



Drug Delivery

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PREFACE

Drug delivery is a concept closely integrated with dosage form and route of administration. This concept is often associated with rationale-based approaches, formulation strategies, drug development technologies, and carriers for facilitating transport of a drug molecule as needed to safely achieve its desired therapeutic effect. During the past two decades, numerous drug molecules with the potential of revolutionizing the treatment of life-threatening diseases have been developed. Despite remarkable advancements, many therapeutically active pharmaceutical ingredients have been dropped from initial screening portfolios because of the lack of an efficient drug delivery method. Recent progress in the field of biotechnology, however, has encouraged researchers and scientists to develop various methods employing effective delivery systems for the administration of biologics. Numerous other technologies are also addressing ways to minimize drug toxicity and reduce adverse effects while maintaining therapeutic drug concentrations and employing suitable therapeutic regimens.

Drug delivery as a field is rapidly expanding and is of vital importance to therapeutics. There is no single text, however, that covers all areas of drug delivery at a level suitable to the needs of undergraduate, graduate, and professional students as well as peers in academia and pharmaceutical research. The majority of current texts either limit themselves to conventional technologies or focus only on a single aspect of drug delivery. This book, therefore, has been designed to thoroughly examine pertinent areas and provide a platform for developing useful concepts for drug delivery.

ORGANIZATION OF THIS TEXT

As a glance at the Contents makes clear, this book provides a very comprehensive overview of the cutting-edge research being carried out in this field with a focus on drug targeting at the molecular, cellular, and organ levels.

The first chapter, “Drug Delivery: An Evolving Concept,” helps the reader understand the evolution of drug delivery concepts and recognize the factors that have an impact on drug discovery and development in pharmaceutical arenas.

Chapter 2, “Barriers to Drug Delivery,” emphasizes the challenges faced by drug delivery scientists. Various barriers to drug delivery and the strategies used to overcome or evade such barriers are discussed in detail. A basic comprehension of these barriers is required to understand the concept behind the design of the delivery systems developed to overcome them.

Chapter 3, “*In Vitro* Models in Drug Discovery and Delivery,” discusses various *in vitro* and *in silico* models used in the estimation of pharmacokinetic parameters of drugs and formulations with a special emphasis on cell culture models.

Chapter 4, “Routes of Drug Delivery,” provides a thorough understanding of the multiple routes of administration utilized to deliver the active ingredient from common pharmaceutical dosage forms. This understanding is important as the factors that must be considered in dosage form design and selection are based not only on the patient being treated but also on the biopharmaceutically relevant advantages and disadvantages of various drug delivery routes.

The focus of Chapter 5, “Novel Drug Delivery Systems,” is the wide variety of novel drug delivery systems that are currently being investigated and currently on the market.

Chapter 6, “Controlled Drug Delivery,” discusses the differences between conventional and controlled drug delivery technologies. This chapter also differentiates controlled dosage forms currently available in the clinic by mechanism of release.

Chapter 7, “Polymers in Drug Delivery,” describes the pharmaceutical applications of polymers in various dosage forms. This chapter allows for better understanding of polymer properties based on composition, molecular weight, and arrangement to facilitate custom design of novel delivery systems.

Chapter 8, “Multifunctional Nanocarriers for Tumor Drug Delivery and Imaging,” aims to provide an overview of recent progress in the rational design of and the engineering of multifunctional systems and to illustrate the cutting-edge technology being employed in such carriers with examples of multifunctional liposomes, micelles, and nanoparticles for cancer diagnosis and treatment.

In the later part of the book, we discuss various aspects of drug delivery technologies that are utilized for various dosing routes. We also discuss how the drugs can be delivered specifically to certain organs.

Chapter 9, “Oral Delivery,” provides an overview of physicochemical and biological barriers in oral delivery. Various oral dosage forms and their performance with respect to bioavailability are extensively discussed.

Chapter 10, “Ocular Drug Delivery,” delves into detailed anatomy and physiology of the eye, the importance of various routes of ocular drug administration, and constraints on conventional ocular therapy. This chapter will aid in acquiring sound knowledge of various approaches to increasing ocular drug absorption. It also discusses recent progress and specific developments relating to various formulation approaches. This chapter also discusses key advances in the application of nanotechnology for gene therapy to the eye.

Chapter 11, “Transmucosal Drug Delivery,” provides an overview of the importance of the transmucosal route and its advantages over traditional methods of drug delivery. This chapter describes the structure of oral mucosa, permeability barriers to drug absorption, and methods of assessing oral mucosal absorption. The chapter also details various drug delivery systems and techniques being used to optimize the delivery across oral mucosa. Commercialized formulations currently available in the market are also detailed.

Chapter 12, “Transdermal Drug Delivery,” describes the anatomical and physiological factors controlling drug transport across skin. Furthermore, active transdermal technologies available to enhance percutaneous absorption and various types of transdermal patches currently available on the market are covered. This chapter also provides methods for patient counseling with regard to the

proper use and precautions necessary with the application of a transdermal drug delivery system.

Chapter 13, “Pulmonary and Nasal Drug Delivery,” reviews the anatomy and physiology of the respiratory tract that governs drug delivery via the nasal and pulmonary routes. This chapter allows the reader to learn pharmaceutical and physiological factors that may affect drug deposition and absorption upon nasal and pulmonary administration. Various devices used to administer drug formulations via the respiratory route are described. A detailed and comprehensive discussion of currently available dosage forms along with recent advancements in nebulizers and metered dose and dry powder inhalers are provided. This chapter will acquaint the reader with various spacer devices and their proper usage, advantages, and disadvantages. Various respiratory drug delivery devices and formulations, as well as patient counseling for inhalational devices and drug products, are also emphasized.

Chapter 14, “Vaginal Drug Delivery,” offers basic understanding of anatomy and physiology of the vagina, physiological and physicochemical factors that may affect vaginal drug absorption, and characteristics of various vaginal drug delivery systems that are currently available on the market or are in the developmental stage.

Chapter 15, “Drug Delivery to the Central Nervous System: Breaking Down the Barrier,” describes the structure and importance of the blood–brain barrier. This chapter offers a detailed understanding of anatomical, physiological, and pharmacological mechanisms by which the blood–brain barrier protects the central nervous system. Furthermore, current strategies for CNS drug delivery, flexibility of novel drug delivery systems, and how they can be tailor–designed to enhance CNS drug delivery are extensively discussed.

Chapter 16, “Gene Delivery: An Essential Component for Successful Gene Therapy,” details the importance of gene therapy that uses a gene–coding sequence as a pharmaceutical agent. Gene therapy requires a method effective in delivering a therapeutic gene into cells and expressing proteins where treatment is needed. Several delivery systems including viral, chemical, and physical methods are discussed. Further, this chapter provides a summary on the pros and cons of each gene delivery system currently available and provides recent perspectives on remaining challenges for future development.

Chapter 17, “Peptide and Protein Drug Delivery,” discusses physicochemical differences between small molecules and protein/peptide drugs. This chapter helps in understanding the challenges faced when formulating a protein/peptide drug for oral delivery and why parenteral delivery is most often needed with such drugs. An overview of the intricacies of insulin that make non–parenteral delivery challenging and the advantages and disadvantages of different alternative routes for delivering protein/peptide drugs are discussed.

Chapter 18, “Drug Metabolomics and Proteomics Analysis in Drug Delivery and Discovery,” describes proteomics and mass spectrometric analysis including sample preparation, isolation, and purification techniques. This chapter also provides an overview of mass spectrometry instrumentation and ionization techniques. It describes top–down protein and bottom–up (shotgun) peptide sequencing and application of mass spectrometry in quantitative proteomics, that is, phosphorylation, glycosylation, and post–translational modifications.

FEATURES AND BENEFITS

Each chapter includes the following elements:

- *Learning Objectives* present the chapter's desired outcomes to the reader.
- *Chapter Outline* provides a preview of the material to be covered.
- *Review Questions* allow readers to apply what has been learned in the chapter and assess their understanding of the content.

INSTRUCTOR RESOURCES

Qualified instructors can receive the full suite of instructor resources, including the following:

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- Chapter Quizzes
- Interactive Glossary
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Ashim K. Mitra
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FOREWORD

Targeted and controlled drug delivery systems can have a massive impact on therapeutic efficacy and safety. These technologies enable maximum benefit from existing drugs and provide opportunities for successful transition to new drug entities. Such advancements have added an entirely new dimension to the pharmaceutical market with sales of these technologies now in the billions of dollars annually. Importantly, multidisciplinary training is needed to understand the interface of biology and chemistry to design novel drug delivery carriers and preparations that are effective and nontoxic. Within this book Dr. Ashim K. Mitra, Dr. Deep Kwatra, and Dr. Aswani Dutt Vadlapudi have done a great job assimilating large amounts of current information about this growing area, bringing together the foremost experts from their respective fields to yield a comprehensive look at drug delivery and its relevant issues.

Drug Delivery contains up-to-date material that will inform both novices as well as advanced learners in the field. A major strength of the book is its logical organization. For example, the human body provides multiple anatomical and physiological barriers to many drugs from easily reaching their target site. The book begins with detailed descriptions of the biological barriers to drug delivery and then covers drug delivery models, routes of administration, and controlled drug delivery systems, making sure the reader first grasps the basic concepts.

Critical for advancement of the field is the creation of novel polymeric materials, which is the subject of next chapter in the book. Here, the different types of polymers and their utilization to form nanoparticles and other novel drug delivery systems are described. The formation and characterization of multifunctional nanocarriers, which can be used for both controlled and targeted drug delivery, are also explained.

Next, specific issues with key routes of administration are detailed in individual chapters. For instance, parenteral, dermal, oral, ocular, pulmonary/nasal, mucosal, and vaginal drug delivery, and delivery to the central nervous system are all given specific attention.

Remarkably, this book also covers modern therapeutic modalities, including gene therapy as well as peptide and protein therapeutics such as antibodies. Delivery of these biologics via conventional carriers poses significant challenges, which are detailed, and numerous techniques are being developed to overcome these temporary hurdles. Moreover, a number of analytical tools are required to test delivery system efficiency, all of which are explained.

Taken together, this book is a very detailed and complete compilation of all the major topics in the field of drug delivery and will prove to be a handy "go-to" reference for students, teachers, and researchers in academia and the pharmaceutical industry.

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Ashim K. Mitra received his PhD in Pharmaceutical Chemistry in 1983 from the University of Kansas. He is currently a Curators' Professor of Pharmacy at the University of Missouri-Kansas City, as well as the Vice Provost for Interdisciplinary Research, Chairman of the Division of Pharmaceutical Sciences, and Co-director of the Vision Research Center at the University of Missouri-Kansas City School of Medicine. For the past three decades he has conducted extensive research in various drug delivery technologies, including ocular drug delivery. He and his research personnel have published more than 315 peer-reviewed research articles in high-impact international journals; published more than 550 abstracts at scientific meetings, including the annual conferences of the American Association of Pharmaceutical Scientists (AAPS), the Society of Toxicology, and The Association for Research in Vision and Ophthalmology (ARVO); have given more than 115 presentations to a wide audience (including several universities, pharmaceutical companies, and scientific organizations); and have been issued nine U.S. patents. Between 2013 and 2014 alone he has edited five books and contributed to more than 60 book chapters. Several of his articles have been recognized as being among the most downloaded articles in their respective journals.

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