11 Diffusion

Chapter Objectives
At the conclusion of this chapter the student should be able to:

1. Define diffusion and describe relevant examples in the pharmaceutical sciences and the practice of pharmacy.
2. Understand the processes of dialysis, osmosis, and ultrafiltration as they apply to the pharmaceutical sciences and the practice of pharmacy.
3. Describe the mechanisms of transport in pharmaceutical systems and identify which ones are diffusion based.
4. Define and understand Fick's laws of diffusion and their application.
5. Calculate diffusion coefficient, permeability, and lag time.
6. Relate permeability to a rate constant and to resistance.
7. Understand the concepts of steady state, sink conditions, membrane, and diffusion control.
8. Describe the various driving forces for diffusion, drug absorption, and elimination.
9. Describe multilayer diffusion and calculate component permeabilities.
10. Calculate drug release from a homogeneous solid.

Introduction

The fundamentals of diffusion are discussed in this chapter. Free diffusion of substances through liquids, solids, and membranes is a process of considerable importance in the pharmaceutical sciences. Topics of mass transport phenomena applying to the pharmaceutical sciences include the release and 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. This chapter treats the fundamental basis for diffusion in pharmaceutical systems.

There are several ways that a solute or a solvent can traverse a physical or biologic membrane. The first example (Fig. 11-1) depicts the flow of molecules through a physical barrier such as a polymeric membrane. The passage of matter through a solid barrier can occur by simple molecular permeation or by movement through pores and channels. Molecular diffusion or permeation through nonporous media depends on the solubility of the permeating molecules in the bulk membrane (Fig. 11-1a), whereas a second process can involve passage of a substance through solvent-filled pores of a membrane (Fig. 11-1b) and is influenced by the relative size of the penetrating molecules and the diameter and shape 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. A second example relates to drug and solvent transport across the skin. Passage through human skin of steroidal molecules substituted with hydrophilic groups may predominantly involve transport through hair follicles, sebum ducts, and sweat pores in the epidermis (Fig. 11-19). 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 11-1c. 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 it is too large for such channel transport, the diffusant may dissolve in the polymer matrix and pass through the film by simple diffusion. Diffusion also plays an important role in drug and nutrient transport in biologic membranes in the brain, intestines, kidneys, and liver. In addition to diffusion through the lipoidal membrane, several other transport

mechanisms have been characterized in biologic membranes including energy-dependent and energy-independent carrier-mediated transport as well as diffusion through the paracellular spaces between

cells. The multitude of mechanisms of transport across various mucosal membranes will be introduced later in this chapter. Several pharmaceutically important diffusion-based processes are covered in this and subsequent chapters.

Key Concept

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 driving force such as a concentration gradient. The mass transfer of a solvent (e.g., water) or a solute (e.g., a drug) forms the basis for many important phenomena in the pharmaceutical sciences. For example, diffusion of a drug across a biologic membrane is required for a drug to be absorbed into and eliminated from the body, and even for it to get to the site of action within a particular cell. On the negative side, the shelf life of a drug product could be significantly reduced if a container or closure does not prevent solvent or drug loss or if it does not prevent the absorption of water vapor into the container. These and many more important phenomena have a basis in diffusion. Drug release from a variety of drug delivery systems, drug absorption and elimination, dialysis, osmosis, and ultrafiltration are some of the examples covered in this and other chapters.

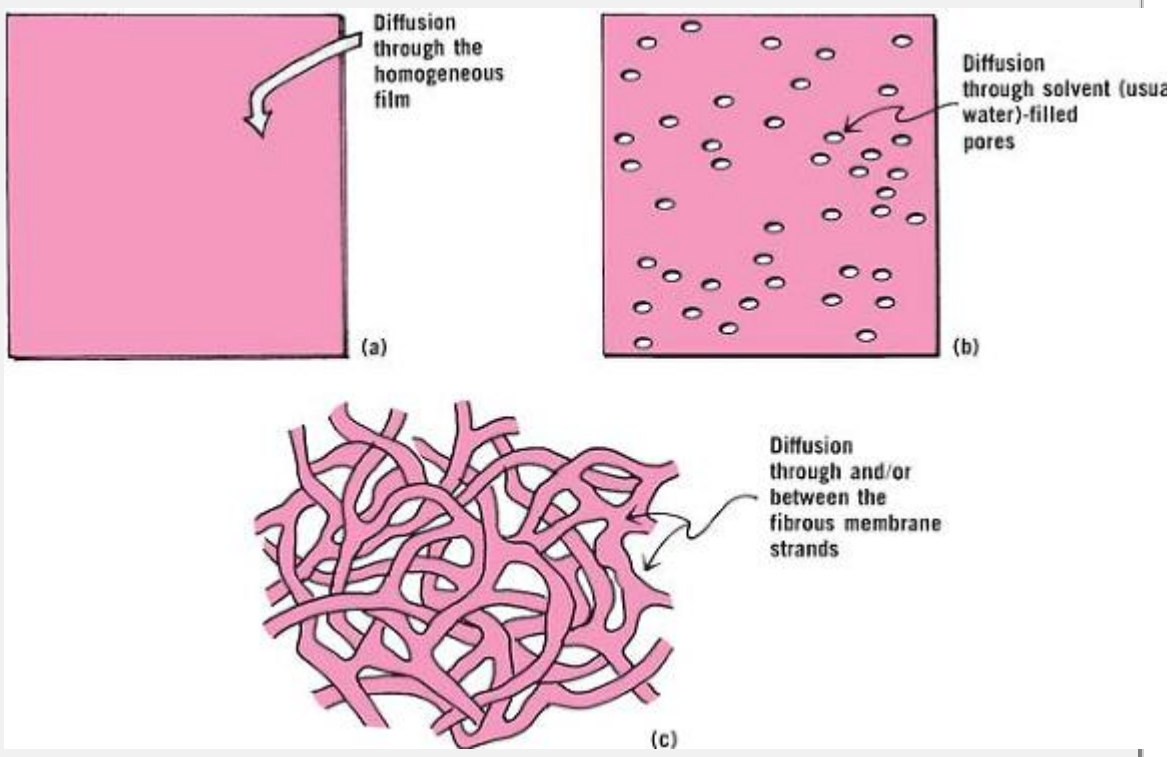

Fig. 11-1. (*a*) Homogeneous membrane without pores. (*b*) Membrane of dense material with straight-through pores, as found in certain filler barriers such as Nucleopore. (*c*) Cellulose membrane used in the filtration process, showing the intertwining nature of the fibers and the tortuous channels.

Drug Absorption and Elimination

Diffusion through biologic membranes is an essential step for drugs entering (i.e., absorption) or leaving (i.e., elimination) the body. It is also an important component along with convection for efficient drug distribution throughout the body and into tissues and organs. Diffusion can occur through the lipoidal bilayer of cells. This is termed *transcellular diffusion*. On the other hand, paracellular diffusion occurs

through the spaces between adjacent cells. In addition to diffusion, drugs and nutrients also traverse biologic membranes using membrane transporters and, to a lesser extent, cell surface receptors. Membrane transporters are specialized proteins that facilitate drug transport across biologic membranes. The interactions between drugs and transporters can be classified as energy dependent (i.e., active transport) or energy independent (i.e., facilitated diffusion). Membrane transporters are located in every organ responsible for the absorption, distribution, metabolism, and excretion (ADME) of drug substances. Specialized membrane transport mechanisms were covered in more detail in Chapter 12(Biopharmaceutics) and Chapter 13 (Drug Release and Dissolution).

Elementary Drug Release

Elementary drug release is an important process that literally affects nearly every person in everyday life. Drug release is a multistep process that includes diffusion, disintegration, deaggregation, and dissolution. These processes are described in this and other chapters. Common examples are the release of steroids such as hydrocortisone from topical over-the-counter creams and ointments for the treatment of skin rashes and the release of acetaminophen from a tablet that is taken by mouth. Drug release must occur before the drug can be pharmacologically active. This includes pharmaceutical products such as capsules, creams, liquid suspensions, ointments, tablets, and transdermal patches.

Osmosis

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 a semipermeable membrane to dilute the solution containing solute and solvent. The passage of solute together with solvent is now called *diffusion* or *dialysis*. Osmotic drug release systems use osmotic pressure as a driving force for the controlled delivery of drugs. A simple osmotic pump

consists of an osmotic core (containing drug with or without an osmotic agent) and is coated with a semipermeable membrane. The semipermeable membrane has an orifice for drug release from the “pump.” The dosage form, after coming in contact with the aqueous fluids, imbibes water at a rate determined by the fluid permeability of the membrane and osmotic pressure of core formulation. The osmotic imbibition of water results in high hydrostatic pressure inside the pump, which causes the flow of the drug solution through the delivery orifice.

Ultrafiltration and Dialysis

Ultrafiltration is used to separate colloidal particles and macromolecules by the use of a membrane. Hydraulic pressure is used to force the solvent through the membrane, whereas 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 nm to several micrometers, removes bacteria from intravenous injections, foods, and drinking water.1 Hwang and Kammermeyer2 defined *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 treating kidney malfunction to rid the blood of metabolic waste products (small molecules) while preserving the high-molecular-weight components of the blood. In ordinary osmosis as well as in dialysis, separation is spontaneous and does not involve the high-applied pressures of ultrafiltration and reverse osmosis.

Diffusion is caused by random molecular motion and, in relative terms, is a slow process. In a classic text on diffusion, E. L. Cussler stated, “In gases, diffusion progresses at a rate of about 10 cm in a minute; in liquids, its rate is about 0.05 cm/min; in solids, its rate may be only about 0.0001 cm/min.”3 A relevant question to ask at this point is, Can such a slow process be meaningful to the pharmaceutical sciences? The answer is a resounding “yes.” Although the rate of diffusion appears to be quite slow, other factors such as the distance that a diffusing molecule must traverse are also very important. For example, a typical cell membrane is approximately 5-nm thick. If it is assumed that a drug will diffuse

into a cell at a rate of 0.0005 cm/min, then it takes only a fraction of a second for that drug molecule to enter the cell. On the other hand, the thickest biomembrane is skin, with an average thickness of 3 μm (Fig. 11-19). For the same rate of diffusion, it would take 600 times longer for the same drug molecule to diffuse through the skin. The time difference in the appearance of the drug on the other side of the skin is known as the lag time. An even more extreme example is the levonorgestrel-releasing implant.4 This long-acting contraceptive has been approved for 5 years of continuous use in human patients. To achieve low constant diffusion rates, six matchstick-sized, flexible, closed capsules made of silicon rubber tubing are inserted into the upper arm of patients. Annual pregnancy rates of Norplant users are below 1 per 100 throughout 7 years of continuous use. Levonorgestrel implants provide low progestogen doses: 40 to 50 μg/day at 1 year of use, decreasing to 25 to 30 μg/day in the fifth year. Serum levels of levonorgestrel at 5 years are 60% to 65% of those levels measured at 1 month of use.4 Although diffusion plays an important role in the successful delivery of levonorgestrel from the Norplant system, drug release from long-acting delivery systems is a function of many other factors as well.

Another pharmaceutically relevant example of diffusion relates to the mixing of a drug in solution with intestinal contents immediately prior to drug absorption across the intestinal mucosa. At first glance, mixing appears to be a simple process; however, several molecular- and macroscopic-level processes must occur in parallel for efficient mixing to occur. It is important to remember that diffusion depends on random molecular motions that take place over small molecular distances. Therefore, other processes are responsible for the movement of molecules over much larger distances and are required for mixing to occur. These processes are called macroscopic processes and include convection, dispersion, and stirring. After the macroscopic movement of molecules occurs, diffusion mixes newly adjacent portions of the intestinal fluid. Diffusion and the macroscopic processes all contribute to mixing, and, qualitatively, the effects are similar. In 1860, Maxwell was one of the first to recognize this when he stated, “Mass transfer is due partly to the motion of translation and partly to that of agitation.”5 Unlike many other phenomena, diffusion in a solution always occurs in parallel with convection. Convection is the bulk movement of fluid accompanied by the transfer of heat (energy) in the presence of agitation. An example of convection relevant to intestinal absorption of drugs is fluid flow down the intestine. Dispersion is also relevant to intestinal flow and is related to diffusion. “The relation exists on two very different levels. First, dispersion is a form of mixing, and so on a microscopic level it involves diffusion of molecules. Second, dispersion and diffusion are described with very similar mathematics.”3 Although it is somewhat difficult to assess intestinal dispersion patterns in humans, they are most likely characterized as “turbulent.” In certain experimental models, such as the single-pass intestinal perfusion procedure6 that is used to estimate the intestinal permeability of drugs in rats, flow conditions are optimized to obtain laminar flow hydrodynamics. Laminar flow conditions are a special example of the coupling of flow and diffusion. In contrast to turbulent flow, when operating under laminar flow conditions a dispersion coefficient can be accurately predicted. In this system, mass transport occurs by radial diffusion (i.e., movement toward the intestinal mucosa) and axial convection (i.e., flow down the length of the intestine).

Steady-State Diffusion

Thermodynamic Basis

Mass transfer is the movement of molecules in response to an applied driving force. Convective and diffusive mass transfer is important to many pharmaceutical science applications. Diffusive mass transfer is the subject of this chapter, but convective mass transfer will not be covered in detail, and the student is referred to other texts.[7,8,9] Mass transfer is a kinetic process, occurring in systems that are not in equilibrium.7 To better understand the thermodynamic basis of mass transfer, consider an isolated system consisting of two sections separated by an imaginary membrane (Fig. 11-2).7 At equilibrium, the temperatures, T, pressures, P, and chemical potentials, μ, of each of two species A and

B are equal in the two sections. If this isolated system is unperturbed, it will remain at this thermodynamic equilibrium indefinitely. Suppose that the chemical potential of one of the species, A, is now increased in section I so that $\mu_{A,I} > \mu_{A,II}$. Because the chemical potential of A is related to its concentration, the ideality of the solution, and the temperature, this perturbation of the system can be achieved by increasing the concentration of A in section I. The system will respond to this perturbation by establishing a new thermodynamic equilibrium. Although it could reestablish the equilibrium by altering any of the three variables in the system (*T*, *P*, or μ), let us assume that it will reequilibrate the chemical potentials, leaving *T* and *P*unaffected. If the membrane separating the two sections will allow for the passage of species A, then equilibrium will be reestablished by the movement of species A from section I to section II until the chemical potentials of section I and II are once again equal. The movement of mass in response to a spatial gradient in chemical potential as a result of random molecular motion (i.e., Brownian motion) is called diffusion. Although the thermodynamic basis for diffusion is best described using chemical potentials, it is mathematically simpler to describe it using concentration, a more experimentally practical variable.

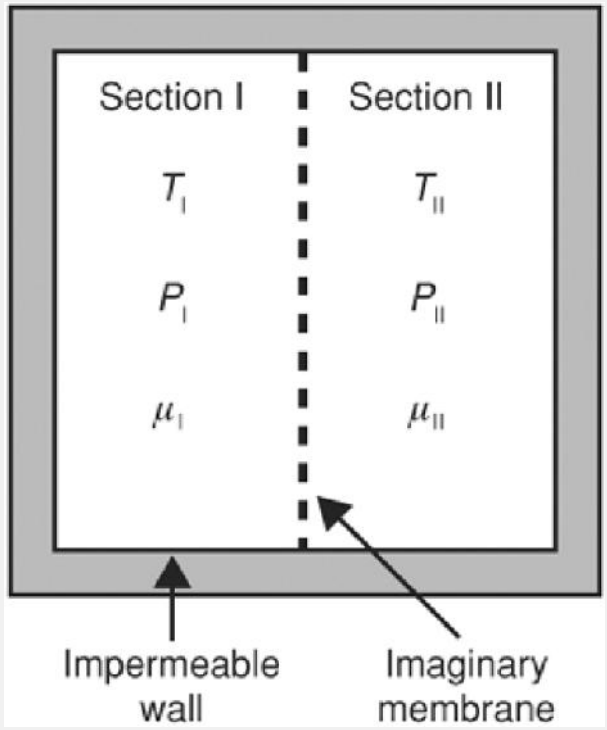

Fig. 11-2. Isolated system consisting of two sections separated by an imaginary permeable membrane. At equilibrium, the temperatures (*T*), pressures (*P*), and chemical properties (μ) of each of the species in the system are equal in the two sections. (Modified from G. L. Amidon, P. I. Lee, and E. M. Topp (Eds.), *Transport Processes in Pharmaceutical Systems*, Marcel Dekker, New York, 2000, p. 13.)84

Fick's Laws of Diffusion

In 1855, Fick recognized that the mathematical equation of heat conduction developed by Fourier in 1822 could be applied to mass transfer. These fundamental relationships govern diffusion processes in pharmaceutical systems. 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*:

$$J = \frac{dM}{S \cdot dt} \qquad (11\text{–}1)$$

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

$$J = -D\frac{dC}{dx} \qquad (11\text{–}2)$$

where *D* is the *diffusion coefficient* of a penetrant (also called the*diffusant*) in cm^2/sec, *C* is its concentration in g/cm^3, and *x* is the distance in centimeter of movement perpendicular to the surface of the barrier. In equation (11-1), the mass, *M*, is usually given in grams or moles, the barrier surface area, *S*, in cm^2, and the time, *t*, in seconds. The units of *J* are g/cm^2 sec. 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 (11-2) signifies that diffusion occurs in a direction (the positive *x* direction) opposite to that of increasing concentration. That is, diffusion occurs in the direction of decreasing concentration of diffusant; thus, the flux is always a positive quantity. Diffusion will stop when the concentration gradient no longer exists (i.e., when *dC*/*dx* = 0).

Although the *diffusion coefficient, D*, or *diffusivity*, as it is often called, appears to be a proportionality constant, it does not ordinarily remain constant. *D* is affected by concentration, 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 (11-2) is known as *Fick's first law*.

Fick's Second Law

Fick's second law of diffusion forms the basis for most mathematical models of diffusion processes. 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 (Figs. 11-3 and 11-4) 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 is, Δ*C*/Δ*t*, as

the flux or amount diffusing changes with distance, Δ*J*/Δ*x*, in the *x*direction, or*

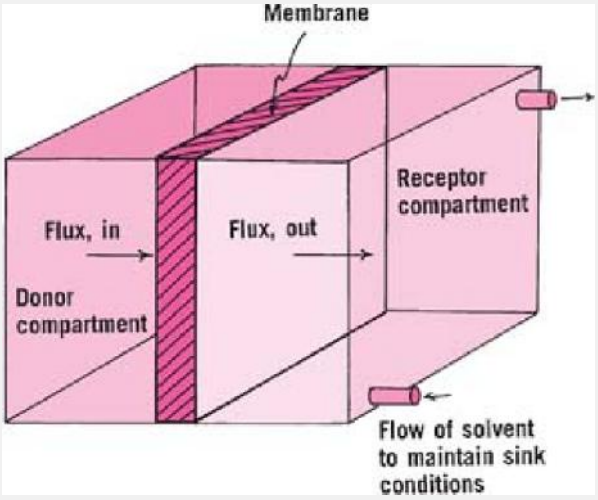

Fig. 11-3. Diffusion cell. The donor compartment contains diffusant at concentration *C*.

$$\frac{\partial C}{\partial t} = -\frac{\partial J}{\partial x} \qquad (11\text{–}3)$$

Differentiating the first-law expression, equation (11-2), with respect to *x*, one obtains

$$-\frac{\partial J}{\partial x} = D\frac{\partial^2 c}{\partial x^2} \qquad (11\text{–}4)$$

Substituting $\partial C/\partial t$ from equation (11-3) into equation (11-4) results in Fick's second law, namely,

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 c}{\partial x^2} \qquad (11\text{–}5)$$

Equation (11-5) 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

$$\frac{\partial C}{\partial t} = D\left(\frac{\partial^2 C}{\partial x^2} + \frac{\partial^2 C}{\partial y^2} + \frac{\partial^2 C}{\partial z^2}\right) \qquad (11\text{–}6)$$

This expression is not usually needed in pharmaceutical problems of diffusion, however, because 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 (11-2), 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 can be described, however, in terms of the second law, equation (11-5). Consider the diffusant originally dissolved in a solvent in the left-hand compartment of the chamber shown in Figure 11-3. 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.

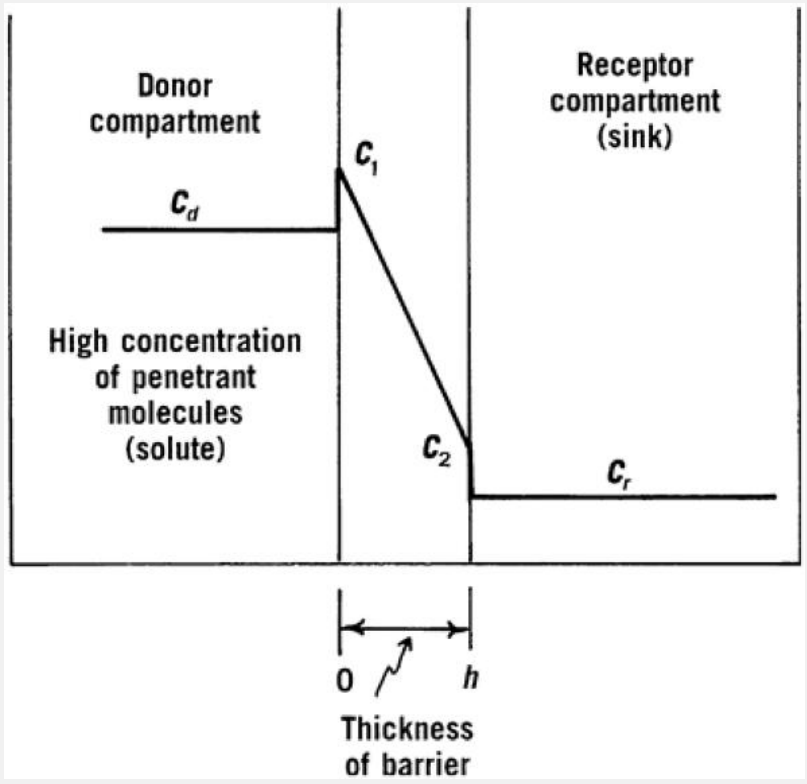

Fig. 11-4. Concentration gradient of diffusant across the diaphragm of a diffusion cell. It is normal for the concentration curve to increase or decrease sharply at the boundaries of the barrier because, in general, C_1 is different from C_d, and C_2 is different from C_r. The concentration C_1 would be equal to C_d, for example, only if*K* -

C_1/C_d had a value of unity.

Originally, the diffusant concentration will fall in the left compartment and rise in the right compartment until the system comes to 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 becomes 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 Fick's second law,

$$\frac{dC}{dt} = D\frac{d^2C}{dx^2} = 0 \qquad (11\text{–}7)$$

C is the concentration of the permeant in the barrier expressed in mass/cm^3. Equation (11-7) demonstrates that because *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

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the membrane, *dC/dx*, is constant, signifying a linear relationship between concentration, *C*, and distance, *x*. This is shown in Figure 11-4 (in which the distance *x* is equal to *h*) for drug diffusing from left to right in the cell of Figure 11-3. 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 "quasistationary" state, and little error is introduced by assuming steady state under these conditions.

Diffusion Driving Forces

There are numerous diffusional driving forces in pharmaceutical systems. Up to this point the discussion has focused on "ordinary diffusion," which is driven by a concentration gradient.8 However, other driving forces include pressure, temperature, and electric potential. Examples of driving forces in pharmaceutical systems are shown in Table 11-1.

Diffusion Through Membranes

Steady Diffusion Across a Thin Film and Diffusional Resistance

Yu and Amidon18 concisely developed an analysis for steady diffusion across a thin film as it relates to diffusional resistance.Figure 11-4 depicts steady diffusion across a thin film of thickness *h*. In this case, the diffusion coefficient is considered constant because the solutions on both sides of the film are dilute. The concentrations on both sides of the film, C_d and C_r, are kept constant and both sides are well mixed. Diffusion occurs in the direction from the higher concentration (C_d) to the lower concentration (C_r). After sufficient time, steady state is achieved and the concentrations are constant at all points in the film as shown in Figure 11-5. At steady state (*dC/dt* = 0), Fick's second law becomes

$$D\frac{\partial^2 e}{\partial z^2} = 0 \qquad (11\text{–}8)$$

Key Concept

Membranes and Barriers

Flynn et al.19 differentiated between a membrane and a barrier. A *membrane* is a biologic or physical "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.

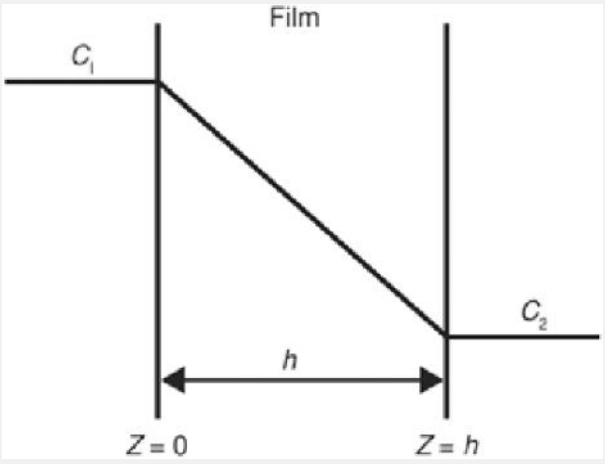

Fig. 11-5. Diffusion across a thin film. The solute molecules diffuse from the well-mixed higher concentration, C_1, to the well-mixed lower concentration, C_2. The concentrations on both sides of the film are kept constant. At steady state, the concentrations remain constant at all points in the film. The concentration profile inside the film is linear, and the flux is constant.

Integrating equation (11-8) twice using the conditions that at $z = 0$, $C = C_d$ and at $z = h$, $C = C_r$, yields the following equation:

$$J = \frac{D}{h}(C_1 - C_2) \qquad \textbf{(11–9)}$$

The term h/D is often called the diffusional resistance, denoted by R. The flux equation can then be written as

$$J = \frac{C_1 - C_2}{R} \qquad \textbf{(11–10)}$$

Although resistance to diffusion is a fundamental scientific principle, permeability is a term that is used more often in the pharmaceutical sciences. Resistance and permeability are inversely related. In other words, the higher the resistance to diffusion, the lower is the permeability of the diffusing substance. In the next few sections the concepts of permeability and series resistance will be introduced.

Permeability

Fick adapted the two diffusion equations (11-2) and (11-5) to the transport of matter from the laws of heat conduction. Equations of heat conduction are found in the book by Carslaw.20 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 reader should have no difficulty in following the discussion of dissolution and diffusion.

If a membrane 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 (Figure 11-4), the first law of Fick can be written as

$$J = \frac{dM}{S\,dt} = D\left(\frac{C_1 - C_2}{h}\right) \qquad \textbf{(11–11)}$$

Table 11-1 Driving Forces in Pharmaceutical Systems

Driving Force	Example	Description	References
Concentration	Passive diffusion	Passive diffusion is a process of mass transfer of individual molecules of a substrate brought about by random molecular motion and associated with a concentration gradient	3
	Drug dissolution	Drug “dissolution” occurs when a tablet is introduced into a solution and is usually accompanied by disintegration and deaggregation of the solid matrix followed by drug diffusion from the remaining small particles	10
Pressure	Osmotic drug release	Osmotic drug release systems utilize osmotic pressure as the driving force for controlled delivery of drugs; a simple osmotic pump consists of an osmotic core (containing drug with or without an osmotic agent) coated with a semipermeable membrane; the semipermeable membrane has an orifice for drug release from the pump; the dosage form, after contacting with the aqueous fluids, imbibes water at a rate determined by the fluid permeability of the membrane and osmotic pressure of core formulation; this osmotic	11

		imbibition of water results in high hydrostatic pressure inside the pump, which causes the flow of the drug solution through the delivery orifice	
	Pressure-driven jets for drug delivery	Pressure-driven jets are used for drug delivery; a jet injector produces a high-velocity jet (>100 m/sec) that penetrates the skin and delivers drugs subcutaneously, intradermally, or intramuscularly without the use of a needle; the mechanism for the generation of high-velocity jets includes either a compression spring or compressed air	12
Temperature	Lyophilization	Lyophilization (freeze-drying) of a frozen aqueous solution containing a drug and a inner-matrix building substance involves the simultaneous change in 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	13

	Microwave-assisted extraction	Microwave-assisted extraction (MAE) is a process of using microwave energy to heat solvents in contact with a sample in order to partition analytes from the sample matrix into the solvent; the ability to rapidly heat the sample solvent mixture is inherent to MAE and is the main advantage of this technique; by using closed vessels, the extraction can be performed at elevated temperatures, accelerating the mass transfer of target compounds from the sample matrix	14
Electrical potential	Iontophoretic dermal drug delivery	Iontophoresis is used to enhance transdermal delivery of drugs by applying a small current through a reservoir that contains ionized drugs; one electrode (positive electrode to deliver positively charged ions and negative electrode to deliver negatively charged ions) is placed between the drug reservoir and the skin; the other electrode with opposite charge is placed a short distance away to complete the circuit, and the electrodes are connected to a power supply; when the current flows, charged ions are transported across the	15, 16

		skin through a pore	
	Electrophoresis	Electrophoresis involves the movement of charged particles through a liquid under the influence of an applied potential difference; an electrophoresis cell fitted with two electrodes contains dispersion; when a potential is applied across the electrodes, the particles migrate to the oppositely charged electrode; capillary electrophoresis is widely used as an analytical tool in the pharmaceutical sciences	17

where $(C_1 - C_2)/h$ approximates dC/dx. The gradient $(C_1 - C_2)/h$within the diaphragm must be assumed to be constant for a quasistationary state to exist. Equation **(**11-11**)** 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 potential influence of multiple resistances on diffusion such as those introduced by aqueous boundary layers (i.e., multilayer diffusion) is covered later in this chapter.

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

$$K = \frac{C_1}{C_d} = \frac{C_2}{C_r} \qquad \textbf{(11–12)}$$

Hence,

$$\frac{dM}{dt} = \frac{DSK(C_d - C_r)}{h} \qquad \textbf{(11–13)}$$

and, if sink conditions hold in the receptor compartment, C_r[congruent] 0,

$$\frac{dM}{dt} = \frac{DSKc_d}{h} = PSC_d \qquad \textbf{(11–14)}$$

where

$$P = \frac{DK}{h}(\text{cm/sec}) \qquad \textbf{(11–15)}$$

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

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:

$$M = PSC_d t \qquad (11\text{–}16)$$

provided 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:

$$\log C_d = \log C_d(0) - \frac{PSt}{2.303V_d} \qquad (11\text{–}17)$$

Example 11-1
Simple Drug Diffusion Through a Membrane
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 $Q = M/S$versus t, the lag time, t_L, is found to be 47.5 min. The original concentration C_0 is 0.003 mmole/cm^3. The amount of steroid passing through the membrane in 4.0 hr is 3.65×10^{-3} mmole.

a. Calculate the parameter DK and the permeability, P. We have

$$Q = \frac{3.65 \times 10^{-3}\ \text{mmole}}{10.36\ \text{cm}^2} = 0.35 \times 10^{-3}\ \text{mmole/cm}^2$$
$$= DK\left(\frac{0.003\ \text{mmole/cm}^3}{0.085\ \text{cm}}\right)\left[4.0\ \text{hr} - \left(\frac{47.5}{60}\right)\text{hr}\right]$$
$$DK = 0.0031\ \text{cm}^2/\text{hr} = 8.6 \times 10^{-7}\ \text{cm}^2/\text{sec}$$
$$P = DK/h = (8.6 \times 10^{-7}\text{cm}^2/\text{sec})/0.085\ \text{cm}$$
$$= 1.01 \times 10^{-5}\ \text{cm/sec}$$

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

$$D = \frac{h^2}{6t_L} = \frac{(0.085)^2\ \text{cm}^2}{6 \times 47.5\ \text{min}}$$
$$= 25.4 \times 10^{-6}\ \text{cm}^2/\text{min}$$

or

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

c. Combining the permeability, Equation (11-15), with the value of D from (*b*), calculate the partition coefficient, K. We have

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

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

Examples of Diffusion and Permeability Coefficients

Diffusivity is a fundamental material property of the system and is dependent on the solute, the temperature, and the medium through which diffusion occurs.20 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 given inTable 11-2. 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 given in Table 11-3. In the chapter on colloids, we will see that the molecular weight and the radius of a spherical protein can be obtained from knowledge of its diffusivity.

Multilayer Diffusion

There are many examples of multilayer diffusion in the pharmaceutical sciences. 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. Finally, membrane permeation studies using Caco-2 or MDCK cell monolayers on permeable supports such as polycarbonate filters are other common examples of multilayer diffusion.

Table 11-2 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	64	14.2	Chloroform (25)

dimer			
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. With permission.

Higuchi32 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, respectively, are shown in Figure 11-6. 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 [equation (11-15)] as the diffusion coefficient,D, multiplied by the partition coefficient, K, and divided by the membrane thickness, h. For a particular lamina i,

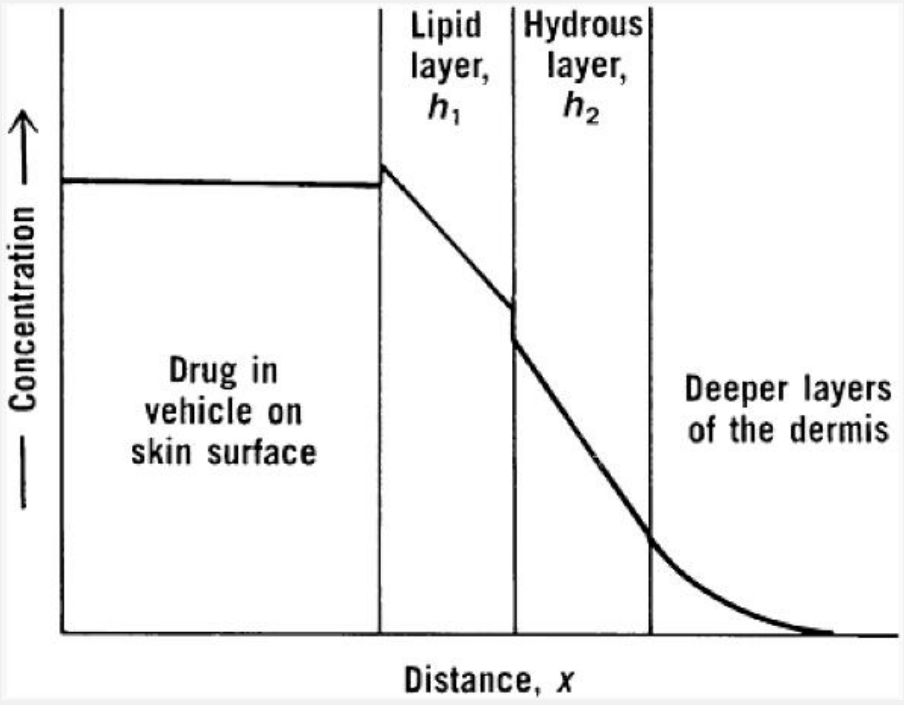

Fig. 11-6. Passage of a drug on the skin's surface through a lipid layer, h_1, and a hydrous layer, h_2, and into the deeper layers of the dermis. The curve of concentration against the distance changes sharply at the two boundaries because the two partition coefficients have values other than unity.

$$P_i = D_i K_i / h_i \qquad (11\text{–}18)$$

and

$$R_i = 1/P_i = h_i/D_iK_i \qquad \textbf{(11–19)}$$

where 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

$$R = R_1 + R_2 + \cdots R_n \qquad \textbf{(11–20}a\textbf{)}$$

$$1/P = 1/P_i + 1/P_2 \cdots + 1/P_n \qquad \textbf{(11–20}b\textbf{)}$$

$$R = 1/P = h_1/D_1K_1 + h_2/D_2K_2 + \cdots + h_n/D_nK_n \qquad \textbf{(11–20}c\textbf{)}$$

where K_i is the distribution coefficient for layer i relative to the next corresponding layer, i + 1, of the system.19 The total permeability for the two-ply model of the skin is obtained by taking the reciprocal of equation **(11–20*c*)**, expressed in terms of two layers, to yield

$$P = \frac{D_1K_1D_2K_2}{h_1D_2K_2 + h_2D_1K_1} \qquad \textbf{(11–21)}$$

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

$$t_L = \frac{\frac{h_1^2}{D_1}\left(\frac{h_1}{6D_1K_1} + \frac{h_2}{2D_2K_2}\right) + \frac{h_2^2}{D_2}\left(\frac{h_1}{2D_1K_1} + \frac{h_2}{6D_2K_2}\right)}{(h_1/D_1K_1 + h_2/D_2K_2)} \qquad \textbf{(11–22)}$$

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

$$t_L = h_1^2/6D_1 \qquad \textbf{(11–23)}$$

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Table 11-3 Drug Diffusion and Permeability Coefficients*

Drug	Membrane Diffusion Coefficient (cm^2/sec)	Membrane Permeability Coefficient (cm/sec)	Pathway	References
Amiloride	—	1.63×10^{-4}	Absorption from human jejunum	21
Antipyrine	—	4.5×10^{-4}	Absorption from human jejunum	22
Atenolol	—	0.2×10^{-4}	Absorption from human jejunum	22
Benzoic acid	—	36.6×10^{-4}	Absorption from rat	23

			jejunum	
Carbamazepine	—	4.3×10^{-4}	Absorption from human jejunum	22
Chloramphenicol	—	1.87×10^{-6}	Through mouse skin	24
Cyclosporin A	4.3×10^{-6}	—	Diffusion across cellulose membrane	25
Desipramine·HCl	—	4.4×10^{-4}	Absorption from human jejunum	22
Enalaprilat	—	0.2×10^{-4}	Absorption from human jejunum	22
Estrone	—	20.7×10^{-4}	Absorption from rat jejunum	23
Furosemide	—	0.05×10^{-4}	Absorption from human jejunum	22
Glucosamine	9.0×10^{-6}	—	Diffusion across cellulose membrane	25
Glucuronic acid	9.0×10^{-6}	—	Diffusion across cellulose membrane	25

Hydrochlorothiazide	—	0.04×10^{-4}	Absorption from human jejunum	22
Hydrocortisone	—	0.56×10^{-4}	Absorption from rat jejunum	23
	—	5.8×10^{-5}	Absorption from rabbit vaginal tract	26
Ketoprofen	2.1×10^{-3}	—	Diffusion across abdominal skin from a hairless male rat	27
Ketoprofen	—	8.4×10^{-4}	Absorption from human jejunum	22
Mannitol	8.8×10^{-6}	—	Diffusion across cellulose membrane	25
Mannitol	—	0.9×10^{-4}	Diffusion across excised bovine nasal mucosa	28
Metoprolol·$^{1}/_{2}$tartrate	—	1.3×10^{-4}	Absorption from human jejunum	22

Naproxen	—	8.3×10^{-4}	Absorption from human jejunum	22
Octanol	—	12×10^{-4}	Absorption from rat jejunum	23
PEG 400	—	0.58×10^{-4}	Absorption from human jejunum	29
Piroxicam	—	7.8×10^{-4}	Absorption from human jejunum	22
Progesterone	—	7×10^{-4}	Absorption from rat jejunum	23
Propranolol	—	3.8×10^{-4}	Absorption from human jejunum	29
Salycylates	1.69×10^{-6}	—	Absorption from rabbit vaginal tract	30
Salycylic acid	—	10.4×10^{-4}	Absorption from rat jejunum	23
Terbutaline·$^{1}/_{2}$sulfate	—	0.3×10^{-4}	Absorption from human jejunum	22
Testosterone	7.6×10^{-6}	—	Diffusion across cellulose	25

			membrane	
Testosterone	—	20×10^{-4}	Absorption from rat jejunum	23
Verapamil·HCl	—	6.7×10^{-4}	Absorption from human jejunum	22
Water	2.8×10^{-10}	2.78×10^{-7}	Diffusion into human skin layers	31

*All at 37°C.

Example 11-2

Series Resistances in Cell Culture Studies

Cell culture models are increasingly used to study drug transport; however, in many instances only the effective permeability, P_{eff}, is calculated. For very hydrophobic drugs, interactions with the filter substratum or the aqueous boundary layer (ABL) may provide more resistance to drug transport than the cell monolayer itself. Because the goal of the study is to assess the cell transport properties of drugs,P_{eff} may be inherently biased due to drug interactions with the substratum or ABL. Reporting P_{eff} is of value only if the monolayer is the rate-limiting transport barrier. Therefore, prior to reporting the P_{eff} of a compound, the effect of each of these barriers should be evaluated to ensure that the permeability relates to that across the cell monolayer. In cell culture systems the resistance to drug transport, P_{eff}, is composed of a series of resistances including those of the ABL (R_{aq}), the cell monolayer (R_{mono}), and the filter resistance (R_f) (Fig. 11-7). Total resistance is additive for a series of layers:

$$R_{eff} = R_{aq} + R_{mono} + R_f \qquad (11\text{–}24)$$

This can be written in terms of the reciprocal of the total permeability:

$$\frac{1}{P_{eff}} = \frac{1}{P_{aq}} + \frac{1}{P_{mono}} + \frac{1}{P_f}$$

$$P_{eff} = \frac{1}{\frac{1}{P_{aq}} + \frac{1}{P_{mono} + \frac{1}{P_f}}} \qquad (11\text{–}25)$$

where P_{eff} is the measured effective permeability, P_{aq} is the total permeability of the ABL (adjacent to both the apical surface of the cell monolayer and the free surface of the filter), and P_f is the permeability of the supporting microporous filter.

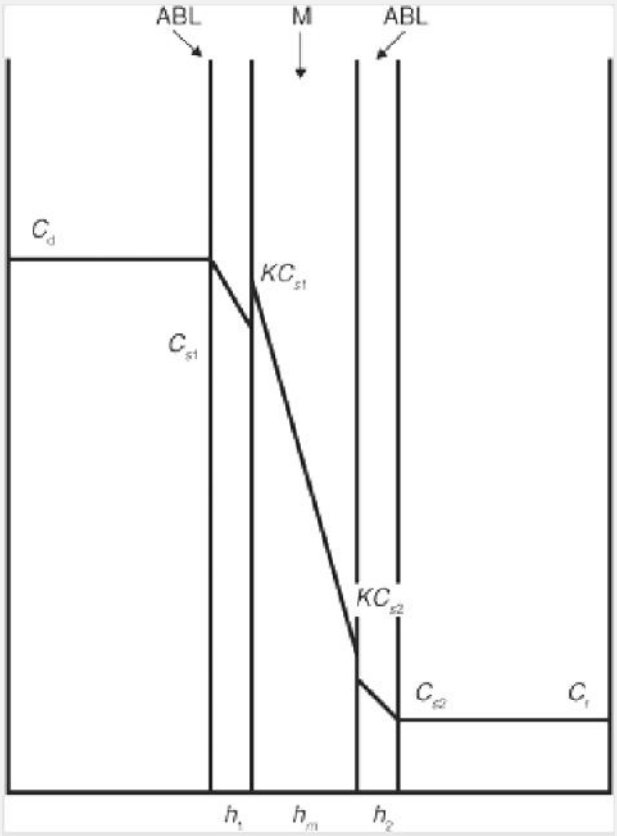

Fig. 11-7. Diffusion of drug across the aqueous boundary layer (ABL) and cell monolayer (M) in a cell culture system.

Permeability across the filter, P_f, can be obtained experimentally by measuring the P_{eff} across blank filters:

$$\frac{1}{P_{eff}^{blank}} = \frac{1}{P_{aq}} + \frac{1}{P_f} \qquad (11\text{–}26)$$

Because P_{aq} is dependent on the flow rate,

$$P_{aq} = KV^n \qquad (11\text{–}27)$$

(where k is a hybrid constant that takes into account the diffusivity of the compound, kinematic viscosity, and geometric factors of the chamber; V is the stirring rate in mL/min; and n is an exponent that varies between 0 and 1 depending on the hydrodynamic conditions in the diffusion chamber), P_f can be calculated using nonlinear regression by obtaining P_{eff} across blank filters at various flow rates.

Similarly, $1/P_f + 1/P_{mono}$ can be determined by measuring the P_{eff} through the cell monolayer at various flow rates and by using nonlinear regression and the equation.

$$P_{eff} = \frac{1}{\frac{1}{P_f} + \frac{1}{P_{mono}} + \frac{1}{KV^n}} \qquad (11\text{–}28)$$

The implicit assumption of this method is that each resistance in series is independent of the other barriers. Therefore, P_{mono} is calculated by difference, using the independently determined P_f. Because P_{aq} is independent of the presence of the monolayer, P_{mono} can be calculated as follows:

$$\frac{1}{P_{mono}} = \frac{1}{P_{eff}} - \frac{1}{P_{eff}^{blank}} \qquad (11\text{–}29)$$

Because the contributions of R_f and R_{aq} vary depending on the nature of the drug, it is important to correct for these biases by reporting P_{mono}. The deviation between P_{mono} and P_{eff} becomes more significant if the flow rate is low (i.e., R_{aq} is high) or if the filter has low effective porosity (i.e., R_f is high). In addition, the permeability of the drug also plays a major role such that the deviation between P_{mono} and P_{eff} becomes more significant for highly permeable compounds.33

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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. 11-8).

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

$$P = \frac{1}{R} = \frac{D_m K D_a}{h_m D_a + 2h_a D_m K} = \frac{1}{h_m/D_m K + 2h_a/D_a} \qquad \textbf{(11–30)}$$

This expression is analogous to equation (11-21). In equation (11-30), 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.34 We thus have

$$J = \frac{1}{S}\frac{dM}{dt} = \frac{D_m K D_a C_1}{h_m D_a + 2h_a D_m K} \qquad \textbf{(11–31)}$$

In equations (11-30) and (11-31), D_m and D_a are membrane and aqueous solvent diffusivities, h_m is the membrane thickness, and h_a is the thickness of the aqueous diffusion layer, as shown in Figure 11-8. M is the amount of permeant reaching the receptor, and S is the cross-sectional area of the barrier. It is important to realize 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

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diffusion layer; the slower the stirring, the thicker is this aqueous layer.

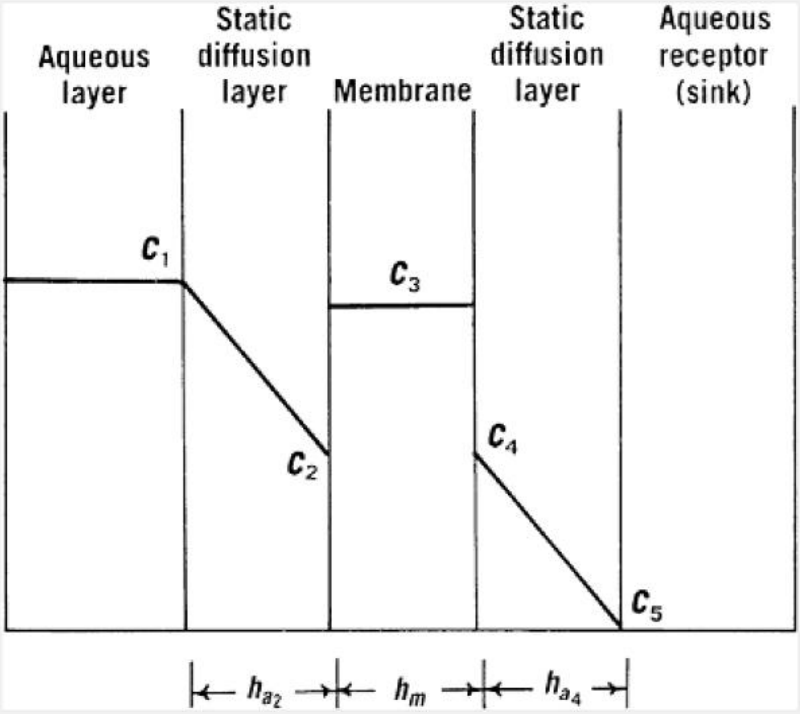

Fig. 11-8. Schematic of a multilayer (three-ply) barrier. The membrane is found between two static aqueous diffusion layers. (From G. L. Flynn, O. S. Carpenter, and S. H. Yalkowsky, J. Pharm. Sci. **61,** 313, 1972. With permission.)

Equation (11-31) 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 is greater than R_a by a factor of at least 10, or correspondingly, P_m is much less than P_a, the rate-determining step (slowest step) is diffusion across the membrane. This is reflected in equation (11-31) when $h_m D_a$ is much greater than $2h_a D_m$. Thus, equation (11-31) reduces to

$$J = \left(\frac{KD_m}{h_m}\right) C_1 \qquad (11\text{–}32)$$

Equation (11-32) represents the simplest case of membrane control of flux.

Aqueous Diffusion Layer Control

When $2h_a KD_m$ is much greater than $h_m D_a$, equation (11-31)becomes

$$J = \left(\frac{D_a}{2h_a}\right) C_1 \qquad (11\text{–}33)$$

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 $2h_a KD_m \gg h_m D_a$, it is observed that membrane control shifts to diffusion layer control when the partition coefficient K becomes sufficiently large.

Example 11-3

Transfer from Membrane to Diffusion-Layer Control

Flynn and Yalkowsky34 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 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. Instead, the gradient is now found in the aqueous diffusion layers, and diffusion-layer control takes over as the dominant factor in the permeation process. The steady-state flux, J, for hexyl *p*-aminobenzoate was found to be 1.60×10^{-7} mmole/cm^2 sec. D_a is 6.0×10^{-6} cm^2/sec and the concentration of the PABA ester, C, is 1.0 mmole/liter. The system is in diffusion-layer control, so equation (11-33) applies. Calculate the thickness of the static diffusion layer, h_a. We have

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

$$h_a = \frac{6.0 \times 10^{-6}\ \text{cm}^2/\text{sec}}{2(1.60 \times 10^{-7}\ \text{mmole/cm}^2\ \text{sec}) \times (1.0 \times 10^{-3}\ \text{mmole/cm}^3)} = 0.019\ \text{cm}$$

One observes from equations (11-32) and (11-33) 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 (11-33) shows that the flux is independent of membrane thickness, h_m, and other properties of the membrane when under static diffusion layer control.

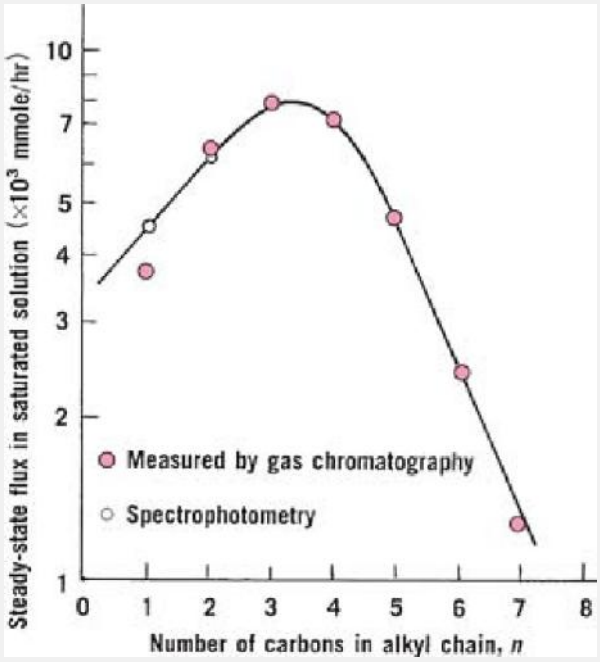

Fig. 11-9. Steady-state flux of a series of *p*-aminobenzoic acid esters. Maximum flux occurs between the esters having three and four carbons and is due to a change from membrane to diffusion-layer control, as explained in the text. (From G. L. Flynn and S. H. Yalkowsky, J. Pharm. Sci. **61,** 838, 1972. With permission.)

The maximum flux obtained in a membrane preparation depends on the solubility, or limiting concentration, of the PABA homologue. The maximum flux can therefore be obtained using equation (11-31) in which C is replaced byC_s, the solubility of the permeating compound:

$$J_{max} = \frac{D_m K D_a}{h_m D_a + 2h_a K D_m} C_s \qquad (11\text{–}34)$$

The maximum steady-state flux, J_{max}, for saturated solutions of the PABA esters is plotted against the ester chain length in Figure 11-9.34 The plot exhibits peak flux between n = 3 and n = 4 carbons, that is, between propyl and butyl *p*-aminobenzoates. The peak in Figure

11-9suggests 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.

By using a well-characterized membrane such as siloxane of known thickness and a homologous series of PABA esters, Flynn and Yalkowsky34 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, influence release rates from sustained-delivery forms, and influence absorption and excretion processes for drugs distributed in the body.

Lag Time Under Diffusion-Layer Control

Flynn et al.19 showed that the lag time for ultrathin membranes under conditions of diffusion-layer control can be represented as

$$t_L = \frac{\left(\sum h_a\right)^2}{6D_a} \qquad (11\text{–}35)$$

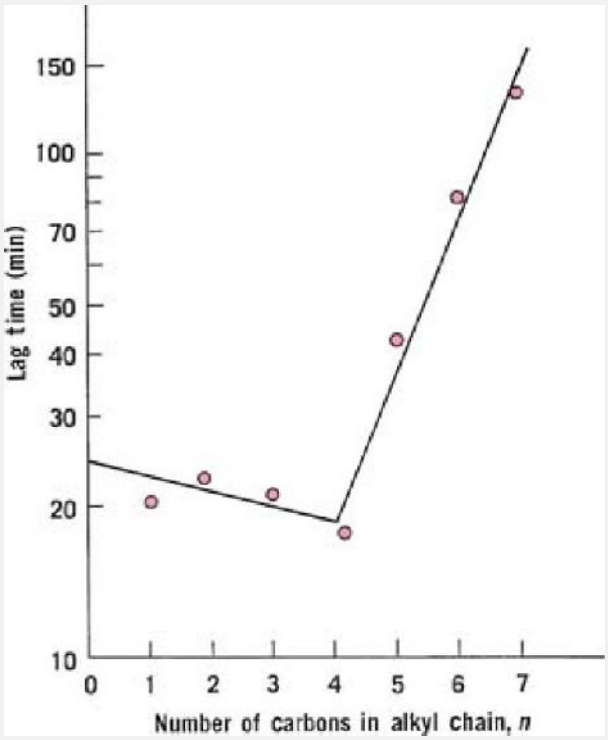

Fig. 11-10. Change in lag time of *p*-aminobenzoic acid esters with alkyl chain length. (From G. L. Flynn and S. H. Yalkowsky, J. Pharm. Sci. **61,** 838, 1972. With permission.)

where $\sum h_a$ is the sum of the thicknesses of the aqueous diffusion layers on the donor and receptor sides of the membrane. The correspondence between t_L in equation (11-35) with that for systems under membrane control, equation (11-32), is evident. The lag time for *thick* membranes operating under diffusion layer control is

$$t_L = \frac{h_m h_{a1} h_{a2} K}{(h_{a1} + h_{a2}) D_a} \qquad (11\text{–}36)$$

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

$$t_L = \frac{h_m h_a K}{2D_a} \qquad (11\text{–}37)$$

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 11-10.34

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Procedures and Apparatus For Assessing Drug Diffusion

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

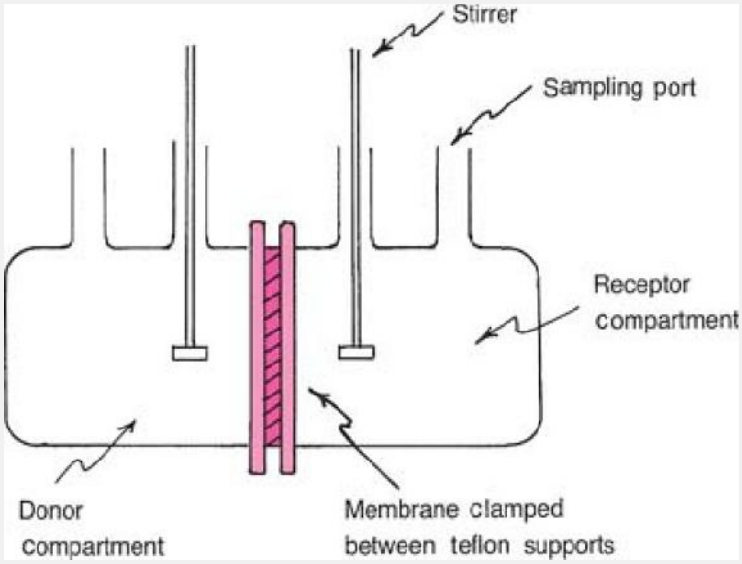


Fig. 11-11. Simple diffusion cell. (From M. G. Karth, W. I. Higuchi, and J. L. Fox, J. Pharm. Sci. **74,** 612, 1985. With permission.)

Diffusion chambers of simple construction, such as the one reported by Karth et al.35 (Fig. 11-11), are probably best for diffusion work. They are made of glass, clear plastic, or polymeric materials, are easy to assemble and clean, and allow visibility of the liquids and, if included, a rotating stirrer. They may be thermostated and lend themselves to automatic sample collection and assay. Typically, the donor chamber is filled with drug solution. Samples are collected from the receiver compartment and subsequently assayed using a variety of analytical methods such as liquid scintillation counting or high-performance liquid chromatography with a variety of detectors (e.g., ultraviolet, fluorescence, or mass spectrometry). Experiments may be run for hours under these controlled conditions.

Biber and Rhodes36 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 can be investigated in two-chamber glass cells similar in design to those used for studying drug

solutions in general. Nasim et al.37 reported on the permeation of 19 aromatic compounds from aqueous solution through polyethylene films. Higuchi and Aguiar38 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.

The sorption of gases and vapors can be determined by use of a microbalance enclosed in a temperature-controlled and evacuated vessel that is capable of weighing within a sensitivity of ± 2 × 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.39 The rate of approach to equilibrium sorption permits easy calculation of the diffusion coefficients for gases and vapors.

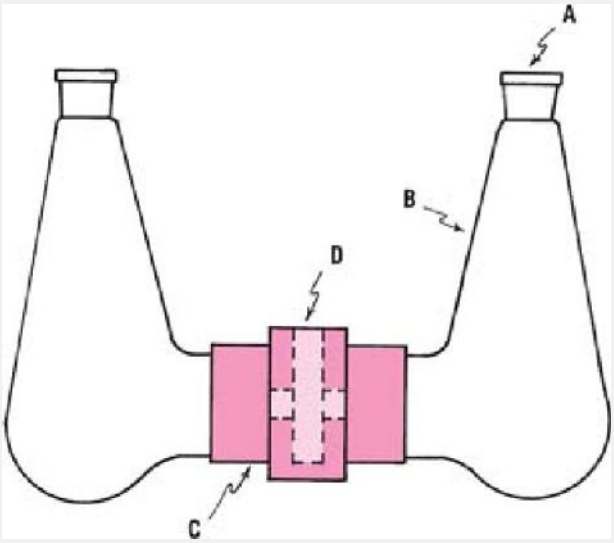


Fig. 11-12. Diffusion cell for permeation through stripped skin layers. The permeant may be in the form of a gas, liquid, or gel. Key: *A*, glass stopper; *B*, glass chamber; *C*, aluminum collar;*D*, membrane and sample holder. (From D. E. Wurster, J. A. Ostrenga, and L. E. Matheson, Jr., J. Pharm. Sci. **68,** 1406, 1410, 1979. With permission.)

In studying percutaneous absorption, animal or human skin, ordinarily obtained by autopsy, is employed. Scheuplein31described 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 to be necessary to determine the low concentrations.

Wurster et al.40 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 11-12. 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 can 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 can also 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.41 Equilibrium solubilities of drug solutes are also required in diffusion studies, and these are obtained as described earlier (Chapter 8).

Addicks et al.42 described a flowthrough cell and Addicks et al.43designed a cell that yields results more comparable to the diffusion of drugs under clinical conditions. Grass and Sweetana44 proposed a side-by-side acrylic diffusion cell for studying tissue permeation. In a later paper, Hidalgo et al.45 developed and validated a similar diffusion chamber for studying permeation through cultured cell monolayers. These chambers (Fig. 11-13 ***a*** and ***b***), derived from the Ussing chamber, have the advantage of employing laminar flow conditions across the tissue or cell surface allowing for an assessment of the aqueous boundary layer and calculation of intrinsic membrane drug permeability.

Biologic Diffusion

Example 11-4

Intestinal Drug Absorption and Secretion

The apparent permeability, P_{app}, of Taxol across a monolayer of Caco-2 cells is 4.4×10^{-6} cm/sec in the apical to basolateral direction (i.e., absorptive direction) and is 31.8×10^{-6} cm/sec from basolateral to apical direction (i.e., secretory direction). Assuming that both absorptive and secretory drug transport occurs under sink conditions ($C_r \ll C_d$), what is the amount of Taxol absorbed through the intestinal wall by 2 hr after administering an oral dose? Assume that the Taxol concentration in the intestinal fluid is 0.1 mg/mL, and following intravenous administration, the initial Taxol concentration in the plasma is 10 μg/mL. How much Taxol will be secreted into the feces 2 hr after dosing? Assume that the effective area for intestinal absorption and secretion is 1 m.2'46'47 We have

$$\frac{dJ}{dt} = \frac{dM}{dt\,A} = P_{app} C_d$$

For intestinal absorption,

$$M_a = P_{app} C_d A t = (4.4 \times 10^{-6}\ \text{cm/sec})(0.1\ \text{mg/mL})(1\ \text{m}^2)(2\ \text{hr})$$
$$= 3.17\ \mu\text{g}$$

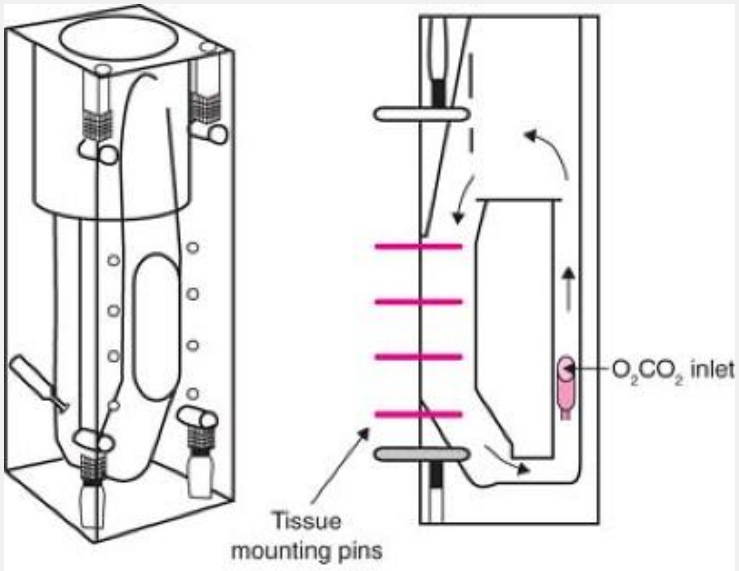
For intestinal secretion,

$$M_e = P_{app} C_d A t = (31.8 \times 10^{-6}\ \text{cm/sec})(10\ \mu\ \text{g/mL})(1\ \text{m}^2)(2\ \text{hr})$$
$$= 2.29\ \mu\text{g}$$

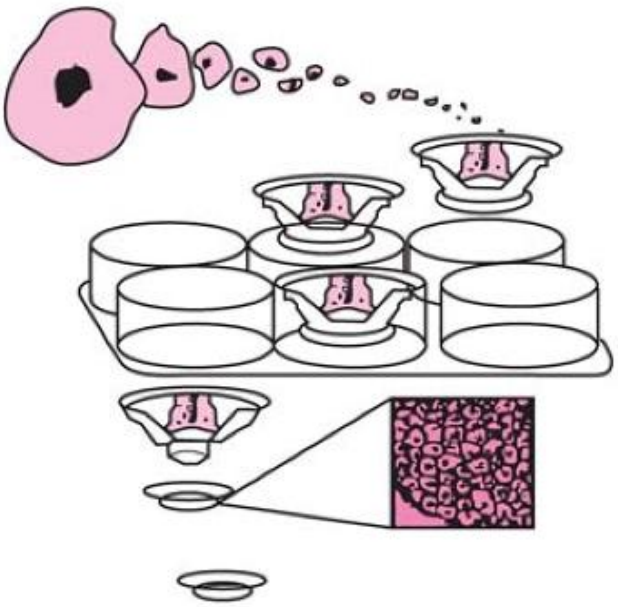
Gastrointestinal Absorption of Drugs

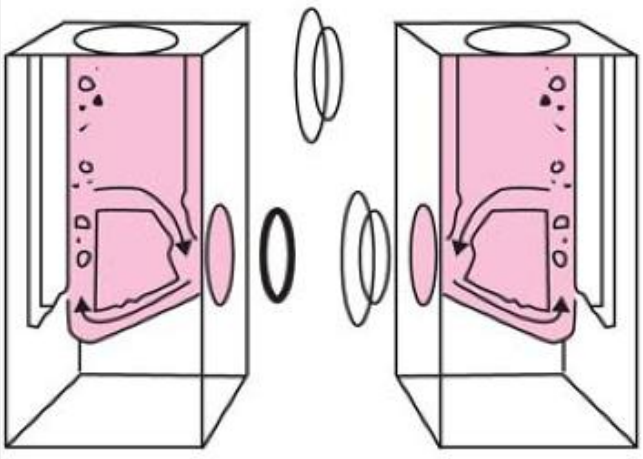
Drugs pass through living membranes according to two main classes of transport, passive and carrier mediated. Passive transfer involves a simple diffusion driven by differences in drug concentration on the two sides of the membrane. In intestinal absorption, for example, the drug travels in most cases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

in the gastrointestinal tract to a region of low concentration in the systemic circulation. Given the instantaneous dilution of absorbed drug once it reaches the bloodstream, sink conditions are essentially maintained at all times.



(a)





( )

Fig. 11-13. (*a*) Sweetana/Grass diffusion cell. Tissue is mounted between acrylic half-cells. Buffer is circulated by gas lift (O_2/CO_2) at the inlet and flows in the direction of arrows, parallel to the tissue surface. Temperature control is maintained by a heating block.

Carrier-mediated transport can be classified as active transport (i.e., requires an energy source) or as facilitated diffusion (i.e., does not depend on an energy source such as adenosine triphosphate). In active transport the drug can proceed from regions of *low*concentration to regions of *high* concentration through the "pumping action" of these biologic transport systems. Facilitative-diffusive carrier proteins cannot transport drugs or nutrients "uphill" or against a concentration gradient. We will make limited use of specialized carrier systems in this chapter 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 for a weak acid,

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

where [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

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

where [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 percentage 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, multiplied by 100:

$$\%\ \text{Ionized} = \frac{I}{I+U} \times 100 \qquad \textbf{(11–38)}$$

Therefore, the Henderson–Hasselbalch equation for weak acids can be written as

$$\frac{U}{I} = 10^{(\mathrm{p}K_a - \mathrm{pH})} = \text{antilog}(\mathrm{p}K_a - \mathrm{pH}) \quad \textbf{(11–39)}$$

or

$$U = I\ \text{antilog}(\mathrm{p}K_a - \mathrm{pH}) \qquad \textbf{(11–40)}$$

Substituting *U* into the equation for percentage ionization yields

$$\%\ \text{Ionized} = \frac{100}{1 + \text{antilog}(\mathrm{p}K_a - \mathrm{pH})} \qquad \textbf{(11–41)}$$

Similarly, for a weak molecular base,

$$\%\ \text{Ionized} = \frac{100}{1 + \text{antilog}(\mathrm{pH} - \mathrm{p}K_a)} \qquad \textbf{(11–42)}$$

Table 11-4 Percentage Sulfisoxazole, pK_a[congruent] 5.0, Dissociated and Undissociated at pH Values

pH	Percentage Dissociated	Percentage 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

In equation (11-41), pK_a refers to the weak acid, whereas in (11-42), pK_a signifies the acid that is conjugate to the weak base.

The percentage ionization at various pH values of the weak acid sulfisoxazole, pK_a [congruent] 5.0, is given in Table 11-4. 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.

The molecular diffusion of drugs across the intestinal mucosa was long thought to be the major pathway for drug absorption into the body. Drug absorption by means of diffusion through intestinal cells (i.e., enterocytes) or in between those cells (i.e., paracellular diffusion) is governed by the state of ionization of the drug, its solubility and concentration in the intestine, and its membrane permeability.

pH-Partition Hypothesis

Biologic membranes are predominantly lipophilic, and drugs penetrate these barriers mainly in their molecular, undissociated form. Brodie and his associates[48] 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.[48,49] 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 governed by Fick's law:

$$-\frac{dM}{dt} = \frac{D_m SK}{h}(C_g - C_p) \qquad (11\text{–}43)$$

where M is the amount of drug in the gut compartment at time t, $D_m$is diffusivity in the intestinal membrane, S is the area of the membrane, K is the partition coefficient between membrane and aqueous medium in the intestine, h is the membrane thickness, $C_g$is the concentration of drug in the intestinal compartment, and C_p is the drug concentration in the plasma compartment at time t. The gut compartment is kept at a high concentration and has a large enough volume relative to the plasma

compartment so as to make C_g a constant. Because C_p is relatively small, it can be omitted. Equation (11-43) then becomes

$$-\frac{dM}{dt} = \frac{D_m S K C_g}{h} \qquad (11\text{–}44)$$

The left-hand side of (11-44) is converted into concentration units, C(mass/unit volume) × V (volume). On the right-hand side of (11-44), the diffusion constant, membrane area, partition coefficient, and membrane thickness are combined to yield a *permeability coefficient*. These changes lead to the pair of equations

$$-V\frac{dC_g}{dt} = P_g C_g \qquad (11\text{–}45)$$

$$-V\frac{dC_p}{dt} = P_p C_g \qquad (11\text{–}46)$$

where C_g and P_g of equation (11-45) are the concentration and permeability coefficient, respectively, for drug passage from intestine to plasma. In equation (11-46), C_p and P_p are corresponding terms for the reverse passage of drug from plasma to intestine. Because the gut volume, V, and the gut concentration, C_g, are constant, dividing (11-45) by (11-46) yields

$$\frac{dC_g/dt}{dC_p/dt} = \frac{P_g}{P_p} \qquad (11\text{–}47)$$

Equation (11-47) demonstrates that the ratio of absorption rates in the intestine-to-plasma and the plasma-to-intestine directions equals the ratio of permeability coefficients.

The study by Turner et al.49 showed 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 Klink50 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 analogues used in clinical practice.

Modification of the pH-Partition Principle

Ho and coworkers51 also showed 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.23 Other complicating factors, such as metabolism of the drug in the gastrointestinal membrane, absorption and secretion by carrier-mediated processes, 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 associates23 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 11-14, known as the modified Doluisio method for in situ rat intestinal absorption. (The original rat intestinal preparation52 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 11-15. 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

$$J = P_{app}(C_b - C_{blood}) \qquad (11\text{–}48)$$

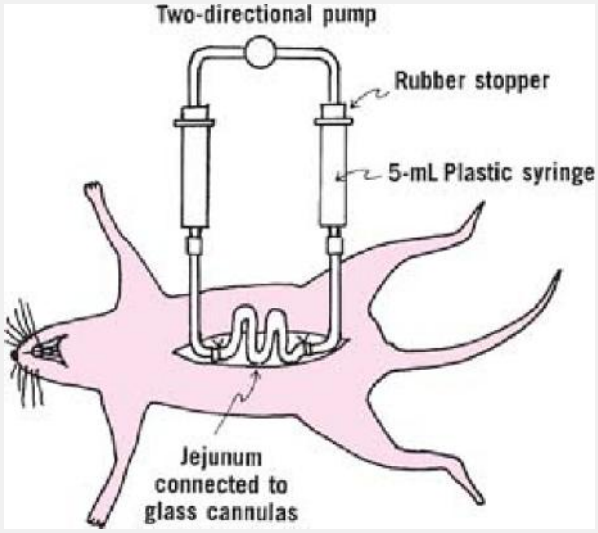


Fig. 11-14. Modified Doluisio technique for in situ rat intestinal absorption. (From N. F. H. Ho, J. Y. Park, G. E. Amidon, et al., in A. J. Aguiar (Ed.), *Gastrointestinal Absorption of Drugs*, American Pharmaceutical Association, Academy of Pharmaceutical Sciences, Washington, D. C., 1981. With permission.)

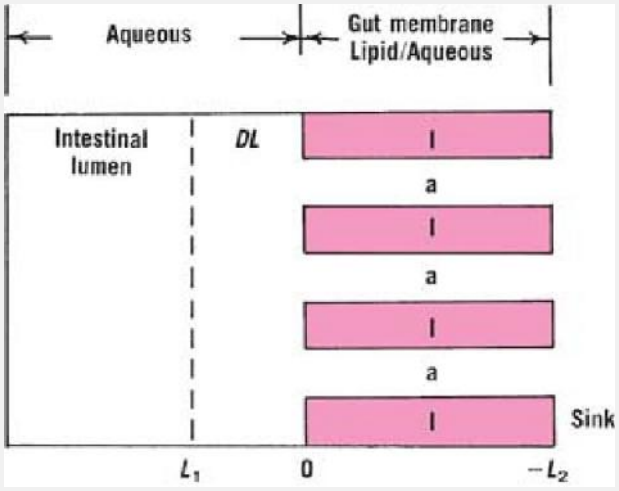


Fig. 11-15. Model for the absorption of a drug through the mucosa of the small intestine. The intestinal lumen is on the left, followed by a static aqueous diffusion layer (DL). The gut membrane consists of aqueous pores (a) and lipoidal regions (l). The distance from the membrane wall to the systemic circulation (sink) is marked off from 0 to $-L_2$; the distance through the diffusion layer is 0 to L_1. (From N. F. Ho, W. I. Higuchi, and J. Turi, J. Pharm. Sci. **61,** 192, 1972. With permission.)

or, because the blood reservoir is a sink, C_{blood} [congruent] 0, and

$$J = P_{app} C_b \qquad (11\text{–}49)$$

where 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

$$P_{app} = \frac{1}{\frac{1}{P_{aq}} + \frac{1}{P_m}} \qquad (11\text{–}50)$$

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

$$J = -\frac{V}{S} \cdot \frac{dC_b}{dt} \qquad (11\text{–}51)$$

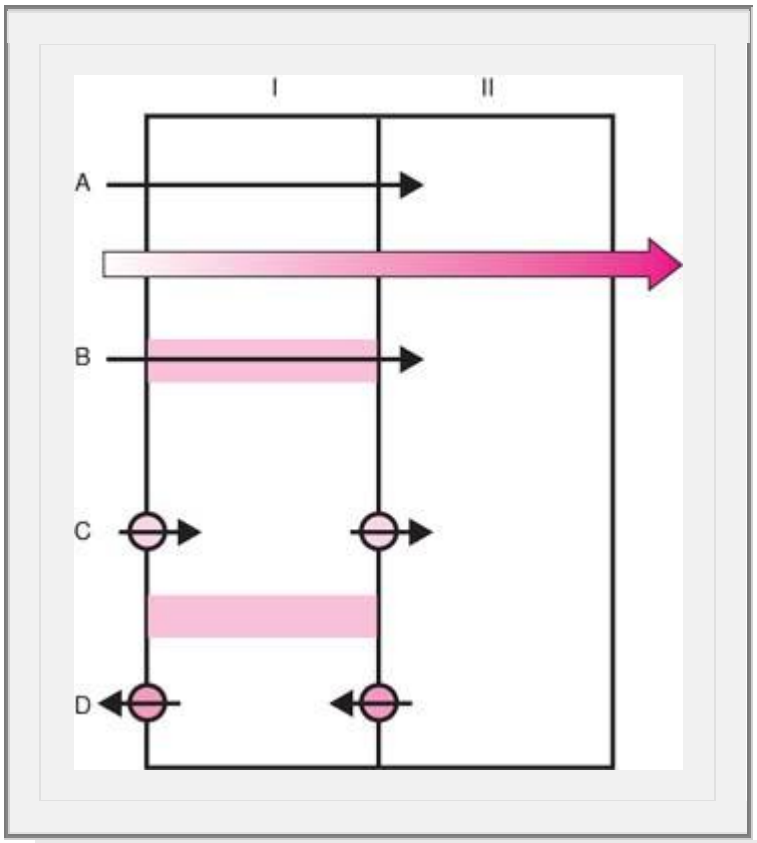
where S is the surface area and V is the volume of the intestinal segment. The first-order disappearance rate, K_u (sec^{-1}), of the drug in the intestine appears in the expression

$$\frac{dC_b}{dt} = -K_u C_b \qquad (11\text{–}52)$$

Substituting equation (11-52) into (11-51) gives

$$J = \frac{V}{S} \cdot K_u C_b \qquad (11\text{–}53)$$

Key Concept
Transport Pathways



Parallel transport pathways are all potential pathways encountered during a particular absorption step. Although many pathways are potentially available for drug transport across biologic membranes, drugs will traverse the particular absorption step by the path of least resistance.

For transport steps in *series* (i.e., one absorption step must be traversed before the next one), the slower absorption step is always the rate-determining process.

and from equations (11-49) and (11-50), together with (11-53), we find

$$P_{app} = \frac{1}{\frac{1}{P_{aq}} + \frac{1}{P_m}} = \frac{V}{S} K_u \qquad (11\text{–}54)$$

or

$$K_u = \frac{S}{V} \cdot \frac{P_{aq}}{1 + \frac{P_{aq}}{P_m}} \qquad (11\text{–}55)$$

Consideration of two cases, (*a*) aqueous boundary layer control and (*b*) membrane control, results in simplification of equation (11-55).

a. When the permeability coefficient of the intestinal membrane (i.e., the velocity of drug passage through the membrane in centimeter per second) 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. Therefore, P_{aq}/P_m will be much less than unity, and equation(11-55) reduces to

$$K_{u,max} = (S/V)P_{aq} \qquad (11\text{–}56a)$$

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.

b. 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(11-55) reduces to

$$K_u = (S/V)P_m \qquad (11\text{–}56b)$$

The rate-determining step for transport of drug across the membrane is now under membrane control. When neither P_{aq} norP_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 11-16 and 11-17 show the absorption studies of *n*-alkanol and *n*-alkanoic acid homologues, respectively, 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.

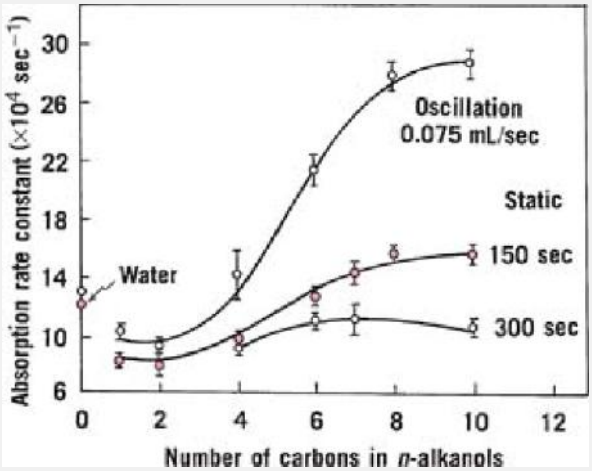


Fig. 11-16. First-order absorption rate constant for a series of *n*-alkanols under various hydrodynamic conditions (static or low stirring rates and oscillation or high stirring fluid at 0.075 mL/sec) in the jejunum, using the modified Doluisio technique. (From N. F. H. Ho, J. Y. Park, W. Morozowich, and W. I. Higuchi, in E. B. Roche (Ed.), *Design of Biopharmaceutical Properties Through Prodrugs and Analogs*, American Pharmaceutical Association, Academy of Pharmaceutical Sciences, Washington, D. C., 1977, p. 148. With permission.)

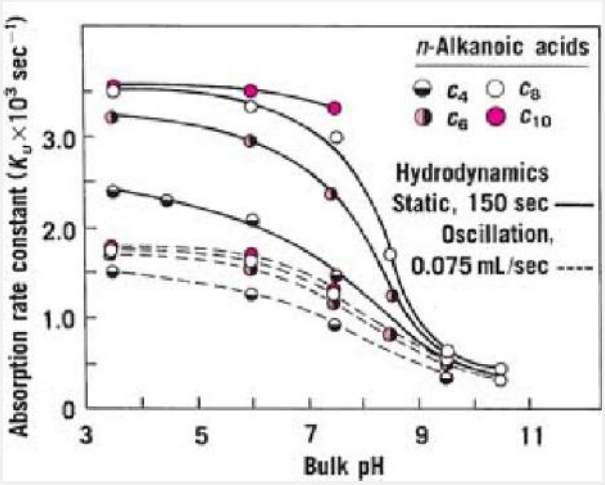


Fig. 11-17. First-order absorption rate constants of alkanoic acids versus buffered pH of the bulk solution of the rat gut lumen, using the modified Doluisio technique. Hydrodynamic conditions are shown in the figure. (From N. F. H. Ho, J. Y. Park, W. Morozowich, and W. I. Higuchi, in E. B. Roche, (Ed.), *Design of Biopharmaceutical Properties Through Prodrugs and Analogs*, American Pharmaceutical Association, Academy of Pharmaceutical Sciences, Washington, D. C., 1977, p. 150. With permission.)

Example 11-5
Small Intestinal Transport of a Small Molecule

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 × 10^{-4} cm/sec, and P_m = 1.1 × 10^{-4} cm/sec. We have

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

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

For a weak electrolytic drug, the absorption rate constant, *K*u, is23

$$K_u = \frac{S}{V} \cdot \frac{P_{aq}}{1 + \dfrac{P_{aq}}{P_0 X_s + P_p}} \qquad (11\text{–}57)$$

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

$$P_m = P_0 X_s + P_p \qquad (11\text{–}58)$$

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

$$X_s = \frac{[H^+]_s}{[H^+]_s + K_a} = \frac{1}{1 + \text{antilog}(pH_s - pK_a)} \qquad (11\text{–}59)$$

for weak acids, and

$$X_s = \frac{K_a}{[H^+]_s + K_a} = \frac{1}{1 + \text{antilog}(pK_a - pH_s)} \qquad (11\text{–}60)$$

for weak bases. Note the relationship between equations (11-59)and (11-41) and between (11-60) and (11-42). 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 solution23 because the membrane of the small intestine actively secretes buffer species (principally $CO_2^{2-}$and HC_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 11-6

Duodenal Absorption Rate Constant

A weakly acidic drug having a K_a value of 1.48 × 10^{-5} is placed in the duodenum in a buffered solution of pH 5.0. Assume $[H^+]_s$ = 1 × 10^{-5} in the duodenum, P_{aq} = 5.0 × 10^{-4}cm/sec, P_0 = 1.14 × 10^{-3} cm/sec, P_p = 2.4 × 10^{-5} cm/sec, and S/V = 11.20 cm^{-1}. Calculate the absorption rate constant, K_u, using equation (11-57).

First, from equation (11-58), we have

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

Then,

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

$$K_u = 2.75 \times 10^{-3}\ \text{sec}^{-1}$$

Example 11-7

Transcorneal Permeation of Pilocarpine

In gastrointestinal absorption (Example 11-5) the permeability coefficient is divided into P_0 for 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 Mikkelson53 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 11-5.

Table 11-5 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	7.66	6.79	8.85

a. Compute the un-ionized fraction, f_B, of pilocarpine at the pH values found in the table, using equation (11-60). 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

$$P = P_B f_B + P_{BH^+} f_{BH^+} \qquad (11\text{–}61)$$

where B stands for base and BH^+ for its ionized or conjugate acid form. Noting that $f_{BH^+} = 1 - f_B$, we can write equation (11-61) as

$$P = P_{BH^+} + (P_B - P_{BH^+}) f_B \qquad (11\text{–}62)$$

Obtain the permeability for the protonated species, P_{BH^+}, and the uncharged base, P_B, using least-squares linear regression on equation (11-62) in which *P*, the total permeability, is the dependent variable and f_B is 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 in the following table:

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 (11-62) gives

$$P = 4.836 \times 10^{-6} + 4.897 \times 10^{-6} f_B$$
$$\text{Intercept} = 4.836 \times 10^{-6} = P_{BH^+}$$
$$\text{Slope} = 4.897 \times 10^{-6} = (P_B - 4.836 \times 10^{-6})$$
$$P_B = 9.733 \times 10^{-6} \text{ cm/sec}$$

c. The ratio P_B/P_{BH}^+ [congruent] 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*) based on the pH-partition hypothesis.

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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 11-18 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.*

Scheuplein54 found that the average permeability constant, P_s, for water into skin is 1.0×10^{-3} cm/hr and the average diffusion constant, D_s, is 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. 11-18, mechanism A rather than B, C, or E). Stratum corneum, normal and even hydrated, is the 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.54 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.55 investigated the percutaneous absorption of a number of steroids. They found that the skin's main barrier to penetration by steroid molecules is the stratum corneum. The diffusion coefficient, D_s, for these compounds is approximately $10^{-11}cm^2/sec$, several orders of magnitude smaller than for most nonelectrolytes. This small value of D_s results in low permeability of the steroids. The addition of polar groups to the steroid molecule reduces the diffusion constant still more. For the polar steroids, sweat and sebaceous ducts appear to play a more important part in percutaneous absorption than diffusion through the bulk stratum corneum.

The studies of Higuchi and coworkers56 demonstrated 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.57

The proper choice of vehicle is important in ensuring bioavailability of topically applied drugs. Turi et al.58 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 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 (*a*) concentration of dissolved drug, C_s, because penetration rate is proportional to concentration; (*b*) the partition coefficient, *K*, between the skin and the vehicle, which is a measure of the relative affinity of the drug for skin and vehicle; and (*c*) 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.58,59

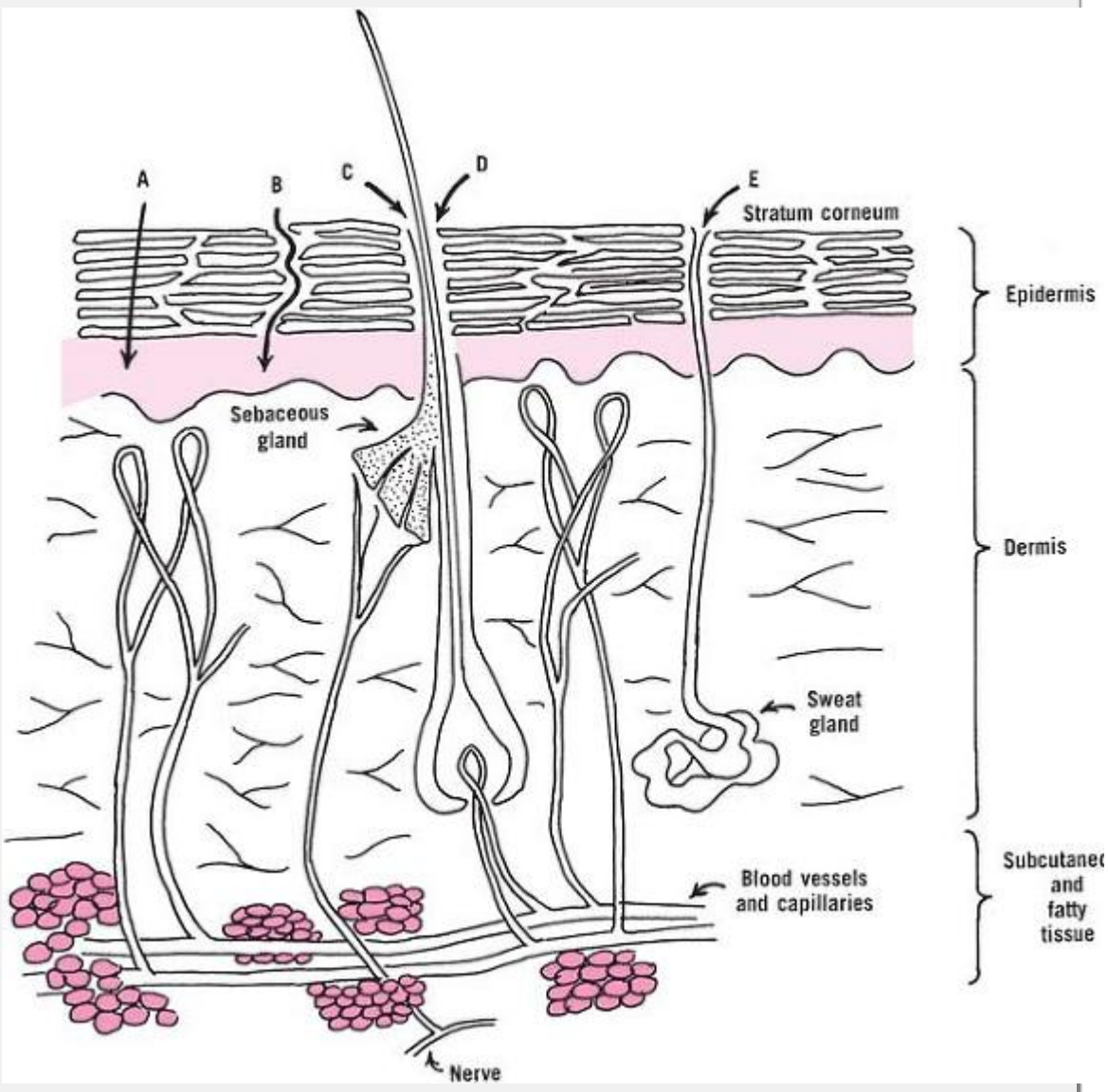

Fig. 11-18. Skin structures involved in percutaneous absorption. Thickness of layers is not drawn to scale. Key to sites of percutaneous penetration: A, transcellular; B, diffusion through channels between cells; C, through sebaceous ducts; D, transfollicular; E, through sweat ducts.

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

$$-\frac{dC_v}{dt} = \frac{SK_{vs}D_sC_v}{Vh} \qquad (11\text{–}63)$$

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

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

$$R_s = h/D_s \qquad (11\text{–}64)$$

and equation (11-63) becomes

$$-\frac{dC_v}{dt} = \frac{SK_{vs}C_v}{VR_s} \qquad (11\text{–}65)$$

In a percutaneous experimental procedure, Turi et al.58 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,

$$-V\frac{dC_v}{dt} = V_R \cdot \frac{dC_R}{dt} \qquad (11\text{–}66)$$

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

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compartment. With this change, equation (11-65) is integrated to yield

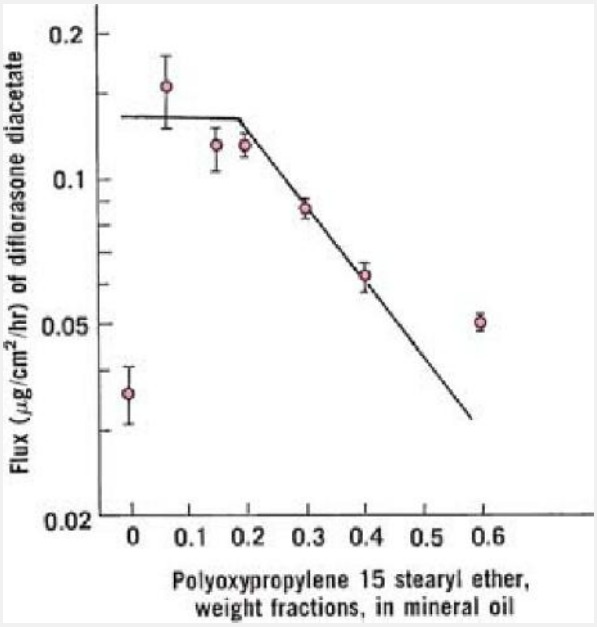

Fig. 11-19. Steady-state flux of diflorasone diacetate in a mixture of polyoxypropylene 15 stearate ether in mineral oil. (From J. S. Turi, D. Danielson, and W. Wolterson, J. Pharm. Sci. **68,**275, 1979. With permission.)

$$M_R = \left(\frac{SK_{vs}C_v}{R_s}\right)t \qquad (11\text{–}67)$$

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

$$J = \frac{M_R}{St} = \frac{K_{vs}C_v}{R_s} \qquad (11\text{–}68)$$

The steady-state flux for a 0.05% diflorasone diacetate formulation containing various proportions (weight fractions) of polyoxypropylene 15 stearyl ether in mineral oil is shown in Figure 11-19. 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 (11-68). 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 can be disregarded. Beyond a critical concentration, about 0.2 weight fraction of polyoxypropylene 15 stearyl ether, penetration rate decreases. The results69 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.

Example 11-8

Diflorasone Diacetate Permeation of Hairless Mouse Skin

A penetration study of 5.0×10^{-3} g/cm^3 diflorasone diacetate solution was conducted at 27°C in the diffusion cell of Turi et al.58 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, $J = M_R/St$, in g/cm, and (*b*) the amount, M_R in µg, of diflorasone diacetate that diffused through the hairless mouse skin in 8 hr.

Using equation (11-68), we obtain

(*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*)

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

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

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

Ostrenga and his associates60 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 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 can be obtained by altering the affinity of the vehicle for the drug.

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 11-20. 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.60 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 have 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.

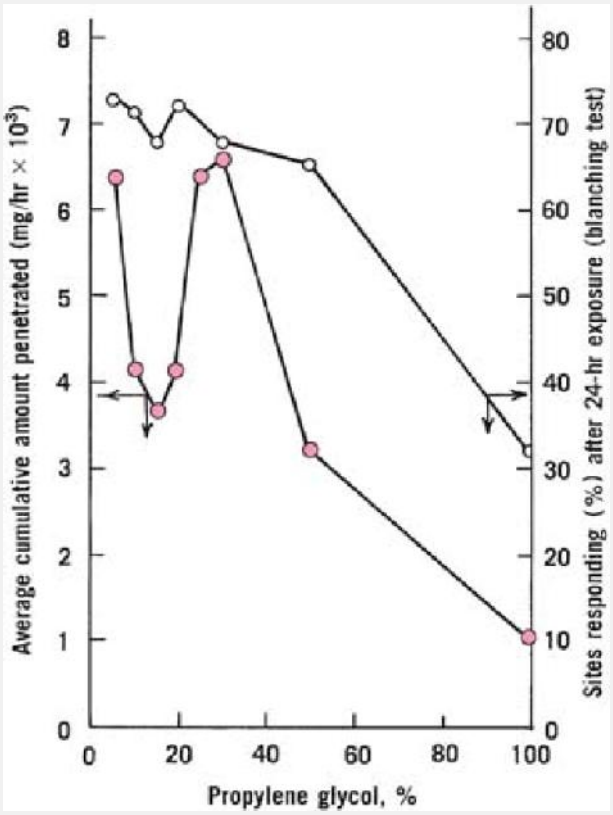

Fig. 11-20. Comparison of in vitro penetration of steroid through a skin section and in vivo skin blanching test. Key: •, in vitro method; ○, in vivo method. (From J. Ostrenga, C. Steinmetz, and B. Poulsen, J. Pharm. Sci. **60,** 1177, 1971. With permission.)

Sloan and coworkers61 studied the effect of vehicles having a range of solubility parameters, *d*, 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 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 were 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 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 Suzuki62 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 ^{32}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 (±0.47 SD) × 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 Suzuki62 found that this surfactant also 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 that 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 Moffat63 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 Higuchi64 applied one of the earlier mass transfer models65 to the analysis of the buccal absorption of *n*-alkanoic acids.66 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:

$$\ln \frac{C}{C_0} = -K_u t \qquad \textbf{(11–69)}$$

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

$$K_u = \frac{S}{V} \cdot \frac{P_{aq}}{1 + \dfrac{P_{aq}}{P_0 X_s}} \qquad \textbf{(11–70)}$$

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the terms of which have been previously defined. Recall that $X_s = 1/(1+10^{pH_s - pK_a})$, or, by equation (11-59), $X_s = 1/[1 + \text{antilog}(pH_s - pK_a)]$ 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, p$K_a = 4.84$, and $pH_s = 4.0$, equations (11-59) and (11-70) 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 agree 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 also 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). In this way the patient is automatically and continuously provided medication or protected from pregnancy for days, weeks, or months.67

Yotsuyanagi et al.68 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. 11-21), 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.

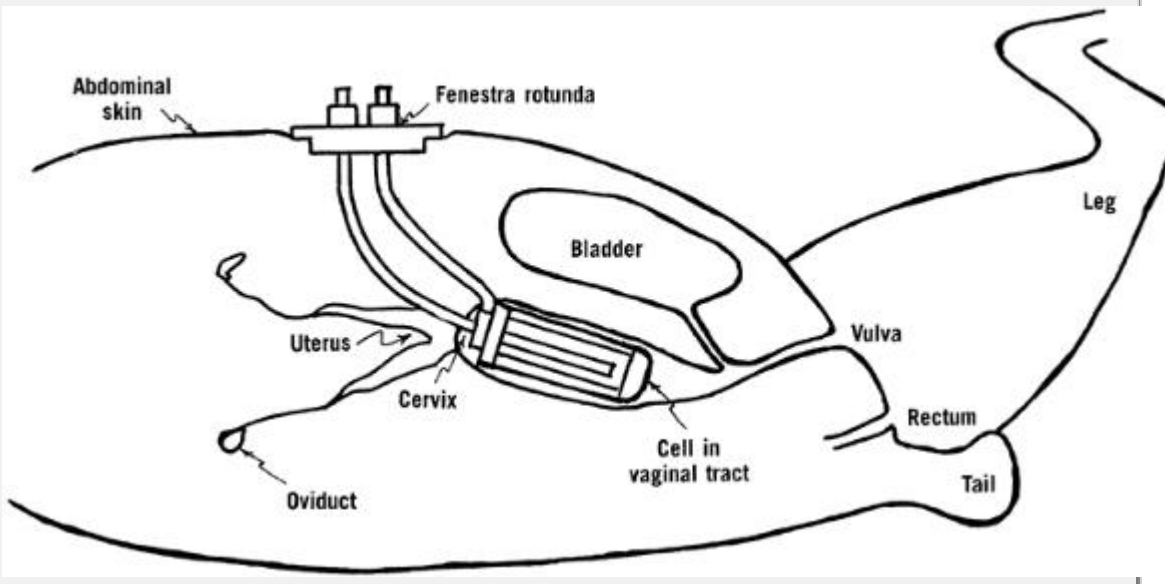

Fig. 11-21. Implanted rib-cage cell in the vaginal tract of a rabbit. (From T. Yotsuyanagi, A. Molakhia, et al., J. Pharm. Sci. **64,** 71, 1975. With permission.)

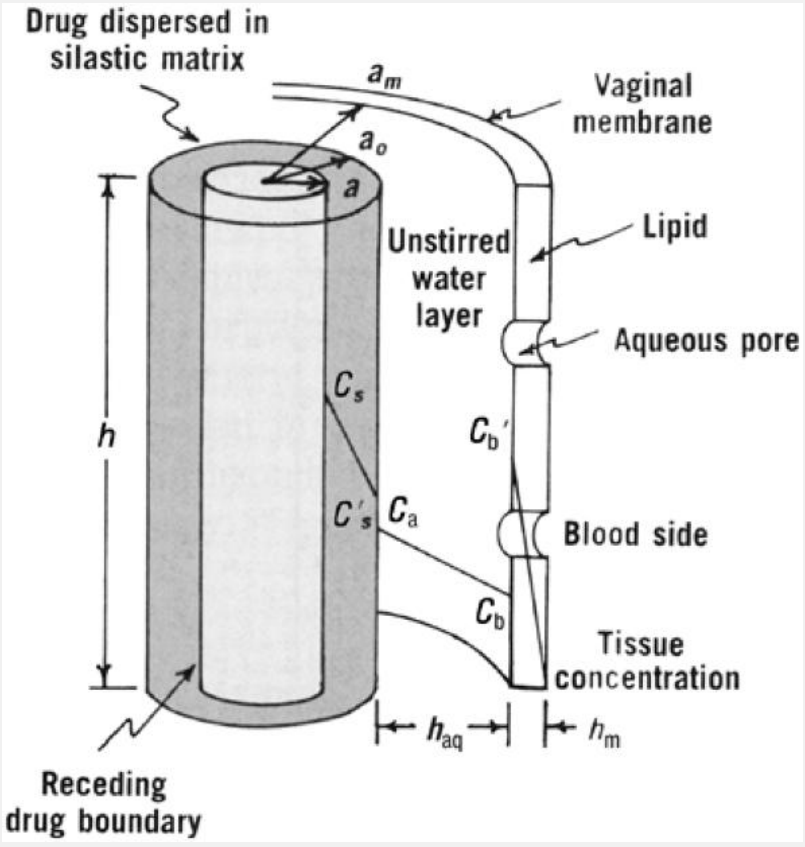

Fig. 11-22. Contraceptive drug in water-insoluble silicone polymer matrix. Dimensions and sections of the matrix are shown together with concentration gradients across the drug release pathway. (From S. Hwang, E. Owada, T. Yotsuyanagi, et al., J. Pharm. Sci. **65,** 1578, 1976. With permission.)

The drug may also be implanted in the vagina in a silicone matrix (Fig. 11-22), and drug release at any time can be calculated using a quadratic expression,[68]

$$\left(\frac{1}{2\pi h a_0^2 A}\right) M^2 + \frac{D_e K_s}{a_0}\left(\frac{1}{P_{aq}} + \frac{1}{P_m}\right) M - (2\pi h D_e C_s t) = 0 \quad \textbf{(11–71)}$$

The method of calculation can be shown, using the data of Hwang et al.,[69] which are given in Table 11-6. When the

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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 cylinder (Fig. 11-21) 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.

Table 11-6 Physical Parameters for the Release of Progesterone and Hydrocortisone from a Silicone Matrix for Vaginal Absorption in the Rabbit[69]

	Progesterone	Hydrocortisone
Solubility in matrix, C_s(mg/cm^3)	0.572	0.014
Diffusion coefficient in matrix, D_e(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}

Equation (11-71) is of the quadratic form $aM^2 + bM + c = 0$, where, for progesterone,

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

$$= 0.000438\text{ mg}^{-1}$$

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

$$\left(\frac{1}{7 \times 10^{-4}\text{ cm/sec}} + \frac{1}{7 \times 10^{-4}\text{ cm/sec}}\right)$$

$$= 0.0587\text{ (dimensionless)}$$

$$c = -2\pi h D_e C_s t = -2(3.1416)(6\text{ cm})$$

$$\times (4.5 \times 10^{-7}\text{ cm}^2\text{/sec})(0.572\text{ mg/cm}^3)$$

$$\times \left(\frac{86{,}400\text{ sec}}{\text{day}}\right)(t\text{ days}) = -0.8384 \times t\text{ (days)}$$

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 × 20 days = -16.77 mg, and

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

$$= 139.8\text{ mg}$$

Okada et al.70 carried out detailed studies on the vaginal absorption of hormones.

Elementary 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.71

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 is covered in great detail in the next chapter.

Zero-Order Drug Release

The flux, J, of equation **(**11-11**)** 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 can 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 11-23shows the

rate of delivery of two steroids from a device providing constant drug activity and what is known as “zero-order release.” For more information about zero-order processes the reader is referred to the chapter on kinetics (Chapter 14). 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.72

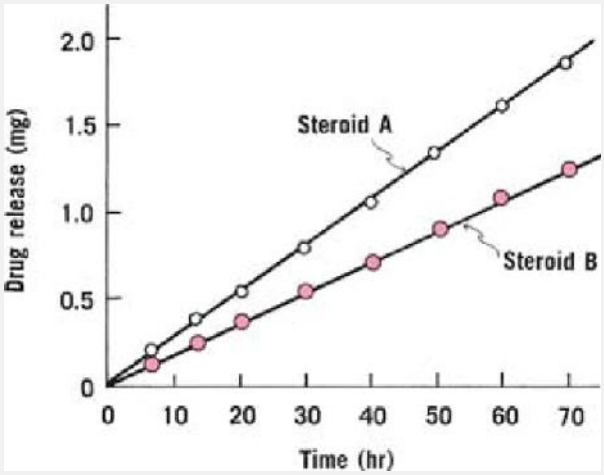

Fig. 11-23. Drug release for two steroids from a matrix or device providing zero-order release. (After R. W. Baker and H. K. Lonsdale, in, A. C. Tanquary and R. E. Lacey (Eds.), *Controlled Release of Biologically Active Agents*, Plenum Press, New York, 1974, p. 30.)

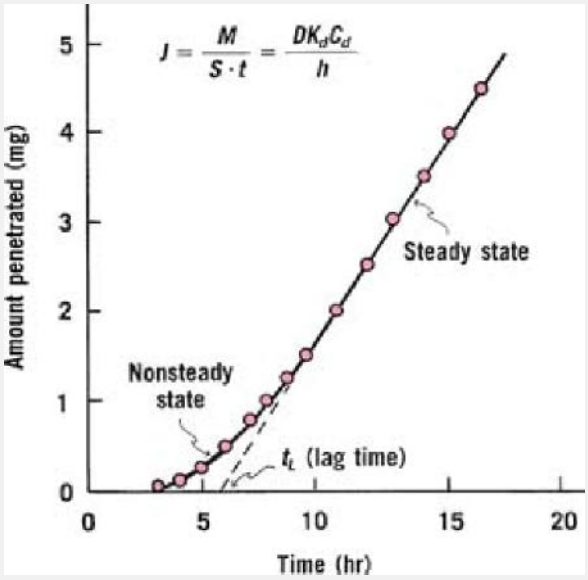

Fig. 11-24. Butyl paraben diffusing through guinea pig skin from aqueous solution. Steady-state and nonsteady-state regions are shown. (From H. Komatsu and M. Suzuki, J. Pharm. Sci.**68,** 596, 1979. With permission.)

Lag Time

A constant-activity dosage form may not exhibit a steady-state process from the initial time of release. Figure 11-24 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 11-23 is convex with

respect 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 11-24, 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 compartment.

In the case of a time lag, the straight line of Figure 11-24 can be represented by a modification of equation (11-13):

$$M = \frac{SDKC_d}{h}(t - t_L) \qquad (11\text{–}72)$$

The lag time, t_L, is given by

$$t_L = \frac{h^2}{6D} \qquad (11\text{–}73)$$

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

$$t_L = \frac{h}{6P} \qquad (11\text{–}74)$$

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 recedes into the tablet as drug is eluted. A schematic illustration of such a device is shown in Figure 11-25a. Figure 11-25b shows a granular matrix with interconnecting pores or capillaries. The drug is leached out of this device by entrance of the surrounding medium.Figure 11-25c depicts the concentration profile and shows the receding depletion zone that moves to the center of the tablet as the drug is released.

Higuchi32 developed an equation for the release of a drug from an ointment base and later73 applied it to diffusion of solid drugs dispersed in homogeneous and granular matrix dosage systems (Fig. 11-25). Fick's first law,

$$\frac{dM}{S\,dt} = \frac{dQ}{dt} = \frac{DC_s}{h} \qquad (11\text{–}75)$$

can 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. Because the boundary between the drug matrix and the 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 (Fig. 11-25a), the boundary of drug (represented by the dashed vertical line in Fig. 11-25c) 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

$$dQ = A\,dh - \tfrac{1}{2}C_s\,dh \qquad (11\text{–}76)$$

Now *dQ* of equation (11-76) is substituted into equation (11-75), integration is carried out, and the resulting equation

is solved for *h*. The steps of the derivation as given by Higuchi32 are

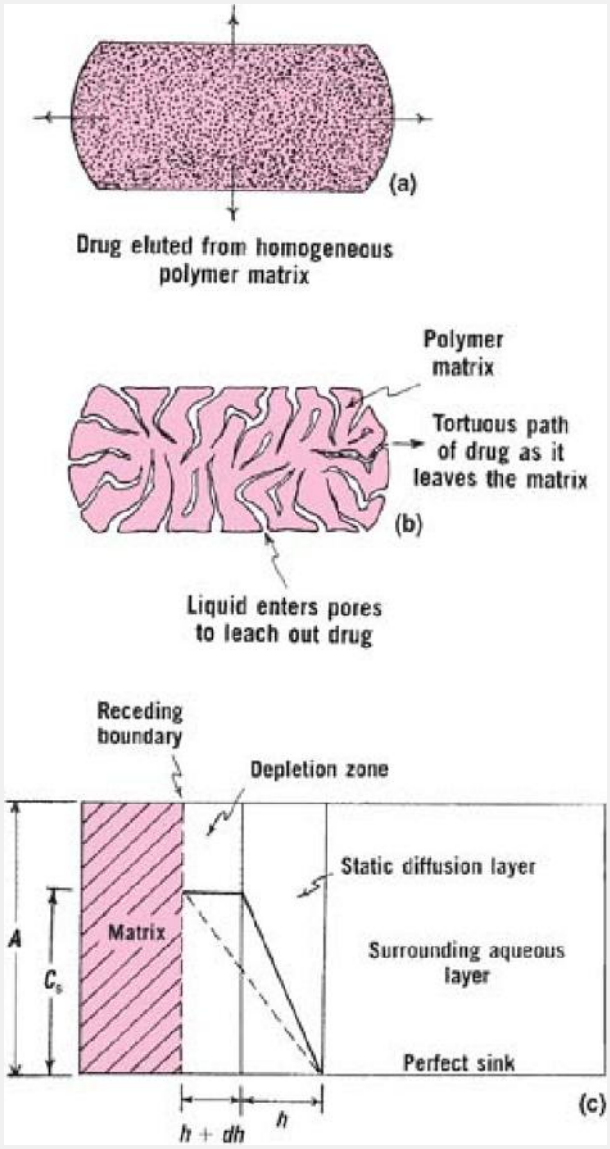

Fig. 11-25. Release of drug from homogenous and granular matrix dosage forms. (*a*) Drug eluted from a homogenous polymer matrix. (*b*) Drug leached from a heterogeneous or granular matrix. (*c*) Schematic of the solid matrix and its receding boundary as drug diffuses from the dosage form. (From T. Higuchi, J. Pharm. Sci.**50,** 874, 1961. With permission.)

$$\left(A - \tfrac{1}{2}C_s\right) dh = \frac{DC_s}{h} dt \qquad \textbf{(11–77)}$$

$$\frac{2A - C_s}{2DC_s} \int h\, dh = \int dt \qquad \textbf{(11–78)}$$

$$t = \frac{(2A - C_s)}{4DC_s} h^2 + C \qquad \textbf{(11–79)}$$

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

$$t = \frac{(2A - C_s)h^2}{4DC_s} \qquad \textbf{(11–80)}$$

$$h = \left(\frac{4DC_s t}{2A - C_s}\right)^{1/2} \qquad \textbf{(11–81)}$$

The amount of drug depleted per unit area of matrix, Q, at time t is obtained by integrating equation (11-76) to yield

$$Q = hA - 1/2\, hC_s \qquad (11\text{–}82)$$

Substituting equation (11-81) into (11-82) produces the result

$$Q = \left(\frac{DC_s t}{2A - C_s}\right)^{1/2} (2A - C_s) \qquad (11\text{–}83)$$

which is known as the Higuchi equation:

$$Q = [D(2A - C_s)C_s t]^{1/2} \qquad (11\text{–}84)$$

The instantaneous rate of release of a drug at time t is obtained by differentiating equation (11-84) to yield

$$\frac{dQ}{dt} = \frac{1}{2}\left[\frac{D(2A - C_s)C_s}{t}\right]^{1/2} \qquad (11\text{–}85)$$

Ordinarily, A is much greater than C_s, and equation (11-84) reduces to

$$Q = (2ADC_s t)^{1/2} \qquad (11\text{–}86)$$

and equation (11-85) becomes

$$\frac{dQ}{dt} = \left(\frac{ADC_s}{2t}\right)^{1/2} \qquad (11\text{–}87)$$

for the release of a drug from a homogeneous polymer matrix–type delivery system. Equation (11-86) 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 11-9

Classic Drug Release: Higuchi Equation

(*a*) What is the amount of drug per unit area, Q, released from a tablet matrix at time t = 120 min? The total concentration of drug in the homogeneous matrix, A, is 0.02 g/cm^3. The drug's solubility C_s is 1.0 × 10^{-3} g/cm^3 in the polymer. The diffusion coefficient, D, of the drug in the polymer matrix at 25°C is 6.0 × 10^{-6} cm^2/sec, or 360 × 10^{-6}cm^2/min.

We use equation (11-86):

$$\begin{aligned} Q &= [2(0.02\ \text{g/cm}^3)(360 \times 10^{-6}\ \text{cm}^2/\text{min}) \\ &\quad \times (1.0 \times 10^{-3}\ \text{g/cm}^3)(120\ \text{min})]^{1/2} \\ &= 1.3 \times 10^{-3}\ \text{g/cm}^2 \end{aligned}$$

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

$$\begin{aligned} dQ/dt &= \left[\frac{(0.02)(360 \times 10^{-6})(1.0 \times 10^{-3})}{2 \times 120}\right]^{1/2} \\ &= 5.5 \times 10^{-6}\ \text{g/cm}^2\ \text{min} \end{aligned}$$

Release from Granular Matrices: Porosity and Tortuosity

The release of a solid drug from a granular matrix (Fig. 11-25b) involves the simultaneous penetration of the surrounding liquid, dissolution of the 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,

$$Q = \left[\frac{D\epsilon}{\tau}(2A - \epsilon C_s)C_s t\right]^{1/2} \qquad (11\text{–}88)$$

where 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, in equation (11-88) 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/cm^3 of drug is extracted from the matrix and the drug's specific volume or reciprocal density is $1/\rho$ cm^3/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

$$\epsilon = \epsilon_0 + A(1/\rho) \qquad \textbf{(11–89)}$$

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

$$\epsilon \cong (A/\rho) \qquad \textbf{(11–90)}$$

Equation (11-88) differs from equation (11-84) only in the addition of ε and τ. Equation (11-84) is applicable to release from a homogeneous tablet that gradually erodes and releases the drug into the bathing medium. Equation (11-88) 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 (11-88), 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 (11-88) 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 release 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.74 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.75

Equation (11-88) has been adapted to describe the kinetics of lyophilization,13 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.

Soluble Drugs in Topical Vehicles and Matrices

The original Higuchi model32,73 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.,76

$$Q^2 + 2DRA^*Q - 2DA^*C_s t = 0 \qquad \textbf{(11–91)}$$

where

$$A^* = A - \frac{1}{2}(C_s + C_v) \qquad \textbf{(11–92)}$$

Q is the amount of drug released per unit area of the dosage form, $D$is an effective diffusivity of the drug in the vehicle, A is the total concentration of drug, C_s is the solubility of drug in the vehicle, C_v is the concentration of drug at the vehicle–barrier interface, and R is the diffusional resistance afforded by the

barrier between the donor vehicle and the receptor phase. A^* is an effective A as defined in equation (11-92) and is used when A is only about three or four times greater than C_s.
When

$$Q^2 \gg 2DRA^*Q \qquad (11\text{–}93)$$

equation (11-91) reduces to one form of the Higuchi equation [equation (11-86)]:

$$Q^2 = (2A^*DC_st)^{1/2} \qquad (11\text{–}94)$$

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

$$Q = [D(2A - C_s)C_st]^{1/2} \qquad (11\text{–}95)$$

The quadratic expression of Bottari, equation (11-91), 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.76 follows.
Because it is a second-degree power series in Q, equation (11-91)can be solved using the well-known quadratic approach. One writes

$$aQ^2 + bQ + c = 0 \qquad (11\text{–}96)$$

where, with reference to equation (11-91), $a = 1$, $b = 2DRA^*$, and $C = -2DA^*C_st$. Equation (11-96) has the well-known solution

$$Q = \frac{-b \pm \sqrt{b^2 - 4ac}}{2a} \qquad (11\text{–}97)$$

or

$$Q = \frac{-2DRA^* + \sqrt{(2DRA^*)^2 + (2DA^*C_st)}}{2} \qquad (11\text{–}98)$$

in which the positive root is taken for physical significance. If a lag time occurs, t in equation (11-98) is replaced by $(t - t_L)$ for the steady-state period. Bottari et al.76 obtained satisfactory value for b and c by use of a least-square fit of equation (11-91) involving the release of benzocaine from suspension-type aqueous gels. The diffusional resistance, R, is determined from steady-state permeation, and $C_v$is then obtained from the expression

$$C_v = R(dQ/dt) \qquad (11\text{–}99)$$

The application of equation (11-91) is demonstrated in the following example.

Example 11-10

Benzocaine Release from an Aqueous Gel

(*a*) Calculate Q, the amount in milligrams of micronized benzocaine released per square centimeter of surface area, from an aqueous gel after 9000 sec (2.5 hr) in a diffusion cell. Assume 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} cm^2/sec. From equation (11-92) we have

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

Then,

$$\begin{aligned} DRA^* &= (9.14 \times 10^{-6} \text{ cm}^2/\text{sec}) \times (8.10 \times 10^3 \text{ sec/cm}) \\ &\quad \times (9.72 \text{ mg/mL}) \\ &= 0.7196 \text{ mg cm}^{-2} \\ DA^*C_st &= (9.14 \times 10^{-6})(9.72)(1.31)(9000) = 1.047 \text{ mg}^2/\text{cm}^4 \\ Q &= -0.7196 + [(0.7196)^2 + 2(1.047)]^{1/2} \text{ mg/cm}^2 \\ &= -0.7196 + [1.616] = 0.90 \text{ mg/cm}^2 \end{aligned}$$

The $Q_{(calc)}$ of 0.90 mg/cm^2 compares well with $Q_{(obs)}$ = 0.88 mg/cm^2.

A slight increase in accuracy can 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/cm^2.
(*b*) Calculate Q using equation (11-95) and compare the result with that obtained in equation (11-94). We have

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

Paul and coworkers77 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,32,73 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 silastic capsule, as depicted in Figure 11-26a, has been used to sustain and control the delivery of drugs in pharmacy and medicine.78,79,80 The release of a drug from a silastic capsule is shown schematically in Figure 11-26b. 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 is 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

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is seen in Figure 11-25b 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.

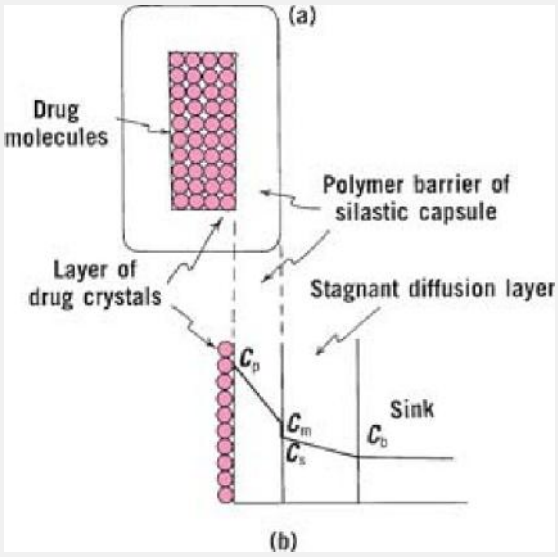

Fig. 11-26. Diffusion of a drug from a silastic capsule. (*a*) Drug in the capsule surrounded by a polymer barrier; (*b*) diffusion of the drug through the polymer wall and stagnant aqueous diffusion layer and into the receptor compartment at sink

conditions. (After Y. W. Chien, in J. R. Robinson (Ed.), *Sustained and Controlled Release Drug Delivery Systems*, Marcel Dekker, New York, 1978, p. 229; and Y. W. Chien, Chem. Pharm. Bull. **24,** 147, 1976.)

To express the rate of drug release under sink conditions, Chien78used the following expression:

$$Q = \frac{K_r D_a D_m}{K_r D_a h_m + D_m h_a} C_p t \qquad \textbf{(11–100)}$$

which is an integrated form analogous to equation (11-31). In equation (11-100), Q is the amount of drug released per unit surface area of the capsule and K_r is the partition coefficient, defined as*

$$K_r = C_s / C_p \qquad \textbf{(11–101)}$$

When diffusion through the capsule membrane or film is the limiting factor in drug release, that is, when $K_r D_a h_m$ is much greater than$D_m h_a$, equation (11-100) reduces to

$$Q = \left(\frac{D_m}{h_m}\right) C_p t \qquad \textbf{(11–102)}$$

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

$$Q = \left(\frac{D_a}{h_a}\right) C_s t = \left(\frac{K_r D_a}{h_a}\right) C_p t \qquad \textbf{(11–103)}$$

The right-hand expression can be written because $C_s = K_r C_p$, as defined earlier in equation (11-101). The rate of drug release, Q/t, for a polymer-controlled process can be calculated from the slope of a linear Q versus t plot and from equation (11-102) 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 11-11

Progesterone Diffusion out of a Silastic Capsule

The partition coefficient, $K_r = C_s/C_p$, of progesterone is 0.022; the solution diffusivity, D_a, is 4.994×10^{-2} cm^2/day; the silastic membrane diffusivity D_m, is 14.26×10^{-2}cm^2/day; the solubility of progesterone in the silastic membrane, C_p, is 513 μg/cm^3; 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/cm^2 per day. Compare the calculated result with the observed value, Q/t = 64.50 μg/cm^2 per day.

Using equation (11-100), we obtain

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

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

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

In the example just given, (*a*) is $K_r D_a h_m$ much greater than$D_m h_a$ *or* (*b*) is $D_m h_a$ much greater than $K D_a h_m$? (*c*). What conclusion can be drawn regarding matrix or diffusion-layer control? First, we have

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

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

Therefore, $D_m h_a$ is much greater than $K_r D_a h_m$, and the system is 93% under aqueous diffusion-layer control. It should thus be possible to use the simplified equation (11-103):

$$\frac{Q}{t} = \frac{K_r D_a C_p}{h_a} = \frac{(0.022)(4.994 \times 10^{-2})(513)}{0.008} = 70.45\ \mu g/cm^2/day$$

Although $D_m h_a$ is larger than $K_r D_a h_m$ by about one order of magnitude (i.e., $D_m h_a / KD_a h_m = 13$), it is evident that a considerably better result is obtained by using the full expression, equation (11-100).

Example 11-12
Contraceptive Release from Polymeric Capsules

Two new contraceptive steroid esters, *A* and *B*, were synthesized, and the parameters determined for release from polymeric capsules are as follows78:

	K_r	D_a (cm^2/day)	D_m (cm^2/day)	C_p ($\mu g/cm^3$)	h_a(cm)	Q/t(obs) ($\mu g/cm^2$/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 (11-100) and the quantities given in the table, calculate values of h_m in centimeter for these capsule membranes. First, we write

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

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

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

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

For capsule *A*,

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

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

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

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Fick's Second Law as a Starting Point

Fick's first law, equation (11-2), 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(11-6),

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 c}{\partial x^2} \qquad (11\text{–}104)$$

must be used. Here we use *u* instead of *C* to express concentration. The symbol ∂ indicates that *partial derivatives* are being used because *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

$$\frac{\partial u}{\partial t} = D\left(\frac{\partial^2 u}{\partial r^2} + \frac{1}{r}\frac{\partial u}{\partial r}\right) \qquad (11\text{–}105)$$

for symmetric diffusion outward from the axis of a cylinder of radius *r*.

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

$$r\frac{\partial u}{\partial t} = D\left(r\frac{\partial^2 u}{\partial r^2} + 2\frac{\partial u}{\partial r}\right) \qquad \textbf{(11–106)}$$

The equations for diffusion in cylinders and spheres are discussed by Crank81 and Jacobs.82 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. 11-27) was used by Graham (1861), one of the pioneers in diffusion studies, to obtain the diffusion coefficient,*D*, for solutes in various solvents. The coefficients for some solutes diffusing through various media are listed in Table 11-2. In the apparatus depicted in Figure 11-27, 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_0. From the experimental values of *u, x*, and *t*, it is possible to determine the diffusion coefficient, *D*, for the solute in the solvent.

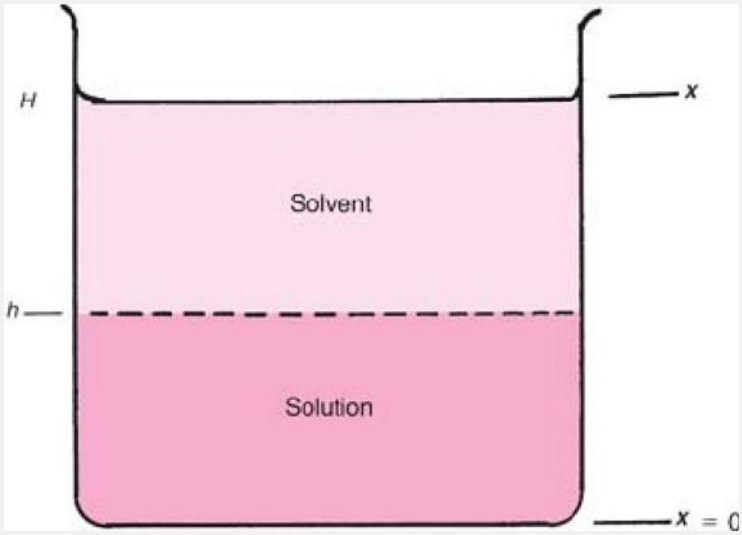

Fig. 11-27. Simple apparatus used by Graham for early diffusion studies. (From M. H. Jacobs, *Diffusion Processes*, Springer-Verlag, New York, 1976, p. 24. With permission.)

Initially—that is, at time *t* = 0 sec—the concentration *u* is equal to u_0(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 be equal to *H*/2, that is, both solution and solvent are of equal volume, the equation for *u* is82

$$u = \frac{u_0}{2} + \frac{2u_0}{\pi}\left[\left(\cos\frac{\pi x}{H}\right)e^{-\pi^2 Dt/H^2} - \frac{1}{3}\left(\cos\frac{3\pi x}{H}\right)e^{-9\pi^2 Dt/H^2} + \cdots\right] \qquad \textbf{(11–107)}$$

Equation **(**11-107**)** 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 **(**11-107**)** becomes cos(π/2) = cos 90° = 0. This leaves only the first cosine term, cos(π/6) = cos 30° = 0.866. Thus, taking *x* = *H*/6, we have

$$u = \frac{u_0}{2} + \frac{2u_0}{\pi}\left(0.866e^{-\pi^2 Dt/H^2}\right) \qquad \textbf{(11–108)}$$

Recall that with trigonometric functions such as cos(π/6), π is given in degrees, that is, π = 180° and π/6 = 30°, whereas in terms such as $2u_0/\pi$ and $e^{-\pi 2Dt/H2}$, the value of π is 3.14159 ….

Example 11-13

Determination of an Aqueous Diffusion Coefficient

A new water-soluble drug, corazole, is placed in a Graham diffusion cell (see Fig. 11-27) at an initial concentration of u_0= 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, *H*, is 5.64 cm. A sample is taken at a depth of *x* = *H*/6 cm at time, *t*, of 4.3 hr (15,480 sec) and is found by spectrophotometric analysis to have a concentration, *u*, of 0.0225 mmole/cm^3. *D* is obtained by rearranging equation (11-108):

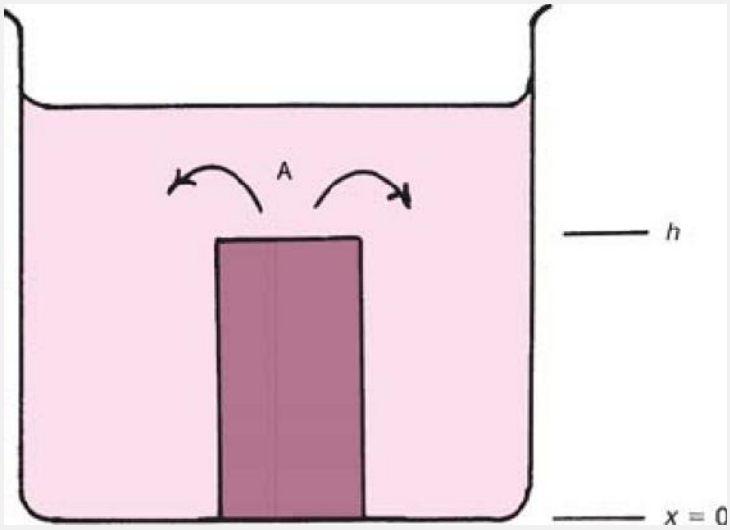

Fig. 11-28. Diffusion apparatus with one open and one closed boundary. (From M. H. Jacobs, *Diffusion Processes*, Springer-Verlag, New York, 1976, p. 47. With permission.)

$$D = -\left[\ln\left(\frac{u - u_0/2}{0.866(2u_0/\pi)}\right)\right] \cdot \frac{H^2}{\pi^2 t}$$

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

$$= 16.47 \times 10^{-5}\ \text{cm}^2/\text{sec}$$

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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 11-28. 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* = 0 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, because 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, $u = u_0$ at $t = 0$.

For a system with one open and one closed surface, the amount, $M_{0,t}$, of solute escaping between time 0 and time t is expressed by the equation82*

$$M_{0,t} = u_0 Ah\left[1 - \frac{8}{\pi^2}\left(e^{-\pi^2 Dt/4h^2} + \frac{1}{9}e^{-9\pi^2 Dt/4h^2} + \cdots\right)\right] \qquad \textbf{(11–109)}$$

where A is the cross-sectional area of the inner cell of height h (seeFig. 11-28), and the other terms have been defined in connection with equations (11-107) and (11-108).

Example 11-14

Drug Diffusion from an Open Boundary

Calculate the total amount, $M_{0,t}$, of the new drug corazole that escapes between times $t = 0$ and $t = 2.70$ hr (9720 sec) from the cell with one open boundary (Fig. 11-28). The area, A, of the cell is 8.27 cm^2 and its height, h, is 2.65 cm. The original concentration, u_0, of the drug in the cell is 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^{-5} cm^2/sec, as found in Example 11-13.

Inserting these values into equation (11-109) yields

$$M_{0,t} = (0.0437\ \text{g/cm}^3 \times 827\ \text{cm}^2 \times 2.65\ \text{cm}) \times \left[1 - \frac{8}{\pi^2}\left(e^{-\frac{\pi^2(16.5\times10^{-5}\ \text{cm}^2/\text{sec})(9720\ \text{sec})}{4\times7.0225\ \text{cm}^2}} + \frac{1}{9}e^{-\frac{9\pi^2(16.5\times10^{-5}\ \text{cm}^2/\text{sec})(9720\ \text{sec})}{4\times7.0225\ \text{cm}^2}} + \cdots\right)\right]$$

$$M_{0,t} = 0.9577 \times 0.53805 = 0.51529\ \text{g}$$

Thus, we arrive at the result that in a cell containing 0.0437 g/cm^3 or 0.9577 g of total drug, 0.5153 g diffuses out in 2.7 hr.

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

Osmotic Drug Release11

Osmotic drug release systems use osmotic pressure as driving force for the controlled delivery of drugs. A simple osmotic pump consists of an osmotic core containing drug with or without an osmotic agent coated with a semipermeable membrane. The semipermeable membrane has an orifice for drug release from the pump. The dosage form, after coming in contact with aqueous fluids, imbibes water at a rate determined by the fluid permeability of the membrane and osmotic pressure of core formulation. This osmotic imbibition of water results in high hydrostatic pressure inside the pump, which causes the flow of the drug solution through the delivery orifice. A lag time of 30 to 60 min is observed in most of the cases as the system hydrates. Approximately 60% to 80% of drug is released at a constant rate (zero order) from the pump.

The drug release rate from a simple osmotic pump can be described by the following mathematic equation:

$$dM/dt = AK/h(\Delta\pi - \Delta p)C \qquad \textbf{(11–110)}$$

where dM/dt is drug release rate, A is the membrane area, K is the membrane permeability, h is the membrane thickness, $\Delta\pi$ and $\Delta p$are the osmotic and hydrostatic pressure differences between the inside and outside of the system, respectively, and C is the drug concentration inside the pump (i.e., dispensed fluid). If the size of the delivery orifice is sufficiently large, the hydrostatic pressure inside the system is minimized and $\Delta\pi$ is much greater than Δp. When the osmotic pressure in an environment is negligible, such as the gastrointestinal

fluids, as compared to that of core, π can be safely substituted for Δπ. Therefore, equation (11-110) can be simplified to

$$dM/dt = AK/h\,\pi C \qquad \textbf{(11–111)}$$

When all the parameters on the right-hand side of equation (11-111)remain constant, the drug release rate from an osmotic device is constant. This can be achieved by carefully designing the formulation and selecting the semipermeable membrane to achieve a saturated drug solution inside the pump so that π and *C* remain constant.

Drug release from osmotic systems is governed by various formulation factors such as the solubility and osmotic pressure of the core component(s), size of the delivery orifice, and nature of the rate-controlling membrane.

Solubility

The kinetics of osmotic drug release is directly related to the solubility of the drug within the core. Assuming a tablet core of pure drug, we find the fraction of the core released with zero-order kinetics from.

$$F(z) = 1 - S/\rho \qquad \textbf{(11–112)}$$

where *F*(*z*) is the fraction released by zero-order kinetics, *S* is the drug's solubility (g/mL), and ρ is the density (g/mL) of the core tablet. Drugs with low solubility (≤0.05 g/mL) can easily reach saturation and would be released from the core through zero-order kinetics. However, according to equation (11-112), the zero-order release rate would be slow due to the small osmotic pressure gradient and low drug concentration. Conversely, highly water-soluble drugs would demonstrate a high release rate that would be zero order for a small percentage of the initial drug load. Thus, the intrinsic water solubility of many drugs might preclude them from incorporation into an osmotic pump. However, it is possible to modulate the solubility of drugs within the core and thus extend this technology to the delivery of drugs that might otherwise have been poor candidates for osmotic delivery.

Osmotic Pressure

Osmotic pressure, like vapor pressure and boiling point, is a colligative property of a solution in which a nonvolatile solute is dissolved in a volatile solvent. The osmotic pressure of a solution is dependent on the number of discrete entities of solute present in the solution. From equation (11-111), it is evident that the release rate of a drug from an osmotic system is directly proportional to the osmotic pressure of the core formulation. For controlling drug release from these systems, it is important to optimize the osmotic pressure gradient between the inside compartment and the external environment. It is possible to achieve and maintain a constant osmotic pressure by maintaining a saturated solution of osmotic agent in the compartment. If a drug does not possess sufficient osmotic pressure, an osmotic agent can be added to the formulation.

Delivery Orifice

Osmotic delivery systems contain at least one delivery orifice in the membrane for drug release. The size of the delivery orifice must be optimized to control the drug release from osmotic systems. If the size of delivery orifice is too small, zero-order delivery will be affected because of the development of hydrostatic pressure within the core. This hydrostatic pressure may not be relieved because of the small orifice size and may lead to deformation of the delivery system, thereby resulting in unpredictable drug delivery. On the other hand, the size of the delivery orifice should not be too large, for otherwise solute diffusion from the orifice may take place. To optimize the size of the orifice, we can use the equation

$$A_s = 8\pi(LV/t)(\eta/\Delta P)^{1/2} \qquad \textbf{(11–113)}$$

where A_s is the cross-sectional area, π = 3.14 …, *L* is the diameter of the orifice, *V*/*t* is the volume release per unit time, η is the viscosity of the drug solution, and Δ*P* is the difference in hydrostatic pressure.

Semipermeable Membrane

The choice of a rate-controlling membrane is an important aspect in the formulation development of oral osmotic systems. The semipermeable membrane should be biocompatible with the gastrointestinal tract. The membrane should also be water permeable and provide effective isolation from the dissolution

process in the gut environment. Therefore, drug release from osmotic systems is independent of the pH and agitational intensity of the gastrointestinal tract. To ensure that the coating is able to resist the pressure within the device, the thickness of the membrane is usually kept between 200 and 300 μm. Selecting membranes that have high water permeability can ensure high hydrostatic pressure inside the osmotic device and hence permit rapid drug release flow through the orifice.

In summary, designing a drug with suitable solubility and selecting a semipermeable membrane with favorable water permeability and orifice size are the key factors for ensuring a sustained and constant drug release rate through an osmotic drug delivery system.

Example 11-15

Osmotic Release of Potassium Chloride

Five hundred mg of potassium chloride was pressed into 0.25 mL of water; the semipermeable membrane thickness is 0.025 cm with an area of 2.2 cm^2. The drug solubility is 330 mg/mL. The density of the solution is 2 g/mL. Here $K\pi = 0.686 \times 10^{-3}$ cm^2/hr, and the diffusion coefficient, D, is 0.122×10^{-3} cm^2/hr. What is the release rate of potassium chloride in this osmotic delivery system?83

Assuming the osmotic pressure is the main driving force of the system, we obtain, using equation (11-111),

$$dM/dt = A/h\, K\, \pi\, C = (2.2\ \text{cm}^2/0.025\ \text{cm})(0.686 \times 10^{-3}\ \text{cm}^2/\text{hr})(330\ \text{mg/mL}) = 19.92\ \text{mg/hr}$$

Correcting for the contribution of diffusion, we obtain

$$dM/dt = A/hC(K\pi + D) = (2.2\ \text{cm}^2/0.025\ \text{cm})(330\ \text{mg/mL})(0.686 \times 10^{-3}\ \text{cm}^2/\text{hr} + 0.122 \times 10^{-3}\ \text{cm}^2/\text{hr}) = 23.5\ \text{mg/hr}$$

Chapter Summary

The fundamentals of diffusion were discussed in this chapter. Free diffusion of substances through liquids, solids, and membranes is a process of considerable importance to the pharmaceutical sciences. A fundamental understanding of the processes of dialysis, osmosis, and ultrafiltration is essential for pharmaceutical sciences. The mechanisms of transport in pharmaceutical systems were described in some detail. Fick's laws of diffusion were also defined and their application described. Important parameters such as diffusion coefficient, permeability, and lag time were discussed and sample calculations were performed to illustrate their use. The various driving forces behind diffusion, drug absorption, and elimination were described as well as elementary drug diffusion. Although many of the treatments in this chapter appear to be highly mathematical because of the extensive use of equations, the equations and their derivations are useful as the student learns about these important pharmaceutical processes at the mechanistic level.

Practice problems for this chapter can be found at thePoint.lww.com/Sinko6e.

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