

Soft Gelatin Capsules II: Oxygen Permeability Study of Capsule Shells

F. S. HOM^{*}, S. A. VERESH, and W. R. EBERT

Abstract □ A method is reported for studying the effects of several factors at room temperature on the oxygen permeability of soft gelatin capsule shell films. The method involves the use of a permeability cell assembly and the spectrophotometric determination of oxygen with an alkaline pyrogallous acid solution. Factors investigated were relative humidity, plasticizers, equilibrium water, an insoluble additive, and film thickness. Results from the effects of film thickness and oxygen partial pressure correlated well with the permeability equation. For greatest stability of encapsulated oxygen-labile materials, it is recommended that the soft gelatin capsule shells be prepared with a low plasticizer concentration and that the finished capsules be stored at low relative humidity.

Keyphrases □ Capsules, soft gelatin—oxygen permeability at room temperature, effects of relative humidity, plasticizers, equilibrium water, insoluble additives, and film thickness □ Soft gelatin capsules—oxygen permeability at room temperature, effects of relative humidity, plasticizers, equilibrium water, insoluble additives, and film thickness □ Oxygen permeability of soft gelatin capsules—effects of relative humidity, plasticizers, equilibrium water, insoluble additives, and film thickness

Information about capsule shell properties is of considerable importance to those concerned with the design and formulation of soft gelatin capsule dosage forms. In a previous paper (1), results and discussion of several factors affecting capsule shell dissolution rate were reported. Results from an investigation of the factors influencing the viscoelastic characteristics of soft gelatin films were presented by Castello and Goyan (2). The present study deals with oxygen permeability behavior of capsule shells. Oxygen uptake by certain drug preparations while in storage or on shelves can lead to undesirable changes.

An example is the USP vitamin A reference standard in soft gelatin capsules. Vitamin A is relatively unstable in air and light; however, the encapsulated contents show no significant loss of potency for 3 years or longer when stored and packaged under the prescribed conditions of temperature and humidity. Results are presented from investigations on factors that influence oxygen permeability of soft gelatin films that could be useful in the design and formulation of capsule shells for oxygen-labile drugs.

A survey of the literature revealed several methods used to measure gas permeability. The usual ASTM method (3) and most commercially available apparatus are not sufficiently sensitive. A commercially available one (4) and the method of Gilbert and Pegaz (5) lack the flexibility and simplicity demanded in the present study. The method developed by Williams *et al.* (6), which was used by Munden *et al.* (7) for their evaluation of polymeric materials, seemed applicable, but little experimental detail was given for the direct application of this procedure. The present study required a sensitive, simple, versa-

tile, and leak-free technique. A method was developed with these criteria based on the method originated by Williams *et al.* (6).

THEORETICAL

The application of Fick's laws for diffusion and Henry's laws for partial pressure relations for gas solubility (8, 9) provides useful equations for gas flux across an intact polymeric film. When permeability occurs at a steady state in the absence of any interaction between gas and film toward the area of decreasing concentration, these equations are:

$$P = DS \quad (\text{Eq. 1})$$

$$P = qh/At(p_1 - p_2) \quad (\text{Eq. 2})$$

where P is a permeability coefficient, D is a diffusion coefficient, and S is a solubility coefficient or Henry's law constant. The quantity of gas (q) that passes through a given film at a given condition depends upon the area (A), thickness (h), partial pressure differential across the film ($p_1 - p_2$), and time (t). Conventionally, the gas permeability coefficient has dimensions of $\text{ml} \times \text{cm}/(\text{cm}^2 \times 24 \text{ hr} \times \text{atm})$. It may be evaluated from the slope of the linear portion of the curve where permeability occurs at a steady state in a plot of milliliters of gas permeated *versus* time in hours. Extrapolation of the linear portion of the curve to the time axis yields the lag time (L). The lag time is related to the diffusion coefficient (10) as follows:

$$D = h^2/6L \quad (\text{Eq. 3})$$

Thus, all three terms in Eq. 1 may be evaluated.

EXPERIMENTAL

Materials—The following were used: gelatin¹ USP (Type B) with 195 Bloom gram gel strength (20–40 mesh size), glycerin USP, titanium dioxide USP, FD&C Yellow No. 5, Teflon film², polyethylene film², mercury, nitrogen, oxygen, plaster of Paris, silicone rubber septum (as used in GC), and reagent grade pyrogallous acid and sodium hydroxide.

Equipment—A permeability cell assembly³, a gas microsyringe⁴, a micrometer, a spectrophotometer⁵, a vacuum pump, and vacuum desiccators were used.

Preparation of Film—The method used to prepare the soft gelatin films was reported earlier (1).

Relative Humidity Systems—The 31, 47, 58, 72, and 80% systems were saturated aqueous solutions of calcium chloride, potassium thiocyanate, sodium bromide, ammonium chloride-potassium nitrate, and ammonium chloride, respectively.

Preparation of Alkaline Pyrogallous Acid Solution—To prepare 2 liters of solution, introduce a magnetic stirrer, 8.0 g of pyrogallous acid, and 20.0 g of sodium hydroxide onto the bottom of the dry, 2-liter bottle without touching each other (Fig. 1). Pour 2 liters of freshly boiled distilled water into the separator on top of the bottle. Then flush the system with nitrogen until the boiled water is cooled to 30° without getting the reagents wet.

Close the system and stop the nitrogen gas. Evacuate the nitrogen gas trapped in the bottle by use of a vacuum pump. Close the

¹ Rousselot Corp., New York, N.Y.

² Cadillac Plastic and Chemical Co., Highland Park, Mich.

³ Quality Glass Apparatus, Ann Arbor, Mich.; other parts were made by the Machine Shop, R. P. Scherer Corp.

⁴ Hamilton Co., Whittier, Calif.

⁵ Beckman model B.

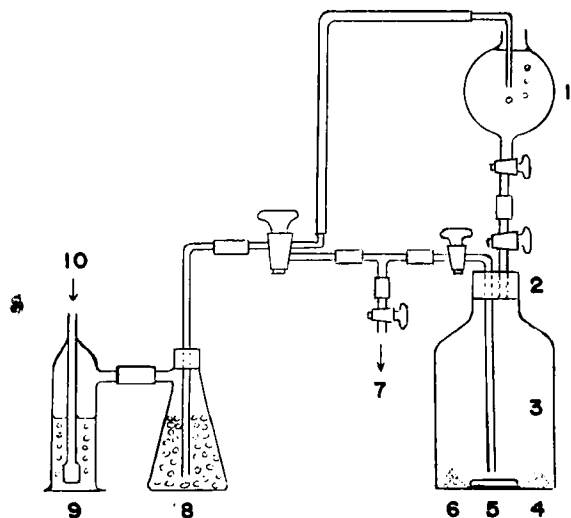


Figure 1—Schematic diagram showing the preparation of alkaline pyrogalllic acid solution. Key: 1, 2-liter funnel; 2, rubber stopper; 3, 2-liter thick wall Pyrex bottle; 4, pyrogalllic acid; 5, magnetic stirrer, 5 cm; 6, sodium hydroxide; 7, vacuum; 8, moisture trap; 9, alkaline pyrogalllic acid trap; and 10, nitrogen gas from tank. All connections are thick wall rubber hose.

system and then allow water to enter the bottle slowly by controlling the stopcock. Mix the solution well by turning on the magnetic stirrer when all of the water has been added without allowing any air to enter the bottle. In this manner, a water clear, colorless solution will be obtained.

Assembling and Filling Permeability Cell—Assemble the

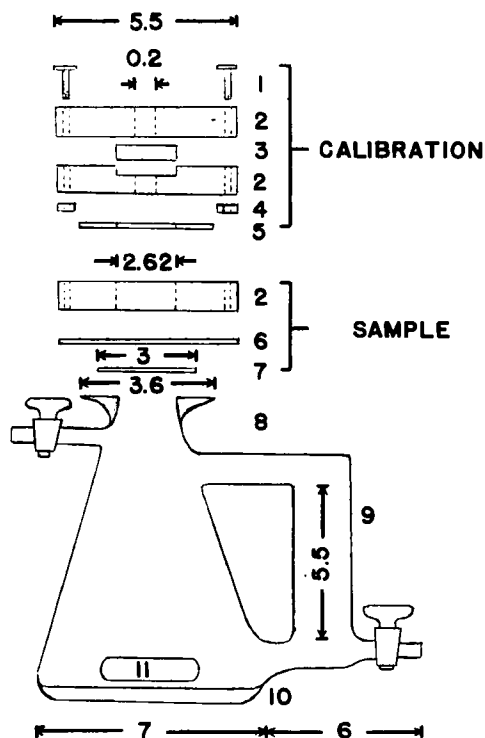


Figure 2—Diagrams of calibration and permeability cell assembly in exploded side views with measurements in centimeters. Key: 1, bolt; 2, Plexiglas plate, 0.612 cm thick; 3, silicone rubber septum; 4, nut; 5, gelatin or lead gasket; 6, soft gelatin film; 7, Teflon film backing, 0.005 cm thick; 8, wide lip 125-ml filtering flask; 9, cell made from 1.6-cm i.d. test tube-type cell; 10, plaster of Paris for leveling and height adjusting; and 11, magnetic stirrer, 2.54 cm.

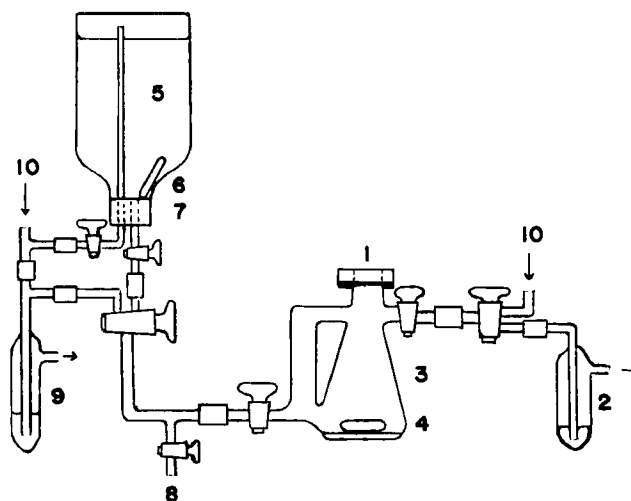


Figure 3—Schematic diagram showing permeability cell filling operation. Key: 1, mercury in cavity; 2, mercury valve trap; 3, assembled permeation cell; 4, magnetic stirrer, 2.54 cm; 5, alkaline pyrogalllic acid solution; 6, magnetic stirrer, 5 cm; 7, rubber stopper; 8, drain; 9, pressure relief valve; and 10, nitrogen gas from tank. All connections are thick wall rubber hose.

cells as shown in Fig. 2, with gelatin film overlapping the outer edge of the Teflon film backing by at least 0.1 cm to serve as a gasket. The permeability area is equal to that of the 2.62-cm diameter machined hole. Fasten, with nylon strings, the assembled films and plate to the top of the flask containing a magnetic stirrer. Fill the cavity on top of the gelatin film with mercury and tape seal to keep the mercury from spilling. Weigh the assembled cell and record its tare weight. Then insert the cell into the system as shown in Fig. 3.

Flush out all traces of air with nitrogen gas by manipulating the several stopcocks. Fill the cell with alkaline pyrogalllic acid solution to within 2 cm of the gelatin film. Weigh the filled cell to determine the weight of the solution and allow the filled cell to stand overnight at room temperature. Make an initial absorbance reading of the filled cell at 425 nm *versus* water after a thorough stirring with the magnetic stirrer. If the initial absorbance reading is less than 0.1, remove the mercury and then place the cell in a pure oxygen atmosphere until the cell solution reads between a 0.10 and 0.15 absorbance value. Replace the mercury on the filled cell and reestablish constancy of the absorbance reading. The filled cell is now ready for the leak test.

Leak Test—The absorbance of the solution in the filled cell was monitored at 425 nm for changes during a period of challenge by pure oxygen at 1 atm. The criterion for a leak-free system was no absorbance change after 2 days under such treatment.

Calibration and Correction Factor—Assemble the calibration cell with a silicone rubber septum between two Plexiglas plates. The hole in the middle of each plate is 0.2 cm in diameter. Fill the cavity on top of the septum with mercury and tape seal. Weigh the assembled cell and fill it with the solution as described in the filling procedure. Establish the weight and the initial absorbance of the solution and ensure that the system is leak free. By use of a gas microsyringe, slowly inject small increments of either pure oxygen or air samples through the mercury and septum into the nitrogen gas phase of the cell. Mix well with the magnetic stirrer until the color has reached equilibrium.

Place the cell in the predetermined position (previously adjusted with plaster of Paris) in the spectrophotometer and read the absorbance at 425 nm *versus* water. A typical standard curve is shown in Fig. 4, in which the change in absorbance at 425 nm is plotted against volume of oxygen added. However, the use of a standard calibration curve required a correction factor because the cells were not matched. A correction factor for each sample cell in relation to the standard cell was obtained from absorbance readings of a common, air-stable, FD&C Yellow No. 5 dye solution.

Permeability Study—After the weight, the absorbance of the solution at 425 nm, and the leak-free condition of the system have been established, remove the tape and mercury from the cell. Place the cell in a desiccator under controlled relative humidity condi-

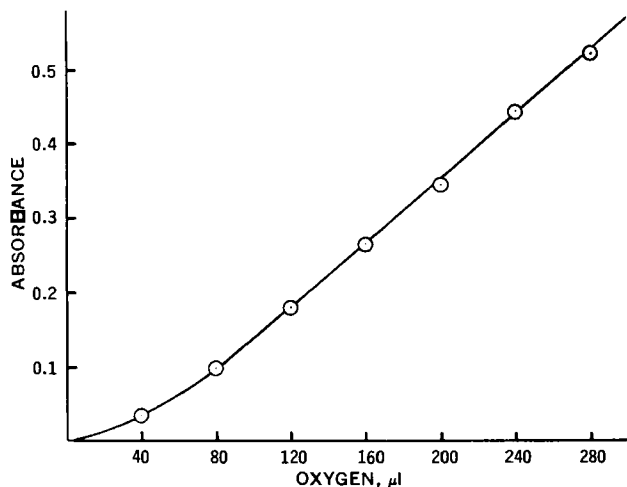


Figure 4—Typical standard calibration curve in a plot of absorbance at 425 nm for 150 g of alkaline pyrogalllic acid solution versus oxygen added in microliters.

tions. Flush the trapped air out of the mercury valve with oxygen from a tank that has been passed through a salt solution system used for adjusting the desired humidity. At appropriate time intervals, remove the cell and make absorbance readings of the solution at 425 nm. At the end of the readings, place the cell in the desiccator and flush the air out with oxygen as before.

The volume of oxygen permeated across the intact film in t hours, V_t , may be calculated from the change in absorbance in t hours, A_t , the standard calibration curve, and the correction factor by use of Eq. 4:

$$V_t = A_t V_s W_u F / A_s W_s \quad (\text{Eq. 4})$$

where A_s is the change in absorbance of W_s grams of standard solution as elicited by V_s milliliters of pure oxygen at 1 atm, W_u is the weight of the sample solution in grams, and F is the ratio of absorbance readings of a common dye solution in the standard cell to that in the sample cell. Results are averages of duplicate runs.

RESULTS AND DISCUSSION

The permeabilities of dry gelatin or collagen films to dry oxygen are extremely low. Lieberman *et al.* (11) made experimental runs with oxygen that gave values consistently in the range of values associated with the permeability cell leakage rates. Hence, to obtain meaningful measurements of oxygen permeability through gelatin, the method used must be leak free, sensitive, and stable. The indigo carmine or FD&C Blue No. 2 method (12, 13) exhibited color instability over the period of an experiment. Preliminary work with the present method showed no indication of color instability but revealed a water vapor problem. Over time the water vapor from the alkaline pyrogalllic acid solution rendered the study of the effect of relative humidity on permeation rate rather difficult. This problem was resolved by the use of a 0.005-cm thick Teflon film as a backing for the soft gelatin film. This complicated the determination of the gelatin film permeability coefficient somewhat, because it seemed that the observed value then had to be corrected for the Teflon contribution.

One may rationalize that if the Teflon film were to have an observable effect, it would manifest itself on the system with the highest permeation rate in a particular study. In line with this reasoning, permeation rates were determined in triplicate for a gelatin film made with 50% glycerin at 80% relative humidity with Teflon film thicknesses of 0.005 and 0.01 cm. There was no significant change in the observed oxygen permeation rates when the Teflon thickness was doubled. This observation is in agreement with results calculated by use of Eq. 5, given by Rogers *et al.* (14) for the Teflon film effect. Thus, oxygen permeation through the soft gelatin film is the rate-limiting factor. Hence, it is not necessary to correct for the Teflon film effect in the observed permeation rates as obtained under the conditions of the present study.

The present study demands that the permeation apparatus be leak free and requires such a test. The use of mercury as a seal ade-

quately prevents oxygen from going through the permeation film. Therefore, there are three other possible sites for leakage: the gasket and the two stopcocks. Hand grinding of each individual stopcock and the use of a small amount of high vacuum stopcock grease help solve this problem. Teflon, polyethylene, and rubber gaskets were found to be inadequate in preventing oxygen leakage. Surprisingly, soft gelatin films make good gaskets and prevent oxygen leakage. Lead gaskets also may be used for this purpose.

Under the conditions of the experiments (film thickness used, *etc.*), the water permeability through the Teflon film is about 200 times slower than through the soft gelatin films. With the use of Teflon backing at the higher relative humidity conditions, the soft gelatin films swell to a measurable degree. For this reason, thickness measurements were made at the beginning and at the end of each run, but only the final thickness was used for permeability calculations.

When the alkaline pyrogalllic acid solution is stored in a leak-free system, it is stable; the change in absorbance is reproducible as shown by standard calibrations done at the beginning and the end of an experiment that may last several weeks. For this reason, the cell systems were tested for leakage by mercury sealing the test film before each oxygen permeation study.

An elaboration of the chemistry of the reaction between oxygen and alkaline pyrogalllic acid is beyond the scope of this paper. Apparently, there are at least two possible reaction pathways. The reaction is rapid, but the color produced is dependent on the oxygen flux. Rapid introduction of a larger bolus of air or oxygen into the system gave erratic results, probably from the formation of irreversible, nonstoichiometric dark-brown colors. In contrast, slow injections from a gas syringe of 40-μl increments of oxygen or an equivalent amount of air produced a reproducible yellow color; the results are typical of those shown in Fig. 4. Apparently, for a 150-g solution, about 80 μl of oxygen was expended before the color production was linear. Therefore, the absorbance of the filled cell was adjusted to between 0.10 and 0.15 before the cell was tested for leakage.

Oxygen permeability studies with Teflon and polyethylene films were designed to test the applicability of the equations, the correlation of experimental results with those available in the literature (15), and the effect of repetitive use of a Teflon film on its oxygen permeability. In preliminary runs with Teflon films, the use of pure oxygen was too rapid for accurate determination of the lag time and the permeability coefficient. Consequently, air was used. When humidity is not a factor, as in this case, air is convenient to use since an experiment can be started and stopped by manipulating the mercury seal on top of the film. However, the oxygen permeability coefficients were calculated for 1 atm of pure oxygen.

Figure 5 shows plots of milliliters of oxygen from air that has permeated through new and used Teflon films *versus* time in

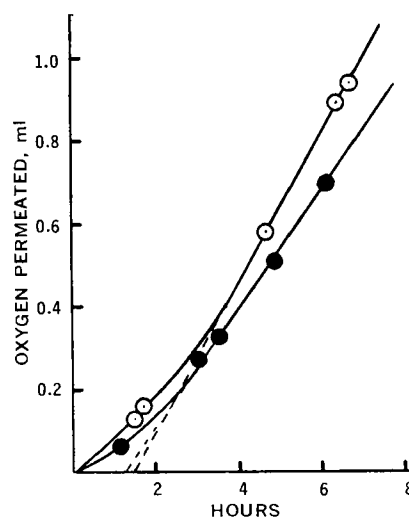


Figure 5—Effects of new (○) and used (●) Teflon films on oxygen permeability rate at room temperature in a plot of milliliters of oxygen at 1 atm permeated across film versus time in hours

Table I—Mean Oxygen Permeability Coefficients and Their Ranges from Duplicate Runs of Teflon and Polyethylene Films Along with Values Taken from Ref. 15

Film	Thick-ness $\times 10^{-3}$ cm	Permeability Coefficient, ml cm/(cm ² 24 hr atm) $\times 10^{-3}$	
		Present Method	Literature (15) Value
New Teflon	5.334	4.18 \pm 0.14	2.95
Used Teflon	5.334	3.15 \pm 0.30	—
Polyethylene	7.620	1.80 \pm 0.07	2.11

hours at room temperature. The extrapolated lag time in both cases is about 1.5 hr. The mean oxygen permeability coefficients with their ranges from duplicate runs of Teflon and polyethylene films are given in Table I along with those available from the literature (15). In consideration of the variability of the films and other parameters used, the results obtained with the present method agree well with the sparse data in the literature. However, the small difference between new and used Teflon film may be significant. It is reasonable to expect a slightly lower oxygen permeability coefficient value for a used film as compared to a new one.

The present study was limited to films made from one sample of gelatin, to a film thickness between 0.04 and 0.1 cm, to room temperature (21 \pm 1°), to 32–63% initial glycerin concentrations, and to 31–80% relative humidity. Oxygen permeability measurements on soft gelatin films made with less than a 30% initial glycerin concentration and conditions of less than 30% relative humidity are extremely slow, time consuming, and inaccurate. Thus, the parameters chosen are such that an experiment usually can be completed in 2–3 weeks.

The mean results from duplicate runs are given in Table II. A typical plot is shown in Fig. 6 of milliliters of pure oxygen at 1 atm that had permeated across the test films, made with 32–63% initial glycerin, versus time in hours under a 72% relative humidity. Figures 5 and 6 resemble those pressure change versus time plots of Higuchi and Aguiar (10) from their study of permeability of fats, waxes, and other enteric coating materials to water vapor. They were able to obtain lag times precisely by extrapolation of the linear portion of the curve to the time axis. Presently, this is the case with Teflon films as shown in Fig. 5; however, an examination of Fig. 6 reveals that the lag times are erratic as compared to those obtained by using Teflon films alone. The reason is that at the beginning of each run the desired relative humidity conditions were

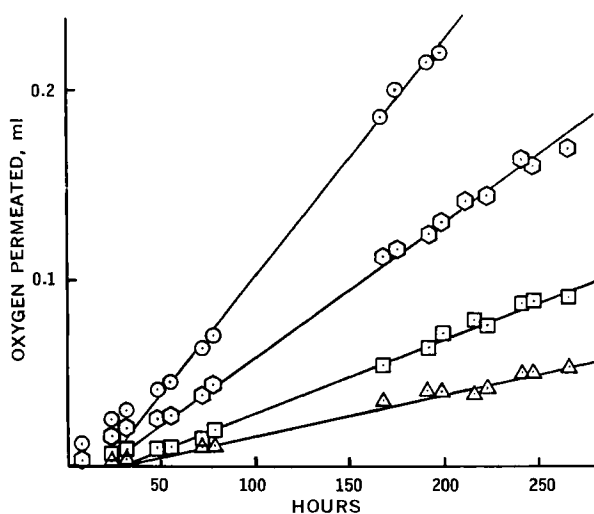


Figure 6—Typical plot showing the rate at room temperature and 72% relative humidity of oxygen at 1 atm permeated across soft gelatin capsule shell films made with initial glycerin concentrations of 32 (Δ), 43 (\square), 53 (\circ), and 63 (\odot) % versus time in hours.

Table II—Mean Values from Duplicate Runs Showing Effects of Glycerin Concentration and Storage Relative Humidity on Oxygen Permeability Coefficients of Soft Gelatin Films at Room Temperature

Relative Humidity, %	Initial Glycerin, %			
	32	43	53	63
	Permeability Coefficient, ml cm/(cm ² 24 hr atm) $\times 10^{-4}$			
31	—	0.14 ^a	—	1.04 ^a
31	—	—	—	0.64
47	—	0.31	0.80	1.58
58	0.51	1.05	1.92	3.98
72	2.40	3.42	5.89	7.97
80	4.00	6.55	9.37	13.35

^a Data obtained by Ox-Tran 100 method (4).

difficult to establish. In the leak test, the gelatin film was sealed with mercury for a number of days. During this time, the gelatin film was able to equilibrate with the water vapor from the solution that had permeated across the Teflon film. After mercury removal to commence the run, the gelatin film required several hours to reach equilibrium with the desired relative humidity conditions. The initial higher moisture gelatin film resulted in a shorter lag time, whereas the equilibrium process lengthened it. As a result, the lag time was neither reproducible nor accurate. However, this has no bearing on the permeability coefficient determination because it is calculated from the slope of the linear portion of the line when the system is at equilibrium and oxygen permeation has reached steady state.

Relative Humidity—Water is part of the composition of gelatin and also is contained in the soft gelatin film. It is reasonable to expect that relative humidity will have an effect on the physical and chemical properties of soft gelatin films. This part of the study was to determine the effect of relative humidity (percent) on the oxygen permeability of soft gelatin films. Figure 7 shows this effect in a plot of the logarithm of the oxygen permeability coefficient of soft gelatin films made with different initial glycerin concentrations versus relative humidity. The values obtained by two different methods correspond quite well. As can be seen, the logarithm of the oxygen permeability coefficient is a linear function of relative humidity. The higher the relative humidity, the exponentially higher is the oxygen permeability for the several initial glycerin concentrations. However, it is surprising that the straight lines, when extrapolated to 100% relative humidity, seem to converge into a single value.

In any event, soft gelatin capsules should be stored below 50% relative humidity in a cool place or at room temperature. Under such storage conditions, oxygen permeability across a soft gelatin capsule shell is limited to very low values under pure oxygen atmospheric conditions (Table II). When stored in air at atmospheric pressure and in a cool, dry place, the oxygen permeability coefficients are about one-fifth of these values or about 1×10^{-5} ml cm/cm² 24 hr atm.

Plasticizers—Glycerin is the most commonly used plasticizer in the manufacture of soft gelatin capsules. As part of the soft gela-

Table III—Mean Oxygen Permeability Coefficients from Duplicate Runs for Soft Gelatin Films Made with Several Different Plasticizers at an Initial 43% Concentration, 72% Relative Humidity, and at Room Temperature Along with Their Corresponding Equilibrium Water Concentration

Plasticizer	Permeability Coefficient, ml cm/(cm ² 24 hr atm) $\times 10^{-4}$	Water, % w/w
Glycerin	3.42 \pm 0.00	23.6
Sorbitol-glycerin (1:1)	1.32 \pm 0.04	22.3
Hexaglycerol	0.71 \pm 0.13	20.0
Decaglycerol	0.67 \pm 0.07	20.0

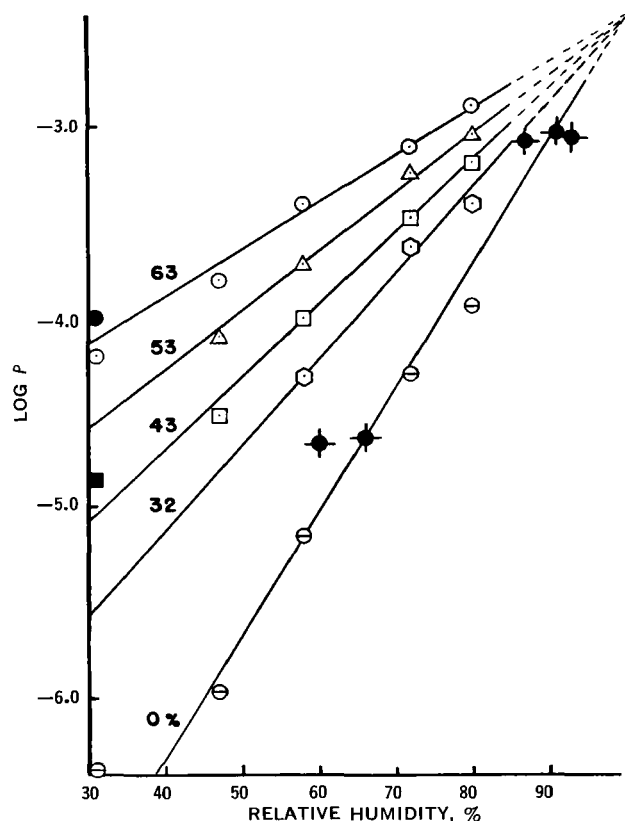


Figure 7—Plot of the logarithm of the oxygen permeability coefficient, P , versus percent relative humidity at room temperature for soft gelatin capsule shell films made with several initial percent glycerin concentrations (given in figure). Solid circle and solid square data were obtained by a commercial method (4). Halved open circle data were obtained by extrapolating lines in Fig. 8 to 0% glycerin. Crossed solid circle data were taken from Ref. 11.

tin composition, it could be expected to affect significantly the oxygen permeability behavior of the capsule shells. Figure 8 is a plot of the logarithm of the oxygen permeability coefficients of soft gelatin films as a function of the initial glycerin concentration (percent) at the several relative humidity conditions. Again, the straight lines indicate that the logarithm of the oxygen permeability coefficients is a linear function of glycerin concentration in soft gelatin films. The higher the initial glycerin in the soft gelatin film, the exponentially higher their oxygen permeability coefficient values will be. However, the initial glycerin concentration of soft gelatin capsule shells is usually below 50%. If the soft gelatin capsules are stored under the recommended conditions (a cool, dry place in air), the oxygen permeability across the capsule shell will be limited to less than a value of 1.6×10^{-5} ml cm/cm² 24 hr atm.

Table III lists the mean oxygen permeability coefficients and their ranges from duplicate runs of soft gelatin films made with glycerin, sorbitol-glycerin (1:1), hexaglycerol, and decaglycerol at an initial 43% plasticizer concentration, 72% relative humidity, and room temperature. If the permeability coefficient of the film made with glycerin is set at 100%, then the ones for sorbitol-glycerin (1:1), hexaglycerol, and decaglycerol will be 38.7, 20.8, and 19.5%, respectively. As can be seen, oxygen appears to be more permeable through gelatin films made with glycerin than with other plasticizers. Therefore, the use of plasticizers such as sorbitol and polyglycerols should be considered in the design and formulation of capsule shells for oxygen-labile drugs.

Equilibrium Water Concentration—Previous discussions on relative humidity and plasticizers could lead to speculation that equilibrium water concentration may be the common factor affecting oxygen permeability across soft gelatin films. In this study, pieces of soft gelatin films that were used in the permeation experiments were suspended with stainless steel wires in identical environmental conditions. The weight of each piece of film was moni-

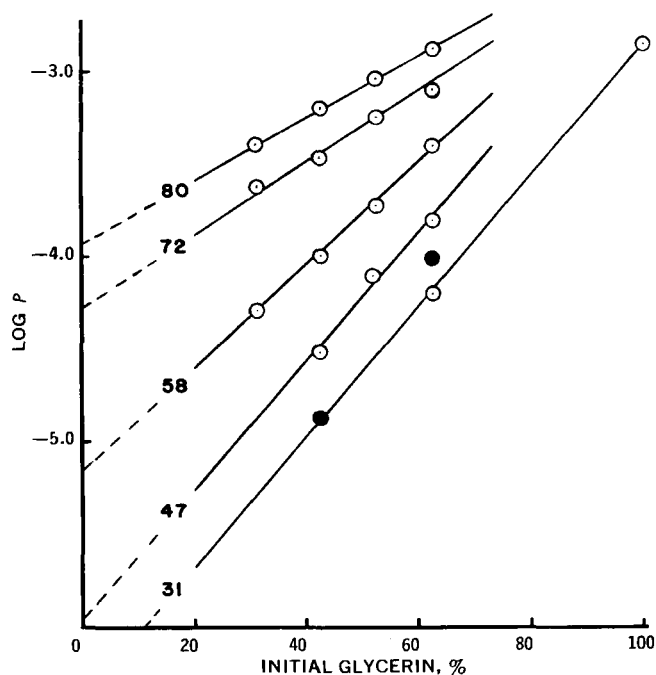


Figure 8—Plot of the logarithm of the oxygen permeability coefficient, P , versus the initial percent glycerin concentration in soft gelatin capsule shell films at room temperature and relative humidity values from 31 to 80% (given in figure). Solid circle data were obtained by a commercial method (4).

tored by periodic weighing. Constant weight was taken as the criterion for equilibrium. Equilibrium water concentration of each piece of soft gelatin film was calculated from knowledge of the final weight, final water content as determined by Karl-Fischer titration, and initial composition. These results are plotted in Fig. 9 for several initial glycerin concentrations and relative humidity conditions. The values for 0% glycerin films were taken from the paper by Bull (16).

For all relative humidity conditions, the equilibrium water concentration is relatively constant between 0 and 40% initial glycerin and then rises with increases in initial glycerin. There seems to be a minimum at about 35% initial glycerin for soft gelatin films stored below 50% relative humidity. This finding is interesting since most soft gelatin capsules in this area are manufactured with this amount of glycerin and stored at this relative humidity. The use of about 35% initial glycerin concentration was determined empirically many years ago. On a more theoretical basis, the glyc-

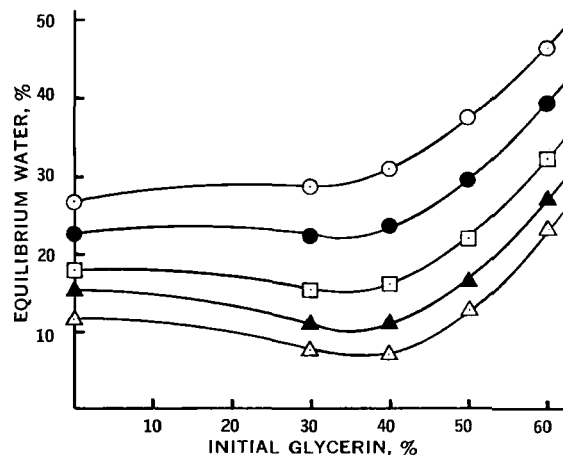


Figure 9—Plot of percent equilibrium water versus percent initial glycerin in soft gelatin films at room temperature and relative humidity of 31 (Δ), 47 (\blacktriangle), 58 (\square), 72 (\bullet), and 80 (\odot) %.

Table IV—Mean Values and Ranges from Duplicate Runs Showing the Effects of a Solid Additive on Oxygen Permeability Coefficients of Soft Gelatin Films at 72% Relative Humidity

Initial Glycerin, %	Permeability Coefficient, ml cm/(cm ² 24 hr atm) × 10 ⁻⁴		Decrease, %
	0% TiO ₂	5% TiO ₂	
43	3.42 ± 0.00	2.61 ± 0.29	23.7
63	7.84 ± 0.51	6.00 ± 1.59	23.5

erin molecule solvates only one hydrophilic group of the gelatin molecule (17). By assuming that each amino acid subunit represents one hydrophilic group and knowing the gelatin composition, a near 1:1 molar ratio of glycerin to amino acid subunit can be calculated for the 35% initial glycerin soft gelatin film.

Without holding the relative humidity conditions constant, the effect of an equilibrium water concentration on oxygen permeability coefficients of soft gelatin films may be shown as in Fig. 10. Here the logarithm of the oxygen permeability coefficients are plotted as a function of the equilibrium mole percent water. The relationship is linear. The reason could be that as the amount of water in the films increases, the water becomes the dominant factor and the curve asymptotically approaches the oxygen permeability coefficient value of water. If the equilibrium water concentration (percent) in Table III were converted to mole percent and the results were plotted *versus* their respective log *P* values in Fig. 10, they would fall on top of the straight line. This indicates that the plasticizers control the equilibrium water concentration in a given soft gelatin film, but their respective equilibrium water concentration has the greatest effect on the oxygen permeability coefficient.

Insoluble Solid Additive—The addition of insoluble solid particles to soft gelatin capsule shells represents an increase in the tortuosity of the path that the permeating gas must flow. The end result is a decrease in the permeability coefficient value as compared to an identical film under the same conditions. The results from such a comparative study are given in Table IV for 0 and 5% titanium dioxide added to soft gelatin films made with 43 and 63% initial glycerin concentrations at 72% relative humidity. The decreases in the oxygen *P* values are 23.7 and 23.5% for the films made with 43 and 63% initial glycerin, respectively. There is little difference in the two results. However, the usual amount of titanium dioxide added to soft gelatin capsule shells is 1% or less. The use of such a small amount of an insoluble additive has a minimal effect on the oxygen permeability coefficient of a given soft gelatin capsule shell. Thus far, the main purpose for using insoluble solid additives in soft gelatin capsules is to obtain pharmaceutical ele-

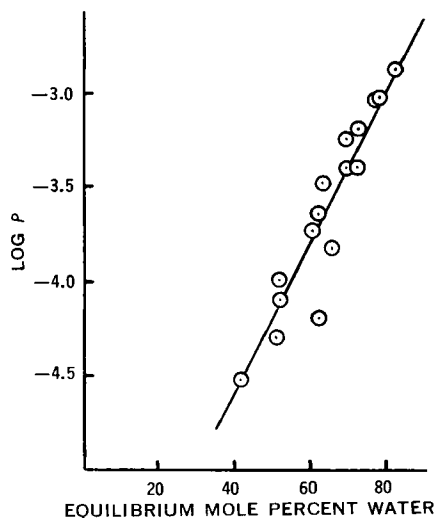


Figure 10—Plot of the logarithm of the oxygen permeability coefficient, *P*, versus the equilibrium mole percent water in soft gelatin capsule shell films at room temperature.

Table V—Nine Separate Runs Showing the Final Film Thickness Effect on Oxygen Permeability Coefficients of Soft Gelatin Films Made with 53% Initial Glycerin at 80% Relative Humidity

Final Film Thickness × 10 ⁻² cm	Oxygen Permeated, ml/(cm ² 24 hr atm) × 10 ⁻²	Permeability Coefficient, ml cm/(cm ² 24 hr atm) × 10 ⁻⁴
4.01	2.26	9.06
4.27	2.17	9.27
5.46	1.72	9.39
5.79	1.59	9.21
6.05	1.58	9.56
7.11	1.24	8.82
7.62	1.33	10.13
9.88	1.06	10.47
9.93	0.85	8.44
Mean ± SD =		9.37 ± 0.62

gance. This purpose may change in the future, especially when more suitable additives are found.

Film Thickness—A rearrangement of Eq. 2 shows that the volume of a gas permeated across a given film is directly proportional to the reciprocal of the film thickness. Table V presents the results from nine separate runs of oxygen volume permeated across soft gelatin films, at a thickness from 4.01 to 9.93 × 10⁻² cm, made with a 53% initial glycerin concentration at 80% relative humidity. Figure 11 shows that the results obey the permeability equation in the form of a straight line going through the origin in a plot of the volume of oxygen permeated *versus* the reciprocal of the final film thickness. Table V also gives the average of the nine oxygen permeability coefficients and its standard deviation: 9.37 ± 0.62 × 10⁻⁴ ml cm/cm² 24 hr atm.

Oxygen Partial Pressure—With reference to Eq. 2, it can be shown that the volume of a gas permeated through a given film is directly proportional to the partial pressure difference (Δp) across the film. In the present method, Δp is equal to p_1 because p_2 is zero or approaches zero. For this reason, it is not difficult to demonstrate the oxygen partial pressure effect on permeability at room temperature. All that is necessary is to subject the same permeability cell system to air and then to pure oxygen. In this manner all variables are the same except the oxygen partial pressure.

Results from such an experiment are depicted in Fig. 12, where the amount of oxygen permeated in milliliters × 10⁻⁴ is plotted against the oxygen partial pressure in atmosphere for cm² × 24

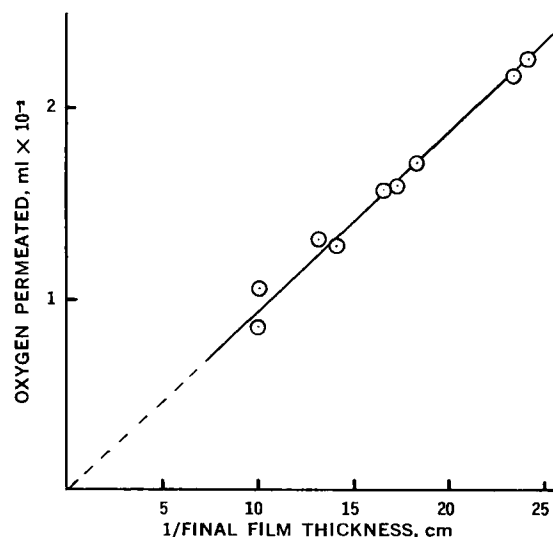


Figure 11—Plot of volume of oxygen permeated versus the reciprocal of film thickness per 24 hr × cm² × atm for soft gelatin films made with 53% initial glycerin at 80% relative humidity.

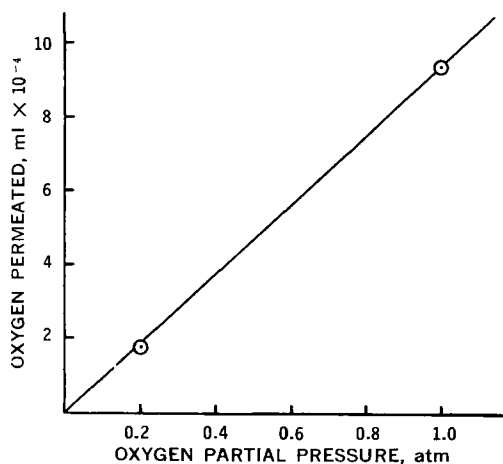


Figure 12—Plot of the volume of oxygen permeated versus oxygen partial pressure per $\text{cm}^2 \times 24 \text{ hr/cm}$ through soft gelatin films made with 53% initial glycerin at 80% relative humidity.

hr/cm through soft gelatin films made with 53% initial glycerin at 80% relative humidity. In accordance with Eq. 2, the plot is a straight line going through the origin and the two points, 0.2 (air) and 1.0 (pure oxygen) atmosphere. Hence, by the use of this oxygen partial pressure effect, it is convenient, where desired, to speed up or to slow down a particular permeability study with the present method.

SUMMARY

A method is described for a study of the effects of various factors on oxygen permeability behavior of soft gelatin capsule shells. The method involves the use of a permeability cell assembly and the spectrophotometric determination of the amount of oxygen permeated into an alkaline pyrogalllic acid solution. The validity of the method was confirmed by a correlation study with a commercially available method and with literature values.

The present method has enabled the investigation, at room temperature, of the influence of relative humidity (percent), types of plasticizers and their concentrations, equilibrium water concentrations, an insoluble solid additive (titanium dioxide), oxygen partial pressure, and film thickness on the oxygen permeability of soft gelatin films. The plasticizer and relative humidity control the equilibrium water concentration, with the latter having the greater effect on oxygen permeability. In a comparative study, the insoluble solid additive appeared to increase the tortuosity of the film and resulted in a decrease in the oxygen permeability coefficient value. The results from the study of the effects of film thickness of soft

gelatin films and oxygen partial pressure correlated well with the permeability equation.

In conclusion, various factors have been demonstrated to influence oxygen permeability of soft gelatin capsule shell films. A knowledge of these relationships is helpful in the formation of soft gelatin capsule shells for the capsulation of oxygen-labile drugs and other materials. For the greatest stability against oxygen degradation of such encapsulated ingredients, it is recommended that the soft gelatin capsule shells be made with a lower concentration of plasticizer and that the finished capsules be stored in a dry, cool place.

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