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IN VITRO SKIN PENETRATION OF TRIAMCINOLONE ACETONIDE FROM LANOLIN ALCOHOL–ETHYL CELLULOSE FILMS

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SUMMARY

In vitro skin penetration of triamcinolone acetonide from lanolin alcohol–ethyl cellulose films has been investigated. These studies were conducted using a diffusion cell and human abdominal skin. During the experiment, the dermal side was kept at 37°C and the epidermal side was exposed to ambient conditions of the room. The lanolin alcohol–ethyl cellulose films contained propylene glycol or hexadecyl alcohol as solvent-plasticizer. At the beginning of each experiment isopropanolic solution of the selected film composition containing [^{3}H]triamcinolone acetonide was applied on the epidermal side. The diffusion across the skin was monitored for 7 days by frequent sampling of the receptor phase composed of normal saline. At the termination of the experiment, the distribution of the steroid between applied vehicle, epidermis and dermis was determined. The penetration data were analyzed to determine if the penetration through the skin or the release from the dosage form was the rate-limiting step. The results of this analysis and the distribution profile of the steroid suggest that the release of the steroid from these matrices was the rate-limiting step for percutaneous absorption. The steady-state penetration rate was found to be proportional to the concentration of the dispersed drug in the vehicle. The effect of drug solubility in the film-vehicle on the rate and extent of penetration of the drug was also investigated.

INTRODUCTION

The use of various polymeric materials in dermatological and pharmaceutical applications has received considerable attention in recent years (Lange and Fang, 1966; Conrady et al., 1971; Loucas and Haddad, 1972; Shaw et al., 1977). Although several polymeric substances have been studied for their film-forming characteristics and potential applica-

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tion in topical delivery systems (Sciarra and Gidwani, 1970; Borodkin and Tucker, 1974), the application of film-forming properties of the non-polymeric high molecular weight substances to dermatologic systems do not appear to have been fully explored.

Recently the film-forming characteristics of lanolin alcohol either alone or in combination with ethyl cellulose have been reported in detail from our laboratory (Iyer and Vasavada, 1978). The in vitro release of triamcinolone acetonide from selected compositions of these matrices containing propylene glycol or hexadecyl alcohol as solvent-plasticizer was found to obey the diffusion-controlled granular matrix model (Higuchi, 1963), as represented by Eqn. 1.

$$Q = \sqrt{\frac{D\epsilon}{\tau}(2A - \epsilon C_s)\, C_s t} \tag{1}$$

where Q is the quantity of drug released after time t per unit exposed area, D is the diffusivity of the drug in the permeating fluid, τ is the tortuosity factor of the capillary system, ϵ is the porosity of the matrix and C_s is the solubility of the drug in the permeating fluid. This equation is applicable only when the release of the drug from the matrix acts as the rate-limiting step for the penetration process. In the situations where the diffusion across the skin barrier acts as the rate-limiting step for the penetration process an expanded form of Fick's law of diffusion has been shown to apply, under certain conditions for the steady-state diffusion across skin. This equation is expressed as below (Higuchi, 1960):

$$\frac{dQ}{dt} = \frac{PC_vD_sA}{h} \tag{2}$$

where dQ/dt is the steady-state rate of penetration, P is the partition coefficient between skin barrier and vehicle, C_v is the concentration of drug dissolved in the vehicle, D_s is the average diffusion coefficient of the drug in the skin barrier, A is the are of skin to which drug is applied, and h is the effective thickness of skin barrier.

The present work describes the in vitro penetration characteristics of triamcinolone acetonide from selected film-forming compositions of lanolin alcohol. This study was designed and conducted to provide a better understanding of the mechanism of drug diffusion during both release and penetration process and to determine if the diffusion from the vehicle or diffusion across the skin was rate-limiting for the absorption of triamcinolone acetonide from the film compositions.

MATERIALS AND METHODS

Materials

The materials used for the penetration of film-forming compositions were lanolin alcohol [1] (m.p. 61–64°C), ethyl cellulose [2], propylene glycol (USP) [3], and hexadecyl alcohol (cosmetic grade, d 0.84) [4]. Triamcinolone acetonide (USP) [5] and [1,2,3(n)-^{3}H]-

[1] Super Hartolan, Croda, Inc., New York, N.Y.
[2] Ethyl Cellulose N-50, Herculus Inc., Wilmington, Delaware.
[3] Ruger Chemical Company, Inc., Irvington, N.J.
[4] Branched chain, Cachalot X0144B, M. Michel and Company, Inc., New York, N.Y.
[5] Johnson and Johnson, Dermatological Div., New Brunswick, N.J.

triamcinolone acetonide [6] were used as the test drug. Isopropyl alcohol (NF) [7] was used as the solvent because of its excellent capacity to solubilize vehicle components including the drug and due to its reported lack of any defatting effects on the skin (Coldman et al., 1969). An aqueous [8] and an organic [9] counting scintillant and a tissue solubilizer [10] were used in these studies. Sodium chloride [11] and thimersol [12] were used in the preparation of the receptor solution.

Preparation of skin

All the penetration experiments utilized human abdominal skin obtained at autopsy since excellent quantitative agreement has been reported with in vivo data (Chowhan and Pritchard, 1978). Immediately following incision the skin was placed in a plastic bag and stored in a freezer for a period up to but not exceeding three months. Before the experiment the skin was allowed to thaw gradually to room temperature, following which the skin was placed on a smooth dissection board with the epidermal surface flat in contact with the board. All subcutaneous fat was completely removed by a scalpel prior to sectioning into 10–12 small pieces (≈2 X 2 cm). The skin from the same donor was utilized for each experiment.

Diffusion assembly

Each piece of skin was mounted in a special glass cell similar to the one described earlier (Franz, 1975). The skin cell consisted of a lower glass chamber with a sampling port. A teflon-coated magnetic bar placed at the bottom expanded portion of the cell provided efficient mixing. The lower chamber had a water jacket which maintained the receptor fluid at a constant temperature. The skin was placed in position between two ball joints of the top and bottom chambers on an O-ring using a pinch-type ground joint clamp. The diffusion area was 2.01 cm^2. A solution containing 0.9% sodium chloride and 0.01% thimersol was heated to expel dissolved gases, cooled to room temperature and 6.2 ml of this solution was pipetted into the bottom chamber bathing the dermal side. The sampling port was closed by a rubber closure and the air bubbles from the dermal side were carefully removed by slightly tilting the cell. Each cell was mounted on a magnetic stirrer. During each run, 12 cells were mounted on 12 magnetic stirrers attached to a laboratory frame. The temperature of fluid in the lower chamber was maintained at 37 ± 0.5°C by circulating water from a constant temperature water circulator [13] through the jacket of each cell. By this arrangement, the epidermal side of the skin was exposed to ambient laboratory conditions while the dermal side was kept at 37 ± 0.5°C to simulate in vivo use conditions. Prior to beginning the experiment by applying the dosage form,

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[6] Amersham/Searle Corp., Arlington Heights, Ill.
[7] Mallinckrodt Chemical Works, St. Louis, Mo.
[8] ACS™, Amersham Corp., Arlington Heights, Ill.
[9] OCS™, Amersham Corp., Arlington Heights, Ill.
[10] NCS*, Amersham Corp., Arlington Heights, Ill.
[11] J.T. Baker Chemical Co., Phillipsburg, N.J.
[12] Sigma Chemical Company, St. Louis, Mo.
[13] Haake Model-FE, VWR Scientific Inc., San Francisco, Calif.

each piece of skin was allowed to stand for 4 h to equilibrate with respect to temperature and relative humidity of the surrounding environment.

Preparation of solutions

Lanolin alcohol, ethyl cellulose, and propylene glycol or hexadecyl alcohol were weighed in required quantities to make 10 ml of 10% w/v solution in a 25 ml beaker. Five milliliters of isopropyl alcohol was added to this and the contents allowed to go into solution by gentle heating. The solution was cooled to room temperature and was transferred to a 10 ml volumetric flask. The required amount of triamcinolone acetonide was then dissolved. The quantity of steroid used was in addition to the 10% w/v concentration of film-formers and plasticizer. This solution was then made up to volume using isopropyl alcohol. Two compositions without any lanolin alcohol and ethyl cellulose were also tested. One contained 0.01% w/v of the steroid in isopropanol and the other contained 0.1% w/v of the steroid and 1.5% w/v propylene glycol in isopropanol (henceforth, referred to as compositions A and B, respectively, in the text).

Determination of in vitro penetration rate

Before each experiment, 0.5 ml of the prepared solution of desired composition was pipetted into a 2 ml beaker containing approximately 5 μCi of [^{3}H]triamcinolone acetonide using a precision pipette. The beaker was covered and the solution was mixed thoroughly. Of this radioactively labeled solution 100 μl was than pipetted on the the skin surface, while a second 100 μl sample was transferred to a scintillation vial for determining the applied dose. This volume was found to be sufficient to spread across the entire exposed surface area of 2.01 cm^2. The volatile isopropanol was allowed to escape in all cases. At selected time intervals following the application of the formulation, the receptor solution was completely removed through the sampling port and cell was refilled with 6.2 ml of fresh saline solution. This was accomplished expeditiously using a disposable syringe with its needle attached to a thin flexible plastic tubing. The complete removal of the bathing fluid at each time interval ensured that the sink conditions were maintained during the course of penetration experiment. One milliliter of the withdrawn receptor solution was pipetted into a scintillation vial and 10 ml of aqueous scintillation fluid was added before counting in a liquid scintillation counter [14]. The amount of quench due to the saline solution was determined using the external standard ratio method. The total amount of steroid penetrated per unit area at different time intervals was calculated by a computer [15] using a Fortran program written for this purpose. The penetration studies were conducted for a period of 7 days, the sampling being more frequent in the first 2 days than the following 5 days. All penetration studies were conducted in duplicate.

Determination of distribution of steroid

At the termination of penetration experiment, 1 ml of isopropanol was added to the

[14] Beckman CPM-100 Liquid Scintillation Counter.
[15] Burroughs B6700.

epidermal surface in each cell and the cells were covered with cover slips for a period of 5 min. During this period the epidermal surface was rinsed of the applied dose remaining and the isopropanolic solution was transferred to a scintillation vial. A second washing was performed with 0.5 ml of isopropanol and this solution was also collected in the same vial. This procedure was repeated in all 12 cells and 10 ml of the organic scintillant was added to the washings in each of the 12 vials. The activity in the vials was then counted. External standard ratio method was employed for calculating counting efficiency using a standard quench curve.

The skin was then removed from the cell and the circular portion which was in contact with the bathing fluid was cut out using a surgical scissor. For each skin sample, the epidermis and dermis were then separated by means of a pair of forceps and collected separately in two scintillation vials. One milliliter of the tissue solubilizer was then pipetted into the vial containing epidermis and 2.5 ml into the vial containing dermis. Digestion of the tissue by the solubilizer to give a clear solution was accomplished by keeping the vials in an oven at 50 ± 1°C for a period of 4 h. Then, 10 ml of the scintillant was added to each vial and the samples were counted. The external standard ratio method was employed for applying quench correction. Standard quench curves were prepared by using fresh samples of dermis and epidermis having similar area as used in the penetration experiments and standard tritiated water of known radioactive concentration.

RESULTS AND DISCUSSION

The penetration data obtained for the two compositions A and B were analyzed by plotting Q (amount penetrated per unit-area) against time. All the plots were made by using the mean Q values obtained from the duplicate runs using a graphics program. Based on this plot, a regression analysis of the steady-state region of the penetration curve was carried out using a regression program since Eqn. 2 is applicable only in the steady-state region of penetration. The regression line was then extrapolated to the time axis to establish the lag times as shown by the dotted lines in Fig. 1. For these two compositions, A and B, penetration across the skin would be expected to be the rate-limiting step for the absorption of steroid. The composition B was formulated to give a near-saturated solution of the steroid in propylene glycol at room temperature after the evaporation of isopropanol. The plot for composition B was curvilinear and revealed two steady-state regions (observed break 67 h). This observation is suggestive of significant time-dependent changes in the interplay of forces governing the penetration of steroid across the skin. The amount of the steroid in the donor phase dropped from 10 to 7.25 μg. About 56.4% of that drop occurred during the first 67 h of the study. Also, the gradual initial diffusion of propylene glycol into the skin might have caused changes in the thermodynamic activity of the drug in the donor phase or changes in the permeability characteristics of stratum corneum. The steady-state penetration rates for compositions A and B were calculated to be 4.52 and 12.67 $\mu g\ cm^{-2}\ h^{-1}$, and the corresponding lag times were found to be 1.84 and 5.70 h (correlation coefficient 0.997), respectively. The reported value for composition B is based upon the first 67 h of penetration profile.

For compositions A and B, at the end of 7 days, the epidermal content of the steroid was found to be more (44.3–55.0%) than the amount remaining on the surface of the

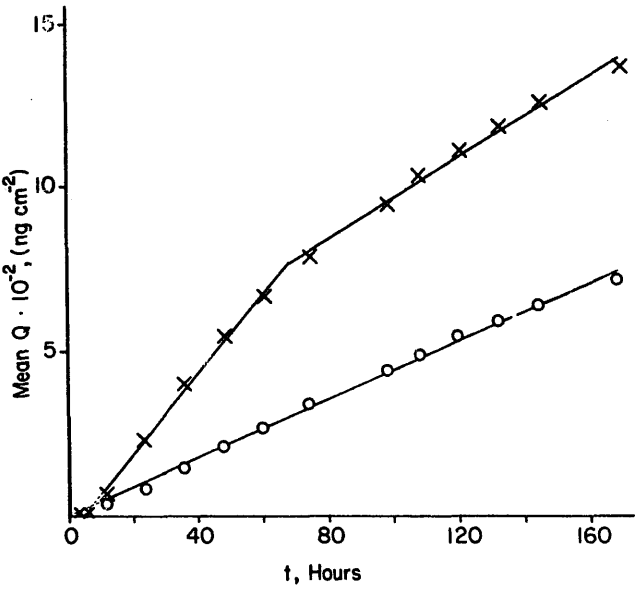

Fig. 1. Q versus t plots of triamcinolone acetonide penetration from non-occluded systems. Key: ○, 0.01% solution in isopropanol; ×, 0.01% solution in isopropanol containing 1.5% w/v of propylene glycol.

skin (15.9–20.0%) or the amount present in the dermis (2.5–7.0%). This would suggest that the penetration of triamcinolone acetonide through the skin for compositions A and B was the rate-limiting step. On the other hand, this might reflect changes in relative solubilities. In view of the poor solubility of triamcinolone acetonide, the transfer of triamcinolone acetonide from the epidermis to the lower water-bearing tissues could be the slow step, resulting in the build up of the steroid concentration in the epidermis.

Effect of drug concentration on the penetration

The minimum concentration of the drug used was at least 4 times its solubility in the matrix. Q versus t plots (Figs. 2 and 3) were made for the matrix compositions tested, under the assumption that the penetration through skin was rate-limiting. A summary of the data obtained by increasing the concentration of the suspended drug in the same composition of the matrix containing propylene glycol or hexadecyl alcohol is shown in Table 1. As can be seen from this table the increase in the concentration of the suspended drug gave a corresponding increase in penetration rate. High correlation coefficients were obtained in the steady-state region of the penetration. There was no notable difference in penetration rate between matrices having propylene glycol and hexadecyl alcohol. The corresponding increase in penetration rate with increases in the concentration of the suspended drug was difficult to explain, if the penetration of the steroid through the skin was assumed to act as the rate-limiting step as was observed for compositions A and B. In theory, penetration should be equal from suspensions containing finely powdered drug (Higuchi, 1960) when the skin barrier is intact and acts as the rate-limiting step.

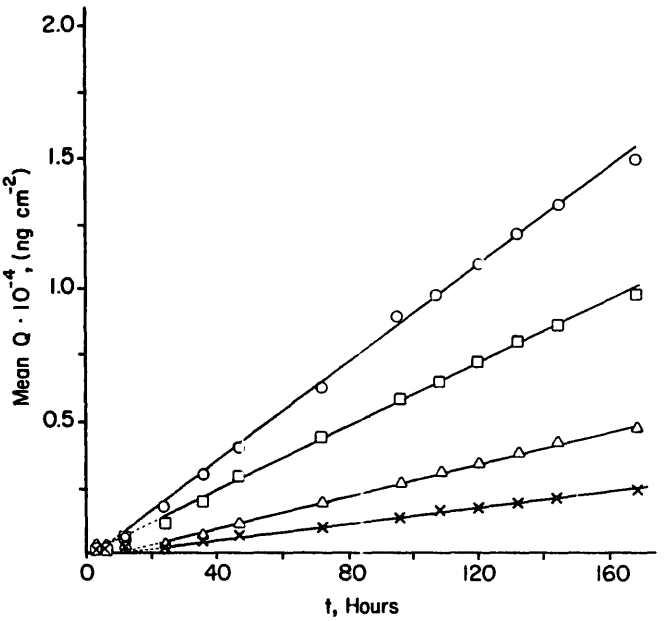

Fig. 2. Q versus t plots of drug penetration from films containing lanolin alcohol–ethyl cellulose–propylene glycol (8.0 : 1.5 : 0.5) at different concentrations of triamcinolone acetonide. Key: ×, 0.50%; △, 0.99%; □, 1.96%; ○, 2.91%.

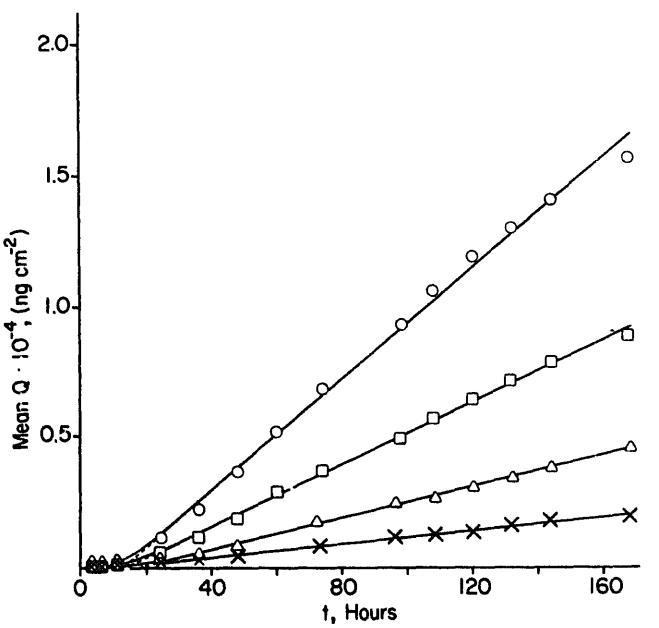

Fig. 3. Q versus t plots of drug penetration from films containing lanolin alcohol–ethyl cellulose–hexadecyl alcohol (8.0 : 1.5 : 0.5) at different concentrations of triamcinolone acetonide. Key: ×, 0.50%; △, 0.99%; □, 1.96%; ○, 2.91%.

TABLE 1

Q VERSUS t TREATMENTS OF TRIAMCINOLONE ACETONIDE PENETRATION DATA FROM FILMS CONTAINING PROPYLENE GLYCOL OR HEXADECYL ALCOHOL

Lanolin alcohol: ethyl cellulose: plasticizer ratio	Drug concentration percent [a]	Steady-state penetration rate [b] ng cm^{-2} h^{-1}	Lag time, hours	Correlation coefficient r [c]
Plasticizer: propylene glycol				
8.0 : 1.5 : 0.5	0.50	15.13	7.04	0.999
8.0 : 1.5 : 0.5	0.99	32.14	13.43	0.999
8.0 : 1.5 : 0.5	1.96	61.55	2.39	0.999
8.0 : 1.5 : 0.5	2.91	95.19	5.45	0.999
Plasticizer: hexadecyl alcohol				
8.0 : 1.5 : 0.5	0.50	12.86	13.21	0.999
8.0 : 1.5 : 0.5	0.99	30.60	20.50	0.999
8.0 : 1.5 : 0.5	1.96	60.32	16.00	0.999
8.0 : 1.5 : 0.5	2.91	106.11	11.81	0.997

[a] Based on weight of drug per weight of dry film.
[b] All steady-state penetration rate values were computed from the regression line drawn from the data obtained by duplicate runs at each level by using TEKTRONIX (Model 4005-1) graphics terminal.
[c] Reported r values are for the steady-state region of the penetration data.

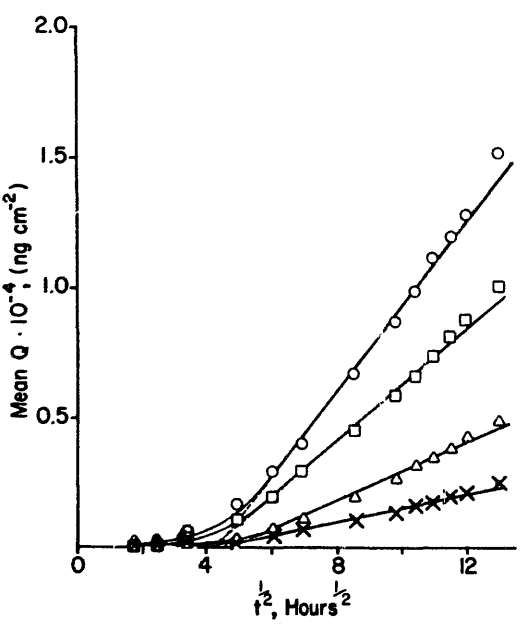

Fig. 4. Q versus $t^{1/2}$ plots of drug penetration from films containing lanolin alcohol–ethyl cellulose–propylene glycol (8.0 : 1.5 : 0.5) at different concentrations of triamcinolone acetonide. Key: X, 0.50%; △, 0.99%; □, 1.96%; ○, 2.91%.

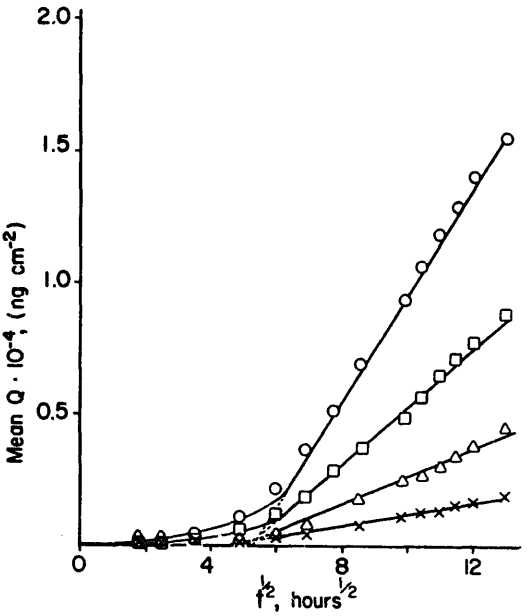

Fig. 5. Q versus $t^{1/2}$ plots of drug penetration from films containing lanolin alcohol–ethyl cellulose–hexadecyl alcohol (8.0 : 1.5 : 0.5) at different concentrations of triamcinolone acetonide. Key: ×, 0.50%; △, 0.99%; □, 1.96%; ○, 2.91%.

TABLE 2

Q VERSUS $t^{1/2}$ TREATMENTS OF TRIAMCINOLONE ACETONIDE PENETRATION DATA FROM FILMS CONTAINING PROPYLENE GLYCOL OR HEXADECYL ALCOHOL

Lanolin alcohol: ethyl cellulose: plasticizer ratio	Drug concentration percent [a]	Steady-state penetration rate (k) [b] ng cm^{-2} $h^{-1/2}$	Lag time, hours	Correlation coefficient r [c]
Plasticizer: propylene glycol				
8.0 : 1.5 : 0.5	0.50	269.54	19.91	0.995
8.0 : 1.5 : 0.5	0.99	571.53	23.18	0.994
8.0 : 1.5 : 0.5	1.96	1099.39	17.79	0.997
8.0 : 1.5 : 0.5	2.91	1689.13	18.93	0.995
Plasticizer: hexadecyl alcohol				
8.0 : 1.5 : 0.5	0.50	228.48	23.02	0.993
8.0 : 1.5 : 0.5	0.99	541.53	26.95	0.989
8.0 : 1.5 : 0.5	1.96	1079.11	25.13	0.993
8.0 : 1.5 : 0.5	2.91	1909.65	23.09	0.997

[a] Based on weight of drug per weight of dry film.

[b] All k values were computed from the regression line drawn from the data obtained by duplicate runs at each level by using TEKTRONIX (Model 4005-1) graphics terminal.

[c] Reported r values are for the steady-state region of the penetration data.

TABLE 3

DISTRIBUTION OF TRIAMCINOLONE ACETONIDE 7 DAYS AFTER APPLICATION FROM FILMS CONTAINING PROPYLENE GLYCOL OR HEXADECYL ALCOHOL

Lanolin alcohol: ethyl cellulose: plasticizer ratio [a]	Drug concentration, percent [b]	Amount penetrated, percent	Amount of applied dose recovered, percent			
			Isopropanol wash of epidermis	Epidermis	Dermis	Percent total recovery
Plasticizer: propylene glycol						
8.0 : 1.5 : 0.5	0.50	9.0 (10.1) [c]	68.6 (67.6)	3.1 (3.6)	0.5 (1.7)	81.2 (83.5)
8.0 : 1.5 : 0.5	0.99	9.1 (10.5)	64.1 (65.2)	3.1 (4.1)	1.4 (2.5)	77.7 (82.3)
8.0 : 1.5 : 0.5	1.96	10.5 (9.4)	73.6 (71.3)	4.5 (3.2)	0.6 (0.5)	89.3 (82.4)
8.0 : 1.5 : 0.5	2.91	9.9 (10.3)	67.1 (68.2)	6.7 (3.4)	0.6 (0.3)	84.3 (82.2)
Plasticizer: hexadecyl alcohol						
8.0 : 1.5 : 0.5	0.50	8.5 (7.3)	65.6 (70.7)	1.9 (1.7)	1.9 (0.6)	78.1 (80.3)
8.0 : 1.5 : 0.5	0.99	9.8 (8.3)	67.7 (72.9)	3.1 (3.0)	1.2 (0.8)	81.8 (85.0)
8.0 : 1.5 : 0.5	1.96	6.2 (11.6)	72.1 (74.9)	6.5 (3.0)	0.7 (1.6)	85.5 (91.1)
8.0 : 1.5 : 0.5	2.91	8.2 (12.7)	73.7 (77.3)	2.8 (2.5)	1.1 (1.0)	85.8 (93.5)

[a] All solutions were apllied as 10% w/v solution of film formers in isopropyl alcohol.

[b] Based on weight of drug per weight of dry film.

[c] The numbers within parentheses represent the values obtained by duplicate run.

The increase in penetration with increase in concentration of the suspended drug suggested that the release of drug from the matrix might have acted as the rate-limiting step for the penetration through the skin and the skin acted as a perfect sink once the equilibration was attained. To further verify this posibility, Q versus $t^{1/2}$ plots of penetration data were made for all matrix compositions tested as shown in Figs. 4 and 5. Q versus $t^{1/2}$ plots were made based on the conclusion that the release of triamcinolone acetonide from these matrices follows diffusion-controlled matrix model (Iyer and Vasavada, 1978). High correlation coefficients were obtained in the steady-state region of penetration as shown in Table 2. The lag times were found to be in the range of 18–27 h.

As in the case of release studies, the penetration rate for the matrices containing hexadecyl alcohol (Table 2) was found to be comparable to matrices containing propylene glycol, even though there is an 8-fold difference in the solubility of the drug in the matrix. This is consistent with the earlier conclusion from the release studies that the diffusion-controlled model was 'granular' (Eqn. 1) and not 'homogeneous'.

Distribution of triamcinolone acetonide at the end of 7 days is shown in Table 3 at all the concentrations studied from the two matrices containing propylene glycol and hexadecyl alcohol, respectively. As can be seen epidermal concentrations of the drug were low (1.9–6.7%) and slightly more than the dermal concentration (0.3–1.7%). The amount remaining in the applied dose was very high, contrary to the values obtained with compositions A and B. This distribution pattern of the steroid supported the view that the release from these film-matrices was the rate-limiting step.

Effect of vehicle composition

Table 4 describes the effect of drug solubility on drug penetration. The variation in solubility was achieved by varying the percentage of propylene glycol in the matrix

TABLE 4

IN VITRO PENETRATION OF 0.10% w/w TRIAMCINOLONE ACETONIDE FROM MATRICES CONTAINING DIFFERENT PERCENTAGES OF PROPYLENE GLYCOL AND LANOLIN ALCOHOL AT 48 AND 120 HOURS AFTER APPLICATION

Lanolin alcohol: ethyl cellulose: propylene glycol ratio	Amount penetrated, percent [a]	
	48 hours	120 hours
8.5 : 1.5 : 0.0	0.2	1.0
8.2 : 1.5 : 0.3	0.3	1.4
8.0 : 1.5 : 0.5	0.4	1.6
7.7 : 1.5 : 0.8	0.5	2.5
7.5 : 1.5 : 1.0	0.7	2.7
7.0 : 1.5 : 1.5	1.0	4.3
6.5 : 1.5 : 2.0	5.2	12.0
6.0 : 1.5 : 2.5	5.0	10.8

[a] All values are expressed as the mean of duplicate runs.

TABLE 5

DISTRIBUTION OF 0.10% w/w TRIAMCINOLONE ACETONIDE 7 DAYS AFTER APPLICATION FROM FILMS CONTAINING VARIOUS CONCENTRATIONS OF PROPYLENE GLYCOL AND LANOLIN ALCOHOL

Lanolin alcohol: ethyl cellulose: propylene glycol ratio [a]	Amount penetrated, percent	Amount of applied dose recovered, percent			
		Isopropanol wash of epidermis	Epidermis	Dermis	Percent accountability
8.5 : 1.5 : 0.0	1.5 (1.8) [b]	63.1 (76.2)	3.1 (2.8)	1.4 (0.8)	69.1 (81.6)
8.2 : 1.5 : 0.3	2.2 (2.6)	65.7 (75.6)	2.9 (4.2)	1.3 (1.7)	72.1 (84.1)
8.0 : 1.5 : 0.5	2.6 (2.5)	85.0 (84.1)	5.6 (7.2)	1.2 (1.8)	94.4 (95.6)
7.7 : 1.5 : 0.8	2.8 (5.4)	82.9 (85.0)	7.0 (8.0)	1.2 (2.0)	93.9 (98.4)
7.5 : 1.5 : 1.0	4.1 (4.7)	79.0 (80.2)	7.0 (6.5)	2.6 (2.9)	92.7 (94.3)
7.0 : 1.5 : 1.5	6.9 (6.1)	69.9 (80.8)	7.5 (6.6)	2.8 (3.2)	85.1 (96.7)
6.5 : 1.5 : 2.0	16.7 (12.8)	63.0 (56.9)	6.4 (7.5)	1.5 (2.3)	87.6 (79.5)
6.0 : 1.5 : 2.5	14.4 (11.2)	65.0 (64.2)	5.1 (6.5)	0.7 (0.8)	85.2 (82.7)

[a] All solutions were applied as 10% w/v solution of film formers in isopropyl alcohol.

[b] The numbers within parentheses represent the values obtained by duplicate run.

between 0 and 25% w/w with a corresponding decrease in the percentage of lanolin alcohol. The ethyl cellulose concentration was kept constant at 15% w/w. The isolatability and integrity of the propylene glycol containing films determined the upper limit of 25% w/w propylene glycol. The steroid concentration of 0.10% w/w was chosen, in part to permit the study over a wide spectrum of solubility ranging from nearly complete suspension to dilute solution.

The reduced penetration of the steroid from film compositions containing 0–10% w/w propylene glycol could be attributed to the insufficient propylene glycol present to dissolve all of the triamcinolone acetonide. This would cause the penetration of the drug into the skin to be diffusion rate-limited causing a reduction in release rate which in turn would be reflected as reduction in the amount of drug penetrated. The diffusion gradients formed within the permeating fluid in the pores and channels of the matrix or in the matrix itself could also be a contributing factor. Similar release and penetration pattern has been reported for fluocinolone acetonide and fluocinonide (Poulsen, 1973).

As can be seen from Table 4 the maximum release was obtained from a system containing 20% w/w of propylene glycol rather than the film containing 15% w/w of propylene glycol, though the latter constituted a near-saturated solution. In this respect the results are at variance from the results of the release studies where the maximum release was obtained from the saturated solution (Iyer and Vasavada, 1978). The amount of penetrated steroid decreased at 25% w/w propylene glycol concentration. This can be explained since at 20 and 25% w/w propylene glycol concentrations the vehicle is probably behaving more as a homogeneous system with the drug in solution rather than as a granular matrix. Such a transition makes the situation more complex and definitive explanation more difficult. In such circumstances, the rate of release is increasing and approaching the rate of penetration and perhaps surpassing it as the propylene glycol is gradually increased to 20% w/w and beyond. The drop in amount penetrated at 25% w/w propylene glycol appears to be due to the drop in thermodynamic activity associated with the dilution of the drug.

The distribution of triamcinolone acetonide at the end of 7 days from these matrices is shown in Table 5. The epidermal concentration was much lower than the concentration remaining in the vehicle-matrix. These observations are comparable to data reported earlier for varying amounts of suspended drug in the same film-vehicle (Table 3).

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