13
Diffusion and Dissolution

Steady-State Diffusion
Procedures and Apparatus
Dissolution
Drug Release
Diffusion Principles in Biologic Systems
Thermodynamics of Diffusion
Fick's Second Law
Diffusion and Ecology

Free diffusion or passive transport of substances through liquids, solids, and membranes is a process of considerable importance in the pharmaceutical sciences. Topics of mass transport phenomena applying to pharmacy are dissolution of drugs from tablets, powders, and granules; lyophilization, ultrafiltration, and other mechanical processes; release from ointments and suppository bases; passage of water vapor, gases, drugs, and dosage form additives through coatings, packaging, films, plastic container walls, seals, and caps; and permeation and distribution of drug molecules in living tissues.

Diffusion. *Diffusion* is defined as a process of mass transfer of individual molecules of a substance, brought about by random molecular motion and associated with a concentration gradient. Flow of molecules through a barrier such as a polymeric membrane is a particularly convenient way to study diffusion processes. The passage of matter through a barrier (Fig. 13-1) may occur by simple molecular permeation or by movement through pores and channels. Molecular diffusion or permeation through nonporous media depends on dissolution of the permeating molecules in the bulk membrane (Fig. 13-1*a*), whereas a second process may involve passage of a substance through solvent-filled pores of a membrane (Fig. 13-1*b*) and is influenced by the relative sizes of the penetrating molecules and the diameter of the pores. The transport of a drug through a polymeric membrane involves dissolution of the drug in the matrix of the membrane and is an example of simple molecular diffusion. Passage of steroidal molecules, substituted with hydrophilic groups, through human skin may predominantly involve transport through hair follicles, sebum ducts, and sweat pores in the epidermis (see Fig. 13-22). Perhaps a better representation of a membrane on the molecular scale is a matted arrangement of polymer strands with branching and intersecting channels as shown in Figure 13-1*c*. Depending on the size and shape of the diffusing molecules, they may pass through the tortuous pores formed by the overlapping strands of polymer. If too large for such channel transport, the diffusant may dissolve in the polymer matrix and pass through the film by simple diffusion.

Dialysis. Hwang and Kammermeyer[1] define *dialysis* as a separation process based on unequal rates of passage of solutes and solvent through microporous membranes, carried out in batch or continuous mode. *Hemodialysis* is used in kidney malfunction to rid the blood of metabolic waste products (small molecules) while preserving the high-molecular-weight components of the blood.

Osmosis. A process related to dialysis, *osmosis* was originally defined as the passage of both solute and solvent across a membrane, but now refers to an action in which only the solvent is transferred. The solvent passes through the semipermeable membrane to dilute the solution containing solute and solvent (see p. 116). The passage of solute together with solvent now is called *diffusion* or *dialysis*.

Ultrafiltration. Ultrafiltration is used to separate colloidal particles and macromolecules by the use of a membrane. Hydraulic pressure is employed to force the solvent through the membrane while the microporous membrane prevents the passage of large solute molecules. Ultrafiltration is similar to a process called *reverse osmosis*, but a much higher osmotic pressure is developed in reverse osmosis, which is used in desalination of brackish water. Ultrafiltration is used in the pulp and paper industry and in research to purify albumin and enzymes. *Microfiltration*, a process that employs membranes of slightly larger pore size, 100 nanometers to several micrometers, removes bacteria from intravenous injections, foods, and drinking wa-

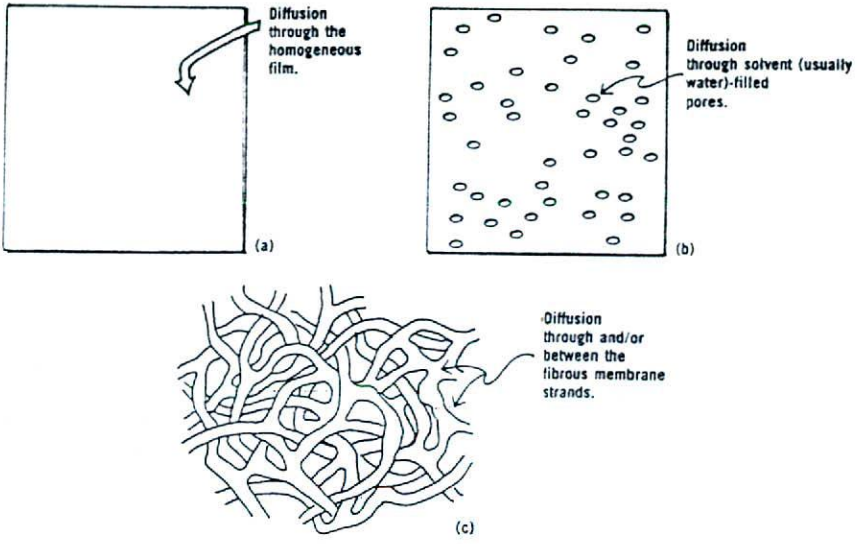


Fig. 13–1. *(a)* Homogeneous membrane without pores. *(b)* Membrane of dense material with straight-through pores, as found in certain filter barriers such as Nucleopore. *(c)* Cellulose membrane used in filtration processes, showing intertwining nature of fibers and tortuous channels.

ter.[2] In ordinary osmosis as well as in dialysis, separation is spontaneous and does not involve the high applied pressures of ultrafiltration and reverse osmosis.

Flynn et al.[3] differentiate between a membrane and a barrier. A *membrane* is a film separating the phases, and material passes by passive, active, or facilitated transport across this film. The term *barrier* applies in a more general sense to the region or regions that offer resistance to passage of a diffusing material, the total barrier being the sum of individual resistances of membranes or the component films of laminae interposed between a donor and a receptor chamber.

STEADY-STATE DIFFUSION

Fick's First Law. The amount M of material flowing through a unit cross-section, S, of a barrier in unit time, t, is known as the flux, J.

$$J = \frac{dM}{S \cdot dt} \qquad (13-1)$$

The flux in turn is proportional to the concentration gradient, dC/dx:

$$J = -D\frac{dC}{dx} \qquad (13-2)$$

in which D is the *diffusion coefficient* of a penetrant (also called the *diffusant*) in cm²/sec, C its concentration in g/cm³, and x the distance in cm of movement perpendicular to the surface of the barrier. In equation (13–1), the mass, M, is usually given in grams or moles, the barrier surface, S, in cm², and the time, t, in seconds. The units on J are g cm^{-2} sec^{-1}. The SI units of kilogram and meter are sometimes used, and the time may be given in minutes, hours, or days. The negative sign of equation (13–2) signifies that diffusion occurs in a direction (the positive x direction) opposite to that of increasing concentration. That is to say, diffusion occurs in the direction of decreasing concentration of diffusant; thus, the flux is always a positive quantity.

The diffusion constant, D, or *diffusivity* as it is often called, does not ordinarily remain constant, for it may change in value at higher concentrations. D is also affected by temperature, pressure, solvent properties, and the chemical nature of the diffusant. Therefore, D is referred to more correctly as a *diffusion coefficient* rather than as a constant. Equation (13–2) is known as *Fick's first law*.

Fick's Second Law. One often wants to examine the rate of change of diffusant concentration at a point in the system. An equation for mass transport that emphasizes the change in *concentration* with time at a definite location rather than the *mass* diffusing across a unit area of barrier in unit time, is known as *Fick's second law*. This diffusion equation is derived as follows. The concentration C in a particular volume element, (see Figs. 13–2 and 13–3) changes only as a result of net flow of diffusing molecules into or out of the region. A difference in concentration results from a difference in input and output. The concentration of diffusant in the volume element changes with time, that

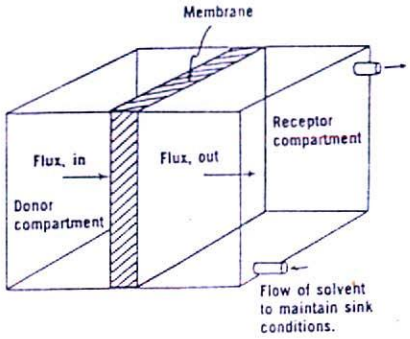


Fig. 13–2. Diffusion cell. Donor compartment contains diffusant at concentration C.

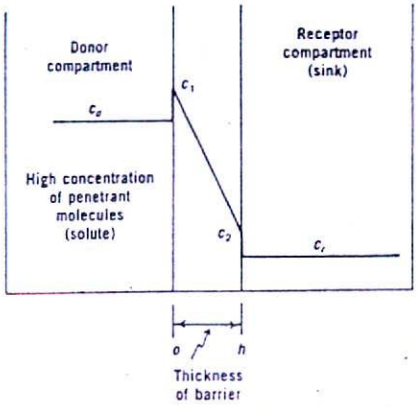


Fig. 13–3. Concentration gradient of diffusant across the diaphragm of a diffusion cell. It is normal for the concentration curve to increase or decrease sharply at the boundaries of the barrier since, in general, c_1 is different from c_d and c_2 is different from c_r. c_1 would be equal to c_d, for example, only if $K = c_1/c_d$ had a value of unity.

is, $\Delta C/\Delta t$, as the flux or amount diffusing changes with distance, $\Delta J/\Delta x$, in the x direction, or*

$$\frac{\partial C}{\partial t} = -\frac{\partial J}{\partial x} \tag{13–3}$$

Differentiating the first-law expression, equation (13–2), with respect to x, one obtains

$$-\frac{\partial J}{\partial x} = D\frac{\partial^2 c}{\partial x^2} \tag{13–4}$$

Substituting $\partial C/\partial t$ from equation (13–3) into equation (13–4) results in Fick's second law, namely

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 c}{\partial x^2} \tag{13–5}$$

Equation (13–5) represents diffusion only in the x direction. If one wishes to express concentration changes of diffusant in three dimensions, Fick's second law is written in the general form

$$\frac{\partial C}{\partial t} = D\left(\frac{\partial^2 C}{\partial x^2} + \frac{\partial^2 C}{\partial y^2} + \frac{\partial^2 C}{\partial z^2}\right) \tag{13–6}$$

This expression is not usually needed in pharmaceutical problems of diffusion, however, since movement in one direction is sufficient to describe most cases. Fick's second law states that the change in concentration with time in a particular region is proportional to the change in the concentration gradient at that point in the system.

Steady State. An important condition in diffusion is that of the *steady state*. Fick's first law, equation (13–2), gives the flux (or rate of diffusion through unit area) in the steady state of flow. The second law refers in general to a change in concentration of diffusant with time, at any distance, x (i.e., a nonsteady state of flow). Steady state may be described, however, in terms of the second law, equation (13–5). Consider the diffusant originally dissolved in a solvent in the left-hand compartment of the cell shown in Figure 13–2. Solvent alone is placed on the right-hand side of the barrier, and the solute or penetrant diffuses through the central barrier from solution to solvent side (donor to receptor compartment). In diffusion experiments, the solution in the receptor compartment is constantly removed and replaced with fresh solvent to keep the concentration at a low level. This is referred to as "sink conditions," the left compartment being the source and the right compartment the sink.

Originally, the diffusant concentration will fall in the left compartment and rise in the right compartment until the system comes to an equilibrium, based on the rate of removal of diffusant from the sink and the nature of the barrier. When the system has been in existence a sufficient time, the concentration of diffusant in the solutions at the left and right of the barrier become constant with respect to time, but obviously not the same in the two compartments. Then within each diffusional slice perpendicular to the direction of flow, the rate of change of concentration, dC/dt, will be zero, and by the second law,

$$\frac{dC}{dt} = D\frac{d^2C}{dx^2} = 0 \tag{13–7}$$

C is the concentration of the permeant in the barrier expressed in mass/cm^3. Equation (13–7) demonstrates that since D is not equal to zero, $d^2C/dx^2 = 0$. When a second derivative such as this equals zero, one concludes that there is no change in dC/dx. In other words, the concentration gradient across the membrane dC/dx is constant, signifying a linear relationship between concentration, C, and distance, x. This is shown in Figure 13–8 (in which the distance x is equal to h) for drug diffusing from left to right in the cell of Figure

*Concentration and flux are often written as $C(x,t)$ and $J(x,t)$, respectively, to emphasize that these parameters are functions of both distance x and time t.

13–2. Concentration will not be rigidly constant but rather is likely to vary slightly with time, and then dC/dt is not exactly zero. The conditions are referred to as a "quasi-stationary" state, and little error is introduced by assuming steady state under these conditions.

Fick adapted the two diffusion equations, (13–2) and (13–5), to the transport of matter from the laws of heat conduction. Equations of heat conduction are found in the book by Carslaw.[4] General solutions to these differential equations yield complex expressions; simple equations are used here for the most part, and worked examples are provided so that the careful reader will have no difficulty in following the arguments of dissolution and diffusion.

If a diaphragm separates the two compartments of a diffusion cell of cross-sectional area S and thickness h, and if the concentrations in the membrane on the left (donor) and on the right (receptor) sides are C_1 and C_2, respectively (Fig. 13–3), the first law of Fick may be written

$$J = \frac{dM}{S\,dt} = D\left(\frac{C_1 - C_2}{h}\right) \qquad (13-8)$$

in which $(C_1 - C_2)/h$ approximates dC/dx. The gradient $(C_1 - C_2)/h$ within the diaphragm must be assumed to be constant for a quasi-stationary state to exist. Equation (13–8) presumes that the aqueous boundary layers (so-called static or unstirred aqueous layers) on both sides of the membrane do not significantly affect the total transport process.

The concentrations C_1 and C_2 within the membrane ordinarily are not known but can be replaced by the partition coefficient multiplied by the concentration C_d on the donor side or C_r on the receiver side, as follows. The distribution or partition coefficient, K, is given by

$$K = \frac{C_1}{C_d} = \frac{C_2}{C_r} \qquad (13-9)$$

Hence,

$$\frac{dM}{dt} = \frac{DSK(C_d - C_r)}{h} \qquad (13-10a)$$

and, if sink conditions hold in the receptor compartment, $C_r \cong 0$,

$$\frac{dM}{dt} = \frac{DSKC_d}{h} = PSC_d \qquad (13-10b)$$

in which

$$P = \frac{DK}{h}\ (\text{cm/sec}) \qquad (13-11)$$

It is noteworthy that the permeability coefficient, also called the *permeability*, P, has units of linear velocity.*

*Confusion arises when the permeability coefficient is defined by $P = DK(\text{cm}^2/\text{sec})$ as used when D and K are not independently known. Equation (13–11), including h in the denominator, is the conventional definition of permeability.

In some cases, it is not possible to determine D, K, or h independently and thereby to calculate P. It is a relatively simple matter, however, to measure the rate of barrier permeation and to obtain the surface area S and concentration C_d in the donor phase and the amount of permeant M in the receiving sink. One can then obtain P from the slope of a linear plot of M versus t:

$$M = PSC_d t \qquad (13-12a)$$

providing that C_d remains relatively constant throughout time. If C_d changes appreciably with time, one recognizes that $C_d = M_d/V_d$, the amount of drug in the donor phase divided by the donor phase volume, and then one obtains P from the slope of log C_d versus t:

$$\log C_d = \log C_d(0) - \frac{PSt}{2.303V_d} \qquad (13-12b)$$

The flux J of equation (13–8) is actually proportional to a gradient of thermodynamic activity rather than concentration. The activity will change in different solvents, and the diffusion rate of a solvent at a definite concentration may vary widely depending on the solvent employed. The thermodynamic activity of a drug may be held constant ($a = 1$) in a delivery form by using a saturated solution in the presence of excess solid drug. Unit activity ensures constant release of the drug at a rate that depends on the membrane permeability and the geometry of the dosage form. Figure 13–4 shows the rate of delivery of two steroids from a device, providing constant drug activity and what is known as "zero-order release." The reader is familiar with zero-order process from a study of kinetics (Chapter 12). If excess solid is not present in the delivery form, the activity decreases as the drug diffuses out of the device, the release rate falls exponentially, and the process is referred to as first-order release, analogous to the well-known reaction in chemical kinetics. First-order release from dosage forms is discussed by Baker and Lonsdale.[5]

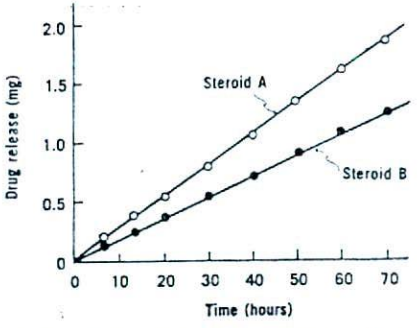


Fig. 13–4. Drug release for two steroids from a matrix or device providing zero-order release. (After R. W. Baker and H. K. Lonsdale, in *Controlled Release of Biologically Active Agents*, A. C. Tanquary and R. E. Lacey, Eds., Plenum Press, New York, 1974, p. 30.)

A constant-activity dosage form may not exhibit a steady-state process from the initial time of release. Figure 13–5 is a plot of the amount of butylparaben penetrating through guinea pig skin from a dilute aqueous solution of the penetrant. It is observed that the curve of Figure 13–5 is convex to the time axis in the early stage and then becomes linear. The early stage is the nonsteady-state condition. At later times, the rate of diffusion is constant, the curve is essentially linear, and the system is at steady state. When the steady-state portion of the line is extrapolated to the time axis, as shown in Figure 13–5, the point of intersection is known as the *lag time*, t_L. This is the time required for a penetrant to establish a uniform concentration gradient within the membrane separating the donor from the receptor compartments.

In the case of a time lag, the straight line of Figure 13–5 may be represented by a modification of equation (13–10):

$$M = \frac{SDKC_d}{h}(t - t_L) \qquad (13-13)$$

The lag time, t_L, is given by

$$t_L = \frac{h^2}{6D} \qquad (13-14a)$$

and its measurement provides a means of calculating the diffusivity D, presuming a knowledge of the membrane thickness h. Also, knowing P, the thickness h can be calculated from

$$t_L = \frac{h}{6P} \qquad (13-14b)$$

Example 13–1. A newly synthesized steroid is allowed to pass through a siloxane membrane, having a cross-sectional area S of 10.36 cm^2 and a thickness h of 0.085 cm, in a diffusion cell at 25° C. From the horizontal intercept of a plot of $Q = M/S$ vs. t, the lag time t_L is found to be 47.5 minutes. The original concentration C_d is 0.003 mmole/cm^3. The amount of steroid passing through the membrane in 4.0 hours is 3.65×10^{-3} mmole.

(a) Calculate the parameter, DK, and the permeability, P.

$$Q = \frac{3.65 \times 10^{-3}\ \text{mmole}}{10.36\ \text{cm}^2} = 0.35 \times 10^{-3}\ \text{mmole/cm}^2$$

$$= DK\left(\frac{0.003\ \text{mmole/cm}^3}{0.085\ \text{cm}}\right)\left[4.0\ \text{hr} - \left(\frac{47.5}{60}\right)\text{hr}\right]$$

$$DK = 0.0031\ \text{cm}^2/\text{hr} = 8.6 \times 10^{-7}\ \text{cm}^2/\text{sec}$$

$$P = DK/h = (8.6 \times 10^{-7}\ \text{cm}^2/\text{sec})/0.085\ \text{cm} = 1.01 \times 10^{-5}\ \text{cm/sec}$$

(b) Using the lag time, $t_L = h^2/6D$, calculate the diffusion coefficient.

$$D = \frac{h^2}{6t_L} = \frac{(0.085)^2\ \text{cm}^2}{6 \times 47.5\ \text{min}}$$

$$= 25.4 \times 10^{-6}\ \text{cm}^2/\text{min}$$

or

$$= 4.23 \times 10^{-7}\ \text{cm}^2/\text{sec}$$

(c) Combining the permeability, Equation (13–11), with the value of D from *(b)*, calculate the partition coefficient, K.

$$K = \frac{Ph}{D} = \frac{(1.01 \times 10^{-5}\ \text{cm/sec})(0.085\ \text{cm})}{4.23 \times 10^{-7}\ \text{cm}^2/\text{sec}} = 2.03$$

Partition coefficients have already been discussed in the chapter on solubility.

Diffusivity depends on the resistance to passage of a diffusing molecule. Gas molecules diffuse rapidly through air and other gases. Diffusivities in liquids are smaller, and in solids still smaller. Gas molecules pass slowly and with great difficulty through metal sheets and crystalline barriers. Diffusivities are a function of the molecular structure of the diffusant as well as the barrier material. Diffusion coefficients for gases and liquids passing through water, chloroform, and polymeric materials are found in Table 13–1. Approximate diffusion coefficients and permeabilities for drugs passing from a solvent in which they are dissolved (water, unless otherwise specified) through natural and synthetic membranes are found in Table 13–2.

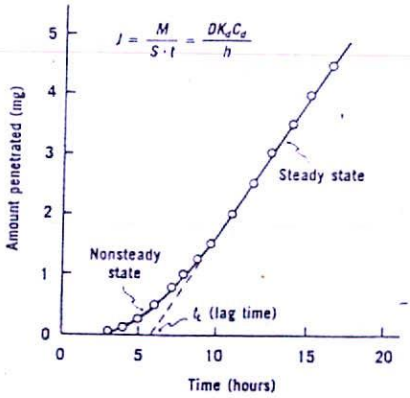


Fig. 13–5. Butyl paraben diffusing through guinea pig skin from aqueous solution. Steady-state and nonsteady-state regions are shown. (From H. Komatsu and M. Suzuki, J. Pharm. Sci. 68, 596, 1979, reproduced with permission of the copyright owner.)

TABLE 13–1. *Diffusion Coefficients of Compounds in Various Media**

Diffusant	Partial Molar Volume (cm^3/mole)	$D \times 10^6$ (cm^2/sec)	Medium or Barrier (temperature, °C)
Ethanol	40.9	12.4	Water (25°)
n-Pentanol	89.5	8.8	Water (25°)
Formamide	26	17.2	Water (25°)
Glycine	42.9	10.6	Water (25°)
Sodium lauryl sulfate	235	6.2	Water (25°)
Glucose	116	6.8	Water (25°)
Hexane	103	15.0	Chloroform (25°)
Hexadecane	265	7.8	Chloroform (25°)
Methanol	25	26.1	Chloroform (25°)
Acetic acid dimer	64	14.2	Chloroform (25°)
Methane	22.4	1.45	Natural rubber (40°)
n-Pentane	—	6.9	Silicone rubber (50°)
Neopentane	—	0.002	Ethycellulose (50°)

*From G. L. Flynn, S. H. Yalkowsky, and T. J. Roseman, J. Pharm. Sci. 63, 507, 1974, reproduced with permission of the copyright owner.

TABLE 13–2. ***Drug Diffusion and Permeability Coefficients***

Drug	Membrane Diffusion Coefficient (cm^2/sec)	Membrane Permeability Coefficient (cm/sec)	Pathway	Temperature (°C)	Reference
Benzoic acid	—	36.6×10^{-4}	Absorption from rat jejunum	37	*a*
Butyl *p*-aminobenzoate	2.7×10^{-6}	—	From aqueous solution through silastic membrane	37	*b*
Chloramphenicol	—	1.87×10^{-6}	Through mouse skin	25	*c*
	—	5.02×10^{-6}	Through mouse skin	37	*c*
Ethynodiol diacetate	3.94×10^{-7} (3.4×10^{-2} cm^2/day)	—	Release from silastic matrix	25	*d*
Estrone	—	20.7×10^{-4}	Absorption from rat jejunum	37	*a*
Fluocinolone acetonide	1.11×10^{-8} (4×10^{-5} cm^2/hr)	—	From 30% propylene glycol–70% water solvent through a polyethylene membrane	25	*e*
Hydrocortisone	—	0.56×10^{-4}	Absorption from rat jejunum	37	*a*
	—	5.8×10^{-5}	Absorption from rabbit vaginal tract	37	*f*
Medroxyprogesterone acetate	3.7×10^{-7}	—	Release from silastic matrix	25	*g*
Nicotinamide	—	1.54×10^{-4}	Absorption from rat jejunum	37	*a*
Octanol	—	12×10^{-4}	Absorption from rat jejunum	37	*a*
Octanoic acid	—	39×10^{-4}	Absorption from rat jejunum	37	*a*
Progesterone	—	7×10^{-4}	Absorption from rabbit vaginal tract	37	*a*
Prostaglandin, 15(S)-methyl-$PGF_{2\alpha}$	—	0.58×10^{-4}	In situ absorption from rat jejunum	37	*a*
Salicylates	1.69×10^{-6}	—	Diffusion across cellulose membrane	37	*h*
Salicylic acid	—	10.4×10^{-4}	Absorption from rat jejunum	37	*a*
Testosterone	—	20×10^{-4}	Absorption from rat jejunum	37	*a*
Water	2.8×10^{-10}	2.78×10^{-7}	Diffusion into human skin layers	37	*i*

a. N. F. H. Ho, J. Y. Park, W. Morozowich and W. I. Higuchi, Physical model approach to design of drugs with improved intestinal absorption, in *Design of Biopharmaceutical Properties Through Pro-drugs and Analogs*, E. B. Roche, Ed., American Pharmaceutical Association, Academy of Pharmaceutical Sciences, Washington, D.C., 1977, Chapter 8, pp. 154–155.
b. G. L. Flynn and S. H. Yalkowsky, J. Pharm. Sci. **61**, 838, 1972.
c. A. J. Aguiar and M. A. Weiner, J. Pharm. Sci. **58**, 210, 1969.
d. Y. W. Chien, in *Sustained and Controlled Release Drug Delivery Systems*, J. R. Robinson, Ed., Marcel Dekker, New York, 1978, Chapter 4.
e. J. S. Turi, D. Danielson and W. Wolterson, J. Pharm. Sci. **68**, 275, 1979.
f. N. F. H. Ho, L. Suhardja, S. Hwang, E. Owada, A. Molokhia, G. L. Flynn, W. I. Higuchi and J. Y. Park, J. Pharm. Sci. **65**, 1578, 1976.
g. T. J. Roseman, J. Pharm. Sci. **61**, 46, 1972; Y. W. Chien, H. J. Lambert and D. E. Grant, J. Pharm. Sci. **63**, 365, 1974.
h. K. F. Farng and K. G. Nelson, J. Pharm. Sci. **66**, 1611, 1977.
i. R. J. Scheuplein, J. Invest. Dermatol. **45**, 334, 1965.

In the chapter on colloids, p. 401, we will see that the molecular weight and the radius of a spherical protein can be obtained from a knowledge of its diffusivity.

PROCEDURES AND APPARATUS

A number of experimental methods and diffusion cells have been reported in the literature. Examples of those used mainly in pharmaceutical and biologic transport studies are introduced here.

Cells of simple construction, such as the one reported by Karth et al.[6] (Fig. 13–6), are probably best for diffusion work. They are made of glass or clear plastic, are easy to assemble and clean, and allow visibility of the liquids and rotating stirrer. They may be thermostated and lend themselves to automatic sample collection and assay. The donor chamber is filled with drug solution. Samples are collected from the receptor compartment in an automatic fraction collector and subsequently assayed spectrophotometrically. Experiments may be run for hours under these controlled conditions.

Biber and Rhodes[7] constructed a Plexiglas three-compartment diffusion cell for use with either synthetic or isolated biologic membranes. The drug was allowed to diffuse from the two outer donor compartments in a central receptor chamber. Results were reproducible and compared favorably with those from other workers. The three-compartment design created greater membrane surface exposure and improved analytic sensitivity.

The permeation through plastic film of water vapor and of aromatic organic compounds from aqueous solution may be investigated in two-chamber glass cells similar in design to those used for studying drug solutions in general. Nasim et al.[8] reported on the permeation of 19 aromatic compounds from aqueous solution through polyethylene films. Higuchi and Aguiar[9] studied the permeability of water vapor through enteric coating materials using a glass diffusion cell and a McLeod gauge to measure changes in pressure across the film.

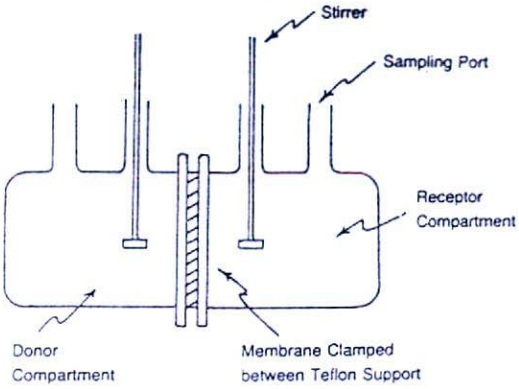


Fig. 13–6. Simple diffusion cell. (After M. G. Karth, W. I. Higuchi and J. L. Fox, J. Pharm. Sci. 74, 612, 1985, reproduced with permission of the copyright owner.)

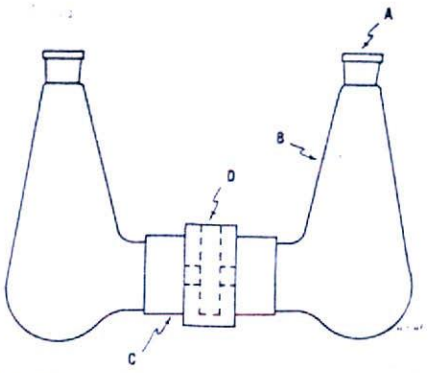


Fig. 13–7. Diffusion cell for permeation through stripped skin layers. The permeant may be in the form of a gas, liquid, or gel. Key: *A*, glass stopper; *B*, glass chamber; *C*, aluminum collar; *D*, membrane and sample holder. (From D. E. Wurster, J. A. Ostrenga and L. E. Matheson, Jr., J. Pharm. Sci. 68, 1406, 1410, 1979, reproduced with permission of the copyright owner.)

The sorption of gases and vapors may be determined by use of a microbalance enclosed in a temperature-controlled and evacuated vessel that is capable of weighing within a sensitivity of $\pm 2 \times 10^{-6}$ g. The gas or vapor is introduced at controlled pressures into the glass chamber containing the polymer or biologic film of known dimensions, suspended on one arm of the balance. The mass of diffusant sorbed at various pressures by the film is recorded directly.[10] The rate of approach to equilibrium sorption permits easy calculation of the diffusion coefficients for gases and vapors.

In studying percutaneous absorption, animal or human skin, ordinarily obtained by autopsy, is employed. Scheuplein[11] described a cell for skin penetration experiments made of Pyrex and consisting of two halves, a donor and a receptor chamber, separated by a sample of skin supported on a perforated plate and securely clamped in place. The liquid in the receptor was stirred by a Teflon-coated bar magnet. The apparatus was submerged in a constant-temperature bath, and samples were removed periodically and assayed by appropriate means. For compounds such as steroids, penetration was slow, and radioactive methods were found necessary to determine the low concentrations.

Wurster et al.[12] developed a permeability cell to study the diffusion through stratum corneum (stripped from the human forearm) of various permeants, including gases, liquids, and gels. The permeability cell is shown in Figure 13–7. During diffusion experiments it was kept at constant temperature and gently shaken in the plane of the membrane. Samples were withdrawn from the receptor chamber at definite times and analyzed for the permeant.

The kinetics and equilibria of liquid and solute absorption into plastics, skin, and chemical and other biologic materials may be determined simply by placing sections of the film in a constant-temperature bath of the pure liquid or solution. The sections are retrieved at various times, excess liquid is removed with absorbant tissue, and the film samples are accurately weighed in tared weighing bottles. A radioactive-counting technique also may be used with this method to analyze for drug remaining in solution and, by difference, the amount sorbed into the film.

Partition coefficients are determined simply by equilibrating the drug between two immiscible solvents in a suitable vessel at a constant temperature and removing samples from both phases, if possible, for analysis.[13] Addicks et al.[14] described a new flow-through cell, Grass and Sweetana[15] proposed a diffusion cell for the study of gastrointestinal permeation, and Addicks et al.[16] designed a cell that yields results more comparable to the diffusion of drugs under clinical conditions. Equilibrium solubilities of drug solutes are also required in diffusion studies, and these are obtained as described earlier (Chapter 10).

DISSOLUTION

Biopharmaceutics and the modern design of dosage forms, as dealt with later in Chapter 19, are based partly on principles of dissolution and diffusion theory. The present chapter lays a foundation for the study of these topics by way of presenting concepts, illustrations, and worked examples. Dissolution is introduced first, followed by examples of diffusion from the literature, with applications of both subjects to pharmaceutical problems.

Dissolution Rate. When a tablet or other solid drug form is introduced into a beaker of water or into the gastrointestinal tract, the drug begins to pass into solution from the intact solid. Unless the tablet is a continguous polymeric device, the solid matrix also

disintegrates into granules, and these granules deaggregate in turn into fine particles. Disintegration, deaggregation, and dissolution may occur simultaneously with the release of a drug from its delivery form. These steps are separated for clarification as depicted in Figure 13–8.

The effectiveness of a tablet in releasing its drug for systemic absorption depends somewhat on the rate of disintegration of the dosage forms and deaggregation of the granules. Ordinarily of more importance, however, is the dissolution rate of the solid drug. Frequently, dissolution is the limiting or rate-controlling step in bioabsorption for drugs of low solubility, because it is often the slowest of the various stages involved in release of the drug from its dosage form and passage into systemic circulation. Dissolution has been reviewed by Wurster and Taylor,[17] Wagner,[18] and Leeson and Carstensen.[19] Release rate processes in general are discussed by W. Higuchi.[20]

The rate at which a solid dissolves in a solvent was proposed in quantitative terms by Noyes and Whitney in 1897 and elaborated subsequently by other workers. The equation may be written as

$$\frac{dM}{dt} = \frac{DS}{h}(C_s - C) \qquad (13-15)$$

or

$$\frac{dC}{dt} = \frac{DS}{Vh}(C_s - C) \qquad (13-16)$$

in which M is the mass of solute dissolved in time t, dM/dt the mass rate of dissolution (mass/time), D the diffusion coefficient of the solute in solution, S the surface area of the exposed solid, h the thickness of the diffusion layer, C_s the solubility of the solid (i.e., concentration of a saturated solution of the compound at the surface of the solid and at the temperature of the experiment), and C the concentration of solute in the bulk solution and at time t. The quantity dC/dt is the dissolution rate and V the volume of solution.

In dissolution or mass transfer theory, it is assumed that an *aqueous diffusion layer* or *stagnant liquid film* of thickness h exists at the surface of a solid undergoing dissolution, as observed in Figure 13–9. This thickness h represents a stationary layer of solvent in which the solute molecules exist in concentrations from C_s to C. Beyond the static diffusion layer, at x greater than h, mixing occurs in the solution, and the drug is found at a uniform concentration, C, throughout the bulk phase.

At the solid surface–diffusion layer interface, $x = 0$, the drug in the solid is in equilibrium with drug in the diffusion layer. The gradient, or change in concentration with distance across the diffusion layer, is constant, as shown by the straight downward-sloping line. This is the gradient represented in equations (13–15) and (13–16) by the term $(C_s - C)/h$. The similarity of the Noyes–Whitney equation to Fick's first law is evident in equation (13–15).

When C is considerably less than the drug's solubility, C_s, the system is represented by *sink conditions*, and concentration C may be eliminated from equations (13–15) and (13–16). Equation (13–15) then becomes

$$dM/dt = DSC_s/h \qquad (13-17)$$

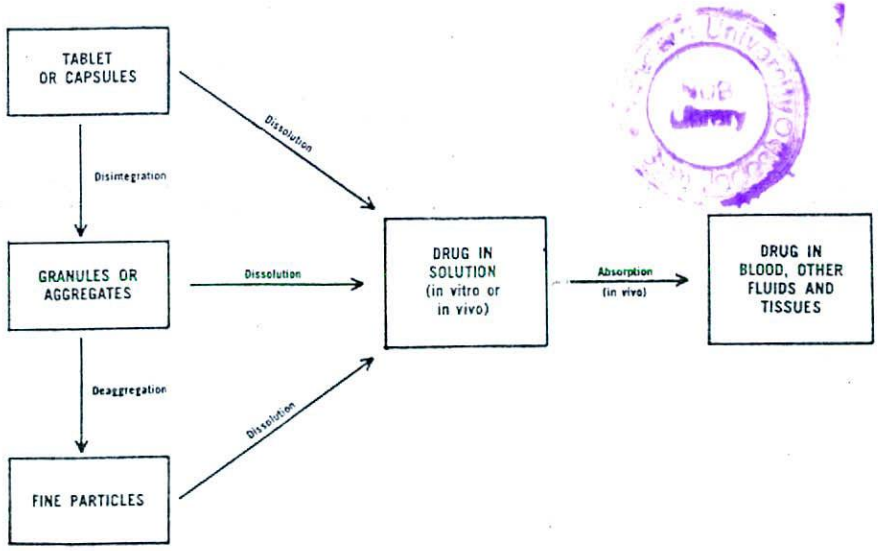


Fig. 13–8. Disintegration, deaggregation, and dissolution stages as a drug leaves a tablet or granular matrix. (From John G. Wagner, *Biopharmaceutics and Relevant Pharmacokinetics*, published by Drug Intelligence Publications, Inc., 1241 Broadway, Hamilton, IL 62341, p. 99, with permission of the copyright owner.)

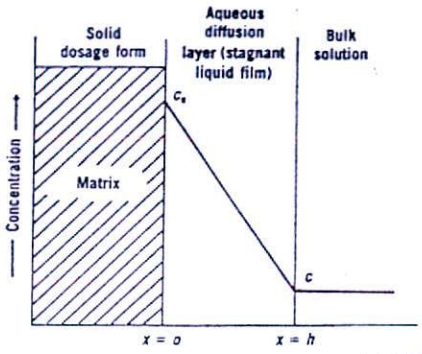


Fig. 13–9. Dissolution of a drug from a solid matrix, showing the stagnant diffusion layer between the dosage form surface and bulk solution.

In the derivation of equations (13–15) and (13–16), it was assumed that h and S were constant, but this is not the case. The static diffusion layer thickness is altered by the force of agitation at the surface of the dissolving tablet and will be referred to later. The surface area S obviously does not remain constant as a powder, granule, or tablet dissolves, and it is difficult to obtain an accurate measure of S as the process continues. In experimental studies of dissolution, the surface may be controlled by placing a compressed pellet in a holder that exposes a surface of constant area. Although this ensures better adherence to the requirements of equations (13–15), (13–16), and (13–17) and provides valuable information on the drug, it does not simulate the actual dissolution of the material in practice.

Dissolution of Tablets, Capsules, and Granules. A number of methods for the in vitro and in vivo testing of dosage forms have been suggested.[21,22] The purpose of an in vitro dissolution study is to provide a fast and inexpensive method that correlates with the performance of a dosage form in human subjects, and a number of studies towards this end have been reported in the literature.[23] Various dissolution apparatus and methods are described in some detail in the latter work.[22] The Hansen paddle equipment and a research apparatus provide two convenient systems, as shown in Figure 13–10*a* and *b*. As observed, the apparatus are similar except that the surface area of the tablet or compacted material in Figure 13–10*b* remains constant as the drug dissolves. This design has advantages in research and product formulation. Furthermore, exact hydrodynamic conditions are maintained by the fixed position of stirrer and sample holder. Much attention has been paid to the rotating disk, a modification of the apparatus in Figure 13–10*b*, in which the tablet in its holder is attached to a rotating shaft of a precision variable-speed motor.[24] The paddle of Figure 13–10*b* is not required in the rotating-disk apparatus. The paddle equipment of Figure 13–10*a* is currently known as the

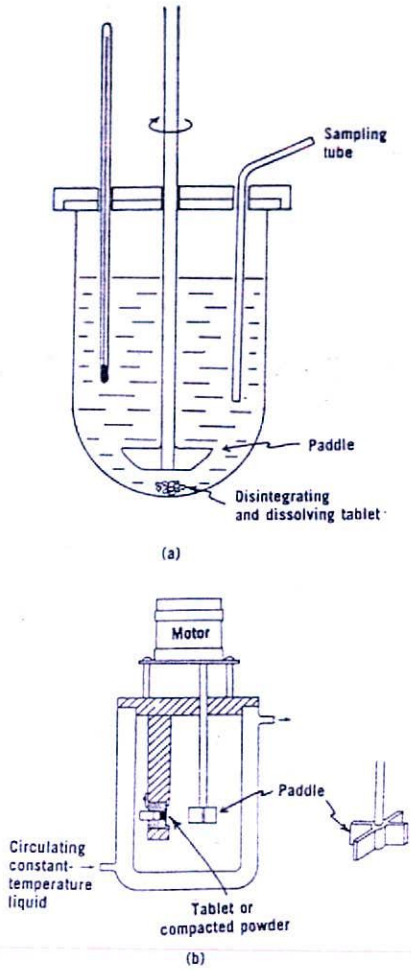


Fig. 13–10. Dissolution apparatus. *(a)* Hansen paddle equipment for granules and tablets. *(b)* Research design to ensure a constant surface area of tablet or compacted powder as the drug dissolves and diffuses out of the dosage form. (From A. P. Simonelli, S. C. Mehta and W. I. Higuchi, J. Pharm. Sci. 58, 538, 1969, reproduced with permission of the copyright owner.)

USP Dissolution Apparatus 2, and a rotating basket apparatus (not shown) is referred to as USP Dissolution Apparatus 1.

In calculating the diffusion coefficient and dissolution rate constant, the application of equations (13–15) to (13–17) is demonstrated by way of the following two examples.

Example 13–2. A preparation of drug granules weighing 0.55 g and having a total surface area of 0.28 m^2 (0.28×10^4 cm^2) is allowed to dissolve in 500 mL of water at 25° C. After the first minute, 0.76 g have passed into solution. The quantity D/k may be referred to as a dissolution rate constant, k.

If the solubility C_s of the drug is 15 mg/mL at 25° C, what is k? From equation (13–17), M changes linearly with t initially, and

$$\frac{dM}{dt} = \frac{760 \text{ mg}}{60 \text{ sec}} = 12.67 \text{ mg/sec}$$

$$12.67 \text{ mg/sec} = k \times 0.28 \times 10^4 \text{ cm}^2 \times 15 \text{ mg/cm}^3$$

$$k = 3.02 \times 10^{-4} \text{ cm/sec}$$

In this example, 0.760 g dissolved in 500 mL after a time of 1 minute or 760 mg/500 mL = 1.5 mg/cm^3. This value is one tenth of the drug's solubility and may be omitted from equation (13–15) without introducing significant error, shown by employing the full equation (13–15):

$$k = \frac{12.67 \text{ mg/sec}}{(0.28 \times 10^4 \text{ cm}^2)(15 \text{ mg/cm}^3 - 1.5 \text{ mg/cm}^3)}$$

$$k = 3.35 \times 10^{-4} \text{ cm/sec}$$

When this result is compared with 3.02×10^{-4} cm/sec, obtained using the less exact expression, it signifies that "sink conditions" are in effect, and the concentration term C may be omitted from the rate equation.

Example 13–3. The diffusion layer thickness in *Example 13–2* is estimated to be 5×10^{-3} cm. Calculate D, the diffusion coefficient, using the relation $k = D/h$.

$$D = (3.35 \times 10^{-4} \text{ cm/sec}) \times (5 \times 10^{-3} \text{ cm})$$

$$= 1.68 \times 10^{-6} \text{ cm}^2\text{/sec}$$

The reader will find additional examples in the book by Carstensen.[25]

Powder Dissolution: The Hixson–Crowell Cube Root Law. For a drug powder consisting of uniformly sized particles, it is possible to derive an equation that expresses the rate of dissolution based on the cube root of the weight of the particles. The radius of the particle is not assumed to be constant.

The particle (sphere) shown in Figure 13–11 has a radius r and a surface area $4\pi r^2$. Through dissolution, the radius is reduced by dr, and the infinitesimal volume of this section lost is

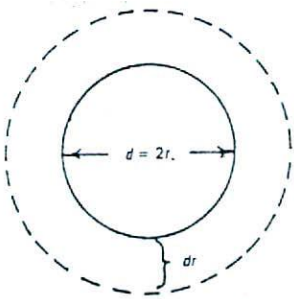


Fig. 13–11. Schematic of a particle, showing change in surface area and volume as the particle dissolves. The volume dV dissolved in dt seconds is given by: thickness × surface area = $dr \times 4\pi r^2$. (After J. T. Carstensen, *Pharmaceutics of Solids and Solid Dosage Forms*, Wiley, New York, 1977, p. 75.)

$$dV = 4\pi r^2 \, dr \qquad (13-18)$$

For N such particles, the volume loss is

$$dV = 4N\pi r^2 \, dr \qquad (13-19)$$

The surface area of N particles is

$$S = 4N\pi r^2 \qquad (13-20)$$

Now, the infinitesimal mass change as represented by the Noyes–Whitney law, equation (13–15), is

$$-dM = kSC_s \, dt \qquad (13-21)$$

in which k is used for D/h as in *Example 13–2*. The drug's density multiplied by the infinitesimal volume change, $\rho \, dV$, may be set equal to dM, or

$$-\rho \, dV = kSC_s \, dt \qquad (13-22)$$

Equations (13–19) and (13–20) are substituted into equation (13–22) to yield

$$-4\rho N\pi r^2 \, dr = 4N\pi r^2 \, kC_s \, dt \qquad (13-23)$$

Equation (13–23) is divided through by $4N\pi r^2$ to give

$$-\rho \, dr = kC_s \, dt \qquad (13-24)$$

Integration with $r = r_0$ at $t = 0$ produces the expression

$$r = r_0 - \frac{kC_s t}{\rho} \qquad (13-25)$$

The radius of spherical particles may be replaced by the mass of N particles by using the relationship (see inside front cover for volume of a sphere).

$$M = N\rho(\pi/6)d^3 \qquad (13-26)$$

in which $d = 2r$, the diameter of the particle. Taking the cube root of equation (13–26) yields

$$M^{1/3} = [N\rho(\pi/6)]^{1/3} d \qquad (13-27)$$

The diameter d of equation (13–27) is substituted for $2r$ into (13–25), giving

$$M_0^{1/3} - M^{1/3} = \kappa t \qquad (13-28)$$

in which

$$\kappa = [N\rho(\pi/6)]^{1/3} \frac{2kC_s}{\rho} = \frac{M_0^{1/3}}{d} \frac{2kC_s}{\rho} \qquad (13-29)$$

M_0 is the original mass of the drug particles. Equation (13–28) is known as the Hixson–Crowell cube root law,[26] and κ is the cube root dissolution rate constant.

Example 13–4. A specially prepared tolbutamide powder of fairly uniformly sized particles, with a diameter of 150 μm*, weighted 75 mg. Dissolution of the drug was determined in 1000 mL of water at 25° C as a function of time. Determine the value of κ, the cube root dissolution rate constant, at each time interval and calculate the average value of κ. The data and results are set forward in Table 13–3.

*The symbol, μm, stands for micrometer and is equal to 10^{-6} meters.

TABLE 13–3. *Dissolution of Tolbutamide Powder*[27]

Time (min)	Concentration Dissolved (mg/mL)	Weight Undissolved (grams) M	$M_0^{1/3} - M^{1/3}$	κ ($g^{1/3}$/min)
0	0	$M_0 = 0.0750$	0	—
10	0.01970	0.0553	0.0406	0.0041
20	0.0374	0.0376	0.0866	0.0043
30	0.0510	0.0240	0.1332	0.0044
40	0.0595	0.0155	0.1724	0.0043
50	0.0650	0.0100	0.2063	0.0041

$$\kappa_{av} = \frac{\Sigma\kappa}{5} = \frac{0.0212}{5} = 0.00424\ g^{1/3}/min$$

In the situation in which the aqueous diffusion layer thickness about a spherical particle is comparable to or larger than the size of the sphere, for example, micronized particles less than 50 μm in diameter, the change in particle radius with time becomes

$$r^2 = r_0^2 - \frac{2DC_s t}{\rho} \qquad (13-30)$$

and the estimated time for complete dissolution, τ, (i.e., when $r^2 = 0$) is

$$\tau = \frac{\rho r_0^2}{2DC_s} \qquad (13-31)$$

Example 13–5. In clinical practice, diazepam injection (a sterile solution of diazepam in a propylene glycol–ethanol–water cosolvent system) is often diluted manyfold with normal saline injection. An incipient precipitation of diazepam occurs invariably upon addition of saline followed by complete dissolution within a minute upon shaking. With C_s in water = 3 mg/mL, $\rho \cong 1.0$ g/mL, and $D = 5 \times 10^{-6}$ cm²/sec, calculate the time for complete dissolution when $r_0 = 10$ μm (10×10^{-4} cm).

$$\tau = \frac{(1\ g/mL)(10 \times 10^{-4}\ cm)^2}{2(5 \times 10^{-6}\ cm^2/sec)(3 \times 10^{-3}\ g/mL)}$$
$$= 33\ sec$$

If $r_0 = 25$ μm, $\tau = 208$ sec.

Convective Diffusion. Convection, the transfer of heat (energy) and the presence of agitation accompanying the movement of a fluid, may be combined with diffusion to provide a *convective diffusion model* for the study of dissolution.[28] The convective diffusion model, unlike the simpler Noyes–Whitney and Nernst–Brünner approaches, takes into consideration such factors as flow rate, mixing (agitation), and the dimensions of the dosage form. Nelson and Shah[29] have investigated the convective diffusion model for the dissolution of alkyl *p*-aminobenzoates as test compounds. De Smidt et al.[30] also used a convective diffusion model in the study of the dissolution kinetics of griseofulvin in solutions of the solubilizing agent sodium dodecylsulfate.

Example 13–6. The above workers[29] introduced a drug dissolution rate approach to model the rates of dissolution of alkyl *p*-aminobenzoates in a specially designed diffusion cell. The model is based on convective diffusion, the equations of which may be used to calculate R, the rate of diffusion or permeation rate:

$$R = 0.808\ D^{2/3} C_s \alpha^{1/3} b L^{2/3} \qquad (13-32)$$

for a *rectangular tablet surface* of width b and length L in the direction of flow, and

$$R = 2.157\ D^{2/3} C_s \alpha^{1/3} r^{5/3} \qquad (13-33)$$

for a *circular tablet surface* of radius r. In these equations D is the diffusivity or diffusion coefficient, C_s is the solubility, and α is the rate of shear as the solvent is pumped over the dissolving surface. The rate of shear is calculated from $\alpha = 6Q/H^2W$, where Q is the flow rate and H and W are the height and width, respectively, of a channel in the diffusion cell to allow the flow of solvent (water) over the dissolving tablet.

Experiments on dissolution rate, R, were carried out at 37° C with rectangular tablet surfaces containing the drug model ethyl *p*-aminobenzoate. The long axis of the rectangular surface was 25.4 mm and the short axis 3.175 mm.

(*a* and *b*) Compute the rate of dissolution R with the long axis L placed perpendicular to the direction of flow, and then with the long axis placed parallel to the direction of flow. The flow rate Q is 14.9 mL/min; the diffusivity and solubility of the drug are $D = 9.86 \times 10^{-6}$ cm²/sec and $C_s = 7.27 \times 10^{-6}$ mole/cm³; and $H^2W = 0.3506$ cm³.

(*c*) The experiment is repeated but using a disk with a circular surface of area equal to the surface area of the rectangle referred to above. Compute R expressing the results in mole/min.

(*d*) What differences do you find between this model and the classic stagnant or unstirred diffusion layer model? You may care to refer to the articles[29] to check the answers given here.

(*a*) The rate of shear is

$$\alpha = 6Q/H^2W = 6 \times 14.9\ cm^3 min^{-1}/0.3506\ cm^3 = 255.0\ min^{-1}$$

For the long axis perpendicular to flow, $b = 2.54$ cm and $L = 0.3175$ cm. Then,

$$R = 0.808(9.86 \times 10^{-6}\ cm^2/sec \times 60\ sec/min)^{2/3} \times (7.27 \times 10^{-6}\ mole/cm^3) \times (255.\ min^{-1})^{1/3} \times (2.54\ cm) \times (0.3175\ cm)^{2/3}$$
$$= 3.10 \times 10^{-7}\ mole/min$$

(*b*) For the long axis parallel to the flow, $b = 0.3175$ cm and $L = 2.54$ cm.

$$R = 0.808(9.86 \times 10^{-6}\ cm^2/sec \times 60\ sec/min)^{2/3} \times (7.27 \times 10^{-6}\ mole/cm^3) \times (255.\ min^{-1})^{1/3} \times (0.3175\ cm) \times (2.54\ cm)^{2/3}$$
$$= 1.55 \times 10^{-7}\ mole/min$$

For the long axis perpendicular to the flow, R is twice the value when the long axis is parallel to the flow, as observed in (*a*) and (*b*) above:

$$R = 3.10 \times 10^{-7}/(1.55 \times 10^{-7}) = 2.0$$

(*c*) The surface area of the rectangular tablet is 2.54 cm × 0.3175 cm = 0.806 cm², which is also the surface area of the circular tablet or disk. Therefore, the radius, r, of the circular surface is $\pi r^2 = 0.806$ or $r = 0.507$ cm., and the rate R of diffusion or permeation for a tablet of circular surface (equation 13–33) is

$$R = 2.157(9.86 \times 10^{-6} \times 60\ cm^2/min)^{2/3} \times (7.27 \times 10^{-6}\ mole\ cm^3) \times (255.\ min^{-1})^{1/3} \times (0.507\ cm)^{5/3}$$
$$= 2.26 \times 10^{-7}\ mole/min$$

(*d*) The convective diffusion model, the *CD* model, which takes into account fluid flow as well as diffusion, has several parameters in common with the classic diffusion model. These include the solubility, C_s, diffusion coefficient or diffusivity, D, and the dimensions of a rectangular or circular surface, b, L, and r. In the classic model, R is proportional to D, while in the *CD* model R is proportional to $D^{2/3}$. In the classic model, R is proportional to the surface area, S, of a rectangle or disk; in the CD model R is proportional to a reduced function of surface area; that is, $bL^{2/3}$ or $r^{5/3}$. A new parameter, α, the rate of shear over the dissolving surface, is introduced in the *CD*

model; it is calculated from the flow rate and the dimension of the diffusion cell.

DRUG RELEASE

Release from dosage forms and subsequent bioabsorption are controlled by the physical chemical properties of drug and delivery form, and the physiologic and physical chemical properties of the biologic system. Drug concentration, aqueous solubility, molecular size, crystal form, protein binding, and pK_a are among the physical chemical factors that must be understood to design a delivery system that exhibits controlled or sustained-release characteristics.[31]

The release of a drug from a delivery system involves factors of both dissolution and diffusion. As the reader has already observed in this chapter, the foundations of diffusion and dissolution theories bear many resemblances. Dissolution rate has been discussed as it influences drug release; the remainder of the chapter emphasizes principles of diffusion as related to the transport of drugs from dosage matrices, through the walls of containers and packages, and into the body by pathways through the gastrointestinal mucosa, skin, vagina, buccal cavity, and other sites of entry into the body.

Drugs in Polymer Matrices. A powdered drug is homogeneously dispersed throughout the matrix of an erodible tablet. The drug is assumed to dissolve in the polymer matrix and to diffuse out from the surface of the device. As the drug is released, the distance for diffusion becomes increasingly greater. The boundary that forms between drug and empty matrix therefore recedes into the tablet as drug is eluted. A schematic illustration of such a device is shown in Figure 13–12*a*. Figure 13–12*b* shows a granular matrix with interconnecting pores or capillaries. The drug is leached out of this device by entrance of the surrounding medium. Figure 13–12*c* depicts the concentration profile and shows the receding depletion zone that moves to the center of the tablet as the drug is released.

Higuchi[32] developed an equation for the release of a drug from an ointment base and later[33] applied it to diffusion of solid drugs dispersed in homogeneous and granular matrix dosage systems (Fig. 13–12).

Fick's first law,

$$\frac{dM}{S\,dt} = \frac{dQ}{dt} = \frac{DC_s}{h} \qquad (13\text{–}34)$$

may be applied to the case of a drug embedded in a polymer matrix, in which dQ/dt* is the rate of drug released per unit area of exposed surface of the matrix. Since the boundary between the drug matrix and the

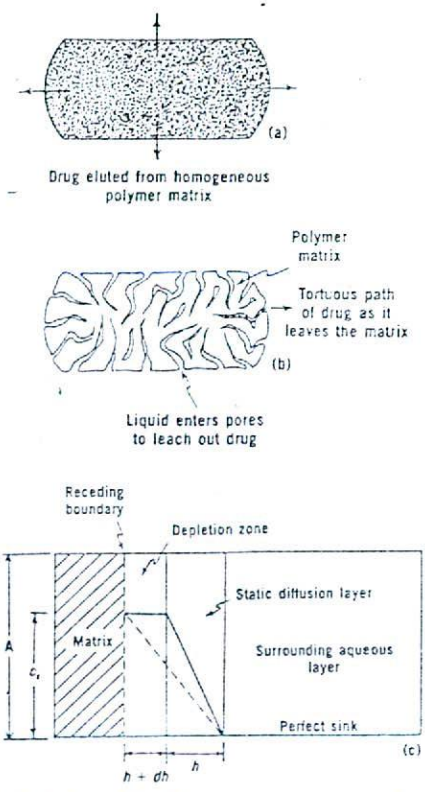


Fig. 13–12. Release of drug from homogeneous and granular matrix dosage forms. *(a)* Drug eluted from a homogeneous polymer matrix. *(b)* Drug leached from a heterogeneous or granular matrix. *(c)* Schematic of the solid matrix and its receding boundary as drug diffuses from the dosage form. (From T. Higuchi, J. Pharm. Sci. 50, 874, 1961, reproduced with permission of the copyright owner.)

drug-depleted matrix recedes with time, the thickness of the empty matrix, dh, through which the drug diffuses also increases with time.

Whereas C_s is the solubility or saturation concentration of drug in the matrix, A is the total concentration (amount per unit volume), dissolved and undissolved, of drug in the matrix.

As drug passes out of a homogeneous matrix, *a* in Figure 13–12, the boundary of drug (represented by the dotted vertical line in Figure 13–12*c*) moves to the left by an infinitesimal distance, dh. The infinitesimal amount, dQ, of drug released because of this shift of the front is given by the approximate linear expression:

$$dQ = A\,dh - \tfrac{1}{2}C_s\,dh \qquad (13\text{–}35)$$

Now dQ of equation (13–35) is substituted into equation (13–34), integration is carried out, and the resulting equation is solved for h. The steps of the derivation as given by Higuchi[32] are

*dM is amount of drug diffusing; dQ is introduced here to represent dM/S, in which S is surface area of the boundary.

$$(A - \tfrac{1}{2}C_s)\,dh = \frac{DC_s}{h}\,dt \qquad (13-36)$$

$$\frac{2A - C_s}{2DC_s}\int h\,dh = \int dt \qquad (13-37)$$

$$t = \frac{(2A - C_s)}{4DC_s}h^2 + C \qquad (13-38)$$

The integration constant, C, may be evaluated at $t = 0$ at which $h = 0$, giving

$$t = \frac{(2A - C_s)h^2}{4DC_s} \qquad (13-39)$$

$$h = \left(\frac{4DC_s t}{2A - C_s}\right)^{1/2} \qquad (13-40)$$

The amount of drug depleted per unit area of matrix, Q, at time t, is obtained by integrating equation (13–35) to yield

$$Q = hA - \tfrac{1}{2}hC_s \qquad (13-41)$$

Substituting equation (13–40) into (13–41) produces the result

$$Q = \left(\frac{DC_s t}{2A - C_s}\right)^{1/2}(2A - C_s) \qquad (13-42)$$

which is known as the *Higuchi equation:*

$$Q = [D(2A - C_s)C_s t]^{1/2} \qquad (13-43)$$

The instantaneous rate of release of a drug at time t is obtained by differentiating equation (13–43) to yield

$$\frac{dQ}{dt} = \frac{1}{2}\left[\frac{D(2A - C_s)C_s}{t}\right]^{1/2} \qquad (13-44)$$

Ordinarily, $A \gg C_s$, and equation (13–43) reduces to

$$Q = (2ADC_s t)^{1/2} \qquad (13-45)$$

and equation (13–44) becomes

$$\frac{dQ}{dt} = \left(\frac{ADC_s}{2t}\right)^{1/2} \qquad (13-46)$$

for the release of a drug from a homogeneous polymer matrix-type delivery system. Equation (13–45) indicates that the amount of drug released is proportional to the square root of A, the total amount of drug in unit volume of matrix; D, the diffusion coefficient of the drug in the matrix; C_s, the solubility of drug in polymeric matrix; and t, the time.

The rate of release, dQ/dt, can be altered by increasing or decreasing the drug's solubility C_s in the polymer by complexation. The total concentration A of drug that the physician prescribes is also seen to affect the rate of drug release.

Example 13–7. (*a*) What is the amount of drug per unit area, Q, released from a tablet matrix at time t = 120 minutes? The total concentration of drug in the homogeneous matrix, A, is 0.02 g/cm³. The drug's solubility C_s is 1.0×10^{-3} g/cm³ in the polymer. The diffusion coefficient D of the drug in the polymer matrix at 25° C is 6.0×10^{-6} cm²/sec or 360×10^{-6} cm²/min.

Equation (13–45) is used:

$$Q = [2(0.02\ \text{g/cm}^3)(360 \times 10^{-6}\ \text{cm}^2/\text{min}) \times (1.0 \times 10^{-3}\ \text{g/cm}^3)(120\ \text{min})]^{1/2}$$

$$= 1.3 \times 10^{-3}\ \text{g/cm}^2$$

(*b*) What is the instantaneous rate of drug release occurring at 120 minutes?

$$dQ/dt = \left[\frac{(0.02)(360 \times 10^{-6})(1.0 \times 10^{-3})}{2 \times 120}\right]^{1/2}$$

$$= 5.5 \times 10^{-6}\ \text{g cm}^{-2}\ \text{min}^{-1}$$

Release from Granular Matrices: Porosity and Tortuosity. The release of a solid drug from a granular matrix (Fig. 13–12*b*) involves the simultaneous penetration of the surrounding liquid, dissolution of drug, and leaching out of the drug through interstitial channels or pores. A granule is, in fact, defined as a porous rather than a homogeneous matrix. The volume and length of the opening in the matrix must be accounted for in the diffusional equation, leading to a second form of the Higuchi equation:

$$Q = \left[\frac{D\epsilon}{\tau}(2A - \epsilon C_s)C_s t\right]^{1/2} \qquad (13-47)$$

in which ϵ is the porosity of the matrix and τ is the tortuosity of the capillary system, both parameters being dimensionless quantities.

Porosity, ϵ, is the fraction of matrix that exists as pores or channels into which the surrounding liquid can penetrate. The porosity term, ϵ, found in equation (13–47) is the total porosity of the matrix after the drug has been extracted. This is equal to the initial porosity, ϵ_0, due to pores and channels in the matrix before the leaching process begins, and the porosity created by extracting the drug. If A g/cm³ of drug is extracted from the matrix and the drug's specific volume or reciprocal density is $1/\rho$ cm³/g, then the drug's concentration, A, is converted to volume fraction of drug that will create an additional void space or porosity in the matrix once it is extracted. The total porosity of the matrix, ϵ, becomes

$$\epsilon = \epsilon_0 + A(1/\rho) \qquad (13-48)$$

The initial porosity ϵ_0 of a compressed tablet may be considered to be small (a few percent) relative to the porosity A/ρ created by the dissolution and removal of the drug from the device. Therefore, the porosity frequently is calculated conveniently by disregarding ϵ_0 and writing

$$\epsilon \cong A/\rho \qquad (13-49)$$

Tablet porosity and its measurement and applications in pharmacy are discussed in more detail on pages 442 to 446.

Equation (13–47) differs from equation (13–43) only in the addition of ϵ and τ. Equation (13–43) is applicable to release from a homogeneous tablet that gradually erodes and releases the drug into the bathing medium. Equation (13–47) applies instead to a drug-release mechanism based upon entrance of the surrounding medium into a polymer matrix, where it dissolves and leaches out the soluble drug, leaving a shell of polymer and empty pores. In equation (13–47), diffusivity is multiplied by porosity, a fractional quantity, to account for the decrease in D brought about by empty pores in the matrix. The apparent solubility of the drug C_s is also reduced by the volume fraction term, which represents porosity.

Tortuosity, τ, is introduced into equation (13–47) to account for an increase in the path length of diffusion due to branching and bending of the pores, as compared to the shortest "straight-through" pores. Tortuosity tends to reduce the amount of drug released in a given interval of time, and so it appears in the denominator under the square root sign. A straight channel has a tortuosity of unity, and a channel through spherical beads of uniform size has a tortuosity of 2 or 3. At times, an unreasonable value of, say, 1000 is obtained for τ, as Desai et al.[34a] have noted. When this occurs, the pathway for diffusion evidently is not adequately described by the concept of tortuosity, and the system must be studied in more detail to determine the factors controlling matrix permeability. Methods for obtaining diffusivity, porosity, tortuosity, and other quantities required in an analysis of drug diffusion are given by Desai et al.[34b]

Equation (13–47) has been adapted to describe the kinetics of lyophilization,[35] commonly called *freeze-drying*, of a frozen aqueous solution containing drug and an inert matrix-building substance (e.g., mannitol or lactose). The process involves the simultaneous change in the receding boundary with time, phase transition at the ice–vapor interface governed by the Clausius–Clapeyron pressure–temperature relationship, and water vapor diffusion across the pore path length of the dry matrix under low temperature and vacuum conditions.

Multilayer Diffusion. Diffusion across biologic barriers may involve a number of layers consisting of separate membranes, cell contents, and fluids of distribution. The passage of gaseous or liquid solutes through the walls of containers and plastic packaging materials is also frequently treated as a case of multilayer diffusion.

Higuchi[32] considered the passage of a topically applied drug from its vehicle through the lipoidal and lower hydrous layers of the skin. Two barriers, in series, the lipoidal and the hydrous skin layers of thickness h_1 and h_2, are shown in Figure 13–13. The resistance R to diffusion in each layer is equal to the reciprocal of the permeability coefficient P_i of that particular layer. Permeability P was defined earlier

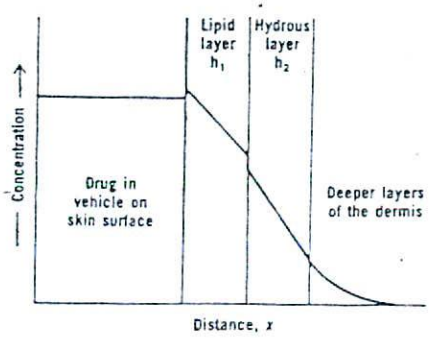


Fig. 13–13. Passage of a drug on the skin's surface through a lipid layer, h_1, and a hydrous layer, h_2, and into the deeper layers of the dermis. The curve of concentration against distance changes sharply at the two boundaries because the two partition coefficients have values other than unity.

(equation [13–11]) as the diffusion coefficient D multiplied by the partition coefficient K, and divided by the membrane thickness, h. For a particular lamina, i,

$$P_i = D_i K_i / h_i$$

and

$$R_i = 1/P_i = h_i/(D_i K_i) \qquad (13-50)$$

in which R_i is the resistance to diffusion. The total resistance R is the reciprocal of the total permeability, P, and is additive for a series of layers. It is written in general as

$$R = R_1 + R_2 + \cdots R_n \qquad (13-51a)$$

$$1/P = 1/P_1 + 1/P_2 \cdots + 1/P_n \qquad (13-51b)$$

$$R = 1/P = h_1/D_1K_1 + h_2/D_2K_2 + \cdots + h_n/D_nK_n \qquad (13-51c)$$

in which K_i is the distribution coefficient for layer i relative to the next corresponding layer, $i + 1$, of the system.[36] The total permeability for the two-ply model of the skin is obtained by taking the reciprocal of equation (13–51c), expressed in terms of two layers, to yield

$$P = \frac{D_1K_1D_2K_2}{h_1D_2K_2 + h_2D_1K_1} \qquad (13-52)$$

The lag time to steady state for a two-layer system is

$$t_L = \frac{\dfrac{h_1^2}{D_1}\left(\dfrac{h_1}{6D_1K_1} + \dfrac{h_2}{2D_2K_2}\right) + \dfrac{h_2^2}{D_2}\left(\dfrac{h_1}{2D_1K_1} + \dfrac{h_2}{6D_2K_2}\right)}{(h_1/D_1K_1 + h_2/D_2K_2)} \qquad (13-53)$$

When the partition coefficients K_i of the two layers are essentially the same and one of the h/D terms, say 1, is

much larger than the other, however, the time lag equation for the bilayer skin system reduces to the simple time lag expression

$$t_L = h_1^2/6D_1 \qquad (13-54)$$

Membrane Control and Diffusion Layer Control. A multilayer case of special importance is that of a membrane between two aqueous phases with stationary or stagnant solvent layers in contact with the donor and receptor sides of the membrane (Fig. 13–14).

The permeability of the total barrier, consisting of the membrane and two static aqueous diffusion layers, is

$$P = \frac{1}{R} = \frac{D_m K D_a}{h_m D_a + 2h_a D_m K}$$

$$= \frac{1}{h_m/D_m K + 2h_a/D_a} \qquad (13-55)$$

This expression is analogous to equation (13–52). In equation (13–55), however, only one partition coefficient K appears, that giving the ratio of concentrations of the drug in the membrane and in the aqueous solvent, $K = C_3/C_4 = C_3/C_2$. The flux J through this three-ply barrier is simply equal to the permeability P multiplied by the concentration gradient $(C_1 - C_5)$, that is, $J = P(C_1 - C_5)$. The receptor serves as a sink (i.e., $C_5 = 0$), and the donor concentration C_1 is assumed to be constant, providing a steady-state flux.[37]

$$J = \frac{1}{S}\frac{dM}{dt} = \frac{D_m K D_a C_1}{h_m D_a + 2h_a D_m K} \qquad (13-56)$$

In equations (13–55) and (13–56), D_m and D_a are membrane and aqueous solvent diffusivities, h_m is the membrane thickness, and h_a the thickness of the aqueous diffusion layer, as observed in Figure 13–14. M is the amount of permeant reaching the receptor, and S is the cross-sectional area of the barrier. It is important to release that h_a is physically influenced by the hydrodynamics in the bulk aqueous phases. The higher the degree of stirring, the thinner is the stagnant aqueous diffusion layer; the slower the stirring, the thicker is this aqueous layer.

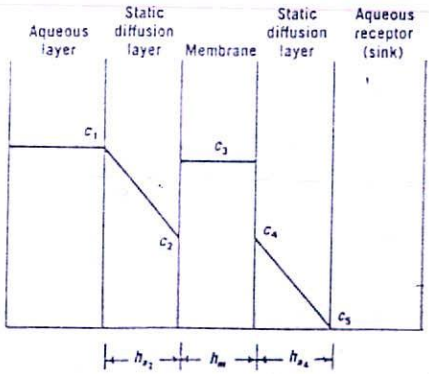


Fig. 13–14. Schematic of a multilayer (three-ply) barrier. The membrane is found between two static aqueous diffusion layers. (From G. L. Flynn, O. S. Carpenter and S. H. Yalkowsky, J. Pharm. Sci. 61, 313, 1972, reproduced with permission of the copyright owner.)

Equation (13–56) is the starting point for considering two important cases of multilayer diffusion, namely, diffusion under *membrane control* and diffusion under *aqueous diffusion layer control*.

Membrane Control. When the membrane resistance to diffusion is much greater than the resistances of the aqueous diffusion layers, that is, $R_m > R_a$ by a factor of at least 10, or correspondingly, $P_m \ll P_a$, the rate-determining step (slowest step) is diffusion across the membrane. This is reflected in equation (13–56) when $h_m D_a \gg 2h_a D_m$. Thus, equation (13–56) reduces to

$$J = \left(\frac{KD_m}{h_m}\right) C_1 \qquad (13-57)$$

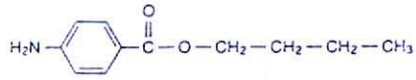
Equation (13–57) represents the simplest case of membrane control of flux.

Aqueous Diffusion Layer Control. When $2h_a K D_m \gg h_m D_a$, equation (13–56) becomes

$$J = \left(\frac{D_a}{2h_a}\right) C_1 \qquad (13-58)$$

and it is now said that the rate-determining barriers to diffusional transport are the stagnant aqueous diffusion layers. This statement means that the concentration gradient that controls the flux now resides in the aqueous diffusion layers rather than in the membrane. From the relationship, $2h_a K D_m \gg h_m D_a$, it is observed that membrane control shifts to diffusion layer control when the partition coefficient K becomes sufficiently large.

Flynn and Yalkowsky[37] demonstrated a transfer from membrane to diffusion-layer control in a homologous series of *n*-alkyl *p*-aminobenzoates (PABA esters). The concentration gradient is almost entirely within the silicone rubber membrane for the short-chain PABA



n-Butyl p-aminobenzoate

esters. As the alkyl chain of the ester is lengthened proceeding from butyl to pentyl to hexyl, the concentration no longer drops across the membrane. Rather, the gradient is now found in the aqueous diffusion layers, and diffusion-layer control takes over as the dominant factor in the permeation process.

Example 13–8. The steady-state flux J for hexyl *p*-aminobenzoate was found to be 1.60×10^{-7} mmole cm^{-2} sec^{-1}. D_a is 6.0×10^{-6} cm^2 sec^{-1} and the concentration of the PABA ester, C, is 1.0 mmole liter^{-1}. The system is in diffusion-layer control, so equation (13–58) applies. Calculate the thickness of the static diffusion layer, h_a.

$$J = \left(\frac{D_e}{2h_e}\right) C \quad \text{or} \quad h_e = \left(\frac{D_e}{2J}\right) C$$

$$h_e = \frac{6.0 \times 10^{-6} \text{ cm}^2 \text{ sec}^{-1}}{2(1.60 \times 10^{-3} \text{ mmole cm}^{-2} \text{ sec}^{-1})} \times$$

$$(1.0 \times 10^{-3} \text{ mmole cm}^{-3}) = 0.019 \text{ cm}$$

One observes from equations (13–57) and (13–58) that, under sink conditions, steady-state flux is proportional to concentration, C, in the donor phase whether the flux-determining mechanism is under membrane or diffusion-layer control. Equation (13–58) shows that the flux is independent of membrane thickness h_m and other properties of the membrane when under static diffusion layer control.

The maximum flux obtained in a membrane preparation depends on the solubility, or limiting concentration, of the PABA homolog. The maximum flux may therefore be obtained using equation (13–56), in which C is replaced by C_s, the solubility of the permeating compound:

$$J_{max} = \left[\frac{D_m K D_a}{h_m D_a + 2h_a K D_m}\right] C_s \qquad (13-59)$$

The maximum steady-state flux, J_{max}, for saturated solutions of the PABA esters is plotted against the ester chain length in Figure 13–15.[37] The plot exhibits peak flux between $n = 3$ and $n = 4$ carbons, that is, between propyl and butyl *p*-aminobenzoates. The peak in Figure 13–15 suggests in part the solubility characteristics of the PABA esters, but primarily reflects the change from membrane to static diffusion layer control of flux. For the methyl, ethyl, and propyl esters, the concentration gradient in the membrane gradually decreases and shifts, in the case of the longer-chain esters, to a concentration gradient in the diffusion layers.

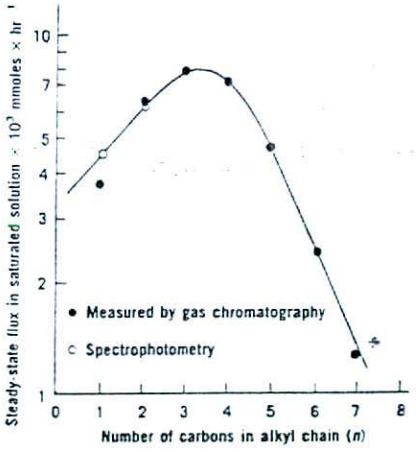


Fig. 13–15. Steady-state flux of a series of *p*-aminobenzoic acid esters. Maximum flux occurs between the esters having three and four carbons and is due to a change from membrane to diffusion-layer control, as explained in the text. (From G. L. Flynn and S. H. Yalkowsky, J. Pharm. Sci. 61, 838, 1972, reproduced with permission of the copyright owner.)

By using a well-characterized membrane such as siloxane of known thickness and a homologous series of PABA esters, these workers[37] were able to study the various factors: solubility, partition coefficient, diffusivity, diffusion lag time, and the effects of membrane and diffusion-layer control. From such carefully designed and conducted studies, it is possible to predict the roles played by various physicochemical factors as they relate to diffusion of drugs through plastic containers, as they influence release rates from sustained delivery forms, and as they influence absorption and excretion processes for drugs distributed in the body.

Lag Time under Diffusion-Layer Control. Flynn et al.[36] showed that the lag time for ultrathin membranes under conditions of diffusion-layer control may be represented as

$$t_L = \frac{(\Sigma h_a)^2}{6D_a} \qquad (13-60)$$

in which Σh_a is the sum of the thicknesses of the aqueous diffusion layers on the donor and receptor sides of the membrane. The correspondence of t_L, equation (13–60), for systems under membrane control (equation [13–57]) is evident. The lag time for *thick* membranes operating under diffusion layer control is

$$t_L = \frac{h_m h_{a1} h_{a2} K}{(h_{a1} + h_{a2}) D_a} \qquad (13-61)$$

When the diffusion layers, h_{a1} and h_{a2}, are of the same thickness, the lag time reduces to

$$t_L = \frac{h_m h_a K}{2D_a} \qquad (13-62)$$

The partition coefficient, which was shown earlier to be instrumental in converting the flux from membrane to diffusion-layer control, now appears in the numerator of the lag-time equation. A large K signifies lipophilicity of the penetrating drug species. As one ascends a homologous series of PABA esters, for example, the larger lipophilicity increases the onset time for steady-state behavior; in other words, lengthening of the ester molecule increases the lag time, once the system is in diffusion-layer control. The sharp increase in lag time for PABA esters with alkyl chain length beyond C_4 is shown in Figure 13–16.

Soluble Drugs in Topical Vehicles and Matrices. The original Higuchi model[32,33] does not provide a fit to experimental data when the drug has a significant solubility in the tablet or ointment base. The model can be extended to drug release from homogeneous solid or semisolid vehicles, however, using a quadratic expression introduced by Bottari et al.[38]

$$Q^2 + 2DRA^*Q - 2DA^*C_s t = 0 \qquad (13-63)$$

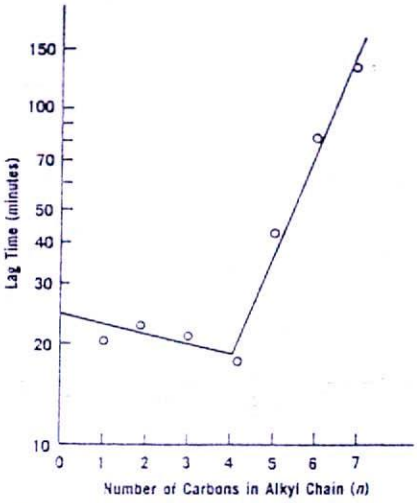


Fig. 13–16. Change in lag time of *p*-aminobenzoic acid esters with alkyl chain length. (From G. L. Flynn and S. H. Yalkowsky, J. Pharm. Sci. 61, 838, 1972, reproduced with permission of the copyright owner.)

in which

$$A^* = A - \tfrac{1}{2}(C_s + C_v) \qquad (13-64)$$

Q is the amount of drug released per unit area of the dosage form, D an effective diffusivity of the drug in the vehicle, A the total concentration of drug, C_s the solubility of drug in the vehicle, C_v the concentration of drug at the vehicle–barrier interface, and R the diffusional resistance afforded by the barrier between the donor vehicle and the receptor phase. A^* is an effective A as defined in equation (13–64) and is used when A is only about three or four times greater than C_s.

When

$$Q^2 \gg 2DRA^*Q \qquad (13-65)$$

equation (13–63) reduces to one form of the Higuchi equation (equation [13–45]):

$$Q = (2A^*DC_s t)^{1/2} \qquad (13-65a)$$

Under these conditions, resistance to diffusion R is no longer significant at the interface between vehicle and receptor phase. When C_s is not negligible in relation to A, the vehicle-controlled model of Higuchi becomes

$$Q = [D(2A - C_s)C_s t]^{1/2} \qquad (13-65b)$$

as derived earlier (p. 336).

The quadratic expression of Bottari (equation [13-63]) should allow one to determine diffusion of drugs in ointment vehicles or homogeneous polymer matrices when C_s becomes significant in relation to A. The approach of Bottari et al.[38] follows.

Being a second-degree power series in Q, equation (13–63) may be solved using the well-known quadratic approach. One writes

$$aQ^2 + bQ + c = 0 \qquad (13-66)$$

in which, with reference to equation (13–63), a is unity, $b = 2DRA^*$, and $c = -2DA^*C_s t$. Equation (13–66) has the well-known solution

$$Q = \frac{-b \pm \sqrt{b^2 - 4ac}}{2a} \qquad (13-67)$$

or

$$Q = \frac{-2DRA^* + \sqrt{(2DRA^*)^2 + (2DA^*C_s t)}}{2} \qquad (13-68)$$

in which the positive root is taken for physical significance. If a lag time occurs, t in equation (13–68) is replaced by $(t - t_L)$ for the steady-state period. Bottari et al.[38] obtained satisfactory values for b and c by use of a least-square fit of equation (13–63) involving the release of benzocaine from suspension-type aqueous gels. R, the diffusional resistance, is determined from steady-state permeation, and C_v is then obtained from the expression

$$C_v = R(dQ/dt) \qquad (13-69)$$

The application of equation (13–63) is demonstrated in the following example.

Example 13–9. (*a*) Calculate Q, the amount in milligrams of micronized benzocaine released per cm² of surface area from an aqueous gel after 9000 seconds (2.5 hours) in a diffusion cell. Assuming that the total concentration A is 10.9 mg/mL, the solubility C_s is 1.31 mg/mL, C_v = 1.05 mg/mL, the diffusional resistance R of a silicone rubber barrier, separating the gel from the donor compartment, is 8.10×10^3 sec/cm, and the diffusivity D of the drug in the gel is 9.14×10^{-6} cm²/sec. From equation (13–64),

$$A^* = 10.9 \text{ mg/mL} - \tfrac{1}{2}(1.31 + 1.05) \text{ mg/mL} = 9.72 \text{ mg/mL}$$

Then

$$DRA^* = (9.14 \times 10^{-6} \text{ cm}^2/\text{sec}) \times (8.10 \times 10^3 \text{ sec/cm})(9.72 \text{ mg/mL})$$
$$= 0.7196 \text{ mg cm}^{-2}$$

$$DA^*C_s t = (9.14 \times 10^{-6})(9.72)(1.31)(9000) = 1.047 \text{ mg}^2/\text{cm}^4$$

$$Q = -0.7196 + \{(0.7196)^2 + 2(1.047)\}^{1/2} \text{ mg/cm}^2$$
$$= -0.7196 + [1.616] = 0.90 \text{ mg/cm}^2$$

The $Q_{(calc)}$ of 0.90 mg/cm² compares well with $Q_{(obs)}$ = 0.88 mg/cm². A slight increase in accuracy may be obtained by replacing t = 9000 sec with t = (9000 − 405) sec, in which the lag time t = 405 sec is obtained from a plot of experimental Q values versus $t^{1/2}$. This correction yields a $Q_{(calc)}$ = 0.87 mg/cm².

(*b*) Calculate Q using equation (13–65*b*) and compare the result with that obtained in (*a*).

$$Q = \{(9.14 \times 10^{-6})[(2 \times 10.9) - 1.31](1.31)(9000)\}^{1/2}$$
$$= 1.49 \text{ mg/cm}^2$$

Paul and coworkers[39] have studied cases in which A, the matrix loading of drug per unit volume in a polymeric dosage form, may be greater than, equal to, or less than the equilibrium solubility C_s of the drug in a matrix. The model is a refinement of the original

Higuchi approach,[32,33] providing an accurate set of equations that describe release rates of drugs, fertilizers, pesticides, antioxidants, and preservatives in commercial and industrial applications, over the entire range of ratios of A to C_s.

A Capsule-Type Device. A silastic capsule, as depicted in Figure 13–17*a*, has become a popular sustained and controlled delivery form in pharmacy and medicine.[40–42] The release of a drug from a silastic capsule is shown schematically in Figure 13–17*b*. The molecules of the crystalline drug lying against the inside wall of the capsule leave their crystals, pass into the polymer wall by a dissolution process, diffuse through the wall, and pass into the liquid diffusion layer and the medium surrounding the capsule. The concentration differences across the polymer wall of thickness h_m and the stagnant diffusion layer of thickness h_a are represented by the lines, $C_p - C_m$ and $C_s - C_b$, respectively. C_p is the solubility of the drug in the polymer and C_m the concentration at the polymer-solution interface, that is, the concentration of drug in the polymer in contact with the solution. C_s, on the other hand, is the concentration of the drug in the solution at the polymer–solution interface, and it is seen in Figure 13–17*b* to be somewhat below the solubility of drug in polymer at the interface. There is a real difference between the solubility of the drug in the polymer and in the solution, although both exist at the interface. Finally, C_b is the concentration of the drug in the bulk solution surrounding the capsule.

To express the rate of drug release under sink conditions, Chien[40] used the following expression:

$$Q = \left[\frac{K_r D_a D_m}{K_r D_a h_m + D_m h_a}\right] C_p t \qquad (13-70)$$

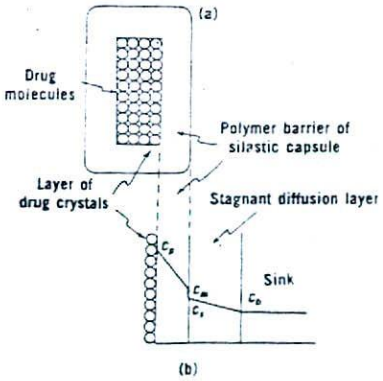


Fig. 13–17. Diffusion of drug from silastic capsule. *(a)* Drug in capsule surrounded by polymer barrier; *(b)* diffusion of drug through polymer wall and stagnant aqueous diffusion layer and into the receptor compartment at sink-conditions. (After Y. W. Chien, in *Sustained and Controlled Release Drug Delivery Systems*, J. R. Robinson, Ed., Marcel Dekker, New York, 1978, p. 229; Chem. Pharm. Bull. 24, 147, 1976.)

which is an integrated form analogous to equation (13–56). In equation (13–70), Q is the amount of drug released per unit surface area of the capsule, and K_r is the partition coefficient, defined as

$$K_r = C_s/C_p \qquad (13-71)^*$$

When diffusion through the capsule membrane or film is the limiting factor in drug release, that is, when $K_r D_a h_m \gg D_m h_a$, equation (13–70) reduces to

$$Q = \left(\frac{D_m}{h_m}\right) C_p t \qquad (13-72)$$

and when the limiting factor is passage through the diffusion layer ($D_m h_a \gg K_r D_a h_m$):

$$Q = \left(\frac{D_a}{h_a}\right) C_s t = \left(\frac{K_r D_a}{h_a}\right) C_p t \qquad (13-73)$$

The right-hand expression may be written because $C_s = K_r C_p$ as defined earlier, in equation (13–71).

The rate of drug release, Q/t, for a polymer-controlled process may be calculated from the slope of a linear Q-versus-t plot, and from equation (13–72) is seen to equal $C_p D_m/h_m$. Likewise, Q/t, for the diffusion-layer–controlled process, resulting from plotting Q versus t, is found to be $C_s D_a/h_a$. Furthermore, a plot of the release rate, Q/t versus C_s, the solubility of the drug in the surrounding medium, should be linear with a slope of D_a/h_a.

Example 13–10. The partition coefficient, $K_r = C_s/C_p$, of progesterone is 0.022; the solution diffusivity $D_a = 4.994 \times 10^{-2}$ cm²/day; the silastic membrane diffusivity $D_m = 14.26 \times 10^{-2}$ cm²/day; the solubility of progesterone in the silastic membrane, C_p, is 513 μg/cm³; the thickness of the capsule membrane, h_m, is 0.080 cm, and that of the diffusion layer, h_a, as estimated by Chien, is 0.008 cm.

Calculate the rate of release of progesterone from the capsule and express it in μg/cm² per day. Compare the calculated result with the observed value, $Q/t = 64.50$ μg/cm² per day. Using equation (13–70),

$$Q/t = \frac{C_p K_r D_a D_m}{K_r D_a h_m + D_m h_a}$$

$$Q/t = \frac{(513\ \mu g/cm^3)(0.022)(4.994 \times 10^{-2}\ cm^2/day)(14.26 \times 10^{-2}\ cm^2/day)}{(0.022)(4.994 \times 10^{-2}\ cm^2/day)(0.080\ cm) + (14.26 \times 10^{-2}\ cm^2/day)(0.008\ cm)}$$

$$Q/t = \frac{0.08037}{0.00123} = 65.34\ \mu g/cm^2\ per\ day$$

In the example just given, (*a*) is $K_r D_a h_m \gg D_m h_a$ or (*b*) is $D_m h_a \gg K D_a h_m$? (*c*) What conclusion can be drawn regarding matrix or diffusion-layer control?

*Contrary to convention, the partition coefficient K_r in equation (13–71) is defined as the water/lipid distribution coefficient. Thus, K_r decreases here as the compound becomes more hydrophobic. The K as used previously, for example, in equations (13–50), (13–55), and (13–61), is the lipid/water distribution coefficient such that K increases with increasing hydrophobicity of the compound. C_m varies with time and eventually equals C_p. Therefore, the equilibrium partition coefficient does not involve C_m, but rather, the equilibrium values C_p and C_s.

$$K_r D_a h_m = 8.79 \times 10^{-5};\ D_m h_a = 1.14 \times 10^{-3}$$

$$D_m h_a/(K_r D_a h_m + D_m h_a) = (1.14 \times 10^{-3})/[(8.79 \times 10^{-5}) + (1.14 \times 10^{-3})] = 0.93$$

Therefore, $D_m h_a \gg K_r D_a h_m$, and the system is 93% under aqueous diffusion-layer control. It should thus be possible to use the simplified equation (13–73):

$$Q/t = \frac{K_r D_a C_p}{h_a} = \frac{(0.022)(4.994 \times 10^{-2})(513)}{0.008}$$

$$= 70.45\ \mu g/cm^2 \text{ per day}$$

Although $D_m h_a$ is larger than $K_r D_a h_m$ by about one order of magnitude (i.e., $D_m h_a/K D_a h_m = 13$), it is evident that a considerably better result is obtained by using the full expression, equation (13–70).

Example 13–11. Two new contraceptive steroid esters, *A* and *B*, were synthesized, and the parameters determined for release from polymeric capsules are[40]

	K_r	D_a (cm²/day)	D_m (cm²/day)	C_p (μg/cm³)	h_a(cm)	$(Q/t)_{obs}$ μg/cm² per day
A	0.15	25×10^{-2}	2.6×10^{-2}	100	0.008	24.50
B	0.04	4.0×10^{-2}	3.0×10^{-2}	85	0.008	10.32

Using equation (13–70) and the quantities in the table given, calculate values of h_m in cm for these capsule membranes.

$$Q/t = \frac{C_p K_r D_a D_m}{K_r D_a h_m + D_m h_a}$$

$$(Q/t)(K_r D_a h_m + D_m h_a) = C_p K_r D_a D_m$$

$$(Q/t)(K_r D_a h_m) = C_p K_r D_a D_m - D_m h_a (Q/t)$$

$$h_m = \frac{C_p K_r D_a D_m - D_m h_a (Q/t)}{(Q/t) K_r D_a}$$

For capsule *A*:

$$h_m = \frac{(100)(0.15)(25 \times 10^{-2})(2.6 \times 10^{-2}) - (2.6 \times 10^{-2})(0.008)(24.50)}{(24.50)(0.15)(25 \times 10^{-2})}$$

$$h_m = \frac{0.0924}{0.9188}\ \text{cm} = 0.101\ \text{cm}$$

Note that all units cancel except cm in the equation for h_m. The reader should carry out the calculations for compound *B*. (*Answer:* 0.097 cm.)

DIFFUSION PRINCIPLES IN BIOLOGIC SYSTEMS

Gastrointestinal Absorption of Drugs. Drugs pass through living membranes according to two main classes of transport, passive and active. Passive transfer involves a simple diffusion driven by differences in drug concentration on the two sides of the membrane. In intestinal absorption, for example, the drug travels in most cases by passive transport from a region of high concentration in the gastrointestinal tract to a region of low concentration in the systemic circulation.

Active transport requires an energy source such as an enzyme or biochemical carrier to ferry the drug across the membrane; transport can proceed from regions of *low* concentration to regions of *high* concentration through the "pumping action" of these biologic transport systems. Other special mechanisms include convective and ion-pair transport. We will make limited use of specialized carrier systems, and will concentrate attention mainly on passive diffusion.

Many drugs are weakly acidic or basic, and the ionic character of the drug and the biologic compartments and membranes have an important influence on the transfer process. From the Henderson–Hasselbalch relationship (p. 169) for a weak acid,

$$\text{pH} = \text{p}K_a + \log \frac{[\text{A}^-]}{[\text{HA}]}$$

in which [HA] is the concentration of the nonionized weak acid and [A^-] is the concentration of its conjugate base. For a weak base, the equation is (p. 170)

$$\text{pH} = \text{p}K_a + \log \frac{[\text{B}]}{[\text{BH}^+]}$$

in which [B] is the concentration of the base and [BH^+] that of its conjugate acid. pK_a is the dissociation exponent for the weak acid in each case. For the weak base, $pK_a = pK_w - pK_b$.

The percent ionization of a weak acid is the ratio of concentration of drug in the ionic form (I) to total concentration of drug in ionic (I) and undissociated (U) form, multipled by 100:

$$\%\ \text{Ionized} = \frac{I}{I + U} \times 100 \qquad (13\text{–}74)$$

The Henderson–Hasselbalch equation for weak acid therefore may be written as

$$\frac{U}{I} = 10^{(\text{p}K_a - \text{pH})} = \text{antilog}\ (\text{p}K_a - \text{pH}) \qquad (13\text{–}75)$$

or

$$U = I\ \text{antilog}\ (\text{p}K_a - \text{pH}) \qquad (13\text{–}76)$$

Substituting U into the equation for percent ionization yields:

$$\%\ \text{Ionized} = \frac{100}{1 + \text{antilog}\ (\text{p}K_a - \text{pH})} \qquad (13\text{–}77)$$

Similarly, for a weak molecular base,

$$\%\ \text{Ionized} = \frac{100}{1 + \text{antilog}\ (\text{pH} - \text{p}K_a)} \qquad (13\text{–}78)$$

In equation (13–77), pK_a refers to the weak acid, while in (13–78), pK_a signifies the acid that is conjugate to the weak base.

The percentage ionization at various pH values of a weak acid, sulfisoxazole, $pK_a \cong 5.0$, is found in Table 13–4. At a point at which the pH is equal to the drug's pK_a, equal amounts are present in the ionic and molecular forms.

TABLE 13–4. *Percent Sulfisoxazole, pK_a – 5.0, Dissociated and Undissociated at Various pH Values*

pH	% Dissociated	% Undissociated
2.0	0.100	99.900
4.0	9.091	90.909
5.0	50.000	50.000
6.0	90.909	9.091
8.0	99.900	0.100
10.0	99.999	0.001

pH-Partition Hypothesis. Biologic membranes are predominantly lipophilic, and drugs penetrate these barriers mainly in their molecular, undissociated form. Brodie and his associates[43] were the first workers to apply the principle, known as the *pH-partition hypothesis*, that drugs are absorbed from the gastrointestinal tract by passive diffusion depending on the fraction of undissociated drug at the pH of the intestines. It is reasoned that the partition coefficient between membranes and gastrointestinal fluids is large for the undissociated drug species and favors transport of the molecular form from the intestine through the mucosal wall and into the systemic circulation.

The pH-partition principle has been tested in a large number of in vitro and in vivo studies, and it has been found to be only partly applicable in real biologic systems.[43,44] In many cases, the ionized as well as the un-ionized form partitions into, and is appreciably transported across, lipophilic membranes. It is found for some drugs, such as sulfathiazole, that the in vitro permeability coefficient for the ionized form may actually exceed that for the molecular form of the drug.

Transport of a drug by diffusion across a membrane such as the gastrointestinal mucosa is represented by Fick's law:

$$-\frac{dM}{dt} = \frac{D_m SK}{h}(C_g - C_p) \qquad (13-79)$$

in which M is the amount of drug in the gut compartment at time t, D_m is diffusivity in the intestinal membrane, S the area of the membrane, K the partition coefficient between membrane and aqueous medium in the intestine, h the membrane thickness, C_g the concentration of drug in the intestinal compartment, and C_p the drug concentration in the plasma compartment at time t. The gut compartment is kept at a high concentration and has a large volume relative to the plasma compartment so as to make C_g a constant. C_p, being relatively small, may be omitted. Equation (13–79) then becomes

$$-\frac{dM}{dt} = D_m SK\, C_g/h \qquad (13-80)$$

The left-hand side of (13–80) is converted into concentration units, C (mass/unit volume) × V (volume). On the right-hand side of (13–80), the diffusion constant, membrane area, partition coefficient, and membrane thickness are combined to yield a *permeability coefficient*. These changes lead to a pair of equations:

$$-V\frac{dC_g}{dt} = P_g C_g \qquad (13-81a)$$

$$-V\frac{dC_p}{dt} = P_p C_g \qquad (13-81b)$$

in which C_g and P_g of equation (13–81*a*) are the concentration and permeability coefficient, respectively, for drug passage from intestine to plasma. In equation (13–81*b*), C_p and P_p are corresponding terms for the reverse passage of drug from plasma to intestine. Since the gut volume V and gut concentration C_g are constant, dividing (13–81*a*) by (13–81*b*) yields

$$\frac{dC_g/dt}{dC_p/dt} = \frac{P_g}{P_p} \qquad (13-82)$$

Equation (13–82) demonstrates that the ratio of absorption rates in the intestine-to-plasma and the plasma-to-intestine directions equals the ratio of permeability coefficients.

In a study by Turner et al.,[44] results show that undissociated drugs pass freely through the intestinal membrane in either direction by simple diffusion, in agreement with the pH-partition principle. Drugs that are partly ionized show an increased permeability ratio indicating favored penetration from intestine to plasma. Completely ionized drugs, either negatively or positively charged, show permeability ratios P_g/P_p of about 1.3, that is, a greater passage from gut to plasma than from plasma to gut. This suggests that penetration of ions is associated with sodium ion flux. Their forward passage P_g is apparently due to a coupling of the ions with sodium transport, which mechanism then ferries the drug ions across the membrane, in conflict with the simple pH-partition hypothesis.

Colaizzi and Klink[45] have investigated the pH-partition behavior of the tetracyclines, a class of drugs having three separate pK_a values, which complicates the principles of pH-partition. The lipid solubility and relative amounts of the ionic forms of a tetracycline at physiologic pH may have a bearing on the biologic activity of the various tetracycline analogs used in clinical practice.

Modification of the pH-Partition Principle. Ho, Higuchi and coworkers[46] also have shown that the pH-partition principle is only approximate, assuming as it does that drugs are absorbed through the intestinal mucosa in the nondissociated form alone. Absorption of relatively small ionic and nonionic species through the aqueous pores and the aqueous diffusion layer in front of the membrane must be considered.[47] Other complicating factors, such as metabolism of the drug in the gastrointestinal membrane, absorption in micellar form, and enterohepatic circulatory effects, must also be

accounted for in any model that is proposed to reflect in vivo processes.

Ho, Higuchi, and their associates[47] have investigated the gastrointestinal absorption of drugs using diffusional principles and a knowledge of the physiologic factors involved. They employed an in situ preparation, as shown in Figure 13–18, known as the modified Doluisio method for in situ rat intestinal absorption. (The original rat intestinal preparation[48] employed two syringes without the mechanical pumping modification.)

The model used for the absorption of a drug through the mucosal membrane of the small intestine is shown in Figure 13–19. The aqueous boundary layer is in series with the biomembrane, which is composed of lipid regions and aqueous pores in parallel. The final reservoir is a sink consisting of the blood. The flux of a drug permeating the mucosal membrane is

$$J = P_{app}\,(C_b - C_{blood}) \qquad (13-83)$$

or, since the blood reservoir is a sink, $C_{blood} \cong 0$;

$$J = P_{app}\,C_b \qquad (13-84)$$

in which P_{app} is the apparent permeability coefficient (cm/sec) and C_b is the total drug concentration in bulk solution in the lumen of the intestine.

The apparent permeability coefficient is given by

$$P_{app} = \frac{1}{\frac{1}{P_{aq}} + \frac{1}{P_m}} \qquad (13-85)$$

in which P_{aq} is the permeability coefficient of the drug in the aqueous boundary layer (cm/sec), and P_m is the effective permeability coefficient for the drug in the lipoidal and polar aqueous regions of the membrane (cm/sec).

The flux may be written in terms of drug concentration C_b in the intestinal lumen by combining with it a term for the volume, or

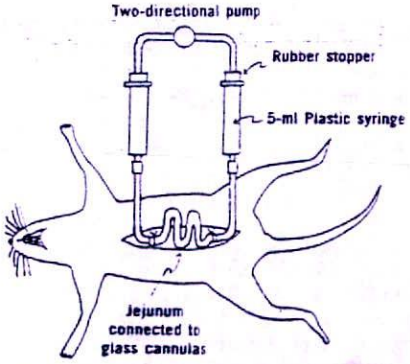


Fig. 13–18. Modified Doluisio technique for in situ rat intestinal absorption. (From N. F. H. Ho et al., in *Gastrointestinal Absorption of Drugs*, A. J. Aguiar, Ed., American Pharmaceutical Association, Academy of Pharmaceutical Sciences, Washington, D.C., 1981, reproduced with permission of the copyright owner.)

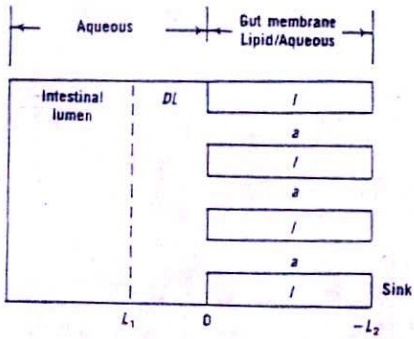


Fig. 13–19. Model for the absorption of a drug through the mucosa of the small intestine. The intestinal lumen is on the left, followed by a static aqueous diffusion layer, *DL*. The gut membrane consists of aqueous pores *a* and lipoidal regions *l*. The distance from the membrane wall to the systemic circulation (sink) is marked off from 0 to $-L_2$; the distance through the diffusion layer is 0 to L_1. (From N. F. H. Ho, W. I. Higuchi and J. Turi, J. Pharm. Sci. 61, 193, 1972, reproduced with permission of the copyright owner.)

$$J = -\frac{V}{S}\cdot\frac{dC_b}{dt} \qquad (13-86)$$

in which S is the surface area and V is the volume of the intestinal segment. The first-order disappearance rate K_u (sec^{-1}) of the drug in the intestine is found in the expression

$$\frac{dC_b}{dt} = -K_u C_b \qquad (13-87)$$

Substituting equation (13–87) into (13–86) gives

$$J = \frac{V}{S}\cdot K_u C_b \qquad (13-88)$$

and from equations (13–84) and (13–85), together with (13–88), yields

$$P_{app} = \frac{1}{\frac{1}{P_{aq}} + \frac{1}{P_m}} = \frac{V}{S}K_u \qquad (13-89)$$

or

$$K_u = \frac{S}{V}\cdot\frac{P_{aq}}{1 + \frac{P_{aq}}{P_m}} \qquad (13-90)$$

Consideration of two cases, (1) aqueous boundary layer control and (2) membrane control, results in simplification of equation (13–90).

(1) When the permeability coefficient of the intestinal membrane (i.e., the velocity of drug passage through the membrane in cm/sec) is much greater than that of the aqueous layer, the aqueous layer will cause a slower passage of the drug and become a rate-limiting barrier. (The slower passage is always the rate-determining process.) Therefore, P_{aq}/P_m will be much less than unity, and equation (13–90) reduces to

$$K_{u,max} = (S/V)P_{aq} \qquad (13-91)$$

K_u is now written as $K_{u,max}$ because the maximum possible diffusional rate constant is determined by passage across the aqueous boundary layer.

(2) If, on the other hand, the permeability of the aqueous boundary layer is much greater than that of the membrane, P_{aq}/P_m will become much larger than unity, and equation (13–90) reduces to

$$K_u = (S/V)P_m \qquad (13-92)$$

The rate-determining step for transport of drug across the membrane is now under membrane control. When neither P_{aq} nor P_m is much larger than the other, the process is controlled by the rate of drug passage through both the stationary aqueous layer and the membrane. Figures 13–20 and 13–21 show the absorption studies of *n*-alkanol and *n*-alkanoic acid homologs that concisely illustrate the biophysical interplay of pH, pK_a, solute lipophilicity via carbon chain length, membrane permeability of the lipid and aqueous pore pathways, and permeability of the aqueous diffusion layer as influenced by the hydrodynamics of the stirred solution.

Example 13–12. Calculate the first-order rate constant, K_u, for transport of an aliphatic alcohol across the mucosal membrane of the rat small intestine if $S/V = 11.2\ cm^{-1}$, $P_{aq} = 1.5 \times 10^{-4}$ cm/sec, and $P_m = 1.1 \times 10^{-4}$ cm/sec.

$$K_u = (11.2)\frac{1.5 \times 10^{-4}\ \text{cm/sec}}{1 + \dfrac{1.5 \times 10^{-4}\ \text{cm/sec}}{1.1 \times 10^{-4}\ \text{cm/sec}}} = 11.2\left(\frac{1.5 \times 10^{-4}}{2.3636}\right)$$

$$K_u = 7.1 \times 10^{-4}\ \text{sec}^{-1}$$

For a weak electrolytic drug, the absorption rate constant K_u is[47]

$$K_u = \frac{S}{V} \cdot \frac{P_{aq}}{1 + \dfrac{P_{aq}}{P_0 X_s + P_p}} \qquad (13-93)$$

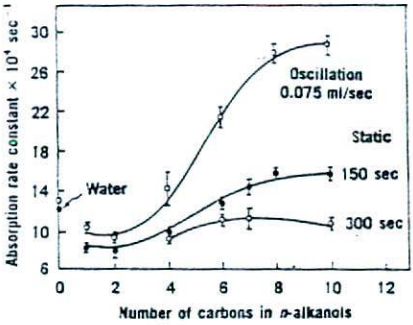


Fig. 13–20. First-order absorption rate constant for a series of *n*-alkanols under various hydrodynamic conditions (static or low stirring rates and oscillation or high stirring of fluid at 0.075 mL/sec) in the jejunum, using the modified Doluisio technique. (From N. F. H. Ho, J. Y. Park, W. Morozowich and W. I. Higuchi, in *Design of Biopharmaceutical Properties Through Prodrugs and Analogs*, E. B. Roche, Ed., American Pharmaceutical Association, Academy of Pharmaceutical Sciences, Washington, D.C., 1977, p. 148, reproduced with permission of the copyright owner.)

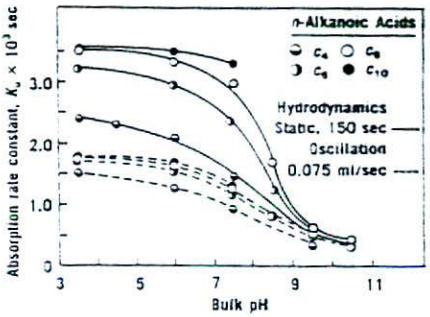


Fig. 13–21. First-order absorption rate constants of alkanoic acids versus buffered pH of the bulk solution in the rat gut lumen, using the modified Doluisio technique. Hydrodynamic conditions are shown in the figure. (From N. F. H. Ho, J. Y. Park, W. Morozowich and W. I. Higuchi, in *Design of Biopharmaceutical Properties Through Prodrugs and Analogs*, E. B. Roche, Ed., American Pharmaceutical Association, Academy of Pharmaceutical Sciences, Washington, D.C., 1977, p. 150, reproduced with permission of the copyright owner.)

in which P_m of the membrane is now separated into a term P_0, the permeability coefficient of the lipoidal pathway for nondissociated drug, and P_p, the permeability coefficient of the polar or aqueous pathway for both ionic and nonionic species.

$$P_m = P_0 X_s + P_p \qquad (13-94)$$

The fraction of nondissociated drug species, X_s, at the pH of the membrane surface in the aqueous boundary is

$$X_s = \frac{[H^+]_s}{[H^+]_s + K_a} = \frac{1}{1 + \text{antilog}(pH_s - pK_a)} \qquad (13-95)$$

for weak acids, and

$$X_s = \frac{K_a}{[H^+]_s + K_a} = \frac{1}{1 + \text{antilog}(pK_a - pH_s)} \qquad (13-96)$$

for weak bases. The student should note the relationship between equations (13–95) and (13–77) and between (13–96) and (13–78). K_a is the dissociation constant of a weak acid or of the acid conjugate to a weak base, and $[H^+]_s$ is the hydrogen ion concentration at the membrane surface, where *s* stands for surface. The surface pH_s is not necessarily equal to the pH of the buffered drug solution[47] since the membrane of the small intestine actively secretes buffer species (principally CO_2^{2-} and HCO_3^-). It is only at a pH of about 6.5 to 7.0 that the surface pH is equal to the buffered solution pH. One readily recognizes that for nonelectrolytes, X_s becomes unity, and also that for large molecules such as steroids, P_p is insignificant.

Example 13–13. A weakly acidic drug having a $K_a = 1.48 \times 10^{-5}$ is placed in the duodenum in a buffered solution of pH 5.0. Assume $[H^+]_s = 1 \times 10^{-5}$ in the duodenum, $P_{aq} = 5.0 \times 10^{-4}$ cm/sec, $P_0 = 1.14 \times 10^{-3}$ cm/sec, $P_p = 2.4 \times 10^{-5}$ cm/sec, and $S/V = 11.20\ cm^{-1}$. Calculate the absorption rate constant, K_u, using equation (13–93). First, from equation (13–94),

Calculate the absorption rate constant, K_a, using equation (13–93). First, from equation (13–94),

$$X_s = \frac{[1 \times 10^{-5}]}{[1 \times 10^{-5}] + 1.48 \times 10^{-5}} = 0.403$$

Then

$$K_a = (11.2)\frac{5.0 \times 10^{-4}}{1 + \dfrac{5.0 \times 10^{-4}}{(1.14 \times 10^{-3})0.403 + 2.4 \times 10^{-5}}}$$

$$K_a = 2.75 \times 10^{-2}\ \text{sec}^{-1}$$

Transcorneal Permeation. In gastrointestinal absorption *(Example 13–12)* the permeability coefficient is divided into P_0 as the lipoidal pathway for undissociated drug and P_p for the polar pathway for both ionic and nonionic species. In an analogous way, P can be divided for corneal penetration of a weak base into two permeation coefficients: P_B for the un-ionized species and P_{BH^+} for its ionized conjugated acid. The following example demonstrates the use of these two permeability coefficients.

Mitra and Mikkelson[45] studied the transcorneal permeation of pilocarpine using an in vitro rabbit corneal preparation clamped into a special diffusion cell. The permeability (permeability coefficient) P as determined experimentally is given at various pH values in Table 13–5.

Example 13–14. (*a*) Compute the un-ionized fraction, f_B, of pilocarpine at the pH values found in Table 13–5, using equation (13–96). The pK_a of pilocarpine (actually the pK_a of the conjugate acid of the weak base, pilocarpine, and known as the pilocarpinium ion) is 6.67 at 34° C.

(*b*) The relationship between the permeability P and the un-ionized fraction f_B of pilocarpine base over this range of pH values is given by the equation

$$P = P_B f_B + P_{BH^+} f_{BH^+} \qquad (13\text{–}97)$$

where B stands for base and BH^+ for its ionized or conjugate acid form. Noting that $f_{BH^+} = 1 - f_B$, equation (13–97) can be written

$$P = P_{BH^+} + (P_B - P_{BH^+})f_B \qquad (13\text{–}98)$$

Obtain the permeability for the protonated species P_{BH^+} and the uncharged base P_B using least-squares linear regression on equation (13–98) in which P, the total permeability, is the dependent variable and f_B the independent variable.

(*c*) Obtain the ratio of the two permeability coefficients, P_{BH^+}/P_B.

Answers:

(*a*) The calculated f_B values are given at the various pH values:

pH, donor solution	4.67	5.67	6.24	6.40	6.67	6.91	7.04	7.40
f_B	0.01	0.09	0.27	0.35	0.50	0.64	0.70	0.84

(*b*) Upon linear regression, equation (13–98) becomes

$$P = 4.826 \times 10^{-6} - 4.897 \times 10^{-6} f_B$$

$$\text{Intercept} = 4.836 \times 10^{-6} = P_{BH^+}$$

$$\text{Slope} = 4.897 \times 10^{-6} = (P_B - 4.836 \times 10^{-6})$$

$$P_B = 9.733 \times 10^{-6}\ \text{cm/sec}$$

(*c*) The ratio $P_B/P_{BH^+} \approx 2$. The permeability of the un-ionized form is seen to be about twice that of the ionized form. The reader should now be in a position to explain the result under (*c*) above based on the pH-partition hypothesis.

TABLE 13–5. ***Permeability Coefficients at Various pH Values***

pH, donor solution	4.67	5.67	6.24	6.40	6.67	6.91	7.04	7.40
$P \times 10^6$ cm/sec	4.72	5.44	6.11	6.81	7.06	7.56	8.79	8.85

Percutaneous Absorption. Percutaneous penetration, that is, passage through the skin, involves (a) dissolution of a drug in its vehicle, (b) diffusion of solubilized drug (solute) from the vehicle to the surface of the skin, and (c) penetration of the drug through the layers of the skin, principally the stratum corneum. Figure 13–22 shows the various structures of the skin involved in percutaneous absorption. The slowest step in the process usually involves passage through the stratum corneum; therefore, this is the rate that limits or controls the permeation.*

Scheuplein[50] found that the average permeability constant, P_s, for water into skin was 1.0×10^{-3} cm/hr and the average diffusion constant, D_s, was 2.8×10^{-10} cm^2/sec. (The subscript, s, on D stands for "skin.") Water penetration into the stratum corneum appears to alter the barrier only slightly, primarily by its effect on the pores of the skin. The stratum corneum is considered to be a dense homogeneous film. Small polar nonelectrolytes penetrate into the bulk of the stratum corneum and bind strongly to its components; diffusion of most substances through this barrier is quite slow. Diffusion, for the most part, is transcellular rather than occurring through channels between cells or through sebaceous pores and sweat ducts (Fig. 13–22, *A* rather than *B*, *C*, and *E*). Stratum corneum, normal and even hydrated, is a most impermeable biologic membrane: this is one of its important features in living systems.

It is an oversimplification to assume that one route prevails under all conditions.[50] Yet after steady-state conditions have been established, transdermal diffusion through the stratum corneum most likely predominates. In the early stages of penetration, diffusion through the appendages (hair follicles, sebaceous and sweat ducts) may be significant. These *shunt* pathways are even important in steady-state diffusion in the case of large polar molecules, as noted in the following.

Scheuplein et al.[51] investigated the percutaneous absorption of a number of steroids. They found that the skin's main barrier to penetration by steroid molecules was the stratum corneum. The diffusion coefficient, D_s, for these compounds was approximately 10^{-11} cm^2/sec, several orders of magnitude smaller than for most nonelectrolytes. This small value of D_s resulted in low permeability of the steroids. The addition of polar groups to the steroid molecule reduced the diffusion constant still more. For the polar steroids, sweat and sebaceous ducts appeared to play a more important part

*Appreciable amounts of some drugs, such as steroids, may also penetrate the skin through sebaceous ducts ordinarily associated with hairs on the skin surface (transfollicular absorption).

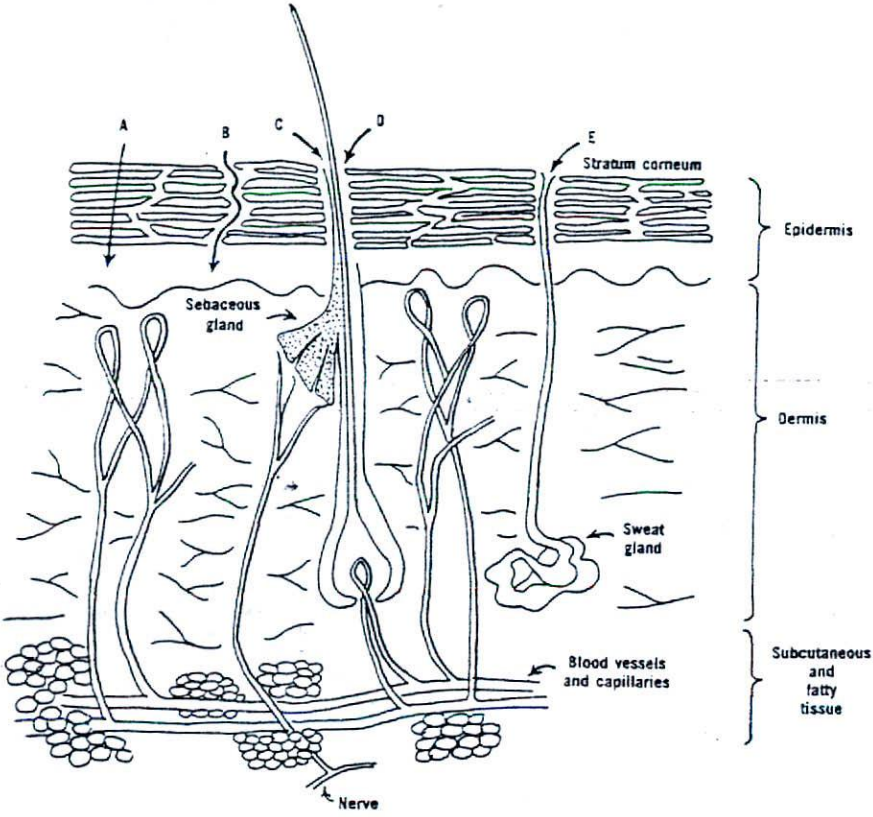


Fig. 13–22. Skin structures involved in percutaneous absorption. Thickness of layers is not drawn to scale. Key to sites of percutaneous penetration: *A*, transcellular; *B*, diffusion through channels between cells; *C*, through sebaceous ducts; *D*, transfollicular; *E*, through sweat ducts.

in percutaneous absorption than diffusion through the bulk stratum corneum.

The studies of Flynn, Higuchi, Ho, and coworkers[52] demonstrate the methods used to characterize the permeability of different sections of the skin. Distinct protein and lipid domains appear to have a role in the penetration of drugs into the stratum corneum. The uptake of a solute may depend on the characteristics of the protein region, the lipid pathway, or a combination of these two domains in the stratum corneum, and depends on the lipophilicity of the solute. The lipid content of the stratum corneum is important in the uptake of lipophilic solutes but is not involved in the attraction of hydrophilic drugs.[53]

The proper choice of vehicle is important in ensuring bioavailability of topically applied drugs. Turi et al.[54] studied the effect of solvents—propylene glycol in water and polyoxypropylene 15 stearyl ether in mineral oil—on the penetration of diflorasone diacetate (a steroid ester) into the skin. The percutaneous flux of the drug was observed to be reduced by the presence of excess solvent in the base. Optimum solvent concentrations were determined for products containing both 0.05% and 0.1% diflorasone diacetate.

The important factors influencing the penetration of a drug into the skin are (1) concentration of dissolved drug C_s, since penetration rate is proportional to concentration; (2) partition coefficient K between the skin and vehicle, which is a measure of the relative affinity of the drug for skin and vehicle; and (3) diffusion coefficients, which represent the resistance of drug molecule movement through vehicle D_v and skin D_s barriers. The relative magnitude of the two diffusion coefficients, D_v and D_s, determines whether release from vehicle or passage through the skin is the rate-limiting step.[54,55]

For diflorasone diacetate in propylene glycol–water (a highly polar base) and in polyoxypropylene 15 stearyl ether in mineral oil (a nonpolar base), the skin was found to be the rate-limiting barrier. The diffusional equation for this system is

$$-\frac{dC_v}{dt} = \frac{SK_{vs}D_sC_v}{Vh} \qquad (13\text{–}99)$$

in which C_v is the concentration of dissolved drug in the vehicle (g/cm^3); S is surface area of application (cm^2); K_{vs} the skin-vehicle partition coefficient of difiorasone diacetate; D_s the diffusion coefficient of the drug in the skin (cm^2/sec); V the volume of the drug product applied (cm^3); and h the thickness of the skin barrier (cm).

The diffusion coefficient and skin barrier thickness may be replaced by a resistance R_s to diffusion in the skin:

$$R_s = h/D_s \qquad (13-100)$$

and equation (13–99) becomes

$$-\frac{dC_v}{dt} = \frac{SK_{vs}C_v}{VR_s} \qquad (13-101)$$

In a percutaneous experimental procedure, Turi et al.[54] measured the drug in the receptor rather than in the donor compartment of an in vitro diffusion apparatus, the barrier of which consisted of hairless mouse skin. At steady-state penetration,

$$-V\frac{dC_v}{dt} = V_R \cdot \frac{dC_R}{dt} \qquad (13-102)$$

The rate of loss of drug from the vehicle in the donor compartment is equal to the rate of gain of drug in the receptor compartment. With this change, equation (13–101) is integrated to yield

$$M_R = \left(\frac{SK_{vs}C_v}{R_s}\right)t \qquad (13-103)$$

in which M_R is the amount of difiorasone diacetate in the receptor solution at time t. The flux, J, is

$$J = \frac{M_R}{S \cdot t} = \frac{K_{vs}C_v}{R_s} \qquad (13-104)$$

The steady-state flux for a 0.05% difiorasone diacetate formulation containing various proportions (weight fractions) of polyoxypropylene 15 stearyl ether in mineral oil is shown in Figure 13–23. The skin–vehicle partition coefficient was measured for each vehicle formulation. The points represent the experimental values obtained with the diffusion apparatus; the line was calculated using equation (13–104). The point at 0 weight fraction of the ether cosolvent is due to low solubility and slow dissolution rate of the drug in mineral oil and may be disregarded. Beyond a critical concentration, about 0.2 weight fraction of polyoxypropylene 15 stearyl ether, penetration rate decreases. The results[54] indicated that one application of the topical steroidal preparation per day was adequate and that the 0.05% concentration was as effective as the 0.1% preparation.

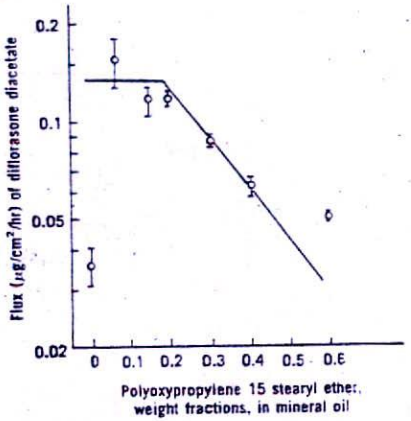


Fig. 13–23. Steady-state flux of difiorasone diacetate in a mixture of polyoxypropylene 15 stearate ether in mineral oil. (From J. S. Turi, D. Danielson and W. Wolterson, J. Pharm. Sci. 68, 275, 1979, reproduced with permission of the copyright owner.)

Example 13–15. A penetration study of 5.0×10^{-3} g/cm^3 difiorasone diacetate solution was conducted at 27° C in the diffusion cell of Turi et al.[54] using a solvent of 0.4 weight fraction of polyoxypropylene 15 stearyl ether in mineral oil. The partition coefficient K_{vs} for the drug distributed between hairless mouse skin and vehicle was found to be 0.625. The resistance R_s of the drug in the mouse skin was determined to be 6666 hr/cm. The diameter of a circular section of mouse skin used as the barrier in the diffusion cell was 1.35 cm.* Calculate (*a*) the flux, $J = M_R/(S \cdot t)$, in g/cm^2/hr, and (*b*) the amount M_R in μg of difiorasone diacetate that diffused through the hairless mouse skin in 8 hours.

Using equation (13–104)

(*a*)

$$J = \frac{K_{vs}C_v}{R_s} = \frac{(0.625)(5.0 \times 10^{-3}\ \text{g/cm}^3)}{6666\ \text{hr/cm}}$$

$$J = 4.69 \times 10^{-7}\ \text{g/cm}^2\text{/hr}$$

(*b*)

$$M_R = J \times S \times t$$

$$M_R = (4.69 \times 10^{-7}\ \text{g/cm}^2\text{/hr}) \times \tfrac{\pi}{4}(1.35\text{cm})^2\ (8\ \text{hr})$$

$$M_R = 5.37 \times 10^{-6}\ \text{g} = 5.37\ \mu\text{g}$$

Ostrenga and his associates[56] studied the nature and composition of topical vehicles as they relate to the transport of a drug through the skin. The varied D_s, K_{vs}, and C_v in order to improve skin penetration of two topical steroids, fluocinonide and fluocinolone acetonide, incorporated into various propylene glycol–water gels. In vivo penetration and in vitro diffusion using abdominal skin removed at autopsy were studied. It was concluded that clinical efficacy of topical steroids can be estimated satisfactorily from in vitro data regarding release, diffusion, and the physical chemical properties of drug and vehicle.

The diffusion, D_s, of the drug in the skin barrier can be influenced by components of the vehicle (mainly solvents and surfactants), and an optimum partition coefficient may be obtained by altering the affinity of the vehicle for the drug.

*The area S of a circle, expressed in diameter, is $S = (\frac{1}{4})\pi d^2$. (See inside front cover.)

The in vitro rate of skin penetration of the drug, dQ/dt, at 25° C is obtained experimentally at definite times, and the cumulative amount penetrating (measured in radioactive disintegrations per minute) is plotted against time in minutes or hours. After steady state has been attained, the slope of the straight line yields the rate, dM/dt. The lag time is obtained by extrapolating the steady-state line to the time axis.

In vitro penetration of human cadaver skin and in vivo penetration of fluocinolone acetonide from propylene glycol gels into living skin are compared in Figure 13–24. It is observed that the shapes and peaks of the two curves are approximately similar. Thus, in vitro studies using human skin sections should serve as a rough guide to the formulation of acceptable bases for these steroidal compounds.

Ostrenga et al.[56] were able to show a relationship between release of the steroid from its vehicle, in vitro penetration through human skin obtained at autopsy, and in vivo vasoconstrictor activity of the drug depending on compositions of the vehicle. The correlations obtained suggest that information obtained from diffusion studies can assist in the design of effective topical dosage forms. Some useful guidelines are (a) all the drug should be in solution in the vehicle, (b) the solvent mixtures must maintain a favorable partition coefficient so that the drug is soluble in the vehicle and yet has a great affinity for the skin barrier into which it penetrates, and (c) the components of the vehicle should favorably influence the permeability of the stratum corneum.

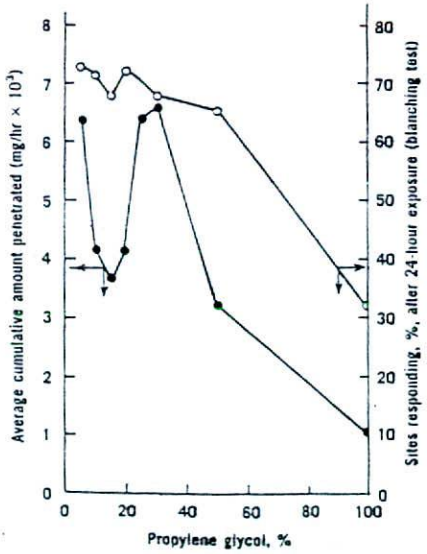


Fig. 13–24. Comparison of in vitro penetration of steroid through a skin section and in vivo skin blanching test. Key: ●, in vitro method: ○, in vivo method. (From J. Ostrenga, C. Steinmetz and B. Poulsen, J. Pharm. Sci. 60, 1177, 1971, reproduced with permission of the copyright owner.)

Sloan and coworkers[57] studied the effect of vehicles having a range of solubility parameters, δ (see pp. 224–228), on the diffusion of salicylic acid and theophylline through hairless mouse skin. They were able to correlate the partition coefficient K for the drugs between the vehicle and skin calculated from solubility parameters (see *Problem 13–16*, p. 359) and the permeability coefficient P, obtained experimentally from the diffusion data. The results obtained with salicylic acid, a soluble molecule, and with theophylline, a poorly soluble molecule with quite different physical chemical properties, were practically the same.

In the studies of skin permeation described thus far, efforts have been made to increase percutaneous absorption processes. It is important, however, that some compounds not be absorbed. Pharmaceutical adjuvants such as antimicrobial agents, antioxidants, coloring agents, and drug solubilizers, although ideally they should remain in the vehicle on the skin's surface, can penetrate the stratum corneum.

Parabens, typical preservatives incorporated into cosmetics and topical dosage forms, may cause allergic reactions if absorbed into the dermis. Komatsu and Suzuki[58] studied the in vitro percutaneous absorption of butylparaben (butyl *p*-hydroxybenzoate) through guinea-pig skin. Disks of dorsal skin were placed in a diffusion cell between a donor and receptor chamber, and the penetration of ^{14}C-butylparaben was determined by the fractional collection of samples from the cell's receptor side and measurement of radioactivity in a liquid scintillation counter.

When butylparaben was incorporated into various vehicles containing polysorbate 80, propylene glycol, and polyethylene glycol 400, a constant diffusivity was obtained averaging $3.63(\pm 0.47$ S.D.$) \times 10^{-4}$ cm^2/hr.

The partition coefficient, K_{vs}, for the paraben between vehicle and skin changed markedly depending upon the vehicle. For a 0.015% (*w/v*) aqueous solution of butyl paraben, K_{vs} was found to be 2.77. For a 0.1% (*w/v*) solution of the preservative containing 2% (*w/v*) of polysorbate 80 and 10% (*w/v*) propylene glycol in water, the partition coefficient dropped to 0.18. There was no apparent complexation between these solubilizers and butylparaben, according to the authors.

The addition of either propylene glycol or polyethylene glycol 400 to water was found to increase the solubility of paraben in the vehicle and to reduce its partition coefficient between vehicle and skin. By this means, skin penetration of butylparaben could be retarded, maintaining the preservative in the topical vehicle where it was desired.

In the case of polysorbate 80, Komatsu and Suzuki[58] found that this surfactant, too, reduced preservative absorption, maintaining the antibacterial action of the paraben in the vehicle. These workers concluded that the action of polysorbate 80 was a balance of complex

factors, which is difficult for the product formulator to predict and manage.

Buccal Absorption. Using a wide range of organic acids and bases as drug models, Beckett and Moffat[59] studied the penetration of drugs into the lipid membrane of the mouths of humans. In harmony with the pH-partition hypothesis, absorption was related to the pK_a of the compound and its lipid–water partition coefficient.

Ho and Higuchi[60] applied one of the earlier mass transfer models[61] to the analysis of the buccal absorption of *n*-alkanoic acids.[62] They utilized the aqueous-lipid phase model in which the weak acid species are transported across the aqueous diffusion layer and, subsequently, only the nonionized species pass across the lipid membrane. Unlike the intestinal membrane, the buccal membrane does not appear to possess significant aqueous pore pathways, and the surface pH is essentially the same as the buffered drug solution pH. Buccal absorption is assumed to be a first-order process owing to the nonaccumulation of drug on the blood side.

$$\ln \frac{C}{C_0} = -K_u t \qquad (13-105)$$

in which C is the aqueous concentration of the *n*-alkanoic acid in the donor or mucosal compartment. The absorption rate constant, K_u, is

$$K_u = \frac{S}{V} \cdot \frac{P_{aq}}{1 + \dfrac{P_{aq}}{P_0 X_s}} \qquad (13-106)$$

the terms of which have been previously defined. Recall that $X_s = 1/(1 + 10^{pH_s - pK_a})$ or by equation (13–95) is $X_s = 1/(1 + \text{antilog}\,(pH_s - pK_a))$ and is the fraction of un-ionized weak acid at pH_s.

With $S = 100$ cm^2, $V = 25$ cm^3, $P_{aq} = 1.73 \times 10^{-3}$ cm/sec, $P_0 = 2.27 \times 10^{-3}$ cm/sec, $pK_a = 4.84$, and $pH_s = 4.0$, equations (13–95) and (13–106) yield for caproic acid an absorption rate constant:

$$K_u = \frac{100}{25}\left(\frac{1.73 \times 10^{-3}}{1 + \dfrac{1.73 \times 10^{-3}}{2.27 \times 10^{-3} \times 0.874}}\right)$$

$$= 3.7 \times 10^{-3}\ \text{sec}^{-1}$$

Buccal absorption rate constants constructed according to the model of Ho and Higuchi agreed well with experimental values. The study shows an excellent correspondence between diffusional theory and in vivo absorption and suggests a fruitful approach for structure–activity studies, not only for buccal membrane permeation but for bioabsorption in general.

Uterine Diffusion. Drugs such as progesterone and other therapeutic and contraceptive compounds may be delivered in microgram amounts into the uterus by means of diffusion-controlled forms (intrauterine device, IUD). In this way the patient is automatically and continuously provided medication or protected from pregnancy for days, weeks, or months.[63]

Ho, Flynn, Higuchi and their associates[64] performed in situ vaginal drug absorption studies using the rabbit doe as an animal model to develop more effective uterine drug delivery systems. A solution of a model drug was perfused through a specially constructed cell and implanted in the vagina of the doe (Fig. 13–25), and the drug disappearance was monitored. The drug release followed first-order kinetics, and the results permitted the calculation of apparent permeability coefficient and diffusion layer thickness.

The drug may also be implanted in the vagina in a silicone matrix (Fig. 13–26) and drug release at any time can be calculated using a quadratic expression.[64]

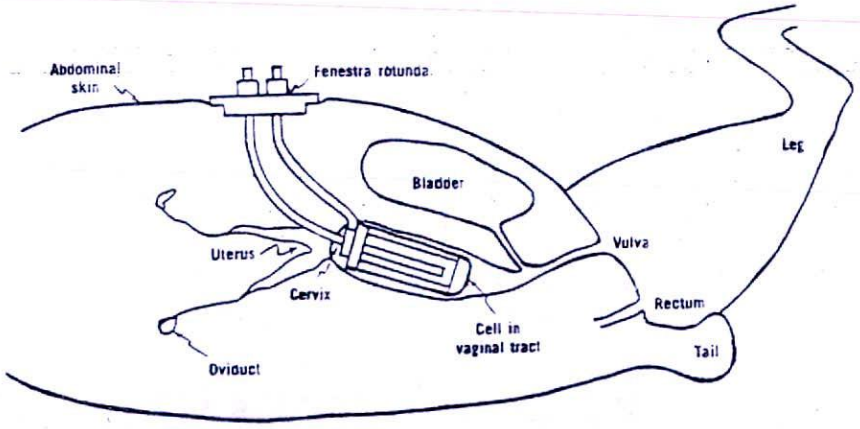


Fig. 13–25. Implanted rib-cage cell in vaginal tract of rabbit. (From T. Yotsuyanagi et al., J. Pharm. Sci. 64, 71, 1975, reproduced with permission of the copyright owner.)

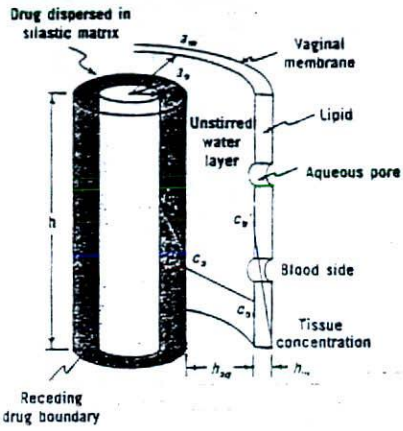


Fig. 13–26. Contraceptive drug in a water-insoluble silicone polymer matrix. Dimensions and sections of the matrix are shown together with concentration gradients across the drug release pathway. (From S. Hwang et al., J. Pharm. Sci. 65, 1578, 1976, reproduced with permission of the copyright owner.)

$$\left(\frac{1}{2\pi h a_0^2 A}\right) M^2 + \frac{D_s K_s}{a_0}\left(\frac{1}{P_{aq}} + \frac{1}{P_m}\right) M - (2\pi h D_s C_s t) = 0 \qquad (13-107)$$

The method of calculation may be shown, using the data of Hwang et al.,[64b] which are found in Table 13–5. When the aqueous diffusion layer, h_{aq}, is 100 μm, the aqueous permeability coefficient P_{aq} is 7×10^{-4} cm/sec; this value is used in the following example. The length h of the silastic cyclinder (see Fig. 13–26) is 6 cm, its radius, a_0, is 1.1 cm, and the initial amount of drug per unit volume of plastic cylinder, or loading concentration, A, is 50 mg/cm^3.

Equation (13–107) is of the quadratic form, $aM^2 + bM + c = 0$, in which, for progesterone,

$$a = \frac{1}{2\pi h a_0^2 A} = \frac{1}{(2)(3.1416)(6\text{ cm})(1.1\text{ cm})^2(50\text{ mg/cm}^3)} = 0.000438\text{ mg}^{-1}$$

$$b = \frac{D_s K_s}{a_0}\left(\frac{1}{P_{aq}} + \frac{1}{P_m}\right) = \frac{(4.5 \times 10^{-7}\text{ cm}^2/\text{sec})(50.2)}{1.1\text{ cm}} \cdot \left(\frac{1}{7 \times 10^{-4}\text{ cm/sec}} + \frac{1}{7 \times 10^{-4}\text{ cm/sec}}\right) = 0.0587\text{ (dimensionless)}$$

$$c = -2\pi h D_s C_s t = -2(3.1416)(6\text{ cm}) \times (4.5 \times 10^{-7}\text{ cm}^2/\text{sec})(0.572\text{ mg/cm}^3) \times \left(\frac{86{,}400\text{ sec}}{\text{day}}\right)(t\text{ days}) = -0.8384 \times t\text{ (days)}$$

How much progesterone is released in 5 days? In 20 days? The quadratic formula to be used here is

$$M = \frac{-b + \sqrt{b^2 - 4ac}}{2a}$$

After 5 days,

$$c = -0.8384\text{ mg/day} \times 5\text{ days} = -4.1920\text{ mg},$$

and

$$M = \frac{-0.0587 + \sqrt{(0.0587)^2 - (4)(0.000438)(-4.1920)}}{2(0.000438)} = 51.6\text{ mg}$$

After 20 days, $c = -0.8384$ mg/day $\times$ 20 days $= -16.77$ mg.

$$M = \frac{-0.0587 + \sqrt{(0.0587)^2 - (4)(0.000438)(-16.77)}}{2(0.000438)} = 139.8\text{ mg}$$

Okada et al.[65] have carried out detailed studies on the vaginal absorption of hormones, as reported in four papers.

THERMODYNAMICS OF DIFFUSION

Permeation of gases, liquids, and solutes through membranes requires an energy of activation (p. 295) for the small molecules to move through the matrix of the barrier material. This fact is expressed in the Arrhenius equation:[66]

$$P = P_0 e^{-E_p/RT} \qquad (13-108)$$

$$\ln P = \ln P_0 - E_p/RT \qquad (13-109)$$

in which P_0 is a factor independent of temperature and proportional to the number of molecules entering the

TABLE 13–5. *Physical Parameters for the Release of Progesterone and Hydrocortisone from a Silicone Matrix for Vaginal Absorption in the Rabbit*[64b]

	Progesterone	Hydrocortisone
Solubility in matrix, C_s (mg/cm^3)	0.572	0.014
Diffusion coefficient in matrix, D_s (cm^2/sec)	4.5×10^{-7}	4.5×10^{-7}
Silicone–water partition coefficient, K_s	50.2	0.05
Permeability coefficient of rabbit vaginal membrane, P_m (cm/sec)	7×10^{-4}	5.8×10^{-5}
P_{aq} (when h_{aq} = 100 μm)	7×10^{-4}	7×10^{-4}
P_{aq} (when h_{aq} = 1000 μm)	0.7×10^{-4}	0.7×10^{-4}

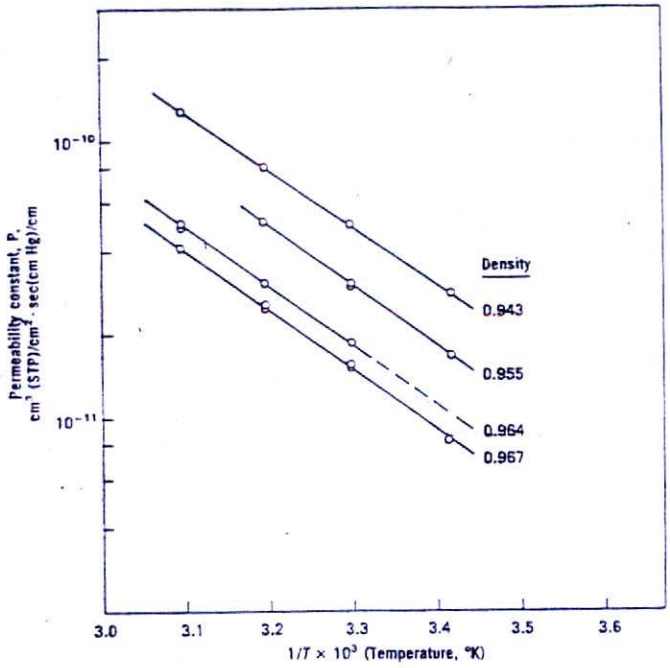


Fig. 13–27. Arrhenius plot for permeability constants of nitrogen permeating polyethylene films of various density. (From A. S. Michaels and R. B. Parker, J. Polym. Sci. 41, 53, 1959.)

film and to the probability that these molecules have sufficient energy to engage in the diffusion process. E_p is the energy of activation for permeation in calories/mole, and R and T have their usual meaning.

Michaels and Parker[67] determined the permeability of oxygen, nitrogen, and other gases in polyethylene films of different densities. The Arrhenius plot (Fig. 13–27) demonstrates the constant energy of activation and corresponding decrease in permeability of nitrogen as density of the polyethylene film is increased by greater short-chain branching of the polymer structure.

E_p values vary from 5 to 20 kcal/mole for permeation through liquids and polymeric barriers, respectively. Higuchi and Aguiar[68] obtained a value of 8 kcal/mole for the permeation of water vapor into wax-like enteric tablet coatings.

Activation energies have also been obtained in the study of the diffusion of liquids across biologic membranes. Blank et al.[69] showed that the apparent activation energies E_p for permeation through human skin (autopsy specimens) by lower alcohols (ethanol to pentanol) and higher or less polar alcohols (hexanol to octanol) are 16.5 kcal/mole and 10 kcal/mole, respectively. The less polar alcohols penetrate the skin more rapidly and exhibit permeability similar to ethers and ketones. The polar compounds with higher activation energies have lower permeability constants, as might be expected. The slopes of the lines in Figure 13–28 may be used to calculate the activation energies with the aid of equation (13–109). The uppermost line has a break at 14.2° C, the penetration of octanol appearing to show a higher activation energy at lower temperatures.

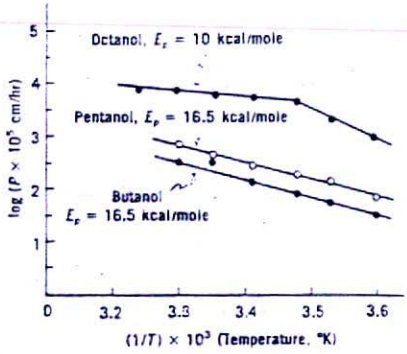


Fig. 13–28. Arrhenius plot (log permeability constant versus reciprocal absolute temperature) for diffusion of normal alkanols through autopsy specimens of human skin. (From I. H. Blank, R. J. Scheuplein and D. J. McFarlane, J. Invest. Dermatol. 49, 582, 1967. © 1967, The Williams & Wilkins Co., Baltimore.)

that is, between 4.6° C ($1/T = 3.60 \times 10^{-3}$) and 14.2° C ($1/T = 3.48 \times 10^{-3}$°K). Temperature dependency of permeation can provide valuable information about the nature of the barrier and the mechanism of transport.

Autian[70] reviewed the importance of plastics in pharmacy and clinical practice and treated the theory of diffusion and sorption of drugs and environmental vapors in polymeric packaging materials. See the chapter by Autian in *Dispensing of Medication*[70] for reference to diffusion in plastic materials as it applies to clinical pharmacy.

FICK'S SECOND LAW

Fick's first law (equation (13–2), p. 325) has been used throughout this chapter as a starting point in the development of equations to describe the diffusion of drugs through natural and polymeric membranes. However, there are many diffusion problems in which the first law of Fick is not applicable, and the second law (equation (13–5), pp. 325, 326),

$$\frac{\partial u}{\partial dt} = D\frac{\partial^2 u}{\partial x^2}$$

must be used. Here we use u instead of C to express concentration. The symbol ∂ signals that *partial derivatives* are being used since u is a function of both t and x. The second law is used to express diffusion in cylinders and spheres, as well as through flat plates. The simplest form of the second law diffusion equation is

$$\frac{\partial u}{\partial t} = D\left(\frac{\partial^2 u}{\partial r^2} + \frac{1}{r}\frac{\partial u}{\partial r}\right) \qquad (13-110)$$

for symmetrical diffusion outward from the axis of a cylinder, in which r is the radius of the cylinder.

For diffusion proceeding symmetrically about the center of a sphere of radius r, the partial differential equation, representing Fick's second law in its simplest form, is

$$r\frac{\partial u}{\partial t} = D\left(r\frac{\partial^2 u}{\partial r^2} + 2\frac{\partial u}{\partial r}\right) \qquad (13-111)$$

The equations for diffusion in cylinders and spheres are discussed by Crank[71] and by Jacobs.[72]

Although the derivation of equations based on Fick's second law is in most cases beyond the mathematical scope of this book, it is of value to present some equations and obtain their solutions. Such exercises give the student practice in calculations for diffusion problems that are more complicated than those derived from Fick's first law.

Diffusion in a Closed System. Determination of *D*. A simple apparatus (Fig. 13–29) was used by Graham (1861), one of the pioneers in diffusion studies, to obtain diffusion coefficients D for solutes in various solvents.

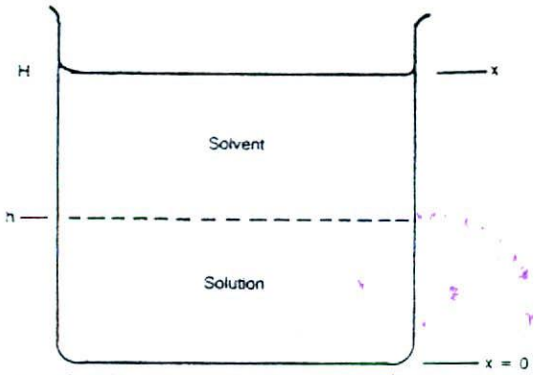


Fig. 13–29. Simple apparatus of Graham for early diffusion studies. (From M. H. Jacobs, *Diffusion Processes*, Springer-Verlag, New York, 1976, p. 24.)

The coefficients for some solutes diffusing through various media are listed in Table 13–1. In the apparatus depicted in Figure 13–29, the height of the solution is h, the combined height of solution and solvent is H, and the distance traversed by the solute is x. The concentration of solute at a position x and time t in the solution is u and its initial concentration is u_o. From the experimental values of u, x, and t, it is possible to determine the diffusion coefficient D for the solute in the solvent.

Initially—that is, at time $t = 0$ sec—the concentration u is equal to u_o (moles or grams per cm^3) in the cell from position $x = 0$ to $x = h$ (cm), and $u = 0$ from $x = h$ to $x = H$. These statements are known as *initial conditions*. In a case in which h is taken equal to $H/2$, that is, both solution and solvent are of equal volume, the equation for u is[72]

$$u = \frac{u_o}{2} + \frac{2u_o}{\pi}\left[\cos\left(\frac{\pi x}{H}\right)e^{-\frac{\pi^2 Dt}{H^2}} - \frac{1}{3}\cos\frac{3\pi x}{H}\,e^{-\frac{9\pi^2 Dt}{H^2}} + \cdots\right] \qquad (13-112)$$

Equation (13–112) is simplified if we choose x, the position of sampling in the cell, to be $H/6$; the second cosine term in the parenthesis of equation (13–112) becomes $\cos(\pi/2) = \cos 90° =$ zero. This leaves only the first cosine term, $\cos(\pi/6) = \cos 30° = 0.866$. Thus, taking $x = H/6$, we have

$$u = \frac{u_o}{2} + \frac{2\,u_o}{\pi}\left(0.866\,e^{-\frac{\pi^2 Dt}{H^2}}\right) \qquad (13-113)$$

The reader is reminded that with trigonometric functions such as $\cos(\pi/6)$, pi is given in degrees; that is, $\pi = 180°$ and $\pi/6 = 30°$, whereas in a term such as $2\,u_o/\pi$ or $e^{-(\pi^2 Dt/H^2}$ the value of π is 3.14159 . . .

Example 13–16. A new water-soluble drug, corazole, is placed in a Graham diffusion cell (see Fig. 13–29) at an initial concentration, $u_o = 0.030$ mmole/cm^3, to determine its diffusion coefficient in water at 25° C. The height of the solution h in the cell is 2.82 cm and the total height of aqueous solution and overlying water is $H = 5.64$ cm. A sample is taken at a depth of $x = H/6$ cm at time $t = 4.3$ hours (15480 sec) and is found by spectrophotometric analysis to have a concentration $u = 0.0225$ mmole/cm^3. D is obtained by rearranging equation (13–113):

$$D = -\left[\ln\left(\frac{u - u_o/2}{0.866(2\,u_o/\pi)}\right)\right] \cdot \frac{H^2}{\pi^2 t}$$

$$= (-0.79113)\frac{(-31.8096)}{(9.8696)(15480)}$$

$$= 16.47 \times 10^{-6}\ \text{cm}^2/\text{sec}$$

Diffusion in Systems with One Open Boundary. The Graham cell for the determination of diffusion coefficients is an example of a closed system. In pharmaceutics, physiology, and biochemistry, systems with one or two open boundaries are of more interest than the closed-boundary system. In 1850 Graham introduced a system with one open and one closed boundary, as shown in Figure 13–30. Insignificant mixing occurs between the solution and the water because of differences in density. The condition at the interface between the solution and the water layer, known as a *boundary condition*, is expressed as "$u = o$ when $x = h$." A second boundary condition states that the change in concentration u with the change in position x is zero, or in mathematical notation, $(\partial u/\partial x) = 0$. This occurs at the bottom of the cell, for the solute cannot pass out through the bottom. In addition to the two boundary conditions, it is useful to specify an *initial condition*, as was done for the closed cell treated earlier. The initial condition is often taken as uniformity of concentration within the solution in the inner vessel of the cell; that is, $u = u_o$ at $t = 0$.

For a system with one open and one closed surface and in which the amount, $M_{o,t}$, of solute escaping between time 0 and time t is expressed by the equation[72]

$$M_{o,t} = u_o A h\left[1 - \frac{8}{\pi^2}\left(e^{-\frac{\pi^2 Dt}{4h^2}} + \frac{1}{9}e^{-\frac{9\pi^2 Dt}{4h^2}} + \cdots\right)\right] \tag{13–114}$$

in which A is the cross-sectional area of the inner cell of height h (see Fig. 13–30), and the other terms have been defined in connection with equations (13–112) and (13–113).

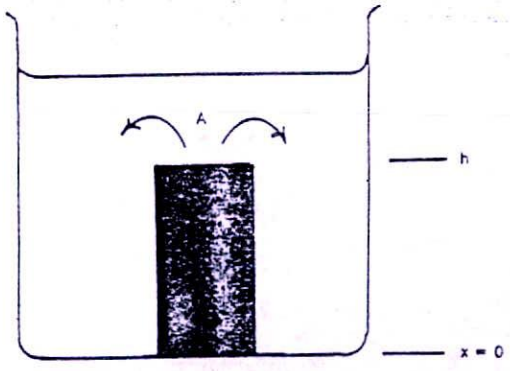


Fig. 13–30. Diffusion apparatus with one open and one closed boundary. (M. H. Jacobs, *Diffusion Processes*, Springer-Verlag, New York, 1976, p. 47.)

Example 13–17. Calculate the total amount $M_{o,t}$ of the new drug corazole that escapes between times $t = 0$ and $t = 2.70$ hours (9720 sec) from the cell with one open boundary (see Fig. 13–30). The area A of the cell is 8.27 cm^2, and its height is $h = 2.65$ cm. The original concentration of the drug in the cell is $u_o = 0.0437$ g/cm^3. The total amount of drug M in the cell is the concentration in g/cm^3 multiplied by $A \times h$, the volume of the cell: 0.0437 g/cm^3 × 8.27 cm^2 × 2.65 cm = 0.9577 g. The diffusion coefficient D of the drug corazole in water at 25° C is 16.5×10^{-6} cm^2/sec, as found in Example 13–16.

Inserting these values into equation (13–114) yields

$$M_{o,t} = (0.0437\ \text{g/cm}^3 \times 8.27\ \text{cm}^2 \times 2.65\ \text{cm}) \times \left[1 - \frac{8}{\pi^2}\left(e^{-\frac{\pi^2(16.5 \times 10^{-6}\ \text{cm}^2/\text{sec})(9720\ \text{sec})}{4 \times 7.0225\ \text{cm}^2}} + \frac{1}{9}e^{-\frac{9\pi^2(16.5 \times 10^{-6}\ \text{cm}^2/\text{sec})(9720\ \text{sec})}{4 \times 7.0225\ \text{cm}^2}} + \cdots\right)\right]$$

$$M_{o,t} = 0.9577\ \text{gram} \times 0.53805 = 0.51529\ \text{gram}.$$

Thus we arrive at the result that in a cell containing 0.0437 g/cm^3 or 0.9577 g of total drug, 0.5155 g diffuses out in 2.7 hours.

The diffusion of macromolecules, such as proteins, is discussed in the chapter on colloids.

DIFFUSION AND ECOLOGY

Diffusional processes have wide application not only in physical and chemical sciences but also in biology, in which living systems, such as animal colonies, are subject to diffusion as well as aggregation or consolidation. Diffusion is a random process by which atoms and molecules, colloidal and coarse particles, and even *living members of populations* diffuse or spread out with time. In the book *Diffusion and Ecological Problems*, Okubo[73] considers such diverse subjects as diffusion and dispersal of spores by the winds, distribution of fish eggs in the sea, migration of turtles, diffusion factors in the homing of birds, insect swarming and fish schooling, and animal movements on their home ranges. An important means of communication between animals is through the release of olfactory or gustatory signals and their transmission through the environment. These processes may be treated in terms of passive diffusion models.

In Figure 13–31, Okubo applies the principles of diffusion to the ventilation of animal burrows. The main opening of the tunnel of the prairie dog is on a mound, and the emergency exit at a lower level. This design apparently provides the most efficient diffusion of air

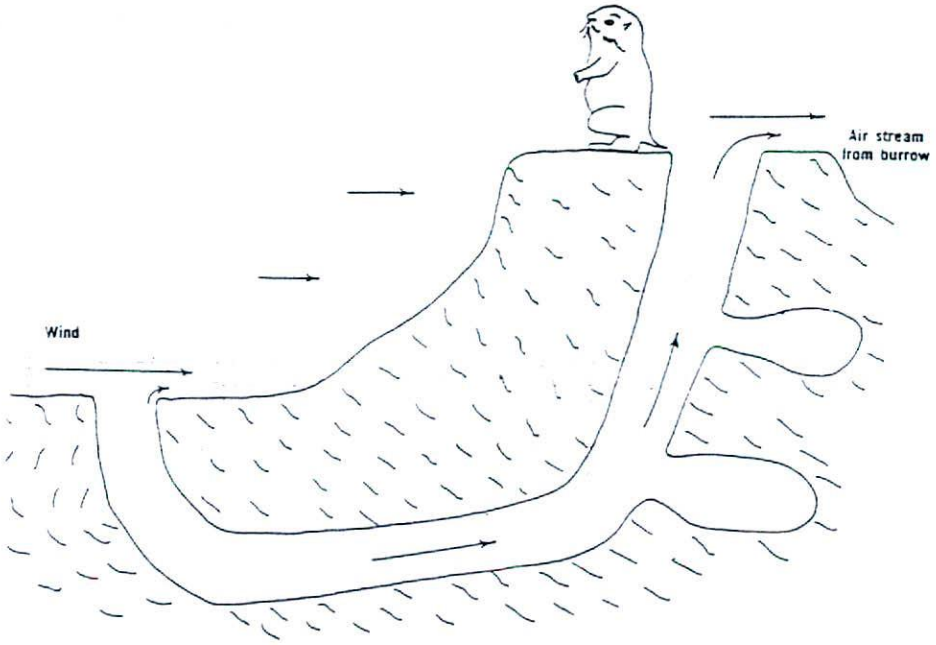


Fig. 13–31. Ventilation of a prairie dog's burrow by action of the wind. (From A. Okubo, *Diffusion and Ecological Problems: Mathematical Models*, Springer-Verlag, Berlin, 1980, p. 43.)

and ventilation for the burrow of the prairie dog. The difference in the height of the two openings produces a "viscous sucking" by the wind on the stagnant air in the burrow, according to Bernoulli's law. This is the principle of the Venturi tube, used to expel liquid medication from a spray atomizer. Diffusion theory has been used by Wilson and Kilgore[74] to calculate the concentration gradient of respiratory gases in small animal burrows. The interested student should see Okubo[73] for other examples of diffusion in biologic systems.

References and Notes

1. S. T. Hwang and K. Kammermeyer, *Membranes in Separations (Techniques of Chemistry)*, A. Weissberger, Ed., Wiley-Interscience, New York, 1975, pp. 23–28.
2. V. T. Stannett et al. Recent advances in membrane science and technology, in *Advances in Polymer Science*, Vol. 32, Springer-Verlag, Berlin, 1979, pp. 71–122; D. R. Paul and G. Morel, Membrane technology, in *Encyclopedia of Chemical Technology*, 3rd Ed., Kirk & Othmer, Eds., Vol. 15, Wiley, New York, 1981, pp. 92–131.
3. G. L. Flynn, S. H. Yalkowsky and T. J. Roseman, J. Pharm. Sci. 63, 479, 1974.
4. H. Carslaw, *Mathematical Theory of the Conduction of Heat*, Macmillan, New York, 1921.
5. R. W. Baker and H. K. Lonsdale, in *Controlled Release of Biologically Active Agents*, A. C. Tanquary and R. E. Lacey, Eds., Plenum Press, New York, 1974, pp. 30–33.
6. M. G. Karth, W. I. Higuchi and J. L. Fox, J. Pharm. Sci. 74, 612, 1985.
7. M. Z. Bíber and C. T. Rhodes, J. Pharm. Sci. 65, 564, 1976.
8. K. Nasim, N. C. Meyer and J. Autian, J. Pharm. Sci. 61, 1775, 1972.
9. T. Higuchi and A. Aguiar, J. Am. Pharm. Assoc., Sci. Ed. 48, 574, 1959.
10. J. Crank and G. S. Park, *Diffusion in Polymers*, Academic Press, New York, 1968, pp. 20–23.
11. R. Scheuplein, J. Invest. Dermatol. 45, 334, 1965.
12. D. E. Wurster, J. A., Ostrenga and L. E. Matheson, Jr., J. Pharm. Sci. 68, 1406, 1410, 1979.
13. Y. C. Martin, *Quantitative Drug Design*, Marcel Dekker, New York, 1978, pp. 76–81.
14. W. J. Addicks, G. L. Flynn and N. Weiner, Pharm. Res. 4, 237, 1987.
15. G. M. Grass and S. A. Sweetana, Pharm. Res. 5, 372, 1988.
16. W. J. Addicks, G. L. Flynn, N. Weiner and C-M. Chiang, Pharm. Res. 5, 377, 1988.
17. D. E. Wurster and P. W. Taylor, J. Pharm. Sci. 54, 169, 1965.
18. J. G. Wagner, *Biopharmaceutics and Relevant Pharmacokinetics*, Drug Intelligence, Hamilton, Ill., 1971, pp. 98–147.
19. L. J. Leeson and J. T. Carstensen, *Dissolution Technology*, Academy of Pharmaceutical Sciences, Washington, D.C., 1974.
20. W. I. Higuchi, J. Pharm. Sci. 56, 315, 1967.
21. J. P. Skelley, G. L. Amidon, W. H. Barr, et al., J. Pharm. Sci. 79, 849, 1991.
22. J. McGinity, S. Stavchansky and A. Martin, Bioavailability in tablet technology, in *Pharmaceutical Dosage Forms: Tablets*, H. A. Lieberman and L. Lachman, Eds. Vol. II, Marcel Dekker, New York, 1981.
23. M. K. T. Yau and M. C. Meyer, J. Pharm. Sci. 70, 1017, 1981; V. P. Shah, V. K. Prasad, T. Alston, B. E. Cabana, R. P. Gural, and M. C. Meyer, J. Pharm. Sci. 72, 306, 1983; P. J. McNamara, T. S. Foster, G. A. Digenis, R. B. Patel, W. A. Craig, P. G. Welling, R. S. Rapaka, V. K. Prasad, and V. P. Shah, Pharm. Res. 4, 150, 1987.
24. G. Levy and B. A. Sahli, J. Pharm. Sci. 51, 58, 1962; J. H. Wood, J. E. Syarto and H. Letterman, J. Pharm. Sci. 54, 1068, 1965; J. H. de Smidt, et al. J. Pharm. Sci. 75, 497, 1986.

25. J. T. Carstensen, *Pharmaceutics of Solids and Solid Dosage Forms*, Wiley, New York, 1977, Chapter III.
26. A. Hixson and J. Crowell, Ind. Eng. Chem. 23, 923, 1931.
27. M. J. Miralles, Dissolution rates of tolbutamide coprecipitates, M. S. Thesis, University of Texas, August, 1980.
28. V. Levich, *Physicochemical Hydrodynamics*, Prentice-Hall, Englewood Cliffs, N.J., 1962.
29. K. G. Nelson and A. C. Shah, J. Pharm. Sci. 64, 610, 1518, 1975.
30. J. H. de Smidt, J. C. A. Offringa and D. J. A. Crommelin, J. Pharm. Sci. 76, 711, 1987.
31. J. R. Robinson, *Sustained and Controlled Release Drug Delivery Systems*, Marcel Dekker, New York, 1978.
32. T. Higuchi, J. Soc. Cosm. Chem. 11, 85, 1960.
33. T. Higuchi, J. Pharm. Sci. 50, 874, 1961.
34. (*a*) S. J. Desai, A. P. Simonelli and W. I. Higuchi, J. Pharm. Sci. 54, 1459, 1965; (*b*) S. J. Desai, P. Singh, A. P. Simonelli and W. I. Higuchi, J. Pharm. Sci. 55, 1224, 1230, 1235, 1966.
35. N. F. H. Ho and T. J. Roseman, J. Pharm. Sci. 68, 1170, 1979.
36. G. L. Flynn, S. H. Yalkowsky and T. J. Roseman, J. Pharm. Sci. 63, 479, 1974.
37. G. L. Flynn and S. H. Yalkowsky, J. Pharm. Sci. 61, 838, 1972.
38. F. Bottari, G. DiColo, E. Nannipieri, et al., J. Pharm. Sci. 63, 1779, 1974; ibid. 66, 927, 1977.
39. D. R. Paul and S. K. McSpadden, J. Memb. Sci. 1, 33, 1976; S. K. Chandrasekaran and D. R. Paul, J. Pharm. Sci. 71, 1399, 1982.
40. Y. W. Chien, in *Sustained and Controlled Release Drug Delivery Systems*, J. R. Robinson, Ed., Marcel Dekker, New York, 1978, Chapter 4; Y. W. Chien, Chem. Pharm. Bull. 24, 147, 1976.
41. C. K. Erickson, K. I. Koch, C. S. Metha and J. W. McGinity, Science, 199, 1457, 1978; J. W. McGinity, L. A. Hunke and A. Combs, J. Pharm. Sci. 68, 662, 1979.
42. Y. W. Chien, *Novel Drug Delivery Systems: Biomedical Applications and Theoretical Basis*, Marcel Dekker, New York, 1982, Chapter 9.
43. B. B. Brodie and C. A. M. Hogben, J. Pharm. Pharmacol. 9, 345, 1957; P. A. Shore, B. B. Brodie and C. A. M. Hogben, J. Pharmacol. Exp. Ther. 119, 361, 1957; L. S. Shanker, D. J. Tocco, B. B. Brodie and C. A. M. Hogben, ibid. 123, 81, 1958; C. A. M. Hogben, D. J. Tocco, B. B. Brodie and L. S. Shanker, ibid. 125, 275, 1959; L. S. Shanker, J. Med. Chem. 2, 343, 1960; L. S. Shanker, Ann. Rev. Pharmacol. 1, 29, 1961.
44. R. H. Turner, C. S. Mehta and L. Z. Benet, J. Pharm. Sci. 59, 590, 1970.
45. J. L. Colaizzi and P. R. Klink, J. Pharm. Sci. 58, 1184, 1969.
46. A. Suzuki, W. I. Higuchi and N. F. H. Ho, J. Pharm. Sci. 59, 644, 651, 1970; N. F. H. Ho, W. I. Higuchi and J. Turi, J. Pharm. Sci. 61, 192, 1972; N. F. H. Ho and W. I. Higuchi, J. Pharm. Sci. 63, 686, 1974.
47. (*a*) N. F. H. Ho, J. Y. Park, G. E. Amidon, et al., in *Gastrointestinal Absorption of Drugs*, A. J. Aguiar, Ed., American Pharmaceutical Association, Academy of Pharmaceutical Sciences, Washington, D.C., 1981; (*b*) W. I. Higuchi, N. F. H. Ho, J. Y. Park, and I. Komiya, in *Drug Absorption*, L. F. Prescott and W. S. Nimmo, Eds., Adis Press, Balgowlah, NSW 2093, Australia, 1981, pp. 35–60; (*c*) N. F. H. Ho, J. Y. Park, W. Morozowich and W. I. Higuchi, in *Design of Biopharmaceutical Properties Through Prodrugs and Analogs*, E. B. Roche, Ed., American Pharmaceutical Association, Academy of Pharmaceutical Sciences, Washington, D.C., 1977, Chapter 8.
48. J. T. Dobrisio, F. N. Billups, L. W. Dittert, E. T. Sugita and V. J. Swintosky, J. Pharm. Sci. 58, 1196, 1969.
49. A. K. Mitra and T. J. Mikkelson, J. Pharm. Sci. 77, 771, 1988.
50. R. J. Scheuplein, J. Invest. Dermatol. 45, 334, 1965; R. J. Scheuplein, J. Invest. Dermatol. 48, 79, 1967; R. J. Scheuplein and I. H. Blank, Physiol. Rev. 51, 702, 1971.
51. R. J. Scheuplein, I. H. Blank, G. J. Brauner and D. J. MacFarlane, J. Invest. Dermatol. 52, 63, 1969.
52. C. D. Yu, J. L. Fox, N. F. H. Ho and W. I. Higuchi, J. Pharm. Sci. 68, 1341, 1347, 1979; ibid. 69, 772, 1980; H. Durrheim, G. L. Flynn, W. I. Higuchi and C. R. Behl, J. Pharm. Sci. 69, 781, 1980; G. L. Flynn, H. Durrheim and W. I. Higuchi, J. Pharm. Sci. 70, 52, 1981; C. R. Behl, G. L. Flynn, T. Kurihara, N. Harper, W. Smith, W. I. Higuchi, N. F. H. Ho and C. L. Pierson, J. Invest. Dermatol. 75, 346, 1980.
53. P. V. Raykar, M-C. Fung, and B. D. Anderson, Pharm. Res., 5, 140, 1988.
54. J. S. Turi, D. Danielson, and W. Wolterson, J. Pharm. Sci. 65, 275, 1976.
55. S. H. Yalkowsky and G. L. Flynn, J. Pharm. Sci. 63, 1276, 1974.
56. J. Ostrenga, C. Steinmetz and B. Poulsen, J. Pharm. Sci. 60, 1175, 1180, 1971.
57. K. B. Sloan, K. G. Siver, and S. A. M. Koch, J. Pharm. Sci. 75, 744, 1986.
58. H. Komatsu and M. Suzuki, J. Pharm. Sci. 68, 596, 1979.
59. A. H. Beckett and A. C. Moffat, J. Pharm. Pharmacol. 20, 239S, 1968.
60. N. F. H. Ho and W. I. Higuchi, J. Pharm. Sci. 60, 537, 1971.
61. A. Suzuki, W. I. Higuchi and N. F. H. Ho, J. Pharm. Sci. 59, 644, 651, 1970.
62. G. L. Flynn, N. F. H. Ho, S. Hwang, E. Owada, A. Motokhia, C. R. Behl, W. I. Higuchi, T. Yotsuyanagi, Y. Shah and J. Park, in *Controlled Release Polymeric Formulations*, D. R. Paul and F. W. Harris, Eds., American Chemical Society, Washington, DC, 1976, pp. 87–122.
63. S. K. Chandrasekaran, H. Benson and J. Urquhart, in *Sustained and Controlled Release Drug Delivery Systems*, J. R. Robinson, Ed., Marcel Dekker, New York, 1978, pp. 572–574.
64. (*a*) T. Yotsuyanagi, A. Molakhia, S. Hwang, N. F. H. Ho, C. L. Flynn and W. I. Higuchi, J. Pharm. Sci. 64, 71, 1975; (*b*) S. Hwang, E. Owada, T. Yotsuyanagi, L. Suhardja, Jr., N. F. H. Ho, G. L. Flynn, W. I. Higuchi and J. V. Park, J. Pharm. Sci. 65, 1574, 1578, 1976.
65. H. Okada, I. Yamazaki, Y. Ogawa, S. Hirai, T. Yashiki and H. Mima, J. Pharm. Sci. 71, 1367, 1982; H. Okada, I. Yamazaki, T. Yashiki and H. Mima, ibid. 72, 75, 1983; H. Okada, T. Yashiki and H. Mima, ibid. 72, 173, 1983; H. Okada, I. Yamazaki, T. Yashiki, T. Shimamoto and H. Mima, ibid. 73, 298, 1984.
66. D. F. Othmer and G. J. Frohlich, Ind. Eng. Chem. 47, 1034, 1955.
67. A. S. Michaels and R. B. Parker, J. Polym. Sci. 41, 53, 1959.
68. T. Higuchi and A. Aguiar, J. Am. Pharm. Assoc., Sci. Ed. 48, 574, 1959.
69. I. H. Blank, R. J. Scheuplein and D. J. McFarlane, J. Invest. Dermatol. 49, 582, 1967.
70. J. Autian, Plastics medication, Chapter 15 in *Dispensing of Medication*, E. W. Martin, Ed., Mack, Easton, Penn., 1971.
71. J. Crank, *The Mathematics of Diffusion*, 2nd Edition, Oxford, Oxford University Press, 1975, Chapters 5 and 6.
72. M. H. Jacobs, *Diffusion Processes*, Springer-Verlag, New York, 1967, p. 45, and p. 49, equation 39 where we use the symbol M to replace Jacobs' term, Q.
73. A. Okubo, *Diffusion and Ecological Problems: Mathematical Models*, Springer-Verlag, Berlin, 1980.
74. K. J. Wilson and D. L. Kilgore, J. Theor. Biol. 71, 73, 1978.
75. S. Esezobo, S. Zubair and N. Pilpel, J. Pharm. Pharmacol. 41, 7, 1989.
76. K. G. Nelson and A. C. Shah, J. Pharm. Sci. 66, 137, 1977.
77. A. C. Shah and K. G. Nelson, J. Pharm. Sci. 64, 1518, 1975; ibid. 76, 799, 1987.
78. Y. W. Chien et al., J. Pharm. Sci. 63, 365, 1974.
79. A. C. Shah and K. G. Nelson, J. Pharm. Sci. 69, 210, 1980.
80. S. Borodkin and F. E. Tucker, J. Pharm. Sci. 64, 1289, 1975.
81. K. F. Farng and K. G. Nelson, J. Pharm. Sci. 66, 1611, 1977.
82. S. S. Davis, Experientia, 26, 671, 1970.
83. A. Adjei, J. Newburger, S. Stavchansky and A. Martin, J. Pharm. Sci. 73, 742, 1984.
84. K. Tojo, C. C. Chiang and Y. W. Chien, J. Pharm. Sci. 76, 123, 1987.
85. A. J. Aguiar and M. A. Weiner, J. Pharm. Sci. 58, 210, 1969.
86. Z. Liron and S. Cohen, J. Pharm. Sci. 73, 534, 1984; ibid. 73, 538, 1984.
87. N. F. H. Ho et al., J. Pharm. Sci. 65, 1578, 1976.
88. C. D. Yu, W. I. Higuchi, N. F. H. Ho, J. L. Fox and G. L. Flynn, J. Pharm. Sci. 69, 770, 1980.

Problems

13–1. The diffusion coefficient of tetracycline in a hydroxyethyl methacrylate–methyl methacrylate copolymer film in a mole ratio of 2:98 is $D = 8.0(\pm 4.7)^{a} \times 10^{-9}$ cm²/sec and the partition coefficient

---

[a] The quantities in parentheses ± are standard deviations. That is, for example, the diffusion coefficient ranges from $(8.0 - 4.7) \times 10^{-9}$ to $(8.0 + 4.7) \times 10^{-9}$ based on a variability of ± 1 standard deviation (4.7) from the mean D value of 8.

K for tetracycline between the membrane and the reservoir is $6.8(\pm 5.9) \times 10^{-3}$. The membrane thickness h of the trilaminar device is 1.40×10^{-2} cm, and the concentration of tetracycline in the core, C_v, is 0.02 g/cm³ of the core material. Using equation (13–73), p. 341, calculate the release rate Q/t in units of $\mu g\ cm^{-2}$ of tetracycline per day.

Answer: $Q/t = 6.71\ \mu g\ cm^{-2}\ day^{-1}$

13–2. Diffusion of fluocinolone acetonide occurred from a 30% propylene glycol–water solution through a circular section of a polyethylene membrane in a two-compartment glass cell. The thickness h of the membrane was 0.076 cm and its diameter was 2.21 cm. The partition coefficient of the drug between the membrane and the solution was 1.23 at 25° C and C_v was 0.025 g/100 cm³. A plot of drug amount (in grams) permeating versus time in hours produced a straight line (after steady state was established) with a lag time t_L of 25.0 hours. Calculate (a) the diffusion coefficient, knowing h and t_L, and (b) dQ/dt in $\mu g/(cm^2\ hr)$, using the expression $dQ/dt = DKC_v/h$.

Answers: (a) 3.85×10^{-5} cm²/hr; (b) $dQ/dt = 1.62 \times 10^{-7}$ g/(cm² hr), or 0.162 $\mu g/(cm^2\ hr)$

13–3. Esezoo et al.[75] studied the effect of concentration of binder on the dissolution rates of acetaminophen tablets using the integrated form of the Noyes–Whitney equation

$$\ln\left(\frac{C_s}{C_s - C}\right) = -kt$$

where C_s is the concentration of the solute at saturation (solubility), C is the concentration at time t, and k is the dissolution rate constant. The data are found in the following table.

Data for *Problem 13–3*

	$\ln\left(\frac{C_s}{C_s - C}\right)$		
t (min)	no binder	2.5% PVP	5% PVP
5	0.125	0.145	0.10
10	0.43	0.29	0.20
15	0.645	0.453	0.30
20	0.86	0.58	0.40
30	1.25	0.87	0.60
40	—	1.16	0.80

Plot $\ln\left(\frac{C_s}{C_s - C}\right)$ (vertical axis) against t and compute the dissolution rate constant k from the slope for the acetaminophen tablets with no binder and in the presence of 2.5% and 5% PVP.

Answer: With no binder, $k = 0.041\ min^{-1}$; with 2.5% PVP, $k = 0.029\ min^{-1}$; with 5% PVP, $k = 0.020\ min^{-1}$

13–4. A new fast-dissolving tolbutamide tablet was prepared and tested for rate of dissolution. The milligram amounts (m) of drug dissolved at various times are given here:

Data for *Problem 13–4*

time (min)	2	4	6	8	10	15
m (mg)	14.4	18.8	21.3	25.9	28.2	32.9

(a) Plot the results on rectangular graph paper (m versus t) and on semilog paper ($\log m$ versus t) and finally plot m versus $t^{1/2}$. Which method yields a straight line?

(b) Using regression analysis and the data that give a linear relationship, calculate the correlation coefficient, the intercept, and the slope, k, the dissolution rate constant.

(c) An intercept gives the value of the ordinate of a graph at the point at which the quantity on the horizontal axis is zero. Hence is it possible that the milligrams of tolbutamide dissolved at 0 $min^{1/2}$ is 3.3872 mg? Give several possible explanations.

Partial Answer: (b) $r^2 = 0.9922$, slope = $k = 7.706\ mg/(min)^{1/2}$, intercept = 3.387 mg

13–5. A 0.625-g sample of acetohexamide powder was dissolved in 1000 cm³ of water in a paddle-type dissolution apparatus at 30° C. The dissolution rate data are found in the table below. They are presumed to follow the Hixson–Crowell law.

Data for *Problem 13–5*

Time (min)	Concentration (mg/mL)	Weight Undissolved in gram (g)	$M_0^{1/3} - M^{1/3}$	κ in $g^{1/3}$/min
0	0	$M_0 = 0.625$	0	—
2	0.159	0.466	0.080	0.040
4	0.288	0.337	0.159	
6	0.390	0.235	0.228	
8	0.468	0.157	0.315	
10	0.528	0.097	0.396	

(a) Calculate κ for each time period to fill in the last column of the table. Then add these separate κ values and divide by the number to obtain an average κ.

(b) Regress $(M_0^{1/3} - M^{1/3})$ versus time in minutes and obtain κ as the slope of the least-squares line. Which of these methods is the better for obtaining κ? Give reasons for your preference.

Answers: (a) $\kappa_{(av)} = 0.0397\ g^{1/3}$/min; (b) $\kappa = 0.0394\ g^{1/3}$/min

13–6. Nelson and Shah[76] applied their convective diffusion model (see *Example 13–6*) to the permeation rate (rate of diffusion), R, of butamben through a dimethicone membrane under conditions of aqueous diffusion layer control (p. 338). For a circular membrane, the permeation rate is given by the convective diffusion (CD) equation:

$$R = 2.157\ D_a^{2/3} C_s \alpha^{1/3} r^{5/3} \qquad (13\text{–}115)$$

where D_a is the diffusivity (diffusion coefficient) of the solute in the aqueous layer, C_s is the solubility, α the rate of shear over the membrane, and r the radius of the circular membrane. The rate of permeation, R, written as dM/dt elsewhere in this chapter, was considered the dependent variable, using the radius of the membrane as the independent variable. The equation obtained by least-squares regression predicts a straight line in a plot of $\log R$ versus $\log r$, holding the other parameters constant.

(a) Prepare the graph of $\log R$ versus $\log r$, compute the slope and intercept, and determine how well they compare with comparable quantities predicted by equation (13–115). The values of the known parameters are $D_a = 6 \times 10^{-6}\ cm^2\ sec^{-1} = 3.60 \times 10^{-4}\ cm^2\ min^{-1}$; $C_s = 9.4 \times 10^{-4}$ mole/liter $= 9.4 \times 10^{-7}$ mole cm^{-3}; and $\alpha = 35.006\ min^{-1}$; the experimental R and r values for the plot are:

Data for *Problem 13–6*

R (mole/min)	1.325×10^{-8}	2.712×10^{-8}	3.881×10^{-8}
r (cm)	0.65	1	1.25

(b) Choose one of the three values of r from the above table and the known parameters given above; substitute these into the least-squares regression equation and into the CD equation (equation (13–115)). Compare your results from these two methods for calculating R. What is the percentage error in these two methods relative to the experimental value of R?

(c) This system is under aqueous diffusion layer control. Compute the thickness h_a of the static aqueous layer, using r = 1.25 cm and $R = 3.881 \times 10^{-8}$ mole $min^{-1} = 6.47 \times 10^{-10}$ mole sec^{-1}.

Notes: In preparation for graphing, be sure to first convert R and r to logarithms. Recall that when converted to logarithmic form in equation (13–115) quantities multiplied together are added. Therefore equation (13–115), written as log R versus r, becomes log (2.157) + 2/3 log D_e + log C_s + 1/3 log α + 5/3 log r, and for D_e, C_s, and α held constant:

$$\log R = \log(2.157\, D_e^{2/3} C_s \alpha^{1/3}) + 5/3 \log r \qquad (13\text{–}116)$$

with the first log term on the right side as the intercept and 5/3 = 1.667 in the second log term as the slope.

Partial Answer: (a) The equation of the linear regression line is $\log R = -7.569 + 1.646 \log r$. The slope, 1.646, and intercept, −7.569, compare well with the values 1.667 and −7.4739 predicted by the convective diffusion (CD) equation (13–115). (b) For r = 1.25 cm substituted into equation (13–116) for the linear regression line:

$$\log R = -7.569 + 1.646 \log(1.25) = -7.4095$$

$R = 3.90 \times 10^{-8}$ mole/min. From the CD equation, $R = 4.87 \times 10^{-8}$ mole/min. The regression equation (13–116) has an error of about 0.5% and the CD equation, (13–115), an error of about 26% in relation to the experimental value of $R = 3.881 \times 10^{-8}$ mole/min. (c) Under aqueous diffusion layer control, p. 338, equation (13–58),

$$J = \frac{dM}{dt}\frac{1}{S} = \left(\frac{D_a}{2\, h_a}\right) C_s;\ R = \frac{dM}{dt} = \left(\frac{S\, D_a}{2\, h_a}\right) C_s = \left(\frac{\pi\, r^2\, D_a}{2\, h_a}\right) C_s;$$

$h_a = 0.0214$ cm. The actual dimethicone membrane thickness is about 0.025 cm.

13–7. Shah and Nelson[77] studied the dissolution rate of alkyl *p*-aminobenzoates using a convective diffusion model (see p. 334 and *Example 13–6*), where for a circular shaped tablet of surface radius r, the equation is

$$R = 2.157\, D^{2/3} C_s \alpha^{1/3} r^{5/3} \qquad (13\text{–}115)$$

D is the diffusivity, C_s the solubility of the drug, and α the rate of shear over the dissolving surface of the tablet. R is the tablet dissolution rate.

(a) If C_s is 9.33×10^{-5} mole/cm^3, α is 255 min^{-1}, r is 0.5012 cm, and R, the measured dissolution rate, 1.553×10^{-6} mole min^{-1}, what is the numerical value of the diffusion coefficient?

(b) One may wish to study the change in the dissolution rate R with a change in the radius r, or regarding the change of another parameter, such as the solubility C_s or the rate of shear α. Because of the exponents in equation (13–115) this is best done by plotting the logarithm of R versus the logarithm of r, holding D, C_s, and α constant. The equation becomes:

$$\log R = \log(2.157 + \tfrac{2}{3}\log D + \log C_s + \tfrac{1}{3}\log \alpha) + \tfrac{5}{3}\log r \qquad (13\text{–}117)$$

Using the data from table (a) below, plot log R versus log r on rectangular coordinate graph paper. If the plot is linear with a slope of 5/3 = 1.667, or approximately so, you have a good indication that the convective diffusion approach is a satisfactory model for the dissolution kinetic study under investigation. Next, one can plot log R versus log C_s, for example, using the data in table (b), while holding D, α, and r constant. What should be the slope of this line?

Data (a) for *Problem 13–7*

R (cm^2/min)	log R	r (cm)	log r
1.26×10^{-7}	−6.90	0.398	−0.40
2.34×10^{-7}	−6.63	0.575	−0.24
4.17×10^{-7}	−6.38	0.794	−0.10

Data (b) for *Problem 13–7*

R (cm^2/min)	log R	C_s (mole/cm^3)	log C_s
1.82×10^{-7}	−6.74	6.31×10^{-4}	−2.20
2.82×10^{-7}	−7.55	9.33×10^{-5}	−3.03
7.94×10^{-9}	−8.10	2.9×10^{-7}	−3.57

The authors show that other properties such as viscosity of the solution may also be tested by the convective diffusion model for their effects on the system.

Answers: (a) $D = 2.39 \times 10^{-4}$ cm^2/min; (b) in a plot of log R versus log r, the slope obtained from regression analysis is 1.732. The theoretical slope is 5/3 = 1.667 because of the final term in equation (13–117). In a plot of log R versus log C_s, the slope should be 1.00 since the exponent on C_s in equation (13–115) or (13–116) is unity. The least-square equation obtained is $\log R = -4.556 + 0.991 \log C_s$. The squared correlation coefficient, r^2, = 0.999.

13–8. The release of ethynodiol diacetate through a silicone dosage form may be calculated using the Higuchi equation,

$$Q/t^{1/2} = [D(2A - C_s)C_s]^{1/2}$$

since diffusion is found in this case to be the rate-limiting factor for drug release. A, the amount of drug per unit volume of the silicone matrix, is 100 g/(10^3 cm^3), the solubility C_s of the drug in the silicone polymer is 1.50 g/(10^3 cm^3), and D, the diffusivity of the drug in the silicone matrix, is 3.4×10^{-2} cm^2/day. Calculate the rate of drug release from the silicone dosage form in units of g/(10^3 cm^2) per day$^{1/2}$.

Answer: 3.182 g/(10^3 cm^2) per day$^{1/2}$

13–9. When C_s is small relative to A, as found in *Problem 13–8*, the Higuchi equation reduces to $Q/t^{1/2} = \sqrt{2DAC_s}$. Recalculate the results of *Problem 13–8* using this abbreviated equation.

Answer: 3.194 g/(10^3 cm^2) per day$^{1/2}$. A value of about 3.1 g/(10^3 cm^2) per day$^{1/2}$ is obtained experimentally.[78]

13–10. The permeation of methyl *p*-aminobenzoate through a dimethicone membrane of thickness h_m = 0.0254 cm was conducted in a laminar flow cell at 25° C.[79] At high flow rates the membrane D_m and aqueous solvent D_a diffusivities are $D_m = 2.72 \times 10^{-6}$ cm^2 sec^{-1} and $D_a = 6 \times 10^{-6}$ cm^2 sec^{-1}. The thickness of the aqueous layer h_a is 0.003 cm, the solubility C of the drug is 1.04×10^{-5} mole/liter, and the partition coefficient K across the drug–membrane interface is 0.26.

(a) By appropriate calculations, suggest whether the flux is controlled by the aqueous diffusion layer or by the membrane.

(b) Compute the flux, J (mole cm^{-2} min^{-1}). See page 338 for membrane and diffusion layer control.

Answers: (a) $2h_aKD_m < h_mD_a$; the process is one of membrane control. Show this to be true by calculating these two quantities. (b) The flux $J = (KD_m/h_m)C$ for membrane control is 1.74×10^{-6} mole cm^{-2} min^{-1}. Using the entire equation (13–59), page 339, we obtain $J = 1.69 \times 10^{-6}$ mole cm^{-2} min^{-1}, which compares favorably with $J = 1.74 \times 10^{-6}$ mole cm^{-2} min^{-1}, the membrane control result.

13–11. A cell contains a silastic membrane with diffusion layers of identical thickness on either side and butyl-aminobenzoate at concentration C = 1.72 mmole/liter or 1.72×10^{-3} mmole/cm^3 in the donor compartment. Calculate the steady-state flux, J, through the membrane in millimoles per cm^2 per hour. The equation that represents the process in which both membrane and diffusion-layer control obtain is

$$J = \frac{D_m K D_a}{h_m D_a + 2 h_a K D_m} C$$

The data obtained from an experiment at 37° C are as follows: $D_m = 2.7 \times 10^{-6}$ cm^2/sec or 0.00972 cm^2/hr, $D_a = 6.0 \times 10^{-6}$ cm^2/sec = 0.02160 cm^2/hr, h_m = 0.006 cm, h_a = 0.0188 cm, and K = 10.3.

Answer: $J = 9.55 \times 10^{-4}$ mmole/(cm^2 hr)

13–12. Borodkin and Tucker[80] studied the diffusion of salicylic acid from a polymer film containing dispersed drug. The kinetics was made

linear with time, i.e., zero order, by laminating a second film, consisting of a hydroxypropylcellulose-polyvinyl acetate membrane of thickness $h_m = 0.0164$ cm to the releasing side of the film with the drug as a reservoir layer.

The drug layer controlled the duration of release, while the nondrug layer consisting of the cellulose membrane served as a rate-controlling membrane. Diffusion through the film is the limiting factor in a drug release, so that equation (13–72) on page 341 applies. Q, the amount of drug released per unit surface area, is given for various times:

Data for *Problem 13–12*

Q (mg/cm^2)	0.46	1.00	1.54	2.19	2.69	3.23	3.54
time (hr)	1	2	3	4	5	6	7

Equation (13–72) may also be written as

$$\frac{dQ}{dt} = \frac{D_m C_p}{h_m} \tag{13–118}$$

the instantaneous rate of release of drug at time t. Integration of this equation and evaluation of the integration constants yields a term for the lag time, t_{lag}:

$$Q = \frac{D_m C_p}{h_m} t - \frac{D_m C_p}{h_m} t_{lag} \tag{13–119}$$

Equation (13–119) shows that a plot of Q against t yields a straight line of slope $= D_m C_p / h_m = k_o$, the apparent zero-order rate constant. The intercept of equation (13–119) is $(D_m C_p / h_m) t_{lag} = k_o t_{lag}$, from which t_{lag} can be computed.

(a) Plot Q versus time, t, from the data given in the table. (b) Regress Q against t and obtain $k_o = D_m C_p / h_m$ (mg cm^{-2}) from the slope and t_{lag} from the intercept. (c) Knowing the lag time and the thickness h_m of the nondrug layer, compute the diffusion coefficient, D_m. You will need the lag time equation (13–14a) from page 328. (d) From the slope obtained in part (b) and the diffusion coefficient D_m calculated in part (c), compute the value of C_p, the concentration of the drug, salicylic acid, in the reservoir layer of the base film.

Answer: (b) $k_o = D_m C_p / h_m = 0.530$ mg cm^{-2} hr^{-1}; $t_{lag} = 0.0539$ hr or 3.23 min; (c) $D_m = 2.31 \times 10^{-7}$ cm^2 sec^{-1} using $h_m = 0.0164$ cm; (d) $C_p = 10.46$ mg cm^{-3}

13–13. Farng and Nelson[61] studied the effect of polyelectrolytes, such as carboxymethylcellulose (CMC), on the permeation rate of sodium salicylate across a cellulose membrane at 37° C. Fick's law may be written to cover this case, assuming the existence of three barriers in series: the membrane and an unstirred liquid diffusion layer on either side. The reciprocal of the permeation coefficient for the three layers is

$$1/P = h_1/D_1 + h_m/\phi D_m K + h_2/D_2 K$$

in which $h_1 = h_2 = 82 \times 10^{-4}$ cm for the two static diffusion layers; $h_m = 46.6 \times 10^{-4}$ cm for the cellulose membrane thickness, $D_1 = 1.33 \times 10^{-5}$ cm^2/sec, $D_2 = 1.11 \times 10^{-5}$/cm^2 sec, and $D_m = 1.69 \times 10^{-6}$ cm^2/sec for the three diffusion coefficients. The partition coefficient K for the salicylate between the solution in compartment 1 (left-hand reservoir) and water in the membrane is 1.16. The volume fraction ϕ of water in the membrane is 0.667. Calculate the permeability P for the salicylate and compare it with $P_{(obs)} = 1.86 \times 10^{-4}$ cm/sec.

Answer: $P_{(calc)} = 2.08 \times 10^{-4}$ cm/sec

13–14. Sulfadiazine, pK_a 6.50 at 25° C, as with all weak acids, shows a variable-percent dissociation as a function of pH. (a) Prepare a table showing the percent dissociated and percent undissociated sulfadiazine at pH 2, 4, 6.5, 7, 8, 10, and 12. (b) Plot the results on rectangular graph paper. (c) Predict the absorption of sulfadiazine from the gut and from the small intestine in terms of the pH–partition hypothesis and from the results obtained in parts (a) and (b).

Partial Answer: Percent dissociation at pH 4 = 0.32%; at pH 8 = 96.93%

13–15. Bile acids are transported across the ileum by active and passive processes.[47] For dilute nonmicellar bile acid solutions, the absorption rate constant is given by equation (13–93):

$$K_v = \frac{S}{V} \frac{P_{aq}}{1 + \dfrac{P_{aq}}{P_o X_a^\circ + P_m^* X_a^-}}$$

in which P_m^* is the permeability constant for the active transport of bile acid anions; P_o the permeability constant of undissociated species undergoing passive diffusion; P_{aq} the permeability constant of the aqueous diffusion layer; and X_a° and X_a^- the fraction of undissociated and anionic species, respectively.

For taurocholic acid, pK_a 2.0, the bile acid is essentially all in the ionic form at pH 6 to 7. Therefore, $X_a^\circ \approx 0$, $X_a^- \approx 1.0$, and K_v becomes

$$K_v = \frac{S}{V} \frac{P_{aq}}{1 + \dfrac{P_{aq}}{P_m^*}}$$

If S/V, the ratio of effective surface area to solution volume, is 10 cm^{-1}, P_{aq} is 2×10^{-4} cm/sec, and P_m^* is 1×10^{-2} cm/sec, what is K_v, the rate constant for the absorption of taurocholic acid across the ileum?

Answer: $K_v = 1.67 \times 10^{-3}$ sec^{-1}

13–16. In situ rat gut permeation experiments were performed at 37° C to determine the influence of the Hildebrand solubility parameter, δ. The rat intestinal preparation is shown in Figure 13–18 and the solubility parameter is defined on page 224. The drug theophylline, with a solubility parameter or delta value, δ_2, of 14 (cal/cm^3)$^{1/2}$ and a molar volume, V_2, of 124 cm^3/mole, was dissolved in the solvent mixtures of polyethylene glycol 400 and water of various polarities as expressed by their solubility parameters, δ_1.

It is postulated that the more alike are the delta values of the drug δ_2 and the solvent mixture δ_1 the greater would be the attraction of solvent and drug and the poorer the release of the drug for absorption. Conversely, when δ_1 and δ_2 are quite different and also when the solubility parameters of the drug δ_2 and the intestinal mucosa δ_c are similar, the drug is readily released from the solvent for bioabsorption.

A partition parameter K_p is obtained in the rat gut experiment from drug absorption k_1 and desorption k_2 rate constants, in which $K_p = k_1/k_2$. The experimental data for this problem are found in the table:

Data for *Problem 13–16*

% PGE 400 in water	Solvent: delta value δ_1(cal/cm^3)$^{1/2}$	$(\delta_1 - \delta_2)$ ($\delta_2 = 14$)	k_1 min^{-1}	k_2 min^{-1}	$K_p = k_1/k_2$	ln K_p
90	11.8	−2.2	0.041	0.028	1.464	0.381
80	13.1	−0.9	0.040	0.039	1.026	0.026
75	13.7	−0.3	0.054	0.083	0.651	−0.429
70	14.4	0.4	0.048	0.075	0.640	−0.446
65	15.0	1.0	0.036	0.064	0.0563	−0.574
60	15.7	1.7	0.037	0.036	1.028	0.028

(a) Plot ln K_p versus $(\delta_1 - \delta_2)$ and note from the curve obtained how the partition parameter varies with the delta value difference $(\delta_1 - \delta_2)$.

(b) Regress ln K_p against $(\delta_1 - \delta_2)$ using a parabolic (quadratic) or better, a cubic least-squares regression procedure. Plot a sufficient number of points, obtained from either the quadratic or the cubic equation, on the graph prepared for (a). This statistical regression analysis should give a smooth line approximating the rough angular

plot obtained from drawing straight lines joining the experimental points in (a).

(c) Calculate a theoretical partition parameter (ln K_p) using the empirical equation suggested by Davis[82]:

$$\ln K_p = \frac{V_2 \phi_1^2}{RT}[(\delta_1 - \delta_2)^2 - (\delta_0 - \delta_2)^2] \qquad (13-120)$$

where V_2, the molar volume of theophylline, is 124 cm³/mole and δ_0 is the solubility parameter of the rat gut membrane, 12.6 $(cal/cm^3)^{1/2}$ as determined in the work of Adjei et al.[83]. R is the gas constant, and T the absolute temperature (37° C or 310° K). The volume fraction (p. 224), ϕ_1, of the solvent mixture is approximately unity in this problem and may be disregarded in equation (13–120). Are the experimental ln K_p values fit better with the ln K_p obtained from solving equation (13–120) or by the ln K_p from the quadratic or cubic regression equation? Observe the points on the graph or the data in your summary table (see below) to answer this part.

Partial Answer: (b) The squared correlation coefficient r^2 had a value of only 0.784 when carrying out parabolic (quadratic) regression, so the quadratic equation was dropped from further consideration. The cubic equation is

$$\ln K_p = -0.4541 - 0.3689\, z + 0.2166\, z^2 + 0.0960\, z^3 \qquad (13-121)$$

and has a satisfactory r^2 of 0.957. The term z in the equation stands for $(\delta_1 - \delta_2)$. (c) The results of calculating ln K_p from equation (13–120) are shown in the following summary table, together with ln K_p (experimental) and ln K_p calculated by carrying out cubic regression (equation 13–121).

Answers for *Problem 13–16*

% PGE 400 in water	Solvent δ_1 $(cal/cm^3)^{1/2}$	$(\delta_1 - \delta_2)$	ln K_p (exp.)	ln K_p (cubic eq.) (13–121)	ln K_p (Eq. (13–120))
90	11.8	−2.2	0.381	0.384	0.579
80	13.1	−0.9	0.026	0.017	−0.231
75	13.7	−0.3	−0.429	−0.327	−0.376
70	14.4	0.4	−0.446	−0.561	−0.362
65	15.0	1.0	−0.574	−0.510	−0.193
60	15.7	1.7	0.028	0.017	0.187

It is seen in the summary table, column 5, that the ln K_p values obtained by cubic regression correspond satisfactorily to the ln K_p (experimental) and the cubic equation, (13–121), can be used to calculate ln K_p and therefore K_p.

The calculated ln K_p values from equation (13–120) (column 6 in the summary table) differ from the experimental ln K_p values, but the principle remains that the largest $(\delta_1 - \delta_2)$, i.e., the largest differences between δ_1 and δ_2, correspond to the greatest ln K_p (experimental) and through the expression $K_p = k_1/k_2$ to the largest absorption rate constants. Conversely, the smallest ln K_p (equation (13–120)) occurs at δ_1 of 13.7 to 14.4 in which region is found the drug's delta value, namely 14.0. Here the solubility parameter of the mixed solvent, PGE 400–water, is sufficiently close to that of the drug, theophylline, to interact with it and hinder the bioabsorption of the drug.

13–17. (a) As a continuation of work on transcorneal permeation of pilocarpine (see *Example 13–14*, p. 346), you are asked to plot the experimentally determined corneal membrane permeability P versus pH (Table 13–5, p. 346) on ordinary rectangular graph paper.

(b) Calculate P(theoretical) (see *Example 13–14*, equation (13–98)) using the values $P_B = 9.733 \times 10^{-6}$ cm/sec and $P_{BH^+} = 4.836 \times 10^{-6}$ cm/sec. The nonionized fraction f_B of pilocarpine at each pH value is calculated from equation (13–96), page 345. Plot P(theoretical) versus pH on the graph prepared under (a). Note that the pH at the inflection point of the sigmoidal line is equal roughly to $pK_a = 6.67$ for the conjugate acid of pilocarpine at 34° C.

(c) Does this sigmoidal curve suggest any relationship to the titration curve of a weak acid, Figure 8–1, page 175, where, at half-neutralization, pH = pK_a?

Partial Answer: (b) at pH 4.67, P(theoretical) = 4.885×10^{-4} cm/sec, and at pH 6.67, P(theoretical) = 7.285×10^{-4} cm/sec. (c) The Henderson–Hasselbalch equation is used on page 176 to arrive at the relationship pH = pK_a at the half neutralization point, and the Henderson–Hasselbalch equation is also used on page 342 to obtain an equation for the percent ionization of a weak acid at various pH values. These remarks should assist you in arriving at your answer.

13–18. The steady-state penetration of progesterone and its hydroxyl derivatives across the intact skin was found to be related to the solubility of the drug in the stratum corneum. The solubility in the stratum corneum and the rate of permeation decrease as the hydrophilicity of the progesterone derivatives increases.[84] The data are found in the following table for the progesterone derivatives numbered 1 through 7:

Data for *Problem 13–18*

Drug no.	1	2	3	4	5	6	7
Solubility (mg/mL)	1.09	2.46	7.97	2.82	12.5	32.4	47.7
Permeability rate ($\mu g/(cm^2\ hr)$)	0.15	0.31	0.97	0.29	0.57	4.73	2.37

(a) Plot the permeability rates dQ/dt, ($\mu g/(cm^2\ hr)$), on the vertical axis against the solubility of the progesterone derivatives on the horizontal axis of three-cycle log–log paper. One may postulate a linear relationship between the steady-state rates of permeation of progesterone and its solubility in the stratum corneum. However, it is found that a linear relationship is obtained only when the data are plotted on a log–log graph, which suggests that the true relationship is a power curve. Let permeability rate dQ/dt be y and the solubility in the stratum corneum be x, and write the power curve relationship:

$$y = ax^b \qquad (13-122)$$

in which a and b are arbitrary constants.

(b) Use a hand calculator or a personal computer to obtain the values of a and b using the data given above.

(c) Now assume a relationship between y and x in the linear form

$$y = a'x + b' \qquad (13-123)$$

and compute a' and b'. Which equation, (13–122) or (13–123), better fits the data?

(d) Why did a log–log fit of the data suggest using the power equation $y = ax^b$?

(e) Do you believe it would be possible to extrapolate results such as these to the transdermal absorption of progesterone derivatives from various ointment bases into intact and damaged or diseased human skin? What factors would need to be taken into consideration?

Partial Answers: (b) $y = 0.111\, x^{1.006}$; (c) $y = 0.0724\, x + 0.2355$

13–19. The percutaneous absorption of chloramphenicol through mouse skin was investigated at various temperatures. Permeability coefficients were recorded together with temperatures as follows:

Data for *Problem 13–19*

Temperature, °C	25	31	37	45
P (cm/min) × 10^4	1.12	1.87	3.01	6.20

Plot the Arrhenius curve and calculate the energy of activation for permeation. Compare your results with those of Aguiar and Weiner,[85] who, in a similar study, found E_a to be 15,000 cal/mole.

Answer: 15,945 cal/mole, or 16 kcal/mole. The answer varies depending on the number of significant figures retained.

13–20. Liron and Cohen[86a] studied the percutaneous absorption of the straight chain fatty acid, propionic acid, through porcine skin. They found that the permeability coefficient, $P = KD/h$ (equation (13–11), p. 327) increased with elevation of the temperature as shown in the table:

Data for *Problem 13–20*

Temperature, °C	15	25	30	37	50
$P \times 10^3$ cm/min	0.81	1.25	1.64	3.00	6.72

Prepare an Arrhenius plot of ln P against reciprocal temperature ($1/T$, °K^{-1}). Obtain the activation energy, E_p, in kcal/mole, and P_o, which is proportional to the number of molecules entering the film and to the probability that these molecules have sufficient energy to engage in the diffusion process. P_o is comparable to the frequency factor A in the field of kinetics (equation (12–72), p. 295).

Answer: E_p = 11.38 kcal/mole; ln P_o = 12.62; $P_o = 3.0 \times 10^5$

13–21. Liron and Cohen[86a] applied Fick's law of diffusion to the percutaneous absorption of a drug. The delivery of valeric (pentanoic) acid from *n*-heptane solution (1 molar) into excised porcine skin was studied in a diffusion cell having a 1 cm^2 cross-sectional area. The following results were obtained:

Data for *Problem 13–21*

Time (hr)	0	0.5	1	2	3	4	5	6
Q, μmole/cm^2	0	1.4	7.6	19.1	34.1	49.1	64.1	79.1

(a) Plot Q, the cumulative penetrated mass per unit area of valeric acid, against time.

(b) Find the flux at the steady state, J_s, from the slope of the linear segment of the cumulative penetrant mass per unit area Q versus time, i.e., for time 2 through 6 hours.

(c) Use J_s and the concentration of valeric acid in the donor phase, C_d, 1000 μmole/cm^3, to calculate the permeability coefficient, P.

(d) Find the lag time t_L from the penetration curve by extrapolating the linear segment to zero penetration per unit cross-section.

(e) Find the diffusion coefficient D from t_L and thickness h of the skin barrier (stratum corneum): h = 15 micrometers (μm).

(f) From the results obtained, calculate the partition coefficient, using equation (13–11), page 327 of this chapter.

(g) Calculate the partition coefficient K using the equation of Davis.[85]

$$\ln K_1 = \frac{V_2 \phi^2}{RT}[(\delta_1 - \delta_2)^2 - (\delta_0 - \delta_2)^2 + (V_d/V_m)] \quad (13\text{–}124)$$

in which V_2 is the molar volume of the solute, R and T have their usual meaning, δ_1 and δ_2 are the solubility parameters for the solute (drug) and solvent, respectively. V_d is the volume of the donor phase, equal to 300 μL, and V_m is the volume of the skin barrier, equal to 1 cm^2 × 0.015 cm = 0.015 cm^3 = 15 μL. In *Problem 13–16*, the approximate equation (13–120) was used, disregarding the final term, ln (V_d/V_m); in the present case it is sufficiently important and cannot be eliminated.

Partial Answers: (b) J_s = 15 μmole/(cm^2 hr); (c) $P = 0.25 \times 10^{-3}$ cm/min; (d) t_L = 40 min; (e) from equation (13–14a), p. 328, $D = 1.6 \times 10^{-10}$ cm^2 sec^{-1}; (f) K = 39.1; (g) K = 43.4

13–22. Hydrocortisone was released from a silicone matrix implanted in the vaginal tract of a rabbit (see pp. 350–351). Calculate the amount of hydrocortisone (mg) released from the vaginal implant in 2.5, 5, 10, 15, 20, 25, 30, and 40 days. Plot the amount released, m (mg), versus time in days. The following data are taken from the work of Ho et al.[87] The solubility of the drug in the polymer matrix, C_s, was 0.014 mg/cm^3; the diffusion coefficient in the matrix, D_s, was 4.5×10^{-7} cm^2/sec; the partition coefficient for silicone/water, K_s, was 0.05; the permeability coefficient of the rabbit vaginal membrane, P_m, was 5.8×10^{-5} cm/sec; P_{aq} was 7×10^{-4} cm/sec; the loading concentration (initial amount of drug per unit volume of plastic cylinder), A, was 100 mg/cm^3; the length h of the silicone cylinder was 6.0 cm., and its radius, a_o, was 1.1 cm.

Partial Answer: 36.63 mg released in 15 days

13–23. The rate at which a solute diffuses out of a single open-boundary cell, Figure 13–30, at time t is equal to the concentration gradient $\partial u/\partial x$ at the open boundary multiplied by $(D \times A)$, the diffusion coefficient of the solute multiplied by the area A of the cell.

The rate R of solute escape is given by

$$R \text{ (g/sec)} = \frac{\partial u}{\partial x}(D \cdot A)$$

$$= \frac{2\,u_o}{h}\left[exp\left(-\frac{\pi^2 Dt}{4h^2}\right) + exp\left(-\frac{9\pi^2 Dt}{4h^2}\right) + \cdots\right](D \cdot A) \quad (13\text{–}125)$$

The area A of the cell is 6.78 cm^2, the cell height h is 3.92 cm, the initial concentration u_o of solute in aqueous solution at 25° C is 0.0628 g/cm^3, the solute's diffusion coefficient in this medium is $D = 9.81 \times 10^{-6}$ cm^2/sec, and the time of diffusion is t = 8560 sec (2.38 hr). Calculate the rate of escape from the cell.

Answer: $R = 3.99 \times 10^{-6}$ g/sec = 2.39×10^{-4} g/min

13–24. A new drug is placed in a Graham closed boundary diffusion cell (see Fig. 13–29) to determine the drug's diffusion coefficient, D. The initial concentration of the drug u_o is 0.0278 g/cm^3 in water at 25° C. The total height of the cell is H = 3.86 cm and the height of the drug solution in the cell is h = 1.93 cm. A sample is taken at a depth of $x = H/3$ at time t = 10,523 sec (2.923 hr) and analyzed for the drug; its concentration u is found to be 0.0173 g/cm^3. Rearrange equation (13–113) so as to calculate D, the drug's diffusion coefficient. (See *Example 13–16.*)

Answer: $D = 12.4 \times 10^{-5}$ cm^2/sec

13–25. Diffusion through the skin may be considered as a multilayer diffusion where the main layers are the stratum corneum, epidermis, and dermis. The stratum corneum is the major diffusional barrier, and epidermis may be significantly less permeable than dermis. Yu et al.[88] performed experiments of permeation of a prodrug of vidarabine to study the diffusional characteristics of the different layers of the skin. Using dermis membranes of mice (average thickness, 350 μm), the lag time t_L for the permeation of the drug was 152.3 sec.

In a second experiment, the stratum corneum was removed with Scotch tape. The permeability coefficient of the stripped skin (P^{ss}) (without stratum corneum) was determined to be 3.74×10^{-6} cm/sec. Finally, the permeability coefficient of the whole skin (stratum corneum, epidermis, and dermis) was 2.98×10^{-4} cm/sec.

(a) Compute the permeability coefficient of the dermis. You will need equation (13–14*b*), page 328, for this part.

(b) Compute the permeability coefficients of the stratum corneum and the dermis. *Hint:* Use equation (13–51*b*), page 337, as a model.

Answers: (a) P (dermis) = 3.8×10^{-5} cm/sec; (b) P (stratum corneum) = 3.0×10^{-5} cm/sec; P (epidermis) = 4.2×10^{-6} cm/sec

[a]These authors are thanked for providing *Problems 13–20* and *13–21*.