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Semisolid Bases containing Hydroxypropyl Cellulose[1,2]

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Intending to explore useful ointment bases containing hydroxypropyl cellulose (HPC), an investigation was made on the spreadability, washing-out time and drug release of combined mixtures of HPC with aqueous glycerine (Aq. G1), propylene glycol (PG) and polyethylene glycol (PEG).

The decrease of the spreadability due to the increase of concentration of HPC was remarkable in the low concentration, declining above 10% (w/v) in HPC/PG and above 14% (w/v) in HPC/PEG. HPC/PEG containing above 12% (w/v) lost the fluidity to take a gel-like state and this gel-like mixture indicated a typical thixotropic phenomenon. The washing-out time increased with the concentration of HPC, and it seemed to be related to the increase of viscosity. With the addition of 30% of zinc oxide as an insoluble drug, the decrease of spreadability was 23% at the largest, which was observed for HPC/Aq.G1. The spread radius at 2 min on the measurement for the sample of HPC/PEG (10: 100, w/v) after heating at 150° for 1 hr was 54% larger than that of the intact one, indicating the structure relating to the thixotropy of the mixture might be crushed by heating. The drug release from each mixture decreased with the increase of concentration of HPC. HPC/PEG showed the fastest drug release at the given spreadability below 4.1 cm.

As a result, it was shown that HPC would provide a promising material as bases for ointments and other semisolid preparations combining properly with Aq.G1, PG and PEG.

In a previous paper,[1] it was shown that hydroxypropyl cellulose (HPC) would be useful as a binder in a tablet making by direct compression combining properly with such disintegrators as potato starch and lactose. HPC dissolves in water and also in some kinds of organic solvents, giving a viscous and clear solution. Therefore, it may be useful to various kinds of pharmaceutical preparations. Actually, methyl cellulose and carboxymethyl cellulose sodium, which are water-soluble derivatives of cellulose as well as HPC, have been used as ointment bases so called "hydrogel bases."

Generally, hydrogel bases can be easily washed out and well adhered to mucous membrane or skin wet with secreting fluid, and thus these are applied to injured skin and also to eyes.[4]

Intending to explore useful ointment bases containing HPC, the present study was attempted to investigate the spreadability, washing-out time and drug release of the combined mixtures HPC/aqueous glycerine (abbriviated to HPC/Aq·Gl),[5] HPC/propylene glycol (HPC/PG) and HPC/polyethylene glycol 400 (HPC/PEG).

Experimental

Materials——Commercial propylene glycol (PG), glycerine J.P. VIII (G1), polyethylene glycol 400 J.P. VIII (PEG), zinc oxide J.P. VIII, agar powder J.P. VIII, gelatin J.P. VIII, and acrinol J.P. VIII were

1) This paper forms Part II of "Pharmaceutical Interactions in Dosage Form and Processing." Preceding paper, Part I: Y. Machida and T. Nagai, *Chem. Pharm. Bull.* (Tokyo), **22**, 2346 (1974).
2) A part of this work was presented at the 94th Annual Meeting of Pharmaceutical Society of Japan, Sendai, April 1974.
3) Location: *Ebara-2-4-41, Shinagawa-ku, Tokyo, 142, Japan.*
4) The Japan Pharmaceutical Association (ed.), "Chozai Shishin," 5th ed., Yakuji Nippo, Inc., Tokyo, 1972, pp. 126—128.
5) Aqueous glycerine consisted of water: glycerine (4: 1, v/v).

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used. Hydroxypropyl cellulose-L (HPC) supplied by Teijin Co. Ltd.[1] was sieved, and the portion passing through 100 mesh sieve was used as the sample.

Preparation of Mixed Sample——i) HPC/Aq.Gl: After HPC was added to glycerine and well stirred, purified water was added and stirred.

ii) HPC/PG: HPC was added gradually into propylene glycol with stirring.

iii) HPC/PEG: HPC was slightly soluble in polyethylene glycol 400 at room temperature. Therefore, the mixture of HPC/PEG was heated to about 90° on a water bath with stirring until the swelled particles of HPC disappeared.

The above three kinds of mixtures were used after kept standing overnight to remove the bubbles in the mixtures. In HPC/PEG containing more than 12% of HPC, however, the bubbles did not completely disappeared.

Measurement of the Spreadability of Mixture——This was done at 22±2° using a Rigosha spreadmeter. The volume of sample was 0.45 ml, and the weight of pressing glass plate was 115 g which was kept horizontally at 1.8 cm height and was dropped upon the measurement. Unless otherwise stated, the "spreadability" was represented by the radius of spread sample at 1 min after the glass plate was dropped.

In order to investigate the effect of insoluble drug on the spreadability of mixtures, zinc oxide was added to HPC/PEG (10: 100, w/v), HPC/PG (12: 100, w/v), and HPC/Aq.Gl (20: 100, w/v) each in concentrations of 10, 20, and 30%, then mixed on an ointment slab to prepare the sample.

In order to investigate the effect of heating on the spreadability of mixtures, 2 g of HPC/PEG (10: 100, w/v) and HPC/PG (12: 100, w/v) each was put in a petri-dish, wrapped with alminum foil, and after keeping at 150° for 1 hr, it was cooled to room temperature to prepare the sample.

In order to investigate the effect of freezing-defreezing on the spreadability of mixtures, the mixtures HPC/PEG (6: 100, w/v) and HPC/Aq.Gl (20: 100, w/v) were frozen in dry-ice/acetone and then defrozen at room temperature to prepare the sample.

Measurement of Washing-out Time of Mixture——The device is shown in Fig. 1. A brass wire of 2.5 mm diameter was adhered with epoxy resin to the glass plate of 3 mm thickness, 50 mm width and 200 mm length. A constant volume of sample was spread on the set position of this glass plate by packing the sample in the rectangular hole of 30 mm width, 10 mm length and 0.4 mm depth of the polyvinyl chloride plate placed on the above glass plate. The glass plate wearing the sample was installed with its brass wire to the stirring device of a Toyama Sangyo T-2HS type disintegration tester for J.P. VIII, and was moved up and down at the pace of 40 times/min in 800 ml of purified water at 37±2°. The sample spread on the glass plate was dissolved gradually and the time when the sample disappeared was measured to indicate the "washing-out time". The disappearance of the sample was observed always from a fixed direction.

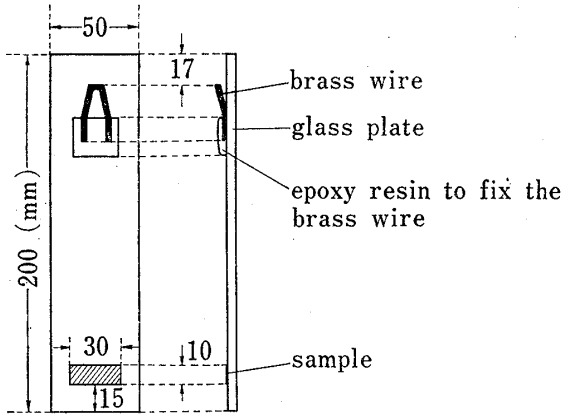

Fig. 1. Device for Measurement of Washing-out Time, which was installed to a Disintegration Tester for J.P. VIII

Measurement of the Drug Release from Mixtures——This was done by modifying the method by Miyazaki, *et al.* applied to the measurement of drug release from a suppository base.[6]

Fifteen ml of 1% (w/v) aqueous solution of agar was poured into each test tube of 1.5 mm diameter to make a gel bed. Then, 0.5 ml of 4% (w/v) aqueous solution of gelatin was added on it to get another gel bed. After 1 ml of each base containing 1% acrinol was set on this gelatin gel bed, the test tubes were kept at 20±2° for 24 hr and the distance of drug penetrated into the agar gel bed was measured. At this temperature, the gelatin layer was not denatured.

Result and Discussion

Relation of the Spreadability of Mixtures to the Concentration of HPC

Fig. 2 shows the change of the radii of samples containing 2, 6, and 20% (w/v) of HPC with the lapse of time after the glass plate of spreadmeter was dropped. HPC/Aq·Gl was of low viscosity and reached the limit of scale of the spreadmeter after about 5 sec in HPC/Aq·Gl (2: 100, w/v) and after 43 sec in HPC/Aq·Gl (6: 100, w/v). Therefore, radius of sample

6) J. Miyazaki and M. Takano, *Nippon Yakuzaishikyokai Zasshi*, 7, 222 (1955).

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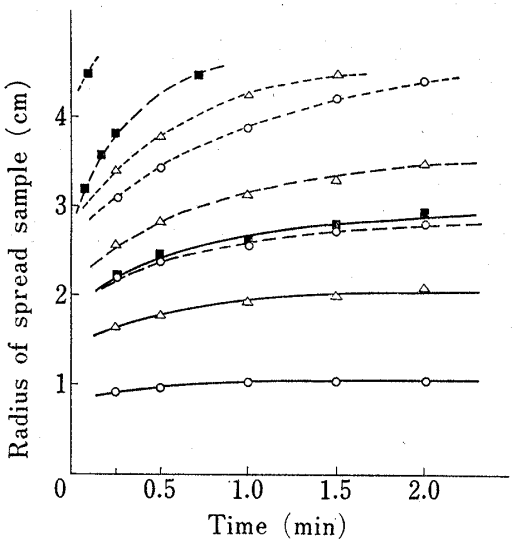

Fig. 2. Spreading Curves of Mixtures

Each symbol represents the mean of 3 determinations.

---■---: HPC/Aq·Gl (2: 100, w/v)
—■—: HPC/Aq·Gl (6: 100, w/v)
—■—: HPC/Aq·Gl (20: 100, w/v)
---△---: HPC/PG (2: 100, w/v)
—△—: HPC/PG (6: 100, w/v)
—△—: HPC/PG (20: 100, w/v)
---○---: HPC/PEG (2: 100, w/v)
---○---: HPC/PEG (6: 100, w/v)
—○—: HPC/PEG (20: 100, w/v)

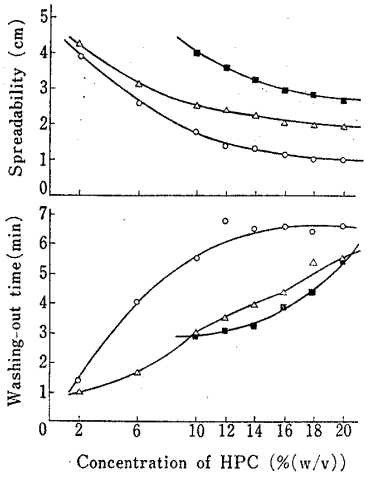

Fig. 3. Relations of the Spreadability and the Washing-out Time of Mixtures to the Concentration of HPC

Each symbol represents the mean of 3 determinations.

—■—: HPC/Aq·Gl
—△—: HPC/PG
—○—: HPC/PEG

of HPC/Aq·Gl after 1 min, *i.e.*, the spreadability defined in this study, was not measured in this concentration region of HPC. The increase of radius of sample with the lapse of time decreased with the increase of concentration of HPC. This decreasing tendency seemed to indicate the "intensity of visco-elasticity" of sample and it was especially remarkable in HPC/PEG.

As shown in Fig. 3, the decrease of spreadability due to the increase of concentration of HPC was remarkable in the low concentration, declining above 10% (w/v) in HPC/PG and above 14% (w/v) in HPC/PEG.

HPC/PEG flowed at room temperature below 10% (w/v) of HPC, but did not above 12% (w/v) and did only upon heating above this concentration. When the hot mixture above 12% (w/v) of HPC was cooled to room temperature on standing, it lost the fluidity to take a gel-like state, and this gel-like mixture got hard with the increase of concentration of HPC. Moreover, this hard gel-like mixture was softened by kneading on an ointment slab and could be spread on the skin with a finger, and then returned to the hard gel-like state again on standing at room temperature. This might belong to a typical thixotropic phenomenon and further investigations should be made in detail.

Washing-out Time of Mixtures and Its Relation to the Spreadability

In HPC/Aq·Gl, the washing-out time was not obtained for the samples containing 2, and 6% (w/v) of HPC because of the high fluidity.

Generally, the washing-out time increased with the concentration of HPC, as shown in Fig. 3. Especially, an exponential increase was observed in HPC/Aq·Gl. The washing-out time of HPC/PG increased almost linearly with the increase of concentration of HPC. In HPC/PEG, a linear increase was observed below 12% (w/v) of HPC and it got to plateau above this concentration.

The increase of washing-out time of each base seemed to be related to the increase of viscosity. Therefore, the plots of washing-out times against the spreadability of samples are

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plotted in Fig. 4. In HPC/Aq·Gl, a comparatively long washing-out time was required in spite of the low viscosity, and also it increased remarkably with the decrease of spreadability. The curve for HPC/PG was similar in tendency to HPC/Aq·Gl. The shortest washing-out time in three kinds of mixtures was given in HPC/PG.

The curve for HPC/PEG was different from the other two, that is, the washing-out time increased linearly with the decrease of the spreadability within the range of about 3.9 cm to 1.4 cm, showing an intermediate washing-out property of the other two, and then the increase of washing-out time reached plateau with the decrease of spreadability.

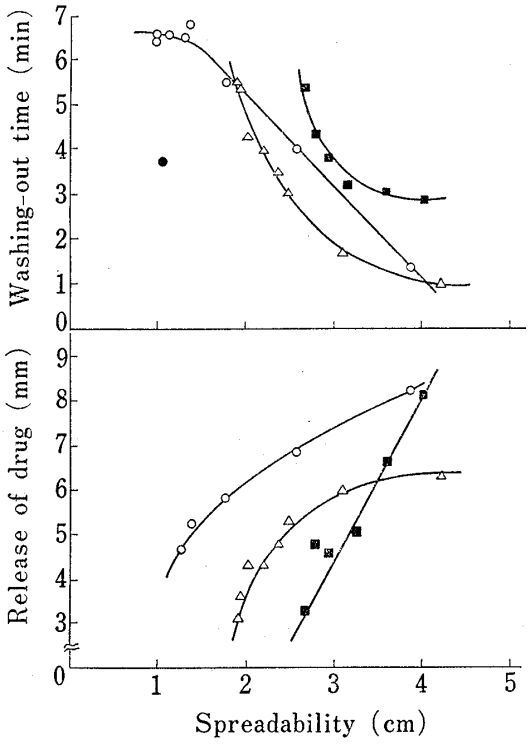

Fig. 4. Relations of the Washing-out Time and the Release of Drug of Mixtures to the Spreadability

Each symbol represents the mean of 3 determinations.

—■—: HPC/Aq·Gl
—△—: HPC/PG
—○—: HPC/PEG
● : Macrogol ointment J.P. VIII

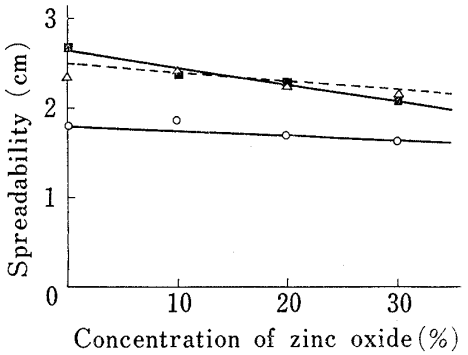

Fig. 5. Effect of the Addition of Zinc Oxide on the Spreadability of Mixtures

Each symbol represents the mean of 3 determinations.

—■—: HPC/Aq·Gl (20: 100, w/v)
---△---: HPC/PG (12: 100, w/v)
—○—: HPC/PEG (10: 100, w/v)

Macrogol ointment J.P. VIII, which consists of PEG 400 and 4000 in equal weight, was also subjected to the measurements, giving the values of 1.05 cm in spredability and 3.7 min in washing-out time. The sample of HPC/PEG having the same viscosity as macrogol ointment J.P. VIII required about twofold washing-out time compared with macrogol ointment J.P. VIII.

Considering the above results, it was estimated that the washing-out time has relation to the viscosity of sample and also to the property of another component added to HPC. The reason why HPC/Aq·Gl showed the comparatively long washing-out time in spite of the low viscosity was explained upon considering that this mixture possesses the aqueous phase and thus may be more affinitive to the glass plate of the hydrophilic nature. Therefore, further investigations should be made using the plates of various materials to get the whole features concerning the washing-out property of the bases.

Effect of the Addition of Insoluble Drug on the Spreadability of Mixtures

An addition of insoluble drug to a semisolid base causes a change of viscosity of the base varying with the particle size and/or the mixing ratio of the drug, often resulting in a preparation too hard to use. In the present study, the change of spreadability of mixtures was investigated with the addition of zinc oxide as an insoluble drug in various concentrations. As shown in Fig. 5, the decrease of spreadability was 23% at the largest, which was observed in HPC/Aq·Gl with the addition of 30% of zinc oxide. The decreases of spreadability in HPC/PG and HPC/PEG were 12% and 11%, respectively, with the addition of 30% of zinc

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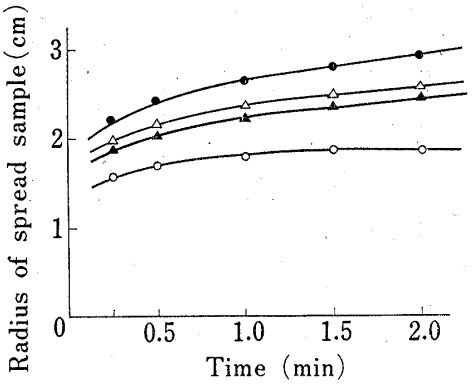

Fig. 6. Spreading Curves of Mixtures after Heating at 150° for 1 hr

Each symbol represents the mean of 3 determinations.
—△—: HPC/PG
—▲—: HPC/PG, after heating
—○—: HPC/PEG
—●—: HPC/PEG, after heating

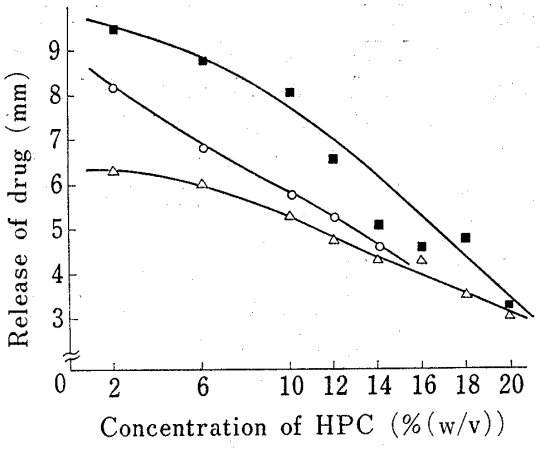

Fig. 7. Relation of the Release of Drug of Mixtures to the Concentration of HPC

Each symbol represents the mean of 3 determinations.
—■—: HPC/Aq·Gl
—△—: HPC/PG
—○—: HPC/PEG

oxide. These were all much smaller than the 36% decrease of spreadability of macrogol ointment J.P. VIII with the addition of zinc oxide in the same concentration.

Although the effect of particle size of drug on the viscosity of mixtures was not studied in present study, the above-mentioned result suggested that the viscosity of these mixtures may depend little on the particle size of the drug added, if the drug has a usual particle size as used in an ointment and also has no special interaction with the mixtures as the bases.

Effect of Heating and/or Freezing-defreezing on the Spreadability of Mixtures

The contamination of ointment with the microorganism is a serious problem especially in an ophthalmic use, and usually ophthalmic ointment bases are sterilized by heating under some conditions, *e.g.*, at 140° for 4 hr,[7] 180° for 1 hr,[7] and or 150° for 1 hr,[8] before use. In the present study, the change of the spreadability of mixtures by heating was examined, excepting HPC/Aq·Gl because it dried up by heating. Fig. 6 shows the plots of the radius of spread sample against the lapse of time after the glass plate of spreadmeter was dropped in the same way as shown in Fig. 2. No significant effect of heating was observed for HPC/PG, while the spread radius at 2 min on the measurement for the sample of HPC/PEG after heating was 54% larger than that of the intact one. This result indicated the visco-elasticity of sample might be affected. In other words, the structure relating to the thixotropy of the mixture was crushed more by the heating than by the kneading.

In connection with this result, the sample of HPC/PEG of the same component after freezing-defreezing gave almost the same spreading curve as the intact one. A similar experiment was done for HPC/Aq·Gl, and no significant difference was observed between the sample after freezing-defreezing and the intact one. Therefore, it was concluded that the structure relating to thixotropy of HPC/PEG may not be affected by freezing-defreezing process.

Drug Release from Bases

The quality of ointment base is evaluated not only by the rheological property and the stability but also by drug releasing property. Generally, a rapid release of drug from ointment base is desirable for the rapid absorption of drug through the skin. Usually, the membrane

7) The Japan Pharmaceutical Association (ed.) "Chozai Shishin," 5th ed., Yakuji Nippo, Inc., Tokyo, 1972, p. 147.
8) Her Majesty's Stationery Office, "British Pharmacopoeia 1973," University Printing House, Cambridge, 1973, p. 200.

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permeation technique is available to *in vitro* study of the drug release from ointment base.[9] The penetrated distance of drug into the agar gel bed from the ointment, which was applied in the present study, was also regarded to be as an indication of the drug releasing property. The present experiment was carried out adding acrinol in the base because this yellow substance is convenient for the measurement and is used often in an ointment.

The result is shown in Fig. 7. In each mixture, the penetrated distance of drug decreased with the increase of concentration of HPC. This decrease of drug release was remarkable in HPC/Aq·Gl. The measurement was carried out also for macrogol ointment J.P. VIII, and the penetrated distance was obtained as 5.2 mm. Therefore, it was shown that these mixtures containing HPC have a drug releasing property similar to macrogol ointment J.P. VIII under the present conditions.

Regarding the relation of the release of drug to the spreadability of mixtures, HPC/Aq·Gl gave the slowest release of drug at the given spreadability below 3.5 cm. This result seemed due to the aqueous phase in HPC/Aq·Gl where acrinol may be apt to stay because of its affinity to water. Moreover, the drug release of this mixture declined linearly with the decrease of spreadability.

On the other hand, HPC/PEG showed the fastest drug release at the given spreadability below 4.1 cm, and also the decreasing tendency of drug release with the decrease of the spreadability of this kinds of mixtures was the least.

Evaluation of the Mixtures as Semisolid Bases

i) **HPC/Aq·Gl**——A comparatively large volume of HPC, *i.e.*, more than 20%, may be required for making a desirable ointment base, still giving a poor washing-out property and drug release. However, since it forms a thin film to coat the skin when applied, it may be useful to applying to cover the injured skin with an addition of some disinfectant. The strength of film and the time required for the formation may depend on the kind of HPC and on the mixing ratio of glycerine to HPC, and thus further examination should be required.

ii) **HPC/PG**——A suitable viscosity as ointment is gained with the addition of HPC in the concentration above 14%. This is inferior to the others in the drug release, but is prepared easily and also gives a good touch making feel clean and compatible without stimulation when applied and thus can be used sufficiently as bases for ointments and other semisolid preparations.

iii) **HPC/PEG**——This is inferior to the others in the washing-out time. However, its drug releasing property is better than the others and the desirable viscosity is gained with the addition of a small amount of HPC, and moreover a gel-like and thixotropic substance is given with the addition of a large amount of HPC. Therefore, this mixture may be utilized not only in ointments but also in suppositories.

Acknowledgement The authors are most grateful to Teijin Co. Ltd. for the generous supply of hydroxypropyl cellulose. Thanks are also given to Messrs. Kiyoshi Nakajima and Masao Kobayashi for their assistance in the experimental work.

9) M. Nakano and N.K. Patel, *J. Pharm. Sci.*, **59**, 985 (1970).

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