DRUG DELIVERY: FUNDAMENTALS & APPLICATIONS

SECOND EDITION

Edited by
ANYA M. HILLERY
KINAM PARK

DRUG DELIVERY:
FUNDAMENTALS & APPLICATIONS
SECOND EDITION

DRUG DELIVERY: FUNDAMENTALS & APPLICATIONS

SECOND EDITION

Edited by

Anya M. Hillery
Saint Louis University - Madrid Campus, Madrid, Spain

Kinam Park
Purdue University, West Lafayette, IN, USA

CRC Press
Taylor & Francis Group
Boca Raton London New York

CRC Press is an imprint of the
Taylor & Francis Group, an **informa** business

CRC Press
Taylor & Francis Group
6000 Broken Sound Parkway NW, Suite 300
Boca Raton, FL 33487-2742

Printed on acid-free paper
Version Date: 20160603

International Standard Book Number-13: 978-1-4822-1771-1 (Paperback)

Visit the Taylor & Francis Web site at
http://www.taylorandfrancis.com

and the CRC Press Web site at
http://www.crcpress.com

Contents

Preface ix
Acknowledgments xi
Editors xiii
Contributors xv

Chapter 1 Historical Introduction to the Field of Controlled Drug Delivery 1
Anya M. Hillery and Allan S. Hoffman

SECTION I Fundamental Issues

Chapter 2 Principles of Controlled Release 25
Yvonne Perrie, Thomas Rades, and Kirsten Graeser

Chapter 3 Improving the Water Solubility of Poorly Soluble Drugs 47
Kohsaku Kawakami and Anya M. Hillery

Chapter 4 Overview of Epithelial Barriers 71
Floriane Laurent, Anya M. Hillery, and Randall Mrsny

SECTION II Parenteral Routes for Drug Delivery and Targeting

Chapter 5 Nanotechnologies for Drug Delivery and Targeting: Opportunities and Obstacles 103
Alexander T. Florence and Daan J.A. Crommelin

Chapter 6 Long-Acting Injections and Implants 137
Jeremy C. Wright and James Matriano

SECTION III Nonparenteral Routes for Drug Delivery and Targeting

Chapter 7 Oral Drug Delivery 171
Anya M. Hillery and David J. Brayden

Chapter 8 Buccal and Sublingual Drug Delivery 201
Marc B. Brown and Viralkumar F. Patel

Chapter 9 Transdermal Drug Delivery 215
Simon R. Corrie and Mark A.F. Kendall

Chapter 10 Nasal Drug Delivery 229
Per Gisle Djupesland and Anya M. Hillery

Chapter 11 Pulmonary Drug Delivery 249
Heidi M. Mansour, Paul B. Myrdal, Usir Younis, Priya Muralidharan, Anya M. Hillery, and Don Hayes, Jr.

Chapter 12 Drug Delivery to the Female Reproductive Tract 279
Patrick F. Kiser, Justin T. Clark, and Jonathan T. Su

Chapter 13 Ophthalmic Drug Delivery 305
Clive G. Wilson, Mariam Badawi, Anya M. Hillery, Shyamanga Borooah, Roly Megaw, and Baljean Dhillon

SECTION IV Emerging Technologies

Chapter 14 Hydrogels 333
Ronald A. Siegel and Carmen Alvarez-Lorenzo

Chapter 15 Drug Delivery to the Central Nervous System 361
Anya M. Hillery

Chapter 16 Gene Delivery Systems 375
Kwang Suk Lim and Sung Wan Kim

Chapter 17 Vaccine Delivery 389
Terry L. Bowersock and Suman M. Mahan

Chapter 18 Theranostic Nanoagents 409
Anthony S. Malamas and Zheng-Rong Lu

Chapter 19 Nanofabrication Techniques and Their Applications in Drug Delivery 425
Erica Schlesinger, Cade Fox, and Tejal Desai

SECTION V Toward Commercialization

Chapter 20 Rational Drug Discovery, Design, and Development 443
Haizhen A. Zhong, Osman F. Güner, and J. Phillip Bowen

Chapter 21 Commercial and Regulatory Development Considerations for Nanomedicines..... 465
Donna Cabral-Lilly and Lawrence D. Mayer

Chapter 22 Marketing Perspectives for Drug Delivery 481
Louise Rosenmayr-Templeton

Chapter 23 Bringing Research to Clinical Application: Lessons from ThermoDox®: A Thermal-Sensitive Liposome for Treatment of Cancer..... 523
David Needham

Chapter 24 Conclusions 587
Anya M. Hillery and Kinam Park

Index..... 603

Preface

Controlled drug delivery systems have evolved over the past six decades, from the sustained-release Spansule® technology of the 1950s to the highly sophisticated and targeted drug delivery systems of today. Numerous drug delivery systems (DDS) have been successfully developed for clinical applications over the years, and the demand for innovative technologies continues to grow, driving a variety of new developments in the field. This book describes the fundamental concepts and underlying scientific principles of drug delivery, current applications of drug delivery technologies, and potential future developments in the field. It is intended to serve both as a core textbook and as a valuable reference source for students, researchers, practitioners, and scientists in disciplines including the pharmaceutical and formulation sciences, chemical and biomedical engineering, materials science, medicine and oncology, the health sciences, and natural sciences.

In common with the first edition,* our aim is to provide a single, comprehensive, easy-to-read reference book that covers all aspects of controlled drug delivery. To this end, considerable attention has been paid to the overall layout and contents of the text. Chapter 1 opens with a historical introduction to the field of controlled drug delivery to provide relevant background details for the subsequent chapters.

Section I: Fundamental Issues serves as a comprehensive introduction to the fundamental concepts that underpin drug delivery and targeting. Chapter 2 describes the principles of controlled release, including the various mechanisms, types, and mathematical models of controlled release. Chapter 3 describes various technologies to enhance the water solubility of poorly soluble drugs, which has important implications for lead development in the drug discovery process, as well as for the formulation, bioavailability, and therapeutic efficacy of poorly soluble drugs. An important objective of this book is to provide a thorough understanding of the multitude of highly complex biological barriers to successful drug delivery and targeting that pertain in vivo. For this reason, an entire chapter (Chapter 4) is dedicated to providing a comprehensive overview of the characteristics and properties of the various types of epithelial interfaces in the body of relevance for drug delivery strategies; the factors that influence drug transport across these interfaces are also described.

Section II: Parenteral Routes for Drug Delivery and Targeting opens with a chapter on nanotechnology, the engineering and manufacturing of materials at the molecular scale, which offers the potential to revolutionize the drug delivery field. Chapter 5 focuses on the application of nanotechnology to drug delivery and targeting, and highlights several areas of opportunity. Various limitations of current drug delivery nanotechnologies are also described, in order to help guide future research; in particular, the anatomical, physiological, and pathological obstacles to the targeting concept are discussed. Chapter 6 describes a variety of long-acting injectables and implant platforms that are currently commercially available or at an advanced stage of development; this chapter also reinforces the general concepts and principles of controlled drug release introduced in Chapters 1 and 2.

Section III: Nonparenteral Routes for Drug Delivery and Targeting describes the major epithelial routes of drug delivery currently under investigation. In keeping with the objective to emphasize an understanding of the biological obstacles for successful drug delivery, each chapter of this section begins with a detailed consideration of the relevant anatomical and physiological barriers pertaining specifically to the route in question, as well as the implications therein to successful drug delivery and targeting via this route. The first epithelial route described is the oral route (Chapter 7), the most common and convenient of the existing administration methods for introducing drugs to the bloodstream. The oral route is discussed with respect to the various mechanisms of controlled release,

* Hillery, A.M., A.W. Lloyd, and J. Swarbrick. 2001. *Drug Delivery and Targeting: For Pharmacists and Pharmaceutical Scientists*. Boca Raton, FL: CRC Press.

regional targeting, strategies for improving bioavailability, and the use of vaccines. These same themes recur through the following chapters on the various other epithelial routes, many of which also serve as alternative portals of drug entry to the systemic circulation. The chapters in Section III deliberately follow a common format, in order to ease understanding and facilitate learning, and also to highlight the many similarities that exist between the various epithelial routes, as well as the unique attributes associated with each specific route.

Section IV: Emerging Technologies covers some of the new and exciting possibilities that are emerging as future directions in the field. Chapter 14 describes hydrogels and their applications to drug delivery, including as microfluidic chips, biosensors, and stimuli-sensitive DDS. A variety of sophisticated delivery approaches for overcoming the blood–brain barrier (BBB) are described in Chapter 15, as a means of delivering therapeutics to the central nervous system (CNS). Chapter 16 describes the most promising delivery vehicles emerging for gene therapy, including recent advances such as gene delivery systems that can target intracellular organelles. Chapter 17 provides a comprehensive account of vaccines, as well as the current and emerging vaccine delivery systems used for various routes of vaccination. The newly emerged field of theranostics, which holds great promise for personalized therapy, is described in Chapter 18, while Chapter 19 describes the leverage of techniques from the microelectronics industry to precisely fabricate DDS in the nanometer range and the application of such nanofabricated systems to drug delivery.

Section V: Toward Commercialization is an entirely new section for this edition, which reflects the onward success and progress of drug delivery in the 15 years since the publication of the first edition, as technology moves "from bench to bedside." Chapter 20 describes the more robust and successful methods currently used in drug discovery, design, and development, with particular emphasis on rationally integrating the drug discovery process with the requirements to optimize successful drug delivery, in order to optimize clinical success. The extensive regulatory development pathway for parenteral nanotechnologies is described in Chapter 21—for those working in the preclinical sector, it offers a comprehensive account of the regulatory hurdles that lie ahead. Chapter 22 provides a thorough analysis of the global drug delivery market and market forces, including the latest trends and developments. Chapter 23 presents an engaging account of the clinical translation of a liposomal product (ThermoDox®, a thermal-sensitive liposome for cancer therapy). It provides an illuminating insight, from the inventor's perspective, into the process—and difficulties—of guiding a DDS through initial funding, development, and preclinical and clinical trials.

In the conclusions of Chapter 24, we discuss some of the future directions for drug delivery and targeting, raise some of the challenges that need to be addressed, and propose some possible solutions and ways forward for research.

In keeping with our aim to produce an accessible, easily comprehensible book, we have endeavored to ensure that the text is clear, concise, and direct. Careful editing has ensured that the final text displays an overall continuity and integrated style. The book is characterized by the ample usage of carefully chosen figures, illustrations, and graphics. Many of the figures have been specially commissioned and are unique and original in the field. Collectively, the artwork greatly assists the clarity and visual appeal of the book, aids understanding, and facilitates our pedagogic, explanatory approach.

We welcome readers' suggestions, comments, and corrections on the text. Finally, we hope that you enjoy reading this book as much as we enjoyed editing it!

Anya M. Hillery
Kinam Park

Acknowledgments

Preparing the second edition of this book has been an exciting, challenging, and very enjoyable project. We are deeply grateful to many people for its successful completion. First and foremost, we thank our chapter contributors, listed on page xv et seq., for their time, effort, expertise, and excellent submissions.

We also thank R. Tyler Gabbard (Purdue University) for his excellent editorial assistance, Carol Cserneczky (Saint Louis University Madrid Campus, IT department) for his highly professional computer expertise, and Fernando Béjar (Saint Louis University Madrid Campus, Marketing and Communication) for his help in preparing some of the illustrations.

We acknowledge the support of our publishers and thank Jill Jurgensen and Barbara Norwitz at Taylor & Francis Group. We express our gratitude to Vijay Bose at SPi Global for the copy editing of this text. Also *mil gracias* to the design team at ICON Brandworks Madrid, Spain, for our stunning front cover.

We sincerely thank our co-editors for the first edition, Professor Andrew Lloyd (University of Brighton, UK) and Professor James Swarbrick (PhamaceuTech Inc.), for their interest and support for this edition. In particular, we have benefited greatly from Jim's encouragement, wise counsel, and good humor.

Finally, AMH thanks Mike, Danny, and Robbie Pinkney, for their brilliant support, encouragement, and patience during the preparation of this text.

Editors

Dr. Anya M. Hillery received her BSc in pharmacy from the School of Pharmacy, Trinity College Dublin, Ireland, in 1990 (awarded the Trinity College Gold Medal of Outstanding Achievement). She was awarded a scholarship by Syntex Research to carry out her PhD in pharmaceutics under the supervision of Professor Sandy Florence at the School of Pharmacy, Brunswick Square, University College London, United Kingdom. She continued with postdoctoral research studies at the Square upon being awarded a Maplethorpe Research Fellowship. Anya took up a lectureship position in Pharmaceutical Sciences at the Department of Pharmacy, University of Brighton, United Kingdom, in 1995, and became a senior lecturer in 1997. This was followed by a move in 1999 to Saint Louis University Madrid Campus, Spain, starting as a lecturer in health sciences, subsequently becoming Director of the Department of Science and Engineering, and then Vice Dean of the university in 2001. After some years at home to raise her young family, she has recently returned to full-time academia at SLU Madrid.

Professor Kinam Park received his PhD in pharmaceutics from the University of Wisconsin–Madison, Madison, Wisconsin in 1983. After his postdoctoral training in the Department of Chemical Engineering at the same university, he joined the faculty of the Department of Industrial and Physical Pharmacy, College of Pharmacy, Purdue University, West Lafayette in 1986. He was promoted to full professor of pharmaceutics in 1994. Since 1998, he has held a joint appointment in the Department of Biomedical Engineering and became Showalter Distinguished Professor of Biomedical Engineering in 2006. His research focuses on oral delivery, drug–device combination products, and long-term microparticle formulations. He is the founder of Akina, Inc. specializing in polymers for drug delivery. He is currently the editor in chief of the *Journal of Controlled Release*.

Contributors

Carmen Alvarez-Lorenzo
Department of Pharmacy and Pharmaceutical Technology
University of Santiago de Compostela
Santiago de Compostela, Spain

Mariam Badawi
Strathclyde Institute of Pharmacy & Biomedical Sciences
University of Strathclyde
Glasgow, Scotland, United Kingdom

Shyamanga Borooah
MRC Centre for Regenerative Medicine
University of Edinburgh
Edinburgh, Scotland, United Kingdom

J. Phillip Bowen
Center for Drug Design
Department of Pharmaceutical Sciences
College of Pharmacy
Mercer University
Atlanta, Georgia, USA

Terry L. Bowersock
Global Biological Research and Development
Zoetis, Inc.
Kalamazoo, Michigan, USA

David J. Brayden
School of Veterinary Medicine
University College Dublin
Dublin, Ireland

Marc B. Brown
MedPharm, Ltd.
Guildford, United Kingdom

Donna Cabral-Lilly
Taaneh, Inc.
Princeton, New Jersey, USA

Justin T. Clark
Department of Biomedical Engineering
Northwestern University
Evanston, Illinois, USA

Simon R. Corrie
Australian Institute for Bioengineering and Nanotechnology
The University of Queensland
St. Lucia, Queensland, Australia

Daan J.A. Crommelin
Department of Pharmaceutical Sciences
Utrecht University
Utrecht, the Netherlands

Tejal Desai
Department of Bioengineering and Therapeutic Sciences
University of California, San Francisco
San Francisco, California, USA

Baljean Dhillon
Centre for Clinical Brain Sciences
University of Edinburgh
and
Princess Alexandra Eye Pavilion
Edinburgh, Scotland, United Kingdom

Per Gisle Djupesland
OptiNose AS
Oslo, Norway

Alexander T. Florence
UCL School of Pharmacy
University College London
London, United Kingdom

Cade Fox
Department of Bioengineering and Therapeutic Sciences
University of California, San Francisco
San Francisco, California, USA

Kirsten Graeser
Roche Research and Early Development, TMo
Roche Innovation Center Basel
F. Hoffmann La Roche, Ltd.
Basel, Switzerland

Osman F. Güner
Center for Drug Design
Department of Pharmaceutical Sciences
College of Pharmacy
Mercer University
Atlanta, Georgia, USA

Don Hayes, Jr.
Departments of Pediatrics and Internal Medicine
The Ohio State University
Columbus, Ohio, USA

Anya M. Hillery
Department of Science and Engineering
Saint Louis University—Madrid Campus
Madrid, Spain

Allan S. Hoffman
Department of Bioengineering
University of Washington
Seattle, Washington, USA

Kohsaku Kawakami
Smart Biomaterials Group, Biomaterials Unit
International Center for Materials Nanoarchitectonics
National Institute for Materials Science
Tsukuba, Japan

Mark A.F. Kendall
Australian Institute for Bioengineering and Nanotechnology
The University of Queensland
St. Lucia, Queensland, Australia

Sung Wan Kim
Department of Pharmaceutics and Pharmaceutical Chemistry
University of Utah
Salt Lake City, Utah, USA

and

Department of Bioengineering
Hanyang University
Seoul, South Korea

Patrick F. Kiser
Department of Biomedical Engineering
and
Department of Obstetrics and Gynecology
Northwestern University
Evanston, Illinois, USA

Floriane Laurent
Department of Pharmacy and Pharmacology
University of Bath
Bath, United Kingdom

Kwang Suk Lim
Center for Controlled Chemical Delivery
Department of Pharmaceutics and Pharmaceutical Chemistry
University of Utah
Salt Lake City, Utah, USA

Zheng-Rong Lu
Department of Biomedical Engineering
Case Western Reserve University
Cleveland, Ohio, USA

Suman M. Mahan
Veterinary Medicine Research and Development
Zoetis, Inc.
Kalamazoo, Michigan, USA

Anthony S. Malamas
National Cancer Institute
National Institutes of Health
Bethesda, Maryland, USA

Heidi M. Mansour
College of Pharmacy
The University of Arizona
Tucson, Arizona, USA

James Matriano
DURECT Corporation
Cupertino, California, USA

Lawrence D. Mayer
Celator Pharmaceuticals, Inc.
Ewing, New Jersey, USA

and

Celator Pharmaceuticals Corporation
Vancouver, British Columbia, Canada

Roly Megaw
MRC Centre for Regenerative Medicine
University of Edinburgh
Edinburgh, Scotland, United Kingdom

Randall Mrsny
Department of Pharmacy and Pharmacology
University of Bath
Bath, United Kingdom

Priya Muralidharan
College of Pharmacy
The University of Arizona
Tucson, Arizona, USA

Paul B. Myrdal
College of Pharmacy
The University of Arizona
Tucson, Arizona, USA

David Needham
Department of Mechanical Engineering and Material Science
Duke University
Durham, North Carolina, USA

and

DNRF Niels Bohr Visiting Professor
Center for Single Particle Science and Engineering
University of Southern Denmark
Odense, Denmark

Kinam Park
Department of Pharmaceutics
and
Department of Biomedical Engineering
Purdue Universty
West Lafayette, Indiana, USA

Viralkumar F. Patel
Department of Pharmacy, Pharmacology, and Postgraduate Medicine
University of Hertfordshire
Hatfield, United Kingdom

Yvonne Perrie
Strathclyde Institute of Pharmacy and Biomedical Sciences
University of Strathclyde
Glasgow, Scotland, United Kingdom

Thomas Rades
Department of Pharmacy
Faculty of Health and Medical Sciences
University of Copenhagen
Copenhagen, Denmark

Louise Rosenmayr-Templeton
Tower Pharma Consulting
Vienna, Austria

Erica Schlesinger
Department of Bioengineering and Therapeutic Sciences
University of California, San Francisco
San Francisco, California, USA

Ronald A. Siegel
Department of Pharmaceutics
and
Department of Biomedical Engineering
University of Minnesota
Minneapolis, Minnesota, USA

Jonathan T. Su
Department of Biomedical Engineering
Northwestern University
Evanston, Illinois, USA

Clive G. Wilson
Strathclyde Institute of Pharmacy & Biomedical Sciences
University of Strathclyde
Glasgow, Scotland, United Kingdom

Jeremy C. Wright
DURECT Corporation
Cupertino, California, USA

Usir Younis
College of Pharmacy
The University of Arizona
Tucson, Arizona, USA

Haizhen A. Zhong
Department of Chemistry
University of Nebraska Omaha
Omaha, Nebraska, USA

1 Historical Introduction to the Field of Controlled Drug Delivery

Anya M. Hillery and Allan S. Hoffman

CONTENTS

1.1 Introduction 1
1.2 Early Drug Delivery Systems 2
1.3 The Spansule® Delivery System: The First Controlled-Release Formulation 3
1.4 Controlled Release Using a Rate-Controlling Membrane 4
1.4.1 Drug Diffusion through a Rate-Controlling Membrane 4
1.4.2 Osmotic Pressure Controlled Release: Water Diffusion through a Rate-Controlling Membrane 7
1.5 Long-Acting Injectables and Implants 9
1.6 Further Developments in Oral Controlled Release 10
1.7 Drugs on Surfaces 11
1.7.1 Heparinized Surfaces 11
1.7.2 Drug-Eluting Stents and Balloons 12
1.7.3 Mucoadhesives 13
1.8 Nanoscale DDS 13
1.8.1 Liposomes 16
1.8.2 Nanoparticle DDS 16
1.8.3 Polyplexes and Lipoplexes 17
1.8.4 Polymeric Micelles 18
1.9 Conclusions 19
References 19

1.1 INTRODUCTION

This chapter presents a historical overview of the field of controlled drug delivery, describing how it grew in the past 60 years from a very small field, to the immense size and importance it represents today for human and animal health. This chapter also highlights many of the people who were involved in the conception and design of the key controlled drug delivery systems (DDS), as well as details about the compositions of the materials used. We begin by considering some of the earliest drug delivery formulations, followed by a discussion of some of the key technologies in the history of controlled drug delivery. It should be noted at the outset that in the early days of controlled drug delivery, the term "controlled release" tended to refer specifically to zero-order drug release obtained via a rate-controlling membrane (RCM), whereas the terms "sustained release" and "extended release" referred to the prolonged drug release obtainable using other DDS such as the oral Spansules® and bioerodible implants. With the passage of time, however, the delineation of these definitions has blurred. Currently, all these terms are used interchangeably, and the term "sustained release" is widely used.

1.2 EARLY DRUG DELIVERY SYSTEMS

Conventional oral delivery systems release the drug immediately in the lumen of the gastrointestinal (GI) tract. The drug then dissolves in the GI fluids and permeates the gut wall to be absorbed into the systemic circulation via the underlying blood capillaries. There is no control over the release of the drug.

An early example of modifying drug release via the oral route was the use of enteric coatings. Tablets can be coated with the so-called enteric polymers, which are nonswelling and hydrophobic at the acidity of the stomach, but become ionized, and then dissolve and release the drug, once they enter the slightly alkaline pH of the intestinal region of the GI tract. Thus, drug release is delayed from the stomach to the small intestine. These "delayed release" coatings are useful to either (1) protect the stomach from drugs that can cause gastric irritation (e.g., aspirin) or (2) protect drugs that can be destroyed in the acidic gastric environment (e.g., some penicillins). Early coatings, introduced in the late 1800s, such as keratin and shellac suffered from storage instability and also, crucially, the pH at which they dissolved was too high for adequate dissolution in the small intestine, so that they were not very effective.

In 1951, cellulose acetate phthalate was introduced as an enteric-coating material (Malm et al. 1951). This polymeric cellulose derivative dissolved at a very weakly alkaline pH, such as found in the small intestine, making it highly suitable for enteric controlled-release applications. Many enteric-coating products followed, including the commercially very successful poly(methacrylates), now marketed as the Eudragit® L and Eudragit® S series by Evonik Industries. Figure 1.1 shows compositions of some enteric-coating polymers.

With respect to parenteral delivery, the development of controlled-release systems began in the 1930s, with the introduction of compressed pellets of hydrophobic compounds, which could provide sustained drug release over time, thereby allowing a reduction in the dosing frequency. Pellets consisting of compressed, finely powdered, estradiol particles were administered via subcutaneous (s.c.) implantation to animals, to cause rapid weight gain in the treated animals. Subsequently, other

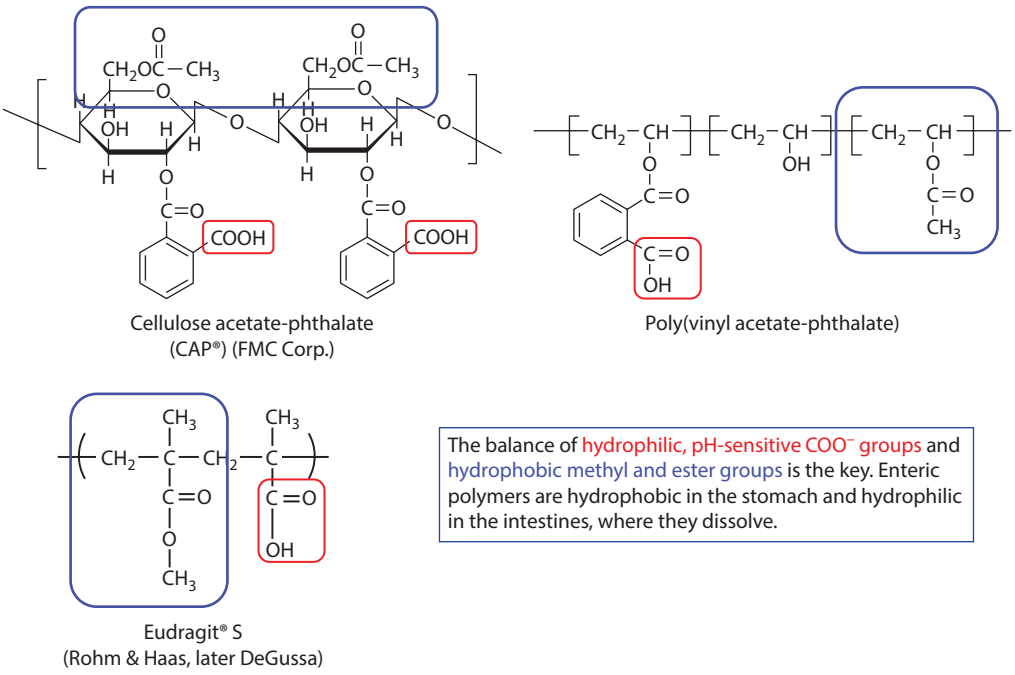


FIGURE 1.1 Enteric-coating polymers.

pellet-type implants were developed using other steroidal hormones. The rate of sustained release of the hydrophobic drugs was determined by the relative hydrophobicity of the pellet (Chien 1982; Hoffman and Wright 2012).

1.3 THE SPANSULE® DELIVERY SYSTEM: THE FIRST CONTROLLED-RELEASE FORMULATION

Even though drug release could be delayed by using enteric coatings, these formulations still featured immediate release of the drug upon removal of the enteric coating. The next stage of technological development was the design of true controlled-release systems, designed to control the drug release rate throughout the lifetime of the formulation. The first of these was the Spansule oral DDS (Figure 1.2), introduced in 1952 by Smith, Kline & French (SKF) for the 12-hour delivery of dextroamphetamine sulfate (Dexedrine®). Each Spansule® capsule contains hundreds of tiny drug-loaded beads, coated with a variable layer of natural waxes, such as carnauba wax, beeswax, or glyceryl monostearate. On ingestion, the outer capsule rapidly disintegrates, liberating the drug-loaded beads. The waxy coating around the beads then gradually dissolves as they transit down the GI tract, to liberate the drug. The rate of drug release is controlled by the thickness and dissolution rate of the waxy coating. A single capsule contains subpopulations of beads with different coating thicknesses, to provide a sustained release of drug over time (Lee and Li 2010).

Subsequently, SKF introduced the cold remedy Contac® 600 (so called because each capsule contained 600 beads), which became the world's leading cold or allergy remedy after its launch in 1960. Each capsule contained four distinct populations of beads: a quarter with no coating, for

The Spansule® system: Sustained oral delivery

FIGURE 1.2 The Spansule system achieved "sustained" drug delivery kinetics over many hours.

immediate drug release; a quarter with a thin waxy coating, which dissolved after 3 hours; a quarter had a thicker coating so that drug release occurred after 6 hours; and the final quarter, with the thickest coating, dissolved after 9 hours. In total, the beads from a capsule provided cold/allergy relief over a sustained 12-hour period. Many advertisements at the time described the Contac® system as "tiny little time pills," which provided "12 hour cold or allergy relief," thereby introducing the general public to the concept of sustained release (Figure 1.2). Since then, many drugs have been reformulated in the Spansule® system, although the original waxy coatings have largely been replaced with more stable and reproducible, slowly dissolving, synthetic polymers.

1.4 CONTROLLED RELEASE USING A RATE-CONTROLLING MEMBRANE

1.4.1 Drug Diffusion through a Rate-Controlling Membrane

Judah Folkman, an MD at Harvard University, was an early pioneer in the field of controlled drug delivery. He was circulating rabbit blood inside a Silastic® (silicone rubber [SR]) arteriovenous shunt, and when he exposed the tubing to hydrophobic anesthetic gases in the atmosphere surrounding the tubing, the rabbits went to sleep. He concluded that the gases were permeating across the SR tubing and absorbing into the blood. He proposed that sealed capsules of SR containing a drug could be implanted to act as a prolonged DDS (Folkman and Long 1964; Folkman et al. 1966; Hoffman 2008).

In this way, a *reservoir* of drug is contained within a RCM. The drug can diffuse out through the reservoir at a controlled rate. If certain conditions are filled, drug release remains constant, "zero order" with time. The principle of the RCM zero-order DDS depends on a RCM that does not vary in permeation properties over the period of use. The zero-order condition also assumes that no significant diffusional resistances will be introduced with time, such as the deposition of a thick layer of scar tissue due to a foreign body response. Then, if the drug concentration–driving force from inside to outside of the device is constant, the delivery rate will be constant over the period of use (Figure 1.3).

Another key pioneer in the origin of the controlled drug delivery field was Alejandro Zaffaroni, a superb pharmaceutical chemist and entrepreneur who had collaborated with Carl Djerassi at Syntex on the synthesis of the steroid levonorgestrel, which was used in the first contraceptive pill. Zaffaroni had been thinking about creating a company devoted to controlled drug delivery. When he heard about Judah Folkman's work, he went to visit him in Boston and Folkman agreed

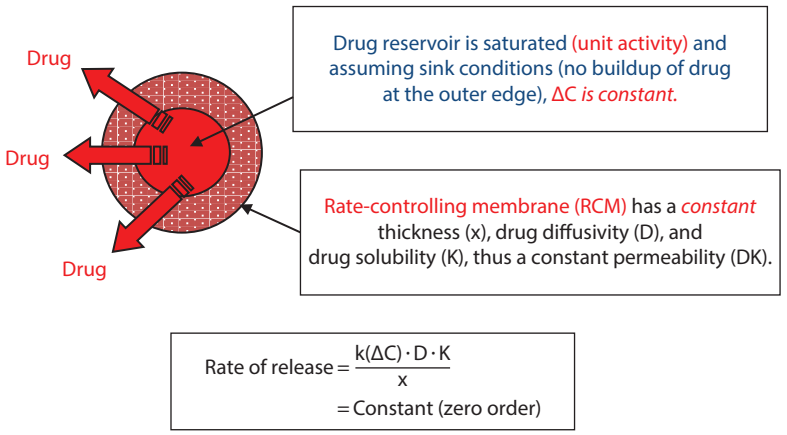


FIGURE 1.3 Membrane-controlled drug delivery systems. Zero-order delivery rate, controlled by a rate-controlling membrane.

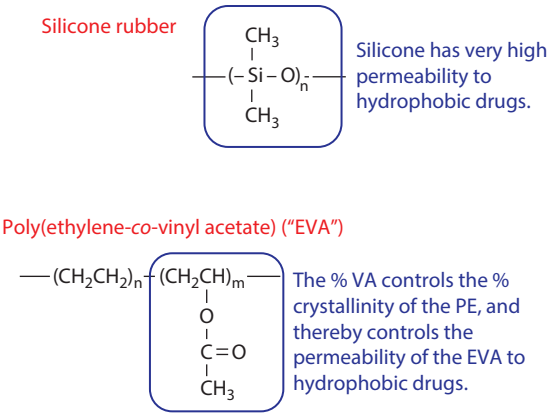


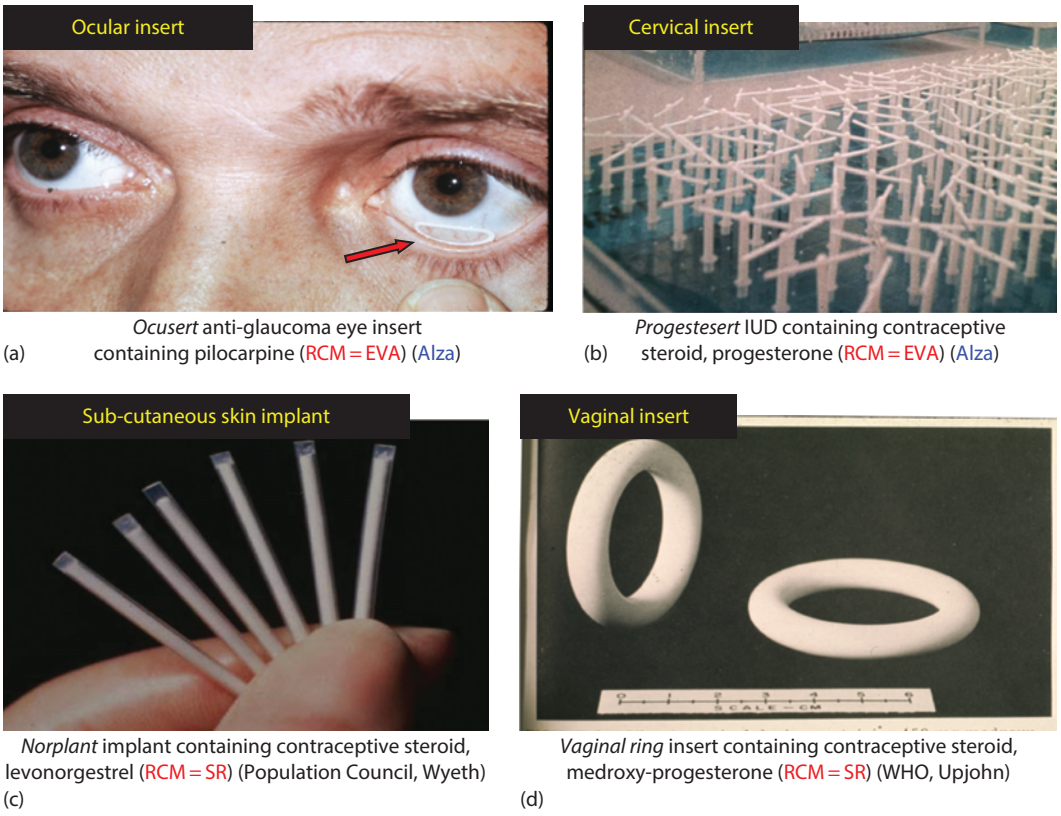
FIGURE 1.4 Silicone rubber and poly(ethylene-*co*-vinyl acetate) were the first polymers to be used as rate-controlling membrane barriers, for the controlled delivery of small hydrophobic drugs.

to become Chairman of the company's Scientific Advisory Board. In 1968, Zaffaroni founded the very first company dedicated to the development of controlled drug delivery materials and devices, which he called Alza, after the first two letters of each of his first and last names. One of the authors (ASH) was invited to become a consultant at Alza and was thus a witness to the origins and growth of the controlled DDS field and met most of the pioneers personally over the years.

The most common materials used as RCMs in the first devices were two polymers, SR and poly(ethylene-*co*-vinyl acetate) (EVA) (Figure 1.4). The EVA RCM is based on the copolymer of ethylene and vinyl acetate (VA). The VA disrupts the crystalline regions of the poly(ethylene) component, creating amorphous regions through which the drug can permeate (a drug cannot permeate through the crystalline region of a polymer). Thus, the higher the VA content of EVA, the higher the permeability of the drug through the EVA membrane. EVA RCMs may typically have as much as 40% VA.

A number of zero-order RCM DDS were developed in the 1970s and were approved for clinical use in the 1980s–1990s (Hoffman 2008). Typically, the drugs delivered were small and relatively hydrophobic, such as a variety of contraceptive steroids, as well as LHRH analogs (for treating prostate cancer) and pilocarpine (for treating glaucoma). Alza's first commercial product, the eye insert, Ocusert®, received FDA approval in 1974. The device released the antiglaucoma drug, pilocarpine, at a constant rate in the eye for 1 week, using an EVA RCM (Figure 1.5a). An EVA RCM was also used in Alza's intrauterine device (IUD), Progestasert®, approved in 1976, which provided zero-order controlled release of the contraceptive steroid progesterone, for over a month (Figure 1.5b).

In addition to the Alza Corp., others such as the Population Council, WHO, Upjohn/Pharmacia Pharmaceuticals, and Planned Parenthood were active in the development, approval process, and marketing of contraceptive drug devices. Norplant® is a controlled DDS birth control device that was developed by Sheldon Segal and Horatio Croxatto at the Population Council in New York in 1966 (Figure 1.5c). The original Norplant® consisted of a set of six small (2.4 mm × 34 mm) SR capsules, each filled with 36 mg of levonorgestrel (a progestin used in many birth control pills), for s.c. implantation in the upper arm. The implanted tubes had a 5-year duration of delivery, after which they had to be explanted surgically. Another set of six tubes could then be implanted if the patient desired it. Norplant® was approved for clinical trials in Chile in 1974 and finally approved from human use in Europe in the 1980s, followed by the United States in 1990. It was withdrawn by Wyeth Pharmaceuticals (who was marketing it in the United States) from the U.S. market in 2002 due to numerous "unwarranted" lawsuits. Production of the original Norplant® was discontinued globally in 2008.



(a) *Ocusert* anti-glaucoma eye insert containing pilocarpine (RCM = EVA) (Alza)

(b) *Progestesert* IUD containing contraceptive steroid, progesterone (RCM = EVA) (Alza)

(c) *Norplant* implant containing contraceptive steroid, levonorgestrel (RCM = SR) (Population Council, Wyeth)

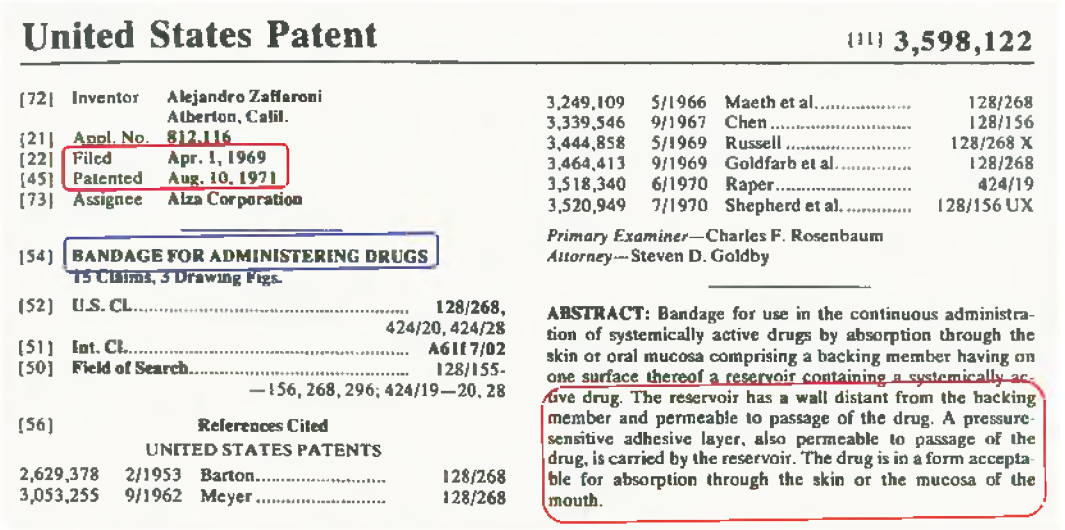
(d) *Vaginal ring* insert containing contraceptive steroid, medroxy-progesterone (RCM = SR) (WHO, Upjohn)

FIGURE 1.5 Examples of early drug delivery devices based on a drug reservoir and a rate-controlling membrane, to effect controlled release. (a) Ocusert®, an eye insert, (b) Progestasert®, an intrauterine device, (c) Norplant®, for subcutaneous implantation, and (d) an early prototype of a vaginal ring. SR, silicone rubber; EVA, poly[ethylene-*co*-vinyl acetate].

In 2006, Organon introduced a single-tube system, Implanon®, using EVA as the RCM. The implant provides controlled release of the contraceptive drug etonogestrel for up to 3 years. More recently, Valera Pharmaceuticals introduced Vantas®, a tubular s.c. implant made of Hydron®, a poly(hydroxyethylmethacrylate) (polyHEMA) hydrogel. The implant provides continuous delivery, for over a year, of the gonadotropin-releasing hormone (GnRH) analog, histrelin acetate, for the treatment of prostate cancer. Similar to Norplant® and Implanon®, the Vantas® implant is nondegradable and has to be surgically retrieved after use.

Vaginal rings were also designed as zero order, RCM, DDS. Gordon Duncan at Upjohn/Pharmacia, with support of the WHO, developed an early example comprising a SR core, loaded with a contraceptive steroid and coated with SR (Figure 1.5d). Although it did not become commercialized, this ring laid the groundwork for the subsequent development of other vaginal rings, such as the Estring® and Femring®, which were approved in the late 1990s for the delivery of estradiol acetate, in the treatment of postmenopausal urogenital symptoms. NuvaRing®, developed at Merck, is made of EVA and has been used clinically to deliver estradiol for treating postmenopausal urogenital symptoms.

Zaffaroni was also interested in the potential of transdermal drug delivery. He patented the controlled delivery rate skin patch as a "Bandage for Administering Drugs" in 1971, shortly after he had founded Alza (Figure 1.6). The Alza skin patch is a reservoir system that incorporates two release mechanisms: an initial burst release of drug from the adhesive layer and zero-order release



United States Patent [11] 3,598,122

[72] Inventor Alejandro Zaffaroni
Atherton, Calif.
[21] Appl. No. 812,116
[22] Filed Apr. 1, 1969
[45] Patented Aug. 10, 1971
[73] Assignee Alza Corporation

[54] BANDAGE FOR ADMINISTERING DRUGS
15 Claims, 3 Drawing Figs.

[52] U.S. Cl. 128/268, 424/20, 424/28
[51] Int. Cl. A61f 7/02
[50] Field of Search ..... 128/155-156, 268, 296; 424/19—20, 28

[56] References Cited
UNITED STATES PATENTS

2,629,378	2/1953	Barton	128/268
3,053,255	9/1962	Meyer	128/268
3,249,109	5/1966	Maeth et al.	128/268
3,339,546	9/1967	Chen	128/156
3,444,858	5/1969	Russell	128/268 X
3,464,413	9/1969	Goldfarb et al.	128/268
3,518,340	6/1970	Raper	424/19
3,520,949	7/1970	Shepherd et al.	128/156 UX

Primary Examiner—Charles F. Rosenbaum
Attorney—Steven D. Goldby

ABSTRACT: Bandage for use in the continuous administration of systemically active drugs by absorption through the skin or oral mucosa comprising a backing member having on one surface thereof a reservoir containing a systemically active drug. The reservoir has a wall distant from the backing member and permeable to passage of the drug. A pressure-sensitive adhesive layer, also permeable to passage of the drug, is carried by the reservoir. The drug is in a form acceptable for absorption through the skin or the mucosa of the mouth.

FIGURE 1.6 Copy of the 1971 Alza patent for transdermal drug delivery using a skin patch ("bandage").

over an extended period (e.g., several days), facilitated by the RCM built into the patch and separating the drug reservoir from the skin surface. The skin patch technology is referred to as a transdermal therapeutic system (TTS). If the RCM does not change in properties during the contact time of the patch on the skin, the drug diffusion rate across the membrane and out of the patch will be constant. The delivery rate from the patch is designed to be much slower than the diffusion of the drug through the stratum corneum (the main resistance in the skin), thus rate control is determined by the patch and not the skin. This was referred to as "putting the major resistance to drug delivery into the device."

Alza developed other types of RCMs that contain micropores, e.g., a stretched polypropylene (PP) membrane (Celgard®), with micropores that may be prefilled with mineral oil or wax. This membrane is used in some controlled-release skin patches. Since PP is highly crystalline, the wax- or oil-filled pores represent the preferred diffusion pathway for the drug. As long as the pore volume and pore interconnections within the microporous RCM do not change with the time of the patch on the skin, the drug diffusion rate across the membrane will be constant. As earlier, if the overall drug delivery rate from the patch is designed to be much slower than that by diffusion through the stratum corneum, the patch will exhibit a zero-order drug delivery rate.

The first controlled delivery skin patch commercially available was Alza's product Transderm-Scop®, approved in 1979 for the transdermal delivery of scopolamine, a drug that alleviates the discomfort of motion sickness. It was developed with the idea that Alza could get funding from the U.S. space program for use of the patch in zero-gravity conditions. Many other TTS patches were subsequently developed by Alza and other companies, allowing once-a-day or even once-a-week dosing, with reduced side effects compared to the oral route (a further description of TTS is given in Chapter 9). It is important to note that some adhesives used to adhere the patch to the skin caused skin irritation.

1.4.2 Osmotic Pressure Controlled Release: Water Diffusion through a Rate-Controlling Membrane

In the 1970s, an alternative method to achieving controlled release was developed, based on the principles of the osmotic pump. It utilizes a constant volume and constant concentration (saturated)

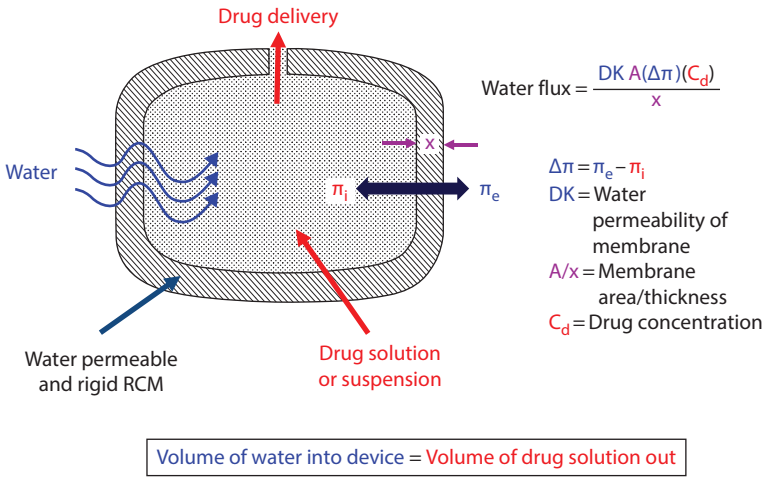


FIGURE 1.7 The elementary osmotic pump. $\Delta\pi$ = the osmotic gradient, i.e., the difference between the osmotic pressure in the surrounding environment ($\Delta\pi_e$) and the osmotic pressure inside the device ($\Delta\pi_i$).

of a drug solution, or dispersion, inside a rigid, semipermeable membrane (the RCM). Water permeates through the RCM into the device, displacing an equal volume of drug solution out of the device, through a microscopic pore created in the membrane. The water permeates into the tablet due to an osmotic pressure difference between the osmotic pressure of water within the body fluids (e.g., the GI tract fluids) and the low osmotic pressure within the saturated drug condition inside. Figure 1.7 shows the elementary osmotic pump (EOP), developed by Felix Theeuwes and colleagues at Alza in 1975, for controlled-release oral drug delivery (Theeuwes 1975).

It is important to emphasize that, while these devices exhibit zero-order drug delivery, they operate on a completely different delivery mechanism from the diffusion-driven, RCM devices described earlier. For osmotic pressure control, the constant drug delivery rate is driven by a membrane-controlled, constant rate of *water* permeation *into* the device (in contrast to *drug* diffusion *out* of the device, as described earlier), which displaces an equal volume of a constant concentration of drug solution through the pore and out of the device. The rate of drug diffusion across the membrane is negligible.

Examples of such osmotic devices include

1. Many types of oral tablets: the oral EOP is shown in Figure 1.7, further examples are described in Chapter 7
2. The implanted Duros® titanium device, developed at Alza and now fabricated and marketed by Durect (see Chapter 6, Figure 6.4)
3. The programmable infusion pump, Alzet®, also developed at Alza and now fabricated and marketed by Durect, which is widely used in preclinical animal studies (see Chapter 6, Figure 6.3)

The exit pore may be formed in drug tablets by a laser beam; it is built into the Duros® implant and Alzet® pump devices. Cellulose acetate is used for the RCM membrane of many peroral drug tablets. A small amount (e.g., 10%) of poly(ethylene glycol) (PEG) of ≈3 kDa MW is added to stimulate the start-up of water permeation into the tablet and reduce somewhat the time lag for drug delivery from the device. In the case of the implanted Duros® device, the RCM is a polyurethane block copolymer, where some blocks are of PEG, to control the rate of water permeation into the implanted titanium cylinder. One drug solution used in the Duros® implant is LHRH, dissolved in a DMSO–water mixed solvent.

1.5 LONG-ACTING INJECTABLES AND IMPLANTS

The earlier *macroscopic* devices (transdermal patches, IUDs, ocular inserts, subdermal implants, etc.) of the 1960s and 1970s were then followed, from the mid- to late 1980s, by newer parenteral DDS in the *microscopic* size range. This period in particular saw important developments in the field of depot DDS: injected or implanted, drug-loaded, polymeric microparticles, wafers, and gels.

In 1974, Robert (Bob) Langer joined the lab of Judah Folkman as a postdoctoral fellow and studied the use of nondegradable polymeric matrix systems, for the sustained release of proteins. In a seminal article in *Nature* in 1976, they showed the sustained release of active proteins from various EVA-based matrices in the rabbit eye (Langer and Folkman 1976). Various proteins (soybean trypsin inhibitor, lysozyme, catalase, insulin, and tumor angiogenesis factor [TAF]), as well as other macromolecules (including heparin and DNA), were dispersed within polymeric matrices of HEMA, EVA copolymer, and PVA and implanted in rabbit corneas. The matrices were capable of releasing biochemically active drug molecules (as demonstrated, for example, by the neovascular response produced by a TAF-loaded implant) for periods exceeding 100 days. This was one of the earliest depot DDS and this pioneering work stimulated much research and interest in the drug delivery field.

The nondegradable depot DDS studied by Langer, Folkman, and others required surgical removal and also tended to be unsuitable for the delivery of hydrophilic drugs. Therefore, further research focused more on the use of degradable polymers, consisting of mixtures of drug/degradable polymer that were implanted or injected into the body and that could release drug for a sustained period of time. These implants and injections could provide "sustained release", rather than the zero order, controlled release of the RCM DDS described earlier.

A variety of options are now possible: (1) long-acting injections (LAIs) of liquid dispersions of solid microparticles, (2) LAIs comprising solutions that subsequently form gel-like masses upon injection, due to the temperature rise or solvent dilution occurring in vivo, and (3) s.c. implants of resorbable, polymer–drug solids, in the forms of wafers, discs, or other shapes.

The polymers used in these systems have most often been based on poly(esters), with the most well-known, and commonly used, degradable polymers in drug delivery being polyesters based on the copolymers of lactic acid and glycolic acid, i.e., poly(lactic-*co*-glycolic acid) (PLGA). Poly(glycolic acid) was prepared and patented by Edward Schmitt and Rocco Polistina at Davis & Geck of American Cyanamid Co. in 1967, for use as a degradable suture, which they named Dexon®. Ethicon, a J&J subsidiary, added lactic acid and prepared the PLGA degradable suture. Ethicon licensed Cyanamid's patent and began the manufacture of a PLGA degradable suture, Vicryl®, which continues today as a highly used, resorbable suture.

Following from their use as biodegradable sutures, PLGA polymers were developed in the 1980s at the Southern Research Institute (SRI) and the University of Alabama as spherical, drug-loaded, microparticle dispersions that were injected subcutaneously as depot DDS (Okada and Toguchi 1995; Anderson and Shive 2012). Lynda Sanders of Syntex also developed several degradable microparticle depot DDS formulations in collaboration with SRI and various companies in the mid- to late 1980s (Sanders et al. 1985).

One of the first companies to market a PLGA microparticle formulation was TAP Pharmaceuticals, a joint venture formed in 1977 between the Abbott Laboratories and the Japanese pharmaceutical company Takeda. They called it Lupron Depot®, a formulation of nafarelin (a GnRH agonist) loaded into PLGA solutions and formed into microparticles. The joint venture was dissolved in 2008 and most of the company merged with Takeda. Abbott ended up with the rights to the Lupron Depot®. PLGAs were subsequently also extensively studied as nanocarriers (NCs) in the 1990s and beyond, as described in Section 1.8.

Other degradable polymers used for depot DDS include poly(caprolactone) (PCL). Poly(ethylene oxide) (PEO) and its block copolymer with poly(ethylene terephthalate) was proposed as a

degradable polymer for use in surgery in the late 1970s (Gilding and Reed 1979). Polyactive®, a block copolymer of poly(ethyleneglycol terephthalate)-*b*-poly(butylene terephthalate) and used for delivery of the anticancer drug, interferon, is based on the work of Jan Feijen at Twente University in the Netherlands (Jorgensen et al. 2006). A further group, the poly(hydroxyalkanoates) are linear poly(esters) formed in a biochemical fermentation process.

The poly(anhydrides) are a family of hydrolytically degradable polymers used in depot DDS that were conceived and synthesized in Bob Langer's laboratory at MIT (Rosen et al. 1983) and implanted in the brain by the surgeon Henry Brem. This work led to the commercial introduction in 1995 of Gliadel®, solid wafers, or discs of poly(anhydride), loaded with the cytotoxic drug, carmustine (*bis*-chloroethylnitrosourea [BCNU]), for the treatment of brain glioblastomas (see also Chapter 15, Section 15.4.2). It is historically interesting to note that Langer and Brem met as postdoctoral fellows in Judah Folkman's laboratory at Harvard Medical School.

Drug–polymer depot DDS formulations may also be injected into the body as a liquid solution of drug plus a "smart" polymer at room temperature, that phase separates to form a solid or a gel in vivo, as the polymer is warmed to body temperature and/or as the polymer solvent is diluted with tissue water (see also Chapter 6, Section 6.2.2). Solvents that have been used in the injectable solutions include *N*-methylpyrrolidone (NMP) and a solvent mixture of benzyl benzoate and benzyl alcohol (BB/BA). Three examples of the drug–polymer solutions that have been developed as depot DDS during the 1990s include the following:

1. Atrix's Atrigel®, an NMP solution of water-insoluble poly(lactic acid) (PLA) + drug. Richard Dunn of Atrix developed this injectable depot DDS in the 1990s; Atrix is now a partner of Pfizer.
2. Alza's Alzamer®, a benzyl benzoate solution of a water-insoluble poly(orthoester) containing a drug.
3. Macromed's ReGel®, an aqueous solution of a temperature-responsive triblock copolymer, PLGA–PEG–PLGA, containing a dispersion of paclitaxel as the drug. Kim, Jeong and collaborators at the University of Utah developed this novel, thermally responsive depot DDS (Jeong et al. 1997).

1.6 FURTHER DEVELOPMENTS IN ORAL CONTROLLED RELEASE

The 1950s and 1960s saw the introduction of a variety of semisynthetic, and synthetic, hydrophilic, gel-forming polymers such as hydroxypropylmethylcellulose (HPMC), hydroxypropyl cellulose, PEO, and Carbopol® by chemical companies such as Dow and Union Carbide. These polymers were "rated" by the FDA as generally recognized as safe (GRAS) materials, as a result of the Food Additives Amendment of 1958. One of the many applications of these polymers was in the field of oral sustained release, in the preparation of "swell and gel" hydrophilic matrix DDS.

In this type of DDS, a drug is dispersed in a hydrophilic polymer, such as HPMC, and compressed into a tablet. As the tablet becomes hydrated in the GI tract, the hydrophilic polymer chains hydrate, relax, and swell, thereby forming an outer, rubbery, viscous gel layer on the tablet surface (Wen et al. 2010). The gel layer slows both water penetration into, and drug diffusion out of, the tablet core. Sustained release of the drug is achieved as the API dissolves in the incoming fluids and then must diffuse out through the viscous, swollen, polymer chains (see also Chapter 7, Section 7.3.1.1). Nowadays, the majority of SR formulations for the oral route are based on "swell and gel" matrix tablets. Although easy to manufacture, drug release from this type of DDS is not zero order; instead, it typically follows first-order kinetics. The amount of drug released decreases with time because the drug diffusional path length through the matrix increases with time.

During the 1980s and 1990s, research focused on improving the delivery profile of the "swell and gel" matrix tablets, by modifying the geometry of the system in such a way as to effect a zero-order release rate. One successful design is called Geomatrix™, designed by Conte et al. at the University of Padua, Italy, and developed by Skye Pharmaceuticals (Conte et al. 1993). It is like a sandwich, with

two outer layers of drug-impermeable, nonswelling polymer that surround a central, drug-loaded, dry polymer layer. The central dry layer gradually swells in vivo, becoming a hydrogel, which releases the drug through the outer, exposed, swollen "edges" of the tablet (see Chapter 7, Figure 7.3). The basis for achieving zero order with this design is understood by examining Fick's equation, as seen in Figure 1.3, and applying it at a moment during the gel swelling as it releases drug:

$$\text{Rate of release} = \left\{ k \cdot A \left(\frac{\Delta C}{x} \right) D \cdot K \right\} \tag{1.1}$$

where

k is a constant
A is the exposed area around the peripheral face of the swelling gel
ΔC is the concentration driving force from the center of the swelling gel to the outer peripheral surface (where C is assumed to be a perfect sink concentration of 0)
x is the gel length from the center to the outer edge of the device that the drug traverses across and out of the device at any moment
D is the drug diffusion coefficient in the swelling gel
K is the drug partition coefficient in the swelling gel

With reference to Equation 1.1, as the gel "swells and gels," a number of interrelated processes occur:

- "A" will increase, which will increase the delivery rate.
- ΔC/x will decrease overall, due to two processes (1) ΔC decreases because drug is being depleted from the gel and (2) the gel thickness, x, increases, as the gel swells. Both these effects will decrease ΔC/x and thus will decrease delivery rate.
- D and K of the drug should both increase with time, as water penetration and swelling increases, especially if the drug is partially polar.

If all these potential increases and decreases in delivery rate just balance out, then the delivery rate will remain constant during the main transit time in the GI tract. This Geomatrix™ DDS technology is currently used in a number of products that are available around the world.

A different mechanism of achieving zero-order controlled release for the oral route has already been described using osmotic pressure to control drug release (Section 1.4.2). Osmotic pressure forces the drug out, in a zero-order controlled fashion, through a tiny laser-drilled orifice in the tablet (Figure 1.7). Since the original EOP described by Theeuwes in 1975, a variety of different sophisticated systems have been developed, utilizing oral osmotic technology (see also Chapter 7, Section 7.3.3).

1.7 DRUGS ON SURFACES

During the 1960s–2000s, a number of different DDS were developed in which drugs were localized onto surfaces, including (1) the anticoagulant heparin, immobilized on blood-contacting surfaces; (2) drug–polymer matrices coated on drug-eluting stent (DES) surfaces; and (3) mucoadhesive-drug formulations that have enhanced residence times on mucosal surfaces.

1.7.1 Heparinized Surfaces

Heparin was the first drug directly adsorbed or linked onto a biomaterial surface. In the late 1960s, it was physically adsorbed by ionic forces to a cationic surfactant (benzalkonium chloride), which was embedded into a graphite coating on the polymer surface (Gott et al. 1968) (Figure 1.8). The coating

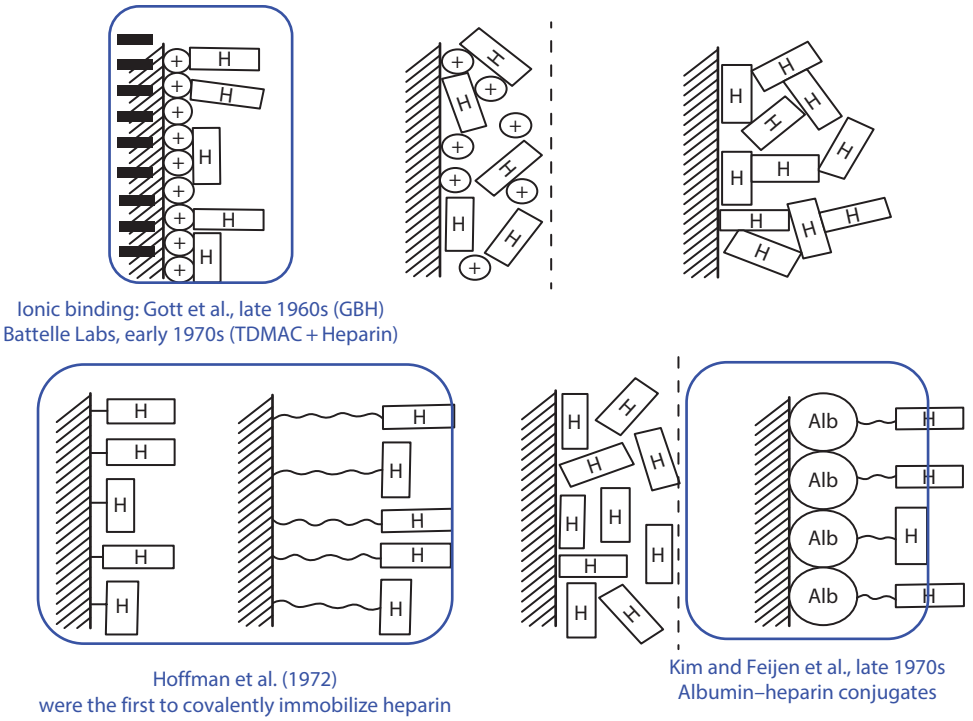


FIGURE 1.8 Heparin-coated polymers were one of the earliest polymeric drug delivery systems (1960s). GBH, graphite–benzalkoniumchloride–heparin; TDMAC, tridodecyl methyl ammonium chloride.

is called "GBH" for "graphite–benzalkoniumchloride–heparin." Heparin molecules are released by ion exchange with chloride ions from the blood plasma.

In the early 1970s, heparin was ionically linked to polymer surfaces by binding it to a cationic surfactant known as "TDMAC" (tridodecyl methyl ammonium chloride), a cationic surfactant that had been physically adsorbed by hydrophobic interactions of the dodecyl groups with surface molecules of the hydrophobic polymer (Figure 1.8). TDMAC was developed at the Battelle labs in Columbus, Ohio by Bob Leininger and Richard Falband, and marketed by Polysciences. Hoffman and colleagues in 1972 were among the first (if not the first) to *covalently* immobilize heparin on polymer surfaces (Hoffman et al. 1972). The heparin remained active, as indicated by its ability to bind antithrombin III and thrombin. They conjugated heparin to the OH groups of poly(HEMA) that had been radiation grafted onto the SR surfaces.

1.7.2 Drug-Eluting Stents and Balloons

Drug–polymer matrices have been coated onto stents and are known as drug-eluting stents, or DES (see also Chapter 6, Section 6.3.5). One of the earliest DES was the Cypher® stent of J&J, which was coated with a thin layer of a blend of poly(*n*-butyl methacrylate) and EVA, containing the smooth muscle cell antiproliferative drug, Sirolimus® (Suzuki et al. 2001). Taxus™, the DES of Boston Scientific and approved by FDA in 2004, uses a thermoplastic triblock elastomer poly(styrene-*b*-isobutylene-*b*-styrene) (SIBS). In this device, the drug paclitaxel is dispersed primarily as discrete nanoparticles (NPs) embedded in the SIBS matrix. Paclitaxel release involves the initial dissolution of drug particles from the paclitaxel/SIBS-coating surface, which exhibits an early burst release, followed by a sustained, slower, release of paclitaxel from the bulk of the coating (Ranade et al. 2004). This coating was developed and patented by Kennedy et al. at Akron University (Kennedy et al. 1990).

There is an active development and marketing of DES with struts that contain periodic "concavities" or roughened patches that are coated or filled with polymer–drug mixtures (e.g., PLA-drug) and provide sustained release of antiproliferative, cytostatic, and antithrombogenic drugs. These types of "patchy coatings" do not leave behind a residue of the polymer coating after the drug is gone.

Drug-eluting, bioresorbable stents (DEBS, also known as BDES) are also under testing; they are composed of a range of slow, bioresorbable polymers such as PLA, PCL, and their copolymers. Tyrosine polycarbonate is a bioresorbable polymer based on the amino acid tyrosine, developed by Joachim Kohn and collaborators (Kohn and Zeltinger 2005). In some cases, the totally bioresorbable stent may be coated with PLA–drug mixtures that release their drug cargoes within days and then resorb, while the stent body disappears much more slowly, allowing the blood vessel to heal from the injury sustained from the initial insertion of the stent into the blocked vessel (Abizaid and Ribamar-Costa 2010). Medtronic Corp. has recently developed a drug-coated balloon (DCB), a catheter containing a balloon that is expanded against a vessel blockage. The balloon is coated with the drug paclitaxel plus urea as an excipient. Called the In. Pact Admiral™, it received FDA approval in 2014 for treating lesions up to 18 cm in length.

1.7.3 Mucoadhesives

Mucoadhesive DDS are designed to adhere to mucosal surfaces, i.e., those epithelial interfaces with an overlying mucus layer, such as the GI tract, the nose, the lungs, the eye, etc. (as described in Section III of this book). A mucoadhesive DDS increases the residence time of a drug dosage form at the targeted mucosal surface, thereby allowing more time for the absorption process, as well as providing a greater concentration gradient to drive the process. To accomplish mucoadhesion, they are designed to interact strongly with the mucus layer, which is rich in secreted, highly hydrophilic glycoproteins. Mucoadhesive drug delivery polymers are similar to mucus in that they are highly hydrophilic, often negatively charged and highly H-bonding with the mucus layer. Poly(acrylic acid) has been a favorite mucoadhesive polymer, beginning with the seminal and pioneering work in the 1980s of Joseph Robinson and Kinam Park (Park and Robinson 1984; Park et al. 2011). Nicholas Peppas has proposed PEGylated methacrylate polymers as mucoadhesives (Serra et al. 2006).

1.8 NANOSCALE DDS

In the 1990s, the size of controlled-release DDS scaled down again so that the *micro* systems of the previous decade made way for technologies in the *nanometer* size range. Drug NCs are individual molecules or assemblies of many molecules, ranging in size from 1 or a few nm, up to several hundreds of nm. These NCs are conjugated to, complexed with, or encapsulate drug molecules.

Three basic technologies stimulated the growth of the field of nanoscale DDS:

1. PEGylation, which provided protection for biomolecular drugs and extended the circulation times of the nanoDDS
2. Active targeting to specific cells, using antibodies and ligands
3. The "enhanced permeability and retention" (EPR) effect, for passive targeting to tumor tissues

These technologies are described briefly here; a more detailed account is given in Chapter 5.

PEGylation. The most widely used synthetic polymer in nanoscale DDS is PEG. In 1969, Frank Davis of Rutgers University wanted to reduce the immunogenicity of the newly developed recombinant protein drugs that were available due to advances in biotechnology and molecular biology. He hypothesized that attaching a hydrophilic polymer might make the proteins less immunogenic. In the early 1970s, he discovered methoxy PEG (mPEG) in a company catalog; mPEG was a very convenient molecule with which to PEGylate a protein drug molecule. The first publication of

a PEG–drug conjugate appeared in 1977, based on the PhD work of Davis's PhD student, Abraham Abuchowski (Abuchowski et al. 1977). Their coupling technology yielded PEG proteins that showed not only reduced immunogenicity, but also much longer circulation times than their non-PEGylated counterparts (Davis 2002).

PEG has been incorporated into a variety of nanoscale DDS as the outer "corona" of the NC, which enhances circulation times, reduces opsonization and removal by the RES in the liver, and may also enhance tumor uptake by the EPR effect. It is important to note, however, that evidence indicates that multiple injections of some PEGylated nanoscale DDS formulations can stimulate the formation of antibodies against PEG (Ishida et al. 2007).

Poly(carboxybetaine) (PCB) is an interesting "stealth-like" polymer that has recently been studied, and its performance compared to PEGylated NPs (Yang et al. 2014). In this study, PEGylated gold NPs were completely removed from the circulation in rats 50 hours after the first injection, or 24 hours after the second injection, which was attributed to IgM recognition, binding, and removal. In contrast, more than 50% of the PCB-coated gold NPs remained in circulation at both time points, demonstrating the potential of a PCB coating to enhance circulation time.

In addition to the work of Frank Davis and colleagues who developed PEG–drug conjugates, it is interesting to note that Helmut Ringsdorf had independently published a prescient article proposing drug–polymer conjugates as new therapeutic entities in 1975 (Ringsdorf 1975) (Figure 1.9).

Kopeček, Duncan, and colleagues in Prague and the United Kingdom designed, synthesized, and tested one of the earliest drug–polymer conjugates, which was based on the water-soluble polymer HPMA. The anticancer drug, doxorubicin, was conjugated to the polymer backbone by a tetrapeptide linkage that was a substrate for a lysosomal enzyme (cathepsin B), as shown in Figure 1.10. This allowed for the release of the drug intracellularly within lysosomes (Kopeček and Kopečková 2010).

Active targeting. The discovery of monoclonal antibodies (mAb) in 1975 by Niels Jerne, Georges Kohler, and Cesar Milstein (Köhler and Milstein 1975) led to their being awarded the 1984 Nobel Prize. mAb can be coupled to drug molecules, or NC DDS, and then used as targeting ligands to

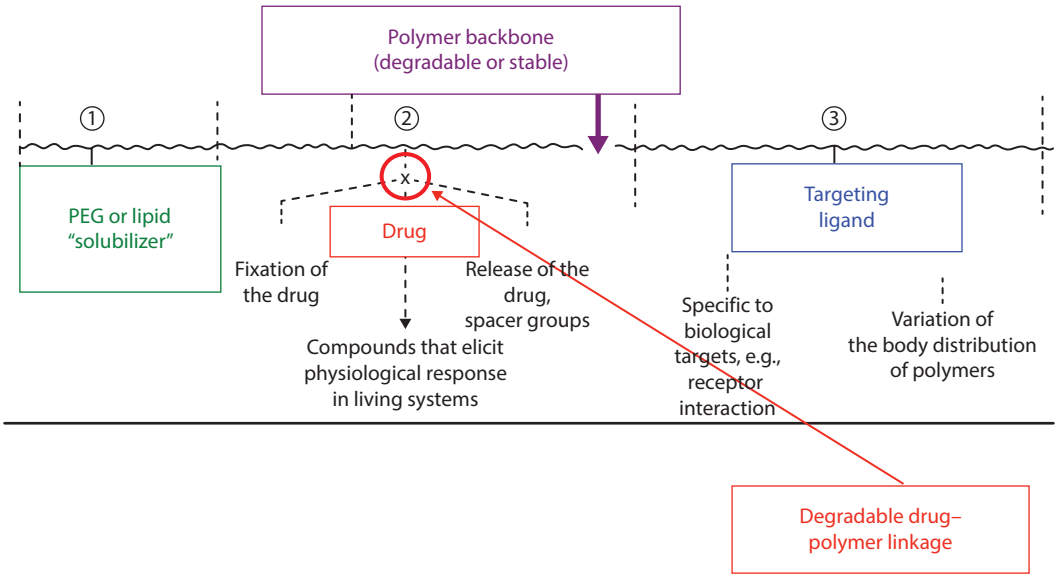


FIGURE 1.9 The components of a pharmacologically active polymer, as proposed by Helmut Ringsdorf in 1975. The polymer backbone can be degradable or stable; other components include (1) a poly(ethylene glycol) or lipid "solubilizer"; (2) the drug, which is attached to the polymer via a degradable linkage; and (3) a targeting ligand.

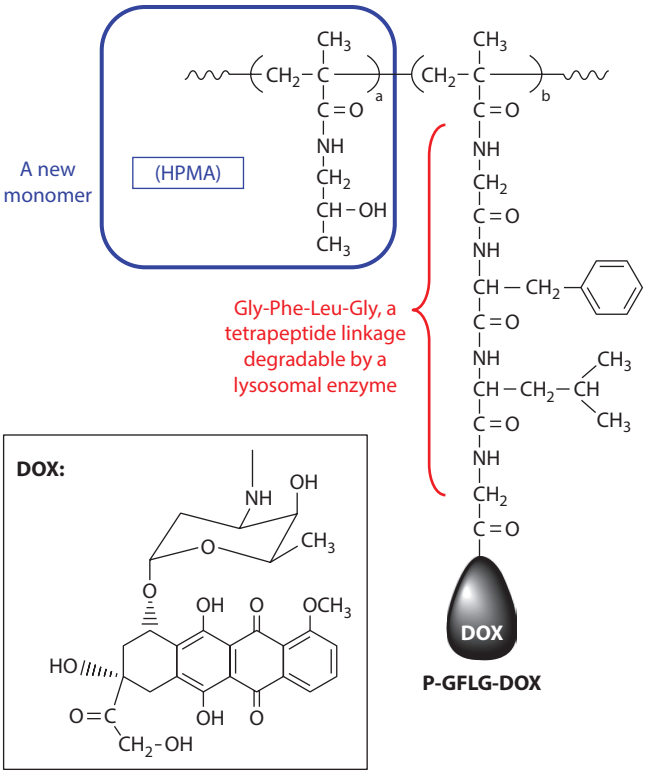


FIGURE 1.10 Drug–polymer conjugate. Poly(hydroxypropyl methacrylamide)–doxorubicin conjugate, with a tetrapeptide biodegradable linker (GFLG).

facilitate the uptake by specific cells. Erkki Ruoslahti and his PhD student Michael Pierschbacher discovered the integrin membrane receptor peptide ligand (RGD) and published it in PNAS in 1984. Many other peptide and small molecule ligands have since been used to target drugs, and NCs, to specific cells.

The EPR effect. From 1984, Hiroshi Maeda and colleagues published findings that showed tumoritropic accumulation of proteins and also their novel drug–polymer conjugate, SMANCS (Maeda et al. 1984; Matsumura and Maeda 1986; Maeda 2001). SMANCS is a conjugate of the polymer styrenemaleic acid (**SMA**) and the anticancer drug neocarzinostatin (**NCS**). They also coined the term "enhanced permeability and retention" (EPR) effect of tumor vasculature, which they described as an intrinsic pathological leakiness of the tumor blood supply, which coupled with poor lymphatic drainage, combine to facilitate the uptake and retention of SMANCS by tumor tissue but not by normal tissue (Figure 1.11).

The EPR effect is claimed to allow "passive targeting" to tumors, i.e., NCs of an appropriate size can passively enter the leaky tumor blood supply and thus accumulate in the tumor tissue. This is in contrast to the "active targeting" described earlier, which necessitates the addition of an appropriate targeting ligand.

Although these three technologies were all discovered around 1975–1984, the field of nanoscale drug delivery did not really begin to emerge until the 1990s. Since the 1990s, synthesis and testing of novel drug NCs continue to be the most active area of R&D in the drug delivery field. In addition, microfabrication techniques, leveraged from the microelectronics industry, are increasingly being used to manufacture NCs of extremely precise geometries and compositions (see also Chapter 19).

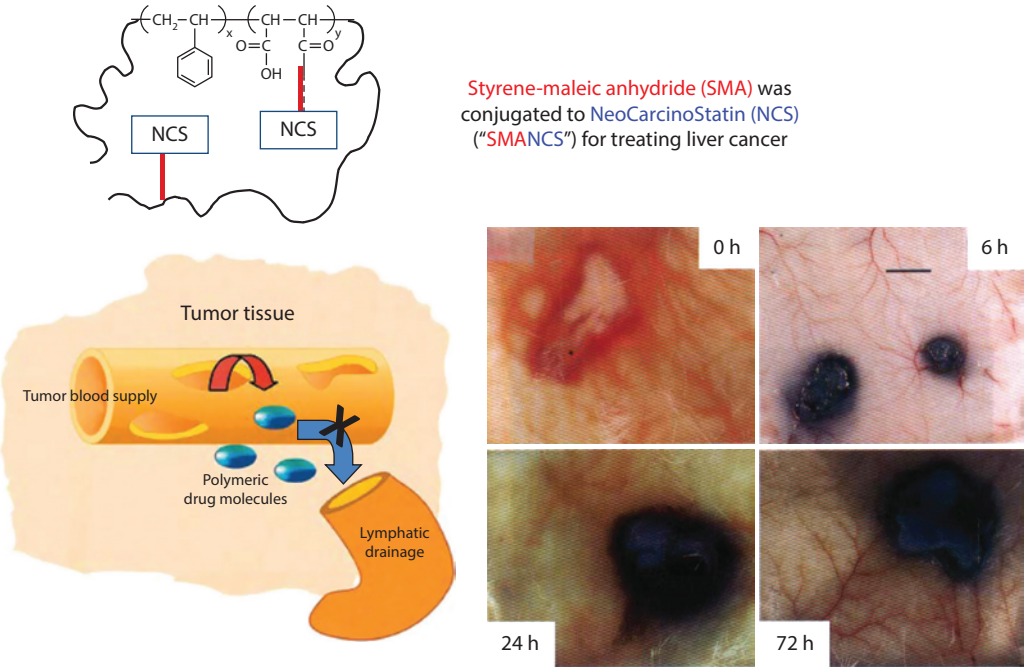


FIGURE 1.11 SMANCS drug–polymer conjugate. The "enhanced permeability and retention" effect for passive targeting to tumor tissues.

NCs come in a wide variety of compositions; they may also be partly, or totally, synthetic or natural. Figure 1.12 shows the basic molecular and NP ingredients of NCs. The synthetic polymeric NCs have a variety of structural compositions, such as homopolymers, random copolymers, block copolymers, and graft copolymers. They may also carry a net charge, e.g., polycations, such as poly(ethyleneimine) and poly(amidoamine), or poly(anions) such as poly(aspartic acid) and poly(propylacrylic acid). Some specific examples of NC are described next.

1.8.1 Liposomes

Since their discovery in 1965 and subsequent application to clinical therapy, liposomes have been a reliable dosage form in the clinic for almost 20 years (Bangham 1995; Torchilin 2005; Allen and Cullis 2013). Liposomes may be PEGylated either by conjugating PEG to either a phospholipid (a component of the liposome bilayer membrane) or a lipid that inserts into the lipid bilayer of a liposome (Figure 1.12).

One of the first liposomal DDS to be approved was the doxorubicin-loaded liposome named Doxil®. Barenholz has published a detailed history of the development of this liposomal DDS (Barenholz 2012). Other marketed liposomal DDS are described in Chapter 5.

1.8.2 Nanoparticle DDS

NPDDS may be drug–polymer mixtures or simply drug NPs with a surfactant stabilizer on their surfaces. Examples of polymeric NP carriers include the pioneering work of Patrick Couvreur on poly(alkylcyanoacrylate) NPs (Lambert et al. 2000). PLGA copolymers, developed as microparticle depot DDS a decade earlier, were also intensively investigated as NCs throughout the 1990s, and this work continues at the present time. PLGA NPs can also be PEGylated and