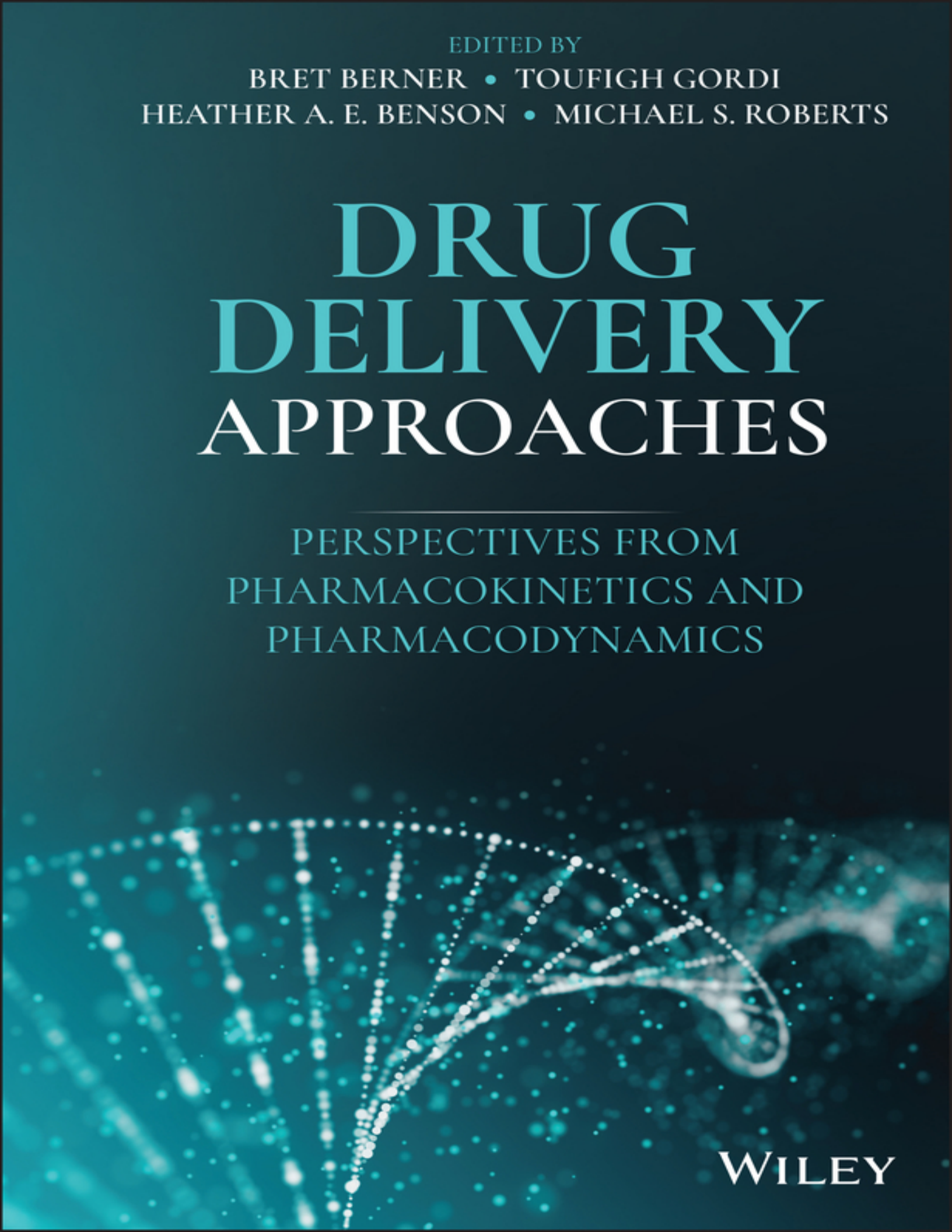


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DRUG DELIVERY APPROACHES

PERSPECTIVES FROM
PHARMACOKINETICS AND
PHARMACODYNAMICS



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Table of Contents

[Cover](#)

[Title Page](#)

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[Preface](#)

[1 Introduction: Utility of Mathematical Models in Drug Development and Delivery](#)

[1.1 Introduction](#)

[1.2 Use of Mathematical Models in Drug Development](#)

[1.3 Noncompartmental Analysis](#)

[1.4 Pharmacokinetic \(PK\) Models](#)

[1.5 Physiologically Based Pharmacokinetic \(PBPK\) Models](#)

[1.6 Pharmacokinetic/Pharmacodynamic \(PK/PD\) Models](#)

[1.7 Systems Pharmacology Models](#)

[1.8 Utility of PK/PD Analysis and Models in Drug Development](#)

[1.9 Discussion](#)

[References](#)

[2 Physiologically Based Models: Techniques and Applications to Drug Delivery](#)

[2.1 Introduction](#)

[2.2 Types of Pharmacokinetic Models](#)

[2.3 Commercial vs. Bespoke PBPK Models](#)

[2.4 Data Sources](#)

[2.5 Applications of PBPK Models](#)

[2.6 Techniques of PBPK Modeling](#)

[2.7 Summary](#)

[References](#)

[3 Oral Delivery and Pharmacokinetic Models](#)

[3.1 Introduction](#)

[3.2 Compartmental Models](#)

[3.3 Empirical Models](#)

[3.4 Physiologically Based Pharmacokinetic Models of Drug Absorption](#)

[3.5 Advanced PBPK Models](#)

[3.6 Intestinal First-pass Drug Metabolism](#)

[3.7 Spatiotemporal Models of Drug Absorption](#)

[3.8 Conclusions](#)

[References](#)

[4 Oral Site-Directed Drug Delivery and Influence on PK](#)

[4.1 Introduction](#)

[4.2 GI Anatomy and Physiology](#)

[4.3 Biopharmaceutics Classification System \(BCS\)](#)

[4.4 Applications and Limitations of Characterization and Predictive Tools](#)

[4.5 Tools to Probe Regional Bioavailability in Humans: Case Studies](#)

[4.6 Rational Formulation Design and Effective Clinical Evaluation: Case Studies Describing How to Achieve Desired Release Modality and Target PK](#)

[4.7 Conclusions](#)

[References](#)

[5 The Vasoconstrictor Assay \(VCA\): Then and Now](#)

[5.1 Introduction](#)

[5.2 Issues and Controversies](#)

[5.3 Conclusions](#)

[References](#)

[6 Topical Delivery: Toward an IVIVC](#)

[6.1 Introduction](#)

[6.2 In Vitro-In Vivo Correlation: Validating the Model of Topical Delivery](#)

[6.3 In Vitro-In Vivo Correlation: Transdermal Delivery](#)

[6.4 In Vitro-In Vivo Correlation: Bioavailability and Bioequivalence](#)

[6.5 Summary](#)

[Disclaimer](#)

[References](#)

[7 Integrated Transdermal Drug Delivery and Pharmacokinetics in Development](#)

[7.1 Introduction](#)

[7.2 Fundamentals of Transdermal Delivery](#)

[7.3 In Vivo Assessment of Drug Input and Pharmacokinetic Disposition](#)

[7.4 In Vitro Testing: Drug Release from Transdermal Systems](#)

[7.5 In Vitro/In Vivo Correlation](#)

[7.6 Clinical Safety and Efficacy Studies for Dermal Drug Development](#)

[7.7 Dosage Form Proportionality Scaling and Dose Proportionality](#)

[7.8 Supporting In Vitro Studies](#)

[7.9 Safety Studies Related to Environmental Conditions Such as Heat and Storage Conditions](#)

7.10 Active Transdermal Systems That Enhance Barrier Penetration

7.11 Conclusion

References

8 Formulation and Pharmacokinetic Challenges Associated with Targeted Pulmonary Drug Delivery

8.1 Progress on Formulations and Devices for Inhaled Drugs

8.2 Challenges for Inhaled Formulations

8.3 Factors Determining the Fate of Inhaled Drugs in the Body

8.4 Pharmacokinetic/Pharmacodynamic Correlation of Inhaled Drugs

8.5 Application of Drug Delivery System for Improving Pharmacokinetic/Pharmacodynamic Parameters of Inhaled Drugs

8.6 Conclusion

References

9 Oral Transmucosal Drug Delivery

9.1 Introduction

9.2 Structure and Physiology of the Oral Mucosa

9.3 Drug Properties Which Influence OTMD

9.4 Buccal and Sublingual Formulations

9.5 Models to Study OTDD

9.6 Feasibility of Systemic Delivery Based on In Vitro Permeation Studies

9.7 Conclusion

References

10 PK/PD and the Drug Delivery Regimen for Infusion in the Critical Care Setting

[10.1 Introduction](#)

[10.2 PK/PD Properties and the Mode of Infusional Drug Delivery for Antibiotics](#)

[10.3 Changes in PK/PD and Infusional Drug Delivery Regimens in Critically Ill Patients](#)

[10.4 Short Intermittent Infusions](#)

[10.5 Extended Infusions](#)

[10.6 Continuous Infusion](#)

[10.7 Conclusions](#)

[References](#)

[11 Virtual Experiment Methods for Integrating Pharmacokinetic, Pharmacodynamic, and Drug Delivery Mechanisms: Demonstrating Feasibility for Acetaminophen Hepatotoxicity](#)

[11.1 Introduction](#)

[11.2 Results](#)

[11.3 Methods](#)

[11.4 Discussion](#)

[References](#)

[12 Personalized Medicine: Drug Delivery and Pharmacokinetics](#)

[12.1 Personalized Medicine](#)

[12.2 Drug Delivery in Personalized Medicine](#)

[12.3 Pharmacokinetic Analysis for Personalized Drug Delivery](#)

[12.4 Challenges and Opportunities in Personalized Drug Delivery](#)

[12.5 Conclusions](#)

[References](#)

[Index](#)

[End User License Agreement](#)

List of Tables

Chapter 1

[Table 1.1 NCA parameter estimates \(geometric mean except for \$t_{\max}\$ given in med...](#)

[Table 1.2 Pharmacokinetic model parameter estimates and associated variabilit...](#)

Chapter 2

[Table 2.1 Example model code.](#)

Chapter 3

[Table 3.1 Parameter values for the traditional PBPK model of intestinal drug ...](#)

Chapter 4

[Table 4.1 Mean \(sd\) fluid volumes \(ml\) throughout the GI Tract.](#)

[Table 4.2 Human intestinal transporters shown to be involved in the transport...](#)

[Table 4.3 Mean and range in transit times in anatomical regions of GI tract.](#)

[Table 4.4 Comparison of FDA, EMA, Canada, and WHO guidances covering the BCS ...](#)

[Table 4.5 Cell-culture models used for drug permeability assessment.](#)

[Table 4.6 Strengths and limitations of ex vivo and in situ intestinal permeab...](#)

[Table 4.7 Applications of PBPK modeling and simulation for oral drug delivery...](#)

[Table 4.8 Comparison of animal and human gastrointestinal systems.](#)

[Table 4.9 Summary of electromechanical capsules and devices utilized to asses...](#)

[Table 4.10 Characterizations of the lipid formulation classification system.](#)

[Table 4.11 Enteric-coating polymers.](#)

Chapter 5

[Table 5.1 Ninety percent confidence intervals \(CIs\) using Locke's method for ...](#)

[Table 5.2 Dose duration used for testing = 400 min and ED₅₀ = 400 minutes.](#)

[Table 5.3 Dose duration used for testing = 200 minutes when ED₅₀ = 400 minute...](#)

Chapter 6

[Table 6.1 Total absorption from an IVIVC study conducted with a harmonized pr...](#)

[Table 6.2 Comparison of primary endpoints for test and reference tretinoin ge...](#)

[Table 6.3 In vitro-in vivo comparison of five generic glucocorticoid test pro...](#)

Chapter 7

[Table 7.1 Different skin permeation rates in static Franz-type diffusion cell...](#)

[Table 7.2 Required or supportive clinical studies in support of transdermal d...](#)

Chapter 8

[Table 8.1 Current use of inhaled drugs for pharmacotherapy.](#)

Chapter 9

[Table 9.1 Examples of oral transmucosal formulations currently available.](#)

Chapter 10

[Table 10.1 Summary of meta-analyses assessing the outcome benefit of continuo...](#)

List of Illustrations

Chapter 1

[Figure 1.1 Mean losmapimod concentration at each time point with standard er...](#)

[Figure 1.2 Schematic presentation of a two-compartment pharmacokinetic model...](#)

[Figure 1.3 An illustration of a physiologically based pharmacokinetics model...](#)

[Figure 1.4 The peak effect lags behind the peak concentration of baicalin an...](#)

[Figure 1.5 A portion of a graphical representation of a type 2 diabetes mode...](#)

[Figure 1.6 Plasma concentration-time profiles of artemether following 25 mg/...](#)

[Figure 1.7 Schematic presentation of a three-compartment model describing th...](#)

[Figure 1.8 Simulated regadenoson plasma concentrations and heart rate in sub...](#)

[Figure 1.9 Regadenoson plasma concentration in subjects with varying degrees...](#)

[Figure 1.10 Individual heart rate changes from baseline vs. regadenoson plas...](#)

[Figure 1.11 Individual ursodiol concentration-time profiles for five infants...](#)

[Figure 1.12 The Bile Acid PhysioPD™ Platform.](#)

[Figure 1.13 \(a\) Gall bladder secretion rate affects initial distribution and...](#)

[Figure 1.14 Schematic presentation of bile acid transporters and their locat...](#)

Chapter 2

[Figure 2.1 **An example PBPK model.** The code for the model in the R language i...](#)

[Figure 2.2 **A flow-limited compartment model with elimination.** This mod...](#)

[Figure 2.3 **Dissolution submodel.** A model where the dissolution rate of an or...](#)

[Figure 2.4 **Hepatic submodel.** A well-stirred hepatic submodel with an impleme...](#)

[Figure 2.5 **Renal submodel.** An implementation of a renal submodel, based on W...](#)

[Figure 2.6 **The effect of free fraction on partition coefficient.** The tissue:...](#)

[Figure 2.7 **Allometric scaling of an organ.** Allometric scaling of a single or...](#)

[Figure 2.8 **Maturation models of glomerular filtration rate \(GFR\).** The relati...](#)

[Figure 2.9 **Sensitivity analysis of AUC predictions for a semi-PBPK model...**](#)

Chapter 3

[Figure 3.1 Time courses of plasma concentration for the first-order absorpti...](#)

[Figure 3.2 Time courses of plasma concentration for the first-order absorpti...](#)

[Figure 3.3 Schematic diagram of the transit compartment model of absorption ...](#)

[Figure 3.4 Time course of plasma concentration for the parallel input first-...](#)

[Figure 3.5 Time courses of plasma concentration and input for the Weibull \(a...](#)

[Figure 3.6 Schematic diagram of the traditional PBPK model of absorption.](#)

[Figure 3.7 Time courses of the fraction of oral dose in the reservoir and in...](#)

Chapter 4

[Figure 4.1 **Gastrointestinal pH profile from one subject using the SmartPill ...**](#)

[Figure 4.2 **Intestinal transporters involved in oral drug absorption.**](#)

[Figure 4.3 **Examples of predictive tools used to estimate intestinal permeabi...**](#)

[Figure 4.4 **Correlation between human jejunal and PAMPA permeabilities.**](#)

[Figure 4.5 **Schematic of drug transport assay in cell monolayers cultured on ...**](#)

[Figure 4.6 **Schematic of a small piece of intestinal epithelial tissue mounte...**](#)

[Figure 4.7 **Schematic of ex vivo everted intestinal sac experiment.** \(a\) Intes...](#)

[Figure 4.8 **Schematic drawing of in situ intestinal perfusion with venous sam...**](#)

[Figure 4.9 Schematic drawing of the Loc-I-Gut instrument.](#)

[Figure 4.10 Comparisons of human and animal bioavailability.](#)

Chapter 5

[Figure 5.1 Typical blanching responses following application of topical cort...](#)

[Figure 5.2 Sigmoidal dose-response curve. \$R_1\$ and \$R_2\$ represent the pharmacody...](#)

[Figure 5.3 Visual response profiles of different dose durations.](#)

[Figure 5.4 Tristimulus colorimetry where the reflected light is recorded in ...](#)

Chapter 6

[Figure 6.1 IVIV ratios of total absorption for all 92 data sets plotted on l...](#)

[Figure 6.2 IVIV ratios of total absorption for 11 fully harmonized data sets...](#)

[Figure 6.3 Comparison of the rate of absorption of estradiol and testosterone...](#)

[Figure 6.4 Comparison of in vitro rate of absorption profiles of prototype f...](#)

Chapter 7

[Figure 7.1 Amount of salicylic acid \(1%\) w/v transported across isolated hum...](#)

[Figure 7.2 AUC and \$C_p\$ profiles vs. time for a 10 cm² transdermal buprenorphi...](#)

[Figure 7.3 Deconvolution of an input rate-limited pharmacokinetic model: eff...](#)

[Figure 7.4 Effect of error on estimation bias resulting from discrete convol...](#)

[Figure 7.5 In vitro vs. in vivo nicotine cumulative release from a nicotine ...](#)

[Figure 7.6 In vivo-in vitro correlation of between the amount of fentanyl hy...](#)

[Figure 7.7 The linear relationship between applied current and amount of fen...](#)

Chapter 8

[Figure 8.1 Design space considerations for development of inhalation product...](#)

[Figure 8.2 Biodistribution of inhaled drugs. Solid and dotted arrows mean tr...](#)

Chapter 9

[Figure 9.1 Schematic of the oral mucosa.](#)

[Figure 9.2 Schematic representation of pathways for oral transmucosal drug d...](#)

Chapter 10

[Figure 10.1 Schematic illustration of the concentration-time profile of diff...](#)

Chapter 11

[Figure 11.1 Mouse Analog components and their organization. \(a\) Mouse Analog...](#)

[Figure 11.2 Events within vHPCs and Analog-mouse relationships. \(A\) Virtual ...](#)

[Figure 11.3 Three of four plausible Mechanisms falsified. \(a\) Only APAP meta...](#)

[Figure 11.4 The relative locations of Hepatocytes are graphed in two differe...](#)

[Figure 11.5 Shown are measurements from identical Mouse Analog experiments d...](#)

[Figure 11.6 Cascading events within Lobules. \(a\) During an experiment that u...](#)

[Figure 11.7 Inhibition of Hepatotoxicity. \(a\) Results are from four experime...](#)

[Figure 11.8 Targeted Attributes: pharmacokinetic similarities. \(a\) Shown are...](#)

Chapter 12

[Figure 12.1 Pharmacotherapy and individualized drug therapy in the context o...](#)

Drug Delivery Approaches

Perspectives from Pharmacokinetics and Pharmacodynamics

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Preface

Drug delivery aims to enable appropriate drug absorption based on the physical and chemical properties, expected dose, and route of administration. For new chemical entities, drug delivery is initially expedient and adapts the dosage form of the active compound to the stage of development based on feedback from the iterative understanding of the pharmacokinetics (PK), pharmacodynamics (PD), and potential sources of variability of the candidate drug. In actual practice, the final formulation is often based at most on the determination of a dose response. Models combining physical and pharmacokinetic properties of a drug candidate with dissolution, in vivo studies, and known transporter and biomarkers have been shown to predict the time course of events successfully in vivo. To improve delivery of older chemical entities, whether controlled release, modified release, temporally or site-controlled delivery, development of a target pharmacokinetic profile to optimize efficacy for duration and/or to reduce adverse events is the starting and ending point for designing a dosage form.

This book discusses the options for drug delivery within the available routes of administration to achieve the target profiles and approaches as defined by these models. It is intended for use by graduate students and novice and skilled practitioners, who are developing either new or repurposed drugs. In particular, this book should prove useful to pharmaceutical scientists and engineers, including formulators, pharmacokineticists, clinical pharmacologists, and those interested in the interaction of these disciplines.

This book begins with an appreciation of modeling of drug absorption and physiological effects and the use of pharmacokinetic and physiologically based models and follows with an introduction to physiological-based pharmacokinetics (PBPK). For the most common route of delivery, oral administration, there are chapters dealing with both PBPK and the multiplicity of options for oral drug delivery dosage forms. Endpoints that may substitute for measures of delivery or efficacy and rigorous skin permeation testing are discussed as targets for topical drug delivery and may have both development and regulatory applications. In the case of systemic transdermal delivery, understanding the pharmacokinetics of the formulation and the drug is essential to guide formulation from earliest conception throughout development. Separate chapters discuss the biological and delivery approaches to pulmonary and mucosal delivery. For emergency care settings, the relationship between parenteral infusion profiles and PK/PD is the key topic discussed. The book concludes with some more recent trends with chapters discussing virtual experiments to elucidate mechanisms and approaches to drug delivery and personalized medicine.

We would like to thank all the authors for their contributions to this book. We wish to especially thank our co-editors, Heather Benson and Michael Roberts, for conception, initiation, and review of this book and our editor at Wiley, Jonathan Rose, for his patience and support during the writing of this book.

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1

Introduction: Utility of Mathematical Models in Drug Development and Delivery

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1.1 Introduction

Models, particularly mathematical models, have been widely used to understand different aspects of human lives for a long period of time. Mathematical models not only can help explain observations, but also aid in predicting outcomes of experiments. Models are frequently used in our daily lives. As an example, consider the following equation as a model:

$$\text{Distance} = \text{Speed} \times \text{Time}$$

Knowing the relationship between distance, speed, and time, we use the model to predict the time to reach our destination on a trip. Furthermore, we plan our daily lives by predicting the time it takes for a trip or a simple question of whether we will be on time for a meeting. For this well-established model, instead of performing the experiment of driving from point A to B to know how long it may take, we can have a good estimate of the time by knowing the distance of the destination is from us and how fast we expect to travel. Models can simplify our

experiments or even alleviate them. The powerful ability of models to predict outcomes of unknown experiments makes them an essential part of a wide range of modern industries, from aviation to auto to computer and financial entities. New airplane designs are tested less than a handful times in the air before large-scale production starts and they are in regular use. New car crash tests are performed in computer simulations before an actual prototype is crash-tested a few times. Models help advance product development at a faster rate and a fraction of the cost associated with actual experiments. It is not surprising that the use of mathematical models has gained widespread attention within the pharmaceutical industry and with regulators. With drug development being a lengthy and enormously expensive process, mathematical models have the potential of optimizing a therapeutic regimen, decreasing costs, and shortening the timelines significantly.

In this chapter, we describe a few mathematical models and their utility in drug development and provide examples of the use of these models in predicting clinical study outcomes or indicating possible causes of the observations, thereby helping researchers focus on areas that have the most impact on the development path of a drug. Within physiologically- based pharmacokinetic (PBPK) in regulatory submissions, only a small fraction, quoted as 6% of PBPK models, focused on drug delivery [\[1\]](#), whether it be food effects or issues in drug absorption. In some exceptional cases, the verification of the PBPK model was sufficient to avoid bioequivalence studies. In this chapter, we focus mostly on models of the drug delivery itself to design or select the target delivery profile or the dosage form itself. Other chapters throughout this book will provide more detailed descriptions of the principles of

developing mathematical models in the drug-development process and for the different routes of drug delivery.

1.2 Use of Mathematical Models in Drug Development

The relationship between dose and effect of a remedy must have been known to ancient healers, who often used mixtures of different herbs and other organic material at certain proportions to combat diseases. Despite significant changes to pharmacological intervention aimed at mitigation of symptoms and curing various diseases, drug-development goals today are strikingly similar: find the dose of a compound that provides the maximum desired effect while avoiding unwanted side effects. This central question of what dose (amount, frequency) is a major reason for late-phase, confirmatory clinical development programs [2]. In early stages of the modern pharmaceutical industry, the focus was on establishing a dose-response relationship. With advances in analytical chemistry to allow measurement of drug concentrations in blood, plasma, urine, or other body fluids, the focus has shifted to elucidating a concentration-response, or in broader form, dose-concentration-response relationships. This shift is logical as the larger observed variability in and the complexity of a dose-response relationship is reduced when investigating the concentration-response. Furthermore, concentration measurements offer the possibility to follow the temporal changes of drug concentrations, thereby providing a tool to understand the time course of the pharmacological effect of a compound. Mathematical models that could describe the time course of drug concentrations were first proposed in late 1930s [3,4]. However, due to the complexity of models required and the lack of computers, only models solved by analytical

solutions could be developed. The perceived complex underlying mathematics resulted in the utility of mathematical models not being appreciated by the medical community. Introduction of physiologically related parameters such as clearance during 1970s made it easier for the medical community to understand and appreciate these models by relating them to the biology of the disease and the pharmacology of the treatment [5]. Furthermore, academic centers contributed to the advancement of general concepts of using mathematical models to describe the time course of drug concentrations in the body (pharmacokinetics, PK) and its effects (pharmacodynamics, PD) [6-8].

Mathematical models have two main functions: describing observations and predicting untested scenarios using simulations. Thus, models are modified when new experimental data becomes available. that are not consistent with the original model. The process of model development involves building simple models based on limited available data. This simple model is then used to guide the design of future studies. Once a new study is performed, the generated data are compared to the simulations by the model to test its validity. If the new data agree with the predictions of the model, the experimental data can be added to the data pool and re-estimate the model parameters using a larger data set. On the other hand, if the model was unable to predict the new data, the underlying assumptions or the model may be modified to include new insights gained through the new experiment. This cycle of learning and testing is an essential part of the model development process and is routinely used in drug development [9,10]. Early development programs of a new drug can be more efficient by developing and enhancing the relevant models, allowing for more accurate and reliable design and prediction of clinical studies.

1.3 Noncompartmental Analysis

Although generally not considered as mathematical modeling, noncompartmental analysis (NCA) of a drug's plasma concentration data over time adds substantial understanding of its PK properties and is therefore briefly described here.

NCA refers to estimating various PK parameters of a compound through simple analysis of its concentration-time profiles at a biological fluid (most commonly plasma), where drug concentrations have been measured. Although the same principles are used when other body fluids, e.g. blood or saliva, are used, in this chapter we will refer to plasma drug levels, the most widely used sample collection medium. [Figure 1.1](#) shows the concentration-time profile of losmapimod, a p38 mitogen-activated protein kinase inhibitor, after intravenous (i.v.) and oral (p.o.) administrations [11]. Since the entire administered dose of the drug is available to the body after an i.v. dose, the bioavailability equals 100% or 1 after an i.v. administration. After a p.o. administration, part of the drug may not reach the systemic circulation due to various reasons: it may degrade in the intestinal tract; it may not be fully absorbed; or drug molecules may be metabolized by enzymes in the gut wall or liver before reaching the circulation. Therefore, the bioavailability of the drug may vary from 0 (not at all bioavailable) to 1 (fully bioavailable). Losmapimod in [Figure 1.1](#) has a bioavailability of 0.62.

transporters

active [105](#)

adenosine triphosphate (ATP)-binding cassette family
(ABC transporters) [104](#)

compounds [105](#)

diffusion gradient [105](#)

efflux [105](#), [106](#)

high capacity [106](#)

human intestinal [106](#), [107](#)

intestinal [105](#), [106](#), [108](#)

low affinity [106](#)

solute carrier family (SLC) [104](#)–106

substances [105](#)

two-compartment model [5](#)

Tyvaso® [318](#)

u

UDP-glucuronosyltransferase (UGT) [136](#)

ultrasound [288](#), [289](#)

v

vancomycin [366](#)–367

vasoconstrictor (VC) [242](#)

vasoconstrictor assay (VCA)

applications [222](#)-224

BE assessment, topical corticosteroid products [221](#),
[236](#)

chromameter assessment [225](#)-226

circadian activity [229](#)

dose-response curve [234](#)-235

ED [50](#) with potency classification, product [235](#)-236

erythema response, application sites [230](#)

generic topical corticosteroid products [236](#)

HSBA [221](#)

market approval, European Union [231](#)-232

occlusion [230](#)

PD response data [228](#)-229

potency ranking, topical corticosteroid products [232](#)-
233

procedures [222](#)-224

sigmoidal dose-response curve [223](#)

topical corticosteroid application [221](#), [222](#)

visual assessment [224](#)-225

visual vs. chromameter assessment [226](#)-227

Ventavis [318](#)

virtual experiment methods

APAP metabolism [393](#)-394, [399](#)

broad requirements [386](#)-388

damage products [395](#)

data types [390](#)

death delay [399](#)

GSH depletion [394](#), [400](#)

iterative refinement (IR) protocol [388](#)-389, [400](#)

liver/lobular form and function [392](#)-393

mouse analogs

NZ-Mechanism [399](#)

validation [391](#)-392

verification [392](#)

mouse body [397](#)-399

PP-to-CV gradients [394](#)

prediction [388](#)

quality assurance and control [390](#)-391

repair events [395](#)-396

sensitivity analyses [396](#)-397

triggering hepatocyte death [395](#)

uncertainty quantification [396](#)-397

visual analog scale (VAS) [292](#)

visual assessment [224](#)-225, [228](#)

W

Wagner–Nelson method [266](#), [277](#)
water-insoluble agents [182](#)
water-soluble polymers [170](#)
Weibull model [83](#)–84
World Health Organization (WHO) [118](#)

X

X-ray powder diffraction [165](#)

Z

zero-order absorption [78](#)