FUNDAMENTALS OF DRUG DELIVERY

Rebecca A. Bader

Syracuse Biomaterials Institute, Syracuse University, Syracuse, NY, USA

1.1 INTRODUCTION: HISTORY AND FUTURE OF DRUG DELIVERY

As depicted in Fig. 1.1, as drug discovery has evolved, the need for innovative methods to effectively deliver therapeutics has risen. In the early 1900s, there began a shift away from the traditional herbal remedies characteristic of the “age of botanicals” toward a more modern approach based on developments in synthetic chemistry [1, 2]. Through the 1940s, drug discovery needs were directed by the needs of the military, that is, antibiotics were developed and produced to treat injured soldiers [3]. As more pharmaceuticals were rapidly identified by biologists and chemists alike, people became more cognizant of the impact therapeutics could have on everyday life. During the late 1940s to the early 1950s, drugs were, for the first time, formulated into microcapsules to simplify administration and to facilitate a sustained, controlled therapeutic effect [4]. For example, Spansules®, microcapsules containing drug pellets surrounded by coatings of variable thickness to prolong release, were developed by Smith Kline and French Laboratories and rapidly approved for use [5]. Many of these early microencapsulation techniques, particularly the Wurster process, whereby drug cores are spray coated with a polymer shell, are still in use today [6, 7].
Although a number of advanced methods for controlled and/or targeted drug delivery were proposed in the 1960s, building on the conventional drug delivery method of microencapsulation, these techniques were not fully implemented until the 1970s [8, 9]. During this decade, biotechnology and molecular biology began to play a significant role in the drug discovery process, culminating in an increased understanding of the etiology of numerous diseases and the development of protein-based therapeutics. Likewise, computer screening, predictive software, combinatorial chemistry, and high throughput screening significantly accelerated the rate at which lead compounds for new therapeutic compounds could be identified [1, 4]. As is discussed further in Chapter 2, drug carrier systems, such as implants, coatings, micelles, liposomes, and polymer conjugates, were proposed to address the growing need to deliver the newly identified therapeutic compounds with maximum efficacy and minimal risk of negative side effects [8, 9] (Fig. 1.2).

In sum, over time, as technology has advanced for drug discovery, there has been a paradigm shift in drug delivery from simplifying the administration of old drugs to creating systems that can make new drugs work. This is particularly true as we continue to identify and develop therapeutics based on proteins and nucleic acids that are difficult to administer in a patient-friendly manner and/or with the necessary site-specificity to reverse adverse consequences. However, as drug delivery technology has advanced for new drugs, many of the old drugs have likewise benefited through increased predictability of pharmacokinetic/pharmacodynamic profiles, decreased side effects, and enhanced efficacy. This text is intended to explain how these advanced drug delivery techniques, particularly those related to the application of polymers, have
improved the efficacy of old and new drugs alike. Chapter 1 serves as the foundation for all subsequent chapters, defining the necessary terminology related to drug delivery and pharmaceutics.

1.2 TERMINOLOGY

1.2.1 Pharmacology

Pharmacology, the science of drugs, is composed of two primary branches, pharmacodynamics and pharmacokinetic. In broad terms, pharmacokinetics refers to what the body does to the drug whereas pharmacodynamics describes what the drug does to the body. In the subsequent sections, a brief overview of these two branches of study are given in order to highlight some of the basic pharmacological terminology frequently encountered in both drug discovery and delivery.

1.2.1.1 Pharmacokinetics. Pharmacokinetics tracks the time course of drugs and drug delivery systems through the body. The processes that impact the temporal and spatial distribution of drugs are absorption, distribution, metabolism, excretion (ADME). Following administration, the drugs are absorbed by the bloodstream,
TABLE 1.1. Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th>Process</th>
<th>Parameter</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>Absorption rate constant ($k_a$)</td>
<td>First-order rate constant for absorption</td>
</tr>
<tr>
<td>Bioavailability ($F$)</td>
<td>Bioavailability ($F$)</td>
<td>The extent of drug absorption</td>
</tr>
<tr>
<td>Distribution</td>
<td>Plasma drug concentration ($C_p$)</td>
<td>The concentration of drug in the plasma</td>
</tr>
<tr>
<td>Volume of distribution ($V_d$)</td>
<td>Volume of distribution ($V_d$)</td>
<td>The mass amount of drug given (dose) divided by the plasma concentration ($C_p$). $V_d$ is an apparent volume with no direct physiological relevance</td>
</tr>
<tr>
<td>Unbound fraction</td>
<td>Unbound fraction</td>
<td>The fraction of drug not bound to protein, that is, pharmaceutically active</td>
</tr>
<tr>
<td>Elimination (metabolism and excretion)</td>
<td>Metabolism rate constant ($k_m$)</td>
<td>First-order rate constant for elimination by metabolism</td>
</tr>
<tr>
<td>Excretion rate constant ($k_{ex}$)</td>
<td>Excretion rate constant ($k_{ex}$)</td>
<td>First-order rate constants for elimination by excretion</td>
</tr>
<tr>
<td>Elimination rate constant ($k_e$)</td>
<td>Elimination rate constant ($k_e$)</td>
<td>$k_e = k_m + k_{ex}$</td>
</tr>
<tr>
<td>Extrarenal (metabolic) clearance</td>
<td>Extrarenal (metabolic) clearance</td>
<td>The volume of plasma cleared of drug per unit time by metabolism</td>
</tr>
<tr>
<td>Renal clearance</td>
<td>Renal clearance</td>
<td>The volume of plasma cleared of drug per unit time by metabolism</td>
</tr>
<tr>
<td>Total clearance</td>
<td>Total clearance</td>
<td>Total clearance = renal clearance + extrarenal Clearance</td>
</tr>
<tr>
<td>Half-life ($t_{1/2}$)</td>
<td>Half-life ($t_{1/2}$)</td>
<td>The time necessary for the plasma drug concentration to be reduced 50%</td>
</tr>
</tbody>
</table>

distributed to tissues and organs throughout the body, and eventually eliminated by metabolism or excretion. Although a summary of these processes with associated parameters is provided in Table 1.1, each of these terms are described in further detail in Section 1.3 [10, 11].

1.2.1.2 Pharmacodynamics. Because pharmacodynamics broadly refers to what the drug does to the body, pharmacodynamics measurements involve looking at toxicity, as well as therapeutic efficacy. These measurements frequently involve examining dose–response curves to determine the optimal range over which drugs can be administered with maximum therapeutic impact and minimal negative side effects. Pharmacodynamics also involves examining the mechanism by which drugs act, that is, drug–receptor interactions. Typically, these studies are used to identify
the amount of drug necessary to reduce interactions of endogenous agonists with the receptor [12]. These concepts related to pharmacodynamics will be explored in greater detail in Section 1.4.

1.2.2 Routes of Administration

The route by which drugs are administered can have a profound impact on the pharmacokinetic properties given in Table 1.1. One of the goals of drug delivery is to facilitate administration by routes that normally have an adverse impact on the associated therapeutic pharmacokinetic properties. For example, as is discussed further in Chapter 2, effective oral administration of numerous drugs is not feasible because of poor uptake through the mucosal epithelial barrier of the intestine and a low resultant bioavailability. Furthermore, orally administered drugs are subject to what is referred to as the first pass effect, whereby the bioavailability is reduced by metabolism within the liver and/or gut wall. Carrier systems have been designed to (i) increase intercellular transport by disrupting the epithelial barrier, (ii) facilitate intracellular transport through targeting of the absorptive epithelial cells, and/or (iii) reduce the destruction of drugs by liver enzymes [13–16].

The most explored routes of drug administration are summarized in Table 1.2. Although 90% of drugs are administered orally due to convenience and high patient compliance, oral drug delivery is associated with low and/or variable bioavailability as a result of the harsh environment of the gastrointestinal tract and the impermeable nature of the mucosal epithelial barrier. In contrast, parenteral forms of administration (intravenous, subcutaneous, and intramuscular) yield rapid effects and high bioavailability (100% for intravenous); however, patient compliance is extremely low as a result of the discomfort because of the injection. Transdermal delivery is

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Advantages</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parenteral</td>
<td>Immediate effects, Reproducible, High bioavailability</td>
<td>Low patient compliance, Often requires a clinician</td>
</tr>
<tr>
<td>Oral</td>
<td>Convenient, High patient compliance</td>
<td>Highly variable, Harsh environmental conditions, Low absorption of many drugs</td>
</tr>
<tr>
<td>Transdermal Pulmonary</td>
<td>Continuous delivery, High absorptive surface area, Rapid absorption of small molecule drugs</td>
<td>Limited to lipophilic drugs, The morphology of the lung tissue makes systemic delivery difficult, Limited absorption of macromolecules</td>
</tr>
<tr>
<td>Nasal</td>
<td>Rapid absorption of lipophilic drugs, High bioavailability of lipophilic drugs</td>
<td>Limited absorption of polar molecules</td>
</tr>
</tbody>
</table>
a favorable route of administration because of high patient acceptability and ready access to the site of absorption; however, this method has historically been limited to small, lipophilic drugs that can passively diffuse through the skin barrier [17, 18]. New techniques are currently being developed to extend transdermal delivery to polar and/or macromolecular compounds. For example, ultrasound and iontophoresis provide a driving force for the passage of small, charged drugs, while electroporation and microneedles disrupt the outermost layer of the skin for delivery of macromolecules, particularly peptides and proteins [19]. Nasal and pulmonary drug deliveries are also attractive routes of administration because of the high potential surface area available for drug absorption; however, as with transdermal delivery, the nature of the epithelial barriers in both regions limits this to lipophilic compounds [17, 18].

1.2.3 Drug Delivery

1.2.3.1 Controlled Release. Controlled drug delivery systems, also referred to as prolonged and sustained release systems, aim to minimize dosing frequency by maintaining the local and/or systemic concentrations of drugs for extended periods of time. Although difficult to achieve, ideal release of drugs from controlled release delivery systems follow zero-order release kinetics, whereby the rate of drug release does not change with time until no drug remains. As a result, constant drug levels within the body can be maintained. A variable release rate with drugs provided to the body at a nonconstant, time-dependent rate is more common. If first-order kinetics are followed, the release rate decreases exponentially with time until the majority of the drug has been released, at which time zero-order release kinetics are approached (Fig. 1.4) [9, 20–23].

1.2.3.2 Active Versus Passive Targeting. Inflammatory tissue and solid tumors both possess an increased vascular permeability that can be exploited for improved drug delivery. The diseased tissue can be passively targeted by developing systems (such as liposomes, micelles, and nanoparticles) with a hydrodynamic radius large enough to prevent renal filtration, but small enough to pass through the leaky vasculature. In cancer, the change in vasculature is accompanied by a reduction in lymphatic drainage, thereby increasing the passive targeting capacity of carrier systems through “enhanced permeation and retention” [24–26]. The site-specificity of drug delivery systems can be further improved through the addition of a ligand, such as an antibody, polysaccharide, or peptide, that will actively target receptors overexpressed in the diseased region [27–30]. The concepts of active and passive targeting will arise throughout this book.

1.3 BASIC PHARMACOKINETICS

1.3.1 Compartment Models

Compartment models are used as a simple method to describe the time course of a drug through a physiological system on administration. One and two compartment
models are depicted in Fig. 1.3. The simplest pharmacokinetic model is the one compartment open model for drugs administered by intravenous (IV) bolus with first-order elimination, that is, the rate at which the amount of drug in the body changes is proportional to the amount of drug remaining in the body. To apply a one compartment open model, the assumption must be made that the drugs are instantaneously, homogenously distributed between tissues on administration, thereby allowing the body to be described as a unit from which drugs are cleared. While the one compartment model for IV bolus administration will be presented herein, more complicated models, such as those required when drugs are not instantaneously distributed, are beyond the scope of this text. Readers are encouraged to look at several excellent textbooks on basic pharmacokinetics for additional information [10, 11, 31]

As mentioned in brief above, elimination after IV bolus administration can be described using a first-order kinetic equation when applying a one compartment model. This equation can be derived by assessing the rate of change for either drug concentration (Eq. 1.1) or drug amount (Eq. 1.2)

\[
\frac{dC_p}{dt} = -k_e C_p 
\]

(1.1)

\[
\frac{dM}{dt} = -k_e M 
\]

(1.2)

where \( C_p \) is the plasma concentration of drug, \( M \) is the mass amount of drug, and \( k_e \) is a first-order elimination rate constant. Although an identical analysis can be applied to the rate of change of drug amount, all subsequent pharmacokinetic parameters will be derived using the rate of change of drug concentration (Eq. 1.1). Thus, integration of Eq. 1.1 gives:

\[
C_{p,t} = C_{p,0}e^{-k_e t} 
\]

(1.3)

Equation 1.3 in conjunction with the area under the curve (AUC) described in Section 1.3.2, serves as a spring board from which other pharmacokinetic parameters are derived. Note that \( C_p \) is not equal to the concentration of drug in other tissues;

Figure 1.3. (a) One and (b) two compartment models can be used to describe the time course of drugs in the body after administration.
however, changes in drug concentration within the plasma are directly proportional
to those in other tissues as a consequence of describing the body as a homogenous,
single compartment.

1.3.2 Bioavailability and Area Under the Curve (AUC)

Bioavailability refers to the rate and extent to which a drug has reached the systemic
circulation for delivery to the site of action. Thus, the most common indicator of
bioavailability is $C_p$. From a plot of $C_p$ versus time, the AUC provides a quantitative
measure of how much drug stays in the body and for how long [10, 31].

For an IV bolus with first-order elimination kinetics, an exact solution for the
AUC can be obtained by analytical integration [10, 31]. For example, consider the
$C_p$ versus time plot shown in Fig. 1.4. As derived in Section 1.3.1, $C_p$ at a given
time can be determined from Eq. 1.3. Using calculus, the AUC is equal to the integral
from $t = 0$ to an infinite time point. Therefore, taking the integral of Eq. 1.3 gives

$$AUC = \int_0^\infty C_p \, dt$$

(1.4)

$$AUC = \int_0^\infty C_{p,0} e^{-k_e t} \, dt = C_{p,0} \left[ \frac{e^{-k_e t}}{-k_e} \right]_0^\infty$$

(1.5)

$$AUC = C_{p,0} \left[ \frac{e^{-k_e \infty} - e^{-k_e 0}}{-k_e} \right]$$

(1.6)

$$AUC = \frac{C_{p,0}}{k_e}$$

(1.7)

![Figure 1.4. After IV bolus administration, elimination can be described using a first-order kinetic equation if a one compartment model is assumed.](image)
Alternatively, \( C_{p,0} \) if and/or \( k_e \) are unknown, the AUC can be found using the trapezoidal rule. Using Fig. 1.4, the AUC for the highlighted segment can be found with
\[
AUC_{1-2} = \frac{C_{p,1} + C_{p,2}}{2} (t_2 - t_1) \quad (1.8)
\]
Extrapolating the first segment to determine \( C_{p,0} \), assuming the last points follow an exponential decay that defines \( k_e \), adding all possible segments together yields.
\[
AUC = AUC_{0-1} + AUC_{1-\text{last}} + AUC_{\text{last}-\infty} \quad (1.9)
\]
\[
AUC = \frac{C_{p,0} + C_{p,1}}{2} t_1 + \frac{C_{p,1} + C_{p,2}}{2} (t_2 - t_1) + \cdots + \frac{C_{p,\text{last}}}{k_e} \quad (1.10)
\]

### 1.3.3 Elimination Rate Constant and Half-Life

The elimination rate constant, \( k_e \), introduced above can be found by converting Eq. 1.3 to natural logarithmic form to give
\[
\ln(C_{p,t}) = \ln(C_{p,0}) - k_e t \quad (1.11)
\]
Thus, \( k_e \) is the slope of a plot of \( \ln(C_p) \) versus time:
\[
k_e = \frac{\ln(C_{p,1}) - \ln(C_{p,2})}{t_2 - t_1} \quad (1.12)
\]
Note that the elimination rate constant includes both excretion and metabolism. From \( k_e \), the half-life, that is, the time necessary to decrease \( C_p \) to one half of \( C_{p,0} \), can be determined. Considering Eq. 1.12 and solving for the time when \( C_{p,2} = C_{p,1}/2 \) gives
\[
t_{1/2} = \frac{\ln 2}{k_e} = \frac{0.693}{k_e} \quad (1.13)
\]
Equation 1.13 shows that the half-life is independent of drug concentration. Thus, regardless of \( C_{p,0} \), the half-life can be used to describe when most of the drug has been eliminated from the body. For example, after five half-lives, \( C_p = C_{p,0}/32 \) and 96.875% of the initial amount of drug in the body has been lost [10, 31].

### 1.3.4 Volume of Distribution

Despite the importance of this parameter in pharmacokinetics, the volume of distribution, \( V_d \), does not have any direct physiological relevance and does not correlate with a true volume. \( V_d \) can be defined as the ratio of dose, \( D \), to the plasma concentration at \( t = 0 \)
\[
V_d = \frac{D}{C_{p,0}} \quad (1.14)
\]
Likewise, \( V_d \) can be obtained by taking the ratio of the mass amount to the concentration of drug at any given time point. If \( V_d \) is high, the drug is highly distributed to tissues/organs throughout the body, rather than being confined primarily to the plasma; while if \( V_d \) is low, the drug is not well distributed to tissue/organs and resides, for the most part, in the plasma [10, 31].

### 1.3.5 Clearance

Drug clearance (CL) is a proportionality constant relating the elimination rate, \( dM/dt \), to the plasma concentration \( C_p \) [10, 31].

\[
CL = \frac{dM}{dt} \cdot \frac{1}{C_p} \quad (1.15)
\]

Substituting in Eq. 1.2 and noting that volume of distribution is equal to the amount of drug divided by the concentration of drug gives

\[
CL = k_e V_d \quad (1.16)
\]

Half-life is related to \( k_e \) through Eq. 1.13. Thus,

\[
CL = \frac{0.693 V_d}{t_{1/2}} \quad (1.17)
\]

### 1.4 Basic Pharmacodynamics

#### 1.4.1 Therapeutic Index and Therapeutic Window

The goal in the development of new therapeutic agents, as well as drug delivery systems, is to maximize efficacy while minimizing the potential for adverse drug events. Thus, dose–response curves, will examine both therapeutic response and toxicity, as shown in Fig. 1.5. The ratio of the median toxic dose (TD_{50}), that is, the dose that causes toxicity in 50% of the population, to the median effective dose (EC_{50}), that is, the dose required to elicit a response in 50% of the population, is referred to as the therapeutic index (TI). A drug with a high TI can be used over a wide range of doses, referred to as the therapeutic window, without adverse side effects. In contrast, a low TI suggests a narrow therapeutic window [12, 32].

#### 1.4.2 Ligand-Receptor Binding

Although some drugs act through chemical reactions or physical associations with molecules within the body, a number of other drugs are used to elicit, change, or prevent a cellular response via ligand-receptor binding interactions. For this mechanism of action, the drug serves as an exogenous ligand that either (i) prevents interactions
Therapeutic window is the dosing range that can be used to safely treat a disease.

of the receptor with an endogenous ligand (e.g., a cytokine or hormone), that is, the drug acts as an antagonist, or (ii) elicits a physiological response equal to or greater than what would result from the binding of an endogenous ligand, that is, the drug acts as an agonist. Ligand (drug)–receptor interactions are governed by affinity, as indicated by the ratio of the association to dissociation rate constants. The inverse of the affinity, that is, the dissociation divided by association rate constant, is referred to as the dissociation constant ($K_D$), the most frequently reported indicator of the strength of drug–receptor interactions [33, 34]. The concept of ligand–receptor binding is critical in understanding how to design a carrier system such that the therapeutic efficacy of the drug can be maintained and/or active targeting can be implemented. Section 1.5.2.2 takes a more quantitative approach toward helping readers understand the importance of drug/drug delivery system–receptor interactions.

1.5 MASS TRANSFER

Learning the basics of mass transfer is critical to understanding how drugs travel through/out of polymeric matrices of carrier systems and through the surrounding tissue. Numerous examples using the principles of mass transfer are given throughout this text. Mass transfer describes the tendency of a component in a mixture to move from a region of high concentration (i.e., the source) to an area of low concentration (i.e., the sink). This transport can occur as a result of molecular mass transfer, or diffusion, whereby movement occurs through a still medium, or convective mass transfer, whereby transfer is promoted by fluid flow. The interested reader is referred to conventional texts on mass transfer and transport phenomena [35–37].

1.5.1 General Flux Equation and Fick’s First Law

The total mass transported can be expressed as the sum of the mass transported by diffusion and the mass transported by bulk motion of the fluid. Considering a mixture
of two species with one dimensional transport along the $z$ axis, the molar flux of species 1, $N_1$, is given by

$$N_1 = J_1 + c_1 v^*$$

(1.18)

where $J_1$ is the flux due to pure diffusion, $c_1$ is the molar concentration, and $v^*$ is the molar average velocity. $v^*$ can be determined as the sum of the velocity contributions from the components in the mixture.

$$v^* = \frac{1}{c} \sum_i c_i v_i = \sum_i x_i v_i$$

(1.19)

where $x_i$ is the mole fraction of species $i$ in the mixture. $c_i v_i$ is equivalent to the molar flux of species $i$ relative to stationary coordinates.

$$N_i = c_i v_i \left( \frac{\text{mol}}{\text{m}^2 \text{s}} \right)$$

(1.20)

Thus, in a binary mixture

$$v^* = \frac{1}{c} \sum_i c_i v_i = \frac{1}{c} (c_1 v_1 + c_2 v_2) = \frac{1}{c} (N_1 + N_2)$$

(1.21)

Referring back to Eq. 1.18, $c_1 v^*$ is the flux generated by processes other than diffusion, such as convection/fluid flow. The flux, owing to diffusion, $J_1$, can also be expressed in the form of Fick’s First Law in one dimension

$$J_1 = -D_1 \frac{dc_1}{dz}$$

(1.22)

where $D_1$ is a proportionality constant referred to as the diffusion coefficient. Combining Eqs. 1.18, 1.21, and 1.22 yields the General Flux Equation [35, 36]:

$$N_1 = -D_1 \frac{dc_1}{dz} + \frac{c_1}{c} (N_1 + N_2)$$

(1.23)

Of note, for dilute solutions, as would be found for a drug moving though a polymer matrix or tissue, the general flux equation reduces to Fick’s first law.

$$N_1 = -D_1 \frac{dc_1}{dz}$$

(1.24)
1.5.2 Mass Conservation and Fick’s Second Law

Referring to Fig. 1.6, consider a material balance on species 1 along diffusion path length $z$ and through fixed cross sectional area for flux $A$.

By conservation of mass in $\text{out} + \text{generation} = \text{accumulation}$, expressed mathematically as

$$N_1 A|_z - N_1 A|_{z+\Delta z} + \psi_1 A \Delta Z = \frac{c_1|_{t+\Delta t,z} - c_1|_{t,z}}{\Delta t} A \Delta Z$$  \hspace{1cm} (1.25)

Division of Eq. 1.25 by $A$, rearrangement, and division by $\Delta Z$ yields

$$-\left[ \frac{N_1|_{z+\Delta z} - N_1|_z}{\Delta Z} \right] + \psi_1 = \frac{c_1|_{t+\Delta t,z} - c_1|_{t,z}}{\Delta t}$$  \hspace{1cm} (1.26)

If the limit of $\Delta Z \to 0$, $\Delta t \to 0$ is taken, the following equation is obtained:

$$-\frac{\partial N_1}{\partial z} + \psi_1 = \frac{\partial c_1}{\partial t}$$  \hspace{1cm} (1.27)

Using Eq. 1.27 with the General Flux Equation (Eq. 1.23), assuming that $D_1$ is constant, gives

$$D_1 \frac{\partial^2 c_1}{\partial z^2} - v^* \frac{\partial c_1}{\partial z} + \psi_1 = \frac{\partial c_1}{\partial t}$$  \hspace{1cm} (1.28)

If the total system density is also constant, Eq. 1.28 can be further simplified to

$$D_1 \frac{\partial^2 c_1}{\partial z^2} - v^* \frac{\partial c_1}{\partial z} + \psi_1 = \frac{\partial c_1}{\partial t}$$  \hspace{1cm} (1.29)

In a situation with no fluid motion ($v^* = 0$) and no productive term ($\psi_1 = 0$), this equation reduces to Fick’s Second Law, which facilitates prediction of concentration changes with time because of diffusion [35, 36].

$$D_1 \frac{\partial^2 c_1}{\partial z^2} = \frac{\partial c_1}{\partial t}$$  \hspace{1cm} (1.30)
Although Fick’s Second Law was derived for one dimension flux in a rectangular coordinate system above, these concepts can readily be extended to spherical and cylindrical coordinate systems (Fig. 1.7). The equations for one dimensional flux in different geometries are summarized in Table 1.3. Detailed derivations of solutions to Fick’s Second Law, including those given for the problems in Section 1.5.2.1, can be found in Crank’s book on the mathematics of diffusion [38].

### 1.5.2.1 Application of Fick’s Second Law in Drug Delivery

Applications of Fick’s Second Law will appear throughout this text; however, two in depth examples will be provided to here to show how Eq. 1.30 can be used to predict the concentration of drug as a function of time and distance away from or through a controlled release system. First, consider a cylindrical hydrogel with a radius of 4 mm and a height of 0.75 mm loaded with keratinocyte growth factor (KGF) at a high concentration \( c_{KGF,0} \) intended for use as a wound healing dressing (Fig. 1.8) [39]. Assuming that diffusion only occurs in one dimension through the surface placed in contact with the wound and taking into account that \( h \ll r \), the system can be modeled with Fick’s Second Law using a rectangular coordinate system.

\[
D_1 \frac{\partial^2 c_1}{\partial z^2} = \frac{\partial c_1}{\partial t} \tag{1.31}
\]
Figure 1.8. KGF release from a cylindrical hydrogel with \( h << r \) can be modeled as one dimensional flux in the \( z \) direction (i.e., a rectangular coordinate system).

If we assume that (i) a high concentration of drug is maintained at the surface of the cylinder, (ii) KGF is not initially present in the underlying tissue, and (iii) there is no KGF at an infinite distance from the cylinder, the following boundary conditions can be applied to determine the drug concentration as a function of time and distance into the underlying tissue.

\[
c_{\text{KGF}}(z, 0) = 0 \quad \text{for} \quad 0 < z < \infty, t = 0 \quad (1.32)
\]

\[
c_{\text{KGF}}(0, t) \quad \text{(surface)} = c_{\text{KGF},0} \quad \text{for} \quad z = 0, t > 0 \quad (1.33)
\]

\[
c_{\text{KGF}}(\infty, t) = 0 \quad \text{for} \quad z = \infty, t > 0 \quad (1.34)
\]

Solving Eq. 1.31 with the method of combination of variables gives the following solution

\[
\frac{c_{\text{KGF}}(z, t) - c_{\text{KGF}}(z, 0)}{c_{\text{KGF},0} - c_{\text{KGF}}(z, 0)} = \text{Erfc}\left(\frac{z}{2\sqrt{D_{\text{KGF}}t}}\right) \quad (1.35)
\]

Which, given that \( c_{\text{KGF}}(z, 0) = 0 \), can be reduced to

\[
\frac{c_{\text{KGF}}(z, t)}{c_{\text{KGF},0}} = \text{Erfc}\left(\frac{z}{2\sqrt{D_{\text{KGF}}t}}\right) \quad (1.36)
\]

Taking \( D_{\text{KGF}} \) to be \( 4.86 \times 10^{-9} \) \( \text{cm}^2\text{s}^{-1} \), the concentration of KGF as a function of distance from the hydrogel wound healing dressing is plotted for several time points in Fig. 1.9.

Next, consider the release of 10 mg of Dramamine from a spherical capsule \( (r = 0.30 \text{ cm}) \) (Fig. 1.10). Using a spherical coordinate system and assuming that diffusion only occurs in the radial direction, Fick's Second Law can be used to predict the change in drug concentration within the capsule over time.

\[
D_1 \left[ \frac{\partial^2 c_1}{\partial r^2} + \frac{2}{r} \frac{\partial c_1}{\partial r} \right] = \frac{\partial c_1}{\partial t} \quad (1.37)
\]
Figure 1.9. Distance of penetration of KGF into the wound site following release from cylindrical hydrogels at three time points (6, 12, and 24 h), as determined from Eq. 1.36.

Figure 1.10. Release of Dramamine from a spherical capsule can be model as one dimensional flux in the radial direction.

The following boundary conditions can be applied assuming that (i) the capsule radius remains constant, (ii) the capsule possesses radial symmetry, and (iii) the drug is immediately swept away from the surface of the capsule on release.

\[ c_d(r, 0) = c_{d,0} \text{ for } 0 < r < R, t = 0 \]  
\[ \frac{\partial c_d(0, t)}{\partial r} = 0 \text{ for } r = 0, t \geq 0 \]  
\[ c_d(R, t)(\text{surface}) = 0 \text{ for } r = R, t > 0 \]  

An analytical solution to Eq. 1.37 can be obtained following the separation of variables method.

\[ \frac{c_d(r, t) - c_{d,0}}{c_d(R, t) - c_{d,0}} = 1 + \frac{2R}{\pi R} \sum_{n=1}^{\infty} \frac{-1^n}{n} \sin \left( \frac{n\pi r}{R} \right) e^{-\frac{D_n^2 \pi^2 t}{R^2}} \]  

(1.41)
which, given that $c_{dramamine}(R, t) = 0$, can be simplified to

$$
\frac{c_d(r, t) - c_{d,0}}{-c_{d,0}} = 1 + \frac{2R}{\pi r} \sum_{n=1}^{\infty} \frac{-1^n}{n} \sin \left( \frac{n\pi r}{R} \right) e^{-\frac{D_d}{\pi^2} \frac{n^2}{R^2} t} \quad (1.42)
$$

Figure 1.11 illustrates the change in Dramamine concentration with distance outward from the center of the capsule for several different time points. Alternatively, by using $r = R$ and $m_{d,0} = c_{d,0} \times (4/3)\pi R^3$, where $m_{d,0}$ is the initial mass amount of Dramamine loaded into the capsule, the equation can be revised to predict the time necessary for near complete drug release. Figure 1.12 uses Eq. 1.43 to demonstrate the fractional release of drug $(1 - m_{d(t)}/m_{d,0})$ as a function of time.

$$
\frac{m_d(t)}{m_{d,0}} = 6 \sum_{n=1}^{\infty} \frac{1}{n^2} e^{-\frac{D_d}{\pi^2} \frac{n^2}{R^2} t} \quad (1.43)
$$

### 1.5.2.2 Fick’s Second Law and Ligand Binding.

As discussed previously, there are many instances, particularly in regard to biologics; efficacy is dependent on the therapeutic agent not only diffusing to the cells within the active site, but also on binding to the cell surface. For these cases, the assumption cannot be made that the drug disappears immediately on reaching the cell, that is, the drug concentration at the surface is equal to 0. Instead, the drug disappears at a rate that is governed by binding kinetics.

Consider the system illustrated in Fig. 1.13. At the surface, the drug can bind to or dissociate from the receptor. This relationship can be described by

$$
C_R + C_L \xrightleftharpoons[k_{off}]{k_{on}} C_R C_L \quad (1.44)
$$
Figure 1.12. Equation 1.43 can be used to predict when most of the Dramamine will be released from the spherical capsule.

\[ \frac{1-m_t}{m_{t,0}} \]

\[ \text{Time (h)} \]

Figure 1.13. For a ligand (i.e., drug) to associate with a cell surface receptor, the drug must first diffuse to the cell surface.

where \( k_{on} \) and \( k_{off} \) are the rate constants of binding and dissociation, respectively; \( C_R \) is the concentration of the receptor; \( C_L \) is the concentration of ligand (drug); and \( C_RC_L \) is the concentration of ligand bound to receptor. At equilibrium, \( C_R \), \( C_L \), and \( C_RC_L \) remain unchanged with time. Thus,

\[
\frac{d(C_RC_L)}{dt} = C_R \cdot C_L \cdot k_{on} - C_RC_L \cdot k_{off} = 0 \quad (1.45)
\]

\[
C_R \cdot C_L \cdot k_{on} = C_RC_L \cdot k_{off} \quad (1.46)
\]

Equation 1.46 can be rearranged and expressed with the equilibrium dissociation constant, \( K_d \).

\[
\frac{C_R'C_L}{C_RC_L} = \frac{k_{off}}{k_{on}} = K_d \quad (1.47)
\]
Likewise, an equilibrium exists between the drug diffusing to and from the receptor, as defined by $k_+$ and $k_-$. Taken together, the overall forward and reverse rate constants are given by $k_f$ and $k_r$, respectively.

By assuming that (i) flux only occurs in the radial direction, (ii) the ligand does not degrade within the physiological solution, (iii) the cell radius remains constant, and (iv) the rate of ligand disappearance is equal to the rate of diffusion at the surface, expressions can be developed to determine $k_f$ and $k_r$. Because there is a constant source (the ligand in solution) and a constant sink (the cell surface), the system is at steady state. Thus, Fick’s second law for a spherical geometry can be written as

$$D_L \left[ \frac{d^2 c_L}{dr^2} + \frac{2}{r} \frac{dc_L}{dr} \right] = 0 \quad (1.48)$$

The following boundary conditions can be applied based on the assumptions given above.

$$c_L(r) = c_{L,0} \text{ for } r = \infty \quad (1.49)$$

$$4\pi R^2 \cdot N_L = k_{on} \cdot C_R \cdot C_L \text{ for } r = R \quad (1.50)$$

The second boundary condition equates the rate of ligand disappearance at the surface, as given by $k_{on} \times C_R \times C_L$, to the rate of diffusion at the surface, as given by the surface area ($4\pi R^2$) times the flux ($N_L$). Thus, this boundary condition can be rewritten as

$$4\pi R^2 \cdot D_L \frac{dc_L}{dr} = k_{on} \cdot C_R \cdot C_L \text{ for } r = R \quad (1.51)$$

Solving with the specified boundary conditions yields the ligand concentration as a function of radius.

$$c_L(r) = \frac{-k_{on} C_R}{4\pi D r + k_{on} C_R} \cdot \frac{1}{r} + c_{L,0} \quad (1.52)$$

If binding is diffusion-limited, that is, $4\pi D r \ll k_{on}$, the rate of ligand disappearance at the cell surface ($r = R$) can be given by

$$\text{Rate of ligand disappearance} = -D(4\pi R^2) \frac{dc_L}{dr} \quad (1.53)$$

Substituting in Eq. 1.52 into Eq. 1.53 gives

$$\text{Rate of ligand disappearance} = 4\pi D \frac{k_{on} C_R}{4\pi D r + k_{on} C_R} \quad (1.54)$$

where $4\pi D r$ is equivalent to $k_-$. By equating the overall rate of ligands diffusing toward and binding to the cell surface receptors, $k_f C_{L,0}$, to Eq. 1.54, the overall rate
constant $k_f$ can be expressed in terms of $k_\perp$, the rate constant for diffusion-limited binding, to $C_Rk_{on}$, the intrinsic binding rate [40, 41].

$$k_f = \frac{k_\perp C_Rk_{on}}{k_\perp + k_{on}C_R} \quad (1.55)$$

As an example, consider that antibody fragments conjugated to PEG can be used for the active, targeted delivery of therapeutics to cancer cells that possess specific cell surface antigens. The hydrodynamic radius and diffusion coefficient of the antibody-PEG fragment in PBS at 37°C have been determined to be 2.5 nm and $8.4 \times 10^{-7}$ cm$^2$ s$^{-1}$ respectively. The intrinsic association constant, $k_{on}$, is $6.1 \times 10^4$ M$^{-1}$ s$^{-1}$ [42]. Assuming that binding is diffusion limited, the transport rate constant, $k_\perp$, and the overall rate constants for ligand binding, $k_f$, for a normal cell that has 20,000 surface receptors ($C_R = 20,000$) and a cancerous cell that has 2,000,000 receptors ($C_R = 2,000,000$) can be determined.

$$k_\perp = 4\pi DR$$

$$k_\perp = 4\pi (8.4 \times 10^{-7} \text{ cm}^2 \text{ s}^{-1})(2.5 \times 10^{-7} \text{ cm})$$

$$k_\perp = 2.64 \times 10^{-12} \text{ cm}^3 \text{ s}^{-1} \text{ ligand}^{-1}$$

$$k_\perp = \frac{2.64 \times 10^{-12} \text{ cm}^3}{\text{ligand}} \times \frac{6.022 \times 10^{23} \text{ ligands}}{\text{mole}} \times \frac{11}{1000 \text{ cm}^3}$$

$$k_\perp = 1.59 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$$

$$k_f = \frac{k_\perp C_Rk_{on}}{k_\perp + C_Rk_{on}}$$

For normal cells:

$$C_R = 20,000$$

$$k_f = 6.90 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$$

For cancer cells:

$$C_R = 2,000,000$$

$$k_f = 1.57 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$$

Thus, the overall forward rate constant for cancer cells is greater than that for normal cells, lending credence to the possibility of active targeting by carrier systems modified with a ligand for receptors overexpressed by diseased cells. Note that while the above calculations were made on a per cell basis, careful attention should be given to units when solving for problems related to ligand binding interactions.
1.6 KEY POINTS

- As drug discovery has evolved to encompass compounds that are less physiologically soluble and/or stable, the need for drug delivery has increased.
- Pharmacokinetics refers to what the body does to the drug, while pharmacodynamics refers to what the drug does to the body.
- The route of absorption can have a profound impact on pharmacokinetic properties.
- Compartmental models can be used to describe the absorption, distribution, metabolism, and excretion of drugs by/from the body.
- In many cases, Fick’s second law can be used to predict the release of a drug from a polymer-based drug delivery system.

1.7 HOMEWORK PROBLEMS

1. Discuss why 100% bioavailability is difficult to obtain by oral drug delivery.
2. Apo2L/TRAIL (tumor necrosis factor-related apoptosis-inducing ligand) has demonstrated anticancer efficacy. Recently, a recombinant, water soluble form of Apo2L/TRAIL was developed for clinical application. Before clinical studies, several in vivo models were used for pharmacokinetic evaluation. For all animals, Apo2L/TRAIL was administered via an IV bolus. The following average data was obtained from chimpanzees administered Apo2L/TRAIL at a dose of 1 mg kg\(^{-1}\) [43].

<table>
<thead>
<tr>
<th>Time, min</th>
<th>(C_p), ng ml(^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>20,000</td>
</tr>
<tr>
<td>20</td>
<td>15,000</td>
</tr>
<tr>
<td>45</td>
<td>9000</td>
</tr>
<tr>
<td>60</td>
<td>6000</td>
</tr>
<tr>
<td>90</td>
<td>2000</td>
</tr>
<tr>
<td>120</td>
<td>900</td>
</tr>
<tr>
<td>180</td>
<td>200</td>
</tr>
</tbody>
</table>

Construct a semi-log plot of serum concentration versus time and determine the best fit exponential equation for the curve. Determine the following pharmacokinetic parameters, assuming a chimpanzee weight of 60 kg:
- a. Elimination rate constant, \(k_e\)
- b. Half-life, \(t_{1/2}\)
- c. Volume of distribution, \(V_d\)
- d. Clearance, CL
3. The diffusion coefficients for the antibiotic cefoperazone through agar gel, fibrin gel, and cerebral cortex tissue were determined by applying a solution of drug in PBS at a concentration of 5 mg ml$^{-1}$ to the top of the appropriate matrix and measuring the concentration as a function of depth at a predetermined time point. Experiments with brain tissue were performed in vivo on rats, while experiments with agar and fibrin gel were performed on matrix prepared in Petri dishes (thickness = 0.5 cm, diameter = 10 cm). The following data was obtained [44]:

<table>
<thead>
<tr>
<th>Matrix</th>
<th>$D$, cm$^2$ s$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agar gel</td>
<td>6.10E−07</td>
</tr>
<tr>
<td>Fibrin gel</td>
<td>7.00E−07</td>
</tr>
<tr>
<td>Cortex tissue</td>
<td>2.50E−08</td>
</tr>
</tbody>
</table>

a. Construct a model of cefoperazone penetration into agar, fibrin, or cortex tissue by (i) drawing the physical situation, (ii) listing at least three assumptions, (iii) specifying the boundary and initial conditions, and (iv) formulating the correct differential equation for mass transfer.

b. Assuming that the correct differential equation and boundary/initial conditions were identified, the analytic solution is

$$c_{\text{Cefazolin}}(z, t) = c_{\text{Cefazolin,0}} \times \text{Erfc} \left( \frac{z}{2\sqrt{Dt}} \right)$$

Construct plots showing (i) the concentration of cefoperazone as a function of depth (0–500 μm) at a time of 30 min and (ii) the concentration of cefoperazone as a function of time (5–30 min) at a depth of 100 μm for agar gel, fibrin gel, and cortex tissue.

4. To control inflammation around implantable glucose sensors, researchers have suggested controlled release of dexamethasone at the site of implantation. In an experimental study with rats, dexamethasone was released from osmotic pumps implanted subcutaneously. Drug delivery from the pump was achieved from the spherical tip (radius = 0.6 mm) of a catheter attached to the pump. The osmotic pump maintains a constant concentration in the catheter tip. The following data was obtained for the concentration versus distance profile of dexamethasone at 6 h after implantation. Distance is expressed as the radial distance ($r$) from the center of the catheter tip, while concentration in the tissue is expressed relative to the concentration at the tip ($C_s$) [45].
a. Construct a model to describe the controlled release of dexamethasone from the spherical tip of the catheter. Draw a picture of the physical system, list at least three assumptions, decide on the most appropriate coordinate system, formulate the differential equation for mass transfer, and specify the boundary/initial conditions.

b. The solution for the release of dexamethasone from the spherical tip of the catheter can be given by

$$\frac{C}{C_s} = \frac{a}{r} \text{erfc} \left[ \frac{r-a}{2\sqrt{Dt}} \right]$$

where \(a\) is the radius of catheter, \(r\) is the distance from the center of the catheter, and \(C/C_s\) is the concentration in the tissue relative to the concentration at the tip.

Given the information about the radius of the catheter tip and the concentration profile of dexamethasone obtained at a time point of 6 h, plot the above equation and determine the diffusion coefficient for dexamethasone.

c. Evidence suggests that dexamethasone can be eliminated from the site of implantation. To account for this, an elimination rate constant \((k_e)\) can be incorporated into the solution for predicting the concentration as a function of radius.

$$\frac{C}{C_s} = \frac{a}{2r} \left\{ \exp \left[ -(r-a) \sqrt{\frac{k}{D}} \right] \text{erfc} \left[ \frac{r-a}{2\sqrt{Dt} - \sqrt{k}t} \right] \right.$$ 

$$+ \exp \left[ (r-a) \sqrt{\frac{k}{D}} \right] \text{erfc} \left[ \frac{r-a}{2\sqrt{Dt} + \sqrt{k}t} \right] \right\}$$

<table>
<thead>
<tr>
<th>(r) (distance from the center of the catheter tip, cm)</th>
<th>(C/C_s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.06</td>
<td>1</td>
</tr>
<tr>
<td>0.085</td>
<td>0.72</td>
</tr>
<tr>
<td>0.110</td>
<td>0.54</td>
</tr>
<tr>
<td>0.135</td>
<td>0.32</td>
</tr>
<tr>
<td>0.16</td>
<td>0.25</td>
</tr>
<tr>
<td>0.21</td>
<td>0.13</td>
</tr>
<tr>
<td>0.26</td>
<td>0.11</td>
</tr>
<tr>
<td>0.31</td>
<td>0.073</td>
</tr>
<tr>
<td>0.36</td>
<td>0.06</td>
</tr>
<tr>
<td>0.41</td>
<td>0.05</td>
</tr>
</tbody>
</table>
Plot this equation using the diffusion coefficient determined in part (b). Comment on whether or not you think elimination plays a significant role in the observed concentration profile.

REFERENCES