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COMMUNICATION

In Vitro Delivery of Fluocinolone Acetonide in FAPG Base

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ABSTRACT

The effects of oleic acid and lauric acid in a mixture of fatty alcohol and propylene glycol (FAPG base) on the percutaneous absorption of fluocinolone acetonide (FA) were investigated by using nude mouse skin and synthetic membrane in vitro. The mixture of 0.9% sodium chloride and methanol (9:1) was used as the receptor phase for the diffusion study. The concentration of FA in the receptor phase was determined by HPLC. The optimal formulation of the FAPG base was obtained with the addition of 5% lauric acid.

INTRODUCTION

Fluocinolone acetonide (FA) is a glucocorticoid which has potent anti-inflammatory and metabolic but negligible mineral-corticoid actions. It is employed topically in the treatment of various dermatoses. In resisting nummular dermatitis, psoriasis, or chronic neurodermatitis, it is usually used as an occlusive dressing (1).

Enhanced activity can be achieved by improved skin penetration of the drug (2). This indicated the importance of the development of a formulation to increase drug penetration. There are two general approaches to enhancing the activity of therapeutic effectiveness of topical ointments. One is to include agents in the vehicles which affect the barrier function of the epidermis to promote penetration of the therapeutic compound (3–11). The other approach is to alter the physical characteristics of the vehicle and thus affect the diffusion of the drug into skin.

The topical vehicle consisting of a mixture of fatty alcohol, propylene glycol, and other excipients is abbreviated as FAPG. It has been used as a topical vehicle for various corticosteroids (12–16), ketoprofen (17), piroxican (18), and indomethacin (19,20). This vehicle can be described as a two-phase system where a continuous, solubilizing phase is distributed in a solid ma-

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trix of fatty alcohol and high molecular weight polyols. This vehicle is named "cream-gel" since it combines the physical properties of gel with cream-like appearance, and the consistency of an emulsion system. We suggested that FAPG base would be a useful vehicle in topical formulation for percutaneous drug administration.

The purpose of this study was to determine the effects of oleic acid and lauric acid in FAPG on the percutaneous absorption of FA through nude mouse skin and synthetic membrane in vitro.

EXPERIMENTAL

Materials

Fluocinolone acetonide (lot 3379/MI) was from Sicor, Italy. Lauric acid (lot M6T7800) was from Nakarai Chem. Ltd., Japan. Propylene glycol (lot 15095) was from PERAX, West Germany. FLUCORT® (lot 6001) was from PANABE, Japan. Stearyl alcohol (lot 24H1025) was from Sigma Chem. Co., USA, and oleic acid (lot K12754871) was from E. Merck Co., Ltd., Germany.

Preparation of FAPG Ointments

FAPG bases containing 0.025% FA were prepared according to the formulas in Table 1. The fatty alcohol and fatty acid were heated at 75 ± 0.5°C, followed by FA which was dissolved in propylene glycol previously heated to the same temperature. The samples were then stored in air-tight aluminum ointment tubes until used.

Analysis Method

All samples were analyzed for the FA content by the high-performance liquid chromatography (HPLC) method described in USP XXII.

Table 1

Formulation of Fluocinolone Acetonide

	Formulation No.		
Composition[a]	1	2	3
Stearyl alcohol	20	20	20
Propylene glycol	30	27.5	27.5
Lauric acid		2.5	
Oleic acid			2.5
Fluocinolone acetonide	0.0125	0.0125	0.0125

[a]In grams.

Content Uniformity

All samples were analyzed for FA content prior to diffusion studies. Only samples with FA content of 100.0 ± 5.0% were used for diffusion studies.

In Vitro Release Studies

Using Synthetic Semipermeable Membrane

A 1.0-g sample of each formulation was accurately weighed and placed in the donor part of the Franz–Chien Diffusion Cell with an aperture of 0.785 cm^2. A semipermeable membrane (Circle AIR/MSP, LJL Sample Exp. Membranes, MSP 987192, 3M, Taiwan, Ltd.) was used as the diffusion barrier. The receptor part contained freshly prepared mixtures of 0.9% sodium chloride:methanol (9:1) at a constant temperature of 37 ± 0.5°C and a stirring speed of 600 rpm. All diffusion studies were carried out in triplicate. The donor part containing the sample was then placed over the semipermeable membrane and diffusion was allowed to take place. Samples were withdrawn at 12-, 18-, 24-, 30-, 36-, and 48-hr intervals, and analyzed for FA contents. The volume of the receptor part was maintained by placing the amount withdraw with an equal volume of the receptor medium. The solution in the receptor cell was kept well mixed with a magnetic stirrer throughout the time of diffusion studies.

The samples withdrawn were analyzed by HPLC. The concentration of FA was determined using a previously constructed standard curve of known concentration of FA in the same receptor medium. Blank ointment samples were run simultaneously to check any interference.

Using Nude Mouse Skin

On the basis of the in vitro release studies conducted with synthetic semipermeable membrane, the formulation with optimum drug release was selected to be used in the study using the freshly excised nude mouse skin. The mice (obtained from Tri-Service General Hospital, Taipei, Taiwan) used were 6 weeks old, females. The skin was excised just prior to the experiments and cleaned using normal saline solution to remove all visceral debris. The skin was then placed over the mouth of the receptor part containing the diffusion medium maintained at 37 ± 0.5°C. The diffusion studies were carried out by withdrawing samples at time intervals of

12, 18, 24, 30, 36, and 48 hr, respectively, and analyzing for FA contents by HPLC.

RESULTS AND DISCUSSION

The results of in vitro diffusion of FA in various stearyl alcohol/propylene glycol bases using a synthetic semipermeable membrane shows that a maximum flux was achieved in the formulation containing 40% stearyl alcohol and 60% propylene glycol. The permeation of FA was increased by incorporating lauric acid or oleic acid as shown in Fig. 1. This indicates that the formulation containing lauric acid has a better permeation than one with oleic acid.

The formulation with optimal diffusion through the synthetic semipermeable membrane (i.e., formulation 2) was selected for the in vitro release of FA through the nude mouse skin. The commercial product FLUCORT® was also used for comparison. The FA release from the two products is shown in Fig. 2. Results show that formulation 2 has the same percutaneous absorption of FA as the commercial product. It is probable that lauric acid in the FAPG base enhances the skin permeation of FA by disrupting the stratum corneum's lipid structure.

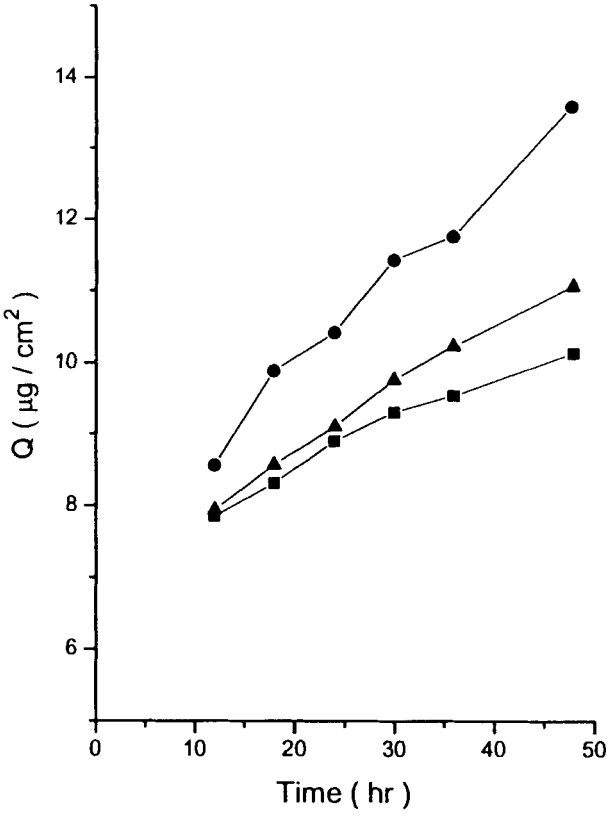

Figure 1. Effect of ointment base on the release of fluocinolone acetonide (synthetic membrane): ---■---, formulation 1; ---●---, formulation 2; ---▲---, formulation 3.

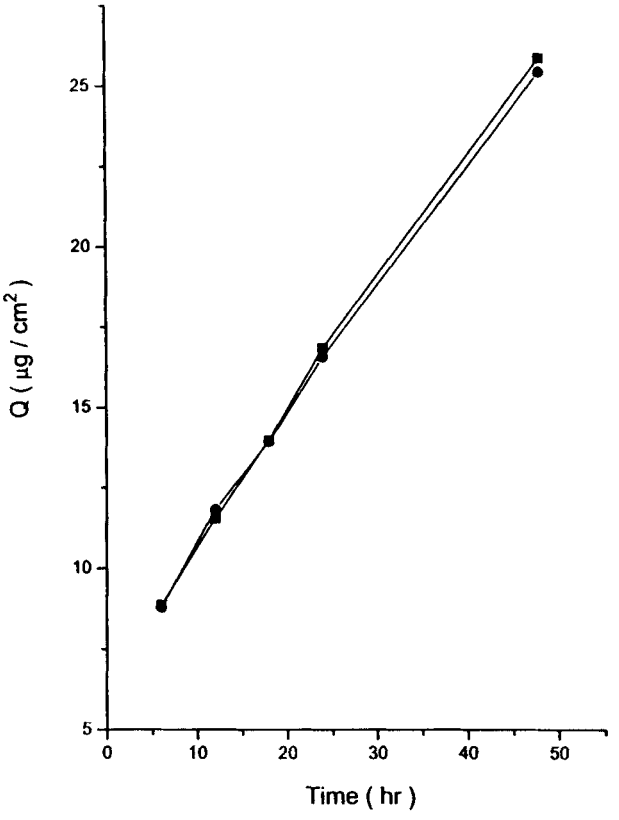

Figure 2. Effect of ointment base on the release of fluocinolone acetonide (nude mouse skin): ---■---, formulation 2; ---●---, FLUCORT.

CONCLUSION

It was concluded that the addition of lauric acid to FAPG base enhanced the in vitro percutaneous absorption of FA from a FAPG base through the synthetic membrane.

If FAPG base is to be used as the vehicle for percutaneous absorption of FA, lauric acid would be a useful additive.

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REFERENCES

1. *Physicians' Desk Reference*, Medical Economic Data, Montvale, NJ, USA, 1992, p. 2296.
2. B. Idson, Drug Costmet. Ind., 137, 30 (1985).
3. R. T. Scheuplein and I. H. Blank, J. Invest. Dermatol., 60, 286 (1973).
4. G. L. Flynn, S. M. Yalkowsky, and J. J. Roseman, JPS, 63, 479 (1974).
5. R. Scheuplein and L. Ross., J. Soc. Cosmet. Chem., 21, 853 (1970).
6. J. P. Astely and M. Levine, JPS, 65, 210 (1976).
7. R. Woodford and B. W. Bary, J. Toxicol. Cut. Ocular Toxical., 5, 167 (1986).
8. D. Southwell and B. W. Bary, J. Invest. Dermatol., 80, 507 (1983).
9. E. R. Cooper, JPS, 73, 1153 (1984).
10. B. J. Aungst, N. J. Rogers, and E. Shefter, Int. J. Pharm., 33, 225 (1986).
11. R. Staughton and W. McClure, Drug Dev. Ind. Pharm., 9, 725 (1983).
12. M. Kate and H. M. Neiman, U.S. patent 3592930, 1971.
13. M. F. Coldman, L. Lockerbie, and E. A. Laws, Br. J. Derm., 85, 573 (1971).
14. M. Henry, Curr. Med. Res. Opin., 2, 27 (1974).
15. J. Ostrenga, J. Naleblian, B. Poulsen, B. Ferrela, N. Mueller, and S. Shastri, J. Invest. Dermatol., 56, 329 (1971).
16. E. L. Rhodes, W. L. Morison, G. B. Skinner, D. W. Borrett, and M. Stoppard, Curr. Med. Res. Opin., 1, 87 (1972).
17. Y.-H. Tsai, Y.-B. Huang, and H.-H. Lin, in *Advances in Pharmaceutics and Pharmaceutical Technology*, 1989, p. 21.
18. L.-R. Hsu, Y. Huang, P.-C. Wu, and Y.-H. Tsai, Chin. Pharm. J., 45(2), 123 (1993).
19. F. Kaiho, Y. Takashi, R. Ichihara, A. Watanabe, T. Yamashita, and T. Kato, Yakugaku Zasshi, 106, 47 (1986).
20. F. Kaiho, H. Normura, E. Makabe, and Y. Kato, Chem. Pharm. Bull., 35, 2928 (1987).