

that in comparison with *Ia*, *Ib* and *Ie* showed more potential in abolishing aconitine-induced arrhythmias, since *Ia* was found to be completely inactive in this respect (1).

The carbonyl absorption bands of the 4-nitro-*N*-[2-(substituted amino)ethyl]-2,6-dimethylbenzamides and their amino analogs appeared in the IR spectra in the lower 1620–1635-cm.<sup>-1</sup> region (Tables I and II), which was somewhat lower than expected for a secondary amide. It was suspected that the shift in frequency was due to the existence in the compounds of an intramolecular hydrogen bonding between the terminal tertiary nitrogen and the amide hydrogen atom. This postulation appeared to gain support from the fact that in the IR spectra of the hydrochloride salt of 4-nitro-*N*-(2-morpholinoethyl)-2,6-dimethylbenzamide and of 4-nitro-*N*-[2-(4-phenyl-1-piperazino)ethyl]-2,6-dimethylbenzamide, the carbonyl absorption bands occurred in the vicinity of 1660 cm.<sup>-1</sup>, a region normally assigned for secondary amide carbonyl absorption. Due to the hygroscopic nature of the hydrochloride salts of *Ib*–*Ie*, it was not possible to prepare these compounds for IR studies.

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## Effect of Environmental Conditions and Polymer Ratio on Water Vapor Transmission through Free Plasticized Cellulose Films

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**Abstract** □ Experiments were conducted to evaluate the effects of changes in the polymer ratio and environmental conditions on the water vapor transmission properties of plasticized films containing combinations of hydroxypropyl methylcellulose and ethylcellulose. Rates of water vapor transmission were calculated from a formula based on Fick's first law of diffusion. Inverse relationships were observed between the rate of water vapor transmission and film thickness for all films studied. In these plasticized systems, the polymer ratio of hydroxypropyl methylcellulose to ethylcellulose produced essentially no difference in the water vapor transmission properties from one film composition to another. Films subjected to a water vapor environment at both film surfaces were more permeable to water vapor than films subjected to a water vapor environment at only one surface. In the thickness range studied, films

subjected to 40 and 50° conditions had lower rates of water vapor transmission than those studied at 30°. The findings of this study demonstrated the presence of another mechanism of vapor transmission, in addition to diffusion, that is apparently related to the hydrophilic character of the film.

**Keyphrases** □ Cellulose films, plasticized—effects of environment and hydroxypropyl methylcellulose–ethylcellulose ratio on water vapor transmission □ Transmission (water vapor) through plasticized cellulose films—effects of environment and hydroxypropyl methylcellulose–ethylcellulose ratio □ Films, plasticized cellulose—effects of environment and hydroxypropyl methylcellulose–ethylcellulose ratio on water vapor transmission □ Permeation of water vapor through plasticized cellulose films—effects of environment and hydroxypropyl methylcellulose–ethylcellulose ratio

All polymer membranes possess the ability to transmit liquids, gases, and vapors, a property termed permeation. This property is an important parameter in determining the potential or actual usefulness of polymeric materials in many pharmaceutical applications. In recent years the pharmaceutical industry has increasingly utilized synthetic, polymeric, film-forming materials as specialized coatings for drug particles and dosage forms, as packaging materials, as topical films and bandage components, as dialysis membranes and filters, and for many other purposes. With the rapid

increase in the use of polymers for pharmaceutical purposes, a corresponding growth of scientific studies concerning the properties of these materials has become increasingly important.

The rate of permeation through films or membranes is highly dependent upon the barrier's nature. Polymeric, film-forming materials with low moisture permeability are said to possess five main characteristics (1): (a) a saturated or nearly saturated carbon chain, (b) a minimum of chain branching, (c) a high degree of lateral symmetry, (d) a fair degree of longitudinal symmetry,

**Table I**—Experimental Environmental Conditions Employed for Water Vapor Transmission Studies

Condition	Temperature	Internal Water Vapor Pressure <sup>a</sup>	Internal Saturated Solution	External Water Vapor Pressure <sup>a</sup>	External Saturated Solution	Water Vapor Pressure Difference <sup>b</sup> ( $\Delta V.P.$ )
A	50°	68.3	NaCl	0.0	Dry	68.3
B	40°	36.9	KI	12.6	KF·2H <sub>2</sub> O	24.3
C	40°	25.0	CrO <sub>3</sub>	0.0	Dry	25.0
D	30°	31.8	H <sub>2</sub> O	8.9	KF·2H <sub>2</sub> O	22.9
E	30°	23.8	NaCl	0.0	Dry	23.8

<sup>a</sup> Water vapor pressure expressed in mm. Hg. <sup>b</sup> Water vapor pressure gradient across the barrier in mm. Hg.

and (e) a very high proportion of relatively small, non-hydrophilic substituents.

According to Lebovitz (2), a polymeric material must fulfill two conditions to be a good barrier: (a) the structure must interfere with the ease of the diffusion process, and (b) the polymer must not possess chain structures similar to the permeant molecules. It has been shown that crystalline structures interfere with gas or vapor permeation (3–5).

One method of reducing drug instability in solid dosage forms has been to coat the product with polymeric materials to prevent the access of moisture or air or both. Some of the first pharmaceutical research concerning the permeation of polymer films was carried out by Higuchi and Aguiar (6), who studied the permeability of water vapor through enteric-coating materials. Their experiments showed that the amount of water vapor transmitted through a film was dependent upon the polarity of the polymeric compounds, with the more polar films having a greater rate of water vapor permeation. The polarity of plasticizers employed in polymeric films was found by Munden *et al.* (7) to affect water vapor transmission properties directly. An inverse exponential relationship between the film thickness and the rate of water vapor transmission was demonstrated for free films of hydrophilic, lipophilic, and combined hydrophilic–lipophilic character (8) and the relationship was found to be more nearly Fickian with less hydrophilic film compositions. Therefore, when a highly polar molecule, such as water vapor, is transmitted through a membrane, the amount of transfer could be expected to be an indication of the hydrophilicity of the membrane material. In a recent study, the water vapor transmission through free polymer films was correlated to the water vapor transmission through applied films of the same substances (9).

This research was conducted to evaluate the effects of changes in the polymer ratio or environmental conditions on the water vapor transmission properties of hydrophilic, plasticized, free film systems containing combinations of hydroxypropyl methylcellulose and ethylcellulose.

## EXPERIMENTAL

**Preparation of Free Film Samples**—The free films were produced from solutions containing various combinations of a methyl hydroxypropyl ether of cellulose<sup>1</sup> and an ethyl ether of cellulose<sup>2</sup> in

ratios of 19:1, 3:1, 1:1, and 1:3, plasticized with 20% w/w, on a film weight basis, of propylene glycol. An organic solvent system consisting of 40 parts (by volume) methylene chloride, 30 parts methanol, and 30 parts isopropanol was used to prepare all polymer–plasticizer solutions. Films were cast on an aluminum foil substrate at ambient conditions (25–29°). Dry films were removed from the foil 12 hr. after pouring and were stored for 6–7 days over desiccant material in vacuum to effect complete dryness.

**Determination of Film Thickness**—Film thickness was calculated from the film density and the weight of a known film area. The density of the films produced from a given formulation was determined by a weight loss method in a nonsolvent, *n*-hexane.

**Apparatus**—The water vapor transmission cell and controlled temperature and humidity chamber previously described by Banker *et al.* (9) were used in these studies. The transmission cell had a capacity of approximately 23 ml., containing 5 ml. of a saturated water vapor pressure maintaining solution. The desired humidity in the chamber was maintained by anhydrous calcium sulfate or a saturated solution of potassium fluoride dihydrate. The experimental conditions are summarized in Table I.

**Determination of Water Vapor Transmission**—The assembled transmission cell, containing the film sample and the water vapor pressure maintaining solution, was placed inside the chamber and immediately weighed on an analytical balance located inside the chamber. The cell was reweighed at various time intervals over at least 72 hr. The amount of moisture transmitted through the membrane was given by the loss of weight of the assembled cell.

## RESULTS AND DISCUSSION

**General Water Vapor Transmission Properties**—The amount of water vapor transmitted across a polymer membrane is influenced by several variables. Four of these variables were studied in this work: (a) polymer–polymer ratio, (b) water vapor pressure gradient, (c) temperature, and (d) film thickness.

The rate of water vapor transmission,  $R_{wvt}$ , was calculated by dividing the amount of moisture crossing the film (in g./hr.) by the product of the exposed surface area (in cm.<sup>2</sup>) and the water vapor pressure differential across the film (in mm. Hg). Therefore,  $R_{wvt}$  is expressed in units of g. cm.<sup>-2</sup> mm. Hg<sup>-1</sup> hr.<sup>-1</sup> and is defined as the amount of moisture transmitted per unit time through a barrier of unit area subjected to a vapor pressure differential of unity.

A linear relationship between the logarithm of  $R_{wvt}$  and the logarithm of film thickness would be expected to exist; and if Fickian diffusion was solely responsible for the water vapor transmission, the slope of such a line would be  $-1$  (10).

A linear relationship between the logarithms of  $R_{wvt}$  and film thickness was observed for all film formulations. However, the slope of the lines obtained indicated that more water vapor was passing through the barrier than Fickian diffusion would predict. This relationship is consistent with that found by Banker *et al.* (8) and can be expressed as a power function:

$$R_{wvt} = c_1 T m_1 \quad (\text{Eq. 1})$$

where  $R_{wvt}$  is as described earlier,  $T$  is the film thickness in centimeters,  $c_1$  is the  $Y$ -intercept in water vapor transmission units, and  $m_1$  is the slope of the line. Deviation from this relationship indicates that the film is not acting as a simple porous barrier, the vapor pressure differential providing the only driving force for permeation. Such deviations result when a facilitated diffusional transport

<sup>1</sup> Methocel 60HG 50 cps., Dow Chemical Co., Midland, Mich.

<sup>2</sup> Ethocel 50 cps., Dow Chemical Co., Midland, Mich.

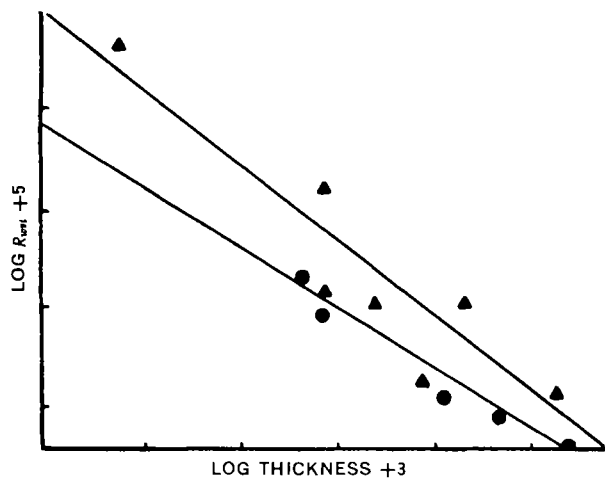


Figure 1—Relationship between  $R_{wvt}$  and film thickness at 40° as a function of the water vapor environment(s) on each side of the film. Key:  $\blacktriangle$ , Condition B; and  $\bullet$ , Condition C.

exists, which in hydrophilic films may be attributed to associations between the water molecules and the polar functional groups on the polymer chain.

All films exhibited a water vapor transmission pattern in which the quantity of water vapor transmitted at any time was decreased by increasing film thickness, and linear relationships were observed between the amount of vapor transmitted and time for any film thickness.

**Effect of Polymer Ratio in Plasticized Films**—Films prepared from four different combinations of hydroxypropyl methylcellulose and ethylcellulose, plasticized with propylene glycol, were studied at Experimental Condition E of Table I. The results of this study indicated that the changes in the polymer-polymer ratio produced essentially no difference in the water vapor transmission properties of the films. A single line, with a slope of  $-0.375$  and a  $Y$ -intercept of  $1.14$ , can represent the  $\log R_{wvt} + 5$  versus  $\log$  thickness  $+3$  graphical relationship for all four polymer combinations. In fairly hydrophilic membranes, such as those obtained from cellulose polymers, it can be postulated that departure from Fickian diffusion may be caused by hydrogen bonding between the hydroxyl groups present in the film and the permeant water vapor molecules. The water molecules would then transfer from one polar site to another across the barrier from the proximal to the distal surface. This "site exchange" mechanism would provide an additional pathway for water molecules to cross the barrier, in addition to the diffusion process, and thus add to Fickian diffusion. In addition, the associated water could produce partial hydration of the film with resultant dilation and swelling, particularly at the proximal film surface exposed to the high water vapor pressure environment. Such dilation and swelling would increase film porosity, if not

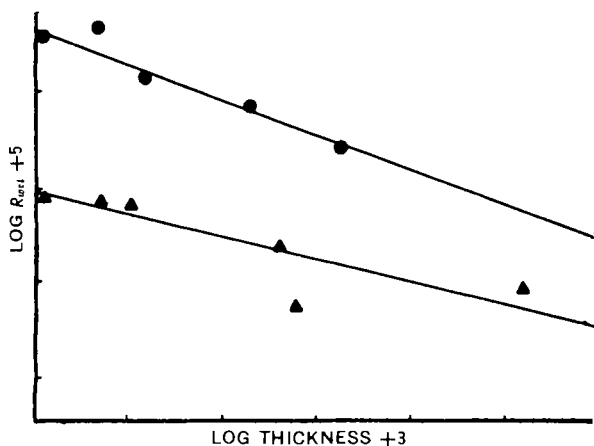


Figure 2—Relationship between  $R_{wvt}$  and film thickness at 30° as a function of the water vapor environment(s) on each side of the film. Key:  $\bullet$ , Condition D; and  $\blacktriangle$ , Condition E.

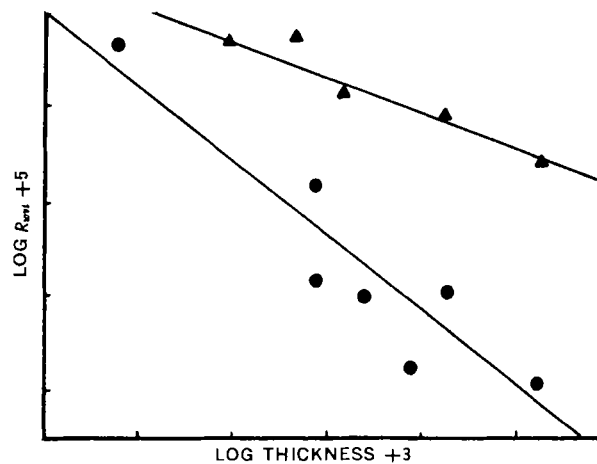


Figure 3—Relationship between  $R_{wvt}$  and film thickness at 30 and 40° with water vapor environment on both sides of the film. Key:  $\blacktriangle$ , Condition D; and  $\bullet$ , Condition B.

throughout the film cross section equally, at least at the moisture-rich surface. Even though the film porosity at the distal film surface might not be substantially affected, if substantial dilation occurred at the proximal surface, the effect would be similar to reducing the effective film thickness, relative to the original film porosity or to that remaining at the distal surface. This effect could exist in addition to a site-exchange-facilitated transport.

In these experiments, it appeared that the hydrophilic effect of the plasticizer, which contained two hydroxyl groups per molecule, overshadowed small differences in hydrophilicity caused by changing the ratio of the polymers. Calculations based on the weight average molecular weight of the polymers support this hypothesis and show that in the 19:1 polymer ratio the plasticizer contributed 58% of the free hydroxyl groups in the film; in the 1:3 ratio, 69% of the free hydroxyl groups of the film was contributed by the plasticizer. Furthermore, in other studies, fairly large differences in the ratio of hydroxypropyl methylcellulose to ethylcellulose in plasticized film samples were found to produce minimal differences in the drug permeation rates through the films or in film solubility (11).

**Effect of Water Vapor Pressure Gradients**—The effect of changing the water vapor pressure environment was studied at the 30 and 40° conditions shown in Table I. The 3:1 polymer ratio was used for this portion of the work, and 20% propylene glycol was included as a plasticizer.

The effect of placing film samples in an environment where there is a water vapor pressure at both surfaces of the barrier (Conditions B and D) as compared to placing the film samples in an environment having water vapor at only one surface (Conditions C and E), but with a nearly equivalent vapor pressure differential, is clearly shown in Figs. 1 and 2. At both 30 and 40°, films having water vapor present at both surfaces had greater rates of water vapor transmission over the thickness range studied in comparison to the films with a water vapor environment at only one surface. This effect was probably caused by an increased total and more uniform cross-sectional swelling of the cellulose polymers exposed to water vapor at both sides of the film when compared to those with one dry side. The films exposed to a dry atmosphere on one surface may be thought of as having one dry surface in equilibrium with the dry atmosphere. The dry surface would not be expected to retain appreciable sorbed water or be substantially hydrated or swollen.

In the other case, where both surfaces are in contact with an atmosphere containing some water vapor, both film surfaces could retain some sorbed water; therefore, both film surfaces would be swollen, and the pore size at the distal surface in films with moisture at both surfaces allows more water vapor to be transmitted across the film. Since the slopes of the lines obtained under Conditions B and C are similar (Fig. 1) and the same can be said for Conditions D and E (Fig. 2), there is an indication that the effect may be primarily controlled by the boundary surface of the film. This being the case, the differences in water vapor transmission properties observed by comparing Conditions B and C or D and E should be essentially independent of the film thickness (12).

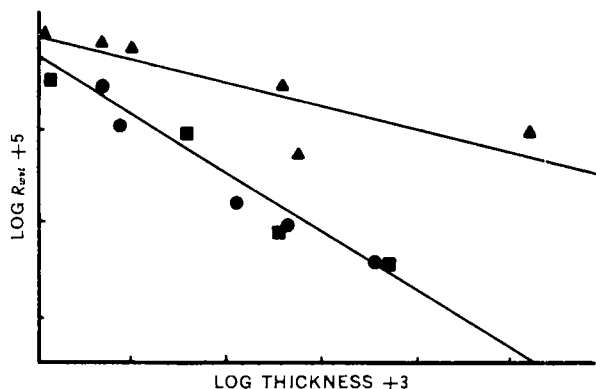


Figure 4—Relationship between  $R_{wvt}$  and film thickness at 30 and 40° with water vapor environment on one side. Key: ■, Condition A; ●, Condition C; and ▲, Condition E.

**Effect of Temperature**—Water vapor transmission studies were conducted using the plasticized 3:1 polymer ratio at all conditions shown in Table I. These experiments demonstrated that either with or without water vapor present at both surfaces of the film, the  $R_{wvt}$  values were greater at 30° than at 40 or 50° (Figs. 3 and 4). Figure 4 also indicates that no further changes in water vapor transmission properties were produced by increasing the temperature from 40 to 50°. Both figures indicate that water vapor transmission was less Fickian at 30° than at either of the elevated temperatures over the thickness range studied.

The probable cause of this phenomenon is that the attractive forces between the hydroxyl groups in the film and the water molecules are reduced at the higher temperatures. At the higher temperatures, a site-exchange phenomenon would be less pronounced and simple Fickian diffusion should predominate, which indeed appeared to be the case (Figs. 3 and 4). The fact that the slopes of the lines produced in either graph are not similar to each other shows that there is a dependence on the film thickness and, therefore, the internal volume of the film. Since the comparative effect is not independent of film thickness, the water vapor transmission is not primarily controlled by the phase boundary of the film (12). This relationship would be consistent with the site-exchange hypothesis.

#### SUMMARY

The results of this study demonstrated the following relationships:

1. In these plasticized systems, the polymer ratio of hydroxypropyl methylcellulose to ethylcellulose produced essentially no differences in the water vapor transmission properties from one film composition to another. In all cases, the water vapor transmission decreased with an increase in film thickness.

2. Increased water vapor permeation values were observed when moisture was present at both sides of the barrier in comparison with

a condition where zero water vapor pressure existed on one side of the film, even though the water vapor pressure differential was approximately the same.

3. A temperature effect was observed in which the rate of water vapor permeation was decreased when the temperature was increased from 30 to 40 or 50°.

These results suggest that two factors in addition to Fickian diffusion are probably involved in controlling the rate at which water vapor crosses these fairly hydrophilic polymer membranes. One factor is a surface or phase boundary effect and is primarily dependent upon the amount of swelling of the cellulose film structure at the distal surface of the film. The second factor is an internal effect of the film and is probably associated with the attraction existing between the hydroxyl groups in the film and the water molecule. This attraction could be responsible for transporting molecules across the film by a site-exchange mechanism.

Results of these experiments could relate to the area of packaging when partially hydrophilic barriers are used and indicate that elevated temperature studies may not accurately reflect occurrences at lower temperatures.

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