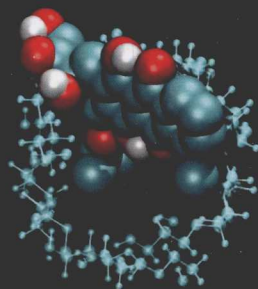
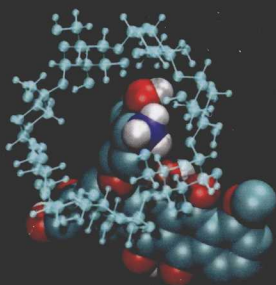
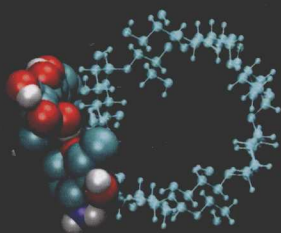


ENGINEERING POLYMER SYSTEMS FOR IMPROVED DRUG DELIVERY



Edited by

REBECCA A. BADER • DAVID A. PUTNAM

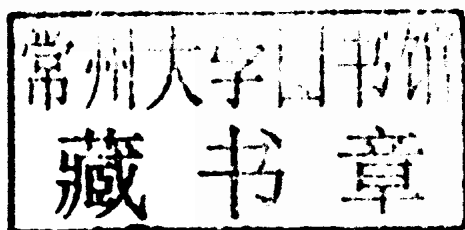
WILEY

ENGINEERING POLYMER SYSTEMS FOR IMPROVED DRUG DELIVERY

Edited by

Rebecca A. Bader

David A. Putnam



WILEY

Cover Design: Wiley

Cover Image: © Horst von Recum and Andrew Fu/Courtesy of Rebecca A. Bader and David A. Putnam

Copyright © 2014 by John Wiley & Sons, Inc. All rights reserved.

Published by John Wiley & Sons, Inc., Hoboken, New Jersey.

Published simultaneously in Canada.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, scanning, or otherwise, except as permitted under Section 107 or 108 of the 1976 United States Copyright Act, without either the prior written permission of the Publisher, or authorization through payment of the appropriate per-copy fee to the Copyright Clearance Center, Inc., 222 Rosewood Drive, Danvers, MA 01923, (978) 750-8400, fax (978) 750-4470, or on the web at www.copyright.com. Requests to the Publisher for permission should be addressed to the Permissions Department, John Wiley & Sons, Inc., 111 River Street, Hoboken, NJ 07030, (201) 748-6011, fax (201) 748-6008, or online at <http://www.wiley.com/go/permission>.

Limit of Liability/Disclaimer of Warranty: While the publisher and author have used their best efforts in preparing this book, they make no representations or warranties with respect to the accuracy or completeness of the contents of this book and specifically disclaim any implied warranties of merchantability or fitness for a particular purpose. No warranty may be created or extended by sales representatives or written sales materials. The advice and strategies contained herein may not be suitable for your situation. You should consult with a professional where appropriate. Neither the publisher nor author shall be liable for any loss of profit or any other commercial damages, including but not limited to special, incidental, consequential, or other damages.

For general information on our other products and services or for technical support, please contact our Customer Care Department within the United States at (800) 762-2974, outside the United States at (317) 572-3993 or fax (317) 572-4002.

Wiley also publishes its books in a variety of electronic formats. Some content that appears in print may not be available in electronic formats. For more information about Wiley products, visit our web site at www.wiley.com.

Library of Congress Cataloging-in-Publication Data:

Engineering polymer systems for improved drug delivery / edited by Rebecca A. Bader, David A. Putnam.
pages cm

Includes bibliographical references and index.

ISBN 978-1-118-09847-9 (cloth)

1. Polymeric drug delivery systems. 2. Polymeric drugs. 3. Polymers in medicine. 4. Drug delivery systems. I. Bader, Rebecca A., 1977- editor of compilation. II. Putnam, David A., 1966- editor of compilation.

RS201.P65E54 2013

615.1—dc23

2013016292

Printed in the United States of America.

10 9 8 7 6 5 4 3 2 1

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 in 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

REFERENCE

1. Attarwala H. TGN1412: from Discovery to Disaster. *J Young Pharm* 2010;2(3):332–6.

CONTRIBUTORS

Rebecca A. Bader Syracuse Biomaterials Institute, Syracuse University, Syracuse, NY, USA

Giuseppe Battaglia Department of Chemistry, University College London, London, UK

Danielle S.W. Benoit Department of Biomedical Engineering, University of Rochester, Rochester, NY, USA

James Blanchette Department of Biomedical Engineering, University of South Carolina, Columbia, SC, USA

Angela Carlson Department of Radiology, Case Western Reserve University, Cleveland, OH, USA

Colleen E. Clark Department of Chemical Engineering, Villanova University, Philadelphia, PA, USA

Noelle K. Comolli Department of Chemical Engineering, Villanova University, Philadelphia, PA, USA

Zhanwu Cui Department of Biomedical Engineering, University of Rochester, Rochester, NY, USA

James C. DiNunzio Pharmaceuticals Division, College of Pharmacy, The University of Texas at Austin, Austin, TX, USA; Hoffmann-La Roche, Inc., Nutley, NJ, USA

Thomas D. Dziubla Department of Chemical and Materials Engineering, University of Kentucky, Lexington, KY, USA

Agata A. Exner Department of Radiology, Case Western Reserve University, Cleveland, OH, USA

Cristina Fante School of Pharmacy, University of Reading, Reading, UK

Andrew S. Fu Department of Biomedical Engineering, Case Western Reserve University, Cleveland, OH, USA

Francesca Greco School of Pharmacy, University of Reading, Reading, UK

Adrian S. Joseph Department of Biomedical Science, The University of Sheffield, Sheffield, UK

Justin M. Keen Pharmaceuticals Division, College of Pharmacy, The University of Texas at Austin, Austin, TX, USA

- David Mastropietro** Department of Pharmaceutical Sciences, College of Pharmacy, Nova Southeastern University, Fort Lauderdale, FL, USA
- James W. McGinity** Pharmaceutics Division, College of Pharmacy, The University of Texas at Austin, Austin, TX, USA
- Srinath Muppalaneni** Department of Pharmaceutical Sciences, College of Pharmacy, Nova Southeastern University, Fort Lauderdale, FL, USA
- Hossein Omidian** Department of Pharmaceutical Sciences, College of Pharmacy, Nova Southeastern University, Fort Lauderdale, FL, USA
- Nisa Patikarnmonthon** Department of Biomedical Science, The University of Sheffield, Sheffield, UK
- David A. Putnam** Department of Biomedical Engineering, Cornell University, Ithaca, NY, USA
- Horst A. von Recum** Department of Biomedical Engineering, Case Western Reserve University, Cleveland, OH, USA
- James D. Robertson** Department of Biomedical Science, The University of Sheffield, Sheffield, UK
- Gregory Russell-Jones** Mentor Pharmaceutical Consulting Pty Ltd, Middle Cove, Australia
- Matthew Skiles** Department of Biomedical Engineering, University of South Carolina, Columbia, SC, USA
- Luis Solorio** Department of Radiology, Case Western Reserve University, Cleveland, OH, USA
- Amy Van Hove** Department of Biomedical Engineering, University of Rochester, Rochester, NY, USA
- Andrew L. Vasilakes** Department of Chemical and Materials Engineering, University of Kentucky, Lexington, KY, USA
- Patricia R. Wardwell** Syracuse Biomaterials Institute, Syracuse University, Syracuse, NY, USA
- Paritosh P. Wattamwar** Teva Pharmaceutical Industries Ltd., West Chester, PA, USA
- Haoyan Zhou** Department of Radiology, Case Western Reserve University, Cleveland, OH, USA

CONTENTS

FOREWORD	xi
PREFACE	xiii
CONTRIBUTORS	xv

PART I INTRODUCTION **1**

1 FUNDAMENTALS OF DRUG DELIVERY **3**

Rebecca A. Bader

1.1	Introduction: History and Future of Drug Delivery	3
1.2	Terminology	5
1.3	Basic Pharmacokinetics	8
1.4	Basic Pharmacodynamics	12
1.5	Mass Transfer	13
1.6	Key Points	23
1.7	Homework Problems	23

2 CHALLENGES OF DRUG DELIVERY **29**

Patricia R. Wardwell and Rebecca A. Bader

2.1	Introduction	29
2.2	History and Challenges of Drug Delivery	30
2.3	Physical Barriers	31
2.4	Metabolic and Chemical Concerns	39
2.5	Physical Properties of Therapeutics	42
2.6	Polymer Carriers as a Solution to Challenges	45
2.7	Key Points	50
2.8	Homework Problems	50

PART II	INJECTABLE POLYMERIC DRUG DELIVERY SYSTEMS	55
3	POLYMER–DRUG CONJUGATES	57
	<i>Cristina Fante and Francesca Greco</i>	
3.1	Introduction	57
3.2	Historical Perspective	58
3.3	Polymer–Drug Conjugates: Biological Rationale	59
3.4	Structural Features of Polymer–Drug Conjugates	62
3.5	Making a Polymer–Drug Conjugate	68
3.6	Current Challenges and Future Perspectives	71
3.7	Key Points	75
3.8	Worked Example	76
3.9	Homework Problems	76
4	POLYMERIC MICROPARTICLES	85
	<i>Noelle K. Comolli and Colleen E. Clark</i>	
4.1	Introduction	85
4.2	The Rationale for Microparticles	86
4.3	Defining the Design Criteria	87
4.4	Polymer Selection	89
4.5	Microparticle Synthesis	91
4.6	Microparticle Characterization Methods	96
4.7	Drug Release from Microparticles	100
4.8	Microparticle Design Examples	108
4.9	Key Points	110
4.10	Worked Example	110
4.11	Homework Problems	111
5	POLYMERIC NANOPARTICLES	117
	<i>Andrew L. Vasilakes, Thomas D. Dziubla, and Paritosh P. Wattamwar</i>	
5.1	Introduction	117
5.2	PNP Design	124
5.3	PNP Formulation Methods and Targeting	128
5.4	Nanoparticle Targeting Overview	133
5.5	PNP Characterization	139
5.6	Major Clinical Achievements	147
5.7	Key Points	148
5.8	Worked Example	149
5.9	Homework Problems	150

6	BLOCK COPOLYMER MICELLES AND VESICLES FOR DRUG DELIVERY	163
	<i>James D. Robertson, Nisa Patikarnmonthon, Adrian S. Joseph, and Giuseppe Battaglia</i>	
6.1	Introduction	163
6.2	Drug Encapsulation and Release	165
6.3	Bioavailability and Biodistribution	166
6.4	Stimuli Responsiveness	170
6.5	The Immune System	174
6.6	Gene Therapy	177
6.7	Cancer Therapy	180
6.8	Conclusions	182
6.9	Key Points	182
6.10	Homework Problems	183

PART III IMPLANTABLE POLYMERIC DRUG DELIVERY SYSTEMS **189**

7	IMPLANTABLE DRUG DELIVERY SYSTEMS	191
	<i>Luis Solorio, Angela Carlson, Haoyan Zhou, and Agata A. Exner</i>	
7.1	Introduction	191
7.2	Nondegradable Polymeric Implants	193
7.3	Biodegradable Polymeric Implants	198
7.4	Conclusions and Future Perspectives	215
7.5	Key Points	216
7.6	Homework Problems	216
8	POLYMERIC DRUG DELIVERY SYSTEMS IN TISSUE ENGINEERING	227
	<i>Matthew Skiles and James Blanchette</i>	
8.1	Introduction	227
8.2	Wound Healing as a Prototype for Adult Tissue Generation	228
8.3	Bioactive Factors in Tissue Engineering and Regenerative Medicine	232
8.4	Delivery of Growth Factors in Tissue Engineering and Regenerative Medicine	248
8.5	Key Points	268
8.6	Worked Example	269
8.7	Homework Problems	270

PART IV	ORAL POLYMERIC DRUG DELIVERY SYSTEMS	283
9	ORAL CONTROLLED-RELEASE POLYMERIC DRUG DELIVERY SYSTEMS	285
	<i>James W. McGinity, James C. DiNunzio, and Justin M. Keen</i>	
9.1	Introduction	285
9.2	Release Mechanisms of Oral Polymeric Dosage Forms	288
9.3	Oral Polymeric Release Modifiers	295
9.4	Manufacturing Technologies and Industrial Applications of Controlled Release	297
9.5	Worked Example	311
9.6	Key Points	314
9.7	Homework Problems	314
10	MUCOADHESIVE DRUG DELIVERY SYSTEMS	319
	<i>Srinath Muppalaneni, David Mastropietro, and Hossein Omidian</i>	
10.1	Introduction	319
10.2	Factors Affecting Mucoadhesion	320
10.3	Polymer–Mucus Interactions	320
10.4	Mucoadhesion Mechanisms	322
10.5	Mucoadhesive Polymers	324
10.6	Novel Mucoadhesive Materials	327
10.7	Mucoadhesion Testing	330
10.8	Drug Release Studies	332
10.9	Mucoadhesive Dosage Forms	332
10.10	Conclusion	334
10.11	Key Points	334
10.12	Homework Questions	337
11	ENHANCED ORAL DRUG DELIVERY THROUGH METABOLIC PATHWAYS	343
	<i>Gregory Russell-Jones</i>	
11.1	Introduction	343
11.2	Uptake of Nutrients from the Intestine	344
11.3	Nutrient Transport in the Intestine	349
11.4	Use of Nutrient Transporters for Drug Delivery	352
11.5	Case Study: The Use of the Vitamin B ₂ Uptake System for Drug Delivery	352
11.6	Key Points	365

11.7	Worked Example	365
11.8	Homework Problems	366

PART V ADVANCED POLYMERIC DRUG DELIVERY 375

12 STIMULI-RESPONSIVE POLYMER DELIVERY SYSTEMS 377

Amy Van Hove, Zhanwu Cui, and Danielle S.W. Benoit

12.1	Introduction	377
12.2	Temperature-Responsive Polymers for Drug Delivery	378
12.3	pH-Responsive Polymers for Drug Delivery	387
12.4	Reduction/Oxidation (Redox)-Responsive Polymers	397
12.5	Enzymatically Responsive Drug Delivery	403
12.6	Key Points	415
12.7	Homework Questions	416

13 AFFINITY-BASED DRUG DELIVERY 429

Andrew S. Fu and Horst A. von Recum

13.1	Introduction	429
13.2	Association Constant	430
13.3	Worked Example	432
13.4	Affinity-Based Drug Delivery Systems	437
13.5	Mathematical Modeling of Affinity-Based Systems	444
13.6	Challenges and Future Directions	448
13.7	Key Points	448
13.8	Homework Problems	449

INDEX 453

PART I

INTRODUCTION

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].

Engineering Polymer Systems for Improved Drug Delivery, First Edition.

Edited by Rebecca A. Bader and David A. Putnam.

© 2014 John Wiley & Sons, Inc. Published 2014 by John Wiley & Sons, Inc.