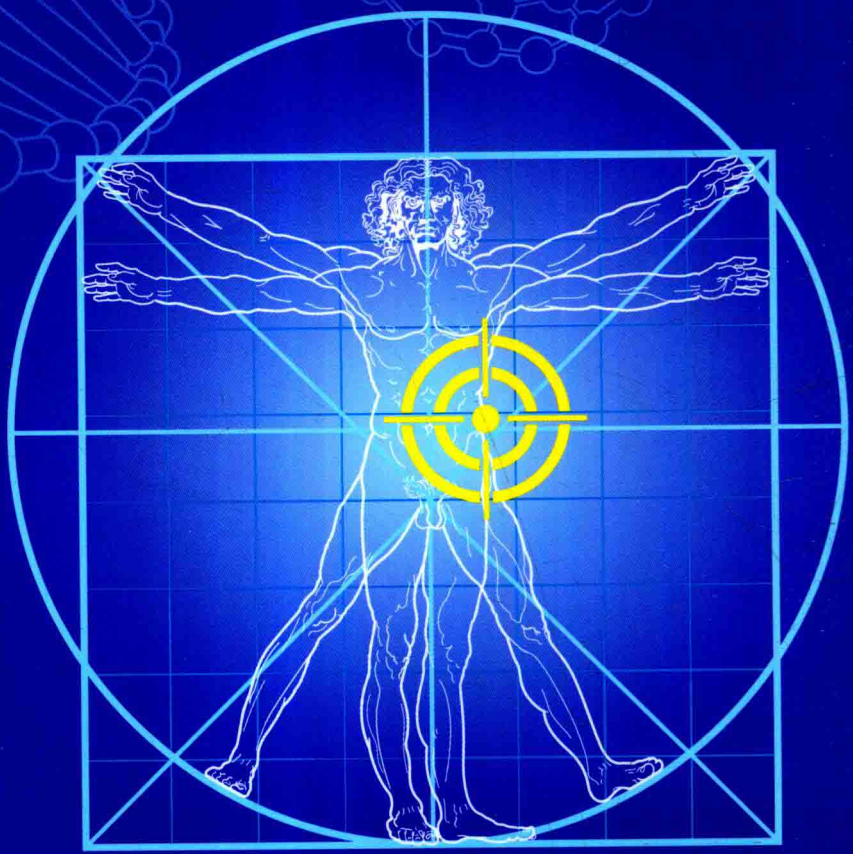
DRUG DELIVERY: FUNDAMENTALS & APPLICATIONS

SECOND EDITION



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SECOND EDITION

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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
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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.

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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*.

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Contents

SECTION V Toward Commercialization

1 Historical Introduction to the Field of Controlled Drug Delivery

Anya M. Hillery and Allan S. Hoffman

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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.

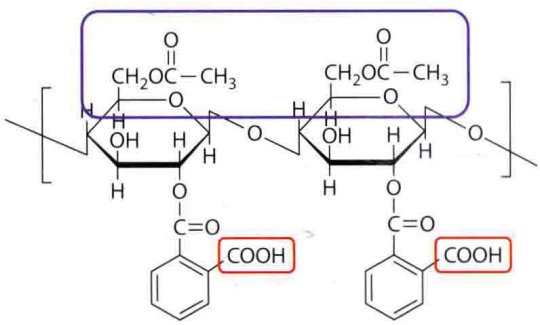
1.2 EARLY DRUG DELIVERY SYSTEMS

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.

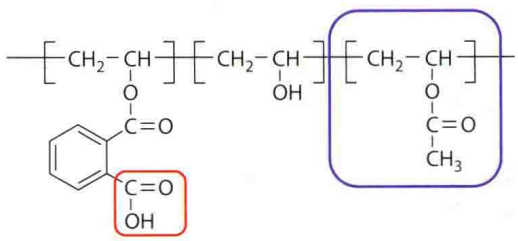
An early example of modifying drug release via the oral route was the use of enteric coatings. Tablets can be coated with the so-called enteric polymers, which are nonswelling and hydrophobic at the acidity of the stomach, but become ionized, and then dissolve and release the drug, once they enter the 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.

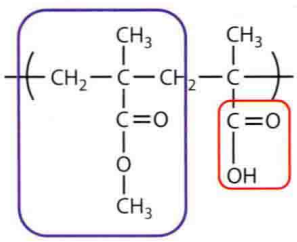
With respect to parenteral delivery, the development of controlled-release systems began in the 1930s, with the introduction of compressed pellets of hydrophobic compounds, which could provide sustained drug release over time, thereby allowing a reduction in the dosing frequency. Pellets consisting of 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



Cellulose acetate-phthalate
(CAP®) (FMC Corp.)



Poly(vinyl acetate-phthalate)



Eudragit® S
(Rohm & Haas, later DeGussa)

The balance of hydrophilic, pH-sensitive COO^- groups and hydrophobic methyl and ester groups is the key. Enteric polymers are hydrophobic in the stomach and hydrophilic in the intestines, where they dissolve.

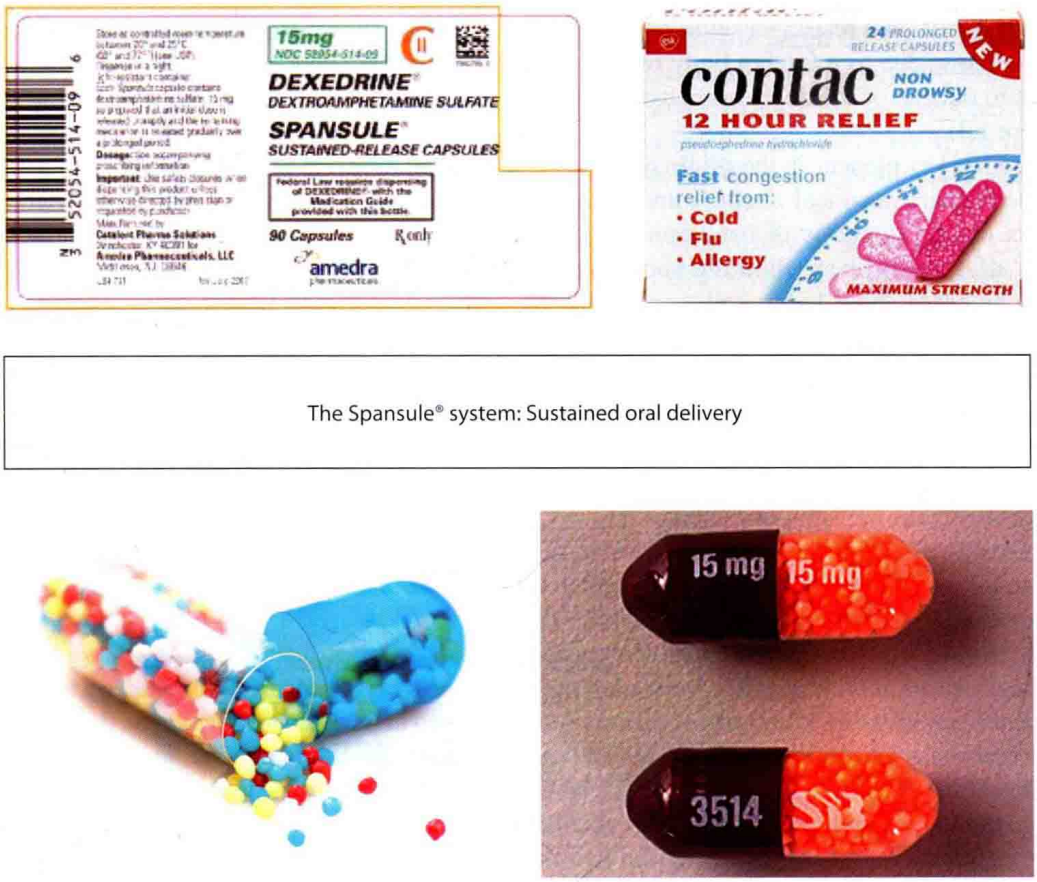
FIGURE 1.1 Enteric-coating polymers.

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.