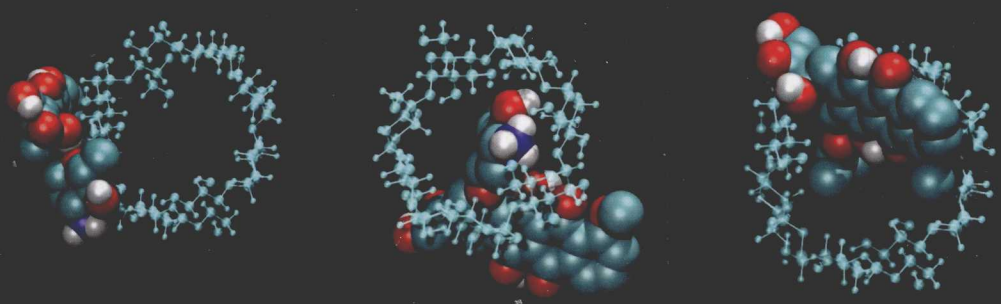
ENGINEERING POLYMER SYSTEMS FOR IMPROVED DRUG DELIVERY



Edited by

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].

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.

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

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.

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REBECCA A. BADER AND DAVID A. PUTNAM

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PART I

INTRODUCTION

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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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