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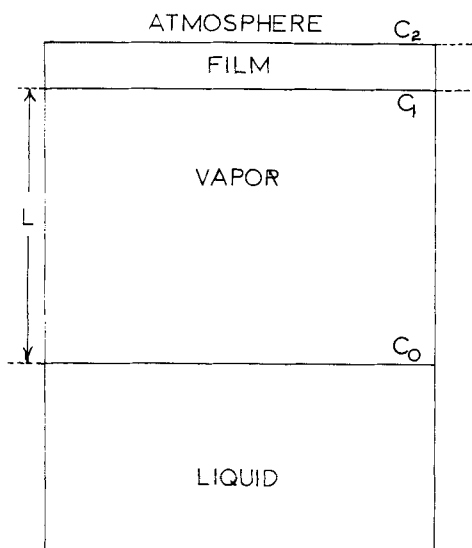
## Theoretical Justification of Reciprocal Rate Plots in Studies of Water Vapor Transmission through Films

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**Abstract** □ A theoretical equation has been developed justifying the graphical representation of vapor permeation data by  $1/\text{rate}$  versus film thickness plots. The permeability coefficient for the film may be determined from the slope of this plot and has units in square centimeters per second. The intercept at zero film thickness is dependent upon the geometry of the experimental design and the diffusion coefficient for the vapor within the diffusion cell. The derivation of the equation assumes a nonequilibrium condition for water vapor in the diffusion cell, as well as the existence of steady-state conditions.

**Keyphrases** □ Water vapor—transmission through films □ Film transmission—water vapor □ Reciprocal rate plots, vapor transmission—theoretical justification □ Polymeric, unplasticized films—water vapor transmission

The passage of water vapor through polymer films, with reference to the free films having potential application as tablet film coatings, has been reported in the



**Figure 1**—Schematic diagram of water vapor transmission cell depicting water concentrations existing at various surfaces.  $C_0$  = concentration of molecules above liquid surface,  $C_1$  = concentration of molecules at inside film surface, and  $C_2$  = concentration of molecules at outside film surface.

pharmaceutical literature (1-3). In the first of these studies (1), a vacuum was created on one side of the film so that a pressure difference existed across the film. More recently (2, 3), the transfer of water vapor through films has been studied in which a water vapor pressure difference existed but in which the total pressure, atmospheric, was the same on both sides of the film. In these investigations (2, 3), a linear relationship was found between the reciprocal of the rate of water vapor permeation and film thickness. In one case (2), the authors stated: "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." The research described by this study and the accompanying theory present a theoretical justification for the linear relationship between the reciprocal of rate of water vapor permeation and film thickness.

#### THEORY

Previous investigations have used equations that relate the rate of vapor transfer to the water vapor pressure differential existing across the film. Alternatively, an expression may be used relating this rate to the concentration difference existing across the film:

$$\frac{R}{a} = \frac{PA \Delta C}{a} \quad (\text{Eq. 1})$$

where  $R$  is the rate of permeation,  $P$  is the permeability coefficient,  $A$  is the area of the film,  $a$  is its thickness, and  $\Delta C$  is the water vapor concentration difference across the film.  $\Delta C$  may be expressed in any suitable units such as molecules. The type of transmission cell used in previous investigations (2, 3) is shown in Fig. 1, where  $\Delta C = C_1 - C_2$ .

In calculating  $\Delta C$ , the diffusion of water vapor from the surface of the liquid to the polymer film must first be considered. Because the distance between the liquid and the film influences the rate of water vapor transmission through the film (4), it can be assumed that the vapor pressure at the film surface is not in equilibrium with the liquid surface, and that a vapor pressure difference exists through this distance. The diffusion through this distance is given by Fick's one-dimensional equation:

$$\frac{\partial C}{\partial t} = \frac{D \partial^2 C}{\partial x^2} \quad (\text{Eq. 2})$$

where  $D$  is the diffusion coefficient for water vapor in air. If a steady state is assumed,

$$\frac{\partial C}{\partial t} = 0 \quad (\text{Eq. 3})$$

Therefore,

$$\frac{D\partial^2 C}{\partial x^2} = 0 \quad (\text{Eq. 4})$$

or

$$\frac{\partial C}{\partial x} = \text{constant} \quad (\text{Eq. 5})$$

$\partial C/\partial x$  may be related to the concentration of water vapor by the equation

$$\frac{\partial C}{\partial x} = \frac{C_1 - C_0}{L} \quad (\text{Eq. 6})$$

where  $L$  is the distance between the liquid surface and the film, and  $C_0$  is the equilibrium concentration of water molecules above the liquid surface (Fig. 1). The steady-state assumption may be justified by observing the rate dependence on the liquid-film distance and the linearity of the rate of water vapor transmission.

The quantity of water that has evaporated and diffused,  $W$ , during time  $t$  is given by

$$W = \frac{-DA't(C_1 - C_0)}{L} \quad (\text{Eq. 7})$$

where  $A'$  is the area of the liquid surface.

Because the diffusion coefficient,  $D$ , may be dependent upon the concentration difference,  $C_1 - C_0$  (5), the diffusion coefficient is more accurately represented by the mean diffusion coefficient,  $\bar{D}$ , of the form

$$\bar{D} = \frac{1}{C_1 - C_0} \int_{C_0}^{C_1} D(c) dc \quad (\text{Eq. 7a})$$

In the absence of data quantifying the concentration dependence of  $D$  on water vapor concentration for the water vapor-air system, only the observed mean value of the diffusion coefficient,  $\bar{D}$ , can be determined.

The concentration of water vapor at the inside surface of the film,  $C_1$ , may then be calculated from the equation:

$$C_1 = C_0 - \frac{WL}{\bar{D}A't} \quad (\text{Eq. 8})$$

If the effective film surface area is assumed to be equal to the liquid surface area, Eq. 8 may be written as

$$C_1 = C_0 - \frac{WL}{\bar{D}At} \quad (\text{Eq. 9})$$

Further assumption of steady-state diffusion within the diffusion cell implies that  $W/t = R$ , where the symbols are as previously defined. As a result, Eq. 9 becomes

$$C_1 = C_0 - \frac{RL}{\bar{D}A} \quad (\text{Eq. 10})$$

If  $C_2$ , the concentration of water outside the film, is maintained at zero,  $\Delta C = C_1$ . Therefore,

$$\Delta C = C_0 - \frac{RL}{\bar{D}A} \quad (\text{Eq. 11})$$

Substituting this relationship for  $\Delta C$  into Eq. 1 and taking the reciprocal yield

$$\frac{1}{R} = \frac{a}{PAC_0} + \frac{L}{DAC_0} \quad (\text{Eq. 12})$$

It can be seen from this equation that a plot of  $1/\text{rate of permeation}$

Table I—Description of the Polymers Employed

Viscosity Grade, cps.	Molecular Weight, $M_n$	Percent Substitution <sup>a</sup>	
		Methoxyl	Hydroxypropoxyl
5-7	11,600	28.0	8.9
50	25,000	30.0	8.6
400	45,300	28.4	9.3

<sup>a</sup> Expressed on a weight basis, as supplied by Dow Chemical Co. (6).

versus film thickness should be linear with a slope of  $1/PAC_0$  and an intercept of  $L/\bar{D}AC_0$ .

## EXPERIMENTAL

**Polymer Selection and Solution Preparation**—Methylhydroxypropoxyl ethers of cellulose,<sup>1</sup> viscosity grades 5-7, 50, and 400 cps., were selected for use in this study (Table I). Their selection was based on their ability to form free unplasticized films, their solubility in aqueous and organic solvent systems, and their widespread commercial use as pharmaceutical coating materials.

Solutions, 3% w/v, were prepared by dispersing the polymers in either deionized water or an organic solvent system consisting of methylene chloride, methyl alcohol, and isopropyl alcohol in a 40:30:30 ratio. The solvents were cooled to 5° prior to polymer addition and were stirred until the dispersions reached room temperature. The solutions were brought to volume and allowed to solvate for a minimum of 24 hr. before use.

**Preparation of Free, Unplasticized Film Samples**—Free films were prepared by pouring the polymer solutions onto a clean, leveled surface of aluminum foil. Film area was controlled by the use of a

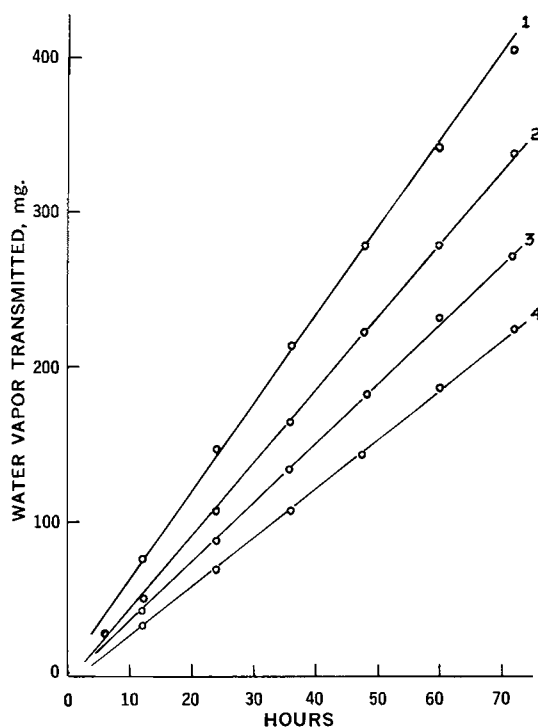


Figure 2—Transmission of water vapor through the cellulose films as a function of time:

Number	Polymer Grade	Solvent	Thickness, in.
1	400 cps.	Water	0.00194
2	400 cps.	Organic	0.00355
3	5-7 cps.	Organic	0.0129
4	5-7 cps.	Organic	0.0176

<sup>1</sup> Methocel 60 HG, Dow Chemical Co., Midland, Mich.

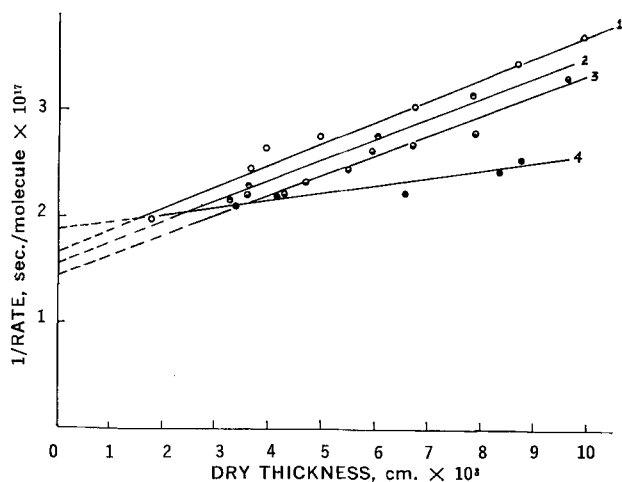


Figure 3—Relationship between the reciprocal of the water vapor transmission rate and film thickness as predicted by Eq. 12:

Number	Polymer	Solvent
1	400 cps.	Water
2	5-7 cps.	Water
3	50 cps.	Organic
4	5-7 cps.	Organic

rectangular 10 × 15-cm. Plexiglas frame, and film thickness was varied by adjusting the volume of the polymer solution employed. Organic cast films were allowed to evaporate for 12 hr. at room temperature before removal from the substrate. Films cast from deionized water were dried in an oven at 50° for 12 hr. before removal from the substrate. Films cast from deionized water, which were dried for 48–60 hr. at room temperature, showed no significant difference in permeation properties compared with those dried in the oven at 50°. The film was removed from the aluminum foil by peeling the substrate away in strips.

Film samples were cut from the sheet with a metal cylinder having an internal diameter of 2.35 cm. Film thickness was determined with a micrometer. The samples were stored in a desiccator over calcium sulfate for 5 days prior to use.

**Transmission Cell and Environmental Chamber**—The type of experimental design used in this study was similar to that used in previous investigations (2, 3).

A saturated solution of sodium tartrate was placed in each transmission cell (Fig. 1), maintaining a relative humidity of 91% at 30° equivalent to a vapor pressure of 28.96 mm. of mercury. Since the film-to-liquid surface was found to be a critical factor in the reproducibility of results, a sufficient volume of the saturated solution (approximately 5 ml.) was utilized to ensure an initial distance of 4.5 cm. between the liquid surface and the film sample. The cells were placed within a glovebox at 30° and maintained at a relative humidity below 3% using anhydrous calcium sulfate. Each cell was weighed on an analytical balance within the glovebox initially and at 12-hr. intervals for a 72-hr. period. The value of  $C_0$ , the equilibrium concentration of vapor existing above the solution having a vapor pressure of 28.96 mm. of mercury, was calculated to be  $9.2 \times 10^{17}$  molecules/cm.<sup>3</sup>, using the ideal gas law.

Table II—Permeability Coefficients for Water Vapor Permeation through Methylhydroxypropoxyl Ethers of Cellulose Films

Polymer	Solvent	Permeability Coefficient, cm. <sup>2</sup> /sec. × 10 <sup>4</sup>
Methylhydroxypropoxyl ethers of cellulose, 5-7 cps.	Organic	7.39
	Water	3.13
Methylhydroxypropoxyl ethers of cellulose, 50 cps.	Organic	3.30
	Water	2.54
Methylhydroxypropoxyl ethers of cellulose, 400 cps.	Organic	3.15
	Water	3.04

Table III—Mean Diffusion Coefficients for Water Vapor—Air Diffusion within the Diffusion Cell for Various Film Systems

Polymer	Solvent	Mean Diffusion Coefficient, cm. <sup>2</sup> /sec.
Methylhydroxypropoxyl ethers of cellulose, 5-7 cps.	Organic	0.166
	Water	0.177
Methylhydroxypropoxyl ethers of cellulose, 50 cps.	Organic	0.189
	Water	0.224
Methylhydroxypropoxyl ethers of cellulose, 400 cps.	Organic	0.162
	Water	0.164
Semifinite column	Free diffusion water in air	0.258 <sup>a</sup>

<sup>a</sup> From Reference 7 corrected to 30° (8).

## RESULTS AND DISCUSSION

The transmission of water vapor through the polymer films was linear with time and dependent on film thickness and composition (Fig. 2). For a given polymer the relationship between 1/rate and film thickness was linear, as predicted by Eq. 12 (Fig. 3). The permeability coefficient,  $P$ , which reflects the interaction of the vapor with the film and its diffusion through the film, can be determined from the slope in Fig. 2, since the slope is  $1/PAC_0$ , and  $C_0$  and  $A$  are constants. The permeability coefficients for films of the three molecular weight grades of the hydroxypropyl methylcellulose polymer, for films cast from both an organic solvent and water, are shown in Table II. Without exception the water-cast films had a lower permeability coefficient, although this difference decreased as the molecular weight of the polymer increased and is probably not significant for the water-cast *versus* organic solvent-cast 400-cps. polymer films.

This approach, *i.e.*, the method of data expression shown in Fig. 3, provides a direct experimental method for determining permeability coefficients. When determined in this manner, the units of  $P$  are square centimeters per second, and the solubility coefficient,  $S$ , in the relationship  $P = DS$  is dimensionless. The linearity of the graphical data (Fig. 3) indicates that  $P$  is independent of film thickness over the range of thickness studied.

The permeability of the film does affect the concentration gradient existing in the diffusion cell. As the permeability of the film decreases and the rate of water vapor transfer through the film decreases, the concentration gradient within the diffusion cell,  $C_0 - C_1$ , decreases, and equilibrium conditions are approached. Conversely, an increase in film permeability increases the concentration gradient,  $C_0 - C_1$ . Although the concentration gradient across the film,  $C_1 - C_2$ , decreases, the increased permeability of the film would result in a greater total flux through the film.

The intercept in Fig. 2,  $L/\bar{D}AC_0$ , is dependent on the geometry of the experimental design and the value of the mean diffusion coefficient,  $\bar{D}$ . Since  $L$  remained essentially constant during the experiment (a maximum change of 1% occurred), the values of  $\bar{D}$  were readily calculated from the intercept values ( $L/\bar{D}AC_0$ ) and are reported in Table III. The values determined for  $\bar{D}$  are lower, although of the same order of magnitude, compared to those for water vapor—air in a semifinite column (Table III) and must reflect the dependence of the diffusion coefficient on water vapor concentration. The linearity of Fig. 3 also indicates that  $\bar{D}$  is a function of concentration only and is not dependent on film thickness. As such, the observed variations in  $\bar{D}$  do not affect the magnitude of the permeability coefficient nor the graphical method used in determining the permeability coefficient.

## SUMMARY AND CONCLUSIONS

In the past, investigators have graphically represented water vapor permeation data by plotting 1/rate *versus* film thickness. A theoretical basis for this relationship was not apparent. A theoretical justification for this relationship has been derived, based on the

observation that an equilibrium does not exist between the liquid surface and the film for water vapor. The resulting equation readily leads to the calculation of a permeability coefficient for the film; the units of  $P$  are the same as the diffusion coefficient, square centimeters per second. A steady state was assumed to exist within the diffusion cell following the lag time. This was justified by the linearity of the graphical data in Fig. 1. The theory was tested with films of unplasticized methylhydroxypropoxyl ethers of cellulose cast from water and an organic solvent and the permeability coefficients were calculated from the slope of  $1/\text{rate}$  versus film thickness. This provides a direct experimental method for easily determining permeability coefficients and, by maintaining constant cell geometry, relative permeability values can be assigned to any film or series of films.

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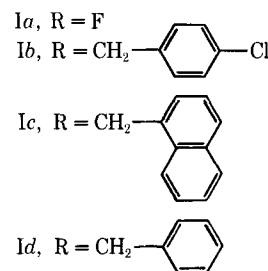
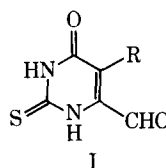
## Potential Anticancer Agents VI: 5-Substituted Pyrimidine-6-carboxaldehydes

CHUNG IL HONG\*, CLAUDE PIANTADOSI†, and J. LOGAN IRVIN

**Abstract** □ A series of 5-substituted pyrimidine-6-carboxaldehydes and their derivatives were synthesized and tested for inhibition of growth of the Ehrlich ascites carcinoma and Ehrlich carcinoma. Further studies included inhibition of incorporation of L-phenylalanine-1-<sup>14</sup>C and formate-<sup>14</sup>C into proteins, and orotic acid-5-<sup>3</sup>H, thymidine-2-<sup>14</sup>C, and formate-<sup>14</sup>C into nucleic acids of the ascitic tumor cells *in vitro*. The following compounds were found to be particularly active as inhibitors: 2-mercapto-4-hydroxy-5-(3-phenylpropyl)pyrimidine-6-carboxaldehyde (VIII-2), 2-mercapto-4-hydroxy-5-(4-phenylbenzyl)pyrimidine-6-carboxaldehyde (VIII-3), and 2-mercapto-4-hydroxy-5-( $\alpha$ -naphthylmethyl)pyrimidine-6-carboxaldehyde (*Ic*). The best compounds of this series are equally as effective as 5-fluorouracil and 2-mercapto-4-hydroxy-5-(4-chlorobenzyl)pyrimidine-6-carboxaldehyde (*Ib*) in inhibiting formate incorporation into DNA and growth of the ascitic tumor. They are more effective than 5-fluorouracil in inhibiting incorporation of formate and orotic acid into RNA, thymidine into DNA, and phenylalanine into proteins. The active compounds also showed a strong inhibitory activity against respiration of the ascitic tumor. Compounds VIII-2 and VIII-3 also inhibited growth of the Ehrlich carcinoma as a solid tumor after subcutaneous transplantation, but in these tests the drugs were more toxic to the host when injected intraperitoneally since the drugs were not preferentially absorbed by the tumor cells in contrast to the tests *versus* the ascites form of the carcinoma.

**Keyphrases** □ Pyrimidine-6-carboxaldehydes, 5-substituted—synthesis □ Anticancer activity—5-substituted pyrimidine-6-carboxaldehydes □ Protein synthesis inhibition—5-substituted pyrimidine-6-carboxaldehydes □ Nucleic acid synthesis inhibition—5-substituted pyrimidine-6-carboxaldehydes □ Tumor aerobic respiration inhibition—5-substituted pyrimidine-6-carboxaldehydes

In earlier studies (1-3) on 5-substituted derivatives of Compound I, it was observed that 5-fluoro (*Ia*) and 4-(4-chlorobenzyl) (*Ib*) substituents resulted in derivatives possessing strong inhibitory activity against the Ehrlich ascites carcinoma.



It was further observed that this series of 5-substituted pyrimidine-6-carboxaldehydes inhibited incorporation of amino acids and formate into proteins, and of orotic acid, thymidine, and formate into nucleic acids of the tumor cells *in vitro* (3). Compound *Ib* was equally as effective as 5-fluorouracil (FU) in inhibiting formate incorporation into DNA and growth of the tumor and more effective than FU in inhibiting incorporation of formate and orotic acid into RNA, thymidine into DNA, and phenylalanine and glycine into proteins. However, Compound *Ib* had only negligible inhibitory activity against the folate reductases.

The fact that an enhanced inhibitory activity was obtained by the introduction of benzyl substituents in the 5-position led to the synthesis of further derivatives of pyrimidine-6-carboxaldehydes containing bulky substituents in the 5-position in order to study the structure-activity relationship of these analogs in the test system.

#### RESULTS AND DISCUSSION

**Chemistry**—The majority of the  $\alpha$ -substituted  $\beta$ -keto esters (VI) were prepared by the alkylation reaction of ethyl  $\gamma,\gamma$ -dimethoxyacetoacetate (IV) with an aralkyl (benzyl or naphthylmethyl) halide