# Permeability of Double-Layer Films I

**TSUNETO KURIYAMA, MICHIHARU NOBUTOKI, and MICHIO NAKANISHI**

**Abstract** □ To make a pharmaceutical preparation that contains a water-unstable ingredient, it is preferable that the preparation be coated with a less permeable film. When rapid disintegration is required, however, the coating film should be made as thin as possible. The present study was carried out on the permeability of the double-layer film in order to create a thin film with sufficient protectivity from moisture. It was found that the permeability of most double-layer films had a directional property and could be made thinner than single films. This finding suggests the potential usefulness in the manufacturing process of pharmaceutical preparations.

**Keyphrases** □ Films, double layer—permeability □ Permeation, water vapor—double-layer films □ Solvent evaporation rate—effect on film

Coating is an important and basic technique which is widely used in the field of pharmaceutics. Film coating of tablets is a typical example. One important purpose of coating is to prevent moisture from permeating into preparations, because decomposition of the ingredient is often attributable to hydrolysis (and oxidation). For protection from moisture, it is of primary importance to select a proper coating agent. Several kinds of coating agents are available, but the selection is not always easy because a coating agent should fulfill various incidental requirements. A coating agent should be soluble in the gastric or intestinal fluids as desired, while its solvents should not react with the ingredients and its water vapor permeability should be as low as possible. The water vapor permeability of a film may be reduced by making the film thicker, but such films may prolong the time of tablet disintegration in the digestive fluids. Therefore, the thickness of the coating film is limited. It may be possible to create a more useful coating film by combining currently available agents. For this purpose, two methods may be feasible: making a film from a mixed solution or combining single films to make a multilayer film. The authors studied the latter and found that the multilayer film had very interesting and useful properties which were worthy of reporting.

To study quantitatively the water vapor permeability of a coating film, it may be advisable to perform an experiment on a simple system such as the free film rather than on a complicated system such as the film-coated tablet. Many reports are available concerning the permeability of a single film (1-5). In this report, the water vapor permeability was measured on the double-layer film as well as its constituent single films in a manner similar to that described by the former reporters.

## EXPERIMENTAL

**Cell for Measuring Water Vapor Permeability**—A cell was assembled according to the method of Patel *et al.* (1). The cell was filled with distilled water and horizontally sealed with a sample film. The initial weight of the cell was accurately measured after 1 hr. of thermal equilibration at a given temperature and humidity environment (generated by the Tabai Lucifer model TL-21P). The cell was again weighed after 20 hr. at the same conditions and the decrease of the weight was calculated. In this experiment, it was necessary to maintain a constant distance between the sample film and the surface of water in the cell to avoid inconsistencies in the data obtained. The shortest possible distance was advisable (6), but for practical reasons the authors used a distance of 1.5 cm.

**Film Preparation**—(*a*) *Single Films*—The coating agents were dissolved in suitable solvents, and the film solutions were then poured on horizontal glass plates equipped with a holding frame around the perimeter. The solvent was allowed to evaporate gradually. In this process, the rate of evaporation was controlled by setting a cover which limited the diffusion of solvent vapor. The thickness of the film was adjusted by changing the concentration (5–15%) and the quantity of the solution poured on the glass plate. Free films were peeled from the plates. Each free film was cut into circles 4 cm. in diameter to make the sample films. These samples were dried in a vacuum for 12 hr. to remove residual solvent.

(*b*) *Double-Layer Films*—It was necessary to use a double-layer free film which contained no air layer between, because an actual multilayer-coating film on the tablet contains no air layer. Two single films, which had the same thickness but were of different types, were selected from the prepared films and combined to form a double-layer film by using a solvent which dissolved only a surface of either film.

**Measurement of Thickness of Film**—The thickness of a single film produced in the manner described was measured with a dial gauge (precision: 0.001 mm.). The thickness of a double-layer film was taken as a total of the thickness of each single film.

**Materials**—Coating agents used are shown in Table I.

**Measurement of Water Vapor Permeability**—Several films were selected to distribute properly the thickness of each film in the range of 0.05–0.4 mm., and their water vapor permeability was measured. Permeability is generally described as follows (8):

$$q = PAt(p_1 - p_2)/l \qquad \text{(Eq. 1)}$$

Quantity ($q$) of water vapor, which passes through a given film at a given temperature, depends upon area ($A$), thickness ($l$), vapor pressure difference ($\Delta p = p_1 - p_2$), and time ($t$). The proportional coefficient ($P$) was termed the permeability coefficient. Permeability ($Q$), which is defined in Eq. 2, was obtained at a given condition:

$$Q = q/At \quad (\text{g./m.}^2\ 24\ \text{hr.}) \qquad \text{(Eq. 2)}$$

Comparison was made on $Q$-values for various samples in terms of 0.3-mm. film thicknesses. It was, of course, very hard to produce a sample film of the exact thickness intended, and $Q$-value depended upon the thickness ($l$) of a film. But because the relationship between $1/Q$ and $l$ was linear, $Q$ for exactly 0.3-mm. thickness was obtained graphically.

## RESULTS AND DISCUSSION

In the case of preparing sample films, the rate of evaporation of the solvent was a problem. Too rapid evaporation produced turbidity in the film, and the water vapor permeability of the film depended upon such turbidity, producing inconsistencies in data. The rate of evaporation was controlled to make the films transparent. All results reported were obtained from transparent sample films.

The relationship between $1/Q$ and $l$ should be a straight line passing through the origin according to Eq. 1. But this experiment revealed that the line did not pass through the origin but intersected

**Table I**—Abbreviations and Solvents of Coating Agents Used

| Abbreviation | Chemical Name | Manufacturer (Specification) | Solvent Used for Making Film |
|---|---|---|---|
| EC | Ethylcellulose | Dow Corning (50 cps.) | Ethyl acetate |
| MC | Methylcellulose | Shin-etsu Chemical Co. (25 cps.) | Methylene chloride + methyl alcohol (1:1) |
| AC | Cellulose acetate | Wako Pure Chemical Co. | Acetone |
| CAB | Cellulose acetate butylate | Eastman Organic Chemicals Co. | Acetone |
| SH | Shellac | Gifu Shellac Manuf. | Methyl alcohol |
| PVA | Polyvinyl alcohol | Hayashi Pure Chemicals (500) | Water |
| HPC | Hydroxypropylcellulose | Freunt Ind. | Methyl alcohol + chloroform (1:1) |
| AEA | Polyvinyl acetate diethylamino acetal | Sankyo Co. | Acetone |
| HECAP | Hydroxyethylcellulose acetate phthalate | Yoshitomi Pharm. Ind. (7) | Acetone |
| CC | Cellulose acetate phthalate-2-diethylaminoethylester | Wako Pure Chemicals | Methyl alcohol |
| CAP | Cellulose acetate phthalate | Wako Pure Chemicals | Acetone |

the ordinate ($1/Q$-axis), indicating that the permeability of coating film does not perfectly agree with the classical theory (Eq. 1).

This fact has been reported also by Patel *et al.* (1), who pointed out that the linear plots resulted for various samples extrapolated to the same point on the abscissa ($l$-axis). However, the latter was not always supported experimentally, as shown in Fig. 1, as Patel himself suspected contingency. In the case of double-layer films also, the relationships between $1/Q$ and $l$ were linear, just as in Fig. 1.

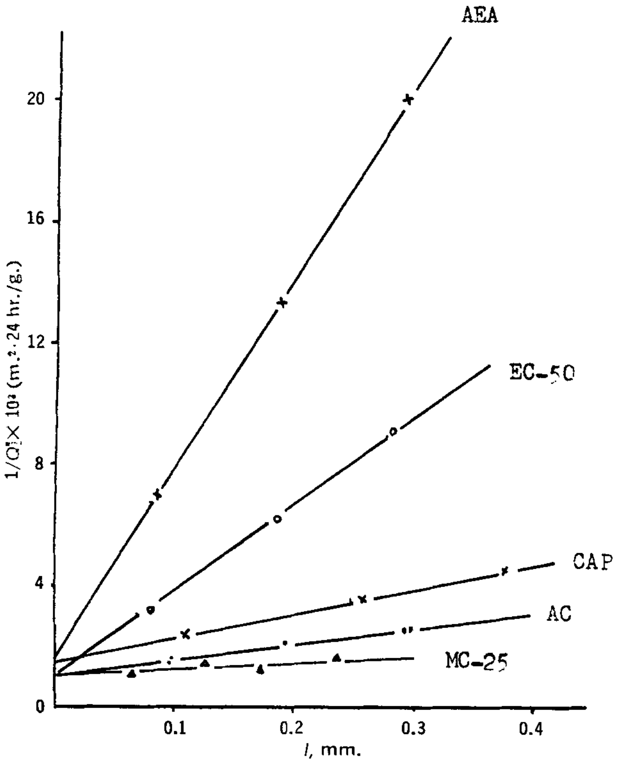


**Figure 1**—*The relationship between the resistance for permeation (1/Q) and the film thickness (l). Temperature, 40°; water vapor pressure of higher pressure side* $p_1$, *5.53 cm. Hg (100% R.H.); water vapor pressure of lower pressure side* $p_2$, *4.20 cm. Hg (76% R.H.).*

Table II shows the results obtained. "Types" in the table are defined in Table III.

Table II shows the permeability for double-layer films as well as that for single-layer films, which are the components of the double-layer films. Differences in permeability were noted even in the same double-layer film, depending upon which layer was set on the side of higher humidity or depending upon the direction of permeation. This property is called "two-sidedness" by Rogers *et al.* (9, 10). In the present report, the double-layer film is expressed as $X + Y$ (or $Y + X$), which means that the film is made from material $X$ and material $Y$, and $X$-layer (or $Y$-layer)—written before the + mark—is set on the side of higher humidity, and $Y$-layer (or $X$-layer) —written after the + mark—is set on the side of lower humidity. In Table III, A, B, C, and D are defined as follows: when $X$ is more permeable than $Y$, A refers to the permeability of $X$ and B refers to that of $Y$; C refers to the permeability observed for $Y + X$, and D to the permeability for $X + Y$. Therefore, A is always larger than B, and C or D is usually between A and B.

It was found, however, that D can be greater than A or that C can be smaller than B in some cases. In Table III, all the possible orders of A, B, C, and D are listed; they are classified into four groups. Twelve orders of A, B, C, and D are called by "types" in this report. Table III also shows the number of cases falling under each "type." Rogers *et al.* (9) and Ninneman and Simerl (10) measured the permeability of double-layer films used for packaging and observed the "two-sidedness." "Two-sidedness" is expressed as C $\neq$ D, according to the definition already mentioned. This property, which was confirmed in the present experiment on coating films, may be useful in pharmaceutics. More concretely, moisture should be minimized in a tablet which contains a water-unstable ingredient; in this sense, it will be practically useful to utilize the "two-sidedness" of the double-layer film for protecting the tablet from moisture. If coating layers are properly combined, the film-coated tablet can be dried easily even at a mild condition and, at the same time, the tablet will absorb little moisture. In addition, Table III indicates a much greater merit of double-layer film coating. Permeability of the double-layer film and that of each layer were compared on the same unit thickness basis in the present experiment. It revealed the

Table II—Water Vapor Permeability[a] of Double-Layer Film and Its Elemental Single Films

| Double-Layer Film Combinations | $Q^b$ | Single Film Name | $Q^b$ | Type[c] | Double-Layer Film Combinations | $Q^b$ | Single Film Name | $Q^b$ | Type[c] |
|---|---|---|---|---|---|---|---|---|---|
| EC-50 + HECAP[d] | 102 | HECAP | 123 | 2 | CAB + MC-25 | 194 | MC-25 | 625 | 8 |
| HECAP + EC-50[e] | 150 | EC-50 | 104 | | MC-25 + CAB | 262 | CAB | 109 | |
| CAB + HECAP | 92 | HECAP | 123 | 2 | CC + PVA | 526 | PVA | 667 | 2 |
| HECAP + CAB | 164 | CAB | 109 | | PVA + CC | 714 | CC | 625 | |
| AEA + HECAP | 74 | HECAP | 123 | 8 | AC + HECAP | 168 | HECAP | 123 | 8 |
| HECAP + AEA | 87 | AEA | 49 | | HECAP + AC | 161 | AC | 385 | |
| CAP + AEA | 132 | CAP | 263 | 8 | CAP + MC-25 | 260 | MC-25 | 625 | 10 |
| AEA + CAP | 80 | AEA | 49 | | MC-25 + CAP | 340 | CAP | 263 | |
| CAB + AEA | 62 | CAB | 109 | 7 | HECAP + CAP | 136 | CAP | 263 | 8 |
| AEA + CAB | 97 | AEA | 49 | | CAP + HECAP | 139 | HECAP | 123 | |
| EC-50 + PVA | 168 | EC-50 | 104 | 8 | AEA + MC-25 | 87 | MC-25 | 625 | 8 |
| PVA + EC-50 | 225 | PVA | 667 | | MC-25 + AEA | 92 | AEA | 49 | |
| AEA + PVA | 69 | PVA | 667 | 8 | AEA + AC | 122 | AC | 385 | 8 |
| PVA + AEA | 142 | AEA | 49 | | AC + AEA | 125 | AEA | 49 | |
| CAB + PVA | 190 | PVA | 667 | 8 | EC-50 + CAB | 112 | CAB | 109 | 11 |
| PVA + CAB | 255 | CAB | 109 | | CAB + EC-50 | 106 | EC-50 | 104 | |
| CAB + AC | 204 | AC | 385 | 8 | CC + MC-25 | 676 | MC-25 | 625 | 11 |
| AC + CAB | 236 | CAB | 109 | | MC-25 + CC | 625 | CC | 625 | |
| CAP + PVA | 296 | PVA | 667 | 8 | CC + HPC | 526 | HPC | 556 | 9 |
| PVA + CAP | 350 | CAP | 263 | | HPC + CC | 625 | CC | 625 | |
| EC-50 + AEA | 75 | AEA | 49 | 7 | CAB + CAP | 141 | CAP | 263 | 8 |
| AEA + EC-50 | 90 | EC-50 | 104 | | CAP + CAB | 167 | CAB | 109 | |
| AC + MC-25 | 427 | AC | 385 | 8 | AC + EC-50 | 213 | EC-50 | 104 | 8 |
| MC-25 + AC | 556 | MC-25 | 625 | | EC-50 + AC | 191 | AC | 385 | |
| MC-25 + PVA | 459 | PVA | 667 | 10 | SH + EC-50 | 15 | EC-50 | 104 | 8 |
| PVA + MC-25 | 625 | MC-25 | 625 | | EC-50 + SH | 19 | SH | 8 | |
| HECAP + PVA | 212 | PVA | 667 | 8 | MC-25 + EC-50 | 244 | EC-50 | 104 | 8 |
| PVA + HECAP | 238 | HECAP | 123 | | EC-50 + MC-25 | 192 | MC-25 | 625 | |
| AC + PVA | 485 | PVA | 667 | 8 | CAP + EC-50 | 179 | EC-50 | 104 | 8 |
| PVA + AC | 649 | AC | 385 | | EC-50 + CAP | 143 | CAP | 263 | |

[a] Measured under the following conditions: temperature, 40°; vapor pressure at higher pressure side $p_1$, 55.3 mm. Hg (100% R.H. at 40°); vapor pressure at lower pressure side $p_2$, 42.0 mm. Hg (76% R.H. at 40°). Every double-layer film is composed of two kinds of single films which have the same thickness. [b] Dimension of permeability $Q$; g./m.$^2$ 24 hr., value obtained for 0.3-mm. thickness both of double-layer and single films. [c] Defined in Table III. [d] HECAP was set at the lower pressure side. [e] EC-50 was set at the lower pressure side.

presence of a particularly interesting effect of the "two-sidedness." as shown in Table III. For example (HECAP + EC-50, HECAP + CAB, CC + PVA), some double-layer films made from the materials $X$ and $Y$ showed greater permeability than that of either $X$ or $Y$ film when water vapor permeated from one direction and, on the contrary, their permeability was smaller than that of either $X$ or $Y$ film when water vapor permeated from the other direction (Group $\alpha$). This means that some double-layer films can accomplish effective protection from moisture when the combined thickness of the layers is less than that of a single film. A coating film on a tablet should be less permeable as well as thinner, because it should effectively protect the ingredients from moisture and be disintegrated quickly in the digestive fluid. These two requirements generally disagree with each other, but the effect of the "two-sidedness" (Group $\alpha$) will be a great help to the reconciliation of these antinomous requirements. The incidence of the Group $\gamma$ is naturally the highest. No case classifiable into Group $\beta$ was found, as was assumed theoretically. Examples of the Groups $\alpha$ and $\delta$ are actually observed.

Table III—Classification of Permeability of Double-Layer Films

| Type | Permeability[a] Larger ← | | → | Smaller | Cases | Group |
|---|---|---|---|---|---|---|
| 1 | C[a] | A[a] | B[a] | D[a] | 0 | $\alpha$ |
| 2 | D | A | B | C | 3 | |
| 3 | A | B | C | D | 0 | $\beta$ |
| 4 | A | B | D | C | 0 | |
| 5 | C | D | A | B | 0 | |
| 6 | D | C | A | B | 0 | |
| 7 | A | C | D | B | 2 | $\gamma$ |
| 8 | A | D | C | B | 20 | |
| 9 | A | C | B | D | 1 | $\delta$ |
| 10 | A | D | B | C | 2 | |
| 11 | C | A | D | B | 2 | |
| 12 | D | A | C | B | 0 | |

[a] A, permeability of more permeable single film; B, permeability of less permeable single film; C, permeability of double-layer film when its more permeable layer was set on the lower vapor pressure side; D, permeability of double-layer film when its more permeable layer was set on the higher vapor pressure side.

## SUMMARY


Water vapor permeability of the coating film, single- and double-layer films, was measured at a certain condition. It was revealed that plotting the relationship between the resistance for permeation ($1/Q$) and the film thickness ($l$) gave a straight line, but the line did not intersect the $1/Q$-axis at the origin, indicating that the permeability of coating film does not perfectly agree with the classical theory. The permeability of the double-layer film varies, depending upon the direction of permeation (two-sidedness). The "two-sidedness" was classified into some groups according to the relationship of permeability of each single film and that of the composite film. The most remarkable characteristic was observed in the Group $\alpha$, which was interpreted to mean that the permeability of the double-layer film from one side and that from the other side are larger or/and smaller than that of any of its elemental single films of the same thickness. This fact is very important and may be useful from the viewpoint of pharmaceutical technology.


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## *NOTES*

# Permeability of Double-Layer Films II

**TSUNETO KURIYAMA, MICHIHARU NOBUTOKI, and MICHIO NAKANISHI**

**Abstract** ☐ Most of the combinations of coating films showed "two-sided" permeability, while this property has not been reported for films composed of hydrophobic layers only. Any coating film is more or less hydrophilic, and its water vapor permeability varies according to the mean humidity condition in which the film is placed. It was found that double-layer films with "two-sidedness" have characteristic relations (as classified into Groups $\alpha$, $\beta$, $\gamma$, and $\delta$) between specificity of permeability and humidity range.

**Keyphrases** ☐ Permeability, two-sided—double-layer films ☐ Double-layer films—permeability, relationship of water vapor, humidity

In the first part of this study, the authors reported the so-called "two-sided" directional property of the water vapor permeability of double-layer films, and classified this property into four groups: $\alpha$, $\beta$, $\gamma$, and $\delta$ (1). In double-layer films with two-sided water vapor permeability of the Group $\alpha$, the permeability is either smaller or greater than that of either component layer, depending on the direction of permeation. The latter feature is a phenomenon that cannot be elucidated in a simple manner. Ninneman and Simerl (2) studied the permeability of multilayer films and introduced the following equation:

$$\Delta p = Q \sum_{i=1}^{n} \frac{l_i}{P_i} \qquad \text{(Eq. 1)}$$

where $\Delta p$ stands for the difference in water vapor pressure between the higher humidity atmosphere and lower humidity atmosphere (*i.e.*, $p_1 - p_2$), $Q$ is the permeability of an $n$-layer film, $l_i$ is the thickness of the $i$th layer in the $n$-layer film, and $P_i$ is the permeability coefficient of the $i$th layer. This equation may estimate the permeability of the multilayer film at a certain condition, where the material and the thickness of each component layer are given. It cannot explain the two-sided property of the multilayer film, however, because the permeability thus calculated is independent of the permutation of component layers of a film. In other words, Eq. 1 is practically applicable to the hydrophobic film only but not to the coating film, which is more or less of a hydrophilic nature.

Equation 3 is derived from Eq. 2 (1), which is known to be applicable to the hydrophobic film.

$$q = P \frac{p_1 - p_2}{l} At \qquad \text{(Eq. 2)}$$

$$\frac{1}{Q} = \frac{At}{q} = \frac{l}{P\,\Delta p} \qquad \text{(Eq. 3)}$$

where $A$ is the area of film through which water vapor is permeated, $t$ is the time of permeation, and $q$ is the quantity of moisture permeated. But Eq. 3 does not always apply to the coating (hydrophilic) film. While $1/Q$ should be proportional to $l$ according to Eq. 3, previously reported experiments (1) revealed that the value of $1/Q$ for $l=0$ did not come to zero in spite of the linearity of the relationship between $1/Q$ and $l$. This finding suggests that the permeability of the coating film is different from that of the usual hydrophobic film and its behavior is rather complex. The two-sided property of the coating film may be attributed to these very facts.

Takeda (3), studying the permeability of cellulose films, introduced the following equation:

$$\frac{1}{Q} = \frac{l}{P\,\Delta p} + \frac{2}{k\,\Delta p} \qquad \text{(Eq. 4)}$$

where $k$ is a coefficient which indicates how easily water molecules drive into the film from the higher humidity atmosphere. This equation explains that the relationship between $1/Q$ and $l$ is not proportional;