Water Vapor Permeation of Selected Cellulose Ester Films

By M. PATEL, J. M. PATEL, and A. P. LEMBERGER

In a study of water vapor permeation of cellulose acetate propionate, cellulose acetate butyrate, and cellulose acetate stearate films it was observed that permeability constant decreased with increasing chain length of the acid moiety. Cellulose acetate hydrogen phthalate films were easily permeated by water vapor at temperatures below 30° and resembled films of cellulose acetate stearate in their permeability at higher temperatures. The rather abrupt change in permeability observed in the temperature range of 30–35° indicates that caution must be exercised in interpreting accelerated aging data at higher temperatures with these films. Mixed films of cellulose acetate hydrogen phthalate and polyethylene glycol 4000 show a minimum permeability constant when polyethylene glycol 4000 is 10–20 per cent by weight of the film.

IN THE LAST several years an increasing interest in and use of polymeric agents which have the unique property of forming films has developed in the pharmaceutical industry. One group of chemical compounds which has merited considerable attention is the group of cellulose derivatives, esters and ethers. The basic patent concerning the use of cellulose acetate hydrogen phthalate for enteric coating was granted to Hiatt in 1940–1941 (1). Antonides and DeKay in 1953 evaluated various types of carboxymethyl celluloses, cellulose acetate, cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate stearate, and cellulose acetate hydrogen phthalate for their enteric properties (2).

The ability of agents, such as cellulose derivatives and other polymers, to form films when deposited from proper solvents is utilized not only for enteric coating but also in the deposition of protective films on tablets as an alternative to sugar coating. With the increasing use of cellulose derivatives as coating materials in the pharmaceutical industry, information on water permeation of such films has become increasingly important. This study reports on water vapor permeation of films of cellulose acetate propionate (CAP), cellulose acetate butyrate (CAB), cellulose acetate stearate (CAS), and cellulose acetate hydrogen phthalate (CAHP). Another aspect of this work deals with water vapor permeation of mixed films of CAHP and polyethylene glycol 4000 (PEG 4000).[1]

Barrer (3) has stated that membranes such as polystyrene (which adsorb little water) behave at low vapor pressures in accordance with Fick's law, and permeation velocity is inversely proportional to film thickness. At higher vapor pressures where increased sorption of water occurs, deviation from Fick's law is observed. In this work the data have been analyzed on the basis of Fick's linear diffusion law in a manner similar to that of Lovegren and Feuge (5). Thus, the permeability constant, P, is defined by

$$P = \frac{W\,a}{At\,\Delta p} \qquad \text{(Eq. 1)}$$

where W is the weight of water in grams diffusing through a film of thickness, a, in centimeters and area, A, in square centimeters during time, t, in hours when the vapor pressure difference across the membrane is Δp in millimeters of mercury. The permeability constant represents the combined effect of diffusion and sorption and is given in units of grams per centimeter per hour per millimeter of mercury.

EXPERIMENTAL

Materials and Apparatus.—Cellulose acetate propionate (16% propionyl), cellulose acetate butyrate (16% butyryl), cellulose acetate stearate, and cellulose acetate hydrogen phthalate (30–40% phthalyl) were used as obtained from Eastman Organic Chemicals. Polyethylene glycol 4000 was used in preparing mixed films with cellulose acetate hydrogen phthalate. Reagent grade sodium chloride, nickel chloride, and magnesium chloride were used to prepare solutions to maintain the desired water vapor pressure within the permeation cell.

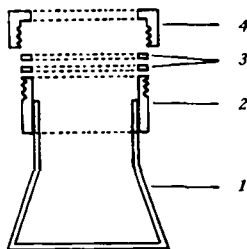The permeation cell is shown in Fig. 1. It consisted of an approximately 20-ml. conical flask

Fig. 1.—Permeation cell. Key: 1, 20-ml. conical flask (29/12 outside ground glass top); 2, tapered aluminum collar; 3, O-ring rubber gaskets; 4, aluminum cap.

TABLE I.—PERMEABILITY CONSTANTS CALCULATED ACCORDING TO EQ. 1

Film Material	Film Thickness, cm. $\times 10^2$	Permeability Constant, Gm. cm.$^{-1}$ hr.$^{-1}$ mm. Hg^{-1} $\times 10^8$	Film Material	Film Thickness, cm. $\times 10^2$	Permeability Constant, Gm. cm.$^{-1}$ hr.$^{-1}$ mm. Hg^{-1} $\times 10^8$
Cellulose acetate propionate (CAP) Temp., 24.5° C. Δp: 23.1 mm. Hg	1.40	73	Δp: 23.0 mm. Hg	2.65	22
	2.15	97		3.50	24
	3.45	96		3.70	23
	4.45	110	CAS Temp., 46.5° C. Δp: 23.0 mm. Hg	1.20	20
	5.58	110		2.50	24
CAP Temp., 36.8° C. Δp: 23.0 mm. Hg	1.35	51		3.55	28
	1.75	56		4.50	27
	2.75	62		5.10	28
	3.90	66	Cellulose acetate hydrogen phthalate (CAHP) Temp., 22.2° C. Δp: 20.1 mm. Hg	1.00	48
	4.25	67		1.90	71
CAP Temp., 45° C. Δp: 21.7 mm. Hg	1.40	39		2.95	89
	1.80	44		3.80	100
	2.75	50	CAHP Temp., 23.5° C. Δp: 21.7 mm. Hg	1.10	48
	3.95	57		2.35	75
Cellulose acetate butyrate (CAB) Temp., 24.5° C. Δp: 23.1 mm. Hg	1.35	60		2.75	82
	1.70	66		4.40	96
	2.50	77	CAHP Temp., 27.5° C. Δp: 21.0 mm. Hg	1.10	32
	3.45	75		1.80	42
	4.25	83		2.90	50
CAB Temp., 36.8° C. Δp: 23.0 mm. Hg	1.70	50		3.70	54
	2.35	59	CAHP Temp., 35° C. Δp: 21.5 mm. Hg	1.05	18
	2.45	64		1.80	24
	3.70	65		2.80	30
	5.15	65		3.65	33
CAB Temp., 46.5° C. Δp: 23.0 mm. Hg	1.75	41	CAHP Temp., 36.8° C. Δp: 23.0 mm. Hg	1.10	14
	2.35	44		1.95	21
	3.45	45		2.65	23
	3.75	49		3.30	28
	4.25	56		4.30	32
	5.15	58	CAHP Temp., 45° C. Δp: 21.8 mm. Hg	1.25	16
Cellulose acetate stearate (CAS) Temp., 24.5° C. Δp: 23.1 mm. Hg	1.20	20		2.10	24
	2.10	22		3.35	32
	3.50	24		4.20	38
	4.50	26	CAHP Temp., 46.5° C. Δp: 23.0 mm. Hg	1.45	16
	5.05	26		2.45	24
CAS Temp., 36.8° C.	1.20	19		3.40	33
	2.10	23		4.00	35

prepared by sealing the end of a male $^{29}/_{42}$ ground-glass joint cut to the proper size. The ground-glass connection was cut to $^{29}/_{12}$; a tapered threaded aluminum collar was fixed to the joint with white shellac. Films were held in a female threaded aluminum cap with a 2.8-cm. opening and sealed

TABLE II.—DATA FOR VARIOUS MIXED CAHP–PEG FILMS

Film Compn., % w/w	Temp., 21° C., Δp 18.7 mm. Hg		Temp., 35° C., Δp 21.5 mm. Hg	
	Thickness, cm. $\times 10^2$	Permeability Constant, Gm. cm.$^{-1}$ hr.$^{-1}$ mm. Hg^{-1} $\times 10^8$	Thickness, cm. $\times 10^2$	Permeability Constant, Gm. cm.$^{-1}$ hr.$^{-1}$ mm. Hg^{-1} $\times 10^8$
CAHP, 95 PEG, 5	1.00	43	0.80	15
	2.00	64	1.90	23
	3.00	79	2.70	28
	3.70	90	3.55	32
CAHP, 90 PEG, 10	0.95	36	0.90	13
	1.70	49	2.15	22
	2.90	67	3.15	28
	3.70	79	3.60	30
CAHP, 80 PEG, 20	0.80	31	0.75	15
	1.75	50	1.80	18
	2.70	66	2.50	21
	3.70	78	3.30	22
CAHP, 70 PEG, 30	0.70	41	0.70	21
	1.70	70	1.50	29
	2.45	85	2.30	34
	3.30	100	3.00	36
CAHP, 60 PEG, 40	0.70	50	0.80	24
	1.75	91	1.60	33
	2.50	110	2.50	38
	3.50	130	3.55	41

to the permeation cell with "O" ring rubber gaskets, 2.8 cm. inner diameter. In an experimental run the permeation cell was placed in a desiccator with magnesium perchlorate as desiccant. Dry air passed through concentrated sulfuric acid, and a calcium chloride tube was circulated through the desiccator during the run to provide agitation and insure that the water vapor pressure in the desiccator was negligible. The assembly was kept in a constant temperature room for determinations at temperatures up to 27°. For higher temperature runs the apparatus was placed in a constant temperature oven. Temperature control was within ±0.5°.

Procedure.—Films were prepared as described below. Sufficient solvent to make 100 ml. of solution was added to 10.0 Gm. of the desired cellulose derivative or to the proper weight ratio mixture of CAHP and PEG 4000. The solution was filtered through glass wool; a sufficient quantity of this solution was poured onto a clean mercury surface in a Petri dish to produce a film of the desired thickness. A perforated piece of filter paper was placed on the Petri dish, and an inverted 6-in. glass funnel was then placed over the assembly. The transparent film deposited as the solvent was permitted to evaporate slowly at room temperature. Solvent employed for CAP and CAB was a 1:1 volumetric mixture of acetone and dry chloroform. Solvent for casting films of CAS was a 3:1 volumetric mixture of acetone and dry chloroform. Acetone was used as solvent for casting CAHP and mixed CAHP–PEG films.

The deposited film was cut into circular disks approximately 3 cm. in diameter with a punch and dried 3–4 days in a desiccator containing magnesium perchlorate. The thickness of the film was measured at ten different locations with a caliper calibrated to 1×10^{-3} cm. The measurements on
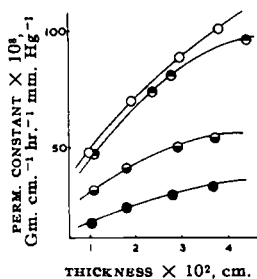

Fig. 2.—Typical curves for permeability constant as a function of thickness. CAHP films. Key: O, 22.2° C.; ⊖, 23.5°C.; ◐, 27.5°C.: ●, 35°C.

the film had to fall within $\pm 1.5 \times 10^{-3}$ cm. of the average to be acceptable.

Ten milliliters of distilled water (21 to 24.5° runs), 10.0 ml. of saturated sodium chloride solution (27°), 10.0 ml. of saturated nickel chloride solution (35 and 36.8°), or 10.0 ml. of saturated magnesium chloride solution (45 and 46.5°) were
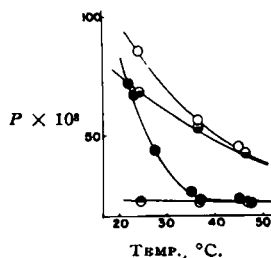

Fig. 3.—Permeability constant as a function of temperature for film thickness of 0.02 cm. Key: O, CAP; ⊖, CAB; ◐, CAS; ●, CAHP.

placed in the permeation cell; the film, mounted in the aluminum collar, was affixed to the cell. The cell was weighed and placed in the desiccator at the proper temperature. Steady state diffusion was achieved in 4–6 hours. Rate of diffusion under steady state conditions was determined by removing the cell from the desiccator periodically and measuring the weight loss. Usually five weighings were sufficient to give a reliable average.

The circular area through which permeation occurred was 6.1 cm.², and the vapor pressure differential under which it occurred, Δp, was equal to the vapor pressure of the solution in the cell. Desiccant was changed on alternate days to insure that the vapor pressure of water on the external side of the film was negligible. Vapor pressure gradient was held approximately constant for all films and at all temperatures studied.

RESULTS AND DISCUSSION

Permeability constants calculated according to Eq. 1 are given in Table I. Temperature and vapor pressure gradient for each series of determinations are as indicated beneath the type of film. Similar data for the various mixed CAHP–PEG films are given in Table II. The order of magnitude of the permeability constants is in agreement with previously reported values (3–5) for similar films. Of the simple films studied, highest permeability constants were observed with CAP films, followed in decreasing order by CAHP, CAB, and CAS when compared at room temperature. At the higher temperatures (35–45°), permeability constants for CAHP films were lower than those obtained for CAB films and approached the magnitude of the permeability constants obtained for CAS films.

Influence of Film Thickness.—The data in Tables I and II show that the permeability constant increases with increasing thickness of film. The magnitude of the effect is greatest with CAP and CAHP films and falls off to a minimum with CAS films. This indicates that CAS films approach Fick's law behavior in their permeability to water vapor. Taylor, Hermann, and Kemp (6) have shown that nonwater absorbing materials offer uniform resistance to passage of water and follow Fick's law of diffusion. When absorption is strong,
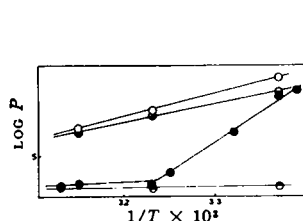

Fig. 4.—Arrhenius type plot for water vapor permeation of cellulose ester films at constant Δp for all temperatures. Key: O, CAP; ⊖, CAB; ⊔, CAS; ●, CAHP.

the pressure gradient across the membrane is no longer uniform, and deviation occurs (7). On the films reported here, CAHP, by virtue of its free carboxyl group could be expected to show significant ability to interact with water. In addition, the other films could be expected to show a decreasing water sorption in the order CAP, CAB, and CAS because of the increasing chain length of the acid

moiety. As the molecular weight of the acid residue increases, hydrophilic activity of the ester film should decrease, with a corresponding decrease in adsorption of water. The relative magnitude of change in permeability constant with increasing film thickness reported here is consistent with this view. Similar results have been reported by others (4, 5).

Influence of Temperature.—Although permeability constant increases with film thickness at all three temperatures studied, the magnitude of the effect falls off rapidly with CAHP, CAP, and CAB films; the decrease is particularly noticeable with CAHP films. On the other hand, permeation of CAS films seems relatively insensitive to temperature changes over the range reported in this work.

From the plots of permeability constant as a function of thickness, as illustrated for several CAHP films in Fig. 2, it was possible to obtain a value for the permeability constant of all films at a given thickness. By plotting permeability constants for these films at a thickness of 0.02 cm. as a function of temperature shown in Fig. 3, the effect of temperature is represented more effectively. It should be pointed out that Δp was held constant over the temperature range studied. The permeability constant for CAHP films reaches that of CAS films at a temperature of approximately 35°, while permeability constants for CAP and CAB films can be visualized as approaching the same limiting value. The abrupt fall in permeability of the CAHP films is interesting to note. That perhaps some change in the physical nature of the film occurs at 35° is further indicated in Fig. 4, where log permeability constant is plotted against the reciprocal of the absolute temperature. The actual significance of the plot is obscure at the present time, but the discontinuity obtained with CAHP films, while CAP, CAB, and CAS films behave linearly over the same region is interesting. Figures 3 and 4 show that accelerated aging studies utilizing higher temperatures must be approached with caution with cellulose derivative films to be sure the effect observed at high temperature is related to aging properties associated with lower temperatures.

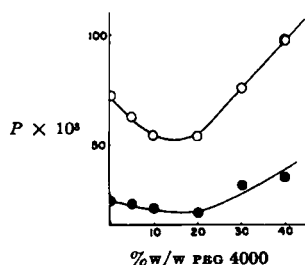**Mixed CAHP–PEG 4000 Films.**—Since various

Fig. 5.—Plot of permeability constant against composition for mixed CAHP–PEG 4000 films. Key: O, 21°C.; ●, 35°C.

plasticizers are commonly used in combination with film forming materials, it was felt that it would be interesting to see what effects might be observed where such an agent was utilized. PEG 4000 was selected because, in addition to plasticizing the cellulose film, it would tend to form a film itself, and thus perhaps provide an alternate pathway for water vapor to permeate. Experimentally determined permeability constants at 21 and 35°

for mixed films of CAHP and PEG 4000 of ratios 95:5, 90:10, 80:20, 70:30, and 60:40 on a weight basis are given in Table II. When these values were plotted against thickness of the film in the same manner as the simple films, permeability constants at a given thickness (0.02 cm.) could be read from the graph. In Fig. 5 these permeability constants are plotted as a function of weight per cent PEG 4000 in the film. At both 21 and 35°, a minimum permeability was observed when the weight per cent of PEG 4000 in the film was approximately 10–20%. Beyond this, minimum further increase in proportion of PEG 4000 in the film resulted in a marked increase in the permeability constant. Deeg and Frosch (4) also reported that plasticizers could enhance or retard permeation of polymer films. The pharmaceutical implication of this observation is that for a given mixture of film forming substances an optimum composition for maximum protective effect against atmospheric moisture may exist. In this particular instance, the optimum combination would be that corresponding to the minimum in the permeability–composition curve. Although it may be entirely coincidental, it is interesting that—calculated on an equivalent weight basis—at approximately 10% by weight of PEG 4000, a 1:1 ratio of ether oxygen to carboxyl exists.

Virtual Resistance to Permeation.—The increase in permeability constant observed upon increasing the thickness of the film suggests that a nonlinear
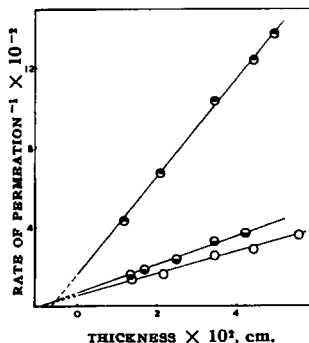
Fig. 6.—Reciprocal of the rate of permeation as a function of thickness for cellulose ester films (24.5° C.). Key: O, CAP; ◑, CAB; ◐, CAS.

concentration gradient exists across these films. If this is the case, it is expected that the rate of diffusion through a given segment, da, of the film will be dependent upon the location of the segment in the film. The reciprocal of the rate of permeation, $(w/t)^{-1}$, for a given film could be considered
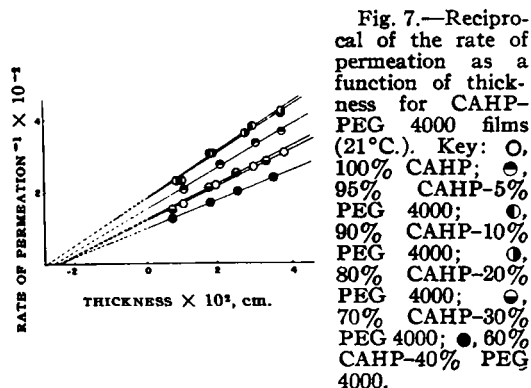
Fig. 7.—Reciprocal of the rate of permeation as a function of thickness for CAHP–PEG 4000 films (21°C.). Key: O, 100% CAHP; ◑, 95% CAHP–5% PEG 4000; ◐, 90% CAHP–10% PEG 4000; ◑, 80% CAHP–20% PEG 4000; ◐, 70% CAHP–30% PEG 4000; ●, 60% CAHP–40% PEG 4000.

as the resistance of the film to permeation by water vapor. An interesting relationship is observed when $(w/t)^{-1}$ is plotted against thickness of film; although no theoretical basis for such a plot can be proposed at the present time, we feel it is worth presenting. Figure 6 shows such plots for the room temperature permeation of simple films of CAP, CAB, and CAS. Figure 7 depicts the curves obtained for CAHP–PEG 4000 films. Whether these relationships are fortuitous or actual remains to be established with future work, but rather good linear plots are obtained. Of particular interest is that these plots extrapolate to the same point on the abscissa within experimental error. Thus, the virtual resistance of these films at zero thickness could be considered equivalent to the resistance of an additional 0.006 to 0.010 cm. for the propionate, butyrate, and stearate films and to an additional 0.025 to 0.028 cm. for the CAHP–PEG 4000 films.

The physical significance (if any) of the virtual resistance observed is obscure. One possibility might be proposed, however. Other workers have reported that when permeation occurs under a gradient where both sides of the film are exposed to water vapor, permeability constants obtained are greater than when water vapor pressure is zero on one side of the film (5, 6). It is known that cellulose fibers in relatively dry conditions shrink, and that this results in a lower permeability constant (8). Since the external environment of our system was an atmosphere of relative humidity equal to zero, the external surface of the film may be dehydrated and offer a significant resistance to the passage of water vapor. The authors intend to explore this observation in future work.

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Studies on Cell Growth and Cell Division III

Action of Azaserine on Cell Division

By KWAN-HUA LEE and YOKO YUZURIHA

The inhibitory action of azaserine on cell division of heat treated *Tetrahymena pyriformis* in a nutrient-free medium is not reversed by either glutamine or formylglycinamide riboside, but is completely reversed by phenylalanine. These findings support our previous report that azaserine exerts its selective inhibitory action on cell division by some means other than by inhibition of any one of those intermediate steps involved in purine synthesis. Diazo-oxo-norleucine (DON), an antibiotic with a close structural analogy to azaserine, has essentially the same biologic activity on cell growth and cell division. Diazouracil, a pyrimidine derivative, inhibits both cell growth and cell division.

IN A PREVIOUS report (1), it was shown that azaserine (*o*-diazoacetyl-*l*-serine) has a selective inhibitory action on cell division of heat treated *Tetrahymena pyriformis* in a nutrient-free medium after the necessary ribonucleic acid and deoxyribonucleic acid have been accumulated. However, the net result of several studies (2,3) was impressively integrated evidence that azaserine exerted its primary inhibition by blocking the *de novo* synthesis of purine. This was further supported by the findings that glutamine reversed azaserine inhibition in a competitive fashion (4) and that azaserine inhibition could be reversed by formylglycinamide riboside (FGAR) and some purines (5–9). In recent years, a large number of natural amino acids and some of their metabolic products have been reported as reversal agents to the inhibitory action of azaserine in various biologic systems (6, 7, 10–12). These findings, together with the result we reported previously (1), indicate that azaserine may block more than one site or it may act as an antagonist of a metabolite involved in a number of biochemical transformations. In the present study we chose to use glutamine, FGAR, and phenylalanine as typical representatives in the study of their effects on the inhibitory action of azaserine on cell division in heat treated *T. pyriformis* and expect to shed some light on the mechanism of action of azaserine. We also studied the action of DON (6-diazo-5-oxo-1-norleucine) and diazouracil (5-