Pharmaceutical Research, Vol. 5, No. 2, 1988

Research Article

Oxygen Diffusion Coefficients in Commonly Used Topical Semisolid Creams

Jonas C. T. Wang,[1,3] Lu-Kwang Ju,[2] and Chester S. Ho[2]

Received April 20, 1987; accepted September 14, 1987

The objective of this paper is to determine oxygen diffusion coefficients, permeabilities, and solubilities in a commonly used o/w topical ointment (similar to USP XXI hydrophilic ointment) and four commercial 1% anthralin creams. A new method developed by Ju and Ho in 1986 by applying a coupled steady-state and unsteady-state analysis for oxygen diffusion through a thin layer of test material on the surface of a membrane-covered polarographic oxygen electrode was used in the study. The results indicate that oxygen diffusion coefficients decrease with an increasing petrolatum concentration in o/w topical creams. The oxygen diffusion coefficients in four commercial creams containing 1% of extremely oxygen-sensitive anthralin were also determined using the same method. The information generated in this study can lead to a better understanding of the diffusion transport mechanism of oxygen in the topical creams and, thus, be useful to the formulation design of oxygen-sensitive drugs in semisolid dosage forms intended for topical, ophthalmic, and parenteral use.

KEY WORDS: steady-state analysis; unsteady-state analysis; USP XXI hydrophilic ointment; phase-volume ratio; 1% anthralin products.

INTRODUCTION

The information regarding diffusion transport of low molecular weight solutes, such as oxygen and carbon dioxide gases, in solutions and semisolid fluids is of great importance in a wide range of areas. These include parenteral solutions, physiological processes, fermentation and biochemical processes, waste disposal systems, polymer processing, semisolid systems, and pharmaceutical manufacture and processing. However, most information related to the gaseous transport in these systems focuses on chemical engineering and bioengineering design and few data are available for pharmaceutical applications.

In the pharmaceutical industry, many drug candidates are prone to oxidation in the atmosphere. To remove oxygen from a formulation becomes an obvious way to prevent the oxidation. Normally, this is done by applying or bubbling an inert gas through the formulation during manufacturing and then adding antioxidants to the formulation. The effect of the vehicle bases on the diffusive transport of oxygen has never become a concern to pharmaceutical scientists. The lack of adequate methodologies and equipment and the need for complicated mathematic manipulation are major obstacles to the measurement of the diffusive transport of oxygen in different vehicle bases.

Ju and Ho (1) recently developed a method of measuring oxygen diffusion in electrolyte solutions with a commercially available membrane-covered polarographic oxygen electrode. The experimental method is capable of simultaneously measuring oxygen diffusion coefficients, permeabilities, and solubilities in aqueous solutions and semisolids by applying a coupled steady-state and unsteady-state analysis for oxygen diffusion through a thin layer of the tested material on the surface of a membrane-covered polarographic oxygen electrode. The method has been proved useful in measuring oxygen diffusion coefficients, permeabilities, and solubilities in aqueous electrolyte solutions (1).

The objective of the study is to determine the diffusive transport of atmosphere oxygen in various topical creams with Ju and Ho's method. Four commercial topical products containing 1% oxygen-sensitive anthralin were also studied in an attempt to evaluate the applicability of Ju and Ho's method to pharmaceutical products. The resulting data would be useful in the formulation selection and processing design for oxygen sensitive molecules to be formulated in semisolid or solution dosage forms. The methodology could also be extended to gases other than oxygen.

THEORY

While a more detailed derivation of this measuring technique is available elsewhere (1), a brief description of the basic theories of this method is worthwhile.

When an electrode of noble metal such as platinum or gold is made 0.6–0.8 V negative with respect to a suitable reference electrode, e.g., the calomel or Ag/AgCl, in a neutral potassium chloride (KCl) electrode solution, dissolved oxygen is reduced at the cathode surface. By separating the cathode, anode, and KCl electrode solution from the test

---

[1] Pharmaceutical Research & Development Division, Bristol-Myers Co., Buffalo, New York 14213.

[2] Department of Chemical Engineering, State University of New York at Buffalo, Buffalo, New York 14260.

[3] To whom correspondence should be addressed.

0724-8741/88/0200-0092$06.00/0

sample with a plastic membrane permeable to oxygen but not to ions, the polarographic oxygen electrode has been successfully employed to measure oxygen partial pressure (p) in gas, liquid, or semisolid (1–4). With proper interpretation, the measurement can be used to characterize transport of oxygen in the test material surrounding the electrode.

Steady-State Analysis

When a thin film of the test material (ointment or cream) is introduced over the surface of a membrane-covered oxygen electrode, a steady-state one-dimensional oxygen diffusion will be established after a while. This diffusion process can be shown as case a in Fig. 1. By neglecting the gas–film resistance, it is reasonable to assume that the material at the gas–material interface is saturated with oxygen in the gas phase and can be regarded as the source of the oxygen diffusion. The sink is the cathode surface, where oxygen is continously engaged in rapid electrochemical reactions. The rate of oxygen consumption due to the reactions is much faster than the rate of diffusion; thus, the oxygen partial pressure at the cathode surface can be treated as nil. Furthermore, the resistance of oxygen transfer in the electrode solution is much smaller than that in the membrane and has usually been neglected for simplicity (3–6). This assumption is valid when the membrane is tightly attached to the cathode surface, which is particularly the case for the oxygen electrode used in the current study. Experimental data obtained by Aiba *et al.* (3) and Linek and Vacek (5) were found to support the assumption that the rate of oxygen transfer in a membrane-covered oxygen electrode is controlled by diffusion of oxygen through the membrane. As a result, the profile of the oxygen diffusion process can be simplified to case b shown in Fig. 1.

It is well known that except operating in high-oxygen concentrations, the current output, R, of the oxygen electrode is proportional to the oxygen flux to the cathode (7–9), that is,

$$R = A\,D_m\left(\frac{\partial C_{O_2}}{\partial x}\right)_{x=0} = A D_m k_m\left(\frac{\partial p}{\partial x}\right)_{x=0} \tag{1}$$

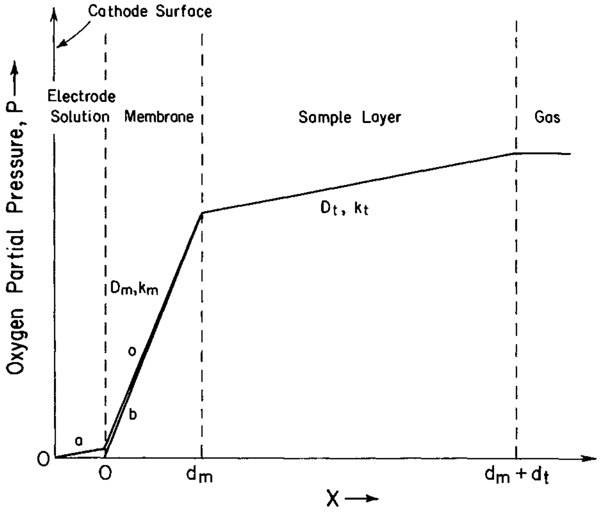

Fig. 1. Schematic of the steady-state oxygen transfer through the membrane-covered electrode immersed in a stationary test material.

where Henry's law

$$C_{O_2} = k_m p \tag{2}$$

has been applied, and subscript m refers to the membrane. As shown by case b in Fig. 1, at steady state the profile of oxygen partial pressure within the membrane is linear. Accordingly, Eq. (1) can be simplified to

$$R = \frac{A\,D_m k_m}{d_m}(p)_{x=d_m} \tag{3}$$

where d_m is the membrane thickness. By solving the steady-state diffusion equation

$$D_t k_t \frac{d^2 p}{dx^2} = 0 \tag{4}$$

with boundary conditions

$$p = p_a \quad \text{at} \quad x = d_m + d_t \tag{5}$$

and

$$D_t k_t \frac{dp}{dX} = \frac{D_m k_m}{d_m} p \quad \text{at} \quad x = d_m \tag{6}$$

where D_t is the oxygen diffusion coefficient, k_t is the oxygen solubility in the sample, d_t is the thickness of the sample layer, and p_a is the oxygen partial pressure in air. The solution for the oxygen partial pressure at the outer surface of the membrane, $(p)_{x=d_m}$, can easily be shown to be

$$(p)_{x=d_m} = \frac{P_a}{[1 + (d_t/d_m)(D_m k_m/D_t k_t)]} \tag{7}$$

By substituting Eq. (7) into Eq. (3), the steady-state current output, R_s, of the electrode can be shown as

$$R_s = \frac{A\,D_m k_m}{d_m}\,\frac{P_a}{[1 + (d_t/d_m)(D_m k_m/D_t k_t)]} \tag{8}$$

According to Eq. (3), the current output of the electrode while exposed to moist air is

$$R_a = \frac{A\,D_m k_m}{d_m} P_a \tag{9}$$

Therefore, Eq. (8) becomes

$$\frac{R_s}{R_a} = \frac{1}{[1 + (d_t/d_m)(D_m k_m/D_t k_t)]} \tag{10}$$

And rearranging Eq. (10) leads to

$$\frac{R_a}{R_s} - 1 = \left(\frac{D_m k_m}{d_m}\right)\left(\frac{d_t}{D_t k_t}\right) \tag{11}$$

For polarographic electrodes, properties of the membrane would not change during a brief period of operation. It is thus possible to obtain the relative oxygen permeability in the test material to that in a reference solution, e.g., pure water, as follows:

$$\frac{D_t k_t}{D_w k_w} = \frac{d_t}{d_w}\cdot\frac{[(R_a/R_s) - 1]_w}{[(R_a/R_s) - 1]_t} \tag{12}$$

where subscript w refers to pure water.

Nonetheless, oxygen diffusion coefficients cannot be directly attained through steady-state analysis unless oxygen solubilities have been predetermined or measured separately. This problem can be solved by coupling the steady-state analysis with an analysis involving the unsteady-state electrode response to a step change of oxygen partial pressure at the gas–cream interface as described below.

Unsteady-State Analysis

As shown in Fig. 1, oxygen diffusion through the thin material film on the membrane-covered electrode can be simplified to a bilayer system, i.e., the test material and the membrane, while neglecting the resistance of oxygen diffusion in the electrode solution. In what follows, reasonable assumptions are sought for further simplification.

By using a ⅜-in.-diameter membrane-covered oxygen electrode with a 25-μm-diameter platinum wire cathode sealed in glass and a bare 500-μm silver wire anode, Goldstick and Fatt (10) measured oxygen diffusion coefficients in aqueous solutions of potassium chloride, bovine serum albumin, and human oxyhemoglobin with the unsteady-state method. Since the cathode area is much smaller than the total membrane surface area, they assumed that the oxygen flux to the electrode is negligible, thus enabling the analysis to be restricted to the liquid layer only. They solved the diffusion equation in the liquid layer by letting the oxygen partial-pressure gradient at the membrane surface be zero. The assumption, however, is not valid for regular oxygen electrodes having large cathodes.

When the thickness of the test material, d_t, is much larger than that of the membrane, d_m, a more general assumption of having linear profiles of oxygen partial pressure within the membrane can be made. It has been shown that for Teflon membranes the minimum ratio of d_t/d_m is about 100 to justify the assumption (1). With this assumption, Eq. (3) can be used to express the current output of the oxygen electrode; and the oxygen partial pressure at the membrane surface, $p(t, x = d_m)$, can be obtained by solving the diffusion equation in the test material:

$$\frac{\partial p}{\partial t} = D_t \frac{\partial^2 p}{\partial x'^2} \tag{13}$$

with initial and boundary conditions as

$$p = p_a\left(\frac{Bx' + 1}{Bd_t + 1}\right) \qquad \text{at } t = 0 \tag{14}$$

$$\frac{\partial p}{\partial x'} = BP \qquad \text{at } x' = 0,\ t > 0 \tag{15}$$

and

$$p = p_f \qquad \text{at } x' = d_{t'},\ t > 0 \tag{16}$$

where

$$x' = x - d_m \tag{17}$$

$$B = \frac{D_m k_m}{d_m} \frac{1}{D_t k_t} \tag{18}$$

Equation (14) describes the steady-state oxygen distribution in the material layer prior to a step change of oxygen partial pressure from p_a to p_f at the gas–material interface. The resulting expression for the transient electrode response under this assumption is thus (1,2)

$$\Gamma = 2 \sum_{n=1}^{\infty} \frac{\xi_n^2 + B'^2}{\xi_n^2 + B'^2 + B'} \frac{\sin\xi_n}{\xi_n} \exp(-\tau\xi_n^2) \tag{19}$$

where

$$\Gamma = \frac{R(t) - R_f(R_s/R_a)}{R_a - R_f} \tag{20}$$

$$\tau = \frac{D_t t}{d_t^2} \tag{21}$$

$$B' = Bd_t \tag{22}$$

and ξ_n's are the positive roots of the transcendental equation,

$$\xi_n\, C_O t\, \xi_n + B' = 0 \tag{23}$$

Γ has the physical meaning of the complementary normalized response subject to a step change in oxygen partial pressure at the gas–liquid interface, τ is the dimensionless time, and B' describes the ratio of the rate of oxygen diffusion in the membrane to that in the test solution when they are exposed to the same oxygen partial pressure differences.

The function Γ (τ, B') as described in Eq. (19) can be determined by solving Eq. (23) numerically with a modified Laguerre method (11). Consequently, the absolute values of oxygen diffusion coefficients in pure water and in test materials can be determined by matching the experimentally obtained transient responses with those theoretically described in Eqs. (19)–(23). Because of a lateral diffusion of oxygen from the electrode solution reservoir to cathode surface, the polarographic electrode used in this study starts to show a significant difference between the upstep (from N_2 to air) response and the downstep (from air to N_2) response after about a 4% drop of Γ (1,12,13). To minimize the error caused by hysteresis of the upstep and downstep responses, it would be more meaningful to assess D_t by measuring the time required to reach a 3% drop of Γ. Figure 2 shows the

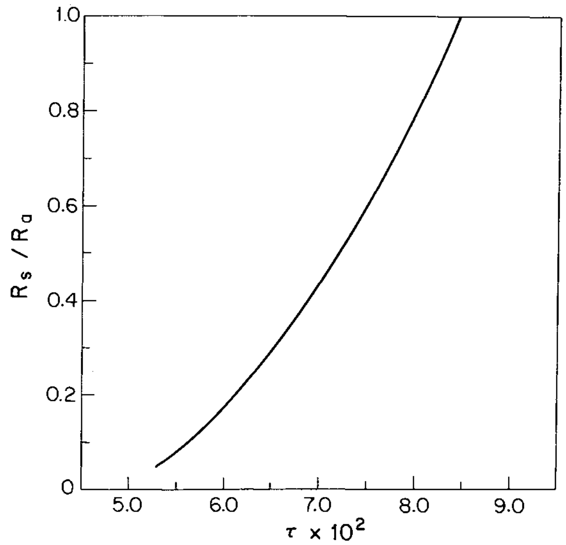

Fig. 2. The normalized steady-state readings of R_s/R_a as a function of the dimensionless time for a 3% drop of Γ under the assumption of linear profiles of oxygen partial pressure within the membrane.

relationship between R_s/R_a and τ. Incorporating the values of R_s/R_a as obtained from steady-state measurements with the results shown in Fig. 2, the oxygen diffusion coefficients in test materials can be determined. By coupling the determined oxygen diffusion coefficients with Eqs. (11) and (12) of the steady-state analysis, the relative oxygen solubility in test materials to that in pure water can then be determined.

EXPERIMENTAL APPARATUS AND PROCEDURE

Experiments were conducted in five hydrophilic ointments (similar to USP XXI hydrophilic ointment) (14) and four commercial 1% anthralin creams, at 22 ± 1°C and 1-atm pressure. The first set of ointments was prepared based upon USP XXI hydrophilic ointment with different amounts of petrolatum, mineral oil, and water, but the total amount of these three ingredients was maintained constant at 78.9%. The composition of the hydrophilic ointments (formulas 1–5) investigated in this experiment is listed in Table I. Experiments were designed to study the influence of different o/w phase–volume ratios on oxygen diffusion coefficients, permeabilities, and solubilities in conventional o/w ointments. Four other commercial 1% anthralin products were studied. These are Lasan HP-1 cream (Lot No. 041405, Stiefel Lab. Inc., Coral Gables, Fla.), 1% Westragel (Lot No. 16VX21, Westwood Pharmaceuticals Inc., Buffalo, N.Y.), 1% Anthraderm (Lot No. 38928, Dermik Lab Inc., Fort Washington, Pa.), and 1% Drithocreme (Lot No. JHB84, American Dermal Corp., Somerset, N.J.). Since these four commercial 1% anthralin products are prepared in different types of vehicle bases (see Table II), it is speculated that the modes of oxygen diffusion in these vehicles could be different.

A scheme of the experimental setup is shown in Fig. 3. The oxygen electrode is the YSI 5739 electrode manufactured by Yellow Springs Instrument Co., Yellow Springs, Ohio. This electrode has a gold cathode and a silver anode, using a half-saturated KCl solution plus Kodak Photo-Flo solution as the electrode solution. To avoid being poisoned, a 25.4-μm-thick FEP Teflon membrane was stretched over the measuring end of the electrode and was held tightly by an O-ring. The current drawn from the electrochemical reaction was translated to the oxygen partial pressure as percentage air saturation with a YSI Model 58 dissolved oxygen meter and was recorded with a Hewlett–Packard 7132A strip-chart recorder.

Table II. Commercial 1% Anthralin Products Used in the Study

Product name	Classification[a]
1% Westragel	O/W microemulsion gel
1% Drithocreme	O/W cream base
1% Anthraderm	Anhydrous petrolatum ointment base
1% Lasan HP-1	W/O cream base

[a] O/W, oil in water; W/O, water in oil.

As shown in Fig. 3, a thin layer of test material was introduced to the sample well over the membrane surface of the oxygen electrode. A three-way valve (Skinner Valve, New Britain, Conn.) which was controlled by an on/off controller was used for instantaneous switch between two gas streams, i.e., air and nitrogen streams, entering the diffusion cell. To prevent the water in the test sample from evaporating, both the air and the nitrogen gases were made saturated with water by passing through humidification bottles prior to entering the diffusion cell. Volumetric flow rates of the gas stream were kept constant at 0.2 liter/min. The gas stream velocity was estimated to be about 17 cm/sec at the mouth of the inlet gas sparger. Evidently, after expansion, the gas velocity over the sample surface will be smaller than this value. During the course of the experiments, no convection has been observed.

The thin sample layer in the diffusion cell was first equilibrated with moist air to obtain steady-state readings, R_s. Then a switch from the entering air to the nitrogen gas was made with the three-way valve. Oxygen dissolved in the test sample in the diffusion cell would either diffuse out through the sample layer or be consumed by electrochemical reactions until a new steady state was to be reached. The transient response of the oxygen electrode was obtained by continuously recording the readings of R during the unsteady-state period. The time for reaching a 3% drop of Γ was accurately measured with a stopwatch. Steady-state readings in moist air, R_a, and in nitrogen, R_f, were obtained by directly exposing the membrane surface to the entering gases.

To ensure that for each measurement the same thickness of test material was employed, the sample surface was flattened to the top of the sample well. With a micromanipulator having a precision of ±2 μm in the vertical direction, the sample layer thickness was repeatedly measured, and an

Table I. Phase–Volume Ratio (ϕ) of the Hydrophilic Ointments[a] Tested

Formula No.	% petrolatum	% water	$\phi = (V_o/V_w)$[b]
1	0	78.9	0.06
2	10	68.9	0.22
3	20	58.9	0.42
4	30	48.9	0.72
5	50	28.9	1.90

[a] The hydrophilic ointment contains white petrolatum and purified water (78.9%), propylene glycol (12%), stearyl alcohol (8.6%), sodium lauryl sulfate (0.1%), and preservatives (0.4%).

[b] V_o is the volume of the oil phase; V_w is the volume of the water phase.

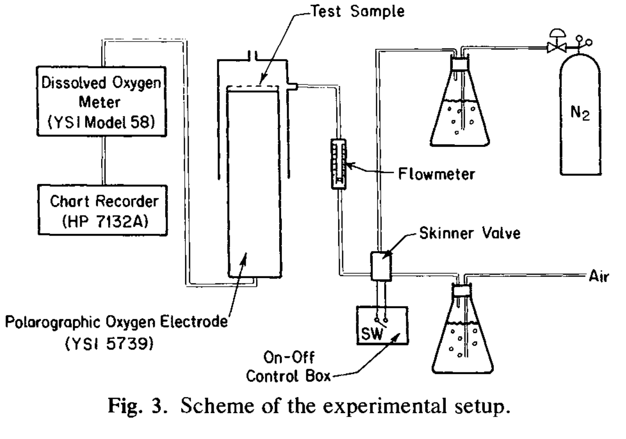

Fig. 3. Scheme of the experimental setup.

average value of 2520.7 μm was obtained. All experiments have been repeated two or three times to ensure reproducibility.

RESULTS AND DISCUSSION

The first set of experiments determined the diffusive transport of oxygen in five formulas similar to USP XXI hydrophilic ointments and the results are shown in Table I. As can be seen, formulas 1–5 differed only in the petrolatum concentration, while the other ingredients were kept constant. The second set of experiments determined oxygen diffusion coefficients of four commercial 1% anthralin products. Each product represents a typical vehicle base of creams commonly used in a topical dosage form.

The transient response curves, $R(t)/R_a$ vs t, and the normalized steady-state readings, R_s/R_a [the values of $R(t)/R_a$ at $t = 0$], determined based on the experimental procedure described under Experimental Apparatus and Procedures for the two sets of studies are shown in Figs. 4 and 5, respectively. Qualitatively speaking, the order of values of oxygen diffusion coefficient and permeability in these investigated systems is clearly illustrated. Numerical data on R_s/R_a and the time needed to reach a 3% drop of Γ, $t_{\Delta 3\%}$, for all these studied systems are further listed in Table III. Also shown in Table III are the results for oxygen diffusion coefficients in test systems, D_t, determined according to Fig. 2. The literature abounds with experimentally determined oxygen solubilities in pure water at different temperatures and pressures (15–17). By taking the published value of 1.298 × 10^{-3} mol/l atm as the oxygen solubility in water at 22°C and 1-atm pressure (18–20), the oxygen permeability in pure water, $D_w k_w$, can be calculated. Accordingly, the oxygen permeabilities, $D_t k_t$, for other test systems can be determined by using Eq. (12) with $d_t/d_w = 1$, and the results are listed in Table III. By dividing the values of $D_t k_t$ by those of D_t, oxygen solubilities in the test systems can be easily obtained as shown in Table III.

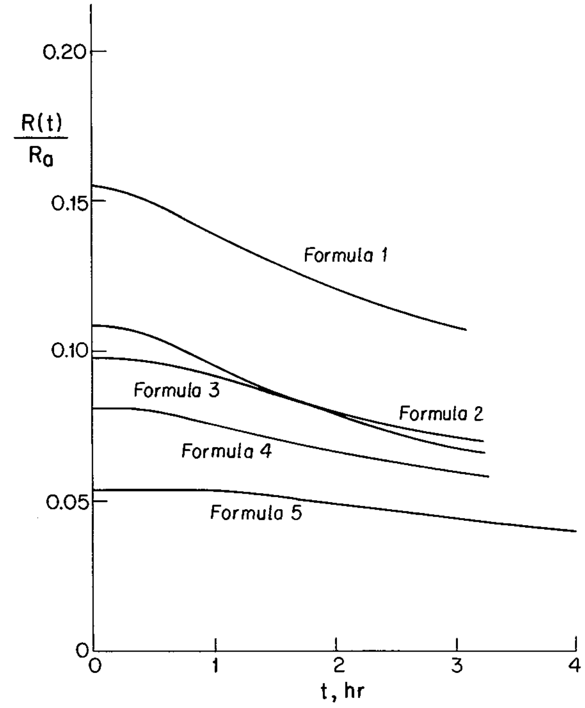

Fig. 4. The transient response curves, $R(t)/R_a$ vs t, of formulas 1–5.

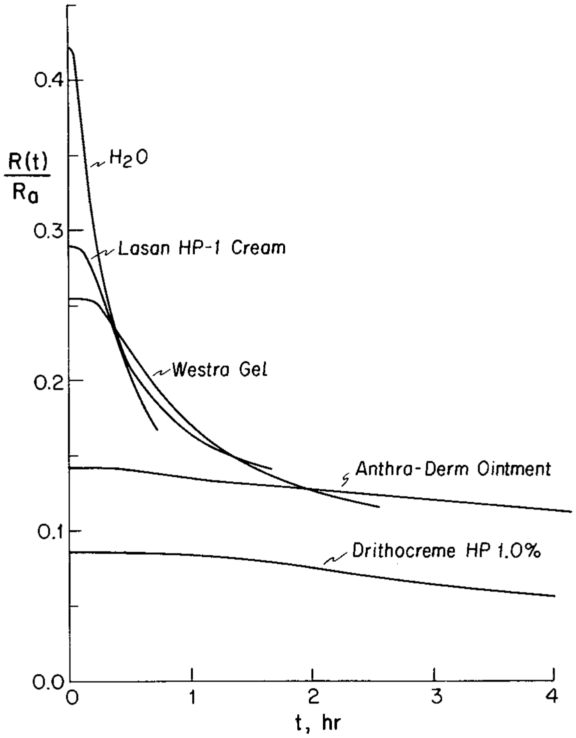

Fig. 5. The transient response curves, $R(t)/R_a$ vs t, of four commercial 1% anthralin products.

Literature values of the oxygen diffusion coefficient in pure water at 25°C have been summarized by Goldstick and Fatt (10) and St. Dennis and Fell (21). Values were found to scatter from 1.87 to 2.60 × 10^{-5} cm²/sec, with a mean of 2.2 × 10^{-5} cm²/sec. The current experimental results for the oxygen diffusion coefficient at 22°C, i.e., 2.09 × 10^{-5} cm²/sec, compares very well with this reported value and values of 2.11 and 2.14 × 10^{-5} cm²/sec obtained in the previous studies (1,2). This lends good support to the reliability and accuracy of the present method and the results obtained in the study.

The oxygen diffusion coefficients in formulas 1–5 in the first set of experiments are illustrated in Fig. 6 by plotting the values of D_t against the petrolatum concentrations in these ointments. A linear decrease in oxygen diffusion coefficients with increased petrolatum concentrations has been observed. This is reasonable because oxygen diffusion is generally poorer in highly viscous, semisolid petrolatum than it is in pure water.

Figure 7 shows the results of the relative oxygen permeabilities, $D_t k_t / D_w k_w$, in these investigated systems against the petrolatum concentrations. The correlation is shown to be a semilog correlation. Similarly to these a semi-log correlation of oxygen permeability with solute concentration has been found in aqueous electrolyte solutions (1).

Since the values of oxygen solubility are further derived from those of the oxygen diffusion coefficient and permeability, diminished accuracy in experimental results of ox-

Table III. Experimental Results for Oxygen Diffusion Coefficient, Permeability, and Solubility in the Investigated Systems

Test material	R_s/R_a (−)	$t_{\Delta 3\%}$ (sec)	$D_t \times 10^6$ (cm^2/sec)	$D_t k_t \times 10^9$ (mol cm^2/l sec atm)	$k_t \times 10^3$ (mol/l atm)
H_2O (N = 4)	0.4210 ± 0.0095	208.55 ± 5.30	20.90 ± 0.53	27.13	1.30
Formula 1 (N = 3)	0.1550 ± 0.0038	1512.0 ± 45.20	2.47 ± 0.07	6.84	2.77
Formula 2 (N = 2)	0.1085 ± 0.0030	1712.8 ± 55.50	2.10 ± 0.07	4.54	2.16
Formula 3 (N = 3)	0.0977 ± 0.0025	2415.5 ± 70.45	1.47 ± 0.04	4.04	2.75
Formula 4 (N = 2)	0.0810 ± 0.0025	2482.4 ± 83.70	1.40 ± 0.05	3.29	2.35
Formula 5 (N = 2)	0.0538 ± 0.0018	5180.1 ± 209.90	0.65 ± 0.03	2.12	3.26
Lasan HP-1 cream (N = 3)	0.2889 ± 0.0065	527.05 ± 14.85	7.79 ± 0.22	1.59	0.20
Westragel (N = 2)	0.2543 ± 0.0071	946.50 ± 31.70	4.25 ± 0.14	1.27	0.30
Anthraderm ointment (N = 2)	0.1420 ± 0.0040	2624.0 ± 113.85	1.29 ± 0.06	6.18	4.79
Drithocreme HP 1.0% (N = 2)	0.0860 ± 0.0029	4248.0 ± 208.15	0.83 ± 0.04	3.51	4.25

ygen solubility is expected. As shown in Table III, no clear trend of variation can be deduced from the experimental data of oxygen solubilities in formulas 1–5. However, values higher than that of pure water are found in all of the investigated systems. Also, a significant difference of the solubility values was found between formula 1 (ϕ = 0.06) and formula 5 (ϕ = 1.90). Obviously, this is dependent upon the volume of the organic phase present in these ointments.

In the second set of experiments, four 1% anthralin products were evaluated using the same method. These products represent four typical vehicle bases commonly used in topical administration: 1% Drithocreme (o/w cream), 1% Westragel (o/w microemulsion gel), 1% Lasan HP-1 (w/o cream), and 1% Anthraderm (anhydrous petrolatum ointment). According to the solubility of anthralin (less than 0.2%), the majority of anthralin in these products is considered to be in a suspension form. And the oxygen consumption due to the solid anthralin can be reasonably assumed to be negligible. The diffusive transport of oxygen in these products is therefore solely dependent upon the vehicle bases.

As can be seen in Table III and Fig. 5, 1% Lasan HP-1 showed the highest oxygen diffusion coefficient at 7.79 × 10^{-6} cm^2/sec, followed by 1% Westragel at 4.25 × 10^{-6} cm^2/sec, 1% Anthraderm at 1.29 × 10^{-6} cm^2/sec, and finally, by 1% Drithocreme at 0.83 × 10^{-6} cm^2/sec. Without knowing the major differences among these creams other than their dosage form, we are not able to make further predictions about the oxygen diffusion processes in these creams. However, the higher values of the calculated oxygen solubility in 1% Drithocreme and Anthraderm reveal their higher oil-phase concentrations as compared to the 1% Lasan HP-1 and Westragel. This further confirms the qualitative trend found in our first set of experiments with ointments of different o/w phase–volume ratios, i.e., the oxygen diffusion coefficient decreases with an increase in the oil-phase concentration in the formulations.

CONCLUSION

From the data generated in this study, it is suggested that Ju and Ho's method of determining the diffusive transport of oxygen is applicable to these pharmaceutical dosage forms. It is believed that the method can also be applied to other semisolid dosage forms, i.e., suspensions, emulsions, and syrups intended for other administration routes. The data also suggested that the diffusive transport of oxygen in semisolid dosage forms is determined not only by the type of the vehicle bases, i.e., o/w creams, o/w microemulsions, w/o creams, or anhydrous bases, but also by the concentration of the oil phase in the formulations. The higher the concentration of the oil phase, the lower the diffusion rate. On the

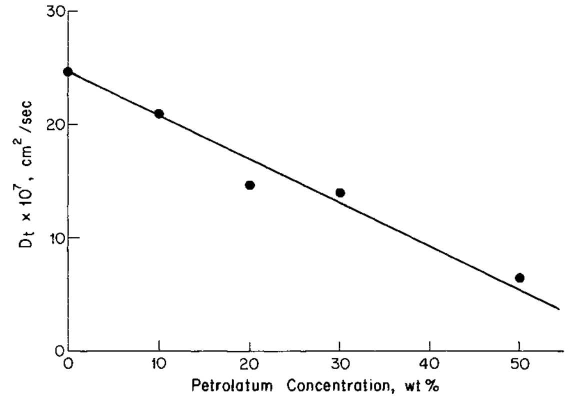

Fig. 6. Values of D_t as a function of the petrolatum concentrations in USP XXI hydrophilic ointment.

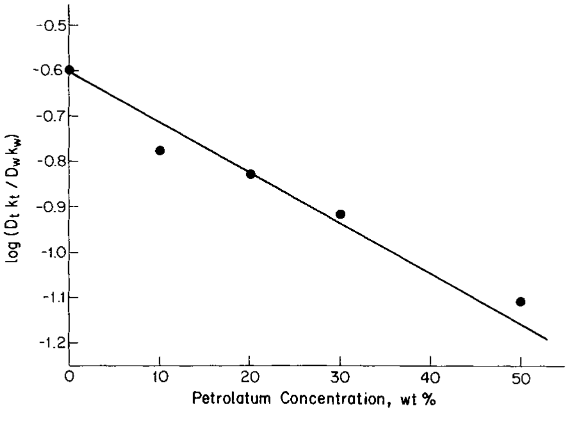

Fig. 7. Values of log $(D_t k_t / D_w k_w)$ as a function of the petrolatum concentrations in USP XXI hydrophilic ointment.

other hand, the oxygen solubilities in these test systems seem to show a reverse trend. Higher oxygen solubilities were usually found in dosage forms with higher oil-phase contents. This study suggests a practical methodology for the determination of the diffusive transport of low molecular weight gases in pharmaceutical solutions and semisolids. The technique described above should allow scientists to have a better grasp on the basic information about the vehicle base itself. It is believed that the information on oxygen diffusive activity could then be used as a reliable criterion for formulation selection and processing design.

NOMENCLATURE

A	A proportionality constant in Eq. (1)
B	A dimensionless parameter as defined in Eq. (18), cm^{-1}
B'	A dimensionless parameter defined in Eq. (22) $(=B\,d_t)$
C_{O_2}	Oxygen concentration, mol/l
D	Oxygen diffusion coefficient, cm^2/sec
d	Thickness, cm
k	Oxygen solubility, mol/l atm
p_m	Oxygen permeability in the membrane
p	Oxygen partial pressure, atm
R	The reading of the oxygen electrode, %
t	Time, sec
$t_{\Delta 3\%}$	Time needed to reach a 3% drop of Γ, sec
x	Distance from the inside surface of the membrane, cm
x'	Distance from the outside surface of the membrane $(=x - d_m)$, cm
Γ	Complementary normalized transient response of the reading of the oxygen electrodes
τ	Dimensionless time $(=D_t t/d_t^2)$
ξ_n	Positive roots of Eq. (23)

Subscripts

a	Air
f	Nitrogen
m	Membrane
w	Water
s	Steady state
t	Test material
o	Oil

REFERENCES

1. C. S. Ho, L. Ju, R. F. Baddour, and D. I. C. Wang (submitted for publication, 1987).
2. M. N. Özisik. *Heat Conduction,* Wiley-Interscience, New York, 1980, Chap. 2.
3. S. Aiba, M. Ohashi, and S. Y. Huang. *Ind. Eng. Chem. Fund.* 7:497–502 (1968).
4. F. G. Heineken. *Biotech. Bioeng.* **13**:599–618 (1971).
5. V. Linek and V. Vacek. *Biotech. Bioeng.* **18**:1537–1555 (1976).
6. K. Akita. *Ind. Eng. Chem. Fund.* **20**:89–94 (1981).
7. R. W. Pittman. *Nature* (*Lond.*) **195**:449–451 (1962).
8. C. E. W. Hahn, A. H. Davis, and W. J. Albery. *Resp. Physiol.* **25**:109–133 (1975).
9. D. G. Maclennan and S. J. Pirt. *J. Gen. Microbiol.* 45:289–302 (1966).
10. T. K. Goldstick and I. Fatt. *Chem. Eng. Prog. Symp. Ser.* **66**:101–113 (1970).
11. M. L. James, G. M. Smith, and J. C. Wolford. *Applied Numerical Methods for Digital Computations with Fortran and CSMP,* 2nd ed., IEP, New York, 1977, Chap. 6, pp. 6.5–6.11.
12. A. A. Benedeck and W. J. Heideger. *Water Res.* 4:627–640 (1970).
13. V. Linek, P. Benes, and V. Vacek. *J. Electroanal. Chem.* **169**:233–257 (1984).
14. *The United States Pharmacopeia XXI,* U.S. Pharmacopoeial Convention, Rockville, Md., 1980.
15. G. A. Truesdale, A. L. Downing, and G. F. Lowden. *J. Appl. Chem.* 5:53–62 (1955).
16. H. Hikita, S. Asai, and Y. Azuma. *Can. J. Chem. Eng.* **56**:371–374 (1978).
17. L. A. Baburin, J. E. Shvinka, and U. E. Viesturs. *European J. Appl. Microbiol. Biotech.* 13:15–18 (1981).
18. A. Seidell. *Solubilities of Inorganic and Metal-Organic Compounds, Vol. II,* Van Nostrand, New York, 1958.
19. R. Battino and H. L. Clever. *Chem. Rev.* **66**:395–463 (1966).
20. Yellow Springs Instrument Co. *YSI Model 58 Dissolved Oxygen Meter Instruction Manual,* Yellow Springs, Ohio, 1981.
21. C. E. St. Dennis and C. J. D. Fell. *Can. J. Chem. Eng.* **49**:885 (1971).