Linearity of Modified USP Procedure—The linearity for the aspirin tablet and buffered aspirin tablet assays was examined. For the aspirin assay, mixtures of varying amounts of aspirin with 0.15 mg of salicylic acid for the aspirin tablet assay and 3.0 mg of salicylic acid for the buffered aspirin tablet assay were determined. The amounts of salicylic acid added were equivalent to the maximum amount allowed by the USP, assuming sample weights equivalent to 50 and 100 mg of aspirin, respectively. For the nonaspirin salicylates assay, mixtures of varying amounts of salicylic acid with 50 mg of aspirin for the aspirin tablet assay and 100 mg of aspirin for the buffered aspirin assay were determined. The amounts of aspirin added represented the quantity specified in the modified USP procedures.

The aspirin assay was linear in the 0–75- and 0–130-mg ranges for the aspirin tablet assay and the buffered aspirin tablet assay, respectively. The nonaspirin salicylates assay was linear in the 0–0.3- and 0–5.0-mg ranges for the aspirin tablet assay and the buffered aspirin tablet assay, respectively.

Precision of Modified USP Procedures—A statistical evaluation of the precision of the modified methods was performed on the assay results of two sets of six accurately weighed preparations. The sets used contained either ~0.15 mg of salicylic acid and 50 mg of aspirin or 0.30 mg of salicylic acid and 100 mg of aspirin (Table II).

Effects of Methanol on Aspirin Assay—Methanol was used in the modified USP aspirin assay to clarify the column eluate, which was often turbid due to the physical removal of water by chloroform from the chromatographic column. Methanol had to be added accurately to both the assay preparation and the standard preparation since the presence of methanol affected the magnitude of the absorbance and the wavelength maximum of the aspirin peak (Table III). Aspirin was stable in this solvent mixture for at least 6 hr. The absorbance of an aspirin solution at 278 nm after this time was 99.5% of the initial value. After 24 hr, however, the absorbance dropped to 75% of the initial value.

Comparison of Modified USP Assay and USP Assay—The results of studies on several commercially available aspirin and buffered aspirin tablets are summarized in Tables IV and V. The results indicate a good correlation between methods.

REFERENCES

(1) "The United States Pharmacopeia," 19th rev., Mack Publishing Co., Easton, Pa., 1975, p. 39.

(2) J. Levine, *J. Pharm. Sci.*, **50**, 506 (1961).

(3) J. Levine and J. D. Weber, *ibid.*, **57**, 631 (1968).

(4) J. D. Weber and J. Levine, *ibid.*, **55**, 78 (1966).

(5) J. D. Weber, *J. Assoc. Off. Anal. Chem.*, **48**, 1151 (1965).

(6) D. E. Guttman, *J. Pharm. Sci.*, **57**, 1685 (1968).

(7) D. E. Guttman and G. W. Salomon, *ibid.*, **58**, 120 (1969).

Evaluation of Lanolin Alcohol Films and Kinetics of Triamcinolone Acetonide Release

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Abstract □ The film-forming potential of lanolin alcohol was evaluated. Inclusion of ethylcellulose in lanolin alcohol improved film integrity. The hardness and modulus of elasticity of these lanolin alcohol–ethylcellulose films were improved by incorporating propylene glycol or cetyl alcohol. *Triamcinolone acetonide release from selected film compositions was* investigated. The data were analyzed from the viewpoint of the first-order kinetic theory and the release from a planar system having a homogeneous or granular matrix. The results suggest that the drug release follows a diffusion-controlled matrix model and a square root of time release profile. The release rate constants were proportional to drug concentration. Drug release was maximal from a system containing the drug in a near-saturated solution.

Keyphrases □ Lanolin alcohol—films, kinetics of triamcinolone acetonide release, topical dosage forms □ Triamcinolone acetonide—release from lanolin alcohol films, kinetics, topical dosage forms, □ Dosage forms, topical—lanolin alcohol films, kinetics of triamcinolone acetonide release □ Glucocorticoids—triamcinolone acetonide, release from lanolin alcohol films, kinetics

Protective films containing therapeutically active agents have been used for dermatological and surgical applications (1–3). An inert polymeric matrix impregnated with pilocarpine has been utilized to achieve prolonged and steady release of the drug for ocular administration (4). In certain dermatological applications, polymeric films containing a drug could offer advantages over conventional dosage forms. These potential advantages include enhanced therapeutic effect, predictable control over rate and extent of absorption, occlusion of the skin surface, and improved patient acceptance.

Although several polymeric substances have been studied for their film-forming characteristics (5–7) and potential application in topical drug delivery systems, the nonpolymeric, high molecular weight substances apparently have not been investigated. Furthermore, the applicability of this concept to topical drug delivery system design has not been explored fully.

THEORETICAL

Drug release from a planar system having a drug dispersed in a homogeneous insoluble matrix was shown (8) to follow:

$$Q = \sqrt{Dt(2A - C_s)C_s} \qquad \text{(Eq. 1)}$$

where Q is the amount of drug released per unit area at time t, D is the drug diffusion coefficient in the matrix, A is the total amount of drug present in the matrix per unit volume, and C_s is the drug solubility in the matrix. The relationship for release from a planar system having a granular matrix was shown to be (9) diffusion controlled and is given by:

$$Q = \sqrt{\frac{D\epsilon}{\tau}(2A - \epsilon C_s)C_s t} \qquad \text{(Eq. 2)}$$

where D and C_s refer to the diffusion coefficient and drug solubility in the permeating fluid, τ is the tortuosity of the matrix, and ϵ is the porosity of the matrix.

Both these equations describe drug release as being linear with the square root of time:

$$Q = kt^{1/2} \qquad \text{(Eq. 3)}$$

where k is the release rate constant. For a homogeneous matrix system:

$$k = \sqrt{D(2A - C_s)C_s} \qquad \text{(Eq. 4)}$$

and for a granular matrix system:

$$k = \sqrt{\frac{D\epsilon}{\tau}(2A - C_s)C_s} \qquad \text{(Eq. 5)}$$

These relationships were confirmed experimentally using plastic and wax matrixes (10–15).

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Table I—Effect of Change in Lanolin Alcohol–Ethylcellulose Ratio on Sward Hardness and Modulus of Elasticity of Films Containing Propylene Glycol at Room Temperature (22 ± 0.5°)

Lanolin Alcohol–Ethylcellulose–Propylene Glycol Ratio[a]	Mean Dry Film Thickness (× 10^3)[b], inches	Constant for Varying Thickness, $K_t \times 10^{10}$	Sward Hardness (R)[c], rocks	Modulus of Elasticity (E), psi (kg/cm^2)
9.50:0.00:0.50	0.189	0.030	2	3.55 (0.25)
9.00:0.50:0.50	0.252	0.068	3	11.47 (0.81)
8.50:1.00:0.50	0.402	0.450	4	44.19 (3.11)
8.00:1.50:0.50	0.724	3.200	4	53.87 (3.79)
7.50:2.00:0.50	1.047	9.000	4	50.16 (3.53)
7.00:2.50:0.50	1.063	9.200	4	51.27 (3.60)
6.50:3.00:0.50	1.425	45.000	3	41.97 (2.95)

[a] All films were cast from a 10% (w/v) solution of film formers in isopropyl alcohol. [b] Thicknesses are expressed as mean values of five measurements. [c] Sward hardnesses are expressed as mean values of three measurements rounded to the nearest whole number.

Table II—Effect of Change in Lanolin Alcohol–Ethylcellulose Ratio on Sward Hardness and Modulus of Elasticity of Films Containing Cetyl Alcohol at Room Temperature (22 ± 0.5°)

Lanolin Alcohol–Ethylcellulose–Cetyl Alcohol Ratio[a]	Mean Dry Film Thickness (× 10^3)[b], inches	Constant for Varying Thickness, $K_t \times 10^{10}$	Sward Hardness (R)[c], rocks	Modulus of Elasticity (E), psi (kg/cm^2)
9.50:0.00:0.50	0.189	0.030	2	3.55 (0.25)
9.00:0.50:0.50	0.193	0.031	3	11.66 (0.85)
8.50:1.00:0.50	0.504	0.850	4	42.52 (2.99)
8.00:1.50:0.50	0.650	2.200	4	51.36 (3.61)
7.50:2.00:0.50	0.480	0.700	4	40.43 (2.84)
7.00:2.50:0.50	0.441	0.600	4	44.80 (3.15)
6.50:3.00:0.50	1.284	30.000	3	38.31 (2.69)

[a] All films were cast from a 10% (w/v) solution of film formers in isopropyl alcohol. [b] Thicknesses are expressed as mean values of five measurements. [c] Sward hardnesses are expressed as mean values of three measurements rounded to the nearest whole number.

This paper reports a preliminary evaluation of films formed by lanolin alcohol. Propylene glycol or cetyl alcohol was used as the plasticizer and primary solvent for the test drug. The films formed by lanolin alcohol in combination with a known film former, ethylcellulose (16), also were tested in the presence of the mentioned plasticizers. The prepared films were evaluated by measuring the hardness and modulus of elasticity.

This paper also describes studies of drug release from the films of selected compositions, showing the effect of change in proportion of film formers and the plasticizer and the nature of the plasticizer. Triamcinolone acetonide was chosen as the model drug.

EXPERIMENTAL

Materials—The materials used for the preparation of the films were lanolin alcohol[1] (mp 61–64°), ethylcellulose[2], propylene glycol USP[3], and cetyl (hexadecyl) alcohol (cosmetic grade, d 0.84)[4]. Triamcinolone acetonide USP (solubility in distilled water at 37° is 0.03 mg/ml)[5] and 1,2,3(n)-^{3}H-triamcinolone acetonide[6] were used as the drugs. The solvents were isopropyl alcohol NF[7] and anhydrous methanol[7] (spectral grade). A premade dioxane cocktail[8] was the scintillation fluid.

Film Preparations—For the initial screening, all films were cast from a 10% (w/v) solution of film former(s) and plasticizer in isopropyl alcohol. The films were cast on the mercury substrate. Sufficient solution was poured within a stainless steel ring (9.2-cm i.d., 3-mm height, which had been placed on a mercury surface contained in a 140 × 10-mm glass petri dish, and the solution was spread evenly across the mercury surface within the area bound by the ring. The petri dish was partially covered with its lid, and the solvent was allowed to evaporate overnight.

The entire operation was carried out in a humidity-controlled room at 30° and 40% relative humidity (RH). Partially covering the petri dish helped to control the solvent evaporation rate and the blistering of the deposited film surface. Film formation was easily noted by observing the mercury substrate after complete solvent evaporation. The film could be retrieved intact by slowly lifting the ring from the mercury substrate. The isolated films were stored between sheets of wax paper in a desiccator.

Determination of Film Hardness and Modulus of Elasticity—Film hardness was determined on film cast on aluminum plates. For each composition tested, a 10% (w/v) solution of film former(s) and plasticizer was prepared in isopropyl alcohol and was cast on an aluminum plate using an applicator[9] with a wet film thickness of ~1 mm. These plates were then dried in a humidity-controlled room at 30° and 40% RH. The exact thickness of the dried film was determined using a thickness measuring gauge[10]. Film hardness was determined using a hardness tester[11]. The rocker was calibrated before each measurement by checking for 100 oscillations on a standard glass plate. From the Sward hardness R (number of oscillations of rocker on the test film), the modulus of elasticity (E) was calculated with:

$$E = \frac{KR^3}{T^3} \qquad \text{(Eq. 6)}$$

The values of the constant K for thickness (T) were obtained from the literature (17).

Solubility Studies—The solubilities of triamcinolone acetonide in propylene glycol and cetyl alcohol were determined at room temperature (22°) and at 37°.

Solubility was determined by adding excess steroid to 25 ml of propylene glycol or cetyl alcohol in 50-ml glass bottles with screw caps. A polytef-coated magnetic bar was placed in each bottle prior to capping it tightly. The bottles were kept in water baths on magnetic stirrers for 6 days. All studies were conducted in triplicate.

Prior to sampling, the stirring was stopped and the excess steroid was allowed to settle. An aliquot was filtered using a filter[12] with 0.22-μm filter paper. The filtration and sampling apparatus was allowed to equilibrate for 48 hr prior to use. The first 5 ml of the filtrate was rejected in each case to avoid any reduction in solubility values due to steroid adsorption in the filter paper (18). All operations were conducted in a constant-temperature room.

The steroid concentration in the solvent was determined using a scanning spectrophotometer[13] after appropriate dilutions of the solvent

[1] Super Hartolan, Croda Inc., New York, N.Y.
[2] Ethyl Cellulose N-50, Hercules Inc., Wilmington, Del.
[3] Ruger Chemical Co., Irvington, N.J.
[4] Branched-chain hexadecyl alcohol, M. Michel and Co., New York, N.Y.
[5] Dermatological Division, Johnson and Johnson, New Brunswick, N.J.
[6] Amersham/Searle Corp., Arlington Heights, Ill.
[7] Mallinckrodt Chemical Works, St. Louis, Mo.
[8] Hydroscint, ICN Chemical and Radioisotope Division, Irvine, Calif.
[9] Multiple-clearance applicator, Gardner Laboratory, Bethesda, Md.
[10] Minitector (model N), Gardner Laboratory, Bethesda, Md.
[11] I.C.I. automatic Sward hardness rocker, Gardner Laboratory, Bethesda, Md.
[12] Swinnex-25, Millipore Filter Corp., Bedford, Mass.
[13] Perkin-Elmer model-202, Coleman Instruments Division, Oak Brook, Ill.

Table III—Effect of Change in Lanolin Alcohol–Propylene Glycol Ratio on Sward Hardness and Modulus of Elasticity of Films at Room Temperature (22 ± 0.5°)

Lanolin Alcohol–Ethylcellulose–Propylene Glycol Ratio[a]	Mean Dry Film Thickness ($\times 10^3$)[b], inches	Constant for Varying Thickness, $K_t \times 10^{10}$	Sward Hardness (R)[c], rocks	Modulus of Elasticity (E), psi (kg/cm^2)
8.50:1.50:0.00	0.669	2.80	3	25.22 (1.77)
8.25:1.50:0.25	0.606	1.12	4	31.58 (2.22)
8.00:1.50:0.50	0.724	3.20	4	53.87 (3.79)
7.75:1.50:0.75	0.755	4.54	4	66.68 (4.69)
7.50:1.50:1.00	0.809	5.52	4	66.58 (4.68)
7.25:1.50:1.25	0.693	3.13	4	59.64 (4.19)
7.00:1.50:1.50	0.874	6.54	4	62.31 (4.38)
6.50:1.50:2.00	0.740	4.05	4	63.12 (4.44)
6.00:1.50:2.50	0.724	3.91	4	65.66 (4.62)
5.50:1.50:3.00	0.622	1.52	4	39.89 (2.80)
5.00:1.50:3.50	0.622	1.52	4	39.89 (2.80)

[a] All films were cast from a 10% (w/v) solution of film formers in isopropyl alcohol. [b] Thicknesses are expressed as mean values of five measurements. [c] Sward hardnesses are expressed as mean values of three measurements rounded to the nearest whole number.

with anhydrous methanol. The steroid solubility was determined at 239 nm in propylene glycol and at 265 nm in cetyl alcohol.

Apparent Solubility in Lanolin Alcohol—The apparent solubility was estimated by determining the effective partition coefficient of the steroid in a lanolin alcohol–water system at 22 and 37°.

About 100–200 mg of the melted lanolin alcohol was coated as a thin film in the bottom of a preweighed, 50-ml, flat-bottom polypropylene beaker and allowed to cool to room temperature. The beaker was weighed again to determine the exact film weight. Then 20 ml of a 0.002% (w/v) mixture of cold and radiolabeled triamcinolone acetonide was added. The beaker was covered with Parafilm and kept in a temperature-controlled water bath until equilibrium was reached. One-milliliter samples were withdrawn from the aqueous phase at suitable intervals into a scintillation vial, and 10 ml of scintillation fluid was added to each. They were then analyzed radiochemically using a liquid scintillation counter[14].

The apparent partition coefficient, K_e, was then determined using the equation proposed previously (19):

$$K_e = \frac{A_1/W_1}{A_a/W_a} = \frac{(A_a' - A_a)W_a}{A_a W_1} \qquad \text{(Eq. 7)}$$

where A_1 and A_a are the amounts of the drug in the lanolin alcohol and in the aqueous phase, respectively; A_a' is the initial amount of drug in water; and W_1 and W_a are the weights of lanolin alcohol and water, respectively.

The apparent solubility was calculated from:

$$K_e = \frac{C_s^1}{C_s^w} \qquad \text{(Eq. 8)}$$

where C_s^1 is the apparent solubility in lanolin alcohol and C_s^w is the solubility in water.

Determination of Release Rate—Lanolin alcohol, ethylcellulose, and propylene glycol or cetyl alcohol were added in required quantities to 5 ml of isopropyl alcohol and allowed to go into solution by gentle heating. The solution was cooled to room temperature, and the required concentration of cold triamcinolone acetonide was added and allowed to go into solution. The radiolabeled steroid (10 μCi) in isopropyl alcohol was added to this solution, and the total volume was made up to 10 ml in a volumetric flask. Two milliliters of this solution was pipetted into a preweighed aluminum petri dish and allowed to spread evenly on the flat bottom (7.5 cm in diameter; area of 44.2 cm^2).

The petri dish was kept on a level surface for 24 hr, and the solvent was allowed to evaporate to form a uniform film of 5–8-μm thickness. Complete solvent evaporation was confirmed by weighing the petri dish to a constant weight. The film-coated petri dish was stored in a desiccator containing anhydrous calcium chloride for at least 24 hr prior to the release studies. The good adherence of the film to the petri dish ensured that only the exposed surface area (44.2 cm^2) was available for release. The film was examined visually at the end of each experiment. No visible pores or "peeling" of the film from the petri dish was observed.

The release studies were conducted in a dissolution assembly[15] with the following modifications. The dissolution flasks were replaced by 1000-ml flat-bottom polypropylene beakers, and the dissolution basket assemblies were replaced by stainless steel stirrers with a propeller diameter of 4.5 cm. The film-coated petri dishes were placed in the bottom of the beakers. The beakers were held in position by Plexiglas disks with central circular ports for the stirrers and a small sampling port. The stirring assembly was set in position, 300 ml of preheated (37°) distilled water was added carefully to each, and the stirring was maintained at 40 rpm. The water bath was maintained at 37°.

One-milliliter samples were drawn frequently over 24 hr and were replaced by 1 ml of distilled water. Each sample was pipetted into a scintillation vial to which 10 ml of scintillation fluid was added. The samples were then analyzed using a liquid scintillation counter. The external standard ratio method was employed for calculation of counting efficiency using a standard quench curve.

The release data were computed and analyzed by a computer[16] using a FORTRAN program. Appropriate corrections were applied for the sample withdrawn, and medium was added. All release studies were conducted in triplicate.

RESULTS AND DISCUSSION

Film Characteristics—Lanolin alcohol was found to form thin, isolatable films. The lanolin alcohol films with a minimum thickness of 65 μm could be easily recovered intact from the mercury substrate. The lanolin alcohol films with less than 65-μm thickness were fragile, and their uniformity and integrity during isolation could not be assured due, in part, to associated tackiness. The inclusion of appropriate amounts of solvent-plasticizer, *e.g.*, propylene glycol or cetyl alcohol, reduced film tackiness. The lanolin alcohol film integrity was enhanced by ethylcellulose. When the solvent-plasticizer concentration was kept constant at 5% (w/w), the modulus of elasticity increased with the increasing proportion of ethylcellulose and a corresponding decrease in the proportion of lanolin alcohol. The modulus of elasticity reached a maximum value at an ethylcellulose concentration of 15% (w/w) with a corresponding lanolin alcohol concentration of 80% (w/w) (Tables I and II).

The effect of variation in the lanolin alcohol–propylene glycol ratio on film properties also was studied while the ethylcellulose content was held constant at 15% (w/w) (Table III). Compositions with 75–77.5% (w/w) lanolin alcohol and 7.5–10% (w/w) propylene glycol produced films with a high modulus of elasticity (Table III). These compositions also gave perceptibly good films. A further increase in the proportion of propylene glycol up to 25% (w/w) with a corresponding decrease in the proportion of lanolin alcohol did not substantially alter the film characteristics. However, an increase in the propylene glycol concentration beyond 25% (w/w) resulted in films that were definitely tacky and had a low modulus of elasticity.

Solubility Studies—Triamcinolone acetonide solubility in propylene glycol at 22 and 37° was 8.04 ± 0.19 and 12.09 ± 0.18 mg/ml, respectively. The solubility in cetyl alcohol at 22 and 37° was 0.92 ± 0.3 and 1.25 ± 0.05 mg/ml, respectively. The solubility values are expressed as the mean ± *SD* of three determinations. The attainment of equilibrium solubility in 3 days was noted by the fact that there was no difference in absorbance between the samples analyzed at the end of 3 and 6 days. Since the cetyl alcohol had a strong absorption at 239 nm, the side of the absorption band was used. Actual measurements of steroid concentration were made at 265 nm after verifying compliance with Beer's law.

[14] Beckman CPM-100 counter.
[15] Hanson Research Corp., Northridge, Calif.
[16] Burroughs B6700.

Table IV—Comparison of *Q versus* $t^{1/2}$ and First-Order Treatments of Triamcinolone Acetonide Release Data from Films Containing Propylene Glycol as Plasticizer at 37 ± 0.5°

Lanolin Alcohol–Ethylcellulose–Propylene Glycol Ratio	Drug Concentration[a], %	*Q versus* $t^{1/2}$ [b]			First Order		
		t_{lag}, min	Correlation Coefficient	$k \times 10^3$, mg cm^2 min$^{-1/2}$	t_{lag}, min	Correlation Coefficient	$K \times 10^3$, min^1
8.0:1.5:0.5	0.50	24.05	0.992	0.405	−54.51	0.990	0.639
8.0:1.5:0.5	0.99	4.70	0.995	1.056	−56.62	0.983	1.169
8.0:1.5:0.5	1.96	0.35	0.994	1.650	−195.74	0.978	0.696
8.0:1.5:0.5	2.91	6.26	0.994	2.849	−113.20	0.986	0.858
8.5:1.0:0.5	0.50	17.14	0.997	0.448	−65.47	0.996	0.764
8.5:1.0:0.5	0.99	−0.53	0.980	1.131	−41.54	0.919	1.833
8.5:1.0:0.5	1.96	7.18	0.996	1.969	−92.23	0.995	0.929
8.5:1.0:0.5	2.91	−0.07	0.979	2.384	−258.55	0.957	0.636

[a] Weight of drug per weight of dry film. Drug concentration exceeded solubility in all cases. [b] All correlation coefficients and k and K values were computed from the regression line drawn from the data obtained by triplicate runs at each level by using the TEKTRONIX (model 4005-1) graphics terminal.

The apparent solubility of triamcinolone acetonide in lanolin alcohol at 22 and 37° was 0.13 ± 0.01 and 0.41 ± 0.01 mg/g, respectively. The attainment of equilibrium in 5 days was noted by running the partitioning experiment for 8 days with daily sampling of the aqueous phase. No further reduction in aqueous phase radioactivity was observed after 5 days.

Release Kinetics—Higuchi (9) showed that the *Q versus* $t^{1/2}$ relationship is common to homogeneous as well as to granular matrix systems during unidirectional leaching or extraction from a simple planar surface (Eqs. 1–5). It is necessary that A be greater than C_s (for homogeneous) or ϵC_s (for granular matrix) by a factor of three or four. A first-order release mechanism in which the release rate is proportional to the amount of drug left in the matrix also might be considered possible for drug release from polymeric systems of this type (11, 15, 16). This can be shown as:

$$\log (Q_\infty - Q) = \frac{-Kt}{2.303} + \log Q_\infty \qquad \text{(Eq. 9)}$$

where Q_∞ is the initial amount of drug present per unit area of the film, Q is the amount of drug present per unit area at time t, and K is the first-order rate constant.

In this study, the release data were analyzed to determine which release mechanism might be operative. The data comparing both of these treatments for triamcinolone acetonide release from matrixes containing propylene glycol as plasticizer are shown in Table IV and Figs. 1 and 2. The linear square root of time plots had high correlation coefficients. The observed lag times were relatively small, and the release rate constant, k, increased with the increase in drug concentration, as predicted by Eqs. 1 and 2. On the other hand, relatively high correlation coefficients also were obtained for the first-order treatment of the release data. However, highly negative lag times and a lack of constancy in the first-order constants (Table IV) strongly point against this mechanism. An initial curvature effect also was noticed in all first-order treatments of the data. A representative plot of the first-order data is shown in Fig. 5. Similar results were seen with systems containing cetyl alcohol as the plasticizer.

Figures 1–4 show the *Q versus* $t^{1/2}$ treatment of the data for different concentrations of triamcinolone acetonide in matrixes containing propylene glycol or cetyl alcohol. All plots show the mean of three observations because of small standard deviations involved in most cases. The maximum amount of drug released varied from 7.6 to 46.0% of its solubility in distilled water at 37°. A good linear fit was observed in all cases, with slight negative deviation at longer time intervals and for higher drug concentrations. This deviation might be due to the exhaustion of the drug in the suspension phase and to the increase in diffusion distance for the

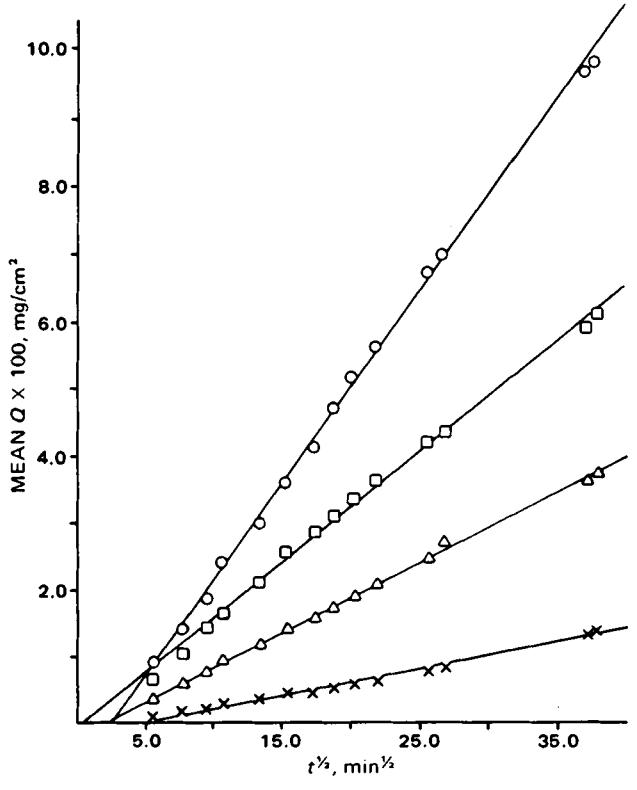

Figure 1—*Drug release from films containing lanolin alcohol–ethylcellulose–propylene glycol (8.0:1.5:0.5) at different concentrations of triamcinolone acetonide. Key: ×, 0.50%; △, 0.99%; □, 1.96%; and ○, 2.91%.*

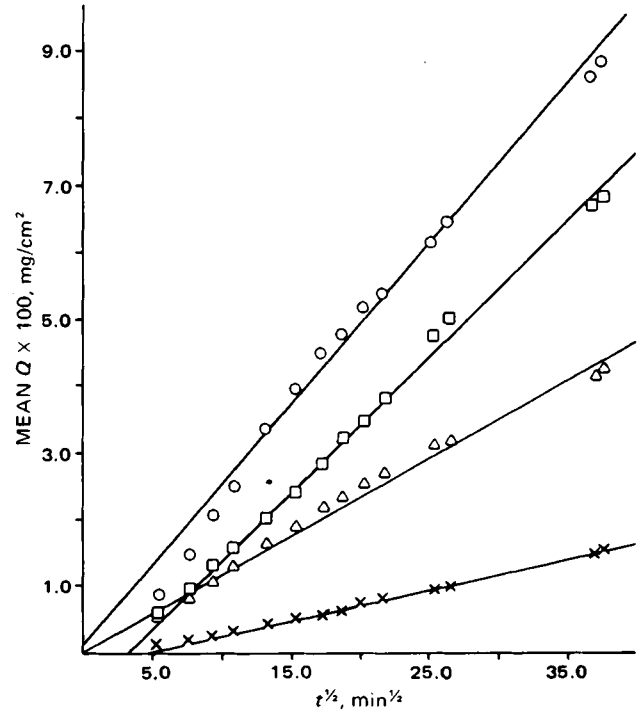

Figure 2—*Drug release from films containing lanolin alcohol–ethylcellulose–propylene glycol (8.5:1.0:0.5) at different concentrations of triamcinolone acetonide. Key: ×, 0.50%; △, 0.99%; □, 1.96%; and ○, 2.91%.*

Table V—*Q versus* $t^{1/2}$ Treatments of Triamcinolone Acetonide Release Data from Films Containing Cetyl Alcohol as Plasticizer at 37 ± 0.5°

Lanolin Alcohol–Ethylcellulose–Cetyl Alcohol Ratio	Drug Concentration[a], %	$k \times 10^3$ [b], mg cm^2 min$^{-1/2}$	t_{lag}, min	Correlation Coefficient
8.0:1.5:0.5	0.50	0.454	5.94	0.990
8.0:1.5:0.5	0.99	1.270	0.52	0.965
8.0:1.5:0.5	1.96	2.116	0.14	0.967
8.0:1.5:0.5	2.91	2.926	−0.07	0.932
8.5:1.0:0.5	0.50	0.540	−3.72	0.957
8.5:1.0:0.5	0.99	0.940	5.26	0.996
8.5:1.0:0.5	1.96	1.940	0.06	0.974
8.5:1.0:0.5	2.91	2.756	1.98	0.982

[a] Weight of drug per weight of dry film. Drug concentration exceeded solubility in all cases. [b] All k values and correlation coefficients were computed from the regression line drawn from the data obtained by triplicate runs at each level by using the TEKTRONIX (model 4005-1) graphics terminal.

drug in the film. The observed lag times never exceeded 1.7% of the total release period (24 hr).

Effect of Drug Concentration—The densities of lanolin alcohol and ethylcellulose were determined to be 0.98 and 1.38 g/ml using the pycnometric method. The weight per weight drug concentrations (Tables IV and V) were converted to weight per volume (A values) concentrations. The effect of the changing the drug concentration on the release rate constant, k, was tested using these concentrations of triamcinolone acetonide for each composition of the film tested. In all cases, the k *versus* A plots were slightly more linear (r = 0.992) than the k *versus* $A^{1/2}$ plots (r = 0.960). While Eqs. 4 and 5 predict a linear relationship between k and $A^{1/2}$, the observed results also could be explained in terms of a granular matrix system alone if the initial porosity were assumed to be very small. Such as assumption appears to be reasonable since these matrixes contain a plasticizer. Higuchi (9) showed that in those instances where initial porosity is very small or where the fraction of the matrix volume occupied by the drug is relatively large, $\epsilon \cong KA$ and Eq. 5 reduces to:

$$k = A\sqrt{\frac{DK}{\tau}(2 - KC_s)C_s} \qquad \text{(Eq. 10)}$$

where K is equal to the specific volume of the drug if A is expressed in terms of grams of drug per milliliter.

Effect of Change in Plasticizer—According to Eq. 4, one would expect k to decrease substantially when the solvent-plasticizer is changed from propylene glycol to cetyl alcohol in view of the nearly eightfold difference in drug solubility in that vehicle. This expectation would be valid if D, the diffusion coefficient of the drug in the matrix, were not altered significantly by the change of the solvent-plasticizer. Alternatively, in the same release medium, Eq. 5 would predict comparable k values for the two systems differing only in the nature of solvent-plasticizer, provided that volume, porosity, and tortuosity of the matrix are not significantly altered. This might well be the case for the systems studied since the k values for the cetyl alcohol systems (Table V) were comparable to those for the propylene glycol systems (Table IV).

Effect of Vehicle Composition—Table VI describes the effect of drug solubilization on drug release by varying the propylene glycol–lanolin alcohol concentration. The steroid concentration (0.10%, w/w) was chosen, in part, to permit this study in films of sufficient integrity. The

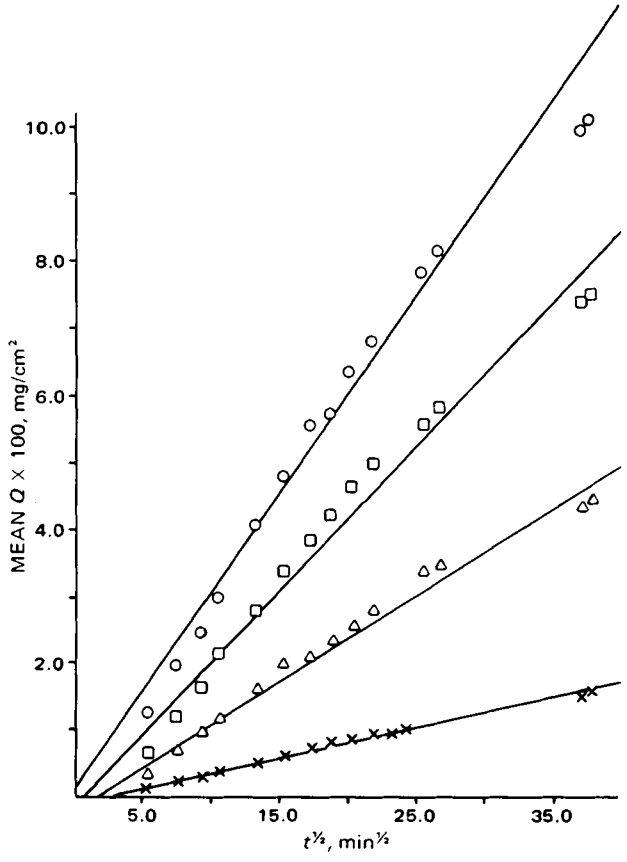

Figure 3—*Drug release from films containing lanolin alcohol–ethylcellulose–cetyl alcohol (8.0:1.5:0.5) at different concentrations of triamcinolone acetonide. Key:* ×, *0.50%;* △, *0.99%;* □, *1.96%; and* ○, *2.91%.*

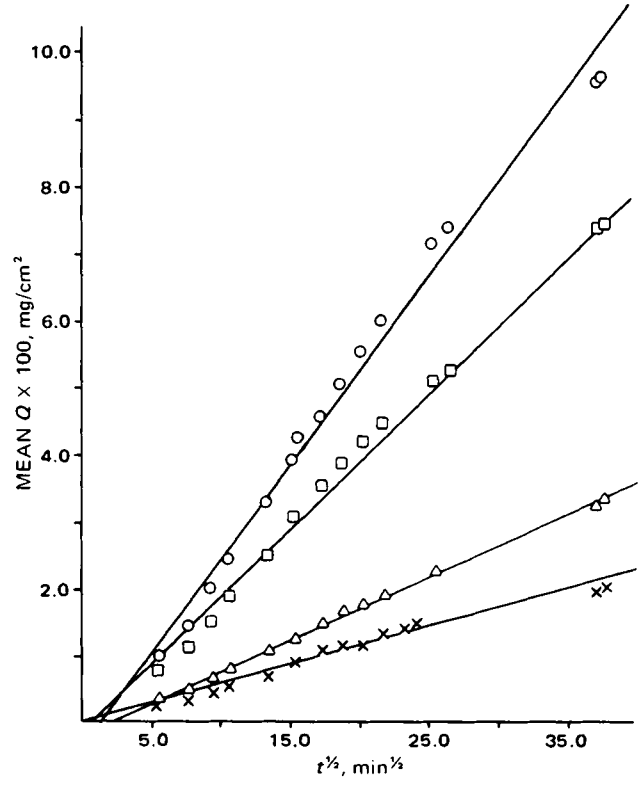

Figure 4—*Drug release from films containing lanolin alcohol–ethylcellulose–cetyl alcohol (8.5:1.0:0.5) at different concentrations of triamcinolone acetonide. Key:* ×, *0.50%;* △, *0.99%;* □, *1.96%; and* ○, *2.91%.*

Table VI—Release of 0.10% (w/w) Triamcinolone Acetonide from Matrixes Containing Different Percentages of Propylene Glycol after 6 hr at 37°

Lanolin Alcohol–Ethylcellulose–Propylene Glycol Ratio	Amount[a] Released, %
8.5:1.5:0.0	37.11 ± 0.62
8.0:1.5:0.5	40.46 ± 1.12
7.7:1.5:0.8	32.38 ± 0.71
7.0:1.5:1.5	30.48 ± 0.29

[a] All values are expressed as the means ± *SD* of three runs.

maximum release of drug was obtained with systems containing the drug in a near-saturated solution (5% propylene glycol). The release rate decreased with systems containing no propylene glycol (major solubilizer) as well as with systems containing the solubilizer in excess of that required to dissolve the steroid completely (8 and 15% propylene glycol). These vehicle effects are consistent with those reported for fluocinolone acetonide from propylene glycol–water gels (20).

Conclusion—This film-forming capability of lanolin alcohol is potentially significant and appears to have remained unrecognized in spite of the use of this material in cosmetic and dermatologic preparations. Additional work is planned to explain its film-forming ability.

The release of suspended triamcinolone acetonide from films of lanolin alcohol in combination with ethylcellulose and propylene glycol or cetyl alcohol followed the diffusion-controlled granular matrix model (9). The *in vitro* skin penetration work in progress may help to determine the rate-limiting step during topical drug absorption.

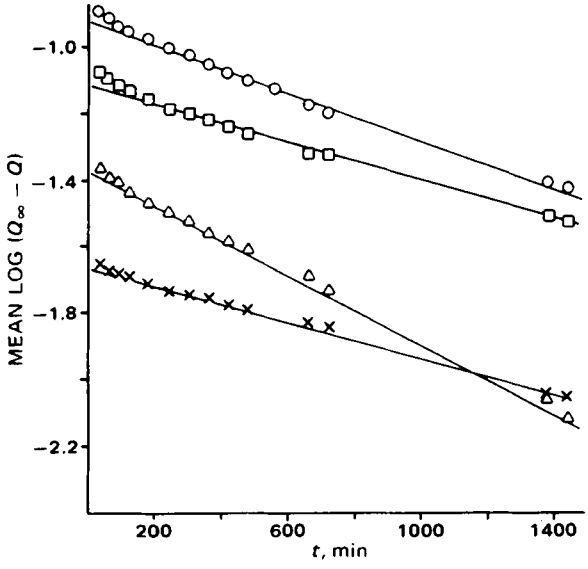

Figure 5—*First-order plots of drug release from films containing lanolin alcohol–ethylcellulose–propylene glycol (8.0:1.5:0.5) at different concentrations of triamcinolone acetonide. Key: ×, 0.50%; △, 0.99%; □, 1.96%; and ○, 2.91%.*

REFERENCES

(1) M. Luongo, J. J. Sciarra, and C. O. Ward, *J. Pharm. Sci.*, **63**, 1376 (1974).

(2) M. J. Groves and J. N. Hague, British pat. 1213295 (1970).

(3) F. E. Gould, U.S. pat. 3,577,516 (1971).

(4) N. Applezweig, U.S. pat. 3,536,809 (1970).

(5) J. J. Sciarra and R. N. Gidwani, *J. Pharm. Sci.*, **61**, 754 (1972).

(6) S. Borodkin and F. E. Tucker, *ibid.*, **64**, 1289 (1975).

(7) J. A. Conrady, Amherst, and C. H. Stockman, U.S. pat. 3,590,118 (1971).

(8) T. Higuchi, *J. Pharm. Sci.*, **50**, 874 (1961).

(9) *Ibid.*, **52**, 1145 (1963).

(10) S. J. Desai, A. P. Simonelli, and W. I. Higuchi, *J. Pharm. Sci.*, **54**, 1459 (1965).

(11) J. B. Schwartz, A. P. Simonelli, and W. I. Higuchi, *ibid.*, **57**, 274 (1968).

(12) *Ibid.*, **57**, 278 (1968).

(13) P. Singh, S. J. Desai, A. P. Simonelli, and W. I. Higuchi, *J. Pharm. Sci.*, **56**, 1542 (1967).

(14) *Ibid.*, **56**, 1548 (1967).

(15) S. Borodkin and F. E. Tucker, *J. Pharm. Sci.*, **63**, 1359 (1974).

(16) J. J. Sciarra and R. N. Gidwani, *J. Soc. Cosmet. Chem.*, **21**, 667 (1970).

(17) R. A. Cass, *J. Paint Technol.*, **38**, 281 (1966).

(18) W. L. Chiou, *Can. J. Pharm. Sci.*, **10**, 112 (1975).

(19) Z. T. Chowhan and R. Pritchard, *J. Pharm. Sci.*, **64**, 754 (1975).

(20) B. J. Poulsen, E. Young, V. Coquilla, and M. Katz, *ibid.*, **57**, 928 (1968).

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