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Studies on drug release from ointments. V. Release of hydrocortisone butyrate propionate from topical dosage forms to silicone rubber

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Summary

The release of hydrocortisone butyrate propionate (HBP) from oil-in-water (o/w) cream and aqueous gels containing propylene glycol and ethanol to silicone rubber as a model for the skin was investigated. The release of HBP from o/w cream or gels was carried out under open or closed conditions at 35°C and 75% RH. The influence of the evaporation of vehicle components of the cream or gels on the release of HBP was examined. The release of HBP from o/w cream and aqueous gel containing propylene glycol under open conditions was lower than that under closed conditions, while the release of HBP from aqueous gel containing ethanol in open conditions was markedly higher than that under closed conditions. These differences in the release of HBP between open and closed conditions were related to changes in the thermodynamic activity of HBP in the vehicle during the release period. The results of HBP release under open conditions were nearly correlated with those of in vivo vasoconstrictor activity. The release method using silicone rubber under open conditions is considered to be useful for the evaluation of topical dosage forms, particularly those containing volatile components.

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Introduction

It has been recognized that the release of drugs from topical dosage forms is affected by the composition of the vehicle and the thermodynamic activity of the drug in the vehicle (Poulsen et al., 1968). In a previous paper (Tanaka et al., 1985), the release of dexamethasone acetate from oil-in-water (o/w) creams was shown to be affected by the state of the drug in the creams.

When a topical preparation is applied to the skin, its composition changes due to evaporation of the ingredients of the vehicle and so, it would be expected that drug release would be affected by this alteration. However, although many investigations concerning the in vitro release of drugs from ointments and gels have been reported (Nakano et al., 1970, Bottari et al., 1974; Poulsen et al., 1968), most of them have been carried out under closed conditions in which the ingredients of the vehicle did not evaporate.

Therefore, in this study, in order to examine the influence of evaporation of the ingredients of a vehicle, the release of a drug, hydrocortisone butyrate propionate (HBP), from cream and aqueous gels containing volatile components under open or closed conditions was determined. Silicone rubber was employed as the receptor phase. The results of in vitro release were compared with the observed human vasoconstrictor activity of the cream and gels.

Materials and Methods

Materials

HBP used was synthesized by Taisho Pharmaceutical Co. Ltd., and its purity was 99.7%. The components of the cream and aqueous gels tested were used as received from the manufacturers. The other materials used were of reagent grade.

Preparation of o/w cream and gels

The formulae of the cream and aqueous gels tested are shown in Table 1. The cream was prepared by adding distilled water, heated to 70°C, to a mixture of the oil components, surfactants and propylene glycol (PG) in which HBP had been dissolved, at the same temperature. The mixture was cooled to room temperature with stirring. Aqueous gels, on the other hand, were prepared as follows. HBP was dissolved in PG and then added to a mixture of distilled water, ethanol, and carboxyvinyl polymer [1]. Ammonia water (10%) was then added to the mixture so that the final pH value of the preparations ranged from 4.5 to 5.5. HBP was considered to be completely dissolved in the cream and aqueous gels since no HBP crystals were observed microscopically during the experimental period.

Release of HBP from cream and aqueous gels

A silicone rubber sheet (area 2.5 × 2.5 cm^2, thickness 0.5 mm) [2] was placed on a slide glass and spread with 100 mg of cream or gel to almost constant thickness. In

[1] Hiviswako 104 (Wako Pure Chemical Industries Ltd., Japan).

[2] Sanko Plastic Co. Ltd., Japan.

TABLE 1

COMPOSITION OF MODEL O/W CREAM AND AQUEOUS GELS

o/w Cream		Gel				
Composition	%(w/w)	Composition %(w/w)	No. 1	No. 2	No. 3	No. 4
HPB	0.1	HBP	0.1	0.1	0.1	0.1
Liquid pretrolatum	10.0	HIVISWAKO 104	1.0	1.0	1.0	1.0
White vaseline	10.0	Ammonia water (10%)	q.s.	q.s.	q.s.	q.s.
Nikkol TS10 [a]	6.0	Ethanol	–	–	–	25.0
Nikkol SS10 [b]	3.0					
Propylene glycol	12.0	Propylene glycol	55.0	80.0	add to 100.0	25.0
Distilled water	add to 100.0	Distilled water	add to 100.0	add to 100.0		add to 100.0

[a] Polyoxyethylene monostearyl sorbitane (Nikko Chemicals Co. Ltd.).
[b] Monostearyl sorbitane (Nikko Chemicals Co. Ltd.).

the case of open conditions, 4 sets for either the cream or gel were stored in an incubator at 35°C and 75% RH [3]. For closed conditions, on the other hand, each set was stored in the same incubator after the sample had been wrapped tightly with polyethylene film. The samples were periodically taken out of the incubator. A silicone rubber sheet to which the vehicle was adhering was washed with distilled water, and then soaked in 5 ml methanol with shaking for 4 h in order to extract the released HBP. Determination of HBP in the methanol solution was performed by high-performance liquid chromatography (HPLC).

Determination of changes in vehicle compositon

The weight of the cream was measured during the release period. Changes in the vehicle composition of gels were determined by weighing and measuring the amounts of water, PG, and ethanol in the residual vehicle during the release period.

The silicone rubber sheet to which residual vehicle was adhering was soaked in 5 ml of Karl Fisher methanol and shaken for 4 h. The amount of water was determined by the method of Karl Fisher Titration and the amounts of PG and ethanol were determined by gas chromatography using a column packed with either Porapak Q [4] or 20% PEG 30M on Chromosorb W [5], respectively.

Evaluation of changes in the thermodynamic activity of HBP in the vehicle

The solubility of HBP in the various vehicles was measured as follows. After an excess of HBP crystals was added to the mixture of PG–water or PG–ethanol–water, the mixture was shaken in an incubator at 35°C for 48 h. It was then passed through

[3] Model EA-33B-A, Isuzu Seisakusho Co. Ltd., Japan.
[4] Water Associates Inc., Massachusetts, U.S.A.
[5] Nippon Chromato Industry Co. Ltd., Japan.

a Millipore filter (0.45 μm). The solubility of HBP in the mixed solvents was measured by HPLC after an appropriate dilution with methanol.

The thermodynamic activity, a, of HBP in the gel was defined (Shahi and Zatz, 1978) as: $a = C_v/C_s$ where C_v is the concentration of HBP in the gel and C_s is the solubility of HBP in the gel. C_s was estimated from solubility data of solvent with the same composition.

HPLC conditions

The amount of HBP in the various solutions was determined by HPLC using a Hitachi 633 liquid chromatograph with a 15 cm × 4 mm i.d. stainless-steel column packed with RiChrosorb RP-18, 10 μm [6]. The other conditions were as follows: eluent, methanol : water (65 : 35); flow rate, 1.0 ml/min; column temperature, 40°C; detector, UV at 254 nm; sensitivity, 0.02–0.16 AUFS; injection volume, 10 μl. HBP standard solutions were prepared using the same solvent as the samples.

Vasoconstrictor activity

The method used was an adaptation of the human vasoconstrictor assay (Coldman et al., 1971). About 50 mg of each sample was applied at random to two sites on the flexor surface of each forearm of 10 healthy volunteers, using a Finn Chamber [7] for patch tests. The total number of test sites was 20 per preparation.

At 2 h after the application of the preparations, the Finn Chamber was removed and the site was wiped with gauze soaked in 70% ethanol. Then, at 4, 6, 8 and 24 h after the application, the blanching of the test site was graded as showing no blanching, slight blanching, distinct blanching, or very distinct blanching (scored as 0, 1, 2 and 3, respectively). The average score for each preparation was obtained by dividing the total score by the number of test sites.

Results and Discussion

Release of HBP from o/w cream

Many in vitro methods of drug release from ointments using membranes and receptor solutions have been reported (Bottari et al., 1974; Nakano and Patel, 1970). In this study, silicone rubber was used as the receptor phase for in vitro release of the drug from the topical vehicle. The amount of HBP released from an o/w cream to the silicone rubber was determined. In order to examine the influence of evaporation of the ingredients of the vehicle, in vitro release was carried out under open and closed conditions in which temperature and humidity were kept constant.

The amounts of HBP released from the o/w cream to silicone rubber under these open and closed conditions are shown in Fig. 1a. Changes in the weight under the same conditions are shown Fig. 1b. The release of HBP from the o/w cream under open conditions was lower than that occurring under closed conditions. The weight

[6] Merck Japan Ltd., Japan.
[7] Epitest Ltd., Helsinki, Finland.

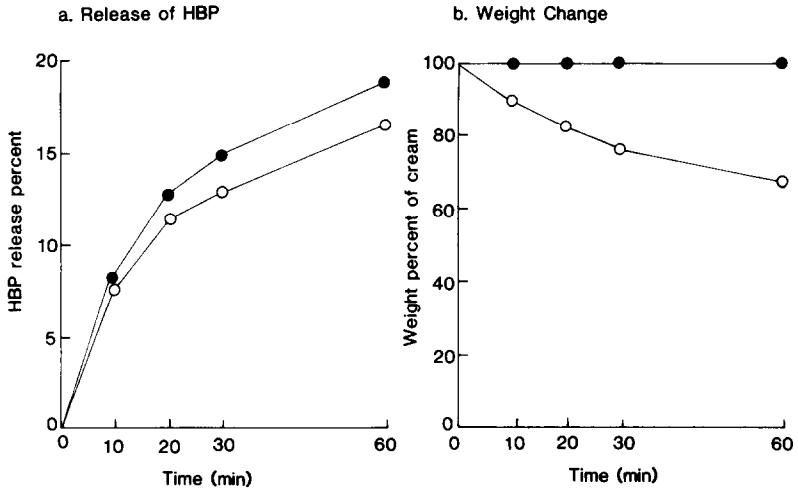

Fig. 1. Release of HBP from o/w cream to silicone rubber and changes in the weight under open (○) and closed (●) conditions at 35°C and 75% RH.

of the o/w cream decreased gradually in open conditions as the release period elapsed. Therefore, it was considered that part of the vehicle had evaporated, thus reducing the release of HBP by changing in the solubility of HBP in the base.

Release of HBP from PG aqueous gels

In order to clarify the influence of evaporation of o/w cream components on the release, the release of HBP from PG aqueous gel was examined as a simple model. The PG content of the gel was more than 55% to dissolve HBP at room temperature.

The release of HBP from 55% PG aqueous gel (no. 1) under open and closed conditions is shown in Fig. 2a. Changes occurring in the composition of the vehicle under the same conditions are shown in Fig. 2b.

The release of HBP from this gel (no. 1) under open conditions was lower than that under closed conditions as in the case of the o/w cream described above. Under closed conditions, the composition showed no changes, but under open conditions, water evaporated, thus increasing the PG/water ratio.

The solubility of HBP in PG-water mixtures increased with PG concentration as shown in Fig. 3. The data were used to estimate the thermodynamic activity in these same gelled mixtures. The thermodynamic activity changes of HBP in the gel are shown in Fig. 4. Under closed conditions, as HBP was released from the gel, the concentration of HBP decreased, and so the thermodynamic activity of HBP in the vehicle also decreased. On the other hand, the concentration of HBP was increased by evaporation of part of the vehicle under open conditions and the PG ratio of the gel increased, thus leading to an increase of HBP solubility in the gel. The thermodynamic activity of HBP in the gel under open conditions therefore decreased more rapidly than that under closed conditions. From these observations, it is considered that the decrease of thermodynamic activity resulting from evaporation of the ingredients causes a reduction in the release of HBP.

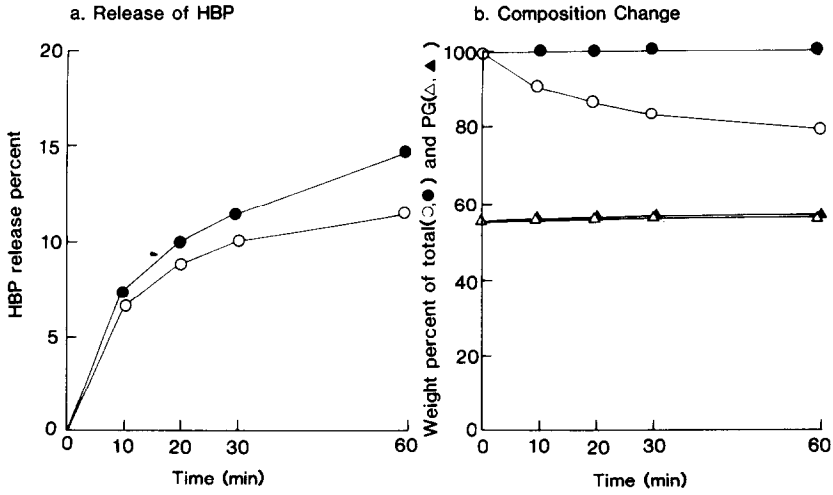

Fig. 2. Release of HBP in 55% PG aqueous gel silicone rubber and changes in the weight and composition under open (○, △) and closed (●, ▲) conditions at 35°C and 75% RH.

The release of HBP from gels of varying PG content under closed conditions is shown in Fig. 5. The release amount of HBP decreased as the PG concentrations increased. The results agreed with those of fluocinolone acetonide in PG aqueous gel previously reported (Poulsen et al., 1968).

The release of HBP from aqueous gel containing ethanol

The release of HBP from an aqueous gel (no. 4) containing a volatile component, ethanol, was examined and the results are shown in Fig. 6a. The release of HBP from

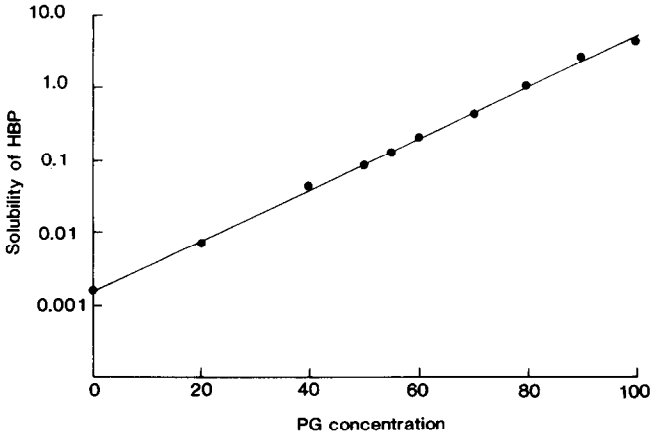

Fig. 3. Solubility of HBP in PG aqueous solutions at 35°C.

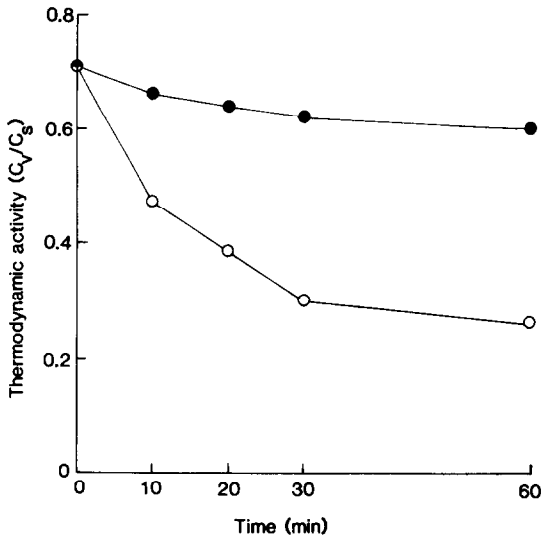

Fig. 4. Changes in the thermodynamic activity of HBP in 55% PG aqueous gel under open (○) and closed (●) conditions at 35°C and 75% RH.

the gel under open conditions was remarkably higher than that under closed conditions. The changes occurring in the composition of the gel under open conditions are shown in Fig. 6b. Ethanol evaporated rapidly causing a subsequent evaporation of water followed by an increase in PG ratio at 60 min. The changes occurring in the thermodynamic activity of HBP in gel stored under open and closed conditions are shown in Fig. 7. The activity decreased gradually under closed conditions as the concentration of HBP in the gel decreased due to its release into the silicone rubber. On the other hand, under open conditions, the activity of HBP

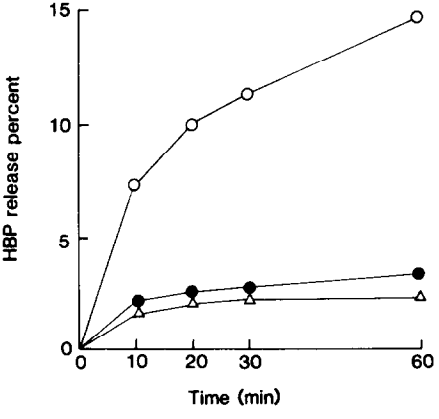

Fig. 5. Release of HBP from aqueous gels of varying PG content to silicone rubber under closed conditions at 35°C and 75% RH PG content of gel; ○, 55%; ●, 80%; △, 98%.

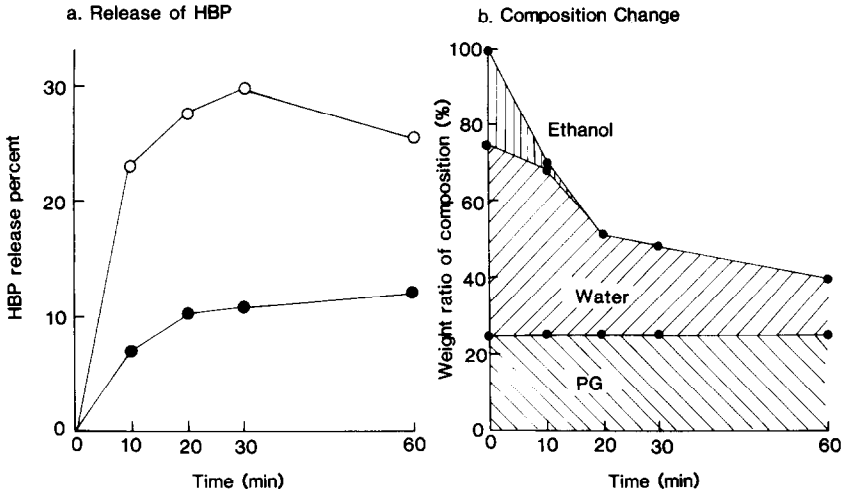

Fig. 6. Release of HBP from aqueous gel (no. 4) containing ethanol to silicone rubber under open (○) and closed (●) conditions and changes in the composition under open conditions at 35°C and 75% RH.

increased rapidly while the solubility of HBP decreased due to evaporation of the ethanol. However, it is considered that the actual activity was lower than the value calculated from the solubility and the concentration in the vehicle because it was observed that the gel became turbid due to HBP crystals. The evaporation of water then caused a decrease of activity as the PG ratio increased. Coldman et al. (1969)

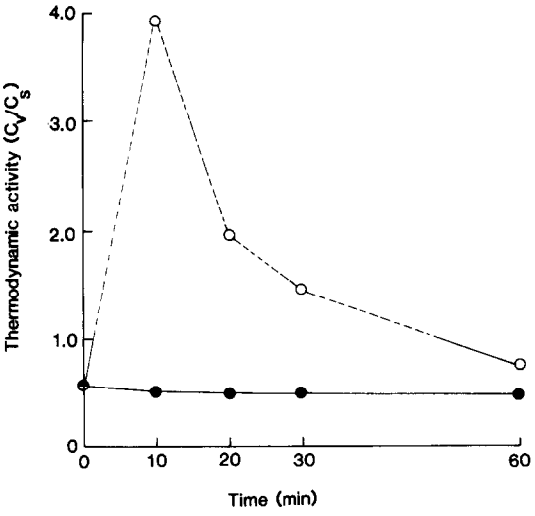

Fig. 7. Changes in the thermodynamic activity of HBP in aqueous gel (no. 4) containing ethanol under open (○) and closed (●) conditions at 35°C and 75% RH. Broken lines are the assumed supersaturated solution of HBP.

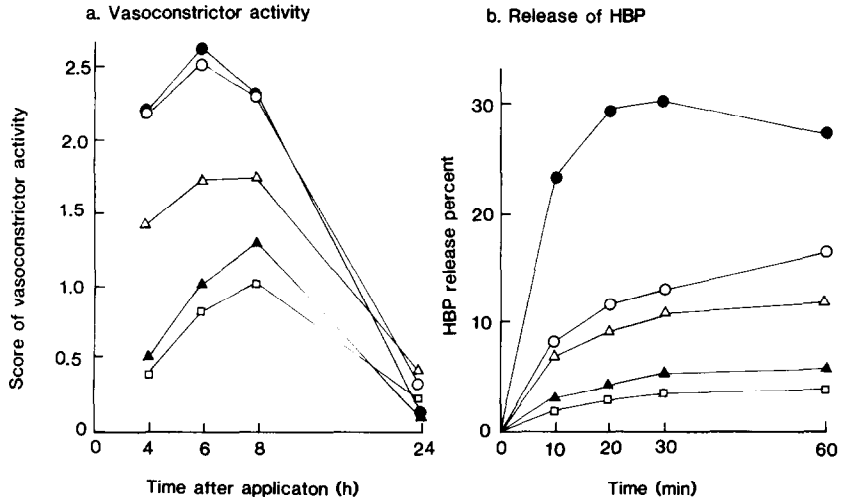

Fig. 8. Vasoconstrictor activity of o/w cream and aqueous gels and release of HBP from them to silicone rubber under open conditions at 35°C and 75% RH. ○, o/w cream; △, 55% PG aqueous gel (no. 1); ▲, 80% PG aqueous gel (no. 2); □, 98% PG gel (no. 3); ●, 25% ethanol : 25% PG aqueous gel (no. 4).

showed that a combination of isopropanol and propylene glycol increased the penetration of steroids through human skin.

These results suggest that the release of a drug under open conditions can be controlled by choosing the volatile ingredients used.

Vasoconstrictor activity

The human vasoconstrictor activity of the cream and aqueous gels was examined and the results were compared with those for in vitro release.

The degree of vasoconstrictor activity of each sample is shown in Fig. 8a. The order of vasoconstrictor activity at 4, 6 and 8 h after application was 25% PG, 25% EtOH aqueous gel (no. 4) > o/w cream > 55% PG aqueous gel (no. 1) > 80% PG aqueous gel (no. 2) > 98% PG gel (no. 3). This order agreed with that of their in vitro release under open conditions shown in Fig. 8b. However, the difference of vasoconstrictor activity between o/w cream and 25% PG, 25% EtOH aqueous gel (no. 4) was less than that of in vitro release. The reason is considered to be that ethanol did not evaporate from the ethanol aqueous gel in the vasoconstrictor study because it was wrapped with a patch test plaster.

Conclusion

Topical preparations are usually applied to the skin under open conditions. In this study, the release of a drug from vehicles containing volatile components was examined using silicone rubber as the receptor phase. Drug release was found to be affected by evaporation of the ingredients and to be improved by choosing the

appropriate ingredients for increasing the thermodynamic activity of the drug in the vehicle as the ingredients evaporate.

References

Bottari, F., Di Colo, G., Nannipieri, E., Saettone, M.F. and Serafini, M.F., Influence of drug concentration on in vitro release of salicylic acid. J. Pharm. Sci., 63 (1974) 1779–1783.

Coldman, M.F., Poulsen, B.J. and Higuchi, T., Enhancement of percutaneous absorption by the use of volatile: nonvolatile systems as vehicles. J. Pharm. Sci., 58 (1969) 1098–1102.

Coldman, M.F., Lockervie, L. and Laws, E.A., The evaluation of several topical corticosteroid preparations in the blanching test. Br. J. Derm., 85 (1971) 381–387.

Nakano, M. and Patel, N.K., Release, uptake, and permeation behavior of salicylic acid in ointment bases. J. Pharm. Sci., 59 (1970) 985–988.

Poulsen, B.J., Young, E., Coquilla, V. and Katz, M., Effect of topical vehicles composition on the in vitro release of fluocinolone acetonide and its acetate ester. J. Pharm. Sci., 57 (1968) 928–933.

Shahi, V. and Zatz, J.L., Effect of formulation factors on penetration of hydrocortisone through mouse skin. J. Pharm. Sci., 67 (1978) 789–792.

Tanaka, S., Takashima, Y., Murayama, M. and Tsuchiya, S., Solubility and distribution of dexamethasone acetate in oil-in-water creams and its release from the creams. Chem. Pharm. Bull., in press.