Sustained Release of Drugs from Ethylcellulose–Polyethylene Glycol Films and Kinetics of Drug Release

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Received April 11, 1978, from the *Pharmacy Department, School of Pharmacy, Hebrew University, Jerusalem, Israel.* Accepted for publication August 22, 1978.

Abstract □ Cast films composed of different ratios of polyethylene glycol and ethylcellulose containing salicylic acid, caffeine, and tripelennamine as model dispersed drugs were prepared and exhibited sustained release. The drug content of the film declined at an apparent first-order rate initially, whereas the drug quantity released was proportional to the square root of time. Data analysis validated the latter treatment, which is in accordance with the diffusional matrix model, and disproved the validity of the apparent first-order conformity. The release rates were independent of film thickness and proportional to drug concentration in pure ethylcellulose films; in polyethylene glycol–ethylcellulose films, a positive deviation from linearity was observed. The logarithm of the rate constant was proportional to the fraction of polyethylene glycol in the film. Unlike in pure ethylcellulose films, the release rate in mixed films was altered by a change in the external fluid pH.

Keyphrases □ Ethylcellulose–polyethylene glycol films—containing model dispersed drugs, drug release kinetics □ Polyethylene glycol–ethylcellulose films—containing model dispersed drugs, drug release kinetics □ Films—ethylcellulose–polyethylene glycol containing model dispersed drugs, drug release kinetics □ Sustained-release films—ethylcellulose–polyethylene glycol, containing model dispersed drugs, drug release kinetics □ Dosage forms, potential—ethylcellulose–polyethylene glycol films, containing model dispersed drugs, drug release kinetics

Incorporation of drugs in inert polymer films during their manufacture affords a possible method of achieving controlled release. Such products can be adapted to topical, oral, and other routes of administration by utilizing them directly or in the form of coatings (1–3). Drug release rates may be altered by variations of the dimensional parameters of the film, the polymer matrix material, and the drug concentration in the film.

Greater changes may be obtained by the use of additive polymers selected on the basis of hydrophilicity properties, such as hydroxypropylcellulose in polyvinyl acetate films (3). Polyethylene glycol 4000 was recently studied in connection with barrier films and drastically increased the permeability of ethylcellulose films in proportion to the amount added (4). Unlike hydroxypropylcellulose, the polyethylene glycol is leachable, introducing porosity and, hence, solvent-occupied regions into the films without loss of barrier properties.

The objective of the present work was to study the influence of polyethylene glycol as a film component on the release of drugs dispersed in ethylcellulose films. While such films might behave diffusionally (5) like ethylcellulose films containing caffeine and salicylic acid (1), the loss of polyethylene glycol could give rise to either homogeneous or heterogeneous release (6).

In the design of controlled-release products, the combination of drug and permeabilizing agent in different quantities has an important influence on the release rate and membrane structure. The presence of two leachable components, one tending to form isolated pores and the other of undetermined pore-forming and plasticizing properties, could give rise to more than one kinetic pattern and could increase the release rate abruptly at a critical porosity value. Films heavily loaded with drugs or permeabilizers might be expected ultimately to show structure breakdown, leading to rapid dissolution-controlled drug release.

The effects of composition on the consistency of release behavior were explored utilizing salicylic acid and caffeine. Their permeabilities were studied in the corresponding barrier film systems. Films containing the basic drug tripelennamine were also included for comparison. Preliminary work showed that these combinations had satisfactory film-forming and release properties (7). The general approach followed that of Borodkin and Tucker (3) in their study on mixed film composition.

EXPERIMENTAL

Materials—Ethylcellulose (N-type) had an ethoxyl content of 47.5–49.0%. The viscosity of a 5% (w/w) solution in toluene–ethanol (80:20 w/w) was 100 cps[1]. Polyethylene glycol 4000[2] was BPC grade. Caffeine, salicylic acid, and tripelennamine hydrochloride were USP grade. The pH 7.00 and 2.00 buffers were USP buffer mixtures.

Film Preparation—The films were cast from a chloroform solution containing 10% (w/w) total drug and polymers on polytef-coated plates, using the techniques of Kanig and Goodman (8). The solvent was allowed to evaporate for 24 hr, the film was removed from the plate and air dried for 24 hr, and the drug content was calculated from the weight ratio of drug and polymers used.

Tripelennamine was added as an oily liquid, prepared from an aqueous solution of the salt by addition of 5 *N* NaOH, extraction with chloroform, and evaporation of the solvent. Spectrophotometric determination of the drug content after solution of specimen films in chloroform gave results that accorded with the weight ratios used in all three systems.

Determination of Release Rate—Films were cut to a circular form 36 cm^2 in area and were weighed accurately. Film thickness was measured in 10 different places with a micrometer[3]. The thickness used did not vary by more than 5% over the film surface. The membranes were attached to glass plates with a silicone pressure-sensitive adhesive[4] and immersed in 500 ml of buffer solution preheated to 37°. (The quantities used afforded sink conditions.) The solution was mixed with a polystaltic pump[5] at a flow rate of 31 ml/min. To avoid water evaporation, the vessels were covered with aluminum foil during the experiments.

Aliquots (5 ml) were withdrawn at various times and replaced by fresh solvent, with corrections being applied in the calculations. The amount of drug released was determined spectrophotometrically[6] at the maximum: salicylic acid at 296 nm, caffeine at 273 nm (both in pH 7 buffer), and tripelennamine at 246 nm in 0.1 *N* HCl.

Experiments were duplicated or triplicated, and mean results were reported. Reproducibility was within 5% of the mean.

THEORETICAL

The release of drugs dispersed in thin films can be treated using the Higuchi (5, 6) equations for diffusion-controlled transport in a polymer matrix. In a planar homogeneous system, the following relationship holds:

$$Q = [D(2A - C_s)C_s t]^{1/2} \quad \text{(Eq. 1)}$$

[1] Hercules, Wilmington, Del.
[2] B.D.H. Ltd., Poole, England.
[3] Tesa Master, Tesa, Switzerland.
[4] Dow Corning Corp., Midland, Mich.
[5] Model MHRK, Watson-Marlow, Falmouth, England.
[6] Unicam SP 1800, Pye Unicam Ltd., Cambridge, England.

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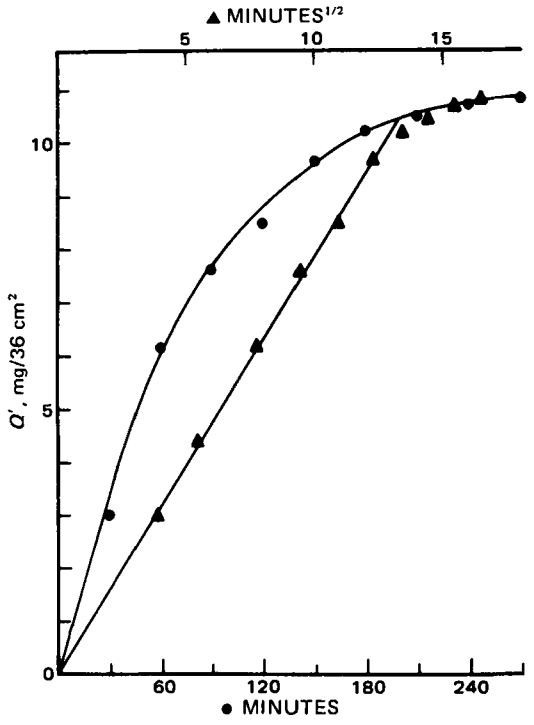


Figure 1—*Drug release into pH 7 buffer from film containing 5% (w/w) caffeine in 4:6 polyethylene glycol–ethylcellulose. (The total drug content was 12 mg.) Key:* ●, Q′ versus t; *and* ▲, Q′ versus $t^{1/2}$.

where Q is the amount of drug released per unit area exposed after time t; and D, A, and C_s are the diffusivity, initial concentration, and solubility of the drug in the matrix, respectively. Where the matrix is granular and the drug is removed from a planar slab by leaching through a capillary network, Q, the amount of drug liberated per unit surface area of matrix into the external medium in time t is given by:

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

where C_s is the solubility and D is the diffusion coefficient of the drug in the leaching medium and ϵ is the porosity and τ is the tortuosity of the matrix.

In the homogeneous case, drug release is directly proportional to the square root of time. Equation 1 then reduces to:

$$Q' = k' t^{1/2} \quad \text{(Eq. 3)}$$

If Q' is the amount of drug released from an area of film S, $Q' = QS$ and $k' = kS$, where k is the release rate constant given by:

$$k = [D(2A - C_s)C_s]^{1/2} \quad \text{(Eq. 4)}$$

Equation 3 also describes the case of the granular matrix if the value of k remains constant throughout the leaching process. Then k is given by:

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

RESULTS AND DISCUSSION

From each film composition studied, the drugs were released at a rate that decreased with time. Treatment of the experimental data on the basis of the diffusion-controlled model indicated that the drug concentration increased linearly with the square root of time in all systems. Figure 1 shows typical Q'–t and Q'–$t^{1/2}$ plots obtained from films containing 5% caffeine with polyethylene glycol 4000 and ethylcellulose in a 4:6 ratio. All of the drugs and films used gave this type of release pattern.

The data also appeared to fit a first-order equation (Eq. 6), used to describe the release from certain polymer films (2, 9):

$$\log A' = \log A - \frac{Kt}{2.303} \quad \text{(Eq. 6)}$$

where A' is the drug content of the film at time t.

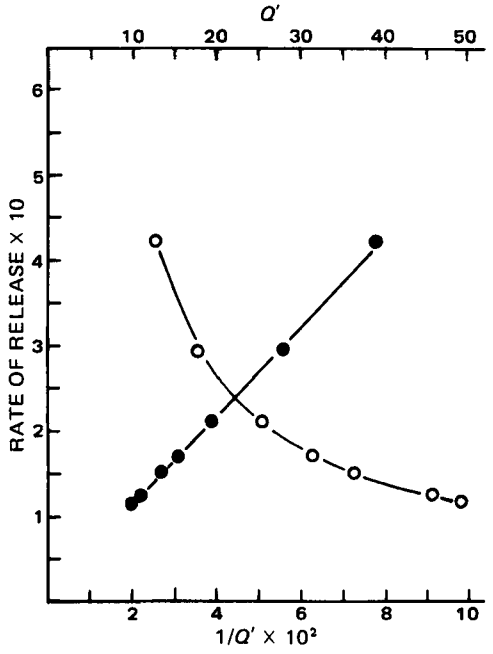


Figure 2—*Plots of release rate into pH 7 buffer of 20% (w/w) salicylic acid from 4:6 polyethylene glycol–ethylcellulose film against the amount of drug release* (Q′) (○) *and the reciprocal of the amount of drug release* (1/Q′) (●).

Table I—Comparison between Linearizations of Release Rate Data [a] by First-Order and Diffusion Treatments for a 20% (w/w) Salicylic Acid in Polyethylene Glycol–Ethylcellulose Film

Polyethylene Glycol–Ethylcellulose Ratio	First Order		Diffusion Control	
	t_{lag}, min	Correlation Coefficient	t_{lag}, min	Correlation Coefficient
0:10	−173	0.987	0.11	0.999
1:9	−174	0.986	0.22	0.999
2:8	−209	0.991	0	0.999
4:6	−141	0.989	0.16	0.998
5:5	−65	0.989	0.32	0.997

[a] Release into pH 7 buffer.

Some typical evaluations of the best statistical lines obtained using the two equations with release data from salicylic acid films are listed in Table I. The diffusion equation gave consistently higher values for the correlation coefficient (0.997–0.999) than did the first-order equation (0.986–0.991).

Lag times for establishment of the apparent linear relations in the two treatments also are included in Table I. They were negligibly short in the diffusion model and unreasonable in the first-order model.

Further evidence bearing upon the relative validity of these two models was obtained by utilizing the differential forms of their rate equations (1, 10). For diffusion control, the rate dQ'/dt is proportional to the reciprocal $1/Q'$, where Q' is the total drug released at a given time:

$$\frac{dQ'}{dt} = \frac{k'^2}{2Q'} \quad \text{(Eq. 7)}$$

For first-order release, the rate is related directly to Q':

$$\frac{dQ'}{dt} = KA - KQ' \quad \text{(Eq. 8)}$$

Release rates were determined by measurement of the slopes of Q' *versus* time curves. When the release rates from a typical film of high leachable content (52%) were plotted as a function of Q' and $1/Q'$, linearity was obtained only in the latter case (Fig. 2), indicating that the process is diffusional.

Similar results were obtained with films containing other drugs and concentrations; some representative data are included in Table II.

Final evidence is provided by plots of log Q' against log t, based on the logarithmic form of the diffusional Eq. 3 (Fig. 3). All film compositions studied gave slopes of 0.5.

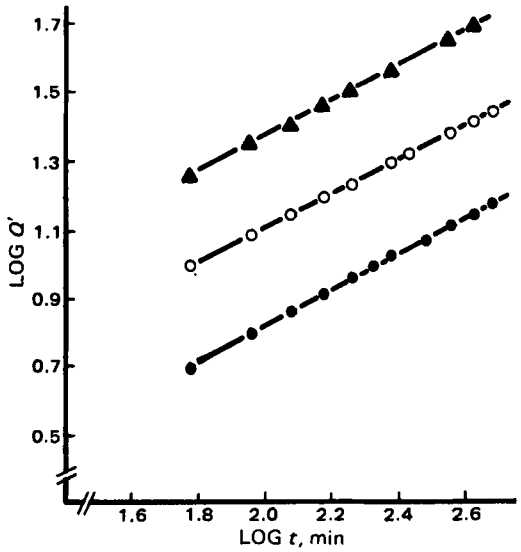


Figure 3—*Relationship of log Q′ to log t. Key: ▲, 20% (w/w) salicylic acid in 4:6 polyethylene glycol—ethylcellulose film (slope = 0.514, r = 0.999); ○, 20% (w/w) salicylic acid in 2:8 polyethylene glycol—ethylcellulose film (slope = 0.499, r = 0.999); and ●, 20% (w/w) tripelennamine in 2:8 polyethylene glycol-ethylcellulose film (slope = 0.526, r = 0.999). (Release was into pH 7 buffer.)*

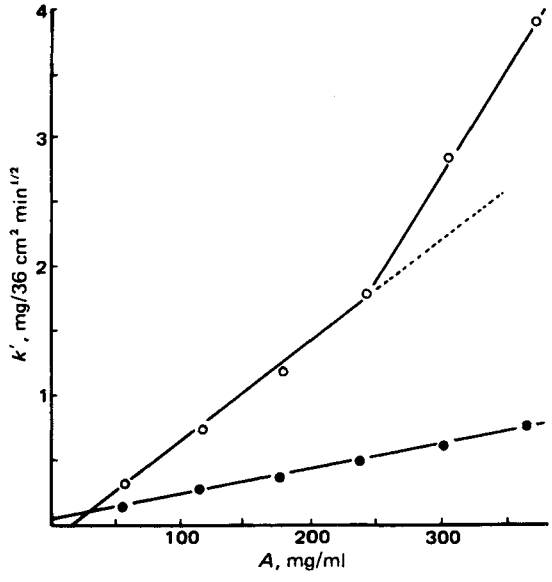


Figure 4—*Relationship of k′ to the initial salicylic acid concentration. Key: ●, ethylcellulose film; and ○, 3:7 polyethylene glycol–ethylcellulose film. (Release was into pH 7 buffer.)*

Experimentally, the linear diffusion model held up to 80–90% drug release, after which the rate decreased progressively. This deviation would be explained by the total exhaustion of solid drug phase from the film, subsequent to which the diffusion gradient would show first-order dependence on drug content. The experimental conditions used ensured that, with all three drugs, ultimate sink concentrations were insignificant compared to drug solubilities in the external buffer solutions. Therefore, the deviation was not the result of an external concentration gradient.

Film Thickness—As expected from Higuchi's equation, film thickness had no influence on the release rate constant (Table III). However, the time for release of half of the drug content of the film, termed the product half-life ($t_{1/2}$), is related to the film thickness. This relationship is indicated conveniently by Eq. 9, derived from Eq. 3, and shows the direct relationship between $t_{1/2}$ and the square of film thickness, h:

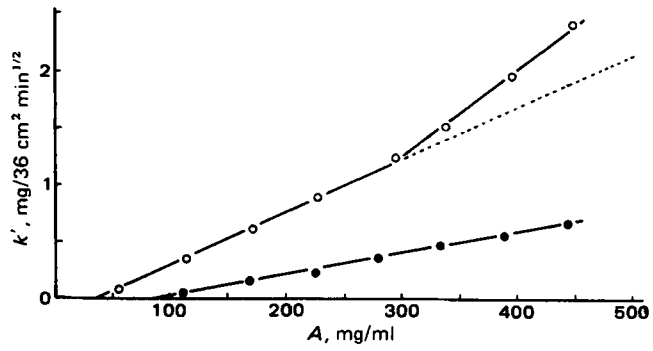


Figure 5—*Relationship of k′ to the initial tripelennamine concentration. Key: ●, ethylcellulose film; and ○, 3:7 polyethylene glycol–ethylcellulose film. (Release was into pH 7 buffer.)*

Table II—Comparison of Parameters of Linearity Obtained from Plots of Release Rate [a] against the Reciprocal Amount ($1/Q'$) and the Amount (Q') of Drug Released

Drug	Concentration[b], % (w/w)	Polyethylene Glycol–Ethylcellulose Ratio	Correlation Coefficient Rate *versus* $1/Q'$	Correlation Coefficient Rate *versus* Q'
Salicylic acid	20	4:6	0.999	0.919
Salicylic acid	20	2:8	0.999	0.959
Tripelennamine	20	4:6	0.991	0.960
Tripelennamine	20	2:8	0.999	0.938
Caffeine	5	4:6	0.993	0.970

[a] Release into pH 7 buffer. [b] Drug in dry film.

$$t_{1/2} = \left(\frac{Ah}{2k}\right)^2 \qquad \text{(Eq. 9)}$$

where A is the initial drug concentration in the film (milligrams per milliliter) and k is the release rate constant (*cf.*, Ref. 3).

The calculated and measured times for 50% drug release from membranes containing 20% salicylic acid and tripelennamine in polyethylene

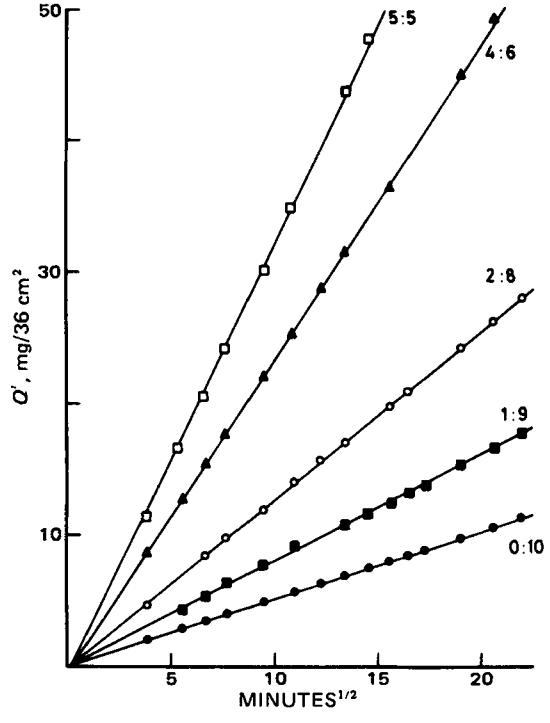
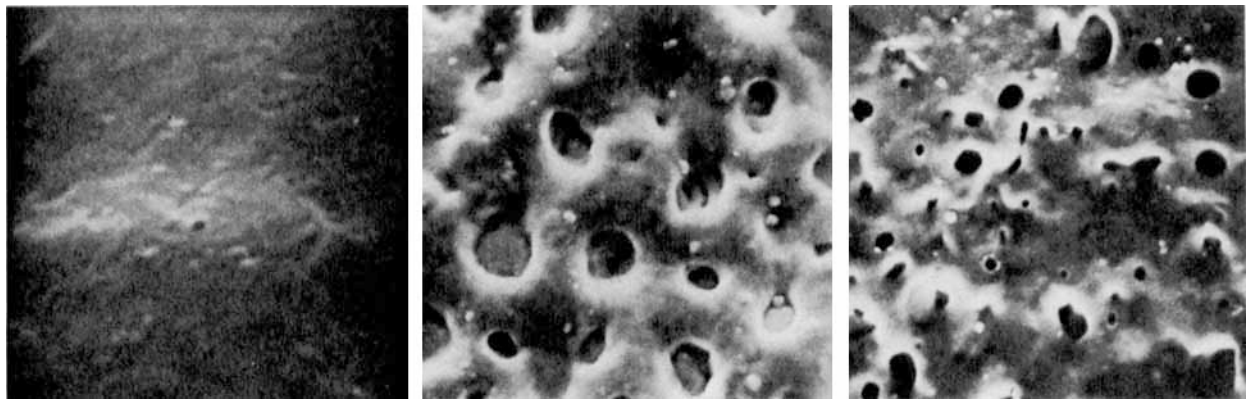


Figure 6—*Drug release into pH 7 buffer from films containing 20% (w/w) salicylic acid at different polyethylene glycol–ethylcellulose ratios. Key: □, 5:5; ▲, 4:6, ○, 2:8; ■, 1:9; and ●, 0:10.*



A B C

Figure 7—*Scanning electron micrographs of films (×5000): Key: A, 20% (w/w) salicylic acid in pure ethylcellulose after release of most of the drug; B, 30% (w/w) polyethylene glycol in ethylcellulose film after leaching out of the hydrophilic component (no drug present); and C, 20% (w/w) salicylic acid in 3:7 polyethylene glycol–ethylcellulose film after release of the drug.*

Table III—Effect of Film Thickness (h) on the Drug Release Rate Constant (k') and Half-Life ($t_{1/2}$) for 1:1 Polyethylene Glycol–Ethylcellulose Films Containing Drugs

System[a]	Film Thickness, mm	k', mg/36 cm^2 min$^{1/2}$	$t_{1/2}$, min Calculated[b]	$t_{1/2}$, min Measured[c]	Correlation Coefficient
Salicylic acid, 20%, pH 7	0.072	3.85	55	58	0.995
	0.100	3.83	107	105	0.997
	0.133	3.90	183	192	0.997
Tripelennamine, 20%, pH 7	0.071	2.38	153	162	0.997
	0.104	2.46	305	299	0.998
	0.128	2.45	466	454	0.996
Tripelennamine, 20%, pH 2	0.069	3.65	61	59	0.999
	0.097	3.57	126	133	0.995
	0.125	3.62	203	212	0.997

[a] Drug concentration by weight in dry film; pH of external solution. [b] Calculated according to Eq. 9. [c] Measured from the experimental graphs at the point corresponding to the release of exactly 50% of the initial drug content of the film.

Table IV—Effect of Polyethylene Glycol–Ethylcellulose Ratio and pH on the Release Rate Constant (k') for Films Containing 20% (w/w) Tripelennamine

Polyethylene Glycol–Ethylcellulose Ratio	Film Thickness, mm	k' (pH 7)[a], mg/36 cm^2 min$^{1/2}$	Film Thickness, mm	k' (pH 2)[a], mg/36 cm^2 min$^{1/2}$
0:10	0.098	0.219	0.087	0.229
1:9	0.089	0.346	0.099	0.405
2:8	0.117	0.723	0.125	0.748
3:7	0.117	0.900	0.124	1.30
4:6	0.071	1.48	0.091	2.39
5:5	0.128	2.45	0.125	3.62
6:4	0.106	4.41	0.097	6.15

[a] Correlation coefficient: 0.995–0.999.

Table V—Effect of Polyethylene Glycol–Ethylcellulose Ratio on the Drug Release Rate Constant (k') for 20% (w/w) Salicylic Acid and 10% (w/w) Caffeine Films

System[a]	Polyethylene Glycol–Ethylcellulose Ratio	Film Thickness, mm	k', mg/36 cm^2 min$^{1/2}$	Correlation Coefficient
Salicylic acid, 20%	0:10	0.057	0.518	0.999
	1:9	0.057	0.793	0.999
	2:8	0.073	1.24	0.999
	3:7	0.087	1.80	0.998
	4:6	0.082	2.69	0.999
	5:5	0.133	3.90	0.997
Caffeine, 10%	0:10	0.085	0.301	0.997
	1:9	0.069	0.491	0.999
	2:8	0.106	0.851	0.995
	3:7	0.102	1.44	0.998
	4:6	0.130	2.51	0.999

[a] Drug concentration by weight in dry film using pH 7 external solutions.

glycol–ethylcellulose (1:1) films are included in Table III and are in excellent agreement.

Drug Concentration—The effect of drug concentration on the release rate constant was tested using eight concentrations of tripelennamine (5–40%) and six concentrations of salicylic acid (5–30%) in pure ethylcellulose and polyethylene glycol 4000–ethylcellulose (3:7) films (Figs. 4 and 5). There was a linear relationship between the release rate constant and the drug concentration in a pure ethylcellulose film. Both diffusion-controlled release models (Eqs. 4 and 5) indicate that the release rate constant should be proportional to the square root of the initial drug concentration, A[7]. However, in systems where the drug is the only extractable component and the initial porosity of the film is negligible, increasing the amount of drug dispersed in the film would increase the porosity by the same factor but would not affect the other parameters. Thus, for these systems, the release rate constants should increase in direct proportion to the drug concentration (6).

Different results were obtained for films composed of ethylcellulose and polyethylene glycol 4000 (Figs. 4 and 5). Although there was a linear relationship between k and A when the drug content was low, a positive deviation was observed at elevated drug concentrations in both drug systems. This result may indicate that other factors are changing with the amount of drug in the film. In particular, leaching out of the polyethylene glycol 4000 and pore formation increase the external film area exposed to the solvent, increase the internal porosity, and decrease the tortuosity. The added contribution of leaching out of the drug to these factors is most significant at high drug concentrations. A similar phenomenon was observed (11, 12) in studies on the release of chlorpheniramine and sodium salicylate from a hydrophilic matrix.

Polyethylene Glycol Content—The effect of an increasing polyethylene glycol content at constant drug concentration was a marked increase in the release rate for all three drugs. Some examples are shown in Fig. 6 for salicylic acid; the other drugs gave a similar pattern.

The slopes of the linear Q–$t^{1/2}$ plots give the diffusional release rate constants (k', Eq. 3) for the individual drug film systems (Tables IV and V).

[7] Subject to the condition that $2A \gg C_s$ or ϵC_s.

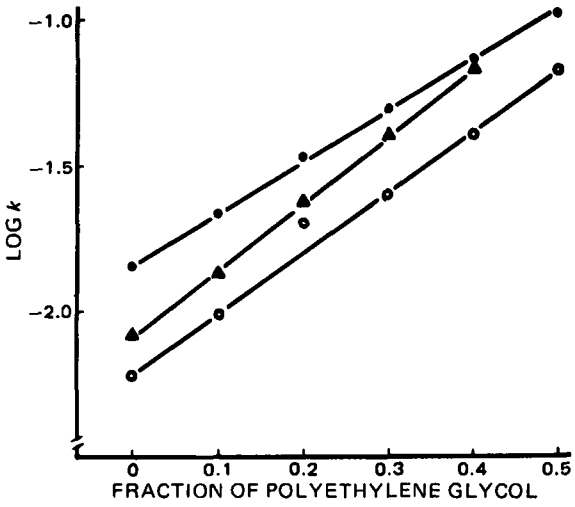


Figure 8—*Relationship of log* k *(release rate constant) to the fraction of polyethylene glycol in the polymer matrix. Key:* ●, *20% (w/w) salicylic acid films;* ○, *20% (w/w) tripelennamine films; and* ▲, *10% (w/w) caffeine films. (Release was into pH 7 buffer.)*

The polyethylene glycol 4000 underwent rapid leaching out, with about 90% being recovered from the water within 15 min for 35-μm film containing 30% of the polyethylene glycol. Scanning electron microscopy (Fig. 7) demonstrated that the loss of polyethylene glycol from polyethylene glycol–ethylcellulose films on leaching with water resulted in the formation of large pores (Fig. 7B) that were not formed in films of the drug in pure ethylcellulose (Fig. 7A). The presence of drug and polyethylene glycol together in ethylcellulose films gave pores on leaching (Fig. 7C) that were indistinguishable from those given by polyethylene glycol–ethylcellulose alone.

With an increase in porosity, the void volume would be expected to be occupied by external solvent diffusing into the film. In most compositions studied, the release rate constants increased drastically with an elevation of the polyethylene glycol content of the film. A plot of the release rate constant, k, against the fraction of polyethylene glycol in the polymer mixture demonstrated a positive deviation. On the other hand, plots of log k against the polyethylene glycol fraction were linear, following Borodkin and Tucker's equation (3):

$$\log k = k_D f_{PEG} + \log k_{EC} \qquad \text{(Eq. 10)}$$

where k_D is a constant specific for each drug and polymer system and drug concentration, f is the fraction of polyethylene glycol, and k_{EC} is the value of the release rate constant in ethylcellulose film. Figure 8 shows graphically the linear relationship of log k to the fraction of polyethylene glycol 4000 in ethylcellulose film for salicylic acid, tripelennamine, and caffeine. The same relation was obtained with hydroxypropylcellulose–polyvinyl acetate films (3).

pH Effects—In films containing polyethylene glycol, the release rate of tripelennamine was altered by a change in the pH of the external fluid. Release was more rapid at pH 2 than at pH 7 (Table IV). The same phenomenon, but in the reverse direction with respect to pH, was observed with salicylic acid; at an ethylcellulose–polyethylene glycol ratio of 6:4, it gave significantly faster release at pH 7 than at pH 1 (Table VI). These drugs would be expected to be converted into their salts or into mixtures of the salts and unionized forms when dissolved in the leaching solvent, according to their pKa values and the buffer pH values.

Table VI—Effect of pH on the Drug Release Rate from Films Containing 20% (w/w) Salicylic Acid

Polyethylene Glycol–Ethylcellulose Ratio	k' (pH 7), mg/36 cm^2 min$^{1/2}$	Correlation Coefficient	k' (pH 1), mg/36 cm^2 min$^{1/2}$	Correlation Coefficient
0:10	0.518	0.999	0.525	0.998
4:6	2.69	0.999	1.85	0.999

With tripelennamine, the salt form would predominate in the test buffers, but the ratio of unionized to ionized drug and, hence, the solubility of the drug in the leaching fluid would be reduced at pH 7 compared to pH 2. Similarly, salicylic acid would be less ionized and less soluble at pH 1. Evidently, ionizable drugs are released at rates related to their solubilities in the leaching solvent.

As the polyethylene glycol–ethylcellulose ratio increases, the differential pH effect becomes more significant. These mixed films behave as granular matrixes in which the solubility and diffusivity of the drug in the permeating fluid determine the release rate. In contrast, pure ethylcellulose films behave as homogeneous matrixes, with drug release being controlled by transport through the ethylcellulose and unaffected by the external pH. This behavior is clearly shown by the identical release rate constants of tripelennamine at pH 2 and 7 and of salicylic acid at pH 1 and 7 in pure ethylcellulose films (Tables IV and VI).

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ACKNOWLEDGMENTS

Abstracted in part from work submitted by Y. Samuelov to the Hebrew University in partial fulfillment of the Doctor of Philosophy degree requirements.

The authors thank the family of the late Mr. Jack Bogush of London, England, for the presentation of a Unicam SP 1800 recording spectrophotometer.