REVIEW ARTICLE

Mass Transport Phenomena and Models: Theoretical Concepts

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"For many years I was troubled by a statement attributed to Faraday, which I have not verified, that he held his theories by his finger-tips so that the least breeze of fact might blow them away. I was troubled because it seemed to me that some theories are more trustworthy and tenable than many facts. When I realized that a fact to Faraday meant something different from what it did to me, that for him a fact was not something he read in a book or a journal, but was something he observed in a laboratory and that Faraday was an exceptionally able observer, my troubles stopped until I began to study membranes. Now I need two handfuls of finger-tips; one for alleged theories and one for alleged facts .... From the first days ... the study of membranes ... has been confused by the misuse of theories. It would be so much better if we called most of them models rather than theories. Then we would not have to defend their truth but only their usefulness. Most of us do need models in order to think. Almost everyone who thinks about membranes first thinks of small holes in a plate which is very thin even compared to the size of the holes. Some biological membranes may be such diaphragms, but synthetic membranes, and many natural ones, have holes which are ·much smaller than the thickness of the membrane. Almost everyone takes as second choice right-circular cylindrical pores, and as a third model lets the pores curve and change in cross-section. I believe that a much more useful model resembles a pile of sand, or brush, or tangled fish-nets in that as many channels run in one direction as any other, and the channels are continually branching and coming together again. There are few if any dead-end pockets or neighbouring points connected only through long loops. The model need hardly be more specific than this .... Many of us are studying synthetic membranes with the hope that they may serve as models for natural membranes. Some-

times I am hopeful that these model studies will give a positive contribution to our knowledge of physiological membrane phenomena. Often I can only admire the methods of the physiologists, but perhaps remind them of Faraday's finger-tips and of the fact that since their phenomena are more complicated than those of the physical chemists, their thinking must be less naive...." G. Scatchard (1)

Membrane transport is a subject of great breadth, diversity, and complexity. Since life itself is dependent on the normal functioning of membranes and membrane transport systems, the barrier properties of membranes are an intense concern of biologists and biologically oriented physical scientists. The essence of the permeability problem facing the bioscientist was succinctly set forth in the introductory thoughts of Scatchard (1)[1]. In particular, Scatchard pointed to the fabrication of models consistent with experimental observations and based on fundamental thermodynamic considerations as a means of furthering comprehension of the phenomena involved. Since pharmacy, defined in its broadest sense, also is concerned with a broad spectrum of physical kinetic processes, the research pharmacist's applications of membrane transport principles are not limited solely to biological areas. The development of formulations that meter predetermined dosages on exact schedules to intended surfaces of absorption is at least partially dependent on sound application of permeation theory. Selection of appropriate packaging materials is another area where barrier properties are of great importance. These areas too can be advanced measurably by a fundamental modelistic point of view. Presenting the conceptual tools to accelerate the modelistic approach is a major goal of this review.

There is an enormity of literature dealing with mass transport. Most extensive compilations (books and reviews) are highly specialized or slanted to the needs of a particular membrane transport problem area. Few have been directed to the specific needs of the medically oriented scientist. This fact has rendered difficult the selection of suitable models for drug delivery and absorption. Therefore, two important purposes of the present review are to provide meaningful criteria for typing membranes and to indicate how different macroscopic fabrics and microstructures influence membrane barrier properties. To accomplish these ends, the various possible components of barriers (*i.e.*, membrane continuum, fillers, crystalline regions, *etc.*) and shunts, pores, diffusion layers, *etc.*, are discussed separately with respect to their influence on barrier resistance and/or permeability. Emphasis is placed on integrating them into an overall barrier property; attention is especially drawn to circumstances where permeabilities and diffusional resistances are additive. By using this ap-

proach, it is often possible to characterize complex membrane structures from the dimensions, arrangements, and diffusional resistances of the component parts.

To accomplish these specified goals, the content of the review has been primarily limited to passive transport (free diffusion) of nonelectrolytes in the absence of bulk flow; therefore, electrochemical gradients, osmotic gradients, thermal gradients, facilitated transport, and active transport are not within its scope. Many excellent reviews of these topics can be found in the literature. In addition to these exclusions, laboratory methodology *per se* is only incidentally covered. Recent discussions on the design and operation of diffusional apparatus may be found in Refs. 2–8.

Before proceeding, it is worthwhile to consider in more detail what makes mastery of transport theory and its applications a valuable tool for the pharmaceutical scientist. Some of the diverse array of membranes and barriers of concern within the greater field of pharmaceutics from the standpoints of drug activity, availability, or formulation development are compiled in Table I. Interest in the membranes depicted spans considerations on structure–activity relationships within drug families and drug absorption by whole animals to controlled drug release and appropriate product packaging. Certain specific problems requiring application of transport theory are presented in Table II. Collectively, these tables give ample evidence that some of the most pressing problems pharmaceutical scientists face are in the mass transport sphere. In this respect the tables, which are representative and hardly complete, speak for themselves. A few of these membranes and problems will be discussed explicitly. Whether expressly considered or not, the theories and approach to membrane transport detailed in this review provide necessary background so that membranes can be better characterized and transport problems can be handled with greater facility.

FUNDAMENTALS OF MEMBRANE PERMEATION

The Modelistic Approach—Total characterization of complex membranes and barriers and the development of suitable models to describe their properties require characterization of each and every independent phase and subphase constituting the barrier system, including the spacial configurations and arrangements of the phases and phase interactions with each other and with the diffusing species under consideration. Based on a conceptual scheme and on information or assumptions about these relationships, the task of building a model is to develop techniques to represent all the existing interrelationships and to sort out those relevant or applicable to a given situation. Where there is a systematic approach to the construction of models, often several alternative models are formulated and the researcher's efforts may be channeled into defining the limitations of each possibility. The result is usually a keener insight into the mechanics of the transport process.

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[1] From the introductory remarks at the 1956 Faraday Society Discussions on Membrane Transport (see Ref. 1).

Table I—Membranes and Barriers of Medical and Pharmaceutical Interest

Biological membranes and barriers:
  Cellular membranes (bacterial and mammalian)
  Mucosal barriers
    GI
    Buccal
    Vaginal, *etc.*
  Skin (epidermis and dermis)
  Cornea
  Whole tissues
Barriers intimately associated with dosage form:
  Films, coatings
  Polymeric containers, seals, stoppers, *etc.*
  Packaging films and laminates
Time and system variable barriers:
  Fluid diffusion layers
  Dosage form boundary layers (in implants, *etc.*)
Theoretical or model membranes:
  Interfacial barriers and monolayers
  Bilayers
  Polymeric barriers
  Fluid partitioning systems

Table II—Dosage Form-Related Mass Transport Problems

Preadministration:
  Leaching or sorption of drug and/or adjuvant by containers or closures
  Leaching of contaminants and/or reactants from packaging materials by the product (heavy metals, plasticizers, *etc.*)
  Sorption and/or permeation of containers, coatings, *etc.*, by undesirable agents from the external environment (moisture, oxygen, *etc.*)
Postadministration:
  Drug delivery from the intact physical system—timed-release properties
  Disintegration (permeation of water into solid matrix)
  Dissolution
  Absorption
  Biological distribution
  Elimination
  Protection (*i.e.*, protective ointments)⁻

Introduction to Membrane Characterization—It is necessary for the purposes at hand to define what constitutes a membrane and what constitutes a barrier and to indicate how these terms differ. A membrane, in the context of this review, is a sheet of solid or semisolid material of fixed dimensions which is insoluble in its surrounding medium and which separates phases that are usually (but not necessarily) fluid. A membrane transport system is created when there is passage (active, facilitated, or passive) of solute across a membrane. The term barrier is more inclusive. It is the region or group of regions within a system, contiguous or physically separated, that offers finite resistance to transport of a substance from a point in one region of a system to another point located at some distance down the diffusional field. Since it is generally convenient to think of mass transport in a unidimensional sense, one usually considers the line traversed as being the shortest path in one plane aligned parallel to the source of diffusional resistance to a similarly aligned plane on the other side of the diffusional field. In this context, the diffusional field or barrier includes unstirred fluid strata and all interfaces as well as all interposed membranes. Flowing or mechanically mixed regions generally offer no diffusional resistance. This assumption cannot be regarded as absolute, however, and each situation must be analyzed on its own merits. The total barrier property of the intervening space between the planes may be considered to be the sum of the individual resistances or barrier properties of its component strata.

The first step in delineating total barrier property is to identify all independent strata that a substance must traverse to pass from one point to another. Here we are considering, for the moment, one-dimensional diffusion, *i.e.*, diffusion along a single vector that is perpendicular to the barrier planes. Independent strata are considered to offer uniform resistance, at least to a first approximation, over their entire thickness. In the extreme, a lamina may be taken as a single molecular distance (9, 10). However, usually thick regions exist where potential energy barriers for each molecular move in the vector of the flux are of constant magnitude, and the full thickness of such regions may be considered as an individual barrier segment.

To describe a barrier in terms of the number and placement of its laminae, it is necessary to develop a convention affording both identification of each distinct segment of a particular composition and classification in terms of the relative positioning of the strata. The simple method of Barrer (11) suffices for most cases. In this notation, each laminate of a given type is given a letter designation. Furthermore, if noncontiguous strata of a given property are repeated in the series, the letter designation is repeated. As an example, consider the situation where a homogeneous membrane is interposed between two like fluid phases, *i.e.*, two aqueous compartments. The first region of potentially significant diffusional resistance is the unstirred fluid region on the high diffusant concentration side of the system. Neglecting interfaces, the membrane is a second laminate and the unstirred fluid region generated at the other membrane interface is a third. Since the fluid regions are comparable in composition, excluding considerations of diffusant concentration, this is an ABA system. If a second membrane of different composition is placed downstream and permeation of the system is considered from the first fluid compartment to a third fluid (aqueous) compartment, the system may be characterized as being ABAACA if the middle fluid compartment is stirred (this will generate a diffusion layer at each membrane interface in the internal compartment) or ABACA if the middle compartment is unstirred and the diffusional resistance is continuous across this compartment's full thickness. As in the situations cited here, it is usually a straightforward process to identify potentially significant diffusional strata. Where there are questions regarding the role of regions such as interfaces or diffusion layers, it is advantageous to include them in the treatment or model. The point where their barrier contributions are truly insignificant eventually becomes mathematically evident and derived permeability expressions are readily simplified.

The next logical step in barrier characterization is to determine the thicknesses of the identified laminae. Often the thicknesses of the membranes in the composite barrier may be measured directly. Effec-

tive diffusion layer thicknesses are a function of solvent viscosity and stirring at a given temperature (12) and also of the molecular volume of the diffusing species. Their widths are usually estimated indirectly during the permeation experiment (13, 14) or by independent experiment using comparable mechanical conditions (15). Direct measurement of diffusion layer thickness on occasion has been accomplished (16). In some cases, particularly in biological systems, barrier strata are highly interdigitated, i.e., the brush border of the GI lining and the juncture of epidermis with dermis. Such cases defy exact mathematical resolution, and effective thicknesses must be assigned. Usually, the error in such approximations is no more than the expected biological variations in permeation experiments, so these approximations suffice in a modelistic approach.

Having identified all participating strata, it is then necessary to characterize each individually with respect to gross physical state (solid, semisolid, or fluid) of the material(s) from which it is constructed and its detailed structure (11, 17). Variations in these details are limitless because segments can be, and often are, multiphasic and of diverse composition. Fluid phases are, to good approximation, homogeneous and of constant diffusional property. Membranes, on the other hand, are generally complex structures requiring more precise analysis and description. Although there is no generally agreed on method of classification, most membranes can be characterized as being composed of three general types of phases: (a) continuous, (b) shunt, and (c) dispersed. These phase types must be further classified as primary, secondary, tertiary, etc., the subclassifications depending on the spacial relationships of each phase to the other phases present.

A primary continuous phase is a phase that is uninterrupted between membrane surfaces as well as laterally or is in the plane perpendicular to the flux vector. Depending on its composition relative to the compositions of associated phases, it may provide an uninterrupted diffusional path for a diffusing species or be operationally impervious and exist as a supporting structure only. A primary shunt phase is one that passes completely through the membrane but that is laterally discontinuous, i.e., a pore or channel. These too may be inert with respect to permeability, may provide parallel diffusional pathways depending on relative compositions, or may be the sole diffusional pathway. Dispersed phases are embedded in continuous phases or shunt phases. They are discontinuous along the flux vector and do not provide an uninterrupted pathway through the membrane or through any of its subphases. If they are also discontinuous laterally, they are fillers or inclusion bodies (biological cases). Fillers are commonly found in synthetic membranes because they favorably influence mechanical properties such as elasticity, permeability, and resistance to tear (18). Dispersed phases that are continuous in the plane perpendicular to the flux vector are also found in synthetic membranes. Netting is sometimes embedded in a membrane structure as a means of reinforce-

ment. The scanning electron micrographs of the 0.45-μm and 0.4-μm membranes in Figs. 1 and 2, respectively, provide examples of the ultrastructure of real membranes[2-4]. Since there can be phases within phases and phases, in turn, within these, it is necessary to designate whether a given identified phase is contributing to the coarsest structural breakdown (primary) or is a subphase of a primary or higher order phase. In this regard, each major phase identified must then be examined for the presence of secondary phases of each type, and these in turn for tertiary phases, etc., until all distinct regions are accounted. Secondary phasic structure is common in real membranes; recourse to characterization of tertiary and finer subclassifications is generally unnecessary.

Once a barrier has been segmented and its segments characterized with respect to structure and composition, it is then necessary to assess the manner in which the diffusing species interacts with the various phases and subphases it must pass through, both on an absolute and relative basis. In other words, diffusivity within a given homogeneous region must be considered, as must adsorption onto or partitioning into all other phases in contact with the particular region under consideration. Subsequent sections provide some means of coping with these aspects. In narration, the process of characterization may seem exceedingly complex; in practice, it is usually manageable, particularly with synthetic membranes. Where membrane properties are indeterminate or too complex for exact physical and chemical description, use of simplifying assumptions and/or hybrid diffusivities still allows for construction of useful models and subsequent membrane typing.

Passive Diffusion: Kinetic and Thermodynamic Considerations—*Diffusion and Probability*—Diffusion is by nature a probabilistic process involving the random movement of molecules. The following description of the classical experiment involving the diffusion of a dye solution into solvent provides a feel for the process. Consider a cylinder half filled with solvent and then layered over with dye solution. Suppose these are separated by a nonpermeable divider which can be removed instantaneously without producing mechanical or other nondiffusive mixing. The following will occur upon removal of the divider. Throughout each medium the molecules will be moving randomly among each other roughly with translational velocities of a rifle bullet, the course of each molecule, solvent and dye alike, being extremely erratic due to multiple elastic collisions with like and unlike molecules in its physical path. In any finite time and in every part of the system, molecules of solvent and solute (where dye exists) will be directed along every vector of a three-dimensional coordinate system. In reference to the plane of interest, namely the dye solution–pure solvent interface, the molecules will be moving laterally within the

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[2] Millipore MF.
[3] Nucleopore.
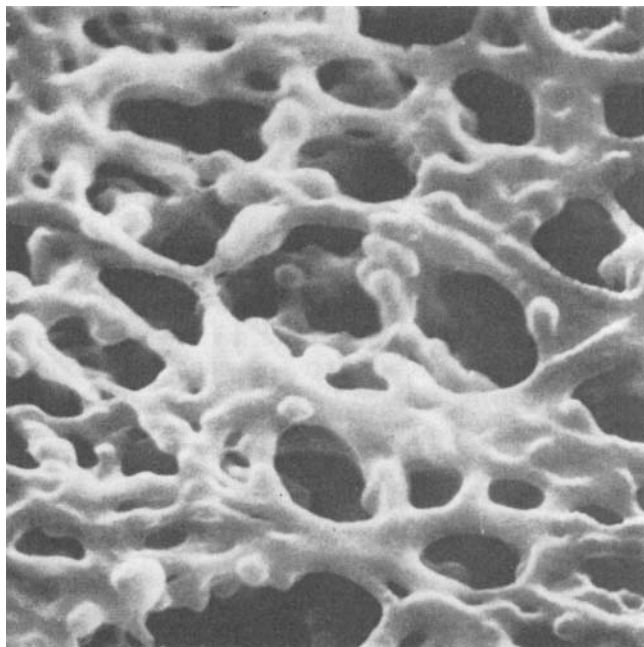[4] Photographs of the Millipore and Nucleopore filters are courtesy of General Electric Co.

Figure 1—*Scanning electron micrograph of a filter (Millipore) rated as 0.45 μm in pore size. The highly porous nature of the structure and the nonlinearity of the "holes" are notable.*

plane as well as in all angles up to and including a right angle through the plane.

In the instant following the removal of the divider between solvent and solution, dye molecules at the interface will either be kinetically thrust back into the bulk of the solution or move laterally within the interface or penetrate the pure solvent. Due to the large numbers of molecules involved, dye molecules will instantaneously follow each of these courses. In this instant, dye molecules leaving the interface to enter the solution phase will be offset by an equal number (statistically speaking) of dye molecules moving from the depth of the solution to the interface. However, dye molecules diffusing into the pure solvent will be offset by only solvent molecules moving in the opposite direction. The random movements of these respective species thus lead to a net penetration of the dye into the pure solvent and solvent into the dye solution. In other words, the deficiency of solute molecules in the direction of pure solvent and the deficiency of solvent molecules in the direction of the solution, coupled with the fact that on the molecular level the system is in a highly dynamic state, cause the components to flow or diffuse into one another nonselectively and randomly. The net mass "movement" results from the concentration gradient of dye, initially across the interface but ultimately expanding through the entire system. In this case, an equal concentration gradient opposite in sign exists simultaneously for the solvent. The slope of the gradient is a reflection of the inequality of concentration across any plane perpendicular to the flux vector and, clearly from the example, the difference in concentration determines the net exchange of component across any chosen plane. In this manner, the rate of movement of mass across a given region is related to the concentration differential of the agent

under consideration over that region. Obviously, the interdiffusion of miscible substances is a spontaneous, irreversible process. The pure components constituting a diffusively equilibrated system cannot be regenerated without doing work on the system.

Thermodynamic Considerations—The tendency toward total randomness by diffusive flow can be equated with an increase in entropy. By thermodynamic definition, a spontaneous process is one where there is an overall decrease in free energy of the system. At isothermal conditions:

$$\Delta G = \Delta H - T \Delta S \qquad \text{(Eq.1)}$$

or the free energy change in the system is equal to the enthalpic change, ΔH, less the product of the absolute temperature, T, and the entropic change, ΔS. In the case of components that form ideal solutions, there will be no enthalpic contribution to diffusive mixing and the entire net change in free energy arises from increased entropy. In all real situations, there will be some enthalpic input into the overall free energy change; however, its magnitude in general will be relatively small and the diffusive process can be regarded as an entropically driven phenomenon.

It is hoped that at this point a picture is forming which, on one hand, describes the individual molecule's movements as being without preferred direction, a so-called random-walk process, but which at the same time, due to the large populations of molecules involved, prescribes that the direction of the total population is relentlessly toward regions of low concentration from relatively concentrated areas. Furthermore, it is implicit that interdiffusion of at least two substances is involved and there must, therefore, be multiple diffusion equations to describe the movement of each species present. For two com-
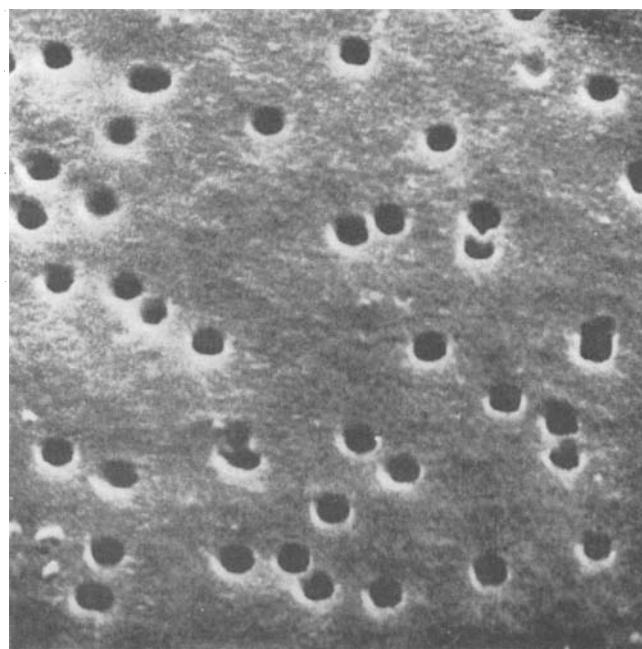

Figure 2—*Scanning electron micrograph of a 0.4-μm filter (Nucleopore). In this filter the pore density is relatively sparse but the pores are compensatingly uniform, linear, and short.*

ponents, two equations are actually necessary. However, since in the absence of a net volume change across the plane of reference the rates of interpenetration are equal in magnitude but opposite in sign, one equation suffices to describe the process and the second equation need not be considered explicitly. It is important to recognize this mutual dependency of the diffusion coefficient on each species. This is particularly true when the molecular species involved are disproportionate in size (*i.e.*, water *versus* protein) because the larger species may be limiting and set the diffusive current for each species at a low value. In the case of diffusion of a substance through a stationary solid or semisolid phase such as a membrane affixed into place in a diffusional apparatus, it is convenient to view the stationary phase as a fixed reference plane and only consider the flux of the mobile penetrant.

Diffusion in An Isotropic Medium—*Fick's First Law*—It was postulated by Bertholot (19) in the early 1800's that the diffusive flow of mass or flux is proportional to a constant times the concentration gradient of the diffusing species across the region of interest. Nearly 50 years later, Fick (20) reformulated this law by analogy to heat transfer and, most importantly, gave credence to the postulate by means of experiment. The first of the two diffusion laws that bear Fick's name is a simple statement of this principle, namely:

$$J = -D\left(\frac{dC}{dx}\right) \qquad \text{(Eq. 2)}$$

The formula explicitly says that the flux, J, of a component across a unit of area in a predetermined reference plane is proportional to the concentration differential across that plane, a conclusion presented intuitively in the preceding discussion. The term D is the proportionality constant, and the negative sign indicates mathematically that the current is in the direction of decreasing concentration. It was initially believed by Fick that D was a constant for a given system. It is now known that D is concentration sensitive, in the general case for reasons paralleling those that lead to deviations at high concentration from the ideal gas laws, osmotic pressure laws, *etc.*, and in specific cases due to the penetrant directly influencing the properties of the diffusion medium (*i.e.*, time- and concentration-dependent effects on polymeric films, *etc.*). For this reason, D is designated a coefficient, not a constant. As expressed in Eq. 2, D is a differential diffusion coefficient.

In certain experimental methods, particularly those used to characterize membranes, an averaged integral diffusion coefficient, $\bar{D}$, is obtained; this is related to the differential coefficient by:

$$\bar{D} = \frac{1}{C_0 - C_h} \int_{C_0}^{C_h} D\, dC \qquad \text{(Eq. 3)}[5]$$

where the thickness of the regions is measured from $x = 0$ to $x = h$. When D is independent of concentration, it is obvious that $D = \bar{D}$. The units of D (or $\bar{D}$) are distance squared per time, preferably square centimeters per second. It is conceptually helpful to translate this to velocity by realizing that, for diffusion through a uniform field of unit thickness (*i.e.*, 1 cm), the diffusivity corresponds to the average distance the diffusing particle travels per unit of time (*i.e.*, centimeters per second) in the direction of flow.

Although the concentration differential, an experimentally easily assessable parameter, is most frequently taken as the driving force in diffusion, the chemical potential differential or activity differential is the fundamental parameter determining the direction and rate of flux. Barrer has derived the relationship between concentration and chemical potential in the following fashion (21). The force acting on a molecule at point x is:

$$F \propto -\frac{d\mu}{dx} \qquad \text{(Eq. 4)}$$

and thus the total force acting on all molecules is:

$$F_{\text{total}} \propto -C\frac{d\mu}{dx} \qquad \text{(Eq. 5)}$$

Assuming flux to be proportional to the total force, one obtains:

$$J = -BC\frac{d\mu}{dx} \qquad \text{(Eq. 6)}$$

where B is a coefficient reflecting the mobility of the diffusing species. The equation relating activity to chemical potential is:

$$\mu = \mu_0 + RT \ln a \qquad \text{(Eq. 7)}$$

where a is activity. Therefore:

$$d\mu = RT\, d[\ln a] \qquad \text{(Eq. 8)}$$

and:

$$J = -BRT\frac{C}{a}\frac{da}{dx} \qquad \text{(Eq. 9)}$$

and, by multiplying by unity in the form dC/dC:

$$J = -BRT\frac{d \ln a}{d \ln C}\frac{dC}{dx} \qquad \text{(Eq. 10)}$$

which, when compared with Fick's first law, yields for the differential diffusion coefficient:

$$D = BRT\frac{d \ln a}{d \ln C} \qquad \text{(Eq. 11)}$$

Both B and $d \ln a/d \ln C$ may be dependent on C and, as Barrer (21) further pointed out, each may in turn depend on x in an inhomogeneous medium. Having introduced these complexities, it is necessary to provide the perspective that in the majority of membrane transport situations of biological and pharmaceutical interest, concentration differentials and integral diffusivities derived therefrom suffice to characterize permeation phenomena in both absolute and relative terms. In other words, activity coefficients are usually confined within a narrow range in a given isotropic medium at the low concentrations one is limited to by the physicochemical and pharmacological natures of drug species.

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[5] In the remainder of the text, the symbol D will be used interchangeably for both differential and integral diffusion coefficients.

Fick's Second Law—Although Fick's first law is a concise mathematical statement, it is not directly applicable to the solution of most permeation problems for it contains three principal variables: J, C, and x (22). Further, J itself is a multiple variable, the net amount of a substance crossing a unit of area of the diffusional reference plane, dM, per unit time, dt. The number of these variables is effectively reduced by one in Fick's second law, which is the fundamental mathematical statement of diffusion and the useful form in resolving most diffusion problems.

When D is independent of x, Fick's second law is readily derived from Fick's first law. Consider the volume element lying between two planes perpendicular to the vector of diffusive flow, x, separated by a distance, ΔX. The rate of entry of diffusant (in units of mass per time) into the volume element per unit of area from the high concentration side is:

$$\frac{dM_{in}}{dt} = -D\frac{d}{dx}\left[C - \frac{\Delta X}{2}\frac{dC}{dx}\right] \quad \text{(Eq. 12)}$$

where C is the concentration in the plane parallel to and equidistant from the two planes prescribing the volume element. Similarly, the loss of mass of diffusant from the low concentration interface may be described by:

$$\frac{dM_{out}}{dt} = -D\frac{d}{dx}\left(C + \frac{\Delta X}{2}\frac{dC}{dx}\right) \quad \text{(Eq. 13)}$$

The terms $C \pm (\Delta X/2)(dC/dx)$ give the concentrations at the planar boundaries of the volume element chosen. The rate of change of mass of diffusing substance in the volume element is obviously equal to the difference in the rate of entry and escape, *i.e.*:

$$\frac{dM_{in}}{dt} - \frac{dM_{out}}{dt} = D\Delta X\frac{d^2C}{dx^2} \quad \text{(Eq. 14)}$$

but this is also equal to the rate of change in concentration within the volume element, dC/dt, times the volume of the element, ΔX (unit area is assumed), and thus:

$$\frac{\left[\dfrac{dM_{in}}{dt} - \dfrac{dM_{out}}{dt}\right]}{\Delta X} = \frac{dC}{dt} = D\frac{d^2C}{dx^2} \quad \text{(Eq. 15)}$$

This is Fick's second law or the differential equation of diffusion for the unidimensional flow case. If more than one-dimensional diffusion is to be considered, it is necessary to assess the net change in mass along the other diffusional vectors by similar methods and, in the notation of rectangular coordinates, Fick's second law may be generalized to:

$$\frac{dC}{dt} = D\left[\frac{d^2C}{dx^2} + \frac{d^2C}{dy^2} + \frac{d^2C}{dz^2}\right] \quad \text{(Eq. 16)}$$

A full derivation of Eq. 16 was presented by Crank (23).

In essence, Fick's second law states that the rate of change in concentration in a volume element within the diffusional field is proportional to the rate of change in concentration gradient at that point in the field, the proportionality "constant" being the diffusivity, D. There are numerous exact solutions of Eq.

15, a particular derivation depending on the boundary conditions imposed by the diffusion problem. Most mathematically tractable cases require or assume invariant diffusivity. Only those situations with obvious bearing on pharmaceutical problems will be discussed here. For more complete coverage and particularly for specifics of the derivations, the reader is referred to Refs. 22–26.

The Simple "Zero-Order" Flux Situation—The solution of Fick's second law for the commonly employed unidimensional experimental situation, where the concentration differential is maintained at a constant value during the course of a run and the diffusant receptor compartment is maintained at essentially zero concentration or a "sink" condition, was provided by Daynes (27) and later generalized by Barrer (28). Considering the diffusive current to be unidirectional, beginning at $x = 0$, the high concentration surface of the membrane, and moving toward the other membrane surface where $x = h$, the boundary conditions are in precise terms: C (concentration) is C_0 (constant) at $x = 0$ for all values of t (time), $C = 0$ at all $x > 0$ for $t = 0$ (initial condition), $C = 0$ at $x = h$ for all values of t (sink condition), and diffusivity, D, is constant. For these conditions, the concentration at any point x (or in a plane through x perpendicular to the flux vector) is given by:

$$C = C_0\frac{x}{h} + \frac{2}{\pi}\sum_{n=1}^{\infty}\frac{C_0}{n}\cos(n\pi)\sin\left(\frac{n\pi x}{h}\right)e^{-n^2\pi^2Dt/h^2} \quad \text{(Eq. 17)}$$

This equation can be solved for the cumulative mass of diffusant per unit area, M, which passes through the membrane in time, t, by the following three steps: (a) differentiation with respect to x to obtain the instantaneous concentration gradient; (b) determination of the flux, dM/dt, at $x = h$; and (c) integration from $t = 0$ to $t = t$. The resulting equation is[6]:

$$M = \frac{DC_0t}{h} - \frac{hC_0}{6} - \frac{2hC_0}{\pi^2}\sum_{n=1}^{\infty}\frac{(-1)^n}{n^2}e^{-n^2\pi^2Dt/h^2} \quad \text{(Eq. 18)}$$

which, as $t \to \infty$, approaches the straight line given by:

$$M = \frac{DC_0}{h}\left(t - \frac{h^2}{6D}\right) \quad \text{(Eq. 19)}$$

In effect, Eq. 19 is the situation where the permeation has attained a steady state, dC/dt at all x within the field is zero, and thus the amount penetrating per unit time is constant. The steady-state flux is readily obtained from Eq. 19 by differentiation and is:

$$\frac{dM}{dt} = \frac{DC_0}{h} \quad \text{(Eq. 20)}$$

Furthermore, if the steady-state line is extrapolated to the time axis, one obtains a value of t (t at $M = 0$) which is:

$$t_L = \frac{h^2}{6D} \quad \text{(Eq. 21)}$$

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[6] The integration constant here and in subsequent derivations is zero due to the choice of boundary conditions.

This intercept is called the lag time, t_L, and it provides estimation of D providing the diffusional field (membrane) thickness is known. The lag time, coupled with the steady-state flux, provides estimates of all the permeation controlling variables because it affords calculation of the membrane surface concentration, C_0. For an isotropic membrane, the steady state is achieved within 1% error when $Dt/h^2 \cong 0.45$, which corresponds to about 2.7 times the lag time, t_L (29). It should be noted that boundary conditions to this point apply to concentrations existing within the membrane, albeit at the surfaces of the membrane. In the typical membrane experiment, one measures concentrations in the external fluids bathing the membrane. In most instances, there is a facile equilibrium between the membrane and the phases contiguous to it. Such equilibria are expressed in terms of solubility coefficients (gaseous contiguous phases) or distribution or partition coefficients (liquid, semisolid, and solid contiguous phases). In other words, it is the usual case that $C_0 = C_0'K$, where C_0' is the applied phase concentration and K is the partition coefficient. Combining this with Eq. 19 yields:

$$M = \frac{DKC_0'}{h}\left[t - \frac{h^2}{6D}\right] \qquad \text{(Eq. 22)}$$

In the case of a gaseous applied phase, pressure or partial pressure of the diffusing gas is used in lieu of concentration and K is the solubility coefficient of the gas in the membranous material. For some materials, e.g., synthetic membranes, the equilibrium coefficient can be obtained independently by equilibrating the membrane material with the applied phase and determining the relative concentrations in each. Alternatively, the distribution can be measured knowing C_0' and determining the steady-state flux and the lag time in a diffusional run (30). Both methods generally yield comparable results, attesting to the fact that the diffusant's interfacial equilibrium between membrane and applied phase is basically instantaneous. For those unusual cases where the equilibrium is not instantaneous, one has in effect an interfacial barrier of significant diffusional resistance so recourse to analysis of barriers in series is necessary.

In many situations of pharmaceutical interest (most biological cases), it is either impossible or experimentally difficult to measure distribution coefficients by either the equilibrium or kinetic (diffusional) method. In such instances, one is limited to characterizing permeability by the composite term, DK, which is often designated as the permeability coefficient, P. When only P can be measured, it is impossible to separate diffusive and gradient (partitioning) contributions to flux. This situation is particularly limiting when relative fluxes of several compounds are being compared. Relative permeabilities are determined by the influences of the structural modifications on both D and K, and one is at a loss to assign the effects to either of these specific parameters.

Since diffusive processes are often thought of and treated as kinetic problems with obvious analogy to

chemical kinetic processes, it is interesting to analyze this common transport problem in these regards. The boundary conditions of constant applied phase concentration, C_0', on one side of the membrane and a receiver sink lead to a zero-order permeation process once the steady state has developed. The zero-order "rate constant" is equal to KD/h.

Short Time Approximation—As stated previously, Eq. 18 converges at large values of t to the straight line given by either Eq. 19 or 22. In circumstances where diffusivities are very small or membranes are very thick, extremely long times are required to attain steady-state conditions and diffusional runs are very lengthy. Protracted experiments are at least analytically inconvenient and, in addition, foster many ancillary but very troublesome problems of analytical origin (instrument stability, overgrowth of microbes, etc.). Furthermore, considering the limited solubilities of some compounds, coupled with concentration requirements for analysis, maintaining a receptor sink condition to a sufficient approximation can be difficult or impossible in some situations. All equations based on the series converging at large values of time would be dubious if not totally inapplicable under these circumstances. Rodgers et al. (31) and Short et al. (32) provided an alternative, although somewhat untested, approach to handle such cases. Collectively they derived a general expression converging at short time by means of a Fourier transformation of Eq. 18 and its integration. The final expression for small t is:

$$\log\frac{M}{\sqrt{t}} = \log\left[\frac{8C_0'K}{h^2\sqrt{\pi}}\right] + \frac{3}{2}\log D - \frac{h^2}{2.3(4)Dt} \qquad \text{(Eq. 23)}$$

A plot of the $\log[M/\sqrt{t}]$ *versus* $1/t$ yields a slope of $h^2/9.2D$, providing an estimate of diffusivity, D, for known membrane thickness, h. The terms M, t, and K have the same meaning as in Eqs. 18–22. This line intercepts with the $\log[M/\sqrt{t}]$ axis at $\log[(8C_0'KD^{3/2})/(\pi^{1/2}h^2)]$ which, in conjunction with the slope, affords individual estimates of all the experimental variables. Rodgers et al. (31) indicated that there is approximately a 1% error by both short time and long time converging series in their respective approximated forms (converged forms) at 2.7 times the standard lag time, t_L. This is taken as the juncture of the validity and applicability of the two equations. In other words, the limit of use of the short time approximation is up to $2.7t_L$, which is about the onset of the steady state and the beginning point of applicability of the long time converging equation. Rodgers et al. (31) also showed that values obtained by the short time approximation for the diffusivity of helium in glass are comparable to those obtained by other investigators using the more conventional diffusional analysis.

Solutions Involving Quasisteady State—To this point, we have dealt with the simplest transport case in an isotropic medium. A more general solution, where there is an initial uniform concentration in the membrane and an initial concentration in the receptor phase, was developed (33). Such cases are solved by the assumption of independent streams; that is,

diffusion from the contiguous phases into the membrane and from the membrane into the external media are solved individually and summed to give the instantaneous concentration at any point, x, in the membrane slab at any arbitrary time, t. When either the applied phase and/or the receptor phase concentrations vary with time, the mathematical analysis is considerably more complicated, and utilizable solutions to Fick's laws are generally limited to conditions after establishment of the concentration gradient across the slab. In other words, after some finite time, an instantaneous or quasisteady state develops and the time course for the diffusional process is initiated and followed after the onset of the quasisteady state. Requisite to successful analysis of these situations are the following conditions:

1. The gradient within the membrane must instantaneously adjust to the external conditions (contiguous phase concentrations).

2. The amount (not concentration) of diffusant in the membrane must be negligible.

These conditions are approached closely for very thin membranes. Ultrathinness is not an absolute requirement, however, as pointed out by Barnes (34). When the conditions are such that there is a linear fall of concentration within the barrier, the instantaneous concentration gradient may be expressed by:

$$-\frac{dC}{dx} = \frac{C_0 - C_h}{h} \qquad \text{(Eq. 24)}$$

where C_0 and C_h are the respective surface concentrations of the membrane. According to Fick's first law, the instantaneous flux per unit area would be:

$$J = \frac{dM}{dt} = -D\frac{dC}{dx} = D\left[\frac{C_0 - C_h}{h}\right] \qquad \text{(Eq. 25)}$$

This can be related to concentrations in the contiguous phases by incorporation of the appropriate partition coefficients. When the amount of material within the membrane is negligibly small compared to that in the external media, the material balance change in the external phases may be represented, respectively, by $(M_D - M)/V_D$ and $(M_R + M)/V_R$, where M_D and M_R are the total amounts of diffusant initially in the high concentration (donor) and low concentration (receptor) contiguous phases, respectively; V_D and V_R are the respective volumes in these phases; and M is the net mass change in the donor phase in time, t (35). On substitution of these expressions into Eq. 25, one obtains:

$$\frac{dM}{dt} = \frac{DK}{h}\left(\frac{M_D - M}{V_D} - \frac{M_R + M}{V_D}\right) \qquad \text{(Eq. 26)}$$

which integrates to:

$$\frac{DK}{h}t = \frac{V_D V_R}{V_D + V_R}\ln\left[\frac{M_D V_R - M_R V_D}{M_D V_R - M_R V_D - (V_D + V_R)M}\right] \qquad \text{(Eq. 27)}$$

When the phase volumes are equal and M_R is zero, Eq. 27 simplifies to:

$$\frac{2DK}{hV}t = -\ln\left[\frac{M_D - 2M}{M_D}\right] \qquad \text{(Eq. 28)}$$

where V is the volume of either phase. Furthermore,

since:

$$\frac{M_D - 2M}{M_D} = \frac{2(M_D - M) - M_D}{M_D} = \frac{2\left(\frac{M_D - M}{V}\right) - \frac{M_D}{V}}{(M_D/V)} \qquad \text{(Eq. 29)}$$

and $(M_D - M)/V$ and M_D/V are the donor concentrations at finite time, t, and at $t = 0$, respectively:

$$\frac{2DK}{hV}t = -\ln\left[\frac{2C' - C_0'}{C_0'}\right] \qquad \text{(Eq. 30)}$$

Therefore, a plot of the log $[(2C' - C_0')/C_0']$ against time yields a straight line with a slope of -0.87 (DK/hV). In situations where these equations are applicable, separation of the partition coefficient, K, and the diffusivity, D, is not possible without an independent measurement of one of these parameters.

A special but important case is derivable from Eq. 27 for the situation where the diffusant is collected into a receptor sink. This is to a first approximation the situation for absorption of soluble drugs from the GI tract since the body acts as an overwhelmingly large reservoir. In this circumstance, V_R may be assumed infinite (very large with respect to V_D) and Eq. 27 simplifies to:

$$\frac{DK}{hV_D}t = -\ln\left[\frac{M_D - M}{M_D}\right] \qquad \text{(Eq. 31)}$$

which, by manipulation similar to the previous case, yields:

$$\frac{DK}{hV_D}t = -\ln\frac{C'}{C_0'} \qquad \text{(Eq. 32)}$$

Diffusive phenomena obeying this relationship correspond to simple first-order processes and, for a given run, the first-order rate constant is given by (DK/hV_D). The conditions in the typical dialysis experiment are also suitable for the use of this mathematical form. In this case, the dialyzed small molecule is continuously flushed from the receptor compartment to maintain the maximum concentration differential throughout the protein purification or other separation procedure.

One further general case should be considered: the situation where a constant concentration is maintained on one side of a membrane system and the concentration on the other side is allowed to approach equilibrium. The boundary conditions are specifically $C_D = C_0$ for all t, $C_R = 0$ (or more generally $C(0_R)$ at $t = 0$, and $C_R > 0$ at t. By analogy to the previous cases, one can write for the flux per unit area:

$$\frac{dM}{dt} = V_R\left(\frac{dC_R}{dt}\right) = \frac{KD}{h}(C_0' - C_R) \qquad \text{(Eq. 33)}$$

This integrates to:

$$\frac{KD}{hV_R}t = -\ln\left[\frac{C_0' - C_R}{C_0' - C(0_R)}\right] \qquad \text{(Eq. 34)}$$

which, when $C(0_R) = 0$, leads to an obvious simplification. Geometry considerations aside, Eq. 34 approximates the cases of absorption of a drug by a small organism in a large drug reservoir (microbes in a beaker of drug solution or goldfish in a tank of

drug solution) or of gases through the lungs, the atmosphere in this latter instance acting as the constant concentration reservoir.

Temperature Effects—Regardless of the diffusional system and the mathematical model required to characterize the same, the temperature dependency in all these instances essentially resides entirely in the temperature dependency of the diffusion coefficient. Partition coefficients (but not gaseous solubility coefficients), volumes, membrane thicknesses, *etc.*, are relatively unaffected by temperature variation. The diffusion coefficient may be written in the form:

$$D = D_0 e^{-Ea/RT} \qquad \text{(Eq. 35)}$$

where D_0 is the hypothetical diffusivity at infinite temperature (from the Y intercept of a plot of log D versus $1/T$) and Ea is the activation energy. Ea is markedly influenced by the nature of the barrier; values range from about 5 kcal/mole for diffusion of low molecular weight nonelectrolytes in liquids to 15–20 kcal/mole for diffusion of comparable compounds in some polymeric structures (36).

Barriers in Series: Diffusion through Laminated Structures—*General Considerations*—Without exception, the systems treated to this point have dealt with situations where concentration gradients are confined entirely within a single isotropic segment of material. For many transport systems, gradients are distributed over several contiguous or noncontiguous strata in a multilayered barrier. Diffusion through a thick segment of a biological tissue like a muscle is one case in point because the diffusing substance must alternately pass through cell membranes and cell cytoplasm. Diffusion through plastic laminates used as packaging materials is another case of pharmaceutical interest. In formulating an attack on characterizing the permeability of stratified barriers, one must consider how the consecutive strata are arranged and characterize the individual physicochemical properties and dimensions of each distinct phase. Zwolinski *et al.* (9) provided a basic approach for analysis of laminates. Using rate theory and a diffusional model which treats diffusion as point-to-point jumps of the diffusing molecules, they derived equations which relate the rate of movement of matter in the steady state to the relative heights of the potential energy barriers encountered in each molecular move. The diffusion constant in a given isotropic field (layer) derived in this analysis is equated to the square of the mean molecular jump distance, λ, times a rate constant, k_i; *i.e.*:

$$D_i = \lambda_i^2 k_i \qquad \text{(Eq. 36)}$$

In extending this analysis, Scheuplein (10) simplified the original expressions, arriving at the following generalized result:

$$\frac{dM}{dt} = \frac{\lambda[C_0' - C_R]}{\dfrac{1}{k_{sm}} + \sum_{i=1}^{n-2} \left(\dfrac{1}{K_i k_i}\right) + \dfrac{1}{k_{sm}'}} = \frac{\Delta C}{\dfrac{1}{P_T}} \qquad \text{(Eq. 37)}$$

where $(n - 2)$ is the total number of barriers exclu-

sive of the interfacial barriers at the extremes of the diffusional field, ΔC is the instantaneous concentration differential across the whole system, k_i is the rate constant in the ith layer as defined by Eq. 36, and K_i is the distribution coefficient in the ith phase with respect to the external phases, which are assumed to be of the same composition. In effect, Eq. 37 states that the reciprocal of the total, complex permeability coefficient, P_T, is equal to the sum of the diffusional resistances encountered in each lamina. In this context, diffusional resistance is equal to the sum thickness of the individual isotropic segment, $N_i \lambda$ (where N_i is the number of unit molecular "jumps" within that part of the field), divided by the diffusion coefficient. The order in which the potential energy barriers are met within the diffusional field does not influence the net steady-state flux across the complex barrier. This latter generalization must only be applied to situations where resistances in all sections of the diffusional field are independent of diffusant concentration. In this situation, the diffusional resistance, R_i, in the ith lamina can be defined by (37):

$$R_i = \frac{1}{P_i} = \frac{h_i}{D_i K_i} \qquad \text{(Eq. 38)}$$

where P_i is the thickness-weighted permeability of the ith segment; and h_i, D_i, and K_i are thickness, diffusivity, and partitional coefficient, respectively. The total diffusional resistance[7] may be computed by:

$$R_T = \frac{1}{P_T} = R_1 + R_2 + \cdots + R_n \qquad \text{(Eq. 39)}$$

or:

$$R_T = \frac{1}{P_T} = \frac{h_1}{D_1 K_1} + \frac{h_2}{D_2 K_2} + \cdots + \frac{h_n}{D_n K_n} \qquad \text{(Eq. 40)}$$

where the distribution coefficients are computed for a given phase with respect to the initial external phase in the system. The terms h_1, h_2, ..., h_n represent the thickness of the individual strata, and D_1, D_2, ..., D_n represent the respective diffusivities in each region. Thus, the composite permeability coefficient for stratified barriers may be obtained with a knowledge of individual thickness and diffusivities of each barrier phase plus the equilibria function between the ith phase and the initial external phase (again we assume the terminal external phase to be the same as the initial external phase). In some cases, these properties may be obtained by independent analysis of the various segments, the properties of the laminate then being formulated from the properties of its component parts. This approach would have particular utility in designing laminated packaging materials to meet predetermined specifications. These equations have been invoked to explain data for many diverse experimental situations.

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[7] It may be noted that the additivity of diffusional resistances in series is analogous to the additivity of sequential electrical resistances. The K values appear as relative capacity terms.

Some particularly good examples may be found in Refs. 9, 10, and 37–42.

Three-Ply Laminate—Derivation of the composite permeability coefficient for a three-ply membrane placed between two well-stirred liquid phases (assuming insignificant diffusion layer resistance), where all membrane strata are of different composition, serves to illustrate the above method. The total resistance encountered by the permeant in traversing the composite barrier, based on Eq. 40, would be:

$$R_T = \frac{1}{P_T} = \frac{h_1}{D_1 K_1} + \frac{h_2}{D_2 K_2} + \frac{h_3}{D_3 K_3} \qquad \text{(Eq. 41)}$$

and:

$$P_T = \frac{(D_1 D_2 D_3)(K_1 K_2 K_3)}{h_1 D_2 D_3 K_2 K_3 + h_2 D_1 D_3 K_1 K_3 + h_3 D_1 D_2 K_1 K_2} \qquad \text{(Eq. 42)}$$

If resistance in one segment is overwhelming, Eq. 42 simplifies to $P_T = (K_i D_i / h_i)$, where i equals 1, 2, or 3, and the composite barrier property is determined by the single high resistance phase. If but one layer is of insignificant diffusional resistance (arbitrarily the third), the overall permeability coefficient becomes:

$$P_T = \frac{D_1 D_2 K_1 K_2}{h_1 D_2 K_2 + h_2 D_1 K_1} \qquad \text{(Eq. 43)}$$

The total permeability coefficient derived here differs from that derived by Barrie *et al.* (42) by the product of the total thickness, $h_1 + h_2 + \ldots + h_n$. In effect, Barrie *et al.* defined the permeability coefficient as an intensive property or averaged property per unit thickness over the total thickness. Recognizing that permeability is not uniform throughout the laminated field, we prefer to view it as the summed property irrespective of total thickness, *i.e.*, as an extensive property. In use (that is, when substituted into a flux equation), the expressions are equivalent because total thickness appears twice and as a ratio in the Barrie *et al.* case and, hence, "cancels."

It is important to realize that, regardless of boundary conditions, a diffusional profile, *i.e.*, a plot of the amount that has penetrated a barrier with respect to time, cannot be used to distinguish between a simple isotropic barrier and a series barrier. For a given experimental condition, profiles obtained with simple and series barriers will be qualitatively the same. Thus, in the absence of knowledge of the diffusional mechanism, standard treatment of the diffusional curve and, particularly, calculation of diffusivity from the Daynes and Barrer lag time relationship must be performed with caution.

Once the series barrier has been described in terms of its complex permeability coefficient, this term may be substituted for the simpler coefficient, KD, in any flux equation previously presented for steady-state or quasisteady-state conditions. The nonstationary state, on the other hand, is exceedingly more complex. This was quantitated for zero-order permeation (constant applied phase concentration and receptor sink, *etc.*) for a three-layer laminate by Barrie *et al.* (42). The lag time for a trilaminate is:

$$t_{L_{1,2,3}} = \left[\frac{h_1^2}{D_1} \left(\frac{h_1}{6 D_1 K_1} + \frac{h_2}{2 D_2 K_2} + \frac{h_3}{2 D_3 K_3} \right) + \frac{h_2^2}{D_2} \left(\frac{h_1}{2 D_1 K_1} + \frac{h_2}{6 D_2 K_2} \right. \right.$$
$$\left. + \frac{h_3}{2 D_3 K_3} \right) + \frac{h_3^2}{D_3} \left(\frac{h_1}{2 D_1 K_1} + \frac{h_2}{2 D_2 K_2} + \frac{h_3}{6 D_3 K_3} \right) + \frac{K_2 h_1 h_2 h_3}{D_1 D_3 K_1 K_3} \right] \Big/$$
$$\frac{h_1}{D_1 K_1} + \frac{h_2}{D_2 K_2} + \frac{h_3}{D_3 K_3} \qquad \text{(Eq. 44)}$$

where h and D are lamina thickness and diffusivity, respectively; and K terms are partition coefficients with respect to the external phases. The subscripts 1, 2, and 3 refer to the order of placement of the layers with respect to the flux vector. When the partition coefficients (solubility coefficients for gases) are comparable and any h_n / D_n term is much greater than the two others, n being 1, 2, or 3, the equation reduces to the simple Daynes and Barrer expression, $h_n^2 / 6 D_n$. In other words, when the diffusional resistance effectively lies in only one of the strata, the remaining strata are shunted out not only with respect to determining steady-state flux but also with respect to determining the duration of the nonstationary state. Numerous other simplifications of Eq. 44 are possible, depending on the relative magnitudes of the h, D, and K values. It may be noted from Eq. 44 that the outer lamina, 1 and 3, may be interchanged without affecting the lag time. However, if the middle phase is relocated in the series, the lag time will in general be altered. This is in contrast to the steady-state flux which will be independent of phase placement.

Membrane-Diffusion Layer Case—One special case involving a trilaminate is of particular importance. Often membrane permeation is from an aqueous phase, through a nonpolar (lipid) membrane, into a second aqueous phase of lesser concentration. Fluid dynamics require the generation of essentially unstirred solvent layers at any stationary surface regardless of stirring conditions (thickness of diffusion layers will depend on stirring but not the existence of the diffusion layers themselves). Thus, in the cited instance, an unstirred aqueous layer will necessarily exist at each membrane surface. From the diffusional standpoint, the system is an ABA trilaminate. This system was recently analyzed (37, 43, 44). The steady-state flux (zero-order boundary conditions) is described by:

$$\frac{dM}{dt} = \left[\frac{K D_M D_{AQ}}{h_M D_{AQ} + (h_{AQ(I)} + h_{AQ(II)}) K D_M} \right] (C_D' - C_R') = P_T \Delta C$$

$$\text{(Eq. 45)}$$

where K is the membrane–water partition coefficient, and the subscripts M and AQ refer to membrane and water, respectively. The terms $h_{AQ(I)}$ and $h_{AQ(II)}$ represent the individual thickness of the two aqueous diffusion layers, and the other terms are as previously defined. In most instances, biological or otherwise, $h_M D_{AQ} \gg K D_M \Sigma h_{AQ}$ and P_T will effectively be $K D_M / h_M$. However, for compounds with high relative lipid solubilities (partition coefficients) and/or for very thin membranes or, in combination with either of these two factors, for the unusual sit-

uations when D_M is of the same magnitude as D_{AQ}, P_T may in effect become $D_{AQ}/\Sigma h_{AQ}$. In the first situation, the concentration gradient is confined entirely within the membrane and the flux and lag time are membrane controlled. In the latter situations, virtually the entire diffusional resistance arises in the diffusion layers and diffusion layer control of permeation is operative[8]. It may be believed by some that increasing "lipophilicity" within a drug family will always produce improved absorption of drugs. Equation 45 states, on the other hand, that there is an upper limit on partition coefficient which, when exceeded, will force the permeation process into diffusion layer control and, once in diffusion layer control, the permeation process is insensitive to partition coefficient. Furthermore, the aqueous diffusivity will decrease as molecular volume is increased, albeit gradually, and the aqueous solubility will drop exponentially with "hydrophobic" derivatization; thus overtitration of "lipophilicity" may actually decrease drug availability. These effects have been experimentally demonstrated and quantitated for the alkyl p-aminobenzoates permeating silicone rubber membranes (37).

Under membrane control and for the zero-order condition, the duration of the nonstationary state is given by the Daynes and Barrer relationship, i.e., $h_M{}^2/6D_M$. For ultrathin membranes operating under diffusion layer control, the lag time will be $(\Sigma h_{AQ})^2/6D_{AQ}$. When the nonpolar membrane is thick and the partition coefficient is sufficiently large to place a permeation process in diffusion layer control, the lag time has been shown to be (44):

$$t_L = \frac{h_M h_{AQ(I)} h_{AQ(II)} K}{[h_{AQ(I)} + h_{AQ(II)}] D_{AQ}}$$ (Eq. 46)

or, when the diffusion layers are of identical thickness:

$$t_L = \frac{h_M h_{AQ} K}{2 D_{AQ}}$$ (Eq. 47)

where h_{AQ} is the thickness of the individual aqueous layer. The appearance of the partition coefficient term in this equation indicates that, once diffusion layer control has been reached, further increases in lipophilicity within a drug series will significantly increase the time for onset of the steady state. It should be kept in mind that partition coefficients grow exponentially with alkyl chain length.

Temperature Effects in Series Barriers—The temperature dependency of the laminated system can be quite complex when the segments offer comparable diffusional resistance and the activation energies of the diffusion coefficients are very different. By substituting $D_0 e^{-Ea/RT}$ terms (see Eq. 35) for D terms in Eq. 45, the permeability coefficient for the membrane-diffusion layer system becomes:

$$P_T = \frac{K D_{0M} D_{0AQ} e^{-(Ea_{AQ} + Ea_M)/RT}}{K D_{0M} e^{-Ea_M/RT} \sum h_{AQ} + D_{0AQ} e^{-Ea_{AQ}/RT} h_M}$$ (Eq. 48)

Since Ea_{AQ} for water is about 5 kcal/mole and Ea_M for many polymers will be as much as 10 or 15 kcal/mole higher, variation of temperature around the critical point where the diffusion resistances in each layer are equal will lead to a change in diffusional mechanism. As temperature is raised, starting 20–30° below the critical point and going to 20–30° above, the system will pass from membrane control to diffusion layer control of flux. A plot of $\log P$ versus $1/T$ will be curvilinear. At small values of $1/T$ (high temperatures), the curve will asymptotically approach a line with a slope of $-Ea_{AQ}/2.3RT$, the diffusion layer activation line. At low temperatures, the slope approached will be $-Ea_M/2.3RT$, indicating membrane control. Thus the temperature dependency in principle can provide much information about the nature of a laminate and the mechanisms of transport. If the diffusional resistance in one layer of the composite barrier dominates over the full temperature span considered, the activation energy will be a function of the diffusivity in that region only and can be used to indicate which layer is rate controlling, providing activation energies are known and are different.

Parallel Pathways: Influence of Shunts and Pores—*General Analysis*—When two or more independent diffusional pathways are linked in parallel in a given diffusional medium, the total diffusional current, J_T, through the composite is simply the sum of the individual currents through the separate routes (45). Thus, for a unit of cross-sectional area, the flux through independent parallel routes, instantaneous or steady state, may be expressed by:

$$J_T = f_1 J_1 + f_2 J_2 + \cdots + f_n J_n$$ (Eq. 49)

where the f_1, f_2, etc., terms give the fractional areas of each route. Therefore, the total flux where independent, parallel pathways exist may be resolved by solving Fick's laws for the operative boundary conditions of the experiment, adjusting for relative areas of the routes, summing over all pathways, and solving for the total area involved. For two parallel, linear routes directly through a membrane, the solution of the flux equations for the zero-order permeation condition with a receptor sink is:

$$M = f_1 \left[\frac{K_1 D_1 C_0'}{h} t - \frac{h C_0' K_1}{6} - \frac{2 h C_0' K_1}{\pi^2} \sum_{n=1}^{\infty} \frac{(-1)^n}{n^2} e^{-n^2 \pi^2 D_1 t/h^2} \right]$$

$$+ f_2 \left[\frac{K_2 D_2 C_0'}{h} t - \frac{h C_0' K_2}{6} - \frac{2 h C_0' K_2}{\pi^2} \sum_{n=1}^{\infty} \frac{(-1)^n}{n^2} e^{-n^2 \pi^2 D_2 t/h^2} \right]$$

(Eq. 50)

which, as $t \to \infty$, approaches the straight line:

$$M = f_1 \frac{K_1 D_1 C_0'}{h} \left(t - \frac{h^2}{6 D_1} \right) + f_2 \frac{K_2 D_2 C_0'}{h} \left(t - \frac{h^2}{6 D_2} \right)$$ (Eq. 51)

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[8] This may seem impossible when $D_M \gg D_{AQ}$. However, if $D_{AQ}/D_M = n$ and there are many times n molecules passing through the membrane for each molecule passing through the aqueous region, the capacity of the diffusion layers becomes flux limiting with the membranes becoming more or less a reservoir between.

The steady-state flux through the parallel routes is thus:

$$J_T = \frac{dM}{dt} = \left[\frac{f_1 K_1 D_1}{h} + \frac{f_2 K_2 D_2}{h}\right] C_0' \quad \text{(Eq. 52)}$$

In general then, for independent, parallel pathways in the steady state:

$$\frac{dM}{dt} = [f_1 P_1 + f_2 P_2 + \cdots + f_n P_n] C_0' \quad \text{(Eq. 53)}$$

where P_1, P_2, ..., P_n are the individual permeability coefficients for each pathway.

Solving Eq. 52 for $M = 0$, one obtains the composite lag time:

$$t_L = \frac{h^2}{6} \left(\frac{f_1 K_1 + f_2 K_2}{f_1 K_1 D_1 + f_2 K_2 D_2}\right) \quad \text{(Eq. 54)}$$

If one of the two possible routes is impervious, the steady-state flux is determined by the fractional area of the permeation available pathway times the rate of permeation through this channel, and the lag time takes the simple Daynes and Barrer form. Membranes containing pores or channels in a rigid, impenetrable superstructure fall into this class.

Unlike series barriers, the diffusional profile (M versus t) may provide *prima facia* evidence for the existence of parallel routes. This occurs when the respective nonstationary-state periods are experimentally separable. In this situation, considering only two routes, the diffusional profile will appear "normal" until the lagging pathway is breached by the permeant, at which time there will be a surge in flux and an approach to a new steady-state line of increased slope. This exact effect has been demonstrated for steroid penetration of human skin (46).

Mechanical Effects—When dealing with pores or channels, two additional mechanical factors must be considered. If the pore is either nonlinear or if it is not oriented perpendicularly within the diffusional field, the effective diffusional path length will exceed the actual thickness of the membrane. This situation is handled by applying a tortuosity factor, τ. The effective thickness of the membrane, H, is computed from:

$$H = \tau h \quad \text{(Eq. 55)}$$

τ having been estimated considering a representative sampling of pores. The second mechanical effect becomes significant when the diffusant's radius approaches the radius of the pores. This leads to hindered diffusion (15, 47–49). This phenomenon is treated in a subsequent section on diffusion through polymers.

Temperature Effects in Parallel Pathways—The temperature dependency for parallel pathways is equally complex to that found for series barriers. Scheuplein (45) thoroughly reviewed the method of analyzing temperature effects for the case of two parallel, independent routes. As in previous analyses, individual diffusion coefficients may be replaced by their $D_0 e^{-Ea/RT}$ forms (Eq. 35), and Eq. 52 becomes:

$$\frac{dM}{dt} = \left[\frac{f_1 K_1 D_{0_1}}{h} e^{-Ea_1/RT} + \frac{f_2 K_2 D_{0_2}}{h} e^{-Ea_2/RT}\right] C_0' \quad \text{(Eq. 56)}$$

Like the case of the laminated barrier, when fluxes through the parallel routes are of the same magnitude at the midpoint of the temperature range of interest and activation energies for each pathway are widely divergent, a curvilinear relationship between log [steady-state flux] and reciprocal temperature is obtained. The curve is inverted in shape from that found for series barriers. A prototype plot may be found in Scheuplein's paper (45).

Scheuplein demonstrated the temperature effects discussed for the permeation of human skin by tritiated water. He provided strong evidence for the existence of pores through the stratum corneum continuum. Activation energies found for each route are 5 kcal for aqueous filled pores, an expectable value based on free diffusion in liquid medium, and 19 kcal for the stratum corneum matrix. Scheuplein's analysis thus shows that the assessment of temperature effects can be a powerful tool in characterizing a membrane and formulating an appropriate model.

Dispersed Phases and Barrier Property— *General Considerations*—The presence of dispersed particles or bodies in the diffusional matrix is another barrier complexity commonly found in pharmaceutical systems. Higuchi and Higuchi (50) previously reviewed the problems associated with this form of heterogeneity, indicating that the theory is applicable to the design of protective ointments, to drug release from semisolid dispersed systems such as solidified emulsions and suspensions (creams and ointments), and to the passage of drugs through biological barriers. Characterization of a membrane containing a dispersed phase necessarily requires full characterization of the dispersed phase itself, including its spatial distribution, its size distribution, its orientation, its shape, its interactions with the diffusing species, and its overall concentration or relative volume. The following analyses will only consider situations where dispersions are uniform within the barrier continuum. Furthermore, the particles will be assumed to be randomly oriented and, in the case of emulsions, spherical in shape. In combination, these features lead to a diffusional field that is isotropic on the macroscopic level. More specific considerations on particle geometry and nonuniform particle distribution may be found in the Higuchi and Higuchi (50) review and in Ref. 51.

Influence of Inert Fillers—The simplest case of filler influence arises when the dispersed phase is diffusionally inactive. Such fillers (here the term is used generally, considering the filler as either solid, liquid, or gas) are referred to as being inert. The inert filler influences the time course of the diffusional profile in basically two ways:

1. It forces the diffusant to stream around the filler, thereby lengthening the average diffusional path.

2. It occupies volume which is excluded as a diffusional path.

As in the case of nonlinear pores, the average path length is adjusted with a tortuosity factor, τ (see Eq. 55). Furthermore, the relative volumes of filler and continuum may be computed in terms of their volume fractions, ϕ_2 and ϕ_1, respectively. Obviously, $\phi_1 = 1 - \phi_2$. Recognizing that the relative cross-sectional

area of the continuum phase is exactly equal to its relative volume (randomness of dispersion is assumed), the steady-state flux equation (zero-order process with a receptor sink) is readily formulated; i.e.:

$$J = \frac{dM}{dt} = \left[\frac{KD}{h}\frac{\phi_1}{\tau}\right] C_0' = \left[\frac{KD(1-\phi_2)}{H}\right] C_0' \quad (Eq.57)$$

The lag time for the zero-order situation as defined is unaffected by the filler volume fraction but is influenced by the increased diffusional path length and is:

$$t_L = \frac{h^2\tau^2}{6D} = \frac{H^2}{6D} \quad (Eq.58)$$

Influence of Adsorptive Fillers—When a filler participates in the diffusion process in a more direct manner, i.e., by sorption of the permeant as it crosses the barrier, it is designated as being active. Sorption here implies either adsorption or absorption. In general, adsorptive influences are less complicated and more readily quantitated. When the adsorption follows Langmuir's isotherm, two distinct dependencies have been formulated: one where the amount adsorbed is directly dependent on concentration and a second representing the plateau of the isotherm where a fixed amount of permeant is adsorbed per unit of filler. The former is designated as the Case I mechanism, and the latter is Case II. The Case I relationship, originally derived by Finger et al. (52), was recently reexamined by Flynn and Roseman (53). For the standard zero-order permeation process, the steady-state flux and lag time equations are:

$$J = \frac{dM}{dt} = \frac{KD(1-\phi_2)}{H} C_0' \quad (Eq.59)$$

and:

$$t_L = \frac{H^2}{6D}(1+z\phi_2) \quad (Eq.60)$$

where z is the adsorptive constant. The steady-state flux equation is identical to Eq. 57, indicating that the steady-state flux is unaffected by the filler short of its influences on effective area for diffusion and effective path length. The lag time is directly related to square of tortuosity, to filler volume fraction, and to filler adsorptive capacity as measured by z. For a given Case I filler, a plot of lag time divided by H^2 against V_2 will have a slope of $1/6D$ and an intercept of $z/6D$, affording in one plot estimates of both D and z. These relationships have been shown to be closely approximated for the permeation of silicone rubber membranes containing a silica filler by ethyl p-aminobenzoate (53, 54).

The Case II adsorptive mechanism was derived by Higuchi and Higuchi (50). The steady-state equation is the same as for the Case I mechanism. The lag time, on the other hand, is considerably different from Case I and is given by:

$$t_L = \frac{H^2}{D}\left[\frac{1}{4} + \frac{Z\phi_2}{2KC_0'}\right] \quad (Eq.61)$$

where Z_{II} is the maximum (saturation) adsorptive

capacity of the filler. The Case I and Case II mechanisms may be differentiated by the donor phase concentration dependency in Case II. When the diffusant is irreversibly bound (Case II) to the adsorbent as may occur in chemisorption, breakthrough of the barrier will be dramatically lengthened at low applied phase concentrations. Higuchi and Higuchi (50) pointed out that the lag time equation for Case II is only approximate in that it reduces to $H^2/4D$ and not to $H^2/6D$ as $Z\phi_2$ approaches zero.

Absorptive, Permeable Fillers—Situations where the filler particles themselves are permeable (i.e., an emulsion) are exceedingly complex and have proven refractory to exact analysis. Such processes involve absorption of diffusant by the filler. It is intuitive that when the filler is permeable a significant flow of material will occur within the filler, and this will affect both transient and steady-state processes. Higuchi and Higuchi (50) derived the following equation for the effective permeability coefficient, P_T, in the steady state, assuming spherical filler particles:

$$P_T = $$

$$\frac{2P_1^2(1-\phi_2) + P_1P_2(1+2\phi_2) - GP_1\left(\frac{P_2-P_1}{2P_1+P_2}\right)^2(2P_1+P_2)(1-\phi_2)}{P_1(2+\phi_2) + P_2(1-\phi_2) - G\left(\frac{P_2-P_1}{2P_1+P_2}\right)^2(2P_1+P_2)(1-\phi_2)}$$

$$(Eq.62)$$

where P_1 and P_2 are the individual permeabilities for the planar case, and ϕ_2 is the dispersed phase volume fraction. The term $(1-\phi_2)$ is the continuum volume fraction, and G is a constant which has a value of about 0.8 based on dielectric constant data for powders and suspensions (Higuchi and Higuchi estimated that G may range down to 0.4 in some instances).

Time Variable Boundaries—*General Considerations*—To this point, transport situations of gradually increasing complexity have been discussed. Further escalation of complexity arises when the barrier's dimensions and/or diffusion properties change in the course of an experimental run. Some systems in which boundaries advance or recede with time, so-called moving boundaries, lend themselves to quantitative analysis. Such systems are exemplified by the following processes: (a) drug release from inert matrixes (55), (b) freeze drying (the receding ice layer) (56), (c) film-forming chemical reactions such as tarnishing of metals (57), and (d) formation of a calcium fluoride layer on tooth enamel (hydroxyapatite) (58).

The first two examples require that the diffusant be transported through a region whose dimension in the flux vector is lengthening due to depletion of diffusant. The latter examples differ in that the diffusant travels through a continuously expanding region (boundary) formed by a chemical reaction of the diffusant and the substrate. With the exception of surface oxidations, there appear to be few examples of these processes outside the pharmaceutical field.

Release from Inert Matrixes—From a pharmaceutical point of view, drug release from inert matrixes represents the most studied system involving moving

boundaries. Mathematical equations have been derived for several different physical situations. With a knowledge of the mechanism of drug release and the appropriate parameters that alter the release process, the researcher is in a better position to design systems to meet a given set of predetermined requirements.

The rate of release of drugs suspended in a stationary matrix (semisolid ointment) was presented by Higuchi (59). Figure 3 depicts the physical model for a planar system. With the assumptions that: (a) a quasisteady state exists, (b) the drug particles are small compared to the average distance of diffusion, and (c) perfect sink conditions exist in the external media, the following equations were derived. The change in amount released per unit area, dM, corresponding to a change in the thickness of the depleted zone, dh, is:

$$dM = W\,dh - \frac{C_s}{2}\,dh \qquad \text{(Eq.63)}$$

where W is the total amount of drug, soluble and undissolved in a unit volume of the matrix, and C_s is the saturation concentration of the drug within the matrix. According to Fick's law, dM is also equal to:

$$dM = \frac{D_s C_s}{h}\,dt \qquad \text{(Eq.64)}$$

where D_s is the diffusion coefficient in the matrix phase. Equating Eqs. 63 and 64, integrating, and solving for h yield:

$$h = \left(\frac{2D_s C_s t}{W - C_s/2}\right)^{1/2} \qquad \text{(Eq.65)}$$

This can be substituted into the integrated form of Eq. 63 to obtain:

$$M = [C_s D_s (2W - C_s)t]^{1/2} \qquad \text{(Eq.66)}$$

and when $W \gg C_s$:

$$M = (2C_s D_s W t)^{1/2} \qquad \text{(Eq.67)}$$

In other words, the amount released is a linear function of the square root of time.

The analogous equation for the release of a single drug from a granular matrix is (55):

$$M = \left(D_a C_a \frac{\epsilon}{\tau}[2W - \epsilon C_a]t\right)^{1/2} \qquad \text{(Eq.68)}$$

where ϵ is the porosity of the matrix, τ is tortuosity, C_a is the solubility of drug in the release medium, and D_a is the diffusivity in the release medium. In this model, the drug is dissolved by a leaching action of the solvent which enters the matrix through connecting capillaries. The corresponding equations, when $W \gg C_a$, for spherical pellets (55) and cylindrical pellets of infinite length (60) are, respectively:

$$F = -\frac{3D_a \epsilon C_a t}{W \tau a_0{}^2} + \frac{3}{2}\left[1 - \left(\frac{a}{a_0}\right)^2\right] \qquad \text{(Eq.69)}$$

and:

$$F = \frac{4D_a \epsilon C_a t}{W \tau a_0{}^2} - \frac{2a^2}{a_0{}^2}\ln\left(\frac{a}{a_0}\right) \qquad \text{(Eq.70)}$$
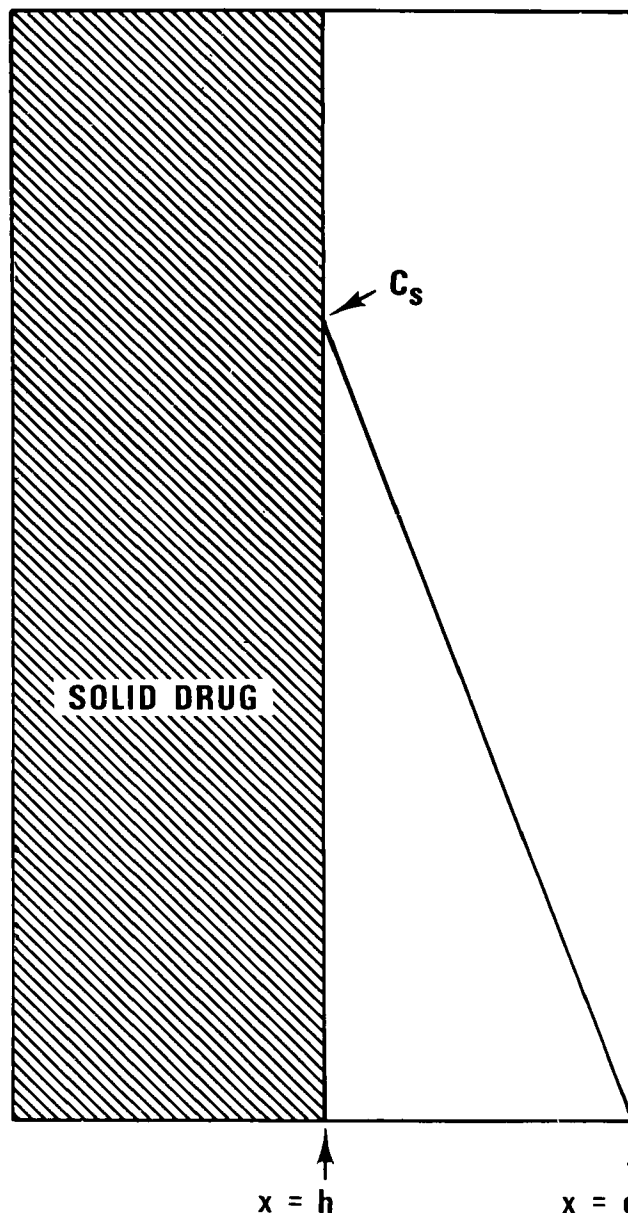
Figure 3—*Physical model for the release of drug suspended in an ointment base under perfect sink conditions (59).*

where F is the fraction of the total amount in the pellet released, a_0 is the radius of the pellet, and a is the radius of the matrix which is unextracted at time, t. When the initial porosity of the matrix is small or the fraction of the matrix volume occupied by the solute is relatively large, ϵ may be represented by W/ρ, where ρ is the density of the drug. In this situation, Eq. 68 reduces to:

$$M = W\left[\frac{D_a}{\tau\rho}\left(2 - \frac{C_a}{\rho}\right)C_a t\right]^{1/2} \qquad \text{(Eq.71)}$$

and, hence, a linear dependency of M upon W is expected. It should also be noted that the fraction of drug released in a given time for the spherical or cylindrical cases is not appreciably different from the planar case until about 50% of the total amount is released (55, 61).

The following equation has been presented (62) for

SOLID
A + B

(a)

REGION 2   **REGION 1**

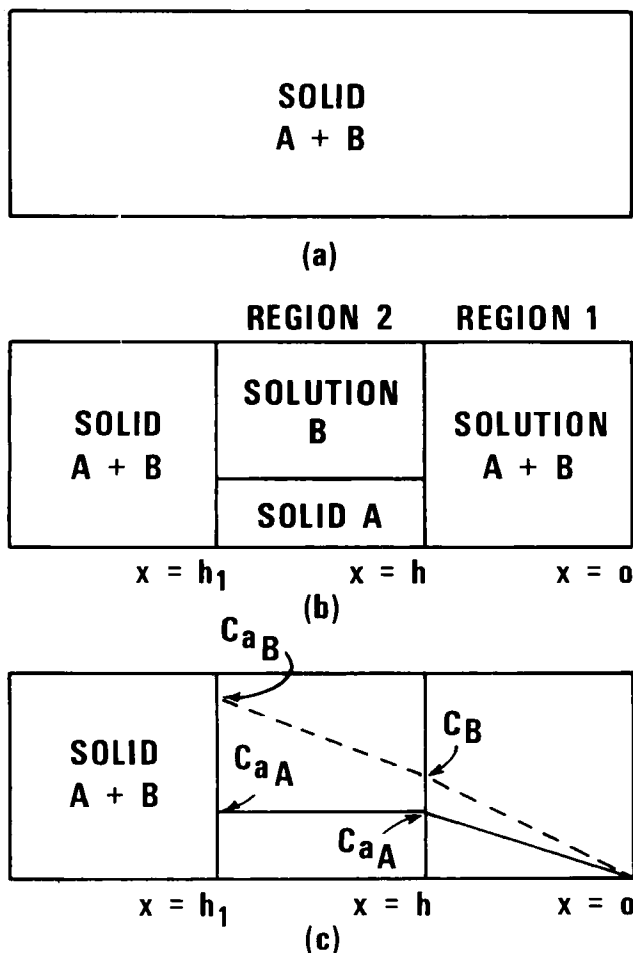| SOLID
A + B | SOLUTION
B | SOLUTION
A + B |
| | SOLID A | |

x = h_1 x = h   x = o

(b)

SOLID
A + B

x = h_1 x = h   x = o

(c)

Figure 4—*Physical model for the release of a mixture of two noninteracting drugs from an inert matrix under perfect sink conditions (73). Key: a, conditions existing at t = 0; b, conditions existing at finite time (t); and c, illustration of the concentration gradients in regions 1 and 2.*

the situation where equilibrium drug binding to the matrix phase occurs but solute does not diffuse through the matrix phase:

$$M = \left[\frac{D_a \epsilon C_a}{\tau} \left[2W - C_a(\epsilon + K - K\epsilon) \right] \right]^{1/2} t^{1/2} \quad \text{(Eq. 72)}$$

where K is the equilibrium partition coefficient, *i.e.*, the drug concentration in solution in the matrix divided by the drug concentration in solution.

The applicability of Eq. 68 to the release of drugs from an inert tablet matrix of polyethylene was tested by Desai *et al.* (63) under controlled experimental conditions. As predicted by theory, a linear relationship was found experimentally when M was plotted against $t^{1/2}$ for the release of sodium salicylate. The effect of W and C_a on the release of drug was in qualitative agreement with theory. However, indirect effects of these two variables along with those of additives and leaching solvent on the porosity and tortuosity terms were noted. Subsequent studies (64) demonstrated that surface-active agents increase the rate of release of solutes by increasing the porosity of the matrix (due to the wetting of channels). When

the constants in Eq. 68 were independently determined, quantitative agreement of data and theory was found. Porosity, however, was not a direct function of the percent of drug in the matrix, and a direct dependence of M upon W as suggested by Eq. 71 was not observed. Furthermore, the choice of the inert matrix strongly influences the observed M *versus* $t^{1/2}$ plots. Polyvinyl chloride releases sodium salicylate four to six times faster than polyethylene, and M *versus* $t^{1/2}$ plots are sigmoidal (65). This atypical behavior was attributed to the slow removal of air from the tablet.

The release of drugs from wax matrixes (66), methyl acrylate–methyl methacrylate copolymer matrixes (67, 68), and hydroxypropyl methylcellulose (69, 70) have also been shown to follow Eq. 68. However, using a sulfanilamide–wax system, calculated tortuosity values were extremely high ($\tau > 1000$) and a more complex model was presented where the permeability characteristics of the drug in the matrix were considered using the Bruggeman equation (71). A receding boundary model has also been proposed to describe the dissolution rates of polyvinylpyrrolidone–sulfathiazole coprecipitates from tablets (72).

The physical model for the simultaneous release of two noninteracting drugs from an inert wax matrix was developed by Singh *et al.* (73). The equations describing the release of each of the two components are based on the physical model given in Fig. 4. The slower moving component's release follows the basic relationship given by Eq. 68. The faster component's release, on the other hand, is described by:

$$M_B = \frac{2 D_{a_B} \epsilon_1 W_A}{\tau_1 k_A} \left[\frac{\frac{\epsilon_2 C_{a_B}}{\tau_2}}{\frac{\epsilon_2}{\tau_2} + \frac{\epsilon_1}{\tau_1} \left[\left(\frac{k_B}{W_B} - \frac{k_A}{W_A} \right) / \frac{k_A}{W_A} \right]} \right] t^{1/2} \quad \text{(Eq. 73)}$$

The subscripts A and B refer to the different drug species, the subscripts 1 and 2 refer to the regions under consideration, the k values are the slopes of the corresponding M *versus* $t^{1/2}$ plots, and C_B is the concentration of drug, B, at the h boundary. Singh *et al.* (74) also derived equations for the case where the two drugs interact to form a complex.

The release of drug from a homogeneous matrix of planar geometry is given by Eq. 66. In this case, the drug dissolves directly in the matrix phase and diffuses through this isotropic environment to the surrounding medium. When the matrix is heterogeneous, that is, when it contains an inert filler, ϕ_1 (the continuum volume fraction) and τ must be included. Equations 69 and 70 are applicable for spherical and cylindrical geometries for this case as long as $W \gg C_s$. Note that C_s, D_s, and ϕ_1 now replace C_a, D_a, and ϵ, respectively. When W approaches C_s, the amount of diffusing component dissolved in the partly extracted matrix must also be considered. The general case relating a (radius of matrix that is unextracted) to time for the spherical case was derived by Higuchi (55):

$$(1 - \alpha) \left[1 + 2 \left(\frac{a}{a_0} \right)^3 \right] - (3 - 4\alpha) \left(\frac{a}{a_0} \right)^2 -$$

$$\alpha \left(\frac{a}{a_0} \right) - \alpha \ln \left(\frac{a_0}{a} \right) = \frac{6 D_s C_s \phi_1 t}{W a_0^2 \tau} \quad \text{(Eq. 74)}$$

where $C_s = \alpha W$. The fraction of drug remaining (F') at t is:

$$F' = \left(\frac{a}{a_0}\right)^3 + \frac{\alpha}{2}\left[\left(\frac{a}{a_0}\right) + \left(\frac{a}{a_0}\right)^2 - 2\left(\frac{a}{a_0}\right)^3\right] \quad \text{(Eq. 75)}$$

As α approaches unity, Eqs. 74 and 75 lose their validity because the quasisteady state necessitates the condition $W \gg C_s$.

Boundary Layers and Matrix Release—In the foregoing derivations involving moving boundaries, it is implicit that the release process is dependent on the properties of the matrix only and is not significantly affected by the external medium (sink) collecting the drug. Due to the presence of solvent boundary layers at surfaces, this may not always be true. Roseman and Higuchi (60) considered the more general system where the solvent (aqueous) diffusion layer is placed in series with the receding drug boundary, much as in the membrane-diffusion layer laminate situation. The expressions relating M to t when $W \gg C_s$ are:

$$M = Wh \quad \text{(Eq. 76)}$$

and:

$$\left[h^2 + \frac{2D_s\phi_1 Kh_a h}{\tau D_a}\right] = \frac{2D_s\phi_1 C_s}{\tau W}t \quad \text{(Eq. 77)}$$

where, again, K is the matrix–solvent partition coefficient, and h_a is the thickness of the solvent diffusion layer. The thickness of the zone of depletion (h) is related to time by Eq. 77 and increases as a function of time as shown in Fig. 5 for the release of medroxyprogesterone acetate from a silicone rubber cylinder. These equations do not predict a linear dependence of M on $t^{1/2}$ at all times unless the condition $h \gg (2D_s\phi_1 h_a K/D_{a\tau})$ is fulfilled. When this occurs, Eqs. 76 and 77 combine to yield Eq. 67, which predicts a linear relationship[9].

The applicability of Eqs. 76 and 77 have been tested by studies on the release of progesterone-type steroids from a silicone polymer (61). Nonlinearity of M versus $t^{1/2}$ plots was found during early stages of the release process. The duration of the nonlinear region was dependent upon the particular steroid studied. With the ratio D_s/D_a presumed to be relatively constant for a class of structurally similar compounds in a given matrix and with h_a fixed by the experimental design, the nature of the M versus $t^{1/2}$ plots are dependent upon the magnitude of K, which is, in turn, strongly dependent upon molecular structure. Further support for this model of drug release can be abstracted from the data of Haleblian et al. (75) for the release of chlormadinone acetate from a silicone polymer. When M versus $t^{1/2}$ plots were made for five different concentrations of micronized drug within the matrix, nonlinearity was observed at early times. In this study, the higher drug loads required a longer time to reach the linear region of the M versus $t^{1/2}$ curve. This finding is consistent with the notion that it requires a longer time at higher drug levels for h to be sufficiently large so that the release process is solely matrix controlled, as given by Eq. 67.
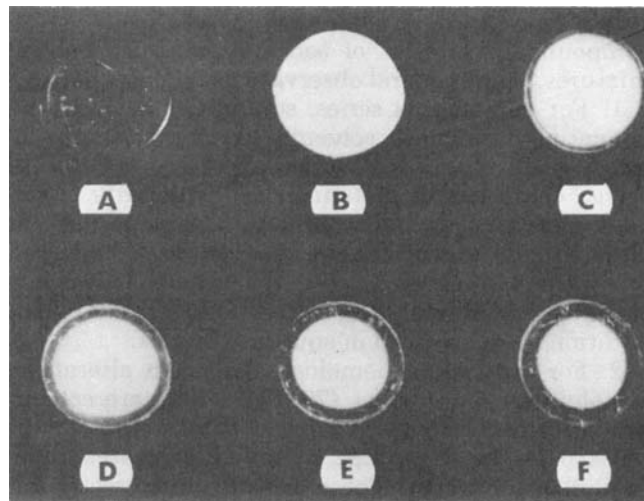

Figure 5—*Cross-sectional views of silicone rubber cylinders (60). Key: A, placebo; B, drug-filled, initial; C, 1 week; D, 2 weeks; E, 3 weeks; and F, 4 weeks.*

INFLUENCE OF SOME SPECIFIC PERMEANT AND BARRIER PROPERTIES ON MASS TRANSPORT

Diffusant Solubility as a Flux-Limiting Factor —*General Solubility Considerations*—Regardless of flux mechanism, it is clear upon examination of all of the permeability expressions that flux is proportional to the concentration differential across the total barrier. This is maximized in a given system for a given permeant when the penetrating agent is present in the applied phase in a saturated state. There are many situations of pharmaceutical interest where this solubility limitation plays a critical role in the transport process. For example, the rate of dissolution of a solid in a given solvent is dependent on its solubility, the barrier for dissolution in most cases being the solvent diffusion layer at the solid's surface. The absorption of slightly soluble drugs from suspensions or from solid dosage forms, the passage of pure gases and vapors across membranes, and the permeation of pure solvents through synthetic containers also involve saturation of the barrier interface in contact with the penetrant. Even in uptake experiments and other situations where saturation is unattained, the solubility of the diffusant is important as a measure of the maximum driving force for transport. Furthermore, since studies concerned with determinations of diffusivity or release from matrixes, *etc.*, often involve permeability from saturated phases, it is necessary to know the solubility to calculate diffusivity or otherwise to quantitate the processes.

A review of solubility theory is beyond the scope of this paper; the reader may want to consult Refs. 76–80 for information along these lines. However, several generalizations regarding chemical structure and its influence on solubility are particularly relevant and will be considered.

Most systematic studies on the solubilities of organic nonelectrolytes have been directed to congeneric solubilities in a given solvent (particularly solubilities of homologs) or to the solubilities of a single

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[9] In Eq. 67, ϕ_1 and τ are unity.

compound in a series of solvents or binary solvent mixtures. Some general observations follow.

1. For homologous series, solubilities decrease exponentially in most solvents as chain length increases (79, 80). Negative slopes of log (solubility) *versus* chain length plots increase as polarity of solvent increases. In hydrocarbons, the slope may be close to zero and it ranges between -0.5 and -0.7 for water. In other words, somewhere between a three- to fivefold decrease in solubility per methylene addition is experienced in aqueous systems.

2. For crystalline homologs, odd–even alterations in solubility are evident (79, 81). These are concurrent with generally decreasing solubility and may be masked in the very large solubility decreases found in aqueous systems. These arise from energetic differences in crystal packing of odd and even chains which lead to odd–even alterations in heats of fusion. Moreover, the behavior of the first few homologs in a series may be aberrant with regard to both slope and odd–even alterations since the nonchain portion of the molecule can assert a disproportionate influence on crystal structure in this instance (81, 82).

3. Solubilities of nonpolar organic compounds are directly influenced by their molecular "hydrophobic" surface area (83). For example, neopentane is more water soluble than n-pentane because it is a more globular molecule offering less total surface to the aqueous environment. The lipid–water partition coefficients of organic homologs and analogs increase exponentially with "hydrophobic" surface area because the affinity for water decreases as the molecules are made more "hydrophobic" and *not* because the absolute lipid affinity is raised.

The emphasis here is on water because water is the principal component of the fluids found in the GI tract and elsewhere in the body as well as the solvent of choice for most liquid pharmaceuticals intended for systemic effects. While most of the comments are made with specific reference to homologs, the properties of analogs would tend to follow the same patterns, albeit less regularly or rigorously. What the solubility phenomena mean with respect to transport was summarized by Flynn and Yalkowsky (37). They combined the zero-order flux equation for the membrane-diffusion layer system with the following homolog relationships:

$$\log S_n = \log S_0 - \delta n \qquad \text{(Eq. 78)}$$

and:

$$\log K_n = \log K_0 + \pi n \qquad \text{(Eq. 79)}$$

where S_n and K_n are the solubility and partition coefficient, respectively, of the homolog of chain length n; and S_0 and K_0 are the solubility and partition coefficient, respectively, of the reference homolog of chain length equal to zero; the latter are often hypothetical values found by taking the Y intercept of the log (solubility) *versus* chain length plot for log S_0 and the Y intercept of the log (partition coefficient) *versus* chain length plot for log K_0. Using this solubility and partitioning reference point, the steady-state flux from saturated solutions for the compound of chain length n in the standard zero-order process may be expressed by:

$$\log J_n = \log S_0 + \log K_0 + (\pi - \delta)n - \log\left[\frac{h_{AQ}}{D_{AQ}} K_0 10^{\pi n} + \frac{h_M}{D_M}\right]$$

$$\text{(Eq. 80)}$$

Often $h_M/D_M \gg (h_{AQ}/D_{AQ})K_0 10^{\pi n}$ for small values of n, in which case the steady-state flux is given by:

$$\log J_n = \log \frac{S_0 K_0 D_M}{h_M} + (\pi - \delta)n \qquad \text{(Eq. 81)}$$

This is the membrane control situation and, where operative, the relative flux of homologs from saturated solutions will depend almost entirely on the relative values of π and δ. Generally, $\delta > \pi$, particularly for biological systems where π is only about 0.2–0.3, and there will be a decreasing flux with increasing chain length for saturated conditions (84). When n gets large, $(h_{AQ}/D_{AQ})K_0 10^{\pi n} \gg h_M/D_M$ and the steady-state flux obtained will be related to solubility by:

$$\log J_n = \log \frac{S_0 D_{AQ}}{h_{AQ}} - \delta n \qquad \text{(Eq. 82)}$$

which, neglecting small changes in aqueous diffusivity of the compounds, indicates that the flux will drop exponentially and in exact parallel to the solubility. Thus, based on literature values of δ, which range from 0.5 to 0.7, a three- to fivefold decrease in steady-state rate of penetration per unit increase in n is experienced. From the standpoint of relative biological activity, a fourfold decrease in rate of supply of drug to the biological "receptor" will often overwhelm other activity-determining factors and the biological activity will plunge precipitously once diffusion layer control is attained, assuming, of course, application in saturated aqueous solutions. The latter assumption is eventually good in all cases because the exponentially decreasing solubility line will of necessity cross any fixed (initial) concentration line at some value of n. Thus, to generalize, there is a practical limit for the adjustment of "hydrophobicity" of homologs and analogs past which the absorption behavior is so seriously affected as to preclude biological activity. It is implicit in this generalization that the membrane-diffusion layer system serves as the model of minimum complexity for the absorption of drugs.

Solubility of Gases—The solubility of pure nonpolar gases and vapors in amorphous nonpolar polymers can generally be described by any of several relationships of the form:

$$\log S = AE + B \qquad \text{(Eq. 83)}$$

where A and B are constants that depend upon the temperature, the gas, and the polymer, respectively. For mixtures of gases, the solubility is usually replaced by the solubility constant, defined as the ratio of the concentration in the polymer phase to that in the gas phase. The heats of solution of gases and vapors are exothermal and tend to increase with solute size and eventually level off for large solutes.

In most cases, heats of solution of gases in nonpolar polymers and in nonpolar liquids can be approximated by:

$$\Delta H_s = V_1(\psi_1 - \psi_2)\Phi_2^2 \qquad \text{(Eq. 84)}$$

where V_1 is the partial molal volume of the solute, ψ_1 and ψ_2 are the solubility parameters of the solute and either the solvent or polymer, and Φ_2 is the volume fraction of solvent or amorphous polymer. Both volumes and solubility parameters for most common polymers and solutes are known (85, 86) or can be estimated by empirical calculations (82, 87). Therefore, for poorly soluble substances, where Φ_2 is approximately unity, it is possible to estimate the heats of solution. For solid dissolution, the heat of solution is dominated by the heat of melting and is thus usually endothermic.

Special Case: Dissolution of Solids—The dissolution of a solid in a fluid medium is described by the Noyes–Whitney equation (88):

$$\frac{dM}{dt} = R_{AQ} \frac{A}{V_B} (S - C_B) \qquad \text{(Eq. 85)}$$

where C_B is the bulk concentration, S is the solubility, M is the weight, A is the surface area of the solute, V_B is the volume of the solution, and R_{AQ} is the resistance of the diffusion layer as described earlier. If, as in the beginning of a dissolution experiment, $C_B \ll S$, Eq. 85 becomes:

$$\frac{dM}{dt} = R_{AQ} \frac{A}{V_B} S \qquad \text{(Eq. 86)}$$

which describes the initial rate of dissolution. The role of aqueous solubility in determining the initial dissolution rates of about 50 drugs and drug-like substances from uniform surface area pellets was illustrated by Hamlin *et al.* (89). Their data show excellent agreement with Eq. 86, the linearity extending over five orders of magnitude.

The solubility of a substrate and, thus, its dissolution rate can be increased significantly in several ways. The addition of surfactants, complexing agents, and solvents and the adjustment of pH can have profound effects on dissolution rates of drugs (89). Complete characterization of such systems must, of course, account for the diffusivity of any micellized or complexed drug and for changes in viscosity that accompany the alteration of solvent composition.

Factors Determining Partition Coefficients— The permeability of a membrane separating two aqueous phases is proportional to the product of the membrane–water partition coefficient and membrane diffusion coefficient of the solute when the membrane provides the sole source of diffusional resistance. Thus, in certain instances, the role of partitioning in determining permeability is similar to the role of absolute aqueous solubility already discussed.

The relationships between partitioning behavior and chemical structure were thoroughly reviewed (90–92). Although the discussion of Leo *et al.* (92) is aimed primarily at octanol–water partitioning, it provides regression equations which can be used to convert octanol–water data to ether–water partition coefficients, chloroform–water partition coefficients, *etc.* Presumably, if enough data were available for biological systems, it would be possible to obtain equations from which membrane–water partition coefficients could be calculated.

In the structural approach to partitioning, a given functional group or other structural component is presumed to have a constant input to the overall partition coefficient of the given whole molecule. By using a reference derivative with a known partition coefficient in the partitioning system of choice, the log (partition coefficients) of a homolog or analog can be calculated by simply summing the group contributions (π values) of the structural modifications with respect to the reference compound and adding these to the log [partition coefficient] of the reference. Fortunately, there is a great parallelism seen for these specific structural effects among differing partitioning systems. This usually makes it possible to assess, at least qualitatively, the effect a given moiety will exert on one partitioning system if its influence on another is known. This is particularly helpful for analyzing data from biological systems, where partition coefficients are often unattainable, because a convenient *in vitro* reference partitioning system may be used to correlate the data and predict optimal properties.

The permeability of many polymers to gases is often more a function of the relative concentration of the gases than their diffusivities, according to Barrer and Chio (93). For example, the diffusivity of helium is almost nine times greater than that of xenon in silicone rubber; yet the permeability of the latter is over 10 times the permeability of helium because of its 100-fold greater solubility. In the case of gases, the distribution function is referred to as the solubility coefficient.

The role of substrate partition coefficients in determining flux is conveniently illustrated by studies on alkyl homologs. The diffusivities of the members of most homologous series in water or artificial membranes generally do not change by more than a slight factor (2 or 3) as the series is ascended over a 10-unit increase in chain length. A 10-unit variation in chain length may be taken as the rough limits of practical chain length manipulation (see section on diffusivity for further conditional factors). However, by examining Eq. 79, it is obvious that over the same 10 methylene unit range, partition coefficients will increase by from 2^{10} ($\simeq 1000$) to 4^{10} ($\simeq 1,000,000$). These numbers correspond, respectively, to π values for a methylene unit of 0.3, which is commonly found for biological membranes (84), and 0.6, which was reported by Davis *et al.* (83) for hexane and similar apolar solvents. Obviously, changes in partitioning dominate diffusivity effects. When measured from solutions of equivalent concentration, the steady-state flux of the homologs will grow essentially as the partition coefficient grows as long as the membrane is the controlling barrier. However, for all membranes that are "lipoid" in character, a point is reached as the partition coefficient is made larger

where the system crosses over to diffusion layer control. As shown by Stehle and Higuchi (43), a plateau in flux is reached at this point for these conditions and flux remains constant upon further alkyl chain length extension, unless, of course, the solubility limitation is also attained, in which case the flux falls exponentially (see previous section).

Garrett and Chemburkar (94) and Flynn and Yalkowsky (37) showed that under membrane control of flux the permeability of alkyl p-aminobenzoates through a silicone rubber membrane parallels the partition coefficients of these compounds between water and a nonpolar solvent. Similarly, Nasim et al. (95) showed that the permeabilities of a variety of substances through polyethylene is proportional to their hexane–water partition coefficients. Other workers correlated permeability of various nonpolar membranes with different oil–water partition coefficients.

Effective Concentrations—Factors that alter compound solubility such as micelle formation, complex formation, and cosolvents also affect the permeation processes by changing the thermodynamic activity of the penetrating substance in either the applied phase or the barrier phases. Since the partition coefficient actually is a ratio of the activity coefficients in the various phases, such effects are directly reflected in measured (or effective) partitioning constants. The influence of complexation, micellization, etc., on permeability of lipid (partitioning) membranes lacks predictability since these processes are complicated in multiphasic systems because all interphase equilibria are simultaneously affected.

Possibly the simplest and best characterized equilibria with respect to permeation of "lipid" membranes are dissociations of weak acids and weak bases. Generally, ionized species formed in such equilibria do not have favorable free energies for transfer to lipid phases and, for all intents and purposes, only nonionized species partition. Thus, the net membrane gradient in membrane control of flux is determined solely by the fraction of unionized drug (diffusant) in the applied phase. In such cases the pH profile for drug permeation is sensitive to the pH profile of the nonionized species[10]. This has been called the pH–partition hypothesis by some authors. The literature is replete with examples illustrating the influence of pH on the transport of both acidic and basic species.

The influence of cosolvents on membrane transport is interesting and of practical importance in the field of topical dosage forms. Garrett and Chemburkar (94) and Yalkowsky and Flynn[11] studied the effect of regularly altering aqueous solvent composition on the transport of several drugs across silicone rubber membranes. For the systems studied, it can be shown that the partition coefficient of a drug between the membrane and any solvent mixture is proportional to the reciprocal of the drug solubility in

the solvent system. Furthermore, a plot of log (reciprocal solubility) versus log (permeability) is linear and has a slope of unity. This indicates that in the systems studied the permeability is directly proportional to the partition coefficient and that the systems are under membrane control of flux. If the permeant is sufficiently nonpolar to produce diffusion layer control, the permeability would be independent of solvent composition.

Self-association of a diffusant into micelles increases the total apparent solubility of a substrate in the aqueous phase and decreases its apparent partition coefficient, but it does not significantly alter the concentration of free drug or its true partition coefficient. Therefore, if the micelle cannot pass through the flux-controlling membrane, its effect on permeability will be small. However, if the dominant resistance is the aqueous diffusion layer, the micelle can play a significant role in the transport process (96–98).

The influence of micelles where the association colloid-forming agent and the diffusant are not the same is a very different matter. When the diffusant has no affinity for the micelle, no appreciable effects will be noted. As the micellar affinity increases, the fraction of unassociated diffusing species will be depleted and the flux will drop proportionally. In the extreme, there may be so little free drug that transport becomes limited by the rate of diffusion of the micelle or the energetics of removing the diffusant from the micelle once at the partitioning surface. The latter interfacial barrier mechanism appears to be operative in the transport of cholesterol and related sterols in the presence of bile acid–lecithin micelles into and out of a hexadecane phase (99). Such processes are orders of magnitude slower than free diffusion.

Complex formation, like micelle formation, alters the apparent solubility and partition coefficient of a substance. If complexation only occurs in the aqueous phase, complexation will influence transport in a manner analogous to micellization. However, if the complex is also stable in the membrane, transport of the complexed form effectively results in a parallel pathway for transport. A complete description must include the stability constant for the complex as well as the diffusivity of free and complexed drug in each phase and the partition coefficient of the drug and complex between phases. The relative magnitudes of these values will determine whether permeability is increased, decreased, or unchanged by complexation. These rather interesting possibilities were effectively separated from one another by Nakano and Patel (100), who studied the effects of alkylamides on the passage of p-nitrophenol across silicone rubber membranes. They found that dimethylacetamide produced no effect on the apparent permeability but that dimethylpropamide, diethylacetamide, and diethylpropamide increased permeability by 11, 29, and 95%, respectively. This point was further illustrated by Bates et al. (101), who showed that certain caffeine–drug complexes, which have lower partition coefficients than the respective free drugs, reduced

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[10] The permeation profile is *superimposable* on the pH profile of the nonionized species only when the partition coefficient is equal to one.
[11] In preparation.

the apparent permeability of the drugs. The apparent permeability of caffeine, on the other hand, was increased as a result of formed complexes that were more hydrophobic than free caffeine.

Factors Affecting Diffusivity—*General Remarks*—In grossly generalized terms, diffusivity is dependent on the state of matter of the diffusing medium, *i.e.*, gas, liquid, or solid. In all theories relating diffusion to the state of matter, it is implicit that no two molecules or atoms may occupy the same point in space at the same time and, thus, diffusion must always be through void spaces in the matter under consideration. In gaseous media, the void space, or free volume as it is often referred to, is thousands of times greater than the physical space occupied by the molecules themselves and the mean free path between molecular collisions is large, leading to large diffusivities. Typical diffusivities in air are on the order of 0.05–1 cm^2/sec at ambient temperature. Thus, the average gas molecule from a large population will cross a centimeter thick barrier of air in from 1 to 20 sec. In condensed fluid phases, the free volume is but a small fraction of that found in the gaseous state; mean free paths and, thus, diffusivities are correspondingly smaller. For example, in liquid water the diffusivities of 10^{-5}–10^{-6} cm^2/sec are common and it would take a molecule somewhere between 1 and 10 years to cross a 1-cm thick, unstirred layer[12]. Solidified polymers generally have even less free volume which, in this case, is dependent on the polymer's density and degree of crystallinity. Diffusivities in polymers are orders of magnitude less than in the fluid state. For all intents and purposes, metallic and ionic crystalline solids are without free volume and are virtually impervious to small molecules at ordinary temperatures. However, small gas molecules (hydrogen, helium, *etc.*), which can "squeeze" through the atoms in the crystalline array, do often penetrate with detectable velocities at ordinary temperature.

In more specific terms, the diffusivity of a substance in a particular medium is a complex phenomenological parameter, which is dependent upon the properties and the degree of interaction between the diffusant and the diffusion medium. The diffusion coefficient, D, is related to the frictional resistance, f, that the diffusing particle experiences in moving through a medium by (26):

$$D = \frac{RT}{f} \qquad \text{(Eq. 87)}$$

The primary effect of structural modification on diffusivity is the alteration of the frictional resistance. However, since structural changes are frequently associated with changes in molecular interaction, a secondary effect is to alter the effective concentration gradient, ΔC. The sensitivity of ΔC and f to molecular modification depends upon the characteristics of both diffusant and barrier. Unfortunately, it is not possible at this time to present a single relationship describing diffusivity in terms of other

known or measurable parameters. To provide a meaningful discussion of diffusivity, this section will be subdivided according to the nature (homogeneity, fluidity, and polarity) of the diffusion medium. Since all possible barriers cannot be covered, a variety of representative systems was chosen so that reasonable extrapolations can be made to media that are not specifically discussed.

Diffusivity in Homogeneous Liquids—In a homogeneous liquid, the frictional resistance that a particle experiences is dependent largely upon its size and shape and on the nature of the solvent. There is a variety of theoretical and empirical correlations of f or D in terms of solvent and solute properties (102–105), but no single equation can account for all experimental data. One of the most useful relationships for the frictional resistance of a particle in a homogeneous fluid is the Sutherland equation (103, 106):

$$f = 6\pi\eta r \left[\frac{2\eta + r\beta}{3\eta + r\beta}\right] \qquad \text{(Eq. 88)}$$

which relates f to solvent viscosity, η; solute radius, r; and a "slip" factor, β. This equation is applicable for spherical particles in sufficiently dilute solution so that solute–solute interactions can be neglected. The slip factor, β, or more properly the coefficient of sliding friction is a measure of the tendency of solvent molecules to adhere to the diffusant. For large particles, the solvent molecules tend to be dragged along with the diffusant and $\beta \rightarrow \infty$. If β is large, Eq. 88 becomes Stokes' law:

$$f = 6\pi\eta r \qquad \text{(Eq. 89)}$$

If, on the other hand, the solvent and diffusant are of similar size, the tendency to slip is large and $\beta \rightarrow 0$ (*i.e.*, there is very little resistance to slip) and Eq. 88 becomes:

$$f = 4\pi\eta r \qquad \text{(Eq. 90)}$$

Equation 90 is particularly applicable to self-diffusion where the solvent and diffusant have identical dimensions. In cases where the solute is smaller than the solvent, it is frequently observed that the frictional resistance is less than $4\pi\eta r$ (106).

It must be realized that the radius to be used in Eqs. 88–90 is not that of the bare molecule but of the hydrodynamic particle (106). The hydrodynamic particle consists of the diffusant molecule plus any solvent or solute (such as a complexing agent) that is adsorbed or bound to the surface or entrapped within the diffusant. If it is known that the diffusant hydrates or complexes, the resultant volume increase must be accounted for in the equations.

The above equations were derived for spherical particles but are applicable to ellipsoids. For oblate (saucer-shaped) and prolate (cigar-shaped) ellipsoids, the equations must be modified to account for the greater surface area and thus the greater resistance that a nonspherical particle experiences. Perrin (107) and Herzog *et al.* (108) independently extended Stokes' law to ellipsoids of revolution. Their results are frequently expressed as the ratio of the frictional resistance of an ellipsoid, f_e, to that of a

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[12] These values are computed from the average molecular velocity, D/h.

sphere of equal volume f (106). For an oblate ellipsoid of major axis, a, and minor axis, b, the frictional ratio, F, is:

$$F = \frac{f_e}{f} = \frac{\sqrt{a^2/b^2 - 1}}{\left(\frac{a}{b}\right)^{2/3} \tan^{-1} \sqrt{a^2/b^2 - 1}} \quad \text{(Eq.91)}$$

and for a prolate ellipsoid with axes (a, b, b):

$$F = \frac{f_e}{f} = \frac{\sqrt{1 - b^2/a^2}}{\left(\frac{b}{a}\right)^{2/3} \ln\left(\frac{1 + \sqrt{1 - b^2/a^2}}{b/a}\right)} \quad \text{(Eq.92)}$$

These functions were shown graphically by Tanford (106) for axial ratios up to 20. These calculations can be extended to a cylinder by approximating the cylinder with a prolate ellipsoid of the same volume. To obtain the axial ratio of the equivalent prolate spheroid, simply multiply the length over the diameter of the cylinder by 0.815 (106). These equations have been demonstrated to be valid for rigid ellipsoidal organic ions ranging from 121 to 367 in molecular weight (109), for linear oligosaccharides containing 1-6 sugar units (110), and for cyclic oligosaccharides (111). Similar equations have also been found useful for linear oligophenylenes (112).

From the above discussion, it can be seen that for solutes whose molar volume, v, is greater than or equal to the molar volume of the solvent, the diffusivity can be expected to range from:
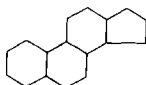
$$D = \frac{kT}{4\pi\eta}\left(\frac{4\pi}{3v}\right)^{1/3} \quad \text{(Eq.93)}$$

for small particles to:

$$D = \frac{kT}{6\pi\eta F}\left(\frac{4\pi}{3v}\right)^{1/3} \quad \text{(Eq.94)}$$

for large particles. Note the correction for nonsphericity in the large particle case. Assuming the viscosity of the solvent to be either known or readily measurable, the only parameters needed to estimate D are the molar volume and the frictional ratio of the diffusant. Although these values are frequently difficult to measure experimentally, they can be estimated with reasonable accuracy. Fortunately, the molar volume of a substance is an additive property of its constituent atoms and functional groups, and it is thus possible to estimate v from the chemical formula of the diffusant. Some workers (104) preferred to calculate the van der Waals' volume of the solute while others (102, 113–117) chose the partial or apparent molal volume; still others (15, 118) determined v from space-filling molecular models. In view of the approximate nature of atomic and group values and the possibility of solvent incorporation into the hydrodynamic particle, it is not possible to justify a theoretical preference for any of these approaches. The partial molal volume is frequently easiest to calculate and has been used extensively in the estimation of protein hydrodynamic properties (106). It has also been used successfully in the calculation of micelle surface charge density (119, 120) and in the estimation of solubility parameters (82). The partial molal volumes of some common atoms and groups are listed in Table III. Many of these

Table III—Partial Molal Volumes of Some Common Atoms and Groups[a]

Atom	Partial Molal Volume, cm³/mole[b]	Group	Partial Molal Volume, cm³/mole[b]
C	9.9	CH₃	19.3
H	3.1	CH₂	16.2
H⁺	−4.5	NH₂	7.7
N	1.5	N(CH₃)₃⁺	66.3
N⁺	8.4	COOH	19.0
O (=O or —O—)	5.5	COO⁻	11.5
O (—OH)	2.3	C₂H₅	35.3
O (diol)	0.4	C₃H₇	51.7
S	15.5	C₄H₉	67.9
P	17.0	C₆H₁₃	100.3
P⁺	28.5	C₈H₁₅	132.7
Li⁺	−5.2	C₁₀H₂₁	165.1
Na⁺	−5.7	C₁₂H₂₅	197.5
K⁺	4.5	C₁₄H₂₉	229.9
Cl⁻	22.3	OCH₂CH₂	37.9
Br⁻	29.2	One ring	−8.1
I⁻	40.8	Two fused rings	−26.4

191.0

[a] From Ref. 13. [b] To convert to Å³ per molecule, divide by 0.6023.

values were originally determined by Traube (121) in 1899.

For nonspherical substrates, the axial ratio can be estimated from bond distances and group radii (122) or from space-filling molecular models. The frictional ratio can then be determined by solving Eqs. 91 and 92. The inclusion of the frictional ratio amounts to less than a 10% correction for all but the most elongated structures and can thus be safely ignored in obtaining a first approximation of D.

In their strictest sense, Fick's laws are valid only in highly dilute solutions where there is absolutely no interaction between solute molecules. Increasing concentration, C, can result in an alteration of the thermodynamic activity coefficient of the diffusant. In general, if the solution and solvent have the same viscosity (123), then:

$$D = D_{c\to0}\left[1 + C\left(\frac{\partial \ln \gamma}{\partial C}\right)\right] \quad \text{(Eq.95)}$$

It is obvious from this equation that if Henry's law is obeyed, D is linearly dependent on C, and if C is small, D is independent of concentration. If the solute concentration is sufficiently high, it can alter the solvent viscosity and thus exert a secondary effect on its own diffusivity. Equation 95 can readily be modified to account for this effect:

$$D = D_{c\to0}\left[1 + C\left(\frac{\partial \ln \gamma}{\partial C}\right)\right]\frac{\eta}{\eta_{c\to0}} \quad \text{(Eq.96)}$$

Certain solutes exhibit critical concentrations at which self-aggregation begins to occur. Critical phenomena are often associated with dramatic changes in $\partial \ln \gamma/\partial C$ and viscosity, but there is another effect which deserves special attention. Once the aggregate (dimer, trimer, or micelle) is formed, the size of the diffusing particle is increased and, conse-

quently, diffusivity is decreased. Specific examples of aggregation in aqueous and nonaqueous solutions and their effects on diffusivity will be discussed in the next two sections.

The presence of materials that can interact with the diffusant will invariably result in a decrease in the diffusion coefficient. The magnitude of the decrease is related to the effective size difference of the diffusant alone and in the presence of the interactant. In general, if a 1:1 complex is formed, there will be only a slight change in D; but if a higher order interaction, such as a drug–micelle complex, is formed, there can be a very marked decrease in diffusivity. Complex and micelle formation are extremely important because of their effect on the partitioning properties of the diffusant. This effect is discussed elsewhere in this review. Specific examples of self-association and association with other solutes will be discussed in the next section.

The observed effect of temperature on diffusivity in homogeneous fluids is a combination of several factors. An increase in temperature results in an intensification of thermal motion of the diffusant. This effect of kT results in a proportional increase in D, as expected from Eq. 87. A more important effect of temperature alteration is the accompanying change in solvent viscosity. For example, a temperature increase from 20 to 30° results in a viscosity change from 1.002 to 0.7975 cps for water (124). This 20% change is much greater than the 3.4% change in the value of kT. A temperature increase could also have an indirect effect on diffusivity by virtue of its structure-breaking effect on complexes and micelles and its effects on molecular activity coefficients. If these indirect effects are small and the effects of temperature are only those predicted by Eqs. 89–94, the energy of activation for diffusion in a solvent is a constant for that solvent.

Diffusivity in Aqueous Solutions—The aqueous diffusivities calculated for some common substrates by Eqs. 93 and 94 which become:

$$D = \frac{4.95 \times 10^{-6}}{v^{1/3}} \qquad \text{(Eq. 97)}$$

and:

$$D = \frac{3.3 \times 10^{-6}}{v^{1/3}F} \qquad \text{(Eq. 98)}$$

in water at 25°, and the partial molar volumes of Table III are listed in Table IV along with the experimentally determined values. In the case of the more nonspherical substrates, the axial ratio was estimated from space-filling molecular models, and the frictional coefficient was calculated *via* Eqs. 91 and 92.

Virtually all of the experimental values of Table IV fall between the diffusivities calculated by Eqs. 97 and 98. As would be expected from the above discussion, the smaller diffusants are better approximated by Eq. 97, whereas the larger ones approach Eq. 98. As can be seen from the table, the shape factor described by Eqs. 95 and 96 is only important for certain special cases. The effect of alkyl chain length on the diffusivity is illustrated for several series in Fig. 6. For each of the six series shown, the diffusivity decreases with chain length. For homologs con-
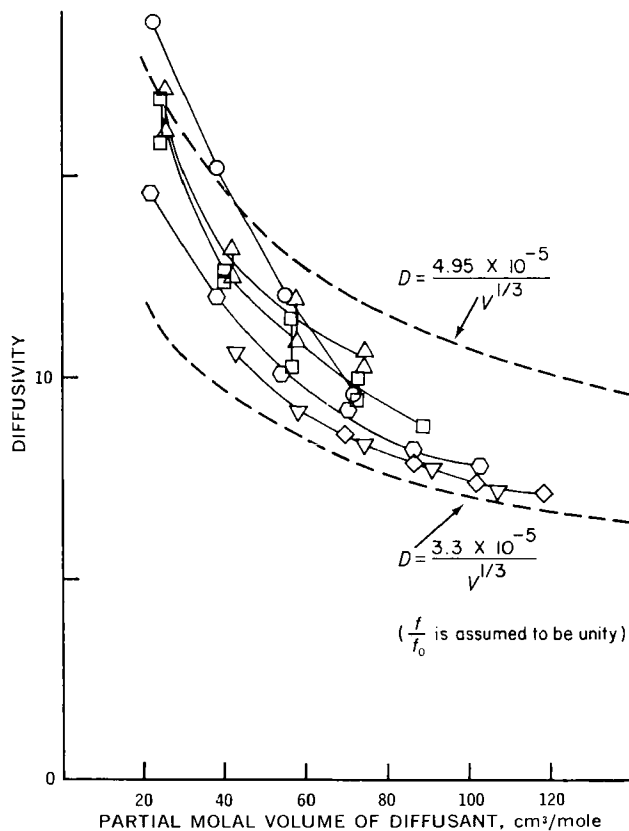

Figure 6—*Diffusivities of some simple homologous series as a function of partial molal volume. The plot indicates that polar moieties increase the hydrodynamic volume of the diffusing species, probably by forming strong hydrogen bridges to adjacent water molecules. Key: O, alkanes; □, alcohols; △, amides; ⊖, acids; ◇, diacids; and ▽, α-amino acids.*

taining four or more carbons, diffusivities are within 25% of the values calculated using Eq. 98.

As would be expected from Eqs. 97 and 98, adding a methylene group to a substance decreases the diffusivity only slightly. The larger the molecule, the more insignificant is the effect of a single methyl group. For most homologous series in a partitioning system, it is probably safe to ignore the increase in diffusivity as the series is ascended because this effect is negligible compared to the change in the partition coefficient that accompanies the chain length elongation. In general, branching tends to make the molecule more compact and thus increases diffusivity.

Horowitz and Fenichel (125, 126) compared several homologous series on the basis of diffusivity at a given molecular weight and concluded that, as a class, the alcohols diffuse more rapidly than amides which, in turn, diffuse faster than alkanes. They concluded that this behavior results primarily from the stabilized aqueous domains (icebergs) that are associated with hydrophobic molecules, the effect presumed larger in hydrocarbons than in alcohols or amides. This explanation seems unlikely because the hydrophobic surface area of a molecule such as ethane is not greatly different from that of ethanol and the latter can have additional water molecules firmly associated with it *via* hydrogen bonding. Indeed, if

Table IV—Calculated and Experimental Aqueous Diffusivities at 25°

Diffusant	Partial Molal Volume, cm³/mole	D_{calc} ($\times 10^6$) $\left(\dfrac{4.95 \times 10^{-5}}{v^{1/3}}\right)$	f/f_0	D_{calc} ($\times 10^6$) $\left(\dfrac{3.36 \times 10^{-5}}{v^{1/3}f/f_0}\right)$	D_{exper} ($\times 10^6$)	Reference
Methane	22.4	17.5	1.00	11.9	18.8	184
Ethane	38.6	14.1	1.00	9.7	15.2	184
Propane	55.2	13.0	1.01	8.6	12.1	184
Butane	71.3	11.9	1.03	7.7	9.6	184
Methanol	24.7	17.0	1.00	11.3	15.8	128
					17.0	185
					13.7	165
Ethanol	40.9	14.3	1.00	9.6	12.4	128
					12.6	185
n-Propanol	57.1	12.8	1.01	8.5	10.2	128
					11.5	185
n-Butanol	73.3	11.8	1.03	7.6	9.5	128
					11.0	185
n-Pentanol	89.5	11.0	1.05	7.0	8.8	165
Isopropanol	57.1	12.8	1.00	8.6	10.2	128
					10.7	185
Isobutanol	73.3	11.8	1.01	7.8	9.3	128
sec-Butanol	73.3	11.8	1.00	7.9	9.2	128
tert-Butanol	73.3	11.8	1.00	7.9	8.8	128
					9.8	185
Formamide	26.0	16.7	1.00	11.1	17.2	185
Acetamide	42.2	14.2	1.00	9.5	13.2	185
Propionamide	58.4	12.7	1.03	8.3	12.0	185
Butyramide	74.6	11.7	1.05	7.5	10.7	185
Isobutyramide	74.6	11.7	1.03	7.6	10.2	185
Formic acid	22.1	17.6	1.00	11.7	14.6	127
Acetic acid	38.3	14.7	1.00	9.8	12.0	127
Propanoic acid	54.5	13.0	1.00	8.7	10.1	127
Butyric acid	70.9	12.0	1.07	7.9	9.2	127
Pentanoic acid	86.9	11.2	1.03	7.2	8.2	127
Hexanoic acid	103.1	10.6	1.05	6.7	7.8	127
Isobutyric acid	70.7	12.0	1.00	8.0	9.5	127
Isopentanoic acid	86.9	11.1	1.00	7.4	8.2	127
Chloroacetic acid			1.00		10.0	127
Hydroxyacetic acid	40.5	14.4	1.00	9.6	9.8	127
Oxalic acid	70.4	12.0	1.00	8.0	8.6	127
Succinic acid	86.6	11.2	1.02	7.3	7.9	127
Adipic acid	102.8	10.6	1.03	6.9	7.4	127
α,ω-Octanedioic acid	119.0	10.0	1.05	6.4	7.1	127
Pyridine	65.8	12.2	1.00	8.2	11.4	3
4-Methylpyridine	82.0	11.4	1.00	7.6	10.8	3
2-Ethylpyridine	98.2	10.7	—	—	9.8	3
4-Ethylpyridine	98.2	10.7	—	—	10.0	3
2-Propylpyridine	114.4	10.2	—	—	8.8	3
4-Propylpyridine	114.4	10.2	—	—	10.0	3
4-tert-Butylpyridine	130.6	9.7	—	—	9.2	3
4-n-Amylpyridine	46.8	9.4	—	—	9.5	3
Glycine	42.9	14.1	1.00	9.4	10.6	128
α-Alanine	59.1	12.7	1.00	8.4	9.1	128
β-Alanine	59.1	12.7	1.00	8.4	9.3	128
α-Aminobutyric acid	75.1	11.7	1.02	7.6	8.3	128
α-Aminopentanoic acid (norvaline)	91.5	11.0	1.03	7.1	7.7	128
α-Aminohexanoic acid (norleucine)	107.7	10.4	1.05	6.6	7.2	128
α-Aminoisobutyric acid	75.1	11.7	1.00	7.8	8.1	128
α-Aminoisopentanoic acid (valine)	91.5	11.0	1.02	7.2	7.7	128
α-Aminoisohexanoic acid (leucine)	107.7	10.4	1.03	6.7	7.3	128
Sererie	60.8	12.5	—	—	8.8	128
Threonine	76.9	11.6	—	—	8.0	128
Asparagine	78.0	11.3	—	—	8.3	128
Proline	81.0	11.4	—	—	8.8	128
Hydroxyproline	89.0	11.3	—	—	8.3	128
Histadine		10.7	—	—	7.3	128
Phenylalanine		10.0	—	—	7.0	128
Tryptophan		9.4	—	—	6.6	128
Sodium lauryl sulfate	235	8.1	1.07	5.0	6.2	135
Dimethyldodecylamine oxide	243	7.9	1.07	4.9	5.7	135
Dodecylbenzenesulfonate	293	7.4	1.10	4.5	6.1	140
Glucose	116[a]	10.1	1.63	6.6	6.8	110
Cellobiose	222[a]	8.3	1.00	5.2	5.2	110
Triose	326[a]	7.2	1.07	4.5	4.2	110
Tetrose	432[a]	6.5	1.09	4.0	3.8	110
Pentose	535[a]	6.1	1.19	3.4	3.2	110
Hexose	639[a]	5.7	1.24	3.1	2.9	110
α-Cyclodextrin	1090[b]	4.8	1.03	3.1	3.4	157
β-Cyclodextrin	1235[b]	4.6	1.04	3.0	3.4	157
					3.2	128

[a] Author's values. [b] From dimensions given in Ref. 15 for overall molecule including hole.

the diffusivities are compared on the basis of molecular volume rather than on molecular weight, a totally opposite conclusion is reached.

When diffusivities are compared on the basis of volume (as in Fig. 6), the alkanes become the most rapidly diffusing materials, with the relative rates being alkanes > alcohols > amides > acids > amino acids > dicarboxylic acids. This order is what would be anticipated if "tightly" hydrogen-bonded water travels with the diffusant and thus increases its hydrodynamic volume. As expected, the effect of such hydration is proportionally lower for large molecules, and the curves appear to merge at volumes greater than 100 cm^3/mole.

Albery et al. (127) showed that there is no significant difference between the diffusivities of nine carboxylic free acids and their anions (Table IV). However, their data for ω-dicarboxylic acids indicate a 5% decrease in diffusivity on complete ionization. This decrease is consistent with the expected repulsion of the negative charges of the dianion which results in a more fully stretched out structure. It is also possible that the di-free acids can form intramolecular hydrogen bonds, which would result in a more compact and possibly less hydrated cyclic structure.

Longsworth (128) compared the diffusivities of zwitterionic glycine and neutral glycolamide which have the same molecular formula. Due to a greater degree of solvation of the former, its diffusivity is nearly 10% less than that of the neutral compound. Wendt and Gosting (129) obtained similar results with alanine and its isomer lactamide. Likewise, Longsworth's data for the diffusion of ortho-, meta-, and para-aminobenzoates show that the diffusivity of the meta-compound, which exists as a zwitterion, is significantly less than the values obtained for the ortho- and para-isomers, which exist in solution as neutral molecules. The fact that the more slowly diffusing species of each of the two above sets of isomers interact more strongly with water is evidenced by their higher degree of electrostriction (increase in the density of neighboring solvent molecules) (130, 131).

Since most aqueous solutions show a negative deviation from Henry's law, the observed diffusivity usually decreases as solute concentration increases. This decrease is frequently enhanced by the increased viscosity that usually accompanies increased solute concentration. Certain compounds such as sucrose for which $\partial \ln \gamma/\partial C$ is positive show a decrease in diffusivity with increasing concentration because of the resultant increase in viscosity (131). In general, however, diffusivities determined at concentrations below 0.10 M are within a few percent of values determined by extrapolation to infinite dilution.

Surfactants such as sodium lauryl sulfate, which tend to form large micelles in aqueous solution, have diffusivities that are highly dependent upon concentration. Below the critical micelle concentration (CMC), the diffusivity of the monomer, D, is essentially independent of concentration. At the CMC, the apparent diffusivity begins to decrease as mi-

celles are formed; at concentrations significantly greater than the CMC, where the number of monomers is negligible compared to the number of micellar surfactant molecules, the diffusivity begins to level off. If the apparent diffusivity, D_{app}, is plotted against reciprocal surfactant concentration, the Y intercept (reciprocal concentration equal to zero) is the diffusivity of the micelle, D_M, in the absence of monomer. This type of plot can be used to determine the CMC from diffusion coefficient data. According to the Stokes–Einstein equation, the ratio of D_M to D is proportional to the cube root of the volume ratio (assuming no shape correction for either monomer or micelle). In the absence of any significant differences in the degree of hydration of monomer and micelle, the volume ratio is equal to the aggregation number, n, of the micelle. Therefore, the diffusivities of micelles and monomer are related by:

$$D_M = r^{1/3}D \qquad \text{(Eq. 99)}$$

Deviations from this relationship have been used (132–134) to estimate various properties of micelles.

A substance that is not surface active can become associated with a surfactant micelle and thereby acquire the hydrodynamic properties of the micelle. This is possible for highly polar diffusants, such as cadmium ions, which are adsorbed on the micelle surface of nonionic surfactants (135) or for nonpolar materials such as testosterone (136), hydrocortisone (137), salicylamide (138), and salicylic and benzoic acids (139), which are incorporated within the micelle, and even for surfactants interacting with oppositely charged surfactants to form mixed micelles (140).

As stated previously, in a homogeneous liquid such as water the effect of temperature upon diffusivity can usually be calculated from Eq. 87. Longsworth (141) found that the ratios of 25° diffusivity to 1° diffusivity of 21 compounds varied between 2.049 and 2.178, in excellent agreement with the calculated value of 2.107. Similar results were obtained by other workers (113, 142) for a variety of solutes. The energies of activation calculated from aqueous diffusion data are generally between 4.5 and 5.0 kcal/mole. As expected from previous discussions, these values are in good agreement with the value of 4.2 kcal for viscous flow of water.

Diffusivity in Nonaqueous Solutions—Ideally the only difference between diffusivities of a substance in various solvents is due to the different viscosities of the solvents. In practice, however, this is not the case. A large solute such as benzoic acid, whose frictional resistance in water is described by Eq. 89, might be of comparable size to solvent molecules of carbon tetrachloride or benzene and thus its frictional resistance would be described by Eq. 90 in these solvents. Also, interactions that can occur in one solvent may not be significant in another. There are a number of compilations of diffusion coefficient data for many nonaqueous solvents (102, 104, 143) as well as a number of semiempirical methods of calculating D in terms of solvent and solute properties (102–105).

Table V—Diffusivities in Chloroform from Longsworth (143) at 25°

Diffusant	Partial Molal Volume, cm³/mole	D_{calc} (× 10⁶) $\left(\dfrac{4.95 \times 10^{-5}}{v^{1/3}}\right)$	f/f_0	D_{calc} (× 10⁶) $\left(\dfrac{3.36 \times 10^{-5}}{v^{1/3}f/f_0}\right)$	D_{exper} (× 10⁶)
Pentane	87	11.2	1.05	7.1	15.7
Hexane	103	10.5	1.06	6.6	15.0
Heptane	120	10.0	1.07	6.2	13.5
Octane	136	9.6	1.08	5.9	12.6
Decane	168	9.0	1.10	5.5	10.8
Dodecane	201	8.5	1.14	5.0	9.5
Hexadecane	265	7.8	1.22	4.3	7.8
Octadecane	297	7.4	1.25	4.0	6.9
Ercosane	330	7.1	1.27	3.7	6.6
Docosane	362	7.0	1.33	3.5	6.2
Octacosane	459	6.4	1.37	3.1	5.3
Dotriacontane	525	6.1	1.35	2.9	4.8
Methanol	25	16.9	1.00	11.3	26.1
Tetramer	100	10.7	1.00	7.1	11.3 0.2 M
Ethanol	35	15.1	1.00	10.1	19.5
Tetramer	100	9.5	1.00	6.4	7.9 0.5 M
Hexadecanol	268	7.8	1.22	4.3	7.4 Dilute
Tetramer	1072	4.9	1.00	3.2	3.7 0.4 M
Acetic acid	32	15.7	1.00	10.4	. . .
Dimer	64	12.4	1.05	7.9	14.2
Hexadecanoic acid	265	7.8	1.22	4.3	. . .
Dimer	530	6.1	1.31	2.9	4.5

Because we are primarily interested in diffusion through water or through membranes, the discussions will be confined to a single nonaqueous solvent, carbon tetrachloride. This solvent has been studied extensively and serves as a model nonpolar phase in which the aggregation behavior of polar solutes can be illustrated. The interactions which occur in carbon tetrachloride likely also occur in nonpolar membranes.

Table V shows the diffusivities obtained by Longsworth (143) for several substances in carbon tetrachloride, along with the values calculated by Eqs. 93 and 94 (coincidentally, carbon tetrachloride and water have nearly the same viscosity at 25° so that Eqs. 97 and 98 can be used directly). Because of the large molecular size of carbon tetrachloride ($V = 315$ cm³/mole) compared to water ($V = 18$ cm³/mole), the diffusivities of solutes whose volume is significantly less than 315 cm³/mole are not adequately described by either of these equations. Solutes of sizes comparable to that of carbon tetrachloride appear to be described by Eq. 93 to a satisfactory extent, and larger solutes have diffusivities between the value expected from Eqs. 93 and 94. Interactions between polar functional groups are extremely important in nonpolar solvents such as carbon tetrachloride or benzene. This is illustrated by some data in Table V. Hexadecanoic acid has nearly the same molar volume as hexadecane, yet, because it exists as a dimer in carbon tetrachloride, its diffusivity is similar to that of dotriconatane, a 32-carbon alkane. Because of the large dimerization constant of organic acids in nonpolar solvents, Longsworth (143) was unable to determine experimentally the diffusivity of the monomeric acid. The constancy of D with concentration suggests that no higher order aggregates of the acids are formed. This is in agreement with the spectral and partitioning data of Aveyard and Mitchell (144). Alcohols, on the other hand, have much smaller association constants, and Longsworth

was able to illustrate dramatic concentration dependencies. The values he obtained for high concentration of hexadecanol suggest that tetramers and possibly higher order aggregates can be formed. This is again in agreement with spectral and partitioning data (145).

Gels—A gel consists of a complex three-dimensional network of polymeric material which imparts rigidity to the phase. The degree of solution structuring and, hence, the solution viscosity is dependent upon the chain length and the degree of cross-linking of the polymer. The presence of the gel substance can modify the observed diffusivity by either interacting with and adsorbing the diffusant on its surface or by mechanically blocking the path of the permeant. Highly concentrated gels can behave as a filter and show diffusional specificity on the basis of diffusant size. The case in which the gel is sufficiently concentrated to act as a filter will be treated in the next section as a porous barrier. In this and the next section, only aqueous gels and aqueous pores will be discussed. The discussion, however, can be applied directly to other systems.

Since in gelatinous and porous media the diffusion occurs only in the fluid phase, the relationship between diffusivity and the other parameters discussed for pure liquid phases are generally applicable. This and the following section will be concerned only with the alteration in diffusivity produced by the presence of the solid phase. The case in which the solid phase is also permeable to the diffusant can be treated as a parallel pathway in accordance with the principles described previously.

The mechanical blockage of diffusion in polymer solutions (obstruction effect) is related to the volume fraction of polymer and not to the degree of polymerization or cross-linking of the polymer. The latter parameters affect only bulk viscosity and not microscopic viscosity, *i.e.*, the viscosity of the entrapped fluid phase. Since the solute travels primarily

through the fluid phase and collides with individual polymer segments, the microscopic viscosity and the number of polymer segments present determine diffusivity. The lack of importance of bulk viscosity was verified by Taft and Malm (146), who showed that the diffusivity of salts through aqueous gelatin solutions before and after setting is unchanged. Lauffer (147) showed, by electrical analogy, that for randomly oriented long thin rods:

$$D_g = \frac{D_w}{1 - \frac{2}{3}\phi} \qquad \text{(Eq. 100)}$$

where D_w and D_g are the diffusion coefficients of the small solute in water and in an aqueous gel containing volume fraction, ϕ, of polymer, respectively. The effect of increasing diffusant size in a polymer solution over and above the effect of size on D_w is slightly to increase the collision diameter and thus the likelihood of an interaction between diffusant and polymer. In other words, small diffusants will be less affected by the presence of polymeric material than large ones.

If the effect of the polymer is strictly mechanical, there should be no specific structural effects (other than size as already mentioned); *i.e.*, polar and nonpolar molecules of the same size should be affected to the same extent. Horowitz and Fenichel (125) determined the diffusivities of a variety of solutes in an aqueous dextran gel. As would be expected from Eq. 100, they found that the ratio of diffusivities in water and in gel to be nearly independent of temperature and of solute size and polarity. Since the gels that they used contained 18.3 ± 0.9% dextran, the expected ratio based on Eq. 100 is 0.82. Their observed ratios of 0.65 ± 0.05 can be explained if it is assumed that about two volumes of water are associated with, or in some way immobilized by, each volume of polymer. This is consistent with the results of Friedman (148) for several nonelectrolytes in gelatin and agar gels, of Langdon and Thomas (149) for anion diffusion, and of Nakayama and Jackson (150) for water self-diffusion in agar gels, who found 3.4 and 3.6 g water immobilized/g dry gel. The amount of immobilized water is diminished at high salt concentration where hydration is reduced.

In addition to decreasing diffusivity by obstructing the permeant's path, a gel can decrease diffusivity by interacting with or adsorbing the diffusant. The adsorption of the diffusant onto the gel substance tends to retard diffusion in much the same way as the passage of a sample along a chromatographic column is slowed by adsorption onto the column. As in the case of the obstruction effect, the adsorption effect is dependent upon the volume fraction, ϕ, of polymer present and not on the viscosity of the solution. If K is the adsorption constant of the diffusant per unit volume of gel, and conditions are such that the gel is not saturated with diffusant, the diffusivity in the presence of an adsorbing polymer, $D_P{}^{\text{ads}}$, is given by (151):

$$D_P{}^{\text{ads}} = \frac{D_w}{1 + K\phi} \qquad \text{(Eq. 101)}$$

For the case in which the gel becomes saturated with diffusant:

$$D_P{}^{\text{ads}} = \frac{D_w}{1 + \frac{K\phi}{k}} \qquad \text{(Eq. 102)}$$

where k is a constant.

Unlike the obstruction effect, the adsorption effect is strongly dependent upon the chemical nature of the diffusant. The value of K is dependent upon the number of adsorptive sites for a given diffusant per unit volume of polymer and on the relative degree of solute attraction of the solvent and the adsorptive sites. In general, the number of sites available to a particular solute depends upon the solute's polar functional groups. For example, a particular polymer might have more sites that are capable of interacting with carboxylates than sites that can bind amines.

For a particular polymer and a series of compounds having the same functional groups (such as a homologous series), the value of K for each member will usually depend upon the solubility of that compound. Therefore, since solubility usually decreases exponentially with chain length (80), the value of K would be expected to increase exponentially as the series is ascended.

If the increase in diffusivity is the result of adsorption of the diffusant, it is possible to counteract this effect by the addition of a competitive adsorbent. Alhaigue *et al.* (152) showed that bovine serum albumin reduced the apparent diffusivity of chloramphenicol significantly and that it was possible to return the diffusivity nearly to its aqueous value by the addition of submicellar amounts of sodium lauryl sulfate.

Pores and Their Influence—As already mentioned, there is no clearcut distinction between diffusion through a dense gel and through a highly porous phase. In either case, when the regions available for diffusion are very large compared to the molecular dimensions of the diffusing species, the previous discussion can be applied directly. However, when ϕ is large, it is frequently more meaningful to characterize the membrane by its porosity, $\epsilon = 1 - \phi$, and a tortuosity factor, τ, as described previously. This section deals with the case in which the diffusing particle diameter approaches the pore diameter and free diffusion can no longer occur. While the discussion will be directed specifically to uniform right circular pores and to dense gels, the principles involved are more generally applicable.

It has been repeatedly observed that the flux of a solute through a small aqueous pore is less than the value calculated from the solute's aqueous diffusivity and the geometry of the pore. The magnitude of the discrepancy between diffusivity in the pore, D_P, and in free solution, D_f, has been shown (47–49) to be related to the spherical solute radius, r_s, and the cylindrical pore radius, r_p, by:

$$\frac{D_P}{D_f} = \left(1 - \frac{r_s}{r_p}\right)^2 \left[1 - 2.104\frac{r_s}{r_p} + 2.09\left(\frac{r_s}{r_p}\right)^3 - 0.95\left(\frac{r_s}{r_p}\right)^5\right]$$

$$\text{(Eq. 103)}$$

The first portion of the Renkin (49) equation was originally proposed by Ferry (153) to account for the statistical likelihood of a particle entering a pore. The remainder of the equation was proposed by Lane and Perry (154) to represent the solvent drag on a solute molecule traversing a narrow pore. It should be noted that according to Eq. 15, $D_P \rightarrow D_f$ as $r_s/r_p \rightarrow 0$ and $D_P \rightarrow 0$ as $r_s \rightarrow r_p$. Equation 103 can be approximated successfully by:

$$\frac{D_P}{D_f} = \left(1 - \frac{r_s}{r_p}\right)^4 \qquad \text{(Eq. 104)}$$

for $r_s/r_p < 0.2$. Beck and Schultz (15) found that these equations adequately described the passage of seven solutes with diverse molecular volumes through right cylindrical pores ranging from 45 to 300 Å in diameter.

It can be seen from Eqs. 103 and 104 that large particles are slowed to a much greater extent than are small ones in their passage through narrow pores. Consequently, substances that differ only slightly in free diffusion coefficients can have D_P values that are greatly different. The technique of differential dialysis capitalizes on this principle and has been used successfully to separate substances differing by only a factor of 2 in molecular weight. It has been shown (155) that the dialysis rates of glucose and sucrose across acetylated membranes (Visking) differ by a factor of 8.6 while the free diffusivities of these sugars differ by only a factor of 1.29. This and other examples of size segregation by dialysis membranes were reviewed (155, 156).

For nonspherical particles, some choice must be exercised in obtaining a value for r_s. Gary-Bobo *et al.* (157) stated that the minimum cross-sectional radius gives better correlation than the equivalent spherical radius $(3r/4\pi)^{1/3}$ for permeation through dense cellulosic membranes. Certainly, in systems that involve bulk flow of solvent, the diffusants can be expected to have a preferential orientation in the direction of flow. But in the absence of bulk flow, where the particles are randomly oriented, it is difficult to justify the use of the cylindrical radius over the equivalent spherical radius. The data (155, 156) for the passage of linear oligosaccharides across acetylated membranes (Visking) show much better correlation with spherical radius than minimum cylindrical radii. Craig and Pulley (155) also found similar dialysis rates for a linear hexose and a cyclohexose, which have very different minimum radii.

This relationship among pore radius, solute radius, and solute diffusivity enabled Solomon and his coworkers (158-160) to calculate an "equivalent pore radius" for a biological membrane. From the diffusivities of several solutes, they calculated an equivalent pore radius of 3.5-4.5 Å for erythrocyte membranes. Similarly, Stein (123) showed that several other biological barriers have equivalent pore radii between 4 and 6 Å. Interestingly, Solomon and Gary-Bobo (158) showed that lipid bilayers, treated with nystatin or amphotericin, also have equivalent pores between 4 and 6 Å in radius.

The validity of the equivalent radius calculation is strictly dependent on the assumption that all solutes permeate only through aqueous pores. It is inappropriate to discuss such a radius for a solute having any reasonable degree of hydrophobicity; consequently, the equivalent pore is of limited value in understanding the permeation of most drug molecules. Additionally, most drugs have radii similar to or greater than the equivalent pore radii of biological barriers and thus are incapable of pore transport.

Diffusivity in Amorphous Isotropic Polymers (Above T_g)—In polymers, it is not possible to relate diffusivity to molecular size by a simple theoretically valid equation such as Eqs. 93 and 94. Although there is a good deal of data available for diffusion coefficients in polymers, the theory is not sufficiently developed to provide a complete theoretical model. Several theoretical and empirical relationships have been developed (161-164) and are of value in certain instances. One major obstacle to quantitating diffusivity in polymers is the inability to describe adequately viscosity for a solid or semisolid. For this reason, most theories must rely upon free volume approaches. These theories emphasize the spaces within the polymer which are available for diffusion of a particle rather than the frictional resistance that the particle experiences. The available data are more consistent with the free volume approach than with a frictional resistance or viscosity approach.

In general, diffusivity in polymers is more sensitive to molecular size (or molecular weight) than in homogeneous liquids. In most polymers, it is possible to relate log D empirically to some function of molecular size. One commonly used relationship is:

$$\log D = -s_v \log v + k_v = -s_M \log M + k_M \qquad \text{(Eq. 105)}$$

where M is molecular weight; v is molecular volume; and s_v, s_M, k_v, and k_M are constants. Whereas s_v in fluid media is a constant equal to one-third [some workers (123, 164) allow s_M to vary between one-third and one-half], s_v can be as high as 4 for polymers (93, 164). Another frequently used relationship is:

$$\log D = -p_v(v) + q_v = -p_M(M) + q_M \qquad \text{(Eq. 106)}$$

where the p's and q's are constants for a particular polymer. Stein and Nir (165) prefer the latter equation because it can be justified on theoretical grounds. However, they also point out the fact that for small variations in molecular size the equations are mathematically similar.

In polymers the value of D is much more sensitive to molecular shape than in liquids. In a liquid, diffusivity decreases with deviation from a spherical shape (*cf.*, Eqs. 95 and 96); in polymers, a sphere usually has a much lower diffusion coefficient than an ellipsoid of the same volume. The chemical nature of the diffusant is of secondary importance to its size and shape for diffusion in nonpolar polymers. Functional groups become important in the situations where interaction can produce an aggregate whose geometry differs significantly from that of the monomer and where there is interaction with fixed sites on filler surfaces.

Table VI—Diffusivities of Alkanes in Some Polymers

Diffusant	Polyisobutylene ($D \times 10^9$)	Natural Rubber 40° ($D \times 10^7$)	Linear Polyethylene 25°	Ethylcellulose 50° ($D \times 10^9$)	Silicone Rubber 50° ($D \times 10^6$)
Methane	—	14.5 (171)	—	—	—
Ethane	—	5.47 (171)	—	—	—
Propane	4.8 (173)	3.4 (171)	—	—	—
n-Butane	3.2 (173)	4.3 (172)	—	11.8 (178)	8.5 (178)
		3.4 (171)	—	—	—
Isobutane	1.5 (173)	2.8 (172)	—	2.1 (178)	7.7 (178)
n-Pentane	2.6 (173)	4.2 (172)	—	5.6 (178)	6.9 (178)
Isopentane	1.3 (173)	2.3 (172)	—	—	—
Neopentane	0.6 (173)	1.4 (172)	—	2.2 (178)	4.3 (178)
n-Hexane	—	—	4.4 (177)	—	—
Isohexane	—	—	2.4 (177)	—	—
3-Methylpentane	—	—	2.4 (177)	—	—
Neohexane	—	—	0.7 (177)	—	—
Cyclohexane	—	—	2.3 (177)	—	—
n-Heptane	3.0 (174)	—	—	—	—
n-Octane	—	—	1.8 (177)	—	—
n-Decane	—	—	0.7 (177)	—	—

The vast majority of studies of the diffusivity of a series of permeants through a polymer involve either gases or normal and branched paraffins. The gases provide a means of studying the effect of size without significantly altering diffusant shape. With the linear paraffins, it is possible to change only one dimension of the permeant while keeping its cross-sectional area constant. The isomeric paraffins enable one to keep volume constant and to study the effects of altering diffusant shape. Most studies using gases show good fit to equations of the form of Eq. 105 or, more often, Eq. 106.

The importance of shape on diffusion in polymers is illustrated by the many studies (93, 161, 166–179) on diffusion of normal isomeric alkane vapors in various polymers. The following general trend in diffusivities is observed (see Table VI): methyl > ethyl > propyl ≥ butyl ≥ pentyl ≥ octyl > isobutyl ≥ isopentyl > neopentyl. In other words, after a minimum chain length is reached (propyl), the addition of a methyl group to extend a linear chain has only a slight effect on D. However, the addition of branched methyl groups tends to reduce the diffusion coefficient significantly.

It is obvious then that neither mass nor molecular volume alone can be satisfactorily correlated with diffusivity for asymmetric solutes in polymers. Michaels and Bixler (179) found that, for purposes of correlation with Eq. 106, the square root of the ratio of molecular volume to the maximum linear dimension of the molecule can be used with satisfactory results. Another means of calculating the effective diameter, d, is to take the diameter of the smallest circle through which the molecule can pass.

The use of d instead of v is frequently less necessary when the correlation is being made by Eq. 105 rather than Eq. 106. This is because log v (or log M) is less sensitive to changes in v or M as these parameters increase. In other words, adding a methyl group to a long chain has only a small effect on log v and no effect on d.

Crank and Park (180) and Park (181, 182) found excellent correlation between log D and v for halo-methanes. In their studies, the more nonspherical haloethanes and especially the halopropanes showed significantly higher values of D than would be expected on a volume basis. The use of the effective diameter improved the correlation somewhat, but best fit was obtained by fitting log D to an empirical function of v and d.

While it is evident that the above studies cannot be described by a single correlative equation, the following generalizations appear to be prevalent in these and other systems: (a) diffusivity decreases with molecular size; (b) diffusivity becomes less sensitive to size as size is increased (this is especially true for increases in length such as accompany the extension of a homologous series); and (c) branched compounds have lower diffusivities than their linear isomers. These findings, as well as the commonly observed temperature and concentration dependencies of D, are all consistent with the free volume theory of Eyring and its many modifications. Basically, these theories relate D to the size and shape of preexisting cavities in the polymer. The partial alignment of polymer chains would result in greater number of cylindrical holes than spherical ones and, thus, can explain the observed shape dependencies of diffusivity.

The size dependencies observed presumably result from the fact that there are a larger number of holes capable of containing a small molecule than there are holes that can accommodate a large penetrant. The different values of s_v, s_M, etc., are thus the result of different distributions of hole sizes in different polymers. A complete detailed discussion of the commonly used free volume theories can be found in Ref. 161 (chap. 4).

In most instances of diffusion in polymers, the effect of temperature is given by an equation identical in form to Eq. 35, thus:

$$D = D_0 e^{-Ea/RT} \qquad \text{(Eq. 107)}$$

where D_0 and Ea are constants. The value of Ea, the energy of activation for diffusion, tends to increase linearly with diffusant size (178) until a plateau value which is characteristic of the polymer is

reached. This was nicely illustrated by Auerbach *et al.* (174) who showed that the energies of octadecane and hexatriconatane are nearly equal in polyisobutylene. This type of behavior was interpreted by Meares (178) as indicating that small solutes can diffuse without the complete rotation of the chain segments which is necessary for diffusion of larger penetrants. The independence of Ea from diffusant size is similar to the situation found in water and other liquids. However, Ea is much larger for polymers than for liquids. Values commonly range from 7 to 20 kcal/mole. As the temperature of an amorphous polymer is lowered below its glass transition point, crystallites begin to form. Since these crystallites are for all practical purposes unavailable for diffusion, they act as impermeable inclusions in the polymeric diffusional field.

Diffusion coefficients in polymers are almost invariably related to diffusant concentration by:

$$D = D_{c=0}e^{Ac} \qquad \text{(Eq. 108)}$$

where A is a constant at any given temperature in a particular polymer. This equation is frequently found to be valid over several orders of magnitude of D. Aitken and Barrer (171) and others observed that A is nearly constant and independent of size for most solutes. Deviations from Eq. 108 will, of course, occur if there is a tendency for the diffusant to self-associate. Certain molecules such as fatty acids and alcohols can aggregate in nonpolar membranes just as they might in nonpolar solvents. Auerbach *et al.* (174) found the following diffusivities in polyisobutylene at 100°: octadecane, 1.97×10^{-7}; octadecanol, 1.56×10^{-7}; octadecanoic acid, 0.74×10^{-7}; and octadecanoyl octadecanoate, 0.46×10^{-7} cm^2/sec. These values have been interpreted as indicating that stearic acid exists almost exclusively as a dimer in the medium. They further suggest a weak association of octadecanol.

If the diffusant is present in sufficient concentration (>1%), it can dilute or solvate the polymer, expanding and "loosening" the polymer matrix, with the swelling producing secondary effects on the permeant's diffusivity, leading to significant deviation from Eq. 108. This effect was recently discussed by Schultz and Asunmaa (183) and will not be pursued here[13].

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