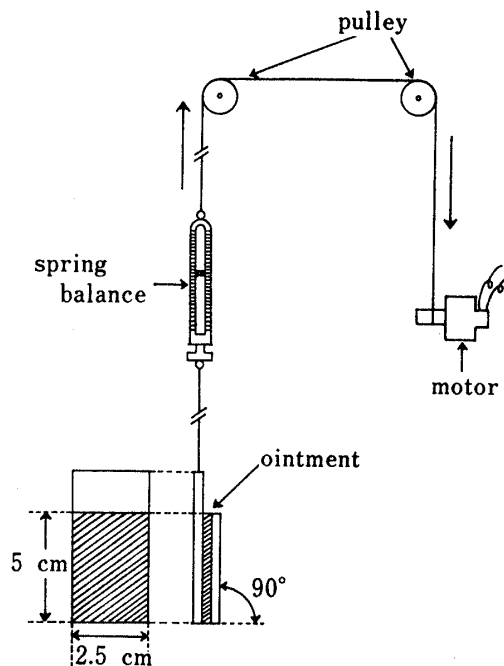


Fig. 1. Schematic Illustration of the Shearing Stickiness Test Apparatus

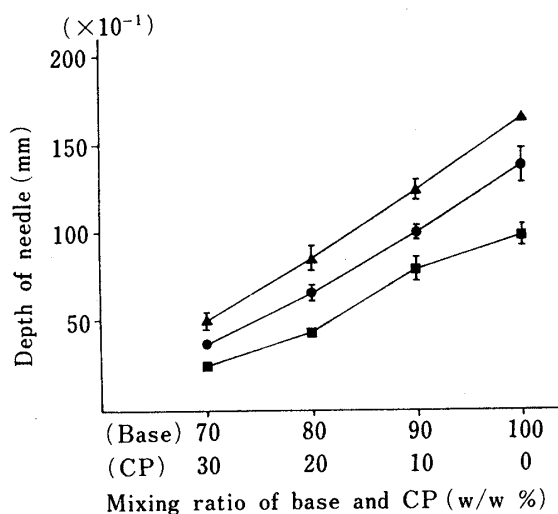


Fig. 2. Depth of Needle Penetration in the Penetrating Test for Various CP-containing Ointments

—●—, white petrolatum; —▲—, hydrophilic petrolatum; —■—, absorptive ointment. Each point represents the mean  $\pm$  S.E. of 5 determinations.

the stickiness of CP ointment to the oral mucosa. In this case too, the shearing stickiness increased with increase in the content of CP in all CP ointments. No difference was detected among the three CP ointments at 0–10% CP. However, at 20–30%, WP-CP ointment had a higher stickiness than the other two emulsion-type CP ointments, *i.e.* HP and AO, in contrast to the case without water. That is to say, because both of the emulsion-type CP ointments formed w/o type micelles with the addition of water, these ointments showed low stickiness. On the other hand, in WP-CP ointment, water was absorbed by CP alone because of the hydrophobic nature of WP. Consequently, the shearing stickiness of WP-CP ointment increased more than did those of the other ointments. From these results, it seemed that WP-CP ointment containing 20–30% CP was the best as regards stickiness to the oral mucosa.

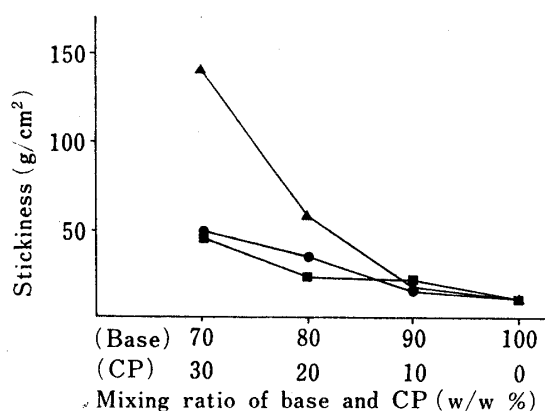


Fig. 3. Stickiness of Various CP-containing Ointments in the Shearing Stickiness Test

—●—, white petrolatum; —▲—, hydrophilic petrolatum; —■—, absorptive ointment.

ointments. In the case of 20–30% CP, the ointments were difficult to apply to the oral mucosa because of the high consistency.

Generally the sticking property of an adhesive plaster is estimated by a 90° or 180° peeling test and so on, but because the sticking property of the ointment could not be estimated by a peeling test, it was estimated in terms of the shearing stickiness using the apparatus shown in Fig. 1. In this test, as shown in Fig. 3, it was recognized that the shearing stickiness increased with increase in the content of CP. Though no difference in the shearing stickiness was detected among the three CP ointments with 0–10% CP, that of HP-CP ointment was over twice those of the other two CP ointments with 20–30% CP.

Fig. 4 shows the results obtained when 10% water was added to each CP ointment in order to investigate the effect of saliva on

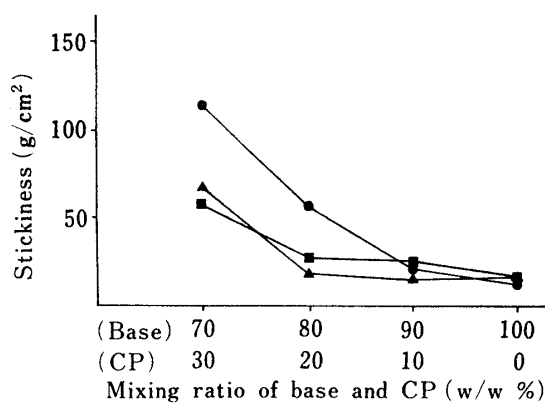


Fig. 4. Effect of Water on Stickiness in the Shearing Stickiness Test

—●—, white petrolatum; —▲—, hydrophilic petrolatum; —■—, absorptive ointment. Water content is 10% in each CP ointment.

### Release of Prednisolone from CP Ointment

The release profiles of prednisolone from CP ointments are shown in Fig. 5 for AO and in Fig. 6 for WP. The release of prednisolone from each ointment at 30% CP was better than that from each original base alone. It was considered that gel formation of CP was caused by water in the cellulose tube, and prednisolone was released easily from this gel-layer. Since no release of prednisolone was obtained without water in the case of 30% CP ointment, the gelation of CP is necessary for the release of prednisolone from CP ointment. In the case of HP-CP ointment, the release of prednisolone was not observed since HP-CP ointment was not gelled because of its poor wettability and high consistency.

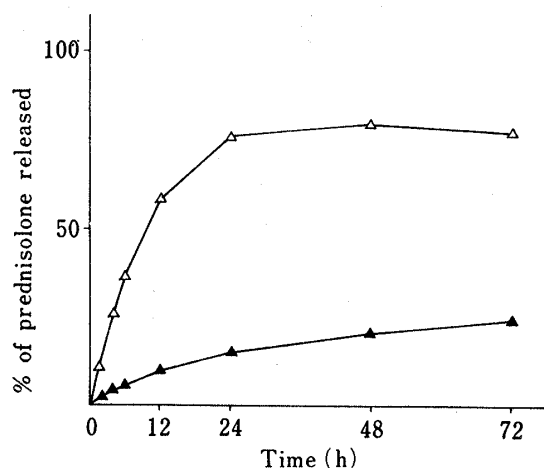


Fig. 5. Effect of CP on Release of Prednisolone through a Cellulose Membrane from CP Ointment with Absorptive Ointment

—△—, CP 30%; —▲—, CP 0%.

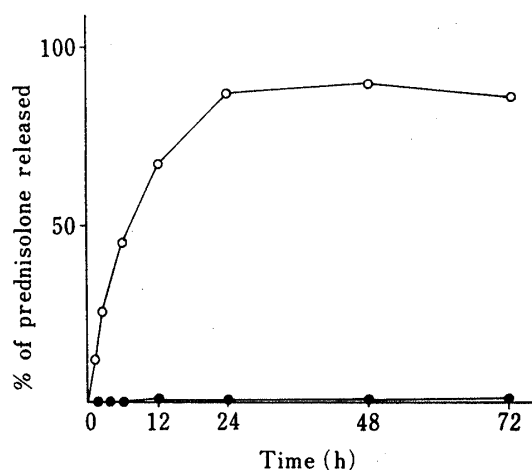


Fig. 6. Effect of CP on Release of Prednisolone through a Cellulose Membrane from CP Ointment with White Petrolatum

—○—, CP 30%; —●—, CP 0%.

### Absorption of Prednisolone from Hamster Cheek Pouch

In addition to the "general method for buccal absorption" reported by Beckett *et al.*,<sup>10)</sup> a method using a glass reflux apparatus was described by Ammo *et al.*<sup>11)</sup> and other procedures have been reported. However, in this ointment study, the above methods could not be employed to measure the amount absorbed. Therefore, we investigated the absorption of prednisolone by measurement of the residual amount of drug in the hamster cheek pouch by reference to the method reported by Tanaka *et al.*<sup>12)</sup>

In the case of AO and HP-CP ointments, no absorption of prednisolone was obtained after 48 h with 0 or 30% CP. Tanaka *et al.*<sup>12)</sup> reported that the absorption of salicylic acid from AO was greater than that from WP. Generally, AO and HP cannot be used on a wet surface. In this study, saline instead of saliva was added to the cheek pouch, so that absorption was not obtained, contrary to the case of Tanaka *et al.*<sup>12)</sup>

On the other hand, in the case of WP-CP ointment, absorption of prednisolone occurred at both 0 and 30% CP, as shown in Fig. 7. At 30% CP, about 18% of the prednisolone was absorbed after 3 h, but no further absorption occurred. In the case of WP original base alone, the absorption increased gradually up to 48 h. It was recognized that these results were related to the results of the release test. The consistency of 30% CP ointment is higher than that of the original base, and thus prednisolone might be absorbed only from the surface in contact with the oral mucosa. It was considered that the absorption of prednisolone took place only from the CP gel-layer formed by added water, so that the absorption rate was very fast, and ceased when no further drug was accessible. Therefore, increased absorption might

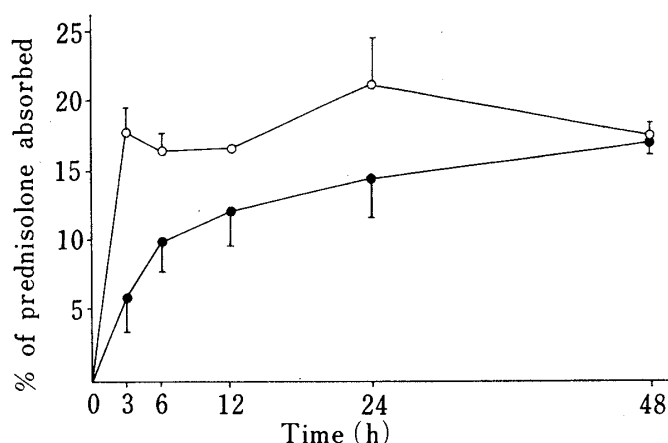


Fig. 7. Change in the Absorption of Prednisolone from Hamster Cheek Pouch after Administration of CP Ointment with White Petrolatum

—○—, CP 30%; —●—, CP 0%.

Each point represents the mean  $\pm$  S.E. of 4 determinations.

be obtained from a thick gel-layer if much water were added.

From the results of stickiness, release and absorption tests, it was recognized that WP-CP 30% ointment was the best ointment for treatment of aphtha among the three CP ointments, though it was difficult to apply to the oral mucosa. The original problem of small absorption area, mentioned in the introduction, was largely overcome. However, the prolonged action especially necessary for systemic action has not yet been obtained. It may be possible to obtain prolonged action by the use of a highly viscous and uniform gel ointment containing CP.

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#### References and Notes

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