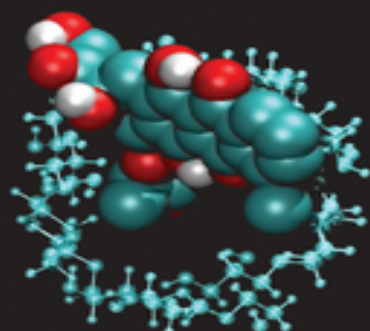
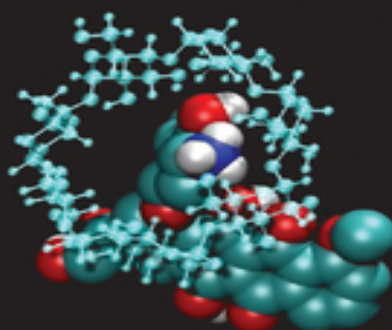
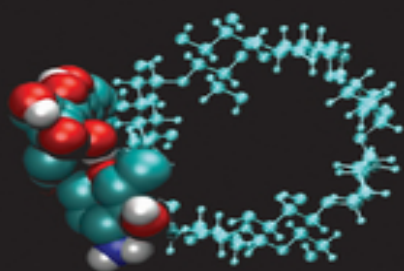


ENGINEERING POLYMER SYSTEMS FOR IMPROVED DRUG DELIVERY



Edited by

REBECCA A. BADER • DAVID A. PUTNAM

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Rebecca A. Bader
David A. Putnam

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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

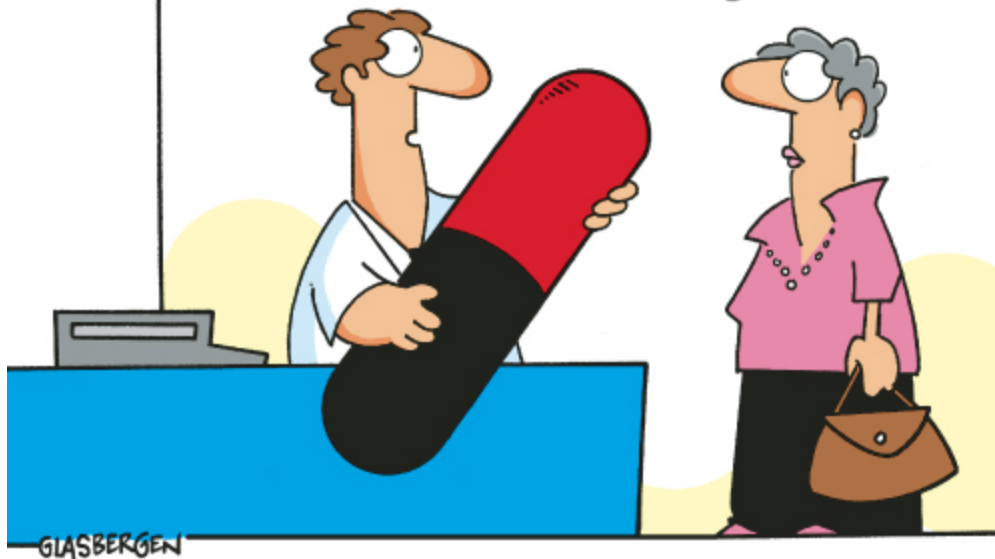
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Preface

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].

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

Pharmacy



**“Each capsule contains your medication,
plus a treatment for each of its side effects.”**

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.

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

Reference

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Part I

Introduction

Chapter 1

Fundamentals of Drug Delivery

Rebecca A. Bader

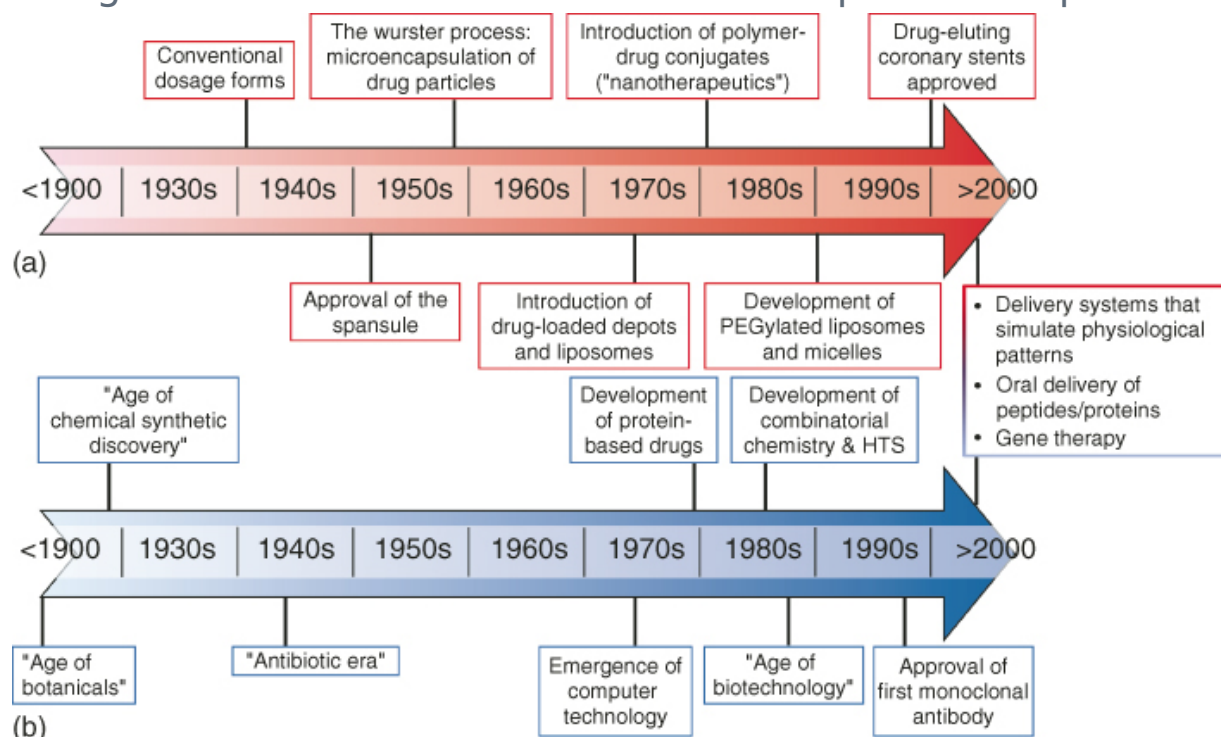
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1.1 Introduction: History and Future of Drug Delivery

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].

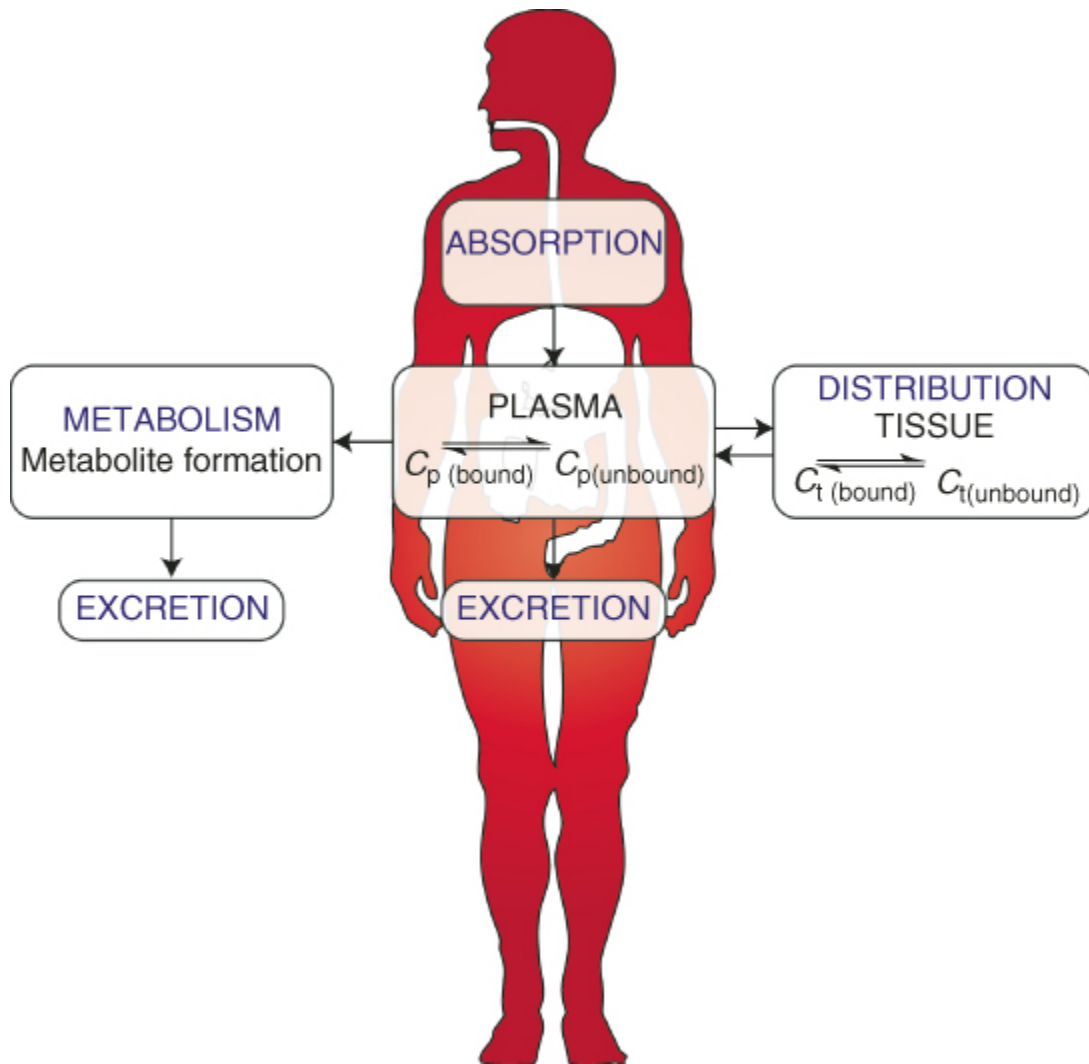
Figure 1.1 Drug delivery (a) and drug discovery (b) have followed similar trajectories with the need for drug delivery rising with the identification of new therapeutic compounds.



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](#)).

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



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 pharmaceuticals.

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, 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].

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%

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 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].

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