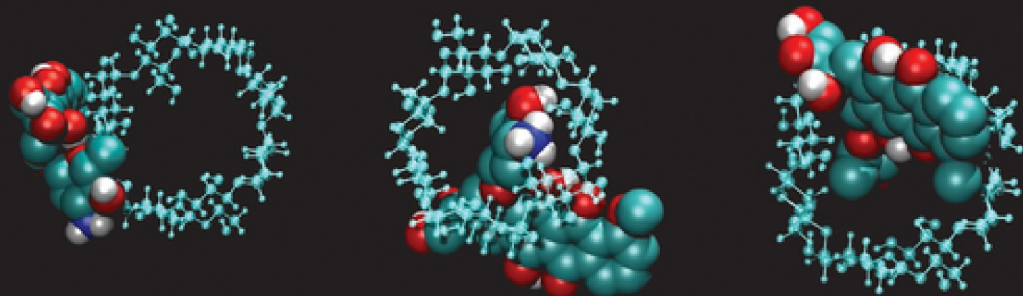# ENGINEERING POLYMER SYSTEMS
FOR IMPROVED DRUG DELIVERY

EDITED BY

REBECCA A. BADER • DAVID A. PUTNAM

WILEY

ENGINEERING POLYMER SYSTEMS FOR IMPROVED DRUG DELIVERY

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CONTENTS

FOREWORD

The body is made up of tens of trillions of human cells and an even greater number of microorganisms, each of which impact health in ways that scientists, physicians, and engineers are still trying to fully comprehend. Overall, the amount of information encoded in each of these cells and their surroundings is staggering, leading to the organization of approximately 7 octillion atoms (a 7 followed by 27 zeros) into a well-oiled, living, breathing, and reproducing machine. Importantly, the myriad of cells in the body do not act in isolation, but rather in concert with one another, sometimes with subsecond precision and timing, forming a countless network of signals and interactions that is nothing short of awe-inspiring.

In contrast, the current state of medicine is somewhat less impressive. Even the most modern medicine is still administered in a way so as to expose a drug to all cells in the body indiscriminately, even though that drug's goal is to elicit a specific response from a specific cell type. In the few instances where this is not the case, any observed cell-specific localization could be completely accidental. Consequently, the total costs to the US Healthcare system associated with side effects from these kinds of drugs (including costs associated with deleterious effects from patients not properly taking these drugs) currently exceeds the amount of money spent on treating both cancer and heart disease combined. It may be surprising to hear that a solution to these problems was described four decades ago with the first demonstration of polymers for the controlled and localized release of biologic molecules. Using polymers that are extremely safe (some of which can completely disappear in the body following action), it was envisioned that it was not only possible to limit a drug's effects to a specific location or specific cell population, but also quite possible to achieve effects over extremely long durations of time, making the common, daily dosing of drugs obsolete. Yet, only a handful of these advanced drug delivery systems have ever been translated to clinical practice given a slower than anticipated learning curve in the understanding of the nature of polymeric delivery systems and the engineering of their behavior.

Most recently, however, there have been exciting advances in understanding and practice in the field of polymeric drug delivery systems so as to increase the effectiveness of new drugs while minimizing (or even completely eliminating) their toxicity and side effects. These advances are built on the foundations laid by the founders and luminaries in the field by the next generation of leaders, many of whom were personally trained by these founders and luminaries.

It is for this reason that I could not have been more excited to hear that Dr. Rebecca Bader and Dr. David Putnam (who are both outstanding teachers and well-respected scholars in the field) have taken on the task of bringing together an impressive team of these next generation leaders to contribute to the book that you are reading right now and to provide an overview of the state of the art in the field of polymeric drug delivery. Also, as expected, Dr. Bader and Dr. Putnam provide excellent historical and topical context in this work as well as a well-grounded understanding of the important current problems in the field. The following chapters (arranged by mode of administration) cover an extremely broad array of advances ranging from micro and nano particulate systems to implantable matrices, to rate controlling membranes, to advanced, stimuli responsive and affinity-based systems. Importantly, each of these chapters has been carefully composed by individuals who have each contributed to the modern understanding of the respective polymeric drug delivery systems. I am excited to have this extremely valuable resource on my bookshelf.

It is also important to mention that given the expected impacts that the information contained in this book will have on the field, I am sure that this volume could not have come at a better time. It is my opinion that we will soon pass a critical point in time where our understanding will lead to drug delivery systems that enable the scores of promising drugs that would have otherwise been discarded. It is also my strong belief that we are extremely close to this critical point. If that is true, the person reading this text right now may very well be one of the ones who will use this information to create the next generation of medical treatments that will improve the quality of life and the cost of healthcare for our children and our grandchildren. Now is indeed a very exciting time in the field, one that has the potential to redefine medicine forever.

STEVEN LITTLE

CHAIRMAN, DEPARTMENT OF CHEMICAL ENGINEERING UNIVERSITY OF PITTSBURGH

PREFACE

Pharmaceutical treatment of disease has evolved from "the botanical era," when herbal remedies were the mainstay, to the present "age of biologics," marked by the use of nucleic acid- and protein-based drugs to alter disease pathology. Although these exciting, new therapeutics offer the possibility of curing diseases that were previously thought to be incurable, a myriad of problems have arisen that have prevented translation to widespread clinical use. Of primary concern is the unwanted delivery of these compounds to normal, healthy tissue, rather than the disease site, which can result in unexpected and/or severe adverse side effects (see Fig. 1). For example, in 2006, TGN1412, a monoclonal antibody that activates T cells, caused multiple organ failure in all six human volunteers recruited for the Phase I clinical trial, despite proven preclinical safety and efficacy. The antibody was intended to target only regulatory T cells to suppress, rather than induce, inflammation, thereby providing an effective treatment for those who suffer from autoimmune diseases such as rheumatoid arthritis. However, TGN1412 instead is thought to have indiscriminately activated T cells throughout the body, leading to an abnormal immune response as well as destruction of healthy tissue [1].

In this example, the question remains as to whether this drug could have been formulated in such a way so as to have enhanced specificity and efficacy, thereby preventing the horrific outcome that was observed. The goal of *Engineering Polymer Systems for Improved Drug Delivery* is to provide an overview of how polymers can be used to control not only what the drug does to the body but also what the body does to the drug. In so doing, polymers provide the key to maximizing the potential of old and new therapeutics alike, including those that would previously be eliminated from consideration as nonviable drug candidates. The cooperation of pharmaceutical scientists and polymer engineers may mark the beginning of an era in which diseases can be treated with increased certainty of a positive outcome.

This book, intended for undergraduate or graduate student instruction, begins with the basics of drug delivery (Chapters 1 and 2), continues through injectable (Chapters 3–6), implantable (Chapters 7 and 8), and oral polymer-based drug delivery systems (Chapters 9–11), and concludes with advanced polymeric drug delivery techniques (Chapters 12 and 13). Each chapter is written so as to give a broad overview of a topic and is concluded with key points, worked problem(s), and homework problems. By taking this approach, we are hopeful that we will inspire the next generation of scientists to make meaningful contributions to the field of drug delivery.

Figure 1. The advent of new therapeutic treatments has been accompanied by an increase an adverse side effects. Our hope is that polymeric drug delivery can help eliminate some of these side effects.

We would like to thank all the authors for their valuable contributions. Special thanks are due to Patricia Wardwell for her help in organizing the chapters, obtaining permissions, and for providing assistance in general.

REBECCA A. BADER AND DAVID A. PUTNAM

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PART I

INTRODUCTION

FUNDAMENTALS OF DRUG DELIVERY

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1.1 INTRODUCTION: HISTORY AND FUTURE OF DRUG DELIVERY

As depicted in Fig. 1.1, as drug discovery has evolved, the need for innovate 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].
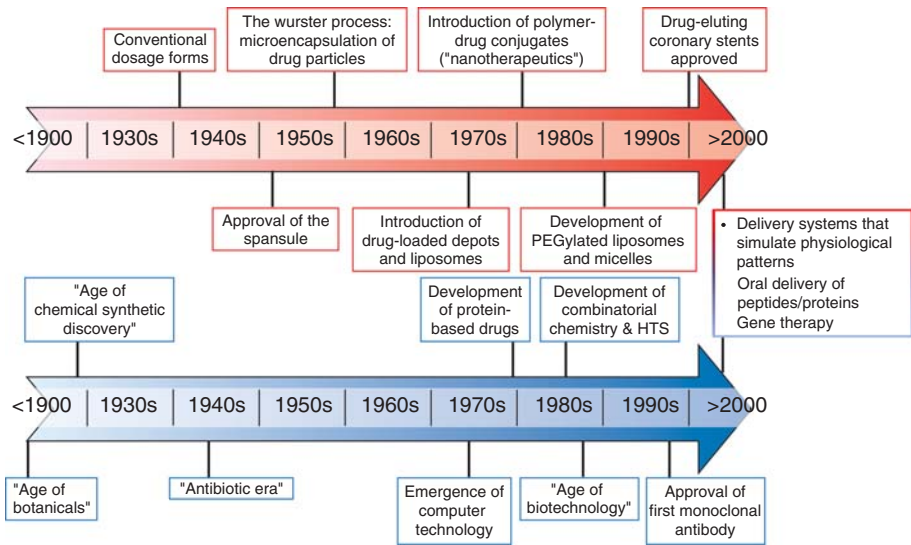
Figure 1.1. Drug delivery (a) and drug discovery (b) have followed similar trajectories with the need for drug delivery rising with the identification of new therapeutic compounds.

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
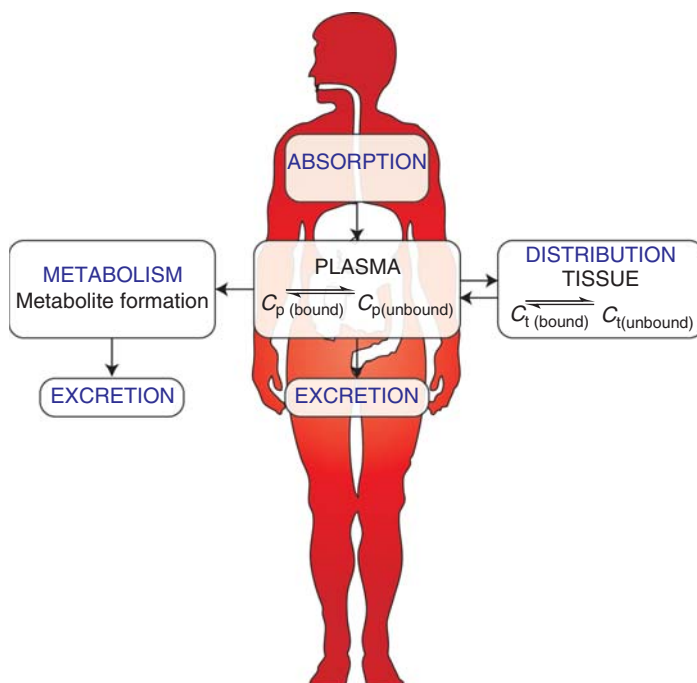
Figure 1.2. The temporal and spatial distribution of drugs is impacted by absorption, distribution, metabolism, and excretion (ADME).

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

Process	Parameter	Definition
Absorption	Absorption rate constant (k_a)	First-order rate constant for absorption
	Bioavailability (F)	The extent of drug absorption
Distribution	Plasma drug concentration (C_p)	The concentration of drug in the plasma
	Volume of distribution (V_d)	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
	Unbound fraction	The fraction of drug not bound to protein, that is, pharmaceutically active
Elimination (metabolism and excretion)	Metabolism rate constant (k_m)	First-order rate constant for elimination by metabolism
	Excretion rate constant (k_{ex})	First-order rate constants for elimination by excretion
	Elimination rate constant (k_e)	$k_e = k_{ex} + k_m$
	Extrarenal (metabolic) clearance	The volume of plasma cleared of drug per unit time by metabolism
	Renal clearance	The volume of plasma cleared of drug per unit time by metabolism
	Total clearance	Total clearance = renal clearance + extrarenal Clearance
	Half-life ($t_{1/2}$)	The time necessary for the plasma drug concentration to be reduced 50%

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 1.2. Routes of Administration for Drug Delivery

Route of Administration	Advantages	Limitations
Parenteral	Immediate effects Reproducible High bioavailability	Low patient compliance Often requires a clinician
Oral	Convenient High patient compliance	Highly variable Harsh environmental conditions Low absorption of many drugs
Transdermal	Continuous delivery	Limited to lipophilic drugs
Pulmonary	High absorptive surface area Rapid absorption of small molecule drugs	The morphology of the lung tissue makes systemic delivery difficult Limited absorption of macromolecules
Nasal	Rapid absorption of lipophilic drugs High bioavailability of lipophilic drugs	Limited absorption of polar molecules

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)

$$\frac{dC_p}{dt} = -k_e C_p \tag{1.1}$$

$$\frac{dM}{dt} = -k_e M \tag{1.2}$$

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:

$$C_{p,t} = C_{p,0} e^{-k_e t} \tag{1.3}$$

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;
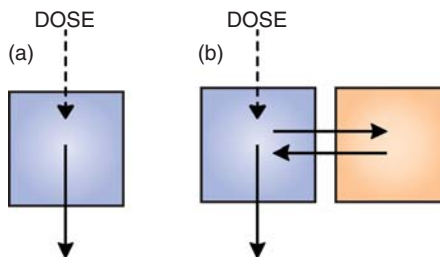

Figure 1.3. (a) One and (b) two compartment models can be used to describe the time course of drugs in the body after administration.

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

$$\text{AUC} = \int_0^\infty C_{p,t} dt \tag{1.4}$$

$$\text{AUC} = \int_0^\infty C_{p,0} e^{-k_e t} dt = C_{p,0} \left[\frac{e^{-k_e t}}{-k_e} \right]_0^\infty \tag{1.5}$$

$$\text{AUC} = C_{p,0} \left[\frac{e^{-k_e \infty} - e^{-k_e 0}}{-k_e} \right] \tag{1.6}$$

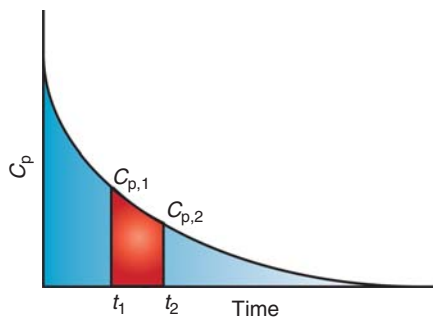$$\text{AUC} = \frac{C_{p,0}}{k_e} \tag{1.7}$$

Figure 1.4. After IV bolus administration, elimination can be described using a first-order kinetic equation if a one compartment model is assumed.

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

$$\text{AUC}_{1-2} = \frac{C_{p,1} + C_{p,2}}{2}(t_2 - t_1) \tag{1.8}$$

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.

$$\text{AUC} = \text{AUC}_{0-1} + \text{AUC}_{1-\text{last}} + \text{AUC}_{\text{last}-\infty} \tag{1.9}$$

$$\text{AUC} = \frac{C_{p,0} + C_{p,1}}{2}t_1 + \frac{C_{p,1} + C_{p,2}}{2}(t_2 - t_1) + \cdots + \frac{C_{p,\text{last}}}{k_e} \tag{1.10}$$

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

$$\text{Ln}(C_{p,t}) = \text{Ln}(C_{p,0}) - k_e t \tag{1.11}$$

Thus, k_e is the slope of a plot of $\text{Ln}(C_p)$ versus time:

$$k_e = \frac{\text{Ln}(C_{p,1}) - \text{Ln}(C_{p,2})}{t_2 - t_1} \tag{1.12}$$

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

$$t_{1/2} = \frac{\text{Ln}2}{k_e} = \frac{0.693}{k_e} \tag{1.13}$$

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 $t = 0$

$$V_d = \frac{D}{C_{p,0}} \tag{1.14}$$

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].

$$CL = \frac{dM}{dt} \cdot \frac{1}{C_p} \tag{1.15}$$

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

$$CL = k_e V_d \tag{1.16}$$

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

$$CL = \frac{0.693 V_d}{t_{1/2}} \tag{1.17}$$

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