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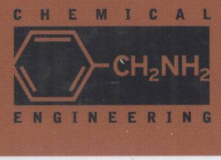

Design of Controlled Release Drug Delivery Systems

- ✔ Mechanisms of controlled release
- ✔ Targeted drug delivery
- ✔ Physiological and biochemical barriers

Xiaoling Li, Ph.D
Bhaskara R. Jasti, Ph.D

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Department of Pharmaceutics and Medicinal Chemistry
Thomas J. Long School of Pharmacy and Health Sciences
University of the Pacific
Stockton, California

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This book is dedicated to our beloved wives, Xinghang Ma and Hymavathy Jasti, and to our children, Richard Li, Louis Li, Sowmya Jasti, and Sravya Jasti. The perseverance and tolerance of our spouses over the years when our eyes were glued on computer screen, and the play-time sacrifice of our children are highly appreciated.

XIAOLING AND BHASKARA

Contributors

Brian Barclay, PE (MSChE). *Engineering Fellow, ALZA Corporation, a Johnson & Johnson Company, Mountain View, Calif.* (CHAP. 7)

Bret Berner, Ph.D. *Vice President, Depomed, Inc., Menlo Park, Calif.* (CHAP. 6)

Shiladitya Bhattacharya, M. Pharm. *Ph.D. Candidate, Department of Pharmaceutics and Medicinal Chemistry, Thomas J. Long School of Pharmacy and Health Sciences, University of the Pacific, Stockton, Calif.* (CHAP. 13)

Ramesh R. Boinpally, Ph.D. *Research Investigator, OSI Pharmaceuticals, Boulder, Colo.* (CHAP. 13)

Rajasekhar Chiruvella, M. Pharm. *College of Pharmaceutical Sciences, Kakatiya University, Warangal, India* (CHAP. 13)

Xin Guo, Ph.D. *Assistant Professor, Department of Pharmaceutics and Medicinal Chemistry, Thomas J. Long School of Pharmacy and Health Sciences, University of the Pacific, Stockton, Calif.* (CHAP. 11)

Manjusha Gutta, M.S. *Department of Pharmaceutics and Medicinal Chemistry, Thomas J. Long School of Pharmacy and Health Sciences, University of the Pacific, Stockton, Calif.* (CHAP. 13)

Bhaskara R. Jasti, Ph.D. *Associate Professor, Department of Pharmaceutics and Medicinal Chemistry, Thomas J. Long School of Pharmacy and Health Sciences, University of the Pacific, Stockton, Calif.* (EDITOR, CHAPS. 2, 3, 9)

Tzuchi "Rob" Ju, Ph.D. *Group Leader, Abbott Laboratories, North Chicago, Ill.* (CHAP. 4)

Jin-Seok Kim, Ph.D *Associate Professor, College of Pharmacy, Sookmyung Women's University, Seoul, South Korea* (CHAP. 10)

Amit Kokate, M.S. *Ph.D. Candidate, Department of Pharmaceutics and Medicinal Chemistry, Thomas J. Long School of Pharmacy and Health Sciences, University of the Pacific, Stockton, Calif.* (CHAP. 2)

Phanidhar Kotamraj, M. Pharm. *Ph.D. Candidate, Department of Pharmaceutics and Medicinal Chemistry, Thomas J. Long School of Pharmacy and Health Sciences, University of the Pacific, Stockton, Calif.* (CHAP. 7)

Ick Chan Kwon, Ph.D. *Principal Research Scientist, Biomedical Research Center, Korea Institute of Science and Technology, Seoul, South Korea* (CHAP. 10)

Xiaoling Li, Ph.D. *Professor and Chair, Department of Pharmaceutics and Medicinal Chemistry, Thomas J. Long School of Pharmacy and Health Sciences, University of the Pacific, Stockton, Calif.* (EDITOR, CHAP. 2)

Puchun Liu, Ph.D. *Sr. Director, Emisphere Technologies, Inc., Tarrytown, N.Y.* (CHAP. 4)

Ravichandran Mahalingam, Ph.D. *Post Doctoral Research Fellow, Department of Pharmaceutics and Medicinal Chemistry, Thomas J. Long School of Pharmacy and Health Sciences, University of the Pacific, Stockton, Calif.* (CHAP. 9)

Venugopal P. Marasanapalle, M.S. *Ph.D. Candidate, Department of Pharmaceutics and Medicinal Chemistry, Thomas J. Long School of Pharmacy and Health Sciences, University of the Pacific, Stockton, Calif.* (CHAP. 2)

Rudi Mueller-Walz, Ph.D. *Head, SkyePharma AG, Muttenz, Switzerland* (CHAP. 8)

Jae Hyung Park, Ph.D. *Full Time Lecturer, College of Environment and Applied Chemistry, Kyung Hee University, Gyeonggi-do, South Korea* (CHAP. 10)

Yihong Qiu, Ph.D. *Research Fellow, Abbott Laboratories, North Chicago, Ill.* (CHAP. 4)

Harish Ravivarapu, Ph.D. *Sr. Manager, SuperGen, Inc., Pleasanton, Calif.* (CHAP. 9)

Appala Raju Sagi, M.S. *Scientist, Corium International, Inc., Redwood City, Calif.* (CHAP. 13)

Anant Shanbhag, M.S. *Chemist II, ALZA Corporation, a Johnson & Johnson Company, Mountain View, Calif.* (CHAP. 3)

Sastry Srikonda, Ph.D. *Director, Xenoport Inc., Santa Clara, Calif.* (CHAP. 7)

Rama A. Shmeis, Ph.D. *Principal Scientist, Boehringer-Ingelheim Pharmaceuticals, Inc., Ridgefield, Conn.* (CHAP. 5)

Amir H. Shojaei, Ph.D. *Director, Shire Pharmaceuticals, Inc., Wayne, Pennsylvania.* (CHAP. 6)

James A. Uchizono, Pharm.D., Ph.D. *Assistant Professor, Department of Pharmaceutics and Medicinal Chemistry, Thomas J. Long School of Pharmacy and Health Sciences, University of the Pacific, Stockton, Calif.* (CHAP. 1)

Andrea Wamsley, Ph.D. *Department of Pharmaceutics and Medicinal Chemistry, Thomas J. Long School of Pharmacy and Health Sciences, University of the Pacific, Stockton, Calif.* (CHAP. 12)

Zeren Wang, Ph.D. *Associate Director, Boehringer-Ingelheim Pharmaceuticals, Inc., Ridgefield, Conn.* (CHAP. 5)

Noymi Yam, M.S. *Senior Research Engineer, ALZA Corporation, a Johnson & Johnson Company, Mountain View, Calif.* (CHAP. 3)

Preface

Discovery of a new chemical entity that exerts pharmacological effects for curing or treating diseases or relieving symptoms is only the first step in the drug developmental process. In the developmental cycle of a new drug, the delivery of a desired amount of a therapeutic agent to the target at a specific time or duration is as important as its discovery. In order to realize the optimal therapeutic outcomes, a delivery system should be designed to achieve the optimal drug concentration at a predetermined rate and at the desired location. Currently, many drug delivery systems are available for delivering drugs with either time or spatial controls, and numerous others are under investigation. Many books and reviews on drug delivery systems based on drug release mechanism(s) have been published. As the technology evolves, it is crucial to introduce these new drug delivery concepts in a logical way with successful examples, so that the pharmaceutical scientists and engineers working in the fields of drug discovery, development, and bioengineering can grasp and apply them easily.

In this book, drug delivery systems are presented with emphases on the design principles and their physiological/pathological basis. The content in each chapter is organized with the following sections:

- Introduction
- Rationale for the system design
- Mechanism or kinetics of controlled release
- Key parameters that can be used to modulate the drug delivery rate or spatial targeting
- Current status of the system/technology
- Future potential of the delivery system

Prior to discussing individual drug delivery system/technology based on the design principles, the basic concepts of pharmacokinetics and biological barriers to drug delivery are outlined in the first two chapters.

For each specific design principle, the contributors also briefly introduce the relevant pharmacokinetics (where necessary) and include the challenges of different biological barriers that need to be overcome.

It is our belief that this book provides distinctive knowledge to pharmaceutical scientists, bioengineers, and graduate students in the related fields and can serve as a comprehensive guide and reference to their research and study.

We would like to thank all the authors for their contributions to this book project. Especially, we would like to thank Mr. Kenneth McCombs at McGraw-Hill for his patience, understanding, and support in editing this book.

XIAOLING LI, PH.D.
BHASKARA R. JASTI, PH.D.
Department of Pharmaceutics and Medicinal Chemistry
Thomas J. Long School of Pharmacy and Health Sciences
University of the Pacific
Stockton, California

ABOUT THE EDITORS

XIAOLING LI, PH.D., is a professor and chair of the Department of Pharmaceutics and Medicinal Chemistry, Thomas J. Long School of Pharmacy & Health Sciences, University of the Pacific, Stockton, California. Professor Li received his Ph.D. degree from the University of Utah and had his postdoctoral training at Ciba-Geigy (now Novartis). His research interest areas are design and synthesis of novel polymers for pharmaceutical and biomedical applications, targeted drug delivery, and transport of drugs across biological barriers. He holds two patents, has published more than 30 papers, and had more than 70 presentations at national and international conferences. He serves as a consultant for various pharmaceutical and biotechnology companies.

BHASKARA R. JASTI, PH.D. is an associate professor in the Department of Pharmaceutics and Medicinal Chemistry, Thomas J. Long School of Pharmacy & Health Sciences, University of the Pacific, Stockton, California. Prior to joining the University of the Pacific, he worked as a staff scientist at Cygnus Therapeutics Systems and as an assistant professor at Wayne State University in the Departments of Pharmacy and Internal Medicine, where he also acted as an assistant director of pharmacology core. His current research interests are identifying the barriers for drug delivery and the design of targeted and mucosal drug delivery systems. Dr. Jasti has published more than 30 papers and presented more than 60 papers at various national and international meetings.

Contents

Chapter

1

Application of Pharmacokinetics and Pharmacodynamics in the Design of Controlled Delivery Systems

James A. Uchizono

Thomas J. Long School of Pharmacy and Health Sciences
University of the Pacific
Stockton, California

1.1 Introduction

In biopharmaceutics, more specifically drug delivery, pharmaceutical scientists generally are faced with an engineering problem: develop drug delivery systems that hit a desired target. The target in pharmacokinetics is generally a plasma/blood drug concentration that lies between the minimum effect concentration (MEC) and minimum toxic concentration (MTC) (Fig. 1.1).

In 1937, Teorell's two articles,[1a,1b] "Kinetics of Distribution of Substances Administered to the Body," spawned the birth of pharmacokinetics. Thus his work launched an entire area of science that deals

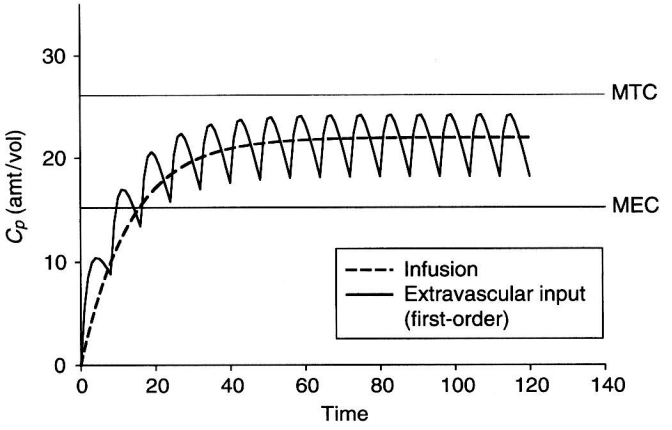

Figure 1.1 Therapeutic window.

with the quantitative aspects that undergird the kinetic foundation of controlled release delivery systems: designing a delivery device or system that achieves a desired drug plasma concentration C_p or a desired concentration profile. To be effective clinically but not toxic, the desired steady-state C_p must be greater than the MEC and less than the MTC. This desired or target steady-state C_p may be achieved by using a variety of dosage forms and delivery/dosage strategies.

1.2 Pharmacokinetics and Pharmacodynamics

Pharmacokinetics and pharmacodynamics provide the time-course dynamics between drug concentration and desired target effect/outcome necessary in the development of optimal drug delivery strategies. The basic premise is that if one is able to model the dynamics governing the translation of drug input into drug concentration in the plasma C_p or drug effect accurately, one potentially can design input drug delivery devices or strategies that maximize the effectiveness of drug therapy while simultaneously minimizing adverse effects. Figure 1.2 shows the relationship between the three main processes that convert the dose into an effect. The pharmacokinetic model translates the dose into a plasma concentration C_p; the link model maps C_p into the drug concentration at the effect site C_e; finally, the pharmacodynamic model converts C_e into the measured effect. For most drugs, C_p is in one-to-one correspondence with the corresponding effect; therefore, most delivery devices can focus primarily on achieving a desired steady-state drug plasma concentration $C_{p,ss}$. Therefore, in this chapter the focus will be on the use of pharmacokinetics to guide the design of controlled release delivery systems that achieve their intended concentration. Some issues arising owing to C_p versus effect nonstationarity (either time- or state-varying pharmacokinetics or pharmacodynamics) will be discussed in the section entitled, "Limitations of Using Pharmacokinetics Only to Design Controlled Release Delivery Systems."

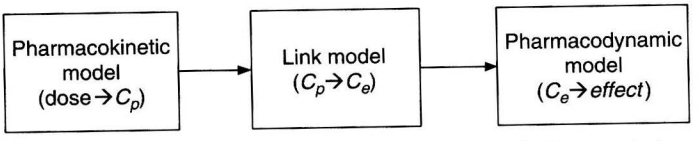

Figure 1.2 Relationship between the pharmacokinetic, link, and pharmacodynamic models.

1.3 LADME Scheme and Meaning of Pharmacokinetic Parameters

The frequently used acronym *LADME*, which stands for liberation, absorption, distribution, metabolism, and excretion, broadly describes the various biopharmaceutical processes influencing the pharmacokinetics of a drug. Since each of aspect of LADME can influence the pharmacokinetics of a drug and ultimately the design of controlled release delivery devices, this section will review and explain the relationship between LADME processes and eight common pharmacokinetic parameters (F, K, V_d, $t_{1/2}$, Cl, k_a, t_{max}, $C_{p,max}$).

Each of the LADME processes can have an impact on a drug's pharmacokinetics profile, some more than others depending on the physicochemical properties of the drug, dosage formulation, route of administration, rates of distribution, patient's specific anatomy/physiology, biotransformation/metabolism, and excretion. From a pharmacokinetics perspective, liberation encompasses all kinetic aspects related to the liberation of drug from its dosage form into its active or desired form. For example, free drug released from a tablet or polymeric matrix in the gut would be liberation. Although liberation is first in the LADME scheme, it does not need to occur first. For example, ester prodrug formulations can be designed to improve gut absorption by increasing lipophilicity. These ester formulations deliver the prodrug into the systemic circulation, where blood esterases or even chemical decomposition cleaves the ester into two fragments, a carboxcylic acid and an alcohol; the desired free drug can be liberated as either the carboxcylic acid or the alcohol depending on the chemical design. Liberation kinetics can be altered by other physicochemical properties, such as drug solubility, melting point of vehicle (suppository), drug dissolution, gastrointestinal pH, etc. Overall liberation kinetics are fairly well known because they generally can be estimated from in vitro experiments. The foundational principles governing the liberation of drug from delivery systems were laid by many, who rigorously applied the laws and principles of physics and physical chemistry to drug delivery systems.[2–12]

1.3.1 Maximum concentration, time to maximum concentration, and first-order absorption rate constant $C_{p,max}$, t_{max}, k_a

Although liberation and absorption can overlap, absorption is much more difficult to model accurately and precisely in pharmacokinetics. A great deal of work in this area by Wagner-Nelson[13–15] and Loo-Riegelman[16,17] reflects the complexities of using pharmacokinetics and diffusion models to describe the rate of drug absorption. Since most drugs are delivered via the oral

route, the gastrointestinal (GI) tract is described briefly. In the GI tract, the source of these complexities lies in the changing environmental conditions surrounding the drug and delivery modality as it moves along the GI tract. Most drugs experience a mix of zero- and first-order kinetic absorption; this mixing of zero- and first-order input results in nonlinearities between dose and C_p (see "Linear versus Nonlinear Pharmacokinetics"). A widely used simplification assumes that extravascular absorption (including the gut) is a first-order process with a rate constant k_a or $k_{e.v}$ or k_{abs}; practically, $C_{p,max}$ and t_{max} are also used to characterize the kinetics of absorption. $C_{p,max}$ (i.e., the maximal C_p) can be determined directly from a plot of C_p versus time; it is the maximum concentration achieved during the absorption phase. t_{max} is amount of time it takes for $C_{p,max}$ to be reached for a given dose [see Fig. 1.14; the equations for $C_{p,max}$ and t_{max} are given in Eqs. (1.28) and (1.29)].

1.3.2 Bioavailability *F*

While pharmacokinetics describing the rate of absorption are quite complex owing to simultaneous kinetic mixing of passive diffusion and multiple active transporters (e.g., P-glycoprotein,[18] amino acid[19]) and enzymes (cytochrome P450s[20–23]) pharmacokinetics describing the *extent* of absorption are well characterized and generally accepted, with area under the C_p curve (AUC) (Eq. 1.1) being the most widely used pharmacokinetics parameter to define extent of absorption. AUC is closely and sometimes incorrectly associated with bioavailability. AUC is a measure of extent of absorption, not rate of absorption; true bioavailability is made up of both extent and rate of absorption. The rate of absorption tends to be more important in acute-use medications (e.g., pain management), and the extent of absorption is a more important factor in chronic-use medications.[24] Frequently, the unitless ratio pharmacokinetics parameter F will be used to represent absolute bioavailability under steady-state conditions or for medications of chronic use.

$$\text{AUC} = \int C_p(t)\,dt \tag{1.1}$$

$$F = \frac{\text{AUC}_{\text{e.v.}} / \text{dose}_{\text{e.v.}}}{\text{AUC}_{\text{i.v.}} / \text{dose}_{\text{i.v.}}} \tag{1.2}$$

In Eq. (1.2), the e.v. and i.v. subscripts stand for extravascular and intravenous, respectively. F is a unitless ratio, $0 < F \leq 1$, that compares the drug's availability given in a nonintravenous route compared with the availability obtained when the drug is given by the intravenous route. F is also known as the fraction of dose that reaches the systemic circulation (i.e., posthepatic circulation).