Linear Drug Release from Laminated Hydroxypropyl Cellulose–Polyvinyl Acetate Films

SAUL BORODKIN ˣ and FLORENCE E. TUCKER

Abstract □ Release of drug from a single-layer film containing dispersed drug follows a diffusion-controlled matrix model, where the quantity released per unit area is proportional to the square root of time. The kinetics may be made linear with time (zero order) by laminating a second film without drug to the releasing side of the film with dispersed drug. In this manner, the drug layer serves as a reservoir and controls the duration of drug release, while the nondrug layer functions as a rate-controlling membrane. Zero-order drug release was demonstrated in such laminated films using 18–45% pentobarbital, methapyrilene, or salicylic acid contained in hydroxypropyl cellulose as the reservoir layer and mixtures of hydroxypropyl cellulose and polyvinyl acetate as the membrane layer. Inverse relationships between the release rate and membrane thickness and between the logarithm of the rate and the percentage of polyvinyl acetate in the membrane layer were observed. Of the three drugs tested, salicylic acid gave the fastest release rates while pentobarbital gave the slowest.

Keyphrases □ Drug release (methapyrilene, pentobarbital, salicylic acid) from laminated hydroxypropyl cellulose–polyvinyl acetate films—linear drug release, effects of membrane thickness and polyvinyl acetate content □ Polymer films, laminated hydroxypropyl cellulose–polyvinyl acetate—linear drug release (methapyrilene, pentobarbital, salicylic acid) □ Laminated hydroxypropyl cellulose–polyvinyl acetate films—linear drug release □ Hydroxypropyl cellulose–polyvinyl acetate films, laminated—linear drug release

The release kinetics of drugs dispersed in films composed of different ratios of hydroxypropyl cellulose and polyvinyl acetate were recently described (1). Drug release followed a diffusion-controlled matrix model, originally suggested by Higuchi (2, 3), where the quantity released per unit exposed area, Q, is proportional to the square root of time, t:

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

where D and C_s refer to the diffusivity and solubility of the drug in the permeating fluid, respectively; A is the initial drug concentration; and τ and ϵ describe the tortuosity and porosity of the matrix, respectively. Although the release rates could be drastically altered by changing the polymer ratio and drug concentration, the Q *versus* $t^{1/2}$ linear relationship was inviolate.

For many dosage applications, linearity with time (zero-order release) would be desirable. Capsules (4), bandages (5), and tapes (6) that provide long-term uniform availability of drugs and pesticides have been described. Zero-order release from these devices appears to be obtained by maintenance of a constant concentration gradient through a membrane from a controlled concentration at the inner surface to zero concentration at the outer surface. This mechanism was recently reviewed (7), and it may be described by the following equation after an initial lag time:

$$\frac{dQ}{dt} = \frac{DC_0}{h} \qquad \text{(Eq. 2)}$$

where D is the diffusion constant through the membrane, C_0 is the concentration at the internal membrane surface, usually at saturation, and h is the membrane thickness. Analogously, zero-order release from a film should be attainable by laminating a polymer layer without drug to the releasing face of a film containing dispersed drug. In this way, the nondrug layer can serve as the rate-controlling membrane, while the drug-containing layer serves as a reservoir to maintain C_0 and the constant gradient.

This paper describes studies of drug release from such laminated films. Pentobarbital, methapyrilene, and salicylic acid contained in hydroxypropyl cellulose were used as the reservoir layers; the membrane layers were composed of different ratios of hydroxypropyl cellulose and polyvinyl acetate.

EXPERIMENTAL

Chemicals—Hydroxypropyl cellulose[1] was a food or pharmaceutical grade with an average molecular weight of 100,000, which gives a viscosity of 75–150 cps as a 5% solution in water. Polyvinyl acetate[2] had an average molecular weight of 500,000 and a viscosity of 90–110 cps as an 8.6% solution in benzene. Pentobarbital sodium and salicylic acid were USP grade, while methapyrilene hydrochloride was NF grade.

The pH 7.0 buffer used in all release rate studies was prepared by dissolving 28.9 g of $Na_2HPO_4 \cdot 7H_2O$ and 8.05 g of $NaH_2PO_4 \cdot H_2O$ in enough water to give 1 liter of solution.

Film Preparation—The reservoir layer films were cast from solutions containing 10% solute (drug plus hydroxypropyl cellulose), with a methylene chloride–methanol mixture (9:1) as the solvent. Hydroxypropyl cellulose was added as a dry powder by slow addition to the vigorously stirring solution. Salicylic acid was added as the dry powder, while pentobarbital and methapyrilene were incorporated from stock methylene chloride solutions prepared from the drug salts.

The pentobarbital stock solution, containing 60.8 mg/ml, was prepared by dissolving 12.0 g of pentobarbital sodium in 50 ml of water, adding 5 ml of concentrated hydrochloric acid, extracting three times with 50-ml portions of methylene chloride, and adjusting the volume of the combined extract to 180 ml. The methapyrilene base solution, containing 58.5 mg/ml, was prepared by dissolving 12.0 g of methapyrilene hydrochloride in 60 ml of water, adding 10 ml of 5 N NaOH, extracting three times with methylene chloride, and adjusting the volume of the combined extract to 180 ml. Films were cast from the solutions at various wet thicknesses

[1] Klucel LF, Hercules, Inc., Wilmington, DE 19899
[2] Gelva V-100, Monsanto Co., St. Louis, MO 63166

(0.64–2.54 mm) by spreading with a knife[3] on Teflon-coated plate glass and allowing the films to air dry at least 24 hr before combining with the membrane layer.

The membrane layers were prepared separately by slowly adding hydroxypropyl cellulose and polyvinyl acetate to a methylene chloride–methanol mixture (9:1) with vigorous stirring to give a solution containing 10% solutes. The solutions were spread on Teflon-coated plate glass with a knife[3], and the films were allowed to air dry at least 24 hr before lamination to the reservoir layer.

The laminated films were prepared by cutting a section (approximately 5 × 5 cm) of the drug reservoir film, measuring its thickness in five places with a micrometer[4], placing it on Teflon-coated plate glass, and spraying one side with methylene chloride. A slightly larger section of the membrane layer, of which the thickness had been previously measured in five places with a micrometer, was immediately pressed on the tacky side of the drug film. The laminated film was allowed to air dry for 24 hr and inspected to assure adhesion between the two layers before use in release rate testing.

Release Rate Determinations—Rectangular films, 2.2 × 4.0 cm (8.8 cm^2), were obtained by cutting a section of the laminated film with a razor blade; a microscope cover glass was used as a template. A thin coating of high vacuum silicone lubricant[5] was applied to a 2.54 × 7.62-cm microscope slide and the exposed face of the drug reservoir layer. The film was then carefully pressed onto the slide with the membrane layer exposed, making sure that all edges adhered and were below the silicone lubricant level but that no lubricant touched the exposed surface. The water repellency of the silicone lubricant covering the film edges prevented any drug release from the edges of the reservoir layer. Studies in which the reservoir layer surface was coated with silicone lubricant and exposed to release conditions showed only insignificant drug dissolution after 7 hr.

The slide was placed film side up at about a 45° angle into a 250-ml beaker in a 37° water bath containing 200 ml of pH 7.0 buffer preheated to 37°. A nonagitated system was selected to eliminate any effect of turbulence on the release rate as well as to prevent any disruption of the film. Periodic assay samples (generally hourly for 8 hr) were obtained by removing the slide, stirring the solution, and pipetting a 5-ml sample. The slide was quickly reinserted, making sure that the film remained completely immersed throughout the release study. The beaker was kept covered[6] except during sampling to prevent evaporation. After 24 hr, the run was terminated and the solution was assayed.

All samples were assayed by UV spectrophotometry[7] after the required dilution in the specific solvent used for each drug. Pentobarbital was assayed at 240 nm in 0.1 *N* NH_4OH, methapyrilene was assayed at 312 nm in 0.1 *N* HCl, and salicylic acid was assayed at 297 nm in 0.1 *N* NaOH.

RESULTS AND DISCUSSION

Drug Release Kinetics—Drug release kinetics from films containing dispersed drug could be changed from linearity with the square root of time to linearity with time (zero order) by laminating a membrane layer to the releasing surface. This effect was demonstrated in many such laminated films using a hydroxypropyl cellulose matrix in the reservoir layer and hydroxypropyl cellulose–polyvinyl acetate composite mixtures in the membrane layer. Figures 1–3 compare drug release from films containing dispersed drug with and without membrane layers. The results of all release rate studies from the laminated films are summarized in Tables I–III. The high correlation coefficients obtained from linear regression analysis (9) of the *Q versus t* treatment attest to the zero-order release kinetics.

The slopes obtained by plotting the amount released per area *versus* time are designated in the tables by an apparent zero-order rate constant, k_0, with the units of milligrams centimeters^{-2} hours^{-1}. Integration of Eq. 2 and evaluation of the integration constant in terms of the lag time (intercept on the time axis obtained when steady-state rate is extrapolated), t_{lag}, yield:

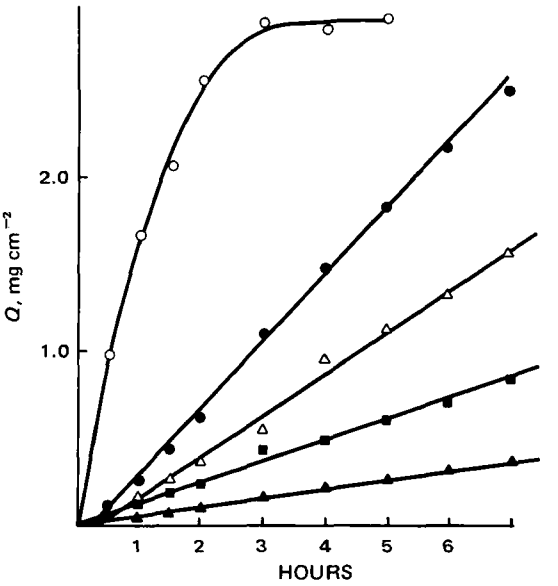

Figure 1—*Drug release from films containing 18.2% pentobarbital in hydroxypropyl cellulose as the reservoir layer. Key:* ○, *no membrane layer;* ●, *0.091-mm hydroxypropyl cellulose–polyvinyl acetate (9:1) membrane;* △, *0.137-mm hydroxypropyl cellulose–polyvinyl acetate (8:2) membrane;* ■, *0.128-mm hydroxypropyl cellulose–polyvinyl acetate (6:4) membrane; and* ▲, *0.093-mm hydroxypropyl cellulose–polyvinyl acetate (4:6) membrane.*

$$Q = \frac{DC_0}{h}t - \frac{DC_0}{h}t_{lag} \qquad \text{(Eq. 3)}$$

For a given film in which the membrane remains intact, D, C_0, and h are constant through most of the release, and the apparent zero-order rate constant may be defined as:

$$k_0 = \frac{DC_0}{h} \qquad \text{(Eq. 4)}$$

and:

$$Q = k_0 t - k_0 t_{lag} \qquad \text{(Eq. 5)}$$

Generally, the lag times were less than 15 min. However, in some cases, especially with methapyrilene as the drug, lag times of greater than 30 min were observed before attainment of steady-state release.

No correlation could be seen between the membrane thickness and lag time, as might be expected from the theoretically developed equation (7):

$$t_{lag} = \frac{h^2}{6D} \qquad \text{(Eq. 6)}$$

It appears likely that other factors, such as hydration of the film or attainment of saturation conditions within the reservoir layer, were more dominant in establishing steady-state conditions and the lag time.

The zero-order relationship would be expected to break down before total drug release when the reservoir layer is no longer able to sustain C_0 at the interface of the two layers. As reflected by the half-lives shown in Tables I–III, none of the laminated films gave complete release in the 7–8-hr release times generally studied. However, in a number of films, the release went well beyond the half-life with no observed deviation from zero-order linearity. In all cases where release was calculated to be incomplete at 24 hr ($t_{1/2} > 12$ hr), the 24-hr assays were in line with those projected by k_0.

Lamination of a membrane layer to a film containing dispersed drug results in slower drug release, as well as a change in kinetics, due to the barrier nature of the membrane layer. This does not mean that all laminated films must release drug at slower rates than nonlaminated films and single- and double-layer films with comparable rates, but different release patterns can be fabricated. Figure 4 compares the release obtained from two salicylic acid films: one a single-layer film following the Q *versus* $t^{1/2}$ linear rela-

[3] Gardner Laboratories, Bethesda, MD 20014
[4] L. S. Starrett Co., Athol, Mass.
[5] Dow Corning Corp., Midland, MI 48640
[6] Parafilm M, American Can Co., Neenak, Wis.
[7] Coleman model 124, Perkin-Elmer Co., Norwalk, Conn.

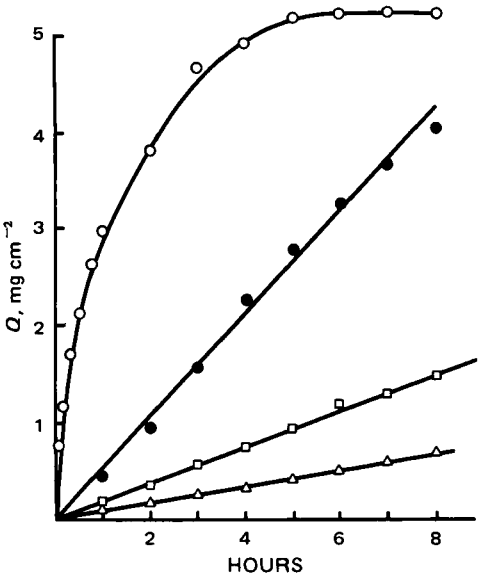

Figure 2—*Drug release from films containing 20% salicylic acid in hydroxypropyl cellulose as the reservoir layer. Key: ○, no membrane layer; ●, 0.164-mm hydroxypropyl cellulose–polyvinyl acetate (8:2) membrane; □, 0.204-mm hydroxypropyl cellulose–polyvinyl acetate (6:4) membrane; and △, 0.164-mm hydroxypropyl cellulose–polyvinyl acetate (4:6) membrane.*

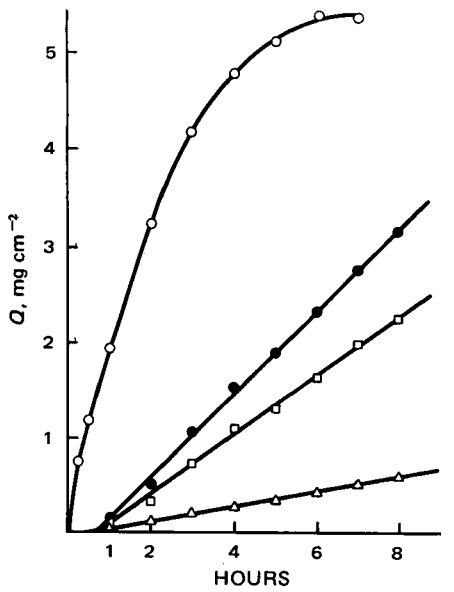

Figure 3—*Drug release from films containing 26.3% methapyrilene in hydroxypropyl cellulose as the reservoir layer. Key: ○, no membrane layer; ●, 0.171-mm hydroxypropyl cellulose–polyvinyl acetate (9:1) membrane; □, 0.160-mm hydroxypropyl cellulose–polyvinyl acetate (7:3) membrane; and △, 0.210-mm hydroxypropyl cellulose–polyvinyl acetate (5:5) membrane.*

tionship and the other a laminated type following zero-order kinetics. Although both gave approximately 60% release in 6 hr, the release kinetics were quite different.

Effect of Membrane Thickness—Equation 4 indicates that the apparent zero-order rate constant, k_0, should be inversely proportional to the membrane layer thickness. Figure 5 shows this relationship using three different thicknesses of pure hydroxypropyl cellulose as the membrane layers; Fig. 6 shows similar results with the much slower releasing hydroxypropyl cellulose–polyvinyl acetate (5:5) membranes.

The linearity of the observed rate constant with the reciprocal of the measured membrane thickness allows calculation of a thickness-independent zero-order constant, k_0', with the dimensions milligrams centimeters^{-1} hours^{-1}, where:

$$k_0' = k_0 h \qquad \text{(Eq. 7)}$$

These values, which should approximate DC_0, are also included in Tables I–III. Their independence of membrane thickness makes them more useful in comparing films of different composition.

The hydrophilic nature of the membrane layer would indicate that the fully hydrated swelled membrane would be the true barrier layer. This would still be consistent with the zero-order release model, although the rate of attaining full hydration might affect the lag time.

During dosage development, it may be beneficial or desirable to increase the initial release of drug. This approach may be necessary to overcome a lag time or to establish a useful therapeutic level which might be followed by a maintenance rate. This can con-

Table I—Zero-Order Release Rates Obtained from Laminated Pentobarbital Films

Membrane: Hydroxypropyl Cellulose–Polyvinyl Acetate Ratio	Membrane: h, mm	Reservoir[a]: Drug, %	Reservoir[a]: h, mm	k_0[b], mg cm^{-2} hr^{-1}	k_0', mg cm^{-1} hr^{-1} × 10^3	$t_{1/2}$, hr	Correlation Coefficient
10:0	0.088	45.5	0.147	0.496 ± 0.028	4.36	8.1	0.998
10:0	0.090	45.5	0.192	0.503 ± 0.030	4.52	10.4	0.998
10:0	0.111	45.5	0.137	0.408 ± 0.040	4.52	8.2	0.994
10:0	0.143	18.2	0.172	0.304 ± 0.013	4.36	6.1	0.999
9:1	0.075	36.4	0.138	0.428 ± 0.043	3.21	6.8	0.994
9:1	0.091	18.2	0.187	0.385 ± 0.021	3.50	5.3	0.998
8:2	0.063	36.4	0.141	0.431 ± 0.036	2.71	6.3	0.993
8.2	0.074	18.2	0.167	0.418 ± 0.031	3.10	4.2	0.997
8:2	0.114	18.2	0.161	0.304 ± 0.030	3.47	5.7	0.995
8:2	0.137	18.2	0.164	0.245 ± 0.020	3.35	7.3	0.996
6:4	0.049	18.2	0.218	0.296 ± 0.010	1.45	8.7	0.999
6:4	0.128	18.2	0.204	0.121 ± 0.008	1.54	14.7	0.997
6:4	0.136	27.3	0.149	0.094 ± 0.013	1.28	23.3	0.990
6:4	0.142	36.4	0.118	0.102 ± 0.008	1.44	22.6	0.995
6:4	0.137	45.5	0.173	0.077 ± 0.002	1.06	52.8	0.999
5:5	0.136	18.2	0.183	0.037 ± 0.002	0.51	51.2	0.999
5:5	0.092	27.3	0.142	0.063 ± 0.002	0.57	33.3	1.000
5:5	0.128	27.3	0.134	0.037 ± 0.001	0.47	51.0	0.999
5:5	0.197	27.3	0.150	0.028 ± 0.002	0.56	76.8	0.998
5:5	0.230	27.3	0.141	0.021 ± 0.001	0.48	96.6	0.999
4:6	0.051	18.2	0.181	0.074 ± 0.003	0.37	24.1	0.999
4:6	0.093	18.2	0.245	0.054 ± 0.003	0.50	40.3	0.998

[a] Reservoir layer composed of pentobarbital in hydroxypropyl cellulose. [b] Slope of Q *versus* t plot ± 95% confidence limits (9).

Table II—Zero-Order Release Rates Obtained from Laminated Salicylic Acid Films[a]

Membrane Layer: Hydroxypropyl Cellulose–Polyvinyl Acetate Ratio	h, mm	k_0[b], mg cm^{-2} hr^{-1}	k_0', mg cm^{-1} hr^{-1} × 10^3	$t_{1/2}$, hr	Correlation Coefficient
10:0	0.176	0.543 ± 0.054	9.56	5.4	0.995
9:1	0.171	0.540 ± 0.058	9.25	5.4	0.994
8:2	0.164	0.530 ± 0.048	8.69	5.5	0.996
7:3	0.169	0.327 ± 0.017	5.53	8.9	0.999
6:4	0.204	0.190 ± 0.012	3.88	15.3	0.998
5:5	0.187	0.156 ± 0.010	2.92	18.7	0.998
4:6	0.164	0.083 ± 0.005	1.36	35.2	0.998
3:7	0.177	0.059 ± 0.001	1.04	49.5	1.000

[a] Reservoir layer composed of 20.0% salicylic acid in hydroxypropyl cellulose with a thickness of 0.256 ± 0.012 mm. [b] Slope of Q *versus* t plot ± 95% confidence limits (9).

Table III—Zero-Order Release Rates Obtained from Laminated Methapyrilene Films[a]

Membrane Layer: Hydroxypropyl Cellulose–Polyvinyl Acetate Ratio	h, mm	k_0[b], mg cm^{-2} hr^{-1}	k_0', mg cm^{-1} hr^{-1} × 10^3	$t_{1/2}$, hr	Correlation Coefficient
10:0	0.173	0.441 ± 0.018	7.63	8.8	0.999
9:1	0.171	0.432 ± 0.019	7.38	9.0	0.999
8:2	0.151	0.495 ± 0.035	7.48	7.8	0.998
7:3	0.160	0.307 ± 0.019	4.91	12.6	0.998
6:4	0.222	0.097 ± 0.011	2.14	40.1	0.996
5:5	0.210	0.071 ± 0.003	1.49	54.5	0.999
4:6	0.179	0.041 ± 0.004	0.74	93.9	0.996
3:7	0.193	0.022 ± 0.005	0.42	176.6	0.987

[a] Reservoir layer composed of 26.3% methapyrilene in hydroxypropyl cellulose with a thickness of 0.259 ± 0.006 mm. [b] Slope of Q *versus* t plot ± 95% confidence limits (9).

ceivably be accomplished by including a low level of drug in the membrane layer.

Reservoir Layer—To achieve the constant concentration gradient in the membrane layer required for zero-order release, the drug layer must continually provide sufficient drug to maintain a constant concentration, C_0, at the inner membrane surface. This condition may be achieved if C_0 is equivalent to saturation and the transfer rate from the reservoir is rapid enough to maintain saturation. Alternatively, C_0 may remain constant through partitioning from a constantly maintained saturated solution phase in the reservoir layer. Such a condition can exist if the reservoir layer contains a high dispersed drug concentration relative to the solution phase level ($A \gg \epsilon C_s$ in terms of Eq. 1) and transfer of drug through the reservoir matrix is faster than loss through the membrane.

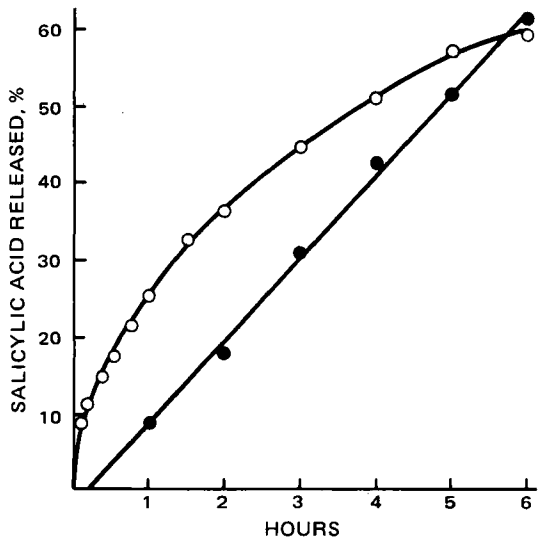

Figure 4—*Comparison of salicylic acid release from single-layer and laminated films. Key: ○, single-layer film composed of 20% drug in hydroxypropyl cellulose–polyvinyl acetate (3:7) (0.156 mm); and ●, laminated film, reservoir is 20% drug in hydroxypropyl cellulose (0.256 mm), and membrane is hydroxypropyl cellulose–polyvinyl acetate (9:1) (0.171 mm).*

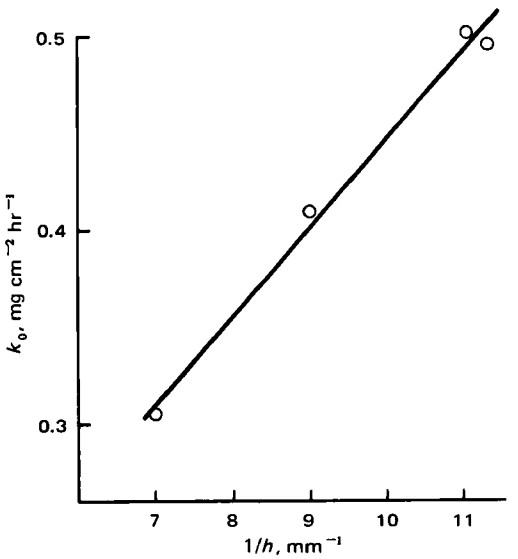

Figure 5—*Relationship of pentobarbital release rate to the reciprocal of membrane layer thickness from laminated films containing pure hydroxypropyl cellulose as the membrane layer.*

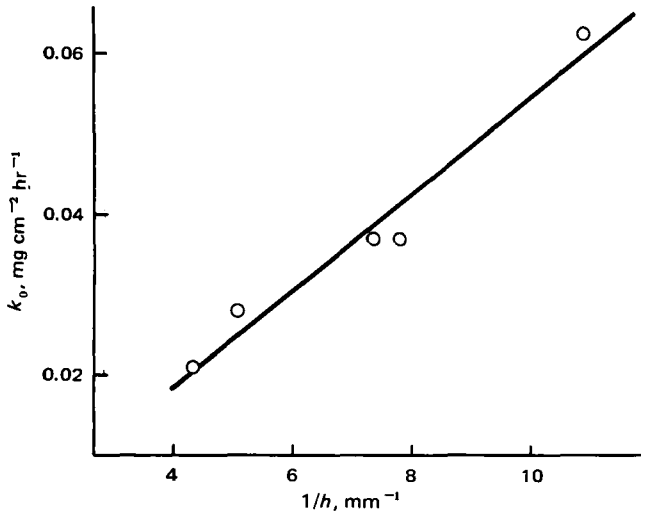

Figure 6—*Relationship of pentobarbital release rate to the reciprocal of membrane layer thickness from laminated films containing hydroxypropyl cellulose–polyvinyl acetate (5:5) as the membrane layer.*

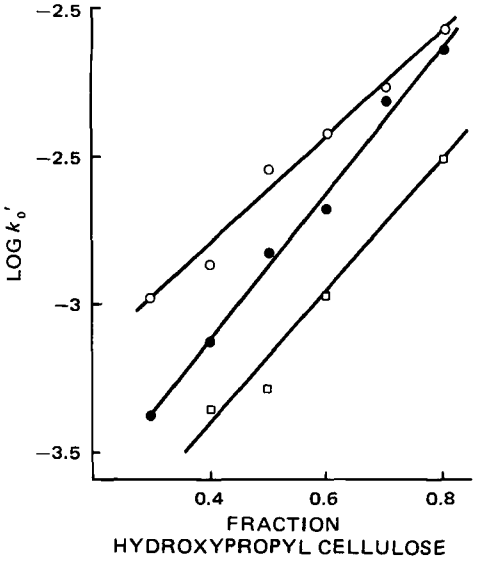

Figure 7—*Relationship of log k_0' to the fraction of hydroxypropyl cellulose in the membrane layer. Key: ○, salicylic acid; ●, methapyrilene; and □, pentobarbital.*

The conditions conducive to maintaining C_0 and zero-order release were achieved by using drug concentrations of greater than 18% and pure hydroxypropyl cellulose as the matrix. This matrix had been shown previously to give the fastest diffusion rates (1). Matrixes with slower diffusion rates were not tested.

The drug concentration in the reservoir layer should not affect the release rate as long as it exceeds the level necessary for maintaining saturation. The data in Table I show that similar k_0' values were obtained for laminated films with similar membrane matrixes but different pentobarbital reservoir concentrations. In studies using less than 10% drug concentration in the reservoir layer and fast releasing membrane layers, zero-order release was not obtained.

Although the drug concentration above the critical level should not affect the release rate, it controls the duration of drug release. The more concentrated the reservoir, the longer it will be able to supply drug to maintain C_0. Similarly, the duration of release, as reflected by the half-life, may be controlled by the thickness of the reservoir layer.

Polymer Ratio in Membrane—As shown in Tables I–III, all three drugs behaved similarly with regard to the hydroxypropyl cellulose–polyvinyl acetate ratio in the membrane layer. Increasing the polyvinyl acetate concentration from 0 to 20% affected the release rate only slightly. Beyond 20%, there was a marked decrease in release rate with further increases in the polyvinyl acetate content, with each 10% reducing the rate by approximately one-third to one-half.

Attempts to relate mathematically the release rate to the hydroxypropyl cellulose–polyvinyl acetate ratio yielded the best results when the logarithm of the thickness-independent rate contant, k_0', was plotted against the fraction of hydroxypropyl cellulose in the membrane (Fig. 7). The relationship may be depicted by the following empirical equation:

$$\log k_0' = k_R F_H + \log (k_0')_p \qquad \text{(Eq. 8)}$$

where F_H is the fraction of hydroxypropyl cellulose in the membrane layer, k_R is the slope specific for a given drug and reservoir, and $(k_0')_p$ is the extrapolated rate constant for a pure polyvinyl acetate membrane ($F_H = 0$). In practice, pure polyvinyl acetate membranes that could be incorporated into laminated films could not be fabricated without plasticizers. Table IV lists the calculated values obtained using Eq. 8. This logarithmic relationship between the rate constant and fraction of hydroxypropyl cellulose in the membrane is quite similar to that found earlier with homogeneous films containing dispersed drug (1).

The greater barrier characteristics obtained with increased polyvinyl acetate percentages in the membrane layer may be attributed to its lower hydrophilicity relative to hydroxypropyl cellulose. Weight gain studies with films suspended in a 100% relative humidity atmosphere at 37° showed very rapid equilibration, with the percentage moisture absorbed increasing with hydroxypropyl cellulose content from 4% with pure polyvinyl acetate to 32% with pure hydroxypropyl cellulose. The lower hydration could cause reduced drug release rates by lower drug solubility, less porosity, or increased tortuosity.

Table IV—Linear Relationship of Log k_0' to Fraction of Hydroxypropyl Cellulose in Membrane Layer

Drug	Concentration in Reservoir Layer, %	Slope (k_R)	$(k_0')_p$, mg cm^{-2} hr^{-1} × 10^3	Correlation Coefficient
Salicylic acid	20.0	1.88	0.282	0.991
Methapyrilene	26.3	2.54	0.074	0.997
Pentobarbital	18.2–45.5	2.29	0.048	0.979

With pure hydroxypropyl cellulose as the membrane layer, it might appear that the membrane would simply be a depleted matrix from a single-phase film and the zero-order release model would not be applicable. However, all results showed zero-order release well beyond the half-life. Apparently, the presence or absence of initial drug imparts sufficiently different characteristics so that the two layers retain individual behavior, with drug saturation in the reservoir layer predominating longer than drug release through the membrane layer.

Drug Effect—With similar polymer compositions, the relative release rates for different drugs in laminated films would be governed primarily by the drug solubility and diffusion coefficient in the membrane layer. The drug solubility in the reservoir layer might also affect C_0 and the release rate through partitioning.

Of the three drugs tested, salicylic acid gave the fastest release rates while pentobarbital gave the slowest. The relatively slower release rates with pentobarbital can be most easily attributed to its much lower solubility in pH 7.0 buffer at 37° (3 mg/ml *versus* greater than 600 mg/ml for methapyrilene and salicylic acid, which are primarily in the ionized form). Although the drug solubility in the external solution should not directly affect the release rate under sink conditions, permeation of buffer into the hydrated membrane layer could give some buffering effect within the membrane.

The faster release rates obtained with salicylic acid relative to methapyrilene may be due primarily to its lower molecular weight (138.1 *versus* 261.4). Since the diffusion coefficient is inversely proportional to the cube root of the molecular weight (10), salicylic acid would give a diffusion coefficient approximately 1.24 times greater than methapyrilene with all other variables equal.

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ACKNOWLEDGMENTS AND ADDRESSES

Received November 21, 1974, from *Pharmaceutical Research and Development, Pharmaceutical Products Division, Abbott Laboratories, North Chicago, IL 60064*

Accepted for publication January 10, 1975.

The authors thank Dr. James Seitz and Mr. Jerold Buddenhagen for their helpful suggestions.

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Pharmacokinetics of Polychlorinated Biphenyl Components in Swine and Sheep after a Single Oral Dose

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Abstract □ Single-dose oral administration of a commercial polychlorinated biphenyl product containing 54% chlorine provided data with which to plot the time course of total polychlorinated biphenyl and individual components in the blood of swine and sheep. Pharmacokinetic parameters describing absorption from the gut and elimination from a two-compartment body system were determined for the components in swine and sheep. The absorption half-time for total polychlorinated biphenyl in swine was 1.13 hr while that for sheep was 3.83 hr. The half-time for disposition of total polychlorinated biphenyl from the central compartment was 4.4 hr in swine and 7.7 hr in sheep; the apparent biological half-life was 62.4 hr in swine and 78.8 hr in sheep. Individual components varied significantly from each other and from total polychlorinated biphenyl in all parameters.

Keyphrases □ Polychlorinated biphenyl components—pharmacokinetics in swine and sheep after single oral dose □ Pharmacokinetics—polychlorinated biphenyls in swine and sheep after single oral dose

The ecological persistence of polychlorinated biphenyls and their continual release into the environment in recent years have created a situation in which contamination of animal feed as well as human food is a constant threat. Since commercial preparations are mixtures of some 200 possible isomers and any given residue probably represents more than a single polychlorinated biphenyl mixture, it becomes important to evaluate the individual components as well as total polychlorinated biphenyl. Furthermore, such a mixture permits the simultaneous comparison of several different compounds in the same animal, and studies using single purified components can be used to assess the extent of interactions within the mixture.

One means of assessing exposure to polychlorinated biphenyls and persistence of the chemicals in the body is by way of blood sampling. Previous studies characterized the polychlorinated biphenyl mixture used (1), developed and refined methods of extraction and analysis (2), and determined pharmacokinetic parameters of individual components in swine and sheep after intravenous administration (3). Reports of investigations of pharmacokinetic parameters after feeding contaminated feed are in preparation.

This paper deals with the time course of polychlorinated biphenyls in the animal body as determined by blood sampling after a single oral dose of a commercial polychlorinated biphenyl containing 54% chlorine[1] to swine and sheep.

EXPERIMENTAL

Three sheep and three swine were given a calculated oral dose of a polychlorinated biphenyl containing 54% chlorine by weight[1] in a gelatin capsule. The dosage was 30 mg/kg for the sheep and 15 mg/kg for the swine; pilot studies indicated that these levels were necessary to provide adequate blood concentrations for analysis.

The sheep were mature ewes of mixed mutton-type breeding and weighed 53.5, 57.0, and 66.5 kg; the swine were of Hampshire-Yorkshire breeding and weighed 48.0, 59.5, and 57.2 kg. Both sheep and swine were maintained in individual steel cages with slot floors. Blood samples were obtained from the sheep by jugular puncture for 7 days and from the swine by femoral venous cannulas, fitted 24 hr prior to dosing, for 2 days.

The levels in swine blood collected after 48 hr were not adequate to permit accurate quantitation, and most of the β values were estimated from only one or two points along with the computer-generated tangent; therefore, the parameters for elimination from the tissue compartment in swine should be viewed with reservation. Further investigations will be conducted to determine these values more accurately.

[1] Aroclor 1254, Monsanto electrical grade No. KB-05-612.