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PART I

INTRODUCTION

1

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].

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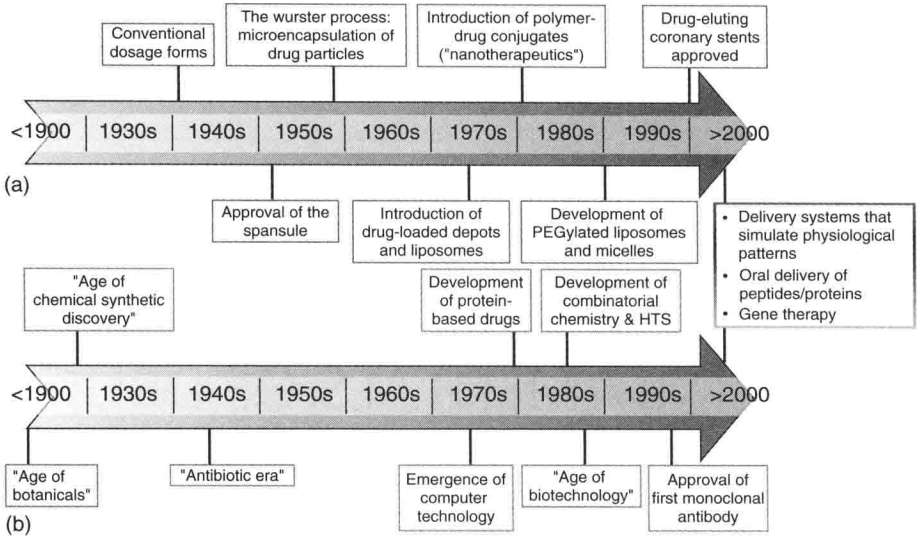

Figure 1.1. Drug delivery (a) and drug discovery (b) have followed similar trajectories with the need for drug delivery rising with the identification of new therapeutic compounds.

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

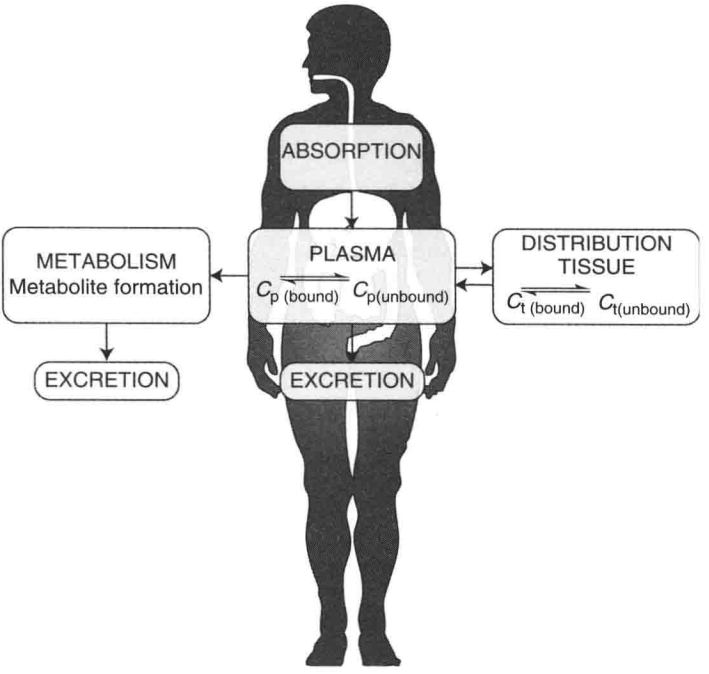

Figure 1.2. The temporal and spatial distribution of drugs is impacted by absorption, distribution, metabolism, and excretion (ADME).

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;

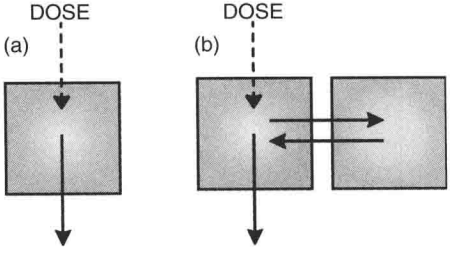

Figure 1.3. (a) One and (b) two compartment models can be used to describe the time course of drugs in the body after administration.

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

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

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

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

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

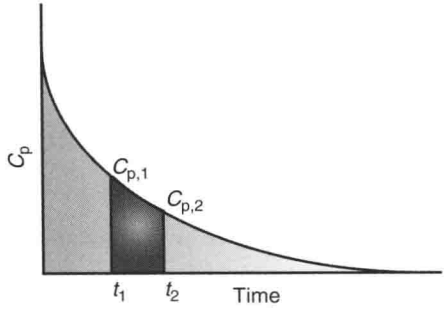

Figure 1.4. After IV bolus administration, elimination can be described using a first-order kinetic equation if a one compartment model is assumed.

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

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

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.

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

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

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

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

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

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

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

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

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 $t = 0$

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