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Percutaneous Absorption Studies of Chloramphenicol Solutions

ARMANDO J. AGUIAR and MICHAEL A. WEINER

Abstract □ An *in vitro* method for measuring the percutaneous absorption of chloramphenicol solutions is described. The apparatus consists essentially of thermostated upper and lower chambers fabricated from methyl methacrylate, with the membrane sandwiched between the chambers. The upper chamber holds the solution containing the drug. The lower chamber allows for a continuous flow of solution which washes away the permeated drug. The two membranes investigated were a filter membrane saturated with peanut oil and a segment of skin obtained from hairless mice. The effect of varying concentrations of surfactants and of propylene glycol on the permeation of chloramphenicol through the barriers is shown. The activation energies for permeation and diffusion of the drug through the filter membrane and for permeation through the skin are evaluated. The partition coefficient is estimated.

Keyphrases □ Chloramphenicol solutions—percutaneous absorption □ Percutaneous absorption—apparatus, *in vitro* determination □ Diagram—*in vitro* percutaneous absorption apparatus □ Sodium lauryl SO_4-effect—chloramphenicol absorption □ UV spectrophotometry—analysis

The vast amount of work carried out in the past on percutaneous absorption has largely dealt with attempts to identify and understand the structure and physicochemical properties of the barrier zone of the skin (1–4), to evaluate factors such as the influence of temperature and hydration on the percutaneous absorption process (5–7), and to study the mechanisms of absorption (8, 9). Other studies (10–12) have been concerned with the relative importance of the transepidermal *versus* the transfollicular routes of diffusion of chemicals through the skin. There have also been studies on the role which topical vehicles play in facilitating or hindering the passage of drugs through the skin (13–15).

There appear to be, however, few studies or techniques which can be used routinely to observe the role which a particular component in a heterogeneous topical vehicle will play on the overall percutaneous absorption of a drug. There are also very few studies dealing with the energies involved in the percutaneous absorption process. The lack of these studies can be partly related to the difficulties of routinely setting up percutaneous absorption studies, and possibly also due to the emphasis given to other factors during the development of a topical vehicle or pharmaceutical product. The emphasis has generally been placed on the compatibility, stability, and appearance of the product, rather than on the influence which the components in the vehicle may have on enhancing or hindering the movement of the drug through the skin.

The present communication is concerned with a relatively easily adaptable dynamic *in vitro* method for measuring percutaneous absorption. Two barriers are evaluated, and the effect of varying the concentrations of surfactants and propylene glycol on the transport of chloramphenicol solutions is demonstrated. The energies involved in the permeation and diffusion processes are measured. A future communication will deal with a correlation of absorption through these barriers with that of excised human skin.

EXPERIMENTAL

Barriers—Whole skin sections stripped from the back and abdomen of male hairless mice[1] were used. The mice with skins clear of lesions and weighing 15–18 g. were sacrificed and the skin removed surgically without injury. The skin was immersed in Ringer's solution and used within 30 min. after removal.

The hairless mice have been used by others in the evaluation of topically applied compounds and have proven to be (16) unusually well adapted for experimentation with topical compounds. It is a healthy animal, and since the skin has no hair, it requires no depilation or shaving process, which often damages the skin. It was also found that the thickness of the skin of animals within a weight range did not vary significantly. There are, however, certain specific

[1] Type HR/HR, Jackson Laboratories, Bar Harbor, Maine.

differences between the mouse and human skin. It has been shown (17) that the epidermal layer is one to three cells thick and is approximately one-third the thickness of the human epidermis. The differences in the thickness would lead to a proportionately faster drug absorption through the mouse than human skin, since cutaneous permeability is thought to be governed by epidermal components (18). The absence of hair also eliminates the transfollicular pathway of absorption, and hence the initial permeation rate will also be different

The synthetic membranes used were prepared from filter membranes[2] impregnated with peanut oil USP. To assure complete wetting of the membrane by the oil, the impregnation was carried out by placing the membrane in a fine-porosity sintered-glass funnel, adding 50 ml. of peanut oil, and drawing a slow vacuum for 30 min. to pull the oil through the membrane. The saturated oil membranes were then immersed in peanut oil and maintained until use.

Materials—The chloramphenicol[3] solutions used in the study at a concentration of 1 mg./ml. were prepared from a single commercial lot of the drug. The polysorbate 80 USP[4] and the propylene glycol USP were used as purchased. The Ringer's solution NF was prepared from reagent grade chemicals. To prevent osmotic flow, the composition and ionic strength of the solutions bathing the two faces of membrane were identical, except for the presence of the drug on the ingoing side of the membrane.

Equipment—Figure 1 is a schematic diagram of the equipment used in the permeation studies. The system consists essentially of a constant-temperature bath (A), jacketed solution reservoir (B), plastic permeation cell (C), polytetrafluorethylene[5] stopcock (F) to control the flow of solutions washing the dermal side, and graduated centrifuge tubes (G) located in a fraction collector.[6]

The permeation cell (Fig. 2) manufactured from methyl methacrylate[7] consisted of two water-jacketed halves. The chambers (A and B) (2.5 cm. deep and 3.3 cm. in diameter) were constructed to hold 25 ml. of solution. The upper chamber A, held the drug solution on the epidermal side of the skin. The solution in this chamber was stagnant during the trial. The solution from the jacketed reservoir was allowed to flow in the lower chamber, washing the diffused drug from the dermal side into the tube located in the fraction collector. The solution in the lower chamber (dermal side) was stirred slowly with a magnetic bar (C) to provide good mixing. The membrane (G) was held and sealed between two rubber O-rings (F) and was supported by two 20-mesh stainless steel screens (J). The screens prevented a bowing out of the membrane during the course of the experiment.

Methodology—For a typical experimental run, the magnetic stirring bar was placed in Chamber B, and the screen and O-ring placed on the top. The membrane was then placed in position (with the epidermal side up in the case of the skin) so that it covered the O-ring completely, stretching it if necessary to insure that it overlapped the O-ring by about 1 cm. all around. The second stainless steel screen was placed carefully over the membrane and centered. The upper cell half with the second O-ring in place was then carefully positioned over the lower half and bolted in place. The assembled cell was then connected to the constant-temperature bath and to the reservoir B (Fig. 1). The solution from the reservoir was allowed to flow to bathe the lower side of the membrane. The flow was cut off when the solution reached the dropping stopcock. With the aid of a 50-ml. syringe and cannula, the upper chamber was then filled with the drug solution.

The flow of the solution from the reservoir B was adjusted to deliver 1 ml./min. The fraction collector was set to change tubes at 15-min. intervals. A typical experimental run was carried out for 4 hr., and the membrane was considered to be viable for this period of time.

Analysis—At the completion of the run, the volume in each centrifuge tube was measured, and an aliquot assayed spectrophotometrically[8] at 278 mμ for chloramphenicol.

[2] Millipore filter membranes, type GS (0.22 μ pore size, 47 mm. diameter) Millipore Filter Corp., Bedford, Mass.
[3] Marketed as Chloromycetin, Parke, Davis & Co., Detroit, Mich.
[4] Marketed as Tween 80, Atlas Chemical Industries, Wilmington, Del.
[5] Teflon, E. I. du Pont de Nemours & Co., Wilmington, Del.
[6] Chromatographic fraction collector with timer, model No. 1205A, Research Specialties Co., Richmond, Calif.
[7] Plexiglas,
[8] Beckman DU-2 spectrophotometer, Beckman Instruments, Inc., Fullerton, Calif.

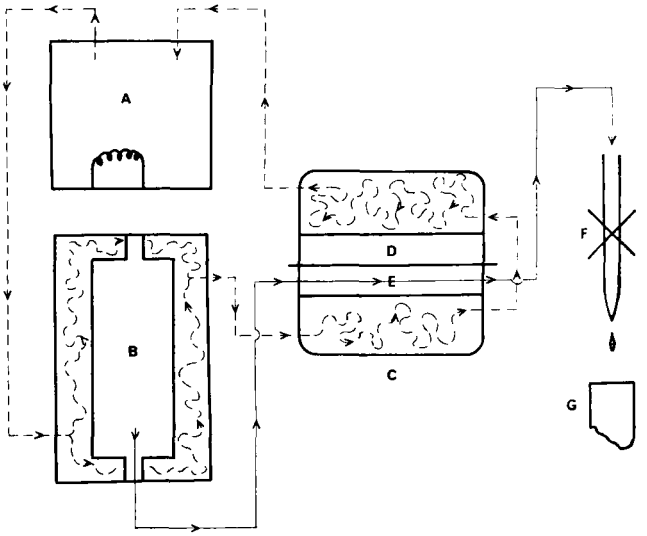

Figure 1—*Schematic diagram of system used for permeation trials: A, water bath with thermostated heater; B, jacketed solution reservoir; C, permeation cell; D, cell upper half; E, cell lower half; F, dropping stopcock; G, tube for collecting sample. The solution flows from the reservoir B, into the lower chamber of the cell C, washing the dermal side of the membrane, into the stopcock F, and is collected in the test tube G located in the fraction collector.*

THEORETICAL CONSIDERATIONS

The permeation of a drug from a solution into and out of the barrier (skin) involves a series of processes (19). Initially the drug partitions between its carrying medium and the exposed surface layer of the barrier. This is followed by diffusion through the barrier. The diffusion also takes place in two steps. The first one is the establishment of a uniform concentration gradient of the drug across the barrier, and the second is the constant uniform diffusion of drug through the barrier after the uniform concentration gradient has been established.

The factors controlling the rate of permeation of a drug through a membrane can be examined by reference to Fick's general law of diffusion which, in essence, states that the driving force which causes the transfer of a substance from regions of high to regions of low concentration is proportional to the concentration gradient. Fick's law (20) is commonly written as follows:

$$dq/dt = -D(dc/dx) \qquad \text{(Eq. 1}$$

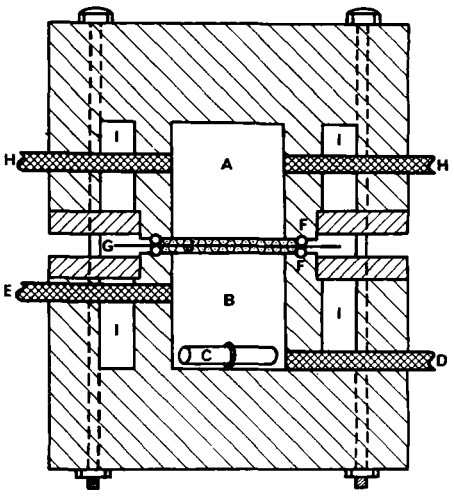

Figure 2—*Detail of permeation cell: A, upper chamber; B, lower chamber; C, magnetic stirring bar; D, lower chamber inlet tube; E, lower chamber outlet tube; F, rubber O-rings; G, membrane; H, upper chamber access tubes; I, water jacketing (note: tubing set-up for water jacketing is not shown on the drawing); J, stainless steel screens.*

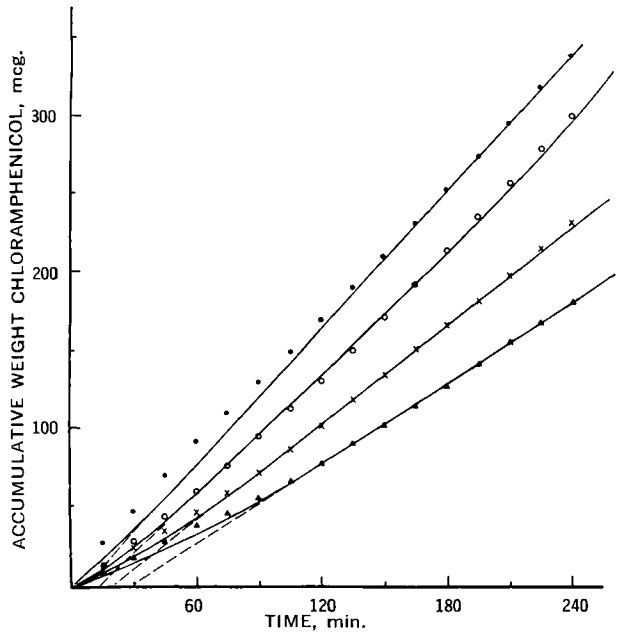

Figure 3—*Plot showing the effect of temperature on the permeation of chloramphenicol (1 mg./ml.) through the filter barrier. Key: ▲, 37°; ×, 45°; ○, 50°; ●, 55°.*

where q represents the amount of a substance diffused, c the concentration of the diffusing drug, t the time of diffusion, and x the diffusion path. D (the diffusion coefficient) is a constant defined by the amount of drug diffusing across unit area per unit time when $(dc)/(dx) = 1$.

Although Fick's law is applicable in experimental situations where a uniform concentration gradient has been established, *i.e.*, in steady-state situations, the steady state is often difficult to achieve experimentally. One then uses (19) the concept of a quasi-steady state. This concept allows treatment of those cases which nearly meet steady-state requirements; *i.e.*, situations where the concentration gradient changes only slightly with time.

Based on a mathematical analysis by Daynes (21), Barrer (22) devised a suitable method of evaluating permeability, diffusivity, and partition coefficients. A barrier is mounted in a diffusion cell and the permeation velocity is determined in the steady state as well as the rate at which that state is approached. The concentration or pressure on the ingoing side of the membrane is constant and is always much greater than that on the outgoing side.

The amount diffusing through is plotted against time. In most cases, these curves emerge from the abscissa with a very small slope which continues over a period of time; the curve then gradually bends upwards and continues as a long straight line. There is an interval before the steady state can be approached due to finite diffusion velocity of the solute (or drug) within the membrane. Provided Fick's law is valid for the transport process, the intercept L made by the asymptotic curve on the axis of time is given by

$$L = \frac{h^2}{D(C_1 - C_2)}\left(\frac{C_1}{6} + \frac{C_2}{3} - \frac{C_0}{2}\right) \qquad \text{(Eq. 2)}$$

for a membrane of thickness h, where C_1 and C_2 are the concentrations of the drug within the ingoing side and outgoing side of the membrane, respectively, and C_0 is the initial uniform concentration of the drug in the membrane. Provided C_0 is zero and C_2 is much less than C_1, and also the diffusion coefficient is independent of concentration of the drug in the barrier then

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

where L is the lag time. Knowing the lag time, the diffusion coefficient D can be calculated using Eq. 3. The apparent permeability constant P can be calculated from the slope of the line obtained by plotting amount *versus* time, and, using the relation $P = -DS$, the solubility or partition coefficient S can be determined.

When dealing with biological membranes such as the skin, it is difficult to measure the thickness h of the membrane. Equation 1 can then be rewritten (23) as

$$\frac{dq}{dt} = \frac{ADS(C_1 - C_2)}{h} \qquad \text{(Eq. 4)}$$

where $(dq)/(dt)$ = rate of movement of solute in mg./min.; A = area of the membrane in cm.^{2}; D = diffusion coefficient; S = partition coefficient; C_1 = concentration of drug on the ingoing (epidermal) side; C_2 = concentration of drug on the outgoing (dermal) side.

Substituting P, the permeability constant, for DS, Eq. 4 can then be rewritten as

$$\frac{dq}{dt} = \frac{AP(C_1 - C_2)}{h} \qquad \text{(Eq. 5)}$$

For a constant thickness, h can be combined with the permeability constant P to give a new constant P_1, the apparent permeability constant, and Eq. 5 can then be rewritten as

$$\frac{dq}{dt} = P_1A(C_1 - C_2) \qquad \text{(Eq. 6)}$$

If $C_1 \gg C_2$, Eq. 6 reduces to

$$\frac{dq}{dt} = P_1AC_1 \qquad \text{(Eq. 7)}$$

If the permeability rate follows Eq. 7, a plot of amount *versus* time should be linear after the quasi-steady state is reached. The slope of the line is equal to $(dq)/(dt)$ and since the other values in Eq. 7 can be easily measured, the apparent permeability constant P_1 can be determined.

RESULTS AND DISCUSSION

Figure 3 shows typical plots of the amount of chloramphenicol permeating as a function of time through the filter membrane impregnated with peanut oil. Each plot shows a lag time followed by a straight line in accordance with the quasi-stationary state concept discussed previously. The variations in the slopes and lag time of similar plots in different determinations were found to be less than 4%. The variations could be ascribed mainly to the difficulties encountered in setting the same flow rate each time from the reservoir through the lower chamber.

The usefulness of measurements such as the one shown in Fig. 3 is related to the postulate that the permeation of a drug through a biological membrane is dependent on the lipoidal solubility of the drug moiety. Since the chloramphenicol molecule is a neutral one, the permeation is not complicated by charge effects and is dependent mainly on the partition coefficient of the drug between the aqueous environment and the lipoidal phase of the barrier.

Some indication of the relative energies involved for the transfer of the drug through barriers such as the ones used in the study is obtained from measurements of the activation energy for the diffusion, permeation, and partition.

Working with permeation of gases through membranes, Barrer (20) showed conclusively that the permeation of a molecule of a gas through a barrier requires an energy of activation to make the molecule enter one face of the barrier and move along a certain path to the other face. He has expressed the phenomenon in an Arrhenius-type equation as follows

$$P = P_0e^{-(EP/RT)} \qquad \text{(Eq. 8)}$$

where P is the permeability constant, P_0 is a factor independent of temperature and proportional to the number of molecules that are available to enter the structure and to the probability that a molecule having a sufficient energy will actually enter the structure. E_p is the energy of activation for permeation, R is a gas constant, and T the absolute temperature.

The equation for temperature dependence of diffusion is also given by an Arrhenius-type equation and can be written as

$$D = D_0e^{-(ED/RT)} \qquad \text{(Eq. 9)}$$

where D is the diffusion coefficient, D_0 is a constant independent of

Table I—Permeability and Diffusion Coefficients of Chloramphenicol Solutions Through the Filter Membrane Saturated with Oil at Various Temperatures

Temp., °C.	$1/T$, °K.	P, cm. min.$^{-1}$	Lag Time, min.	D, cm.^{2} min.$^{-1}$
37	0.00322	0.95×10^{-4}	30	1.09×10^{-6}
45	0.00314	1.17×10^{-4}	19	1.72×10^{-6}
50	0.00310	1.35×10^{-4}	14	2.34×10^{-6}
55	0.00305	1.56×10^{-4}	10	3.27×10^{-6}

temperature or the diffusion coefficient at absolute zero, and E_D is the energy of activation for diffusion.

If P behaves as Eq. 8 and D behaves as Eq. 9 and since $P = -DS$ it is necessary that the partition coefficient exhibit the same functional variation with temperature. Hence it would require that

$$S = S_0 e^{-(\Delta H/RT)} \qquad \text{(Eq. 10)}$$

where S_0 is a constant, and ΔH is the heat of solution in the membrane which is related to the partition coefficient.

The concepts developed by Barrer can be extended in an analogous manner to the permeation of chloramphenicol in solution. The variation of the diffusion and permeability coefficients of chloramphenicol through the filter membrane saturated with peanut oil was determined by carrying out experiments at 37, 45, 50, and 55°. The results are summarized in Fig. 3, which shows the progressive increase in the permeation rate with increase in temperature. The plot also shows that the lag time decreases progressively as the temperature increases, and, therefore, the diffusion coefficients calculated from Eq. 3 should also increase. The thickness h of the membrane, measured with a micrometer caliper was found to be 0.014 cm.

The permeability and the diffusion coefficients calculated from the data presented in Fig. 3 are summarized in Table I.

The apparent activation energies for permeation and diffusion of chloramphenicol through the filter membrane were calculated from the slope of plots of the logarithm of permeation and diffusion coefficients *versus* the reciprocal of absolute temperature shown in Fig. 4. The apparent activation energy for permeation of chloramphenicol through the membrane was found to be 5,800 cal./mole and the apparent activation energy for diffusion was found to be 13,400 cal./mole. By difference the apparent heat of solution was found to be 7,600 cal./mole, a very reasonable value.

It is interesting to speculate on the relationships between the apparent activation energies involved for the permeation and diffusion processes. As the activation energies derived from an Arrhenius-type equation involve the concept of the probability of a molecule accruing enough energy to overcome a barrier, the smaller apparent activation energy for permeation *versus* that for diffusion must involve the partition coefficient. It is reasonable to assume from the relative magnitude of the energies involved that the solubility has a negative temperature dependence as shown in Fig. 5. The greater temperature dependence of the diffusion coefficient *versus* that of the permeability coefficient is also evident from Table I. It is apparent that the diffusion coefficient changes much more rapidly as the temperature increases than does the permeability function.

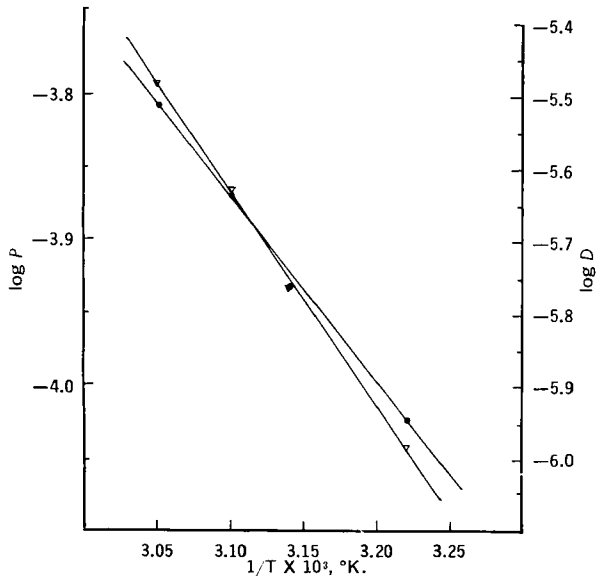

Figure 4—*Arrhenius-type plot for permeation and diffusion of chloramphenicol through the filter membrane saturated with peanut oil. Key: ●, permeation coefficient; ▽, diffusion coefficient.*

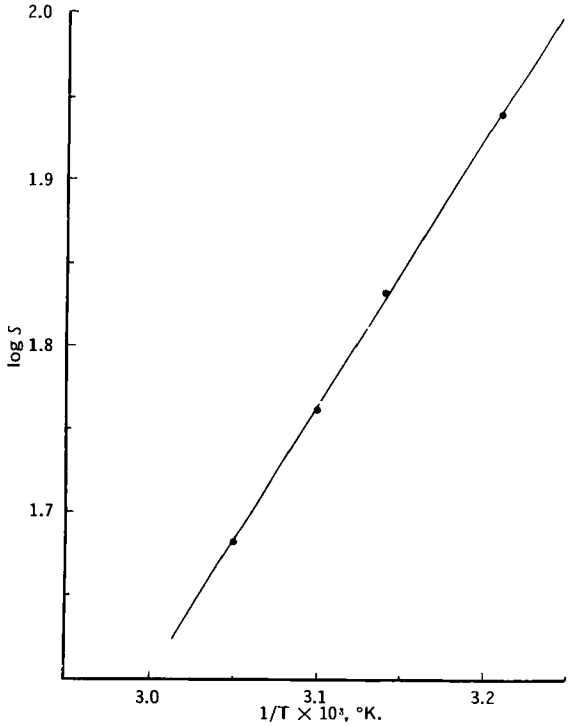

Figure 5—*Arrhenius-type plot showing negative temperature dependence of partition coefficient of chloramphenicol in the filter membrane saturated with peanut oil.*

The effect of temperature on the permeation of chloramphenicol through the skin of hairless mice is shown in Fig. 6. The apparent absence of lag time in these plots can perhaps be ascribed to the small thickness of the stratum corneum of the skin. It is also conceivable that the experimental procedure used in the study is not sufficiently sensitive to measure the drug which has permeated through the barrier before the apparent steady-state condition is established.

The permeation coefficients calculated from the slopes of the lines in Fig. 6 are summarized in Table II.

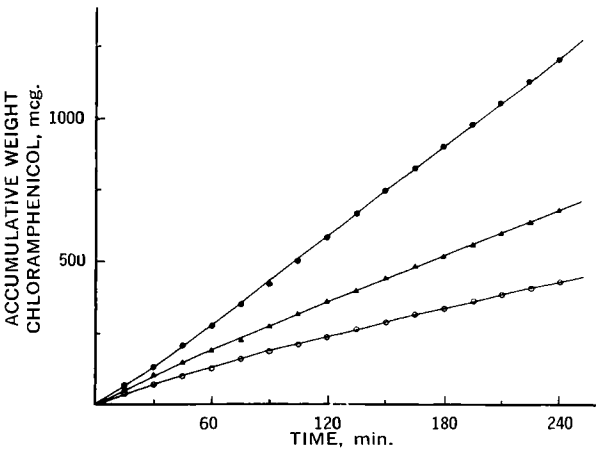

Figure 6—*Plot showing the effect of temperature on the permeation of chloramphenicol (1 mg./ml.) through the skin of hairless mice. Key: ○, 31°; ▲, 37°; ●, 45°.*

Table II—Permeability Coefficients of Chloramphenicol Solution Through the Skin of Hairless Mice at Various Temperatures

Temp., °C.	1/T, °K.	P, cm. min.$^{-1}$
31	0.00329	1.87×10^{-4}
37	0.00322	3.01×10^{-4}
45	0.00314	6.20×10^{-4}

From the slope of a plot of the logarithm of the permeation coefficient *versus* the reciprocal of the absolute temperature, shown in Fig. 7, the apparent activation energy for permeation was found to be 15,900 cal./mole.

The addition of 0.2% sodium lauryl sulfate to the solution significantly affected the permeation rate of chloramphenicol through the filter membrane saturated with peanut oil. The marked increase in permeation shown in Table III and Fig. 8 can possibly be ascribed to the influence which the surfactant has on the membrane. It appears that the presence of surfactant changes either the physical surface of the membrane or influences the partition coefficient by lowering the interfacial tension of the lipoidal surface. The presence of sodium lauryl sulfate also changes the temperature dependence of

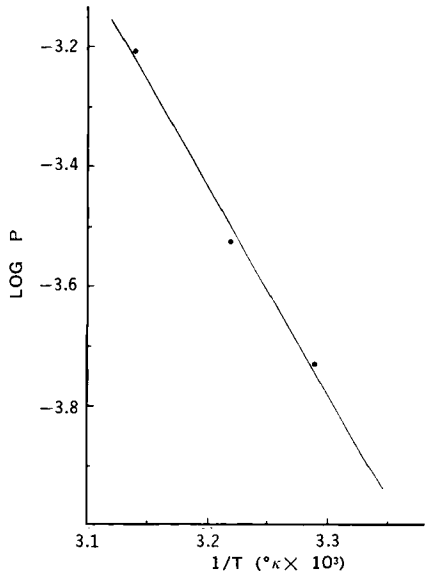

Figure 7—*Arrhenius-type plot for permeation of chloramphenicol through the skin of hairless mice.*

permeation as is evident from the data. It appears that the surfactant lowers the activation energy needed for the molecules to cross the barrier; therefore, raising the temperature has little effect on the permeation rate.

The effect of adding sodium lauryl sulfate on the permeation rates of chloramphenicol through the skin of hairless mice is summarized in Table IV and Fig. 9. At a concentration of 0.2% of the surfactant, which is slightly above the critical micelle concentration, the permeation rate was found to be about twice as fast as that without surfactant. Increasing the concentration of sodium lauryl sulfate to 0.4% increases the rate only sightly more than that seen with the 0.2% concentration.

It seems that two factors are involved in the relationship between

Table III—Effect of Sodium Lauryl Sulfate on Permeation of Chloramphenicol (mg./ml.) Solutions Through Filter Membrane Saturated with Peanut Oil

Temp., °C.	Concn. of Sodium Lauryl Sulfate, %	Permeability Coeff., cm. min.$^{-1}$
37	0	0.095×10^{-3}
37	0.2	0.663×10^{-3}
45	0.2	0.651×10^{-3}

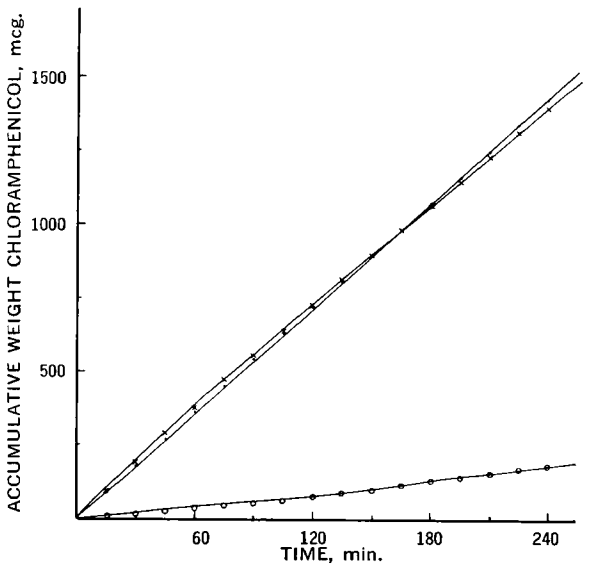

Figure 8—*Plot showing the effect of the addition of sodium lauryl sulfate on the permeation of chloramphenicol (1 mg./ml.) through the filter barrier. Key: ○, control at 37°; ●, 0.2% sodium lauryl sulfate at 37°; ×, 0.2% sodium lauryl sulfate at 45°.*

the presence of sodium lauryl sulfate and the permeation rate of chloramphenicol through the skin of hairless mice. At concentrations below the critical micelle concentration, it is conceivable that the surfactant lowers the activity of the drug by complexation or other interactions. As the critical micelle concentration is approached and passed, less of the surfactant is available for com-

Table IV—Effect of Various Concentrations of Sodium Lauryl Sulfate on the Permeation Rate of Chloramphenicol Through the Hairless Mice Skin at 37°C.

Concn. of Sodium Lauryl Sulfate, %	Permeability Coeff., cm. min.$^{-1}$
0	0.682×10^{-3}
0.02	0.298×10^{-3}
0.20	1.252×10^{-3}
0.40	1.455×10^{-3}

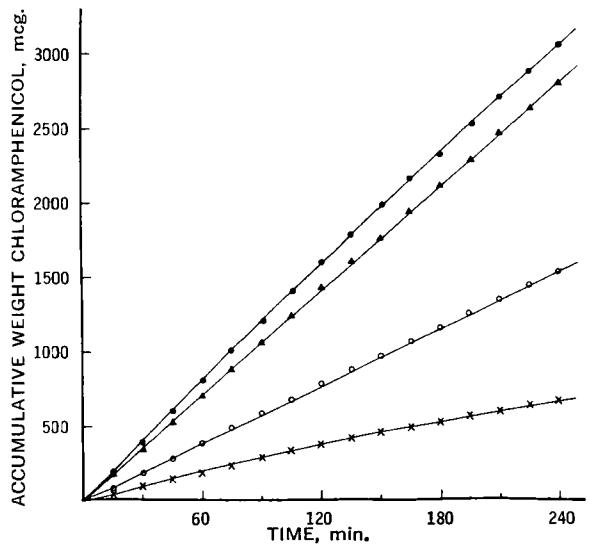

Figure 9—*Plot showing the effect of the addition of sodium lauryl sulfate on the permeation of chloramphenicol (1 mg./ml.) through the skin of hairless mice at 37°. Key: ○, control; ×, 0.02% sodium lauryl sulfate; ▲, 0.20% sodium lauryl sulfate; ●, 0.40% sodium lauryl sulfate.*

Table V—Effect of Various Concentrations of Polysorbate 80 on the Permeation Rate of Chloramphenicol Through the Skin of Hairless Mice at 37°C.

Concn. of Polysorbate 80, %	Permeability Coeff., cm. min.$^{-1}$
0	0.682×10^{-3}
0.2	0.609×10^{-3}
0.5	0.757×10^{-3}
1.0	1.048×10^{-3}

plexation. There is also the possibility that at higher concentrations of surfactant, the stratum corneum layer of the skin is dismantled, or physically altered, or possibly the surface layer is wetted and hydrated, increasing the permeation rate.

Polysorbate 80 (a nonionic surfactant) at concentrations higher than the critical micelle concentration has a similar influence on the permeation of chloramphenicol through the skin, although its effect is not as great as that seen with the sodium lauryl sulfate. The data are summarized in Table V and Fig. 10, which show a slight decrease in the rate at 0.2% concentration and an increase at the higher concentrations.

In contrast to the surfactants, the addition of propylene glycol at a concentration of 20% (v/v) decreased the permeation by about a third as is evident from Fig. 11. Increasing the concentration of propylene glycol from 20 to 40% did not alter the permeation rate. Propylene glycol apparently influences the permeation rate of chloramphenicol by lowering the activity of the drug in solution, through complexing or some such interaction. It apparently does not affect the property of the membrane.

SUMMARY AND CONCLUSIONS

The system used in the study was found to yield reproducible results. Activation energies for diffusion, permeation, and the heat of solution for passage of the drug through the filter membrane saturated with oil were determined. The activation energy for permeation of chloramphenicol through the skin of hairless mice was measured. The effect of various additives on the permeation rate of chloramphenicol in solution was demonstrated. The cell can be modified to hold an ointment in its upper chamber in place of a solution, and the release of a drug from the ointment can be studied.

The skin of hairless mice was found to be a suitable barrier for evaluation of the effect of surfactants and propylene glycol on the permeation of chloramphenicol. Future studies will attempt to correlate the permeation properties of the barriers studied with that of excised human skin.

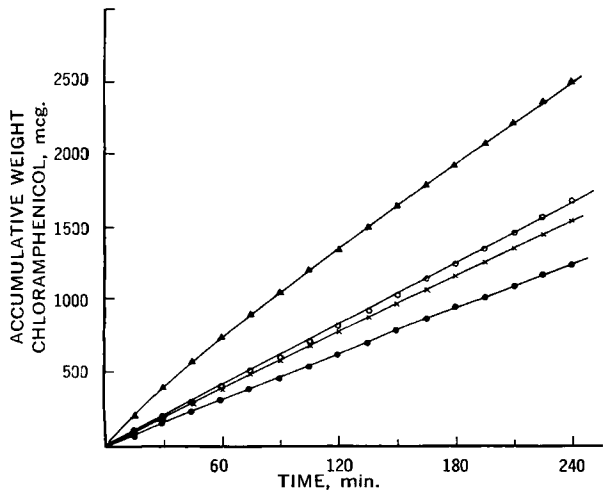

Figure 10—*Plot showing the effect of the addition of polysorbate 80 on the permeation of chloramphenicol (1 mg./ml.) through the skin of hairless mice at 37°. Key: ×, control; ●, 0.20% polysorbate 80; ○, 0.50% polysorbate 80; ▲, 1.00% polysorbate 80.*

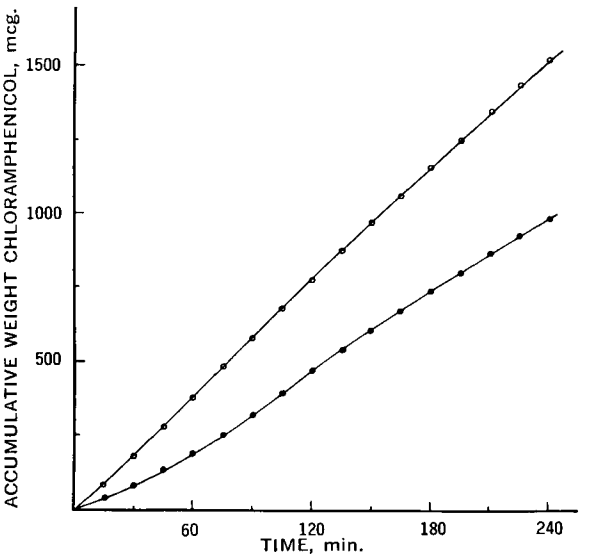

Figure 11—*Plot showing the effect of the addition of propylene glycol on the permeation of chloramphenicol (1 mg./ml.) through the skin of hairless mice at 37°. Key: ●, control; ○, 20% (v/v) propylene glycol.*

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