Evaluation of Selected Physical Constants of Polymeric Films and Proposed Kinetics of Drug Release

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Abstract □ The formulation of an aerosol occlusive dressing presents several complex problems which must be solved before one can arrive at a single combination having the ability to control the rate at which medication is released from a polymeric film. These films must first be evaluated on the basis of their water vapor transmission, hardness, modulus of elasticity, alkali resistance, and stability to degradation by exposure to UV radiation. The plasticizer was found to have an effect upon the water vapor transmission of some films. The physical properties of the film also can be varied within limits by the incorporation of suitable plasticizers. These films were also found to be compatible with a commonly used aerosol propellant blend, dichlorodifluoromethane/trichlorofluoromethane (50:50). A specially designed apparatus and method for the *in vitro* determination of the rate of drug release was developed. A kinetic model based on the Noyes–Whitney relationship was used, and the rate of drug release of cetylpyridinium chloride and benzalkonium chloride from various films was determined. Drug release from both sustained- and prolonged-release films followed first-order kinetics. It was found that films cast from polymeric solutions containing 0.3% by weight of cetylpyridinium chloride and benzalkonium chloride were best suited for evaluation of drug release.

Keyphrases □ Polymer films—physical constants and kinetics of drug release, formulation of aerosol dressing □ Films, polymeric—physical constants and kinetics of drug release, formulation of aerosol dressing □ Aerosol occlusive dressing—evaluation of physical constants of polymeric films, kinetics of drug release proposed □ Drug release—from polymeric film formulated as aerosol dressing □ Physical constants—polymeric films, considerations for an aerosol formulation

The availability of a drug for penetration through the skin depends upon the rate of its release from a vehicle. If the vehicle is a polymeric film, it may be possible to control the rate of release of a therapeutically active substance for subsequent penetration through the skin. This control may be possible through use of an aerosol spray such as a "spray-on bandage." The formulation of an aerosol occlusive dressing presents several complex problems which must be solved before one can arrive at a single product having the ability to control the rate at which medication is made available. To achieve this, the selected polymers must be evaluated for various physical properties before any studies can be initiated on the kinetics of the drug release. A preliminary evaluation of the polymers in combination with plasticizers was conducted by measuring the hardness, modulus of elasticity, and flexibility of the selected films cast from a solution of treated polymers. The data obtained provided the basis for the initial screening of the films. Those films selected for further study were then evaluated for alkali and water resistance, stability to degradation by exposure to UV radiation, and compatibility of polymers with various propellant blends.

THEORY

One primary requirement for topical therapy is that the drug incorporated into a vehicle must reach the skin surface at an adequate rate for either penetration into the skin or superficial action as desired (1). The enhanced percutaneous absorption of topical steroids induced by occlusion of the skin surface with a plastic film to give greater contact between vehicle and skin has been attributed to epidermal maceration and increased skin temperature (2). Medicated occlusive dressings applied in aerosol form offer a significant improvement over those topical preparations which normally require occlusion of the skin surface with a plastic barrier following the application. In studying the influence of vehicles on the rate of penetration of steroids through human skin, Feldmann and Maibach (3) showed that dimethyl sulfoxide increases the penetration of steroids fourfold. Furthermore, by comparing the effect of occlusion to that of dimethyl sulfoxide on the percutaneous penetration, they were able to demonstrate that the occlusion increased the penetration of steroids more than any vehicle, including dimethyl sulfoxide. Occlusive vehicles induced the greatest degree of equilibrium hydration in the stratum corneum through sweat accumulation at the skin vehicle interface (4).

Shelmire (1) demonstrated that the rate of diffusion of a drug from the vehicle to the intact skin surface was determined by the degree of hydration of the stratum corneum and the miscibility of the vehicle with sweat. Baker (5) quantitatively measured the occlusivity of the topical vehicles in terms of their ability to suppress transepidermal water loss, indicating that the miscibility of vehicle with skin secretion is related to the water vapor permeability of the vehicle. Vehicles miscible with sweat are considered relatively less occlusive than those immiscible with sweat. Completely occlusive vehicles, therefore, offer resistance to water vapor permeation through the skin and consequently interfere with normal physiological functions of the skin. Jacobi and Maruszewski (6) termed the process of gas and water vapor exchange through the skin as "breathing" and showed that branched-chain organic compounds having the property of making occlusive films porous are responsible for the breathing qualities of the vehicles. It was reported that the diffusion of a drug from a vehicle into the skin surface and subsequent penetration of that drug through the stratum corneum are functions of the partition coefficient of the drug between the stratum corneum and vehicle and of the relative solubility of the drug in the vehicle (7–9).

Higuchi (7) proposed an approximated relationship for an idealized system between the steady-state rate of penetration and various properties of a fairly water-soluble drug. On the basis of this work, the authors indicated that the rate of penetration is a function of thermodynamic activity of the drug in the vehicle. Since the drug release is a function of thermodynamic activity, the penetration of the drug through the skin depends on the rate of its release from the vehicle. Since the drug depot in the vehicle, on activation by the natural perspiration process, very slowly releases drug at a constant rate to the skin surface, the release rate may be considered as a rate-limiting step in the absorption of the drug. The application of polymeric films from an aerosol form may interfere with the biochemistry of the integument due to prolonged adherence; therefore, it is imperative that the selected polymeric model films intended for topical application as an aerosol bandage be evaluated simultaneously for water vapor transmission and drug release.

The mechanism of water vapor transmission through polymeric film is a complex phenomenon. It is governed by both Fick's law and Henry's law. The rate of transmission depends on the absorption of the moisture by the undersurface of the film and its diffusion

across the surface at a given pressure. Under steady-state conditions, the rate of flow of water vapor is expressed by Fick's law:

$$f = -D(dc/dx) \qquad \text{(Eq. 1)}$$

where f = amount of water vapor in mg. permeating through a unit area in cm.^{2} per unit time of 24 hr., D = diffusion constant, and dc/dx = concentration gradient in the direction of flow. For substances following Henry's law, at a given temperature where the diffusion constant is independent of water vapor concentration, Eq. 1 can be integrated as follows:

$$f\,dx = -D\,dc \qquad \text{(Eq. 2)}$$

$$-\int_{x_2}^{x_1} f\,dx = \int_{c_2}^{c_1} D\,dc \qquad \text{(Eq. 3}a\text{)}$$

or:

$$\int_{x_1}^{x_2} f\,dx = \int_{c_2}^{c_1} D\,dc \qquad \text{(Eq. 3}b\text{)}$$

Therefore:

$$f(x_2 - x_1) = D(c_1 - c_2) \qquad \text{(Eq. 4)}$$

and:

$$f = D\frac{(c_1 - c_2)}{(x_2 - x_1)} \qquad \text{(Eq. 5)}$$

where c_1 and c_2 are steady-state concentration of water vapor under and above the film, respectively; and $x_2 - x_1 = T$ = thickness of the film. Therefore, $f = [D(c_1 - c_2)]/T$. But according to Henry's law, $c = sp$, where s = solubility coefficient for the water vapor in the polymeric film and p = pressure of the water vapor. Therefore:

$$(c_1 - c_2) = s(P_1 - P_2) \qquad \text{(Eq. 6)}$$

$$\frac{(c_1 - c_2)}{T} = s\frac{(P_1 - P_2)}{T} \qquad \text{(Eq. 7)}$$

$$f = Ds\frac{(P_1 - P_2)}{T} \qquad \text{(Eq. 8)}$$

where $Ds = P$ (permeability coefficient), and:

$$f = P\frac{(P_1 - P_2)}{T} = P\frac{\Delta P}{T} \qquad \text{(Eq. 9)}$$

where ΔP = pressure differential. Therefore, P (permeability coefficient) $= fT/\Delta P$.

Since the transmission is an inverse function of film thickness, the expression is corrected to a standard thickness of 0.1 mm. so that:

$$P = \frac{fT}{0.1 \text{ mm.}\,(\Delta P)} \qquad \text{(Eq. 10)}$$

and if fT/0.1 mm. $= F$ = amount of water vapor in mg. permeating through 0.1-mm. thick film per unit area in cm.^{2} per unit time of 24 hr., then $P = F/\Delta P$ since $F = wT/(A)(0.1$ mm.), where w = weight in mg. and A = area in cm.^{2}. Then $P = F/$(pressure differential) = mg./cm.^{2} per 0.1-mm. thickness per 24 hr. per mm. Hg. F is also known as flux.

The permeability coefficient (P) is defined as milligrams of water that permeate through a 0.1-mm. thick film per unit area in cm.^{2} per unit pressure drop each 24 hr. after a steady state of diffusion has been established under the experimental conditions of temperature and pressure (10).

Singh *et al.* (11) showed that matrix permeability and the rate of permeation of the matrix by the solvent can individually limit the drug release rate. This would seem to indicate that the drug release is controlled by the rate of solvent penetration, which is itself influenced by the degree of wetting or contact angle.

According to the Noyes-Whitney equation (12) for determining the rate of solution of a solid:

$$\frac{dC}{dt} = k(C_s - C_t) \qquad \text{(Eq. 11)}$$

where C_s = concentration of the saturated solution, C_t = concentration of the drug in solution at time t, and k = rate constant, an increase in C_s would result in an increase in solution rate. Hence, the determination of C_s of the drug becomes a major factor in the evaluation of solution rates. The constant k is dependent upon the surface area of the exposed solid, the intensity of the agitation, temperature, and structure of the surface depending on the cross-linking of the molecules. For the most part, the surface area, the intensity of agitation, and temperature are held constant; under these conditions, the rate constant k depends only on the nature of the solid.

Upon integration:

$$\int dC/(C_s - C_t) = \int k\,dt \qquad \text{(Eq. 12)}$$

Therefore:

$$\int 1/(C_s - C_t)dC = \int k\,dt \qquad \text{(Eq. 13)}$$

and:

$$\int \frac{(1/C_s)dC}{(1 - C_t/C_s)} = \int k\,dt \qquad \text{(Eq. 14)}$$

Since the value of C_t/C_s is less than 1, when $1 - C_t/C_s = U$, then $dU/dC = 1/C_s$ and $dC = -dUC_s$.

On substitution, the integral becomes:

$$\frac{-dU}{U} = k\,dt \qquad \text{(Eq. 15)}$$

Therefore, $-\ln U = kt$, $\ln 1/U = kt$, $\ln 1/(1 - C_t/C_s) = kt$, and $\ln C_s/(C_s - C_t) = kt$. By rearranging terms, $C_s/(C_s - C_t) = e^{kt}$ and $(C_s - C_t) = C_s e^{-kt}$, which is an exponential decay function. Since:

$$\ln C_s - \ln (C_s - C_t) = kt \qquad \text{(Eq. 16)}$$

therefore:

$$\ln (C_s - C_t) = -kt + \ln C_s \qquad \text{(Eq. 17)}$$

and:

$$\log (C_s - C_t) = -\frac{kt}{2.303} + \log C_s \qquad \text{(Eq. 18)}$$

From Eq. 18, when log $(C_s - C_t)$ is plotted *versus* time, the slope of the curve equals $-k/2.303$ or $k = -$ slope $\times$ 2.303.

When C_t is negligible, the Noyes-Whitney equation reduces to:

$$\frac{dC}{dt} = kC_s = \text{constant (zero order)} \qquad \text{(Eq. 19)}$$

This is possible only under perfect sink conditions where an excess of solvent is always present to maintain a subsaturated solution. Equation 19 can also be written in terms of concentration of the drug in the film, provided $C_s = A_0$, where A_0 represents the initial drug concentration in the film:

$$\frac{dC}{dt} = kA_0 - (A_0 - A) = kA \qquad \text{(Eq. 20)}$$

Equations 18 and 20 were applied to the release of gentian violet from selected films by Sciarra and Gidwani (13). The experimental data were fitted to these equations, and it was noted that the rate of release of gentian violet from the films followed first-order kinetics.

This investigation is primarily concerned with the determination of the effect of plasticizers on the water transmission of polymeric films. A relatively simple method for the determination of water vapor transmission was developed. The values for the hardness, alkali resistance, flexibility, and modulus of elasticity for the films

Table I—Water Vapor Transmission of Films Prepared from Polyamide 1540 at 37°

Plasticizer	Weight Percent, PHR[a]	Hours	Flux (F), mg.
Hexadecyl alcohol	10	24	8.91
		48	16.43
		72	23.50
		96	30.76
Hexadecyl alcohol	20	24	14.80
		48	27.40
		72	38.50
		96	49.40
Hexadecyl alcohol	30	24	18.70
		48	35.95
		72	52.55
		96	69.35
Tributyl citrate	10	24	10.96
		48	20.71
		72	30.64
		96	39.64
Multisterol mixture	10	24	5.18
		48	11.40
		72	18.28
		96	24.88

[a] Parts of plasticizer per 100 parts of total weight of film.

were previously reported by the authors (13). Furthermore, it may be possible to relate the water vapor transmission to the release of drugs from the film as well as to prolong the drug release and thereby maintain most effectively the thermodynamic activity of the drug in the underlying tissues with relatively small amounts of drug. The existence of a significant degree of interaction between ionic drugs and nonionic surfactants (14) very clearly demonstrates a considerable influence of the binding on the release of drug from the formulation (15). This might be particularly true in the formulation of spray-on bandages where nonionic esters such as plasticizers are often employed to impart flexibility fo the films. Flexibility of the film is based upon a subjective analysis. Several drugs were selected for this study on the basis of their solubility in suitable solvents rather than their therapeutic value. In this manner, direct measurements can be made. Cetylpyridinium chloride and benzalkonium chloride were selected since it has been reported that these substances tend to bind to nonionic agents and inert plastic matrixes. Finally, a study of the *in vitro* release of the drugs from selected model polymeric films intended for topical application as an aerosol spray was made.

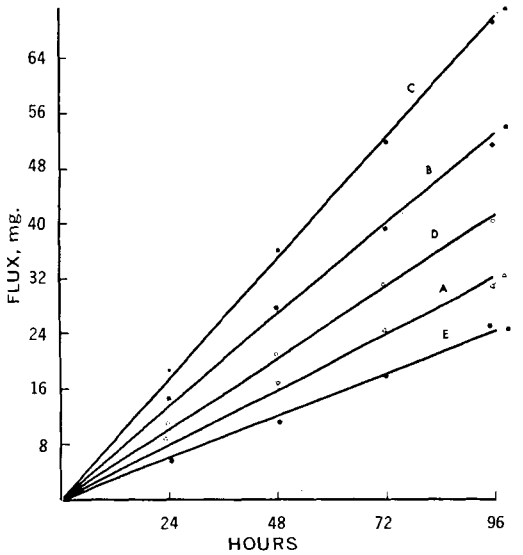

Figure 1—*Water vapor transmission of films prepared from polyamide 1540. Key: A, hexadecyl alcohol, 10 PHR; B, hexadecyl alcohol, 20 PHR; C, hexadecyl alcohol, 30 PHR; D, tributyl citrate; and E, multisterol mixture. (In all figure legends, PHR = parts of plasticizer per 100 parts of total weight of film.)*

Table II—Water Vapor Transmission of Films with High Flux Value at 37°

Film	Plasticizer	Weight Percent, PHR[a]	Hours	Flux (F), mg.
Ethylcellulose	Hexadecyl alcohol	10	24	76.0
			48	156.0
			72	238.0
			96	317.5
Ethylcellulose	Hexadecyl alcohol	20	24	59.5
			48	117.8
			72	177.5
			96	237.5
Ethylcellulose	Hexadecyl alcohol	30	24	61.5
			48	122.5
			72	183.0
			96	245.5
Acrylic resin	Unplasticized	—	24	57.3
			48	114.0
			72	170.7
			96	221.5
Mixed polymer (2.5 parts of polyamide 1155 and 2 parts ethylcellulose)	Tributyl citrate	10	24	68.5
			48	126.0
			72	175.5
			96	224.5

[a] Parts of plasticizer per 100 parts of total weight of film.

EXPERIMENTAL

Several film-forming agents were selected for initial screening. These included an acrylic resin[1]; polyamides 1155[2], 1533[3], 1536[4], and 1540[5]; and ethylcellulose[6]. The plasticizers studied included a multisterol mixture[7], tributyl citrate[8], and hexadecyl alcohol[9]. These films were selected based upon their insolubility in water so as to eliminate any effect due to solution of the film in desorbing media.

Preparation of Model Films—The films were cast from a 5% by weight solution of the film-forming agent and plasticizer. The acrylic resin, polyamide 1155, and ethylcellulose were dissolved in absolute ethyl alcohol; the polyamide 1533, 1536, and 1540 resins were dissolved in isopropyl alcohol. Twenty milliliters of the solution was poured onto the surface of mercury contained in a 150 × 20-mm. petri dish, which was then covered with an inverted glass funnel. Clearance was provided for the escape of the solvent vapors by raising the base of the funnel just above the resting surface. The funnel was an aid in controlling the rate of evaporation of the solvent and reduced the blistering of the surface of the deposited film. The resulting films were removed from the surface of the mercury and stored in a desiccator for 24 hr. before they were used.

Determination of Water Vapor Transmission—The rate of water vapor transmission was determined by slightly modifying the ASTM E-96-66 method (16). The determination was carried out in a 120-ml. (4-oz.) jar filled with demineralized water. A circular opening with a diameter of 2 cm. was cut at the center of the screw cap of the test jar. High vacuum silicone grease was applied on the under surface of the cap, and the film to be tested was mounted so that it adhered to the cap most tenaciously. The area of the film that covered the bereft portion of the cap represented the actual area of test film subjected to water vapor transmission. A rubber

[1] Caboset 525, B. F. Goodrich Chemical Co., Cleveland, Ohio.
[2] Polymid 1155, Lawler Chemicals, Inc., Krumbhaar Resin Div., Chicago, Ill.
[3] Emerez 1533, Emery Industries, Inc., Cincinnati, Ohio.
[4] Emerez 1536, Emery Industries, Inc., Cincinnati, Ohio.
[5] Emerez 1540, Emery Industries, Inc., Cincinnati, Ohio.
[6] Ethylcellulose N-10, Hercules Powder Co., Wilmington, Del.
[7] Amerchol L-101, American Cholesterol Products, Inc., Edison, N. J.
[8] Citroflex 4, Pfizer and Co., Inc., New York, N. Y.
[9] Enjay Chemical Co., Elizabeth, N. J.

Table III—Water Vapor Transmission of Films with Low Flux Value at 37°

Film	Plasticizer	Weight Percent, PHR[a]	Hours	Flux (F), mg.
Polyamide 1533	Hexadecyl alcohol	10	24	10.03
			48	19.75
			72	29.10
			96	38.28
Polyamide 1536	Unplasticized	—	24	9.65
			48	19.20
			72	29.10
			96	38.48
Polyamide 1155	Hexadecyl alcohol	10	24	11.37
			48	21.32
			72	32.37
			96	42.82
Polyamide 1155	Tributyl citrate	10	24	16.60
			48	33.10
			72	64.90
			96	49.45
Polyamide 1155	Multisterol mixture	10	24	9.55
			48	20.10
			72	30.90
			96	41.80

[a] Parts of plasticizer per 100 parts of total weight of film.

gasket was also fitted into the cap and the edges of the jar were coated with high vacuum grease to prevent possible leaks. The distance between the surface of the water and the under surface of the film was maintained at 20 ± 5 mm. The cap was gently replaced and the jar was tightly closed to ensure complete sealing of the assembly.

The jar was then accurately weighed and placed in the heated vacuum desiccator containing anhydrous calcium sulfate[10] as desiccant. The jar was then surrounded by eight perforated 120-ml. (4-oz.) cans containing anhydrous calcium sulfate. The desiccator was closed and maintained at the specified temperature. Under these conditions, the relative humidity under the film was 100%, and above the film it was zero. Therefore, Δp, the vapor pressure differential, became equal to the vapor pressure of the water at the specified temperature. The water vapor permeated from the lower 100% humidity section through the film to the upper zero humidity section. The jar was accurately weighed periodically to determine the weight loss, which would be equal to the amount of water that permeated through the film. The thickness of the films was measured with a micrometer caliper having an accuracy of ±0.01 mm.

To prevent the defacing or deformation of the test films, the thickness was measured at the end of the determination. The results of the water vapor transmission of each type of film over a period of 96 hr. is shown in Tables I–III and represent the average of three determinations. The water vapor transmission plots are shown in Figs. 1–3. Permeability coefficients, P, were calculated from the slopes of the lines in accordance with the equation $P = (\text{slope}/P) \times 24$ and are given in Table IV.

Determination of Degradation from Exposure to UV Radiation—The clear, dried test films were mounted on cardboard slides. After the initial IR spectra of the mounted films were recorded on an IR spectrophotometer[11], the films were irradiated with longwave UV light for 24 hr. by exposing them in the opaque box to a lamp[12]. Following irradiation, the IR spectra of the exposed films were recorded. The spectra of the films before and after radiation were examined for any appearance of additional absorption bands.

Aerosol Formulation—A preliminary study was made to determine the compatibility of the various films with fluorinated hydrocarbons used as aerosol propellants. Product concentrates were prepared by dissolving the resins in suitable solvents with the aid of heat, if necessary. The resin solution was then transferred to an aerosol container and trichlorofluoromethane (Propellant 11) was added. After sealing a suitable valve in place, the air was removed from the container and it was pressurized with dichlorodifluoromethane (Propellant 12). Five percent of the polymer was mixed with 25% of the solvent and 70% of a blend of Propellant 12/11 (50:50), all on a weight basis.

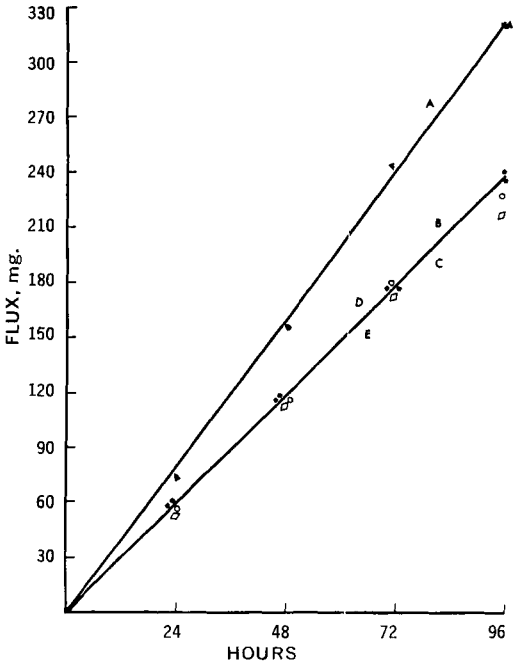

Figure 2—*Water vapor transmission of films with high flux value. Key: A, ethylcellulose/hexadecyl alcohol, 10 PHR; B, ethylcellulose/hexadecyl alcohol, 20 PHR; C, ethylcellulose/hexadecyl alcohol, 30 PHR; D, acrylic resin unplasticized; and E, mixed polymer/tributyl citrate, 10 PHR.*

Determination of Absorption Spectra and Beer's Plot—Absorption spectral curves for each drug used in this study were made by plotting the absorbance *versus* the wavelength, using a double-beam spectrophotometer[13]. The wavelengths at which maximum absorption occurred were determined for these drugs. Maximum absorption for cetylpyridinium chloride and benzalkonium chloride

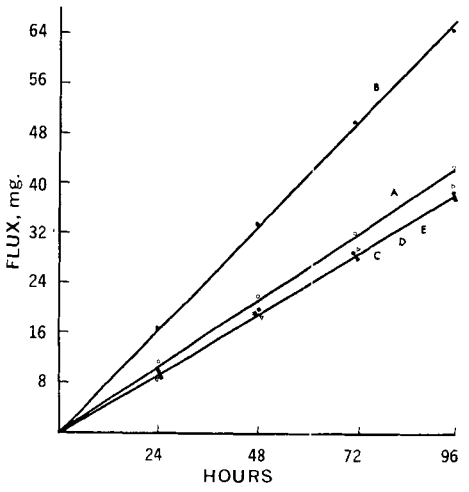

Figure 3—*Water vapor transmission of films with low flux value. Key: polyamide 1155/hexadecyl alcohol, 10 PHR; B, polyamide 1155/tributyl citrate, 10 PHR; C, polyamide 1155/multisterol mixture, 10 PHR; D, polyamide 1533/hexadecyl alcohol, 10 PHR; and E, polyamide 1536, unplasticized.*

[10] Drierite, W. A. Hammond Drierite Co., Xenia, Ohio.
[11] Perkin-Elmer model 700.
[12] Produces maximum emission at a wavelength of 3660 Å. The distance between film and light source was approximately 22 cm. Black Raymaster lamp, George W. Gates and Co., Inc., Franklin Square, N. Y.
[13] Coleman-Hitachi model 124.

Table IV—Comparison of Permeability Coefficients (P)

Film	Plasticizer	Weight Percent, PHR[a]	Slope	$P = \frac{\text{slope} \times 24}{48^b}$
Polyamide 1533	Hexadecyl alcohol	10	0.400	0.20
Polyamide 1536	Unplasticized	—	0.400	0.20
Polyamide 1540	Hexadecyl alcohol	10	0.334	0.17
Polyamide 1540	Hexadecyl alcohol	20	0.540	0.27
Polyamide 1540	Hexadecyl alcohol	30	0.750	0.38
Polyamide 1540	Tributyl citrate	10	0.430	0.22
Polyamide 1540	Multisterol mixture	10	0.260	0.13
Ethylcellulose	Hexadecyl alcohol	10	3.300	1.65
Ethylcellulose	Hexadecyl alcohol	20	2.500	1.25
Ethylcellulose	Hexadecyl alcohol	30	2.500	1.25
Polyamide 1155	Hexadecyl alcohol	10	0.439	0.22
Polyamide 1155	Tributyl citrate	10	0.680	0.34
Polyamide 1155	Multisterol mixture	10	0.439	0.22
Acrylic resin	Unplasticized	—	2.500	1.25
Mixed polymer[c]	Tributyl citrate	10	2.500	1.25

[a] Parts of plasticizer per 100 parts of total weight of film. [b] Vapor pressure of water at 37.5°. [c] Consists of 2.5 parts polyamide 1155 and 2 parts ethylcellulose.

occurred at 260 and 285 nm., respectively. Individual graphs were prepared for each specific drug by plotting absorbance *versus* the known concentration. Linear plots were obtained, indicating that the drugs followed the Beer–Lambert relationship. All measurements were made using water as the solvent.

Determination of Initial Drug Concentration (A_0) of Film—The initial drug concentration in the films was determined spectrophotometrically[14]. The blank solution was prepared by dissolving the drug-free film in *n*-butyl alcohol. This solution was used as the reference standard. The sample solution was prepared in a similar manner using the test film that contained drug. The absorbance of the sample against the reference was measured, and the concentration was determined by consulting the appropriate Beer plot.

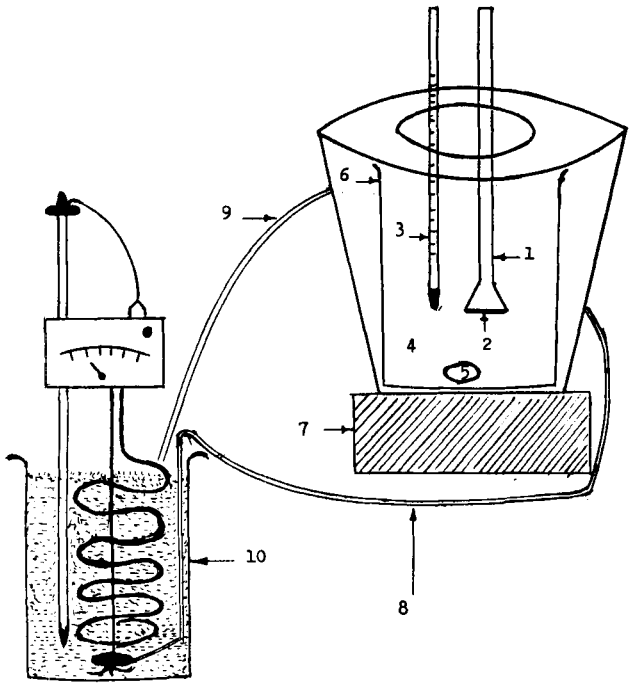

Figure 4—*Schematic diagram of the apparatus used to measure drug release rates from polymeric films. Key: 1, glass-stoppered tube; 2, test film; 3, thermometer; 4, desorbing solvent; 5, magnetic stirring bar; 6, water-jacketed glass beaker; 7, magnetic stirrer; 8, inlet for water jacket; 9, outlet for water jacket; and 10, constant-temperature water bath equipped with circulating pump.*

[14] Using either the Coleman-Hitachi double-beam spectrophotometer, model 124, or the Bausch & Lomb Spectronic 20, depending on whether the absorbance occurred in the UV or visible region.

***In Vitro* Release Rate Determination**—The method used was similar to the method previously reported (13). The model films containing drug were mounted on the flat head of the glass-stoppered tube using a bonding agent[15]. This acted as a bond between the undersurface of the film and the contact surface of the flat-head stopper. A thin layer of the bonding agent was applied over a hard surface, and the flat head of the stoppered glass tube was gently placed on the top of it. As the tube was pulled away from the treated surface, the contact surface of the flat head picked up a thin coat of the adhering matter. Then, on pressing the flat head of the tube firmly against the specimen film, the latter adhered to the former. This unit was then allowed to cure overnight in an oven at 45 ± 5°. Finally, the periphery of the flat head was trimmed with a sharp blade to remove the excess film. This tube was then placed in the water-jacketed beaker containing 300 ml. of desorbing solvent maintained at 37 ± 0.5°. The solution was agitated by means of a magnetic stirring bar. The entire assembly was then placed on a magnetic stirrer. The temperature of the desorbing solvent in the beaker was kept constant by circulating water from the constant-temperature bath equipped with a stir pump around the beaker (Fig. 4).

Aliquot samples of the solvent were withdrawn at various time intervals and analyzed spectrophotometrically for the concentration of drug present. After the absorbance was measured, the samples were placed back into the beaker to maintain a constant volume. Absorbances were measured at 260 and 285 nm. for cetylpyridinium chloride and benzalkonium chloride, respectively.

The determinations were made in 0.225% sodium chloride solution and in demineralized water for the drugs incorporated into

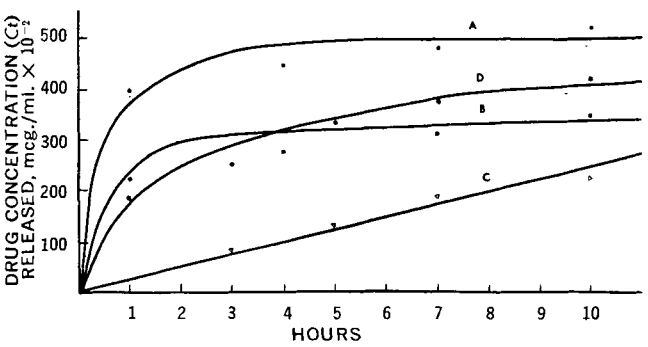

Figure 5—*Release profile for ethylcellulose film containing hexadecyl alcohol, 30 PHR. Key: A, cetylpyridinium chloride/demineralized water; B, cetylpyridinium chloride/0.225% sodium chloride; C, benzalkonium chloride/0.225% sodium chloride; and D, benzalkonium chloride/demineralized water.*

[15] EA-40 epoxy-bonding agent, Smooth-On, Inc., Gillette, N. J.

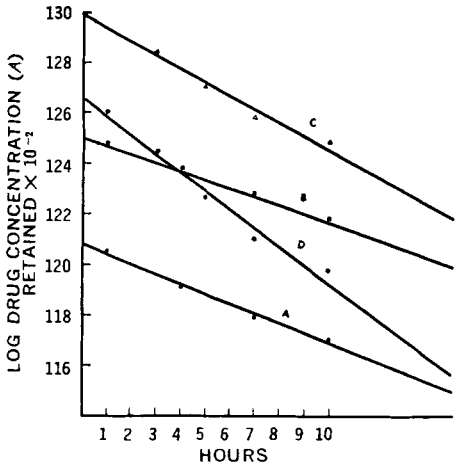

Figure 6—*Apparent first-order profile for ethylcellulose film containing hexadecyl alcohol, 30 PHR. Key: A, cetylpyridinium chloride/demineralized water; B, cetylpyridinium chloride/0.225% sodium chloride; C, benzalkonium chloride/0.225% sodium chloride; and D, benzalkonium chloride/demineralized water.*

ethylcellulose films. Drugs incorporated into the polyamide 1155 films utilized 0.45% sodium chloride solution and demineralized water as the desorbing solvent. The mixed polymer was evaluated in demineralized water only. Three hundred milliliters of desorbing solvent was used in all cases. These results are shown in Figs. 5–11. Two determinations were made for each variable.

DISCUSSION

A profile of water vapor transmission through various films containing different plasticizers was given. The plots produced a straight line which intersected the origin, indicating that there existed a steady state of permeation through the films. As the amount of plasticizer was increased, the water vapor transmission of polyamide 1540 films was increased while the flexibility was decreased. This may be attributed to the porosity-contributing qualities of the plasticizer. From these data, it seems that the water vapor transmission is proportional to the amount of plasticizer in the film. However, in the case of ethylcellulose films, it was noted that water vapor transmission decreased while plasticizer increased. Flexibility was found to increase. It is possible that water vapor transmission is not only a function of the amount of plasticizer but is also a function of flexibility. The mixed polymer produced a film which was highly permeable to water vapor. This may have been due to a lower degree of crystallinity resulting from the mixture. The acrylic resin was also noted to produce films with high permeability coefficients. A previous report (13) presented data regarding the flexibility, hardness, and modulus of elasticity of these films.

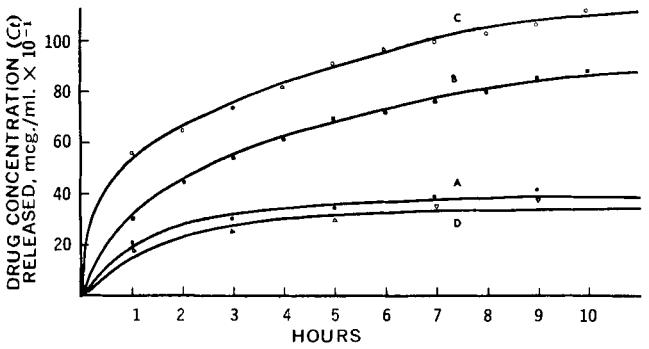

Figure 7—*Release of cetylpyridinium chloride from polyamide 1155. Key: A, hexadecyl alcohol, 10 PHR/0.45% sodium chloride; B, hexadecyl alcohol, 10 PHR/demineralized water; C, tributyl citrate, 10 PHR/demineralized water; and D, tributyl citrate, 10 PHR/0.45% sodium chloride.*

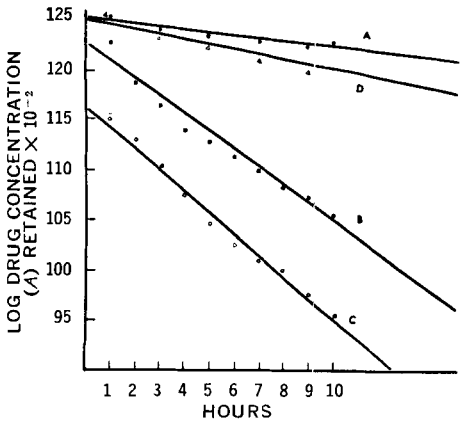

Figure 8—*Apparent first-order profile for cetylpyridinium chloride. Key: A, hexadecyl alcohol, 10 PHR/0.45% sodium chloride; B, hexadecyl alcohol, 10 PHR/demineralized water; C, tributyl citrate, 10 PHR/demineralized water; and D, tributyl citrate, 10 PHR/0.45% sodium chloride.*

The examination of IR spectra of the films both before and after exposure to UV radiation indicated that the films were fairly stable under these conditions. Very few changes were noted in the absorption bands. Some changes were noted in the bands at wave numbers of 1700, 1750, 1050, and 960 $cm.^{-1}$ but none of the changes was appreciable.

All of the films were found to be compatible with the aerosol propellants. Clear solutions were produced in all cases. However, further formulation studies are indicated to develop suitable spray patterns, particle size, and spray rate.

Preliminary investigations showed that, due to the hydration effect, the solubility of certain drugs in water decreased with an increasing concentration of sodium chloride. In addition, the vapor pressure above the solution decreased with an increase in salt concentration. It was also found that the rate of drug release in 0.9% sodium chloride was so slow that the sensitivity of the measurement was limited. Furthermore, a reasonable drug release occurred when the concentration of sodium chloride was reduced to 0.45%. To accelerate the drug release in quantities sufficient for detection, 0.45% of sodium chloride solution was used instead of 0.9% for the *in vitro* studies. Due to some complex formation of the drug with polymers, an optimum concentration for each specific drug had to be maintained in the polymeric film so that the drug being released could be measured over a reasonable period of time. It can be seen from a plot of log (*A*) as a function of time (Figs. 6, 8, and 10) that the plot is linear, indicating that the drug release followed first-order kinetics. Moreover, the profile of drug release for mixed polymers shows nonlinearity (Fig. 11), possibly due to some complex mechanism of drug release. The first-order rate constants, *k*, were calculated from the slope of the linear plot ac-

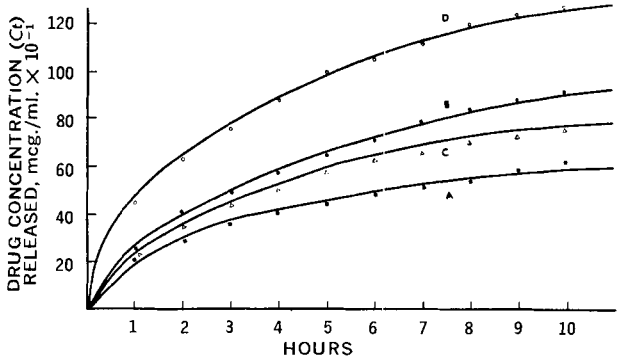

Figure 9—*Release of benzalkonium chloride from polyamide 1155. Key: A, hexadecyl alcohol, 10 PHR/0.45% sodium chloride; B, hexadecyl alcohol, 10 PHR/demineralized water; C, tributyl citrate, 10 PHR/0.45% sodium chloride; and D, tributyl citrate, 10 PHR/demineralized water.*

Table V—Rate of Release (k) of Drugs from Selected Films

Film	Plasticizer	Weight Percent, PHR[a]	—Cetylpyridinium Chloride— k, hr.$^{-1}$	$t_{1/2}$, hr.	—Benzalkonium Chloride— k, hr.$^{-1}$	$t_{1/2}$, hr.
Ethylcellulose	Hexadecyl alcohol	30	8.60×10^{-3}[b]	80.0	16.0×10^{-3}[b]	43.0
			7.60×10^{-3}[c]	91.0	12.6×10^{-3}[c]	55.0
Polyamide 1155	Hexadecyl alcohol	10	4.15×10^{-2}[b]	16.7	8.00×10^{-2}[b]	8.7
			8.00×10^{-3}[d]	87.0	4.15×10^{-2}[d]	16.7
Polyamide 1155	Tributyl citrate	10	4.90×10^{-2}[b]	14.2	14.7×10^{-2}[b]	4.7
			12.6×10^{-3}[d]	55.0	5.75×10^{-2}[d]	12.0

[a] Parts of plasticizer per 100 parts of total weight of film. [b] Demineralized water. [c] 0.225% sodium chloride solution. [d] 0.45% sodium chloride solution.

cording to:

$$k = -\text{slope} \times 2.303 \qquad \text{(Eq. 21)}$$

and the half-life, $t_{1/2}$, for the drugs were then calculated on the basis of the relationship:

$$t_{1/2} = \frac{0.693}{k} \qquad \text{(Eq. 22)}$$

These are shown in Table V.

It was found that the drug release from polyamide 1155 was suppressed by 0.45% of sodium chloride in demineralized water. There was no drug release at all from ethylcellulose film in the 0.45% sodium chloride solution. Therefore, 0.225% of sodium chloride solution was used as a desorbing solvent to study the *in vitro* drug release from ethylcellulose films. This anomalous behavior of inhibiting the drug release by sodium chloride solution can be explained by the inability of the salt solution to wet the polymeric film as effectively as demineralized water. The poor wetting qualities of sodium chloride solution could be attributed to its high contact angle and high surface tension. It is, therefore, apparent that the drug release is controlled by the degree of wetting or hydration of the film and by the rate of solvent penetration. It can be noted that ethylcellulose produced films with excellent flexibility and water vapor transmission but with poor drug release qualities. On the other hand, polyamide 1155 produced films that exhibited no detectable binding to the drugs. As a result, it was decided to form a mixed polymer from these two resins. The mixed polymer produced films with balanced properties of water vapor transmission and drug release. These observations appear to be consistent with electron theory of covalent bonding. Polyamide 1155 is polar in nature and carries a negative center of electricity. This electronegativity of the resin is attributed to its amide group, which has two pairs of electrons in the oxygen atom and one pair of electrons in the nitrogen atom. These surplus electron pairs have a tendency to associate with positively charged ions deficient in electrons. Thus, both oxygen and nitrogen atoms of the amide group share their lone pairs of electrons with cations of the outside groups, forming complex ions through ion-dipole interaction. This type of complexation is the result of coordination (dative-covalent) linkages. On the other hand, ethylcellulose carries a positive center of electricity due to the presence of polar hydroxyl groups which are responsible for binding of drugs. It is also evident that the drugs are weakly bound by the polyamide 1155 film and strongly bound by ethylcellulose films. This indicates that the magnitude of binding is also influenced by the number of binding sites available in the polymer structure for the interaction with the drugs. When polyamide 1155 and ethylcellulose are mixed, they neutralize each other's charges, leaving the mixed polymer with no residual charges to form a complex with drugs. With this mixture it is possible that a higher degree of hydration will take place.

All the data presented in this study, with the exception of data on the mixed polymer, show that the drug release follows first-order kinetics. For *in vitro* drug release to be exponential, the plot of log A *versus* time should yield a straight line, and the y intercept at zero time should correspond to log A_0 (initial concentration). But the typical apparent first-order profiles show that the values of the y intercepts are, in fact, less than the predicted values. It seems apparent from the drug release profiles that one portion of the drug is released immediately and the other portion exponentially. The initial release is faster than the remainder which follows the first-order kinetics. This may be attributed to the presence of surface drug which may be ignored. There is, therefore, a lag time before the rate follows a first-order process. Hence the linear portion of the curve is the rate-determining step for the drug release. Since the rate release during the first 60 min. (lag time) was indeterminate,

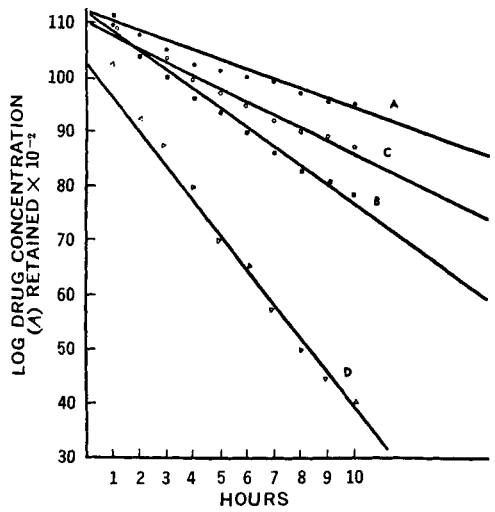

Figure 10—*Apparent first-order profile for benzalkonium chloride. Key: A, hexadecyl alcohol, 10 PHR/0.45% sodium chloride; B, hexadecyl alcohol, 10 PHR/ demineralized water; C, tributyl citrate, 10 PHR/0.45% sodium chloride; and D, tributyl citrate, 10 PHR/ demineralized water.*

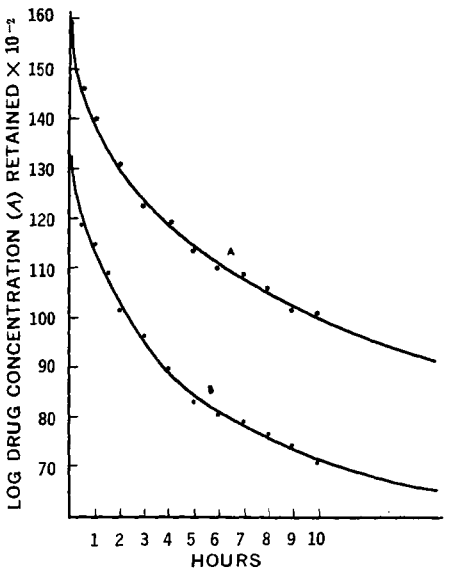

Figure 11—*Nonlinear plot for mixed polymer/tributyl citrate, 10 PHR. Key: A, cetylpyridinium chloride/demineralized water; and B, cetylpyridinium chloride/demineralized water.*

the rate-limiting step permitted the determination of relative rate constants and half-lives for the drugs studied. There possibly may be two processes involved: transportation of the drug by hydration followed by release of drug from the surface of the film.

The drug release of such type may be expressed mathematically by the following equations:

$$\text{total amount released} = \text{amount released immediately} + \text{amount released exponentially} \quad \text{(Eq. 23}a\text{)}$$

$$C_t = A_0C_i + AC_e \quad \text{(Eq. 23}b\text{)}$$

where:

C_t = total amount of drug released at any time t
A_0 = original amount of drug in the film
C_i = fraction of the original amount of drug released immediately
A = amount of the drug remaining in the film
C_e = fraction of the remainder drug released exponentially

But:

$$A_0C_i + A = A_0 \quad \text{(Eq. 24}a\text{)}$$

$$A_0C_i = A_0 - A \quad \text{(Eq. 24}b\text{)}$$

$$C_t = (A_0 - A) + AC_e \quad \text{(Eq. 24}c\text{)}$$

Again, $(A - AC_e)$ = amount of drug remaining after the AC_e amount is released:

$$A - AC_e = Ae^{-kt} \quad \text{(linear portion of curve)} \quad \text{(Eq. 25}a\text{)}$$

$$AC_e = A - Ae^{-kt} \quad \text{(Eq. 25}b\text{)}$$

$$AC_e = A(1 - e^{-kt}) \quad \text{(Eq. 25}c\text{)}$$

$$C_t = (A_0 - A) + (1 - e^{-kt}) \quad \text{(Eq. 25}d\text{)}$$

This is the same as $Y = mX + C$. Therefore, the plot C_t *versus* $(1 - e^{-kt})$ should be linear, intersecting at $(A_0 - A)$.

It is apparent from these equations that the rate constant, k, is calculated from the slope of the linear portion of the curve which is the rate-determining step. Initial drug release $(A_0 - A)$ is dependent on the lag time of the system. As the lag time or the quantity $(A_0 - A)$ approaches zero, the straight line tends to intersect through the origin. If this does occur, then the value of the y intercept is the same as the predicted value according to the first-order plot:

$$\log A = \frac{-kt}{2.303} + \log A_0 \quad \text{(Eq. 26)}$$

In the case of the mixed polymer, the plots of log A *versus* time are nonlinear and exhibit marked curvature. The curve emerges with a slope and then gradually bends and continues as a straight line. The nonlinearity shows that the rates of drug release are complicated, and the equation for such releases becomes more complex. This could be expressed mathematically as:

$$C_t = A_0C_i + A_1C_{e_1} + A_2C_{e_2} + \ldots \quad \text{(Eq. 27)}$$

It can be seen from the first-order profiles that the drug release proceeds in successive steps, indicating that the mechanism of the drug release becomes complex. This complicated behavior of drug release from the mixed polymer may be due to the low degree of binding of drugs by the mixed polymer or to a higher degree of hydration. The rate was so complicated due to total elimination of drug from the binding sites that it was impractical to determine the rate constant for the system.

SUMMARY

The influence of selected polymers on the rates of drug release was investigated with the objective of assessing the nature of binding of the drugs. Cetylpyridinium chloride and benzalkonium chloride were selected to illustrate the relative magnitude of binding to polymers. The films with a more pronounced tendency to complexation with the drugs exhibited slow rates of release. Conversely, the films with a lesser tendency to complexation with drugs exhibited relatively faster rates of release. The values of appropriate rate constants were determined in the presence and absence of sodium chloride in the desorbing solution. On the basis of these results, two polymers were selected to form a mixed polymeric film. The mechanism of drug release from the mixed polymeric film was shown to be complex. A special apparatus and method for *in vitro* determination of the rates of drug release were developed. A kinetic model based on the Noyes–Whitney relationship was used, and the rate of drug release in aqueous media from various films was determined. The drug release was found to proceed by first-order kinetics for the calculation of the first-order rate constants and half-lives for the drugs studied.

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