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Highly Viscous Gel Ointment Containing Carbopol for Application to the Oral Mucosa[1)]

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A new type of highly viscous ointment containing Carbopol-934 (CP) for application to the oral mucosa was formulated. The release properties of Brilliant Blue FCF (B.B. FCF) and the absorption of sodium salicylate through the oral mucosa from the ointment were studied.

In release test using the agar gel bed method, there was no significant difference in % release of B.B. FCF after 12 h from ointments containing glycerin and polyethylene glycol (PEG) as excipients. However, the form of the ointment containing glycerin was maintained for 24 h whereas the ointment containing PEG liquefied. The 50% release time (T_{50}) decreased with increase of glycerin content, but the difference of water absorption was negligible. Therefore, the release rate of B.B. FCF was related to the consistency of CP gel ointment rather than to water absorption.

In vivo absorption of sodium salicylate from the ointment in hamster cheek pouch was also investigated. Absorption was fast from both 12.5 and 20% CP ointments, and the drug absorption was sustained for 5 h from 12.5% CP ointment.

Keywords——Carbopol-934; gel ointment; oral mucosa; agar gel bed method; Brilliant Blue FCF; hamster cheek pouch; sodium salicylate

The authors have investigated oral mucosal dosage forms containing Carbopol-934 (CP),[2-4)] which stick to the oral mucosa. In a previous report,[4)] it was recognized that drug release occurred only from the gel layer formed by saliva with ointment consisting of white petrolatum and CP (WP-CP ointment). However, it was necessary to cover the ointment with a hydrophobic membrane to protect the ointment from removal by the saliva and to form a gel with the drug solution beforehand in order to get good absorption of the drug through the oral mucosa. Under these conditions, little saliva entered the ointment.

Generally, the content of CP in gel ointments is from 1 to 10% and has never been over 10% in dermatological bases. In this study, we prepared a highly viscous CP gel ointment that could stick to the oral mucosa. In an *in vitro* experiment, Brilliant Blue FCF (B.B.FCF) was used as a water-soluble pigment to investigate the release properties from this gel ointment by reference to the method reported by Machida *et al.*[5)] In an *in vivo* experiment, sodium salicylate, a freely water-soluble drug, was used to investigate the systemic drug absorption in hamster cheek pouch by reference to the method reported by Tanaka *et al.*[6)]

Experimental

Preparation of CP Gel Ointment——CP gel ointment was prepared using glycerin or polyethylene glycol (PEG) as an excipient. PEG used was a mixture of 400 and 4000 in a mixing ratio of 2:1. In the release test, the ointment contained 1 g of CP, 3 g of glycerin or PEG and 1 ml of 0.5% B.B.FCF aqueous solution, 20, 60 and 20 w/w%, respectively. Experiments were also done with contents of 4, 5 and 6 g of glycerin.

Release Test Using Agar Gel Bed Method——About 500 mg of CP gel ointment was applied to the surface of a 30 ml gel bed of 1% agar in aqueous solution in a Petri dish of 90 mm diameter. The applied area of ointment was 20 × 20 mm and the thickness of ointment was 0.5 or 1.5 mm. The agar gel bed was kept in an incubator at 37 ± 1 °C

and the ointment was removed after 2, 4, 6, 8, 12 or 24 h. Each ointment was dissolved in water to make to 200 ml and the residual concentration of B.B.FCF thus released was calculated.

Water Absorption Test——CP gel ointment was applied to an aluminium foil of 20 × 20 × 0.5 mm thickness and kept in an incubator at 60 ± 0.1 °C. The weight was measured at 2, 4, 6, 8 and 24 h and the % of water absorbed was calculated.

***In Vivo* Absorption of Sodium Salicylate in Hamster Cheek Pouch**——Male golden hamsters weighing 80—100 g were anesthetized with Nembtal® and Phanobal®. The inside of the cheek pouch was cleaned with a tampon and about 0.5 g of gel ointment was administered through a 1 ml syringe so as to reach the inside tip of the cheek pouch. The changes in the amount of drug remaining in the cheek pouch and of the plasma levels were investigated using sodium salicylate as a model drug. Sodium salicylate was added as a solution to the bases at a concentration of 2%.

Determination of Plasma Salicylate Levels——The blood was collected from the jugular vein, and plasma was obtained by centrifugation at 3000 rpm for 10 min. To 0.5 ml of this plasma, 0.12 ml of 6 N HCl was added. After precipitation of protein, 10 ml of 1,2-dichloroethane was added. The mixture was shaken for 15 min and centrifuged at 3000 rpm for 10 min. Next, 3 ml of water and 0.25 ml of iron reagent (1 g of $Fe(NO_3)_3\ 9H_2O$ was dissolved in 0.07 N nitric acid to make 100 ml) were added to 5 ml of 1,2-dichloroethane, and the mixture was shaken for 10 min and centrifuged at 3000 rpm for 10 min. The colored upper phase was measured photometrically at 530 nm.

Determination of Residual Sodium Salicylate in Cheek Pouch——The whole residual ointment in the cheek pouch was taken and mixed sufficiently; 20 ml of water was added to a 100 mg sample (weighed exactly), and the salicylic acid extracted was determined photometrically in the same way as for the plasma level measurement.

Results and Discussion

Release Test Using the Agar Gel Bed Method

Figure 1 shows the results of a release test from CP gel ointment containing glycerin or PEG. There was no difference between the two cases after 12 h, but a significant difference was seen after 24 h (t-test; $p < 0.05$). The form of the gel ointment containing glycerin was retained

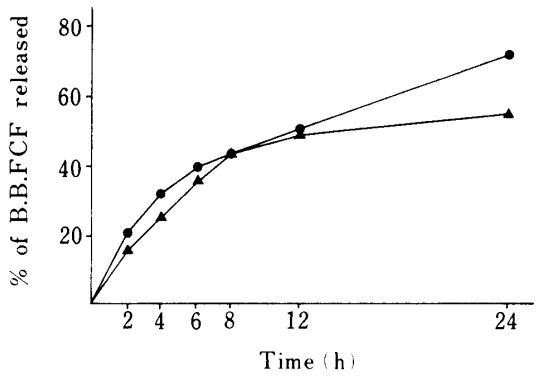

Fig. 1. Release Profiles of B. B. FCF from CP Gel Ointments Containing Glycerin or PEG by the Agar Gel Bed Method

—▲—, glycerin; —●—, PEG. (Each point represents the mean of 4 determinations.)

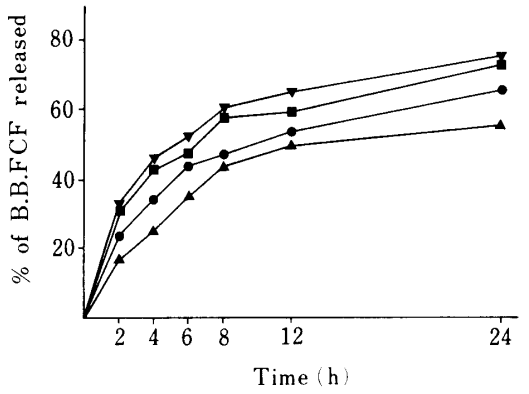

Fig. 2. Release Profiles of B. B. FCF at Various Contents of CP

—▲—, 20%; —●—, 16.67%; —■—, 14.29%; —▼—, 12.5%. (Each point represents the mean of 4 determinations.)

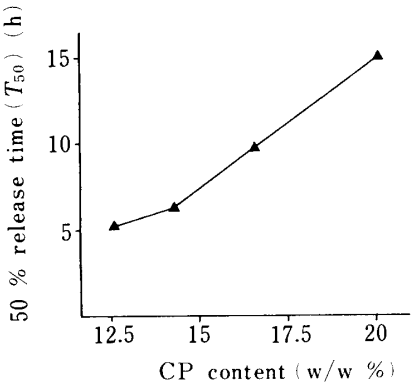

Fig. 3. Relation between T_{50} and CP Contents in Release Test

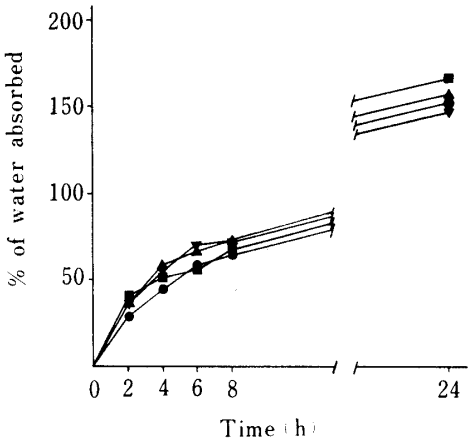

Fig. 4. Water Absorption Profiles of CP Gel Ointments at Various Contents of CP

—▲—, 20%; —●—, 16.67%; —■—, 14.29%; —▼—, 12.5%. (Each point represents the mean of 5 determinations.)

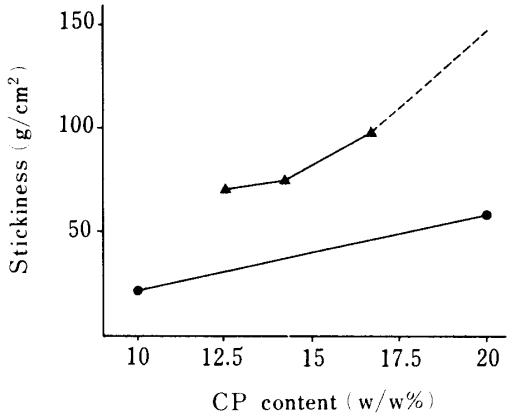

Fig. 5. Relation between CP Content and Stickiness in the Shearing Stickiness

—▲—, gel ointment; —●—, WP-CP olintment.

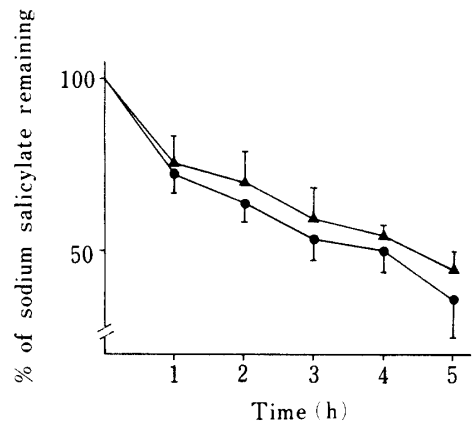

Fig. 6. Change of % of Sodium Salicylate Remaining after Administration of CP Gel Ointment

—▲—, 20%; —●—, 12.5%. (Each point represents the mean ±S.D. of 6 determinations.)

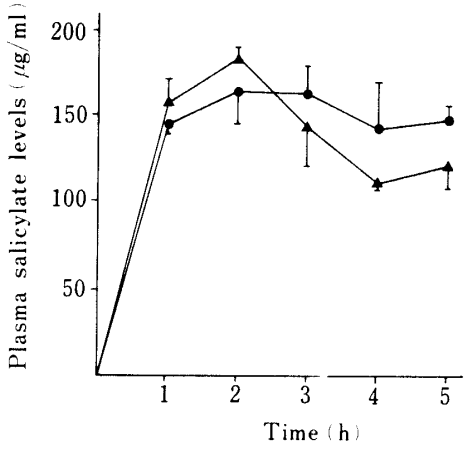

Fig. 7. Change of Plasma Salicylic Acid Levels after Administration of CP Gel Ointment

—▲—, 20%; —●—, 12.5%. (Each point represents the mean ±S.D. of 3 determinations.)

for 24 h, whereas the ointment containing PEG liquefied. In practice the ointment is unlikely to be applied in the oral cavity for 24 h. However, glycerin was used as an excipient of this CP gel ointment in further experiments.

As shown in Fig. 2, the percentage of B.B.FCF released was increased with a decrease of CP, and Fig. 3 shows the relation between the 50% release time (T_{50}) and the content of CP. T_{50} was calculated by the use of a log normal distribution. An approximately linear relationship was obtained between T_{50} and the content of CP (20, 16.67 and 14.29%). T_{50} for 12.5% CP was the smallest among the four. The thickness of ointment was 1.5 mm in this test, but the same result was obtained in the case of 0.5 mm thickness, which may be more appropriate in practice.

Water Absorption of CP Gel Ointment

As shown in Fig. 4, the CP content had no effect on the results in the water absorption test. Thus, the difference of T_{50} among CP gel ointments were due to the changes in the consistency and not to change in the water absorption. Therefore, under low moisture conditions, the release of the drug from CP gel ointment was better than that from WP-CP

ointment reported previously.[4]

Accordingly, the shearing stickiness of CP gel ointment was measured by means of the apparatus used in the previous report.[4] As shown in Fig. 5, the shearing stickiness of the gel ointment of 20% CP was over 150 g/cm^2 and was greater than that of WP-CP ointment containing 30% CP (WP-CP 30% ointment). The stickiness of the gel ointment of 12.5% CP was greater than that of WP-CP 20% ointment. In the case of WP-CP 20% ointment, application to the oral mucosa was difficult because of its high consistency, while this was not the case with the gel ointment of 14.29% CP.

In Vivo Absorption Test Using Hamster Cheek Pouch

The *in vivo* absorption test using a hamster cheek pouch was carried out as described in the previous report.[4] The percentage of sodium salicylate remaining and the plasma salicylate levels are shown in Figs. 6 and 7, respectively. The absorption test was carried out in two CP gel ointments containing 12.5 and 20% CP. The absorption of salicylic acid from 12.5% CP ointment was larger than that from 20% CP ointment. The absorption rate from both ointments was fast, and in the case of 12.5% CP ointment, the plasma level was well sustained for 5 h. It is considered that the drug absorption from a highly viscous gel ointment might be sufficient when the ointment is covered with a hydrophobic membrane. Therefore, in the case of this CP gel ointment, there was no need for gelation with saliva to make the absorption of the drug increase, and also the optimum pH could be selected easily, because the drug was added as a solution.

Further investigation is desirable to prepare a formulation with a more protective hydrophobic membrane and which sticks more adhesively to the oral mucosa.

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References and Notes

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