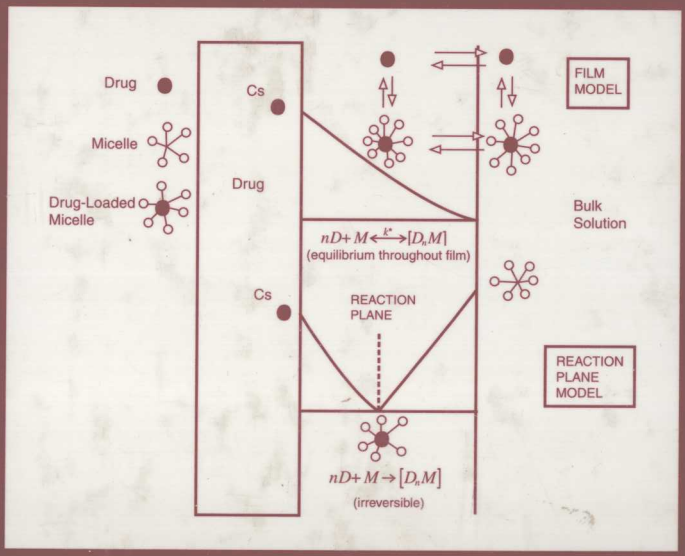
DRUGS AND THE PHARMACEUTICAL SCIENCES VOLUME 102

Transport Processes in Pharmaceutical Systems



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MARCEL DEKKER, INC. NEW YORK • BASEL

ISBN: 0-8247-6610-5

This book is printed on acid-free paper.

Headquarters
Marcel Dekker, Inc.
270 Madison Avenue, New York, NY 10016
tel: 212-696-9000; fax: 212-685-4540

Eastern Hemisphere Distribution
Marcel Dekker AG
Hutgasse 4, Postfach 812, CH-4001 Basel, Switzerland
tel: 41-61-261-8482; fax: 41-61-261-8896

World Wide Web
http://www.dekker.com

The publisher offers discounts on this book when ordered in bulk quantities. For more information, write to Special Sales/Professional Marketing at the headquarters address above.

Current printing (last digit):
10 9 8 7 6 5 4 3 2 1

PRINTED IN THE UNITED STATES OF AMERICA

Preface

A fundamental understanding of transport phenomena has become increasingly important to pharmaceutical scientists during the past 20 years. Applications range from drug and nutrient transport across cell membranes, drug dissolution and absorption across biological membranes, whole body kinetics, and drug release from polymer reservoirs and matrices to heat and mass transport associated with freeze drying and hygroscopicity. Two factors often obscure a basic understanding in this field. First is the diversity of applications, with their differing language and objectives. The second is the often blurred distinction between the transport processes and the thermodynamics and kinetics of the system under consideration. A full development of any system requires that both the thermodynamic and kinetic reaction factors, as well as the transport processes, be fully understood. It is the aim of this volume to present a unified approach such that the common basic principles involved in many applications are clearly presented.

Our purpose is to discuss those areas of transport phenomena that have direct relevance and application to the pharmaceutical sciences. The book can be divided into roughly four sections, with Part I, Chapters 1–5, presenting basic transport processes, including drug dissolution; Part II, Chapters 6–10, presenting various aspects of biological transport; Part III, Chapters 11–15, presenting transport in polymers and drug delivery systems; and Part IV, Chapters 16 and 17, presenting heat and mass transfer in freeze drying and hygroscopicity. This illustrates the breadth of coverage in this monograph.

In our courses, we cover some aspects of all topics in this book. This is appropriate for students who become involved in drug discovery and research and development. The chapters are comprehensive in covering the diversity of applications of each subject. Each section of this book could be a monograph on its own. However, with the material presented in these chapters a scientist would be able to enter the entire literature and understand current research papers.

The level of mathematics and physical chemistry required for understanding each chapter varies greatly. Chapters 3, 4, 6–9, 11, 13, and 14 require only

basic algebra and physical chemistry at an undergraduate level. However, we have attempted to minimize the actual mathematical detail. The solution to mathematical problems in this book and arising from research problems, in general, is greatly aided by the availability of sophisticated mathematical software that can handle any of the problems presented in this book on a personal computer. Students who have taken the time to learn one or more of these software packages have found them useful for handling problems in this book, as well as for much more complex problems involving numerical solutions to ordinary and partial differential equations. We encourage the use of this software but do not require it in our graduate courses.

We want to thank the authors for their contributions to this monograph. In addition, we would like to thank the following graduate students in the Department of Pharmaceutical Chemistry at the University of Kansas: Melissa Beck-Westemeyer, Jutima Boonleang, Sirirat Choosakoonkriang, Joshua Cooper, Anita Freed, Andrew Gawron, Victor Guarino, Karen Hamilton, Bradley Hanson, Susan Hovorka, Erin Hugger, Lisa Kueltzo, Brian Lobo, Antonie Rice, Sun Wei, Waree Tiyaboonnai, Christopher Wiethoff, Anne Wolka and Jerry Yang. These students helped to edit several of the chapters of this book, and their concern with clarity and attention to detail are much appreciated. Finally, in addition to individuals who have contributed chapters to this monograph, we particularly want to thank Ms. Iris Templin, whose management, follow-up, and editing made possible the successful completion of this monograph.

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Contents

1
Principles of Mass Transfer

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I. INTRODUCTION TO MASS TRANSFER

Mass transfer is the movement of the molecules of a fluid in space in response to applied driving forces. This chapter describes the fundamental principles on which mass transfer theory is based. The chapter begins by describing the thermodynamic basis for mass transfer, together with an approach to posing and solving mass transfer problems (Sections I.A and I.B). Diffusion and convection are then defined, and the theories and models used to describe diffusive (Section III) and convective (Section II) mass transfer are presented. Finally, the effects of multiple driving forces on mass transfer are discussed (Section IV). This discussion includes information on combined convection and diffusion, on the influences of electrical potential gradients, and on combined heat and mass transfer. The chapter is intended to be an overview of fundamental principles that will be assumed in subsequent chapters. To that end, references to the later chapters are provided whenever possible, a glossary of common terms in mass transfer is included (Section VI), and references to recommended texts are provided (Section VII).

A. Thermodynamic Basis for Mass Transfer

Mass transfer is a kinetic process, occurring in systems that are not at equilibrium. To understand mass transfer from a thermodynamic perspective, consider the isolated system shown in Figure 1. The system is bounded by an impermeable insulating wall which prevents the transfer of matter, heat, or mechanical energy between the system and the external environment. The system is subdivided into

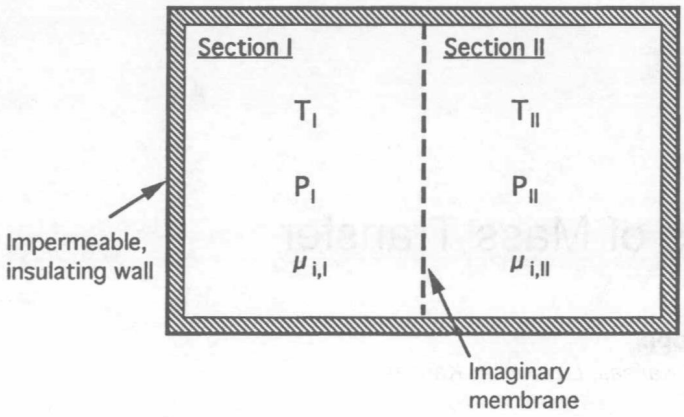

Figure 1 Isolated system consisting of two sections separated by an imaginary permeable membrane. At equilibrium, the temperatures (T), pressures (P), and chemical potentials of each species i (μ_i) are equal in the two sections.

two sections of equal volume, labeled I and II. The sections are separated by an imaginary membrane, indicated by the dashed line, which is completely permissive to the transfer of mass, heat, and mechanical energy. Thermodynamics assures us that the following conditions are both necessary and sufficient for section I to be in equilibrium with section II: (1) their temperatures are equal ($T_I = T_{II}$), (2) their pressures are equal ($P_I = P_{II}$), and (3) the chemical potentials of the species present are equal ($\mu_{i,I} = \mu_{i,II}$ for all species i).

If this isolated system is unperturbed, it will remain at this thermodynamic equilibrium indefinitely. Consider now a particular hypothetical perturbation of the system away from this equilibrium condition, in which the pressure in section I is increased (so that $P_I > P_{II}$) while the temperatures and all chemical potentials remain equal in the two sections. Thermodynamics asserts that as a result of this perturbation the system will change in an attempt to establish a new equilibrium condition. This can happen in a number of ways, through changes in any or all of the variables shown in Figure 1. However, one of the simplest changes that can be imagined is the re-equilibration of the two pressures P_I and P_{II}, with no change in the values of the temperatures or chemical potentials. If the imaginary membrane is fully permeable to the fluids in the system, the re-equilibration of the pressures will occur through the flow of fluid from section I to section II, which will continue until the values of P_I and P_{II} are again equal. This flow of fluid in response to a spatial gradient in pressure is called *convection.*

Similarly, the system can be perturbed from equilibrium by altering the

equality of chemical potentials. Suppose that the chemical potential of one of the species, A, is now increased in section I, so that $\mu_{A,I} > \mu_{A,II}$. Recall that the chemical potential of A is related to its concentration, the ideality of the solution, and the temperature, so that this perturbation may occur, for example, by increasing the concentration of A in section I. Again, the system will change in order to establish a new equilibrium, and again, one of the simplest changes that can be imagined is the re-equilibration of the chemical potentials of species A, with no change in the other variables. If the imaginary membrane is permeable to species A, the re-equilibration will occur through the movement of A from section I to section II, which will continue until the chemical potentials are again equal. In this case, the movement occurs as a result of the random, thermally induced Brownian motion of the molecules of A, since there is no gradient in pressure to cause bulk flow of the fluid. An analogous process will occur in a box containing black and white marbles, initially segregated by a vertical divider, when the divider is removed and the box is shaken vigorously. This movement of mass in response to a spatial gradient in chemical potential, and as the result of the random thermal motion of molecules, is called *diffusion.*

B. The Systems Approach to Mass Transfer Problems

The theories that have been developed to describe mass transfer arise from the law of conservation of mass, which states that mass can be neither created nor destroyed. According to this law, the total mass in a particular region in space can increase only by the addition of mass from the surroundings and can decrease only by the loss of mass back to them. Processes such as radioisotope decay and nuclear fission are exceptions to this law, since they involve the interconversion of matter and energy. In the absence of nuclear decay, however, the law of conservation of mass holds and is broadly applicable to mass transfer problems.

In order to apply this law, the "region in space" must be defined carefully and specifically for the problem of interest. In the discussion that follows, this carefully defined region in space will be called the *system.* While the definition of the system is subject to a degree of investigator discretion, a judicious choice often can simplify a seemingly complex problem. Generally speaking, the system should be selected so that it is a single-phase, homogeneous region with well-defined boundaries and (if possible) spatially invariant physical properties. For example, in describing mass transfer in a chromatographic column, the system might be defined as the fluid in the column, excluding the solid packing material and the column walls.

When the system has been defined, an equation can be written to state the law of conservation of mass. Such a "total mass balance equation" can be given in verbal form as

$$\begin{array}{l}\text{Rate of change}\\ \text{of total mass in}\\ \text{the system}\end{array} = \begin{array}{l}\text{Rate of mass}\\ \text{gain from}\\ \text{surroundings}\end{array} - \begin{array}{l}\text{Rate of mass}\\ \text{loss to}\\ \text{surroundings}\end{array} \qquad (1)$$

Note that the equation includes rates of gain and loss rather than total amounts. As a result, the mathematical form will be a differential equation rather than an algebraic one. The differential form is preferred in almost all mass transfer problems, because variations in the rates with position and time can be incorporated accurately. Each term in the equation will take on a specific functional form depending on the parameters and mass transfer characteristics of the problem of interest.

In addition to the total mass balance, equations can be written to describe changes in each of the individual chemical species, or "components," that are present. As with the total mass, the mass of a component can be altered by exchange with the surroundings. However, it can also be affected by chemical reactions occurring within the system, converting one component to another. The total mass of the system is not affected by such interconversions, since the mass of reactants consumed is exactly equal to the mass of products formed. In verbal form, the "component mass balance" for a particular component A in the system is

$$\begin{array}{l}\text{Rate of change}\\ \text{of mass A}\\ \text{in the system}\end{array} = \begin{array}{l}\text{Rate of gain}\\ \text{of A from}\\ \text{surroundings}\end{array} - \begin{array}{l}\text{Rate of loss}\\ \text{of A to}\\ \text{surroundings}\end{array} \pm \begin{array}{l}\text{Rate of gain}\\ \text{or loss of A}\\ \text{by reaction}\end{array} \qquad (2)$$

Note that in the component mass balance the kinetic rate laws relating reaction rate to species concentrations become important and must be specified. As with the total mass balance, the specific form of each term will vary from one mass transfer problem to the next. A complete description of the behavior of a system with n components includes a total mass balance and $n - 1$ component mass balances, since the total mass balance is the sum of the individual component mass balances. The solution of this set of equations provides relationships between the dependent variables (usually masses or concentrations) and the independent variables (usually time and/or spatial position) in the particular problem. Further manipulation of the results may also be necessary, since the natural dependent variable in the problem is not always of the greatest interest. For example, in describing drug diffusion in polymer membranes, the concentration of the drug within the membrane is the natural dependent variable, while the cumulative mass transported across the membrane is often of greater interest and can be derived from the concentration.

In many problems, the system ultimately will reach a time-invariant state in which the total mass and/or the masses of the components are no longer changing. This condition is called the *steady state*. In mass transfer problems, the math-

ematical condition for the steady state is that all derivatives with respect to time are equal to zero. This is a fairly restrictive definition of the steady state. Oscillatory steady states, in which the dependent variable changes in a periodic manner with constant frequency and amplitude, are allowed in fields such as clinical pharmacokinetics (e.g., oral dosing to steady state) and electrical engineering. The simpler "zero time derivatives" definition is sufficient for most mass transfer problems, however. Steady-state solutions to mass transfer problems can be obtained by solving the set of differential equations when time derivatives are set equal to zero. This simplifies the mathematics considerably, in many cases reducing ordinary differential equations (ODEs) to algebraic ones, and partial differential equations to ODEs. While these steady-state solutions contain no information about the dynamics of the system, they often provide useful information about its long-term, steady behavior.

Solving mass transfer problems can be of great practical value to pharmaceutical scientists. At the simplest level, the solutions can describe experimental data in terms of fundamental material properties. In many cases, the numerical values of the material properties can then be calculated. For example, for the membrane transport problem described above, the solution of a mass transfer problem allows the investigator to relate the experimentally measured permeability of the membrane to the diffusion and partition coefficients, fundamental material properties of the system. On a more basic level, solving mass transfer problems enables the investigator to develop predictive models of system behavior in the absence of data. These can then be used as a theoretical guide to the design of experiments, identifying important parameters and their probable relationships.

The remaining sections of this chapter provide examples of mass transfer models, presented using the systems approach described above. In many cases, the models are of such importance that they are regarded as theories in their own right. These basic models are also the foundation for the more specific applications in the subsequent chapters of this book.

II. CONVECTION

Convection is mass transfer that is driven by a spatial gradient in pressure. This section presents two simple models for convective mass transfer: the stirred tank model (Section II.A) and the plug flow model (Section II.B). In these models, the pressure gradient appears implicitly as a spatially invariant fluid velocity or volumetric flow rate. However, in more complex problems, it is sometimes necessary to develop an explicit relationship between fluid velocity and pressure gradients. Section II.C describes the methods that are used to develop these relationships.

A. Stirred Tank Models

One of the simplest models for convective mass transfer is the stirred tank model, also called the continuously stirred tank reactor (CSTR) or the mixing tank. The model is shown schematically in Figure 2. As shown in the figure, a fluid stream enters a filled vessel that is stirred with an impeller, then exits the vessel through an outlet port. The stirred tank represents an idealization of mixing behavior in convective systems, in which incoming fluid streams are instantly and completely mixed with the system contents. To illustrate this, consider the case in which the inlet stream contains a water-miscible blue dye and the tank is initially filled with pure water. At time zero, the inlet valve is opened, allowing the dye to enter the

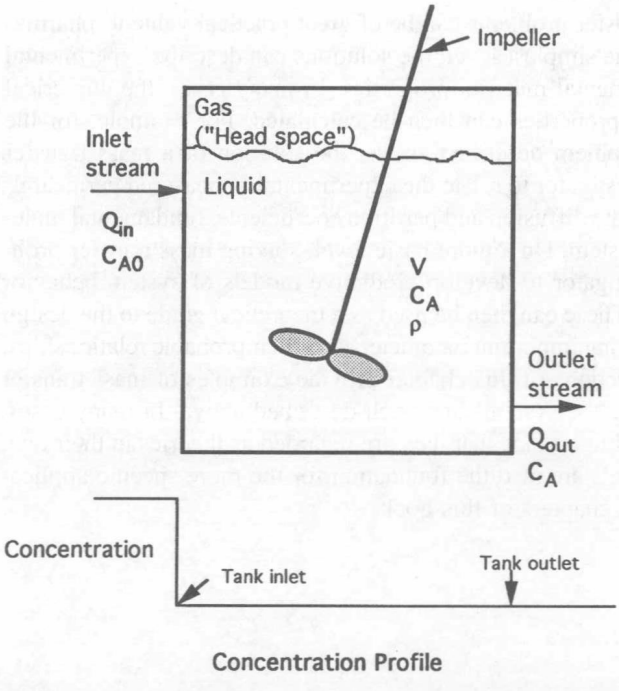

Figure 2 The stirred tank, a simple model for convective mass transfer. The liquid in the tank is characterized by its volume (V), density (ρ), and the concentrations of the components (C_A). Liquid enters through the inlet stream at a flow rate Q_{in} and concentration C_{A0}. Liquid exits through the outlet stream at volumetric flow rate Q_{out} and concentration identical to that in the tank (C_A). The concentration profile below the tank shows the step change in concentration encountered as the inlet stream is mixed with tank contents of lower concentration.

tank. As the first drop of dye enters the tank, it is mixed instantly and completely with the water, imparting a uniform light blue color. Because the distribution of dye in the tank is uniform, the fluid entering the exit stream at this instant also is of the same light blue color. The continued addition of dye to the tank through the flowing inlet stream will gradually darken the color of the fluid in the tank, until both the tank and the exit stream are the same color as the inlet stream.

This simple example illustrates two important features of stirred tanks: (1) the concentration of dissolved species is uniform throughout the tank, and (2) the concentration of these species in the exit stream is identical to their concentration in the tank. Note that a consequence of the well-stirred behavior of this model is that there is a step change in solute concentration from the inlet to the tank, as shown in the concentration profile in Figure 2. Such idealized behavior cannot be achieved in real stirred vessels; even the most enthusiastically stirred will not display this step change, but rather a smoother transition from inlet to tank concentration. It should also be noted that stirred tank models can be used when chemical reactions occur within the tank, as might occur in a flow-through reaction vessel, although these do not occur in the simple dye dilution example.

Mass balance equations can be developed to describe mass transfer in the stirred tank. The system is defined as the fluid within the tank, excluding any headspace above the fluid and the solid tank itself. The total mass balance on this sytem, given above in verbal form as Eq. (1), takes the following form when fluid density (ρ) is assumed to be constant:

$$\frac{d(\rho V)}{dt} = \rho(Q_{in} - Q_{out}) \tag{3}$$

where V is the volume of fluid in the tank, t is time, and Q_{in} and Q_{out} are the volumetric flow rates of the inlet and exit streams. When the fluid volume, V, is constant, the derivative on the left-hand side is equal to zero, and the total mass balance states simply that the inlet and exit flow rates are equal ($Q_{in} = Q_{out} = Q$). Similarly, a component mass balance can be written for each chemical species that enters or exits the tank. For example, for a species A that is present in the inlet stream at a constant concentration C_{A0}, the component mass balance is

$$\frac{d(C_A V)}{dt} = Q(C_{A0} - C_A) - R \tag{4}$$

where C_A is the uniform concentration of dye in the tank and R is the rate of loss or gain of A due to chemical reaction. In this equation, note that fluid flowing from the tank has a concentration C_A, a consequence of the well-stirred model. Solution of this equation requires the specification of the kinetics of the reaction as well as an initial condition of the form "At $t = 0$, $C_A = \beta$," where β is a