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In Vitro Release of Salicylic Acid from Lanolin Alcohols–Ethylcellulose Films

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Abstract □ Lanolin alcohols–ethylcellulose films were investigated as a potential drug delivery system for the controlled release of salicylic acid. The effects of changes in film composition, drug concentration, drug solubility, and stirrer speed on the *in vitro* release of salicylic acid have been examined. The drug release has been found to obey a diffusion-controlled matrix model and square root of time release profile both in the suspension and solution cases.

Keyphrases □ Salicylic acid—*in vitro* release from lanolin alcohols–ethylcellulose films, drug diffusion □ Lanolin alcohols—films with ethyl cellulose, *in vitro* release of salicylic acid, drug diffusion □ Ethylcellulose—films with lanolin alcohols, *in vitro* release of salicylic acid, drug diffusion □ Drug diffusion—*in vitro* release of salicylic acid from lanolin alcohols–ethylcellulose films

The film-forming potential of nonpolymeric materials such as lanolin alcohols, which are extensively used in cosmetic and pharmaceutical formulations, has been recently investigated in our laboratory (1). Lanolin alcohols were found to form isolatable thin films on a mercury substrate. The incorporation of small percentages of ethylcellulose, a known film former (2), and a plasticizer such as propylene glycol with lanolin alcohols was found to give tack-free films of improved quality.

Effective utilization of nonpolymeric substances such as lanolin alcohols in film-forming composition holds considerable promise for a variety of reasons. Such delivery systems could be designed and formulated to provide sustained drug delivery. The potential hazards associated with monomeric impurities in polymers are avoided. Nonpolymeric materials are easy to manipulate and compound, and are relatively easy to obtain in a state of definable composition. They also can be washed from the skin with relative ease using soap and water.

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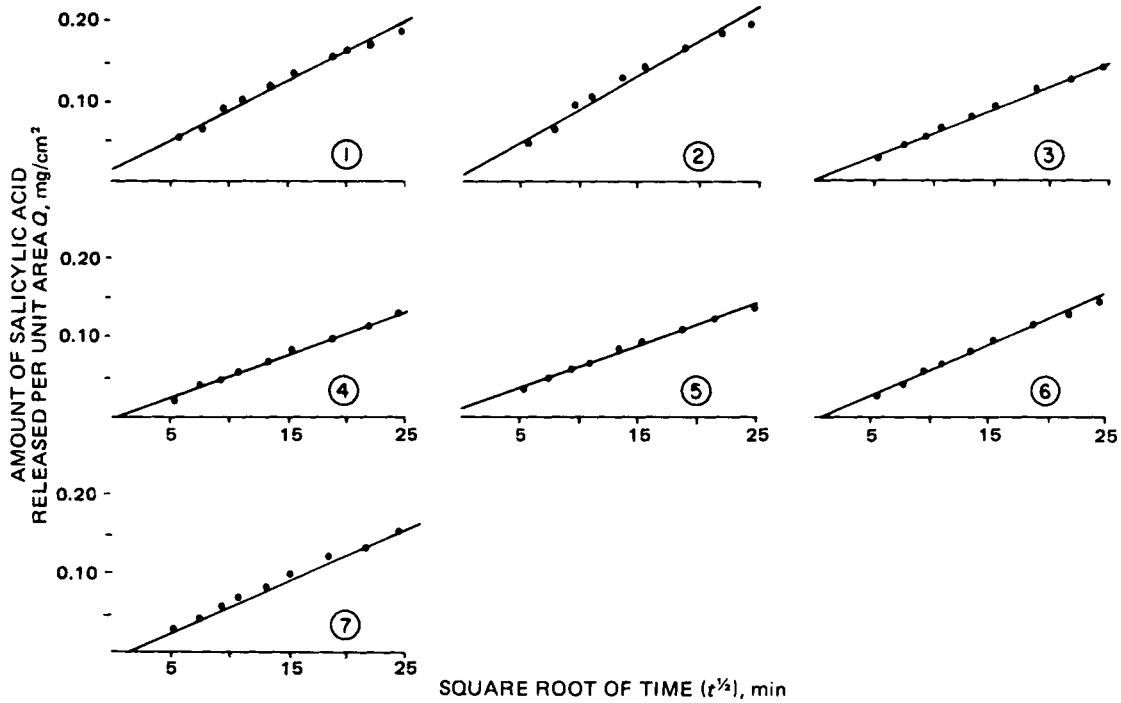

Figure 1—*Release of salicylic acid from films 1–7. Key: (1)* r = 0.992, b = 7.11; *(2)* r = 0.990, b = 7.82; *(3)* r = 0.998, b = 0.11; *(4)* r = 0.999, b = 5.76; *(5)* r = 0.993, b = 5.63; *(6)* r = 0.997, b = 6.34; *(7)* r = 0.999, b = 6.46.

It is the purpose of this study to investigate the *in vitro* release of salicylic acid (a known keratolytic agent) from selected lanolin alcohols–ethylcellulose film compositions with or without propylene glycol as a solvent–plasticizer.

THEORETICAL

In the present study, salicylic acid is assumed to be uniformly dispersed in the film matrix. The solubility of salicylic acid in lanolin alcohols or ethylcellulose is considered negligible based on preliminary work.

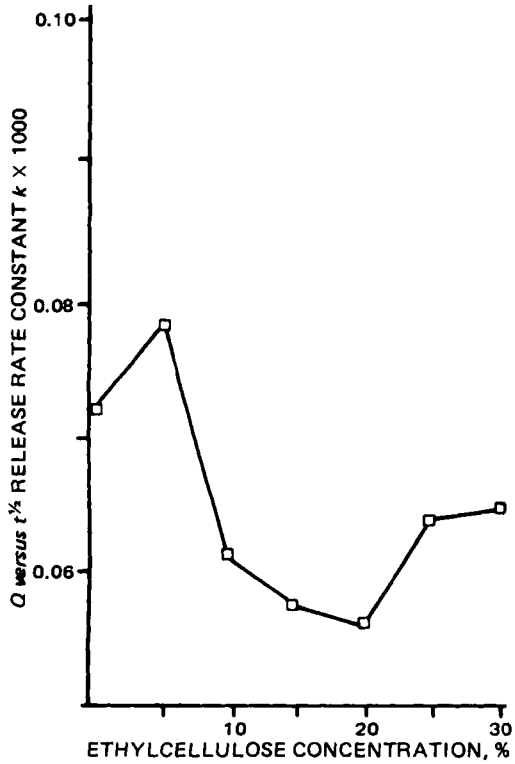

Figure 2—*Effect of vehicle composition on the release rate.*

The release from a planar system having a drug dispersed in a granular matrix has been shown by Higuchi (3) to follow a diffusion-controlled mechanism described by the relationship:

$$Q = \left[\frac{D}{\tau}(2A - \epsilon C_s)C_s \cdot t\right]^{1/2} \quad \text{(Eq. 1)}$$

where Q is the amount of drug released per unit area at time t, D and C_s refer to the diffusion coefficient and solubility of the drug in the permeating fluid, respectively, τ refers to the tortuosity and ϵ to the porosity of the matrix, and A is the amount of drug present in the matrix per unit volume. This equation describes drug release as being linear with the square root of time:

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

where k is the rate constant of release:

$$k = \left[\frac{D\epsilon}{\tau}(2A - \epsilon C_s)C_s\right]^{1/2} \quad \text{(Eq. 3)}$$

The release of drug from a granular matrix in which the drug is present as a solution was shown by Desai *et al.* (4) to be:

$$Q = 2\epsilon C_0\left[\frac{Dt}{\tau\pi}\right]^{1/2} \quad \text{(Eq. 4)}$$

with the rate constant of release:

$$k = 2\epsilon C_0\left[\frac{D}{\tau\pi}\right]^{1/2} \quad \text{(Eq. 5)}$$

where C_0 is the solution concentration and the other parameters are as defined earlier. This equation is applicable when the drug released from the vehicle is <50%.

EXPERIMENTAL

Materials—Lanolin alcohols[1] (mp 61–64°C, *d* 0.98 g/mL), ethylcellulose[2] (*d* 1.38 g/mL), propylene glycol USP[3], and salicylic acid USP[4] (*d* 1.44 g/mL) were used as received. The solvents used were anhydrous methanol[5] (spectral grade) and isopropyl alcohol[5].

Solubility Studies—The solubility of salicylic acid in propylene glycol was determined at room temperature (22°C) and 37°C by adding excess

[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] Amend Drug and Chemical Co., Irvington, N.J.
[5] Mallinckrodt Chemical Works, St. Louis, Mo.

Table I—Calculated Values for Selected Parameters

Film	Film Composition[a]	Film Density[b], g/mL	Film Volume, mL	A, mg/mL	C_s, mg/mL
1	97.5:0:2.5	0.992	0.202	24.812	0.0167
2	92.5:5:2.5	1.012	0.205	25.324	0.0173
3	87.5:10:2.5	1.032	0.192	25.813	0.0165
4	82.5:15:2.5	1.052	0.186	26.300	0.0163
5	77.5:20:2.5	1.072	0.181	26.828	0.0162
6	72.5:25:2.5	1.092	0.176	27.300	0.0160
7	67.5:30:2.5	1.112	0.181	27.828	0.0168

[a] Proportion of lanolin alcohols, ethylcellulose, and salicylic acid expressed as % w/w. [b] Based on density (g/mL) of lanolin alcohols (0.98), ethylcellulose (1.38), and salicylic acid (1.44).

Table II—Release of Salicylic Acid from Lanolin Alcohols–Ethylcellulose Films

	Q versus $t^{1/2}$		
Film	Release Rate Constant (k) × 1000, mg/cm²·min$^{1/2}$	Intercept, min	r
1	7.11	−6.47	0.992
2	7.82	−2.80	0.990
3	6.11	1.06	0.998
4	5.76	4.87	0.999
5	5.63	−0.15	0.993
6	6.34	0.97	0.997
7	6.46	6.43	0.999

salicylic acid to 20 mL of propylene glycol contained in 50-mL screw-capped glass bottles. A polytef-coated magnetic bar was placed in each of the bottles prior to sealing. The contents of the bottle were then stirred in water baths for a period of 4 d to ensure attainment of equilibrium. All studies were conducted in triplicate.

Prior to sampling, the stirring was stopped and salicylic acid was allowed to settle. An aliquot was then filtered[6]. The filtration and sampling apparatus were equilibrated at 22°C or 37°C for a period of 48 h, and all operations were conducted in a constant-temperature room. Actual measurements of salicylic acid concentration were made using a scanning spectrophotometer[7] at 305 nm[8] after appropriate dilutions with anhydrous methanol to ensure compliance with Beer's Law.

Preparation of Solutions—Solutions containing appropriate amounts of lanolin alcohols, ethylcellulose, salicylic acid, and propylene glycol (if added) were prepared in the following manner. Weighed amounts of ethylcellulose were sprinkled onto 25 mL of isopropyl alcohol over a 2-h period with gentle stirring at 50–55°C. The lanolin alcohols were then dissolved in a similar manner. Prior to addition of the salicylic acid, the solutions were cooled to room temperature, transferred to a 50-mL volumetric flask, allowed to stand for 24 h, and the final volume was adjusted with isopropyl alcohol to give a 10% w/v solution.

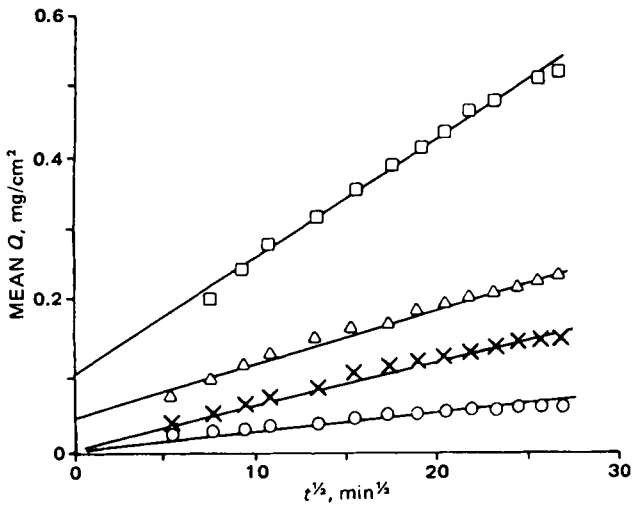

Figure 3—*Drug release from films containing lanolin alcohols–ethylcellulose (8.5:1.5) at different concentrations of salicylic acid. Key: (□) 9.09% w/w; (△) 4.76% w/w; (×) 2.91% w/w; and (○) 0.99% w/w.*

[6] Swinnex-25, 0.22-μm filter; Millipore Corp., Bedford, Mass.
[7] Perkin-Elmer model 202; Coleman Instruments Div., Oakbrook, Ill.
[8] Note that λ_{max} for the aqueous system was 297 nm.

Table III—Effect of Change in Drug Concentration on the Release Rate Constant for Films Containing Lanolin Alcohols and Ethylcellulose at a Ratio of 8.5:1.5

Drug Conc.[a], %	A, mg/cm³	Q versus $t^{1/2}$ [b] Intercept, min	r	$k \cdot 10^{-2}$, mg/cm³·min$^{1/2}$
0.99	10.25	0.20	0.985	0.189
2.91	30.74	0.44	0.991	0.576
4.76	51.23	−24.58	0.991	0.740
9.09	102.46	−35.00	0.990	1.642

[a] Weight of drug per weight of dry film. [b] All correlation coefficients 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.

Preparation of Films—Two milliliters of an appropriate 10% w/v solution was transferred onto a preweighed glass petri dish (area = 18.1 cm²), placed on a flat surface at room temperature. The petri dishes were kept partially covered for 48 h to ensure slow and uniform evaporation of the solvent and to prevent blistering of the film, this also ensured uniform distribution of drug particles in the film matrix. Complete evaporation was ensured by drying to a constant weight. The film-coated petri dishes were stored in a desiccator (anhydrous calcium chloride) for at least 24 h prior to the release studies.

Release Studies—The release studies were conducted following the method reported previously (1), at 37 ± 0.5°C and a stirring rate of 40 rpm. Three-milliliter samples were drawn at definite intervals over a period of 10 h and, each time, replaced with an equal volume of distilled water. The salicylic acid concentrations were determined spectrophotometrically at 297 nm[9]. The unidirectional release of salicylic acid from the films was ensured by good adherence of the film to the bottom of the petri dish, as confirmed by frequent visual examinations during and at the termination of the release studies. No evidence of peeling was ever recorded. All release studies were conducted in triplicate.

RESULTS AND DISCUSSION

The solubility of salicylic acid in propylene glycol at 22°C and 37°C was found to be 0.481 ± 0.028 and 0.543 ± 0.025 g/mL, respectively; values are expressed as the mean ±SD of three measurements. The solubility of salicylic acid in lanolin alcohol or ethylcellulose was found to be negligible. The film compositions studied are described at appropriate locations in the text.

Release from Films Containing Solid Drug—Adherence of drug release to the Q *versus* $t^{1/2}$ relationship requires that the drug concentration in the film matrix far exceeds solution drug concentration at the interface ($A \gg C_s$ or $\epsilon\ C_s$). In the systems studied, this criterion was satisfied (Table I). The release data were examined in terms of the Higuchi model for a granular matrix. The correlation coefficient (r) for the regression line and the values of the intercept (time) were used as the principal criteria for evaluation.

Q *versus* $t^{1/2}$ plots for films 1–7 containing 2.5% w/w drug are shown in Fig. 1. On examination of the release data for compliance with the Higuchi model (Table II), it was observed that the correlation coefficients were consistently high (0.990–0.999). Three film compositions (*i.e.*, 1, 2, and 5) had negative intercepts, but the values were relatively small. Negative intercepts may be attributed to the immediate release of the drug present on the film surface. The calculated release rate constant

[9] Bausch and Lomb Spectronic 710.

Table IV—*Q versus* $t^{1/2}$ Treatment of Salicylic Acid Release Data from Films Containing Dissolved Drug in Solution

Film Composition[a]	Drug Conc.[b], %	C_0 mg/cm^3	t_{lag}, min	r	$k \cdot 10^{-2}$ [c], mg/cm^2·min$^{1/2}$
7.5:1.5:1.0	0.99	10.30	−0.04	0.996	0.180
7.5:1.5:1.0	2.91	30.90	−0.05	0.985	0.516
7.5:1.5:1.0	4.76	51.50	−12.22	0.982	0.776

[a] Proportion of lanolin alcohols, ethylcellulose, and propylene glycol expressed as % w/w. [b] Weight of drug per weight of dry film. [c] All correlation coefficients 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.

represents the steady-state region. The variation of rate constant as a function of the film composition is shown in Fig. 2. Interestingly, the release rate constant increased at first with inclusion of ethylcellulose and then declined sharply with increases in ethylcellulose concentration, passing through a minimum value at ~15–20% ethylcellulose before increasing again. Increases in the concentration of ethylcellulose (>20% w/w) resulted in an increased rate of drug release, with a tendency to level off at ~30% ethylcellulose concentration.

Analysis of release data from films containing a fixed proportion of lanolin alcohol and ethylcellulose but varying drug concentrations of salicylic acid (Table III, Fig. 3) further supported earlier observations favoring the Higuchi model. A test previously used by Schwartz *et al.* (5) was then applied. By taking the logarithm, Eq. 2 can be rewritten as:

$$\log Q = \log k + \tfrac{1}{2}\log t \qquad \text{(Eq. 6)}$$

If the Higuchi model indeed described the release mechanism, the slope of log Q *versus* log t plots should be 0.5. The calculated values for the slope ranged from 0.42 to 0.53 with a mean of 0.49.

The effect of change in drug concentration on release rate constant, k, was tested using the four drug concentrations of salicylic acid for one film composition (Table III, Fig. 3). The k *versus* A plot was found to be more linear ($r = 0.996$) than k *versus* $A^{1/2}$ plot ($r = 0.850$). Although Eq. 1 predicts a linear relationship between k and $A^{1/2}$, the observed results could also be explained in terms of Eq. 1 if the initial porosity of the granular matrix was assumed to be very small. Higuchi (3) has shown that if the fraction of the matrix volume occupied by the drug is relatively large or if the initial porosity of the matrix is very small, $\epsilon = VA$ where V is the specific volume of the drug if A is expressed in terms of grams per milliliter. Eq. 3 then reduces to:

$$k = A\frac{DV}{\tau}(2 - VC_s)\,C_s \qquad \text{(Eq. 7)}$$

predicting a direct proportionality between k and A.

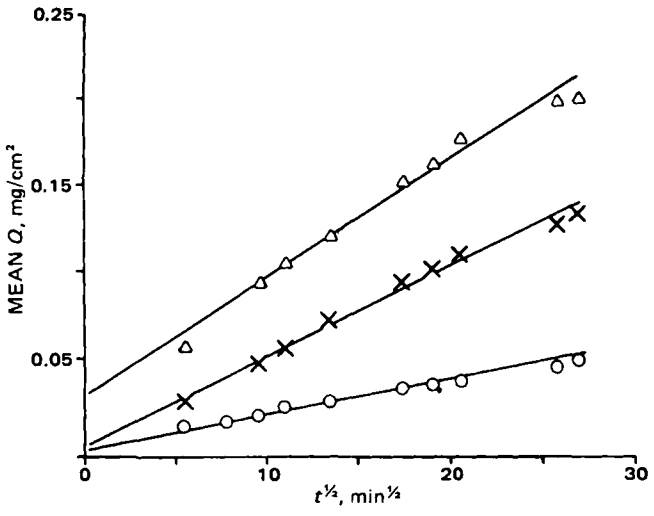

Figure 4—*Drug release from films containing lanolin alcohols–ethylcellulose–propylene glycol (7.5:1.5:1.0) at different concentrations of salicylic acid in solution. Key: (△) 4.76% w/w; (×) 2.91% w/w; and (○) 0.99% w/w.*

Drug Release from Film Matrices Containing the Drug in Solution—The release studies were conducted from lanolin alcohols–ethylcellulose films containing 10% w/w propylene glycol as solvent for the drug. The three drug concentrations examined were 0.99, 2.91, and 4.76% w/w, respectively. In each case the drug concentration was well below the saturation solubility of salicylic acid in propylene glycol. Furthermore, comparative examination of films with and without propylene glycol further established that the drug was in fact in solution.

The Q *versus* $t^{1/2}$ treatment of data showed linearity, but not as good as in the suspension case (Table IV, Fig. 4). It should be noted that the drug released rose to 71%, which was well above the constraints imposed on Eq. 5. The lag times were extremely small except in the case of films containing 4.76% w/w of drug. Equation 5 predicts a linear relationship between k and C_0 for the same system containing different concentrations of the drug in solution. Analysis of the data in Table IV revealed that there is an excellent linear correlation between k and C_0.

The release of both propylene glycol and salicylic acid is not predicted or accounted for by Eqs. 4 and 5. The square root of time dependency would be expected whether or not propylene glycol is released faster than the drug.

This study further demonstrated the potential application of lanolin alcohols–ethylcellulose films in controlled drug-delivery systems. Kinetic analysis suggests that the unidirectional release of salicylic acid from these films (whether the drug was suspended or in solution) follows a diffusion-controlled granular matrix model. The rate and extent of drug release from these films can be effectively manipulated by varying the drug concentration, film composition, and choice of solvent–plasticizer.

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