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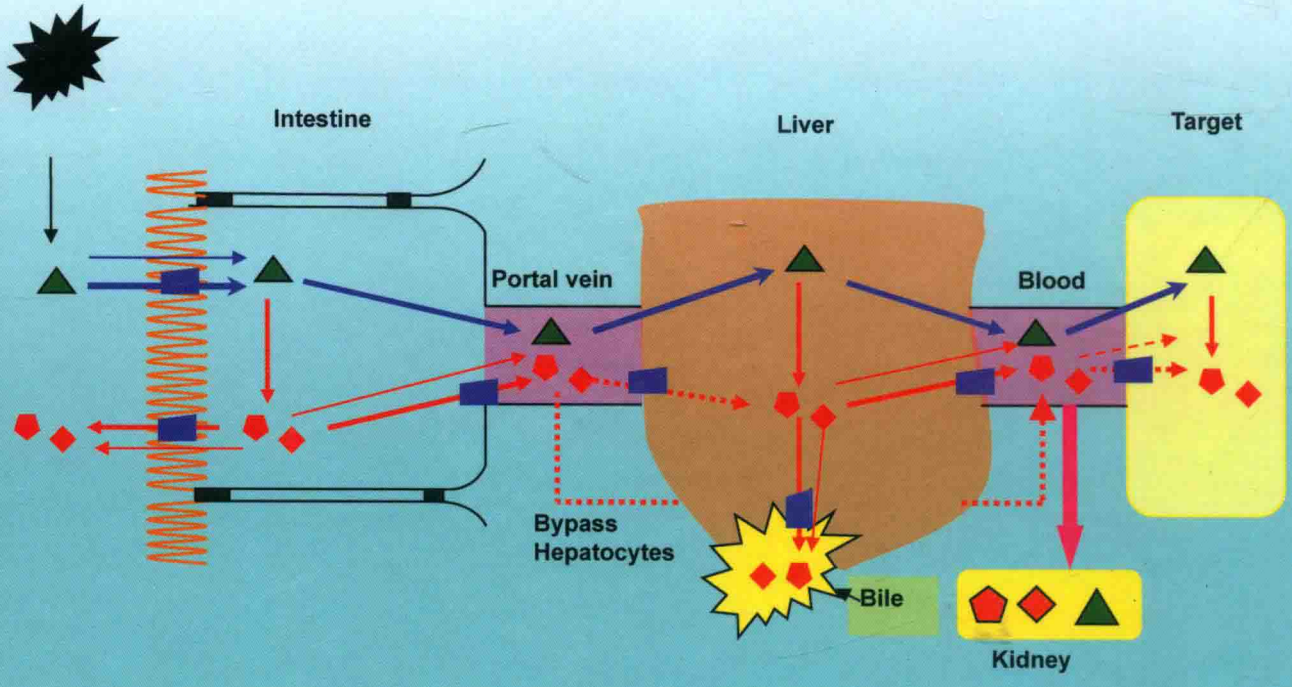
ORAL BIOAVAILABILITY

Basic Principles, Advanced Concepts, and Applications

Edited by
Ming Hu and Xiaoling Li



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A complete list of the titles in this series appears at the end of this volume.

Dedicated to my dad Zhengye Hu whose inspiration lives on with this book,
to my mom Qihua Chang whose constant love and encouragement persists to this date,
to my wife Yanping Wang whose company endears constant push for perfection, and
to my children Vivian and William whose energy and noise are missed now they are in college.

—Ming Hu

Dedicated to my grandmother Yunzhi Su,
my parents Bailing Li and Jie Hu,
my wife Xinghang, and
my children Richard and Louis
for their unconditional love, encouragement, and understanding.

—Xiaoling Li

FOREWORD

In Spring of 1983, I took a position at The University of Michigan. There I met my first Chinese student, Ming Hu, from mainland China, and began a personal and professional relationship that has lasted for nearly 30 years. He is now a Professor at the University of Houston and one of the two editors of this book. I am very pleased to have observed his contributions to science and his success as a scientist over the nearly 30 years I have known him and followed his career. It is a pleasure to write this foreword for this book coedited by Ming and his former classmate at Shanghai Medical University, Prof Xiaoling Li at University of the Pacific.

This book has two purposes, to give readers a contemporary understanding of the science of oral bioavailability and to present the state-of-the-art tools that can be used to advance the science of oral bioavailability and solve problems in the development of drug products for oral administration. It presents the advances in the science of oral bioavailability over the last five decades. This multidisciplinary scientific field has steadily progressed from an emphasis on physical sciences such as solubility and solid state properties, to incorporating the significant recent advances in the biological sciences that emphasize transporters, enzymes, and the biological and physiological processes that influence their expression and function.

I will note some of the evolutionary and perhaps revolutionary steps this field of oral bioavailability has taken over last five decades. In the 1960s and 1970s, application of the physical sciences to the problem of oral drug delivery produced the first wave of major advances that shaped the development of the modern commercial oral dosage form and the science of oral bioavailability. Important physicochemical principles and strategies such as manipulation of dissolution via physical manipulation of the drug and drug product and chemical modification using prodrugs were developed. These approaches are routinely considered and applied in the drug product development process today. The principles governing sustained and controlled release formulations were developed in those "early" years (e.g., Higuchi equation), and have become widely applied in the later decades of the twentieth century. In the 1980s, important progress in the science of oral bioavailability was led by the development of two critical absorption models, rat intestinal segment perfusion model (developed in my laboratory) and Caco-2 cell mono-layer culture model (developed in Dr Ronald T. Borchardt's lab). Prof Hu studied in both laboratories, and was an early contributor to the development of both of these systems for the study of oral absorption. These methods have since become widely adapted by the pharmaceutical industries. This set the basis for predicting oral absorption and partitioning bioavailability into its component process, dissolution/release, transport/permeation, and metabolism, notability distinguishing absorption and systemic availability. During the 1980s, major advances were also made in the study of metabolism in the intestine as well as the liver, particularly the cytochrome *P*450s and resultant potential drug–drug interaction mechanisms. In addition to predicting oral absorption, my laboratory also pioneered the concept of exploiting the intestinal mucosal cell peptide transporter (hPEPT1) to improve the oral absorption of polar drugs by making a prodrug, chemically combining the drug and an amino acid with a peptide-bond like structure. This mechanistic concept is the basis for the absorption of many polar drugs and prodrugs. The development of several approved prodrugs including valacyclovir and valganciclovir, while originally empirical, is based on these

transport mechanisms. In the 1990s, I established the concept of the Biopharmaceutical Classification System (BCS), partitioning drugs into classes for drug development and drug product regulation. This BCS approach has found wide use in drug discovery, development as well as regulation. It has been adapted by regulatory authorities and governments around the world as a basis for the regulation of drug product quality.

During this same period, the US Food and Drug Administration began the mandate of requiring studies that predict drug–drug interactions based on the sciences that were developed during the past two decades. Study of efflux transporters began in the 1990s and has exploded in the twenty-first century. While efforts to make an inhibitor of *p*-glycoprotein for anticancer application have not produced an approved drug, it is likely that the future will see such a development. The explosion in the study of transporters is ongoing, with the recent addition of efflux transporters such as multidrug resistance-related proteins (MRPs), breast cancer resistant protein (BCRP), and uptake transporters such as organic anion transporting peptides (OATP), organic anion transporters (OATs), and carboxylic acid transporter (CAT). Such advances in our mechanistic understanding of oral bioavailability will most certainly lead to future advances in therapy.

The advances in the science of oral bioavailability is driven by the needs to develop orally administered drugs, which remains the most acceptable patient compliant means of administering drugs to patients across the globe today. Although the scientific basis was most often the pursuit of industrial scientists, a lack of rapid advancement in the science of oral bioavailability became recognized as a hurdle in the drug development process in the early 1990s as many highly potent compounds (high affinity ligands), for example, HIV *in vitro* were inactive in humans. In a timely or even a watershed event, the National Institute of Health in 1994 organized a conference on "Oral Bioavailability," where scientists of various backgrounds were organized to address the complex problem facing potent yet poorly bioavailable drug candidates, particularly anti-HIV candidates. Senior managements in many of the major pharmaceutical companies became aware of and recognized the importance of "bioavailability" as the pharmaceutical industry was working hard to fast track the development of anti-HIV drugs. This led to investment by the pharmaceutical industries in the technology and scientists to tackle this oral delivery problem. While actual numbers can be hard to obtain and interpret, my impression is that the attention to bioavailability has led to the decrease in the percentage of clinical trial failures due to oral bioavailability problems. Looking even further into the future, I believe the science of oral bioavailability will be driven by the needs for personalized medicine, individualized treatment plan tailored to patients, and by the commercial need to increase the efficiency and efficacy of oral drug product development. This book provides a comprehensive survey of the modern study of the science of oral bioavailability in the twenty-first century.

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PREFACE

Since the concept of bioavailability has been introduced, significant progress has been made in understanding the science of oral bioavailability and in improving the oral delivery of drugs. Yet, we also find that there is still much to be discovered to have a good handle on oral bioavailability. As a subject, bioavailability encompasses the knowledge and technologies from various disciplines. A pharmaceutical scientist in a specific research area will benefit from a treatise on the topic. Hence, the objective of this book is to provide the framework for fundamental concepts and contemporary practice of bioavailability in pharmaceutical research and drug development.

It is our belief that this book provides both the basic concepts to a novice and the advanced knowledge to veteran pharmaceutical scientists and graduate students in related research fields. Chapter 1 gives a high level summary of this book. The basic concepts of bioavailability are covered in Chapter 2–13. From Chapter 14 to 26, the advanced concepts of bioavailability are discussed in greater depth. Various approaches and methods for improving and studying bioavailability are highlighted in Chapter 27 to 33. The comprehensive coverage of topics on bioavailability in this book offers readers a choice of logically building their knowledge on bioavailability from basic concepts to advanced applications or *à la carte* based on their specific needs.

A book with such diverse contents requires a multidisciplinary effort. Without the efforts of contributors from different areas, this book would have not been a reality. We would like to personally thank all authors for their contributions and patience during the completion of this book project. Sincere thanks are gratefully extended to Mr Jonathan Rose at John Wiley and Sons, Inc. and Dr Binghe Wang (the book series editor) for their patience, understanding, support, and confidence in us. We would also like to express our appreciations to Mrs. Kathy Kassab for her invaluable secretarial assistance, and to Haseen Khan for her tireless effort in the book production. Finally, we would like to thank the world renowned scientist and leading expert in bioavailability, Prof Gordon L. Amidon for writing an insightful and inspiring forward for this book.

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CONTENTS

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BARRIERS TO ORAL BIOAVAILABILITY—AN OVERVIEW

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1.1 INTRODUCTION

Oral bioavailability of a drug is a measure of the rate and extent of the drug reaching the systemic circulation and is a key parameter that affects its efficacy and adverse effects. Therefore, study of oral bioavailability has received considerable attention in scientific arena. Unfortunately, we are unable to predict bioavailability as *a priori* to this date, although we have made significant progress in understanding various components of this complex puzzle, including solubility (e.g., aqueous solubility), partition coefficients (e.g., octanol/water), absorption (e.g., permeability across the Caco-2 cell membrane), metabolism (e.g., microsome-mediated phase I metabolism), and excretion (e.g., efflux via *p*-glycoprotein). However, understanding a few of these components would not allow us to accurately predict a drug candidate's bioavailability in humans. Therefore, oral bioavailability remains to be a highly experimental parameter that eludes prediction from modern computational or experimental approaches, although some preliminary progress has been made in recent years. Continued progress to develop a better and more thorough understanding of physicochemical and biochemical profiling of drug or drug-like molecules would be needed to alleviate the problems associated with bioavailability, and some progress has been made in the last decade (Ho and Chien, 2009). Poor oral bioavailability is also one of the leading causes of failures in clinical trials. This is because compounds with low bioavailability would have a highly variable exposure between individuals. If a compound has an average bioavailability of 5%, it would easily vary in the range of 0.5–10%, a 20-fold difference. This difference makes the selection of an appropriate dose particularly difficult since too little may yield no impact and too much could result in toxicity, which is not acceptable for most drugs that desire chronic administration.

The reasons why oral bioavailability is such a challenge for development of drugs or drug-like substances (e.g., nutraceuticals) are several-fold: first, many physicochemical and biological factors contribute to the bioavailability of a compound; second, many scientific disciplines are involved but few, if any, scientists are good at more than one specific area; third, reliable scaling from animal models to humans is often absent; and fourth, oral bioavailability is often seriously affected by diet and polypharmacy, neither of which can be adequately controlled in a standard clinical trial, considering the diversity of the population—the elderly and seriously ill patients. In addition, we are normally able to gain access only to limited body fluids such as blood and urine, and fluids surrounding the target tissues/cells are often not accessible. This limitation makes bioavailability, a measure of the extent and rate of absorption and the elimination processes,

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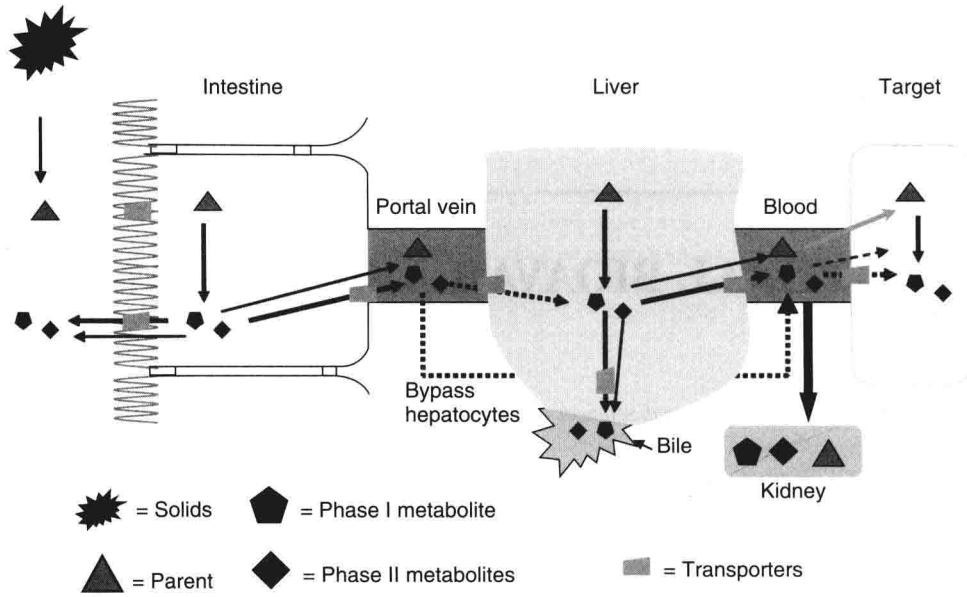

Figure 1.1 Organ bioavailability barriers to drugs. The processes that include dissolution from the solids to molecules, transport of the dissolved molecules via passive and carrier-mediated uptake transporters into the cells, and phase I and phase II metabolism inside the enterocytes and beyond are depicted. Drug metabolism mostly occurs in the liver. Drug elimination is mainly via bile and kidney, so other elimination route (e.g., exhalation) is not shown. (*See insert for color representation of the figure.*)

really representing only systemic blood exposure to drugs (Fig. 1.1). Therefore, it is not surprising that bioavailability would sometimes not satisfactorily correlate with efficacy.

Oral bioavailability remains a major challenge to the development of nutraceuticals and naturally derived chemopreventive agents. For example, many scientists are interested in developing plant-derived polyphenols into chemopreventive agents. Polyphenols are derived from plants and consumed in the form of fruits, vegetables, spices, and herbs. In different regions of the world, a large percentage of dietary polyphenols are consumed in the form of flavonoids from various sources of food intake, although cultural and dietary habit dictates which forms of polyphenols are consumed (Fletcher, 2003; Slavin, 2003; Aggarwal *et al.*, 2007). On the other hand, a large percentage of population do not take sufficient quantities of fruits and vegetables for a variety of reasons (Adhami and Mukhtar, 2006). Therefore, scientists are interested in developing a pill that will mimic the effects of ingesting fruits and vegetables. Yet, today their effort has not produced a single polyphenolic chemopreventive agent; the unsuccessful attempt may be attributed to the poor bioavailability of polyphenols (usually <5%). Poor bioavailability makes the evaluation of a chemopreventive agent a particular challenge, since the clinical trials for chemopreventive agents often involve a large population for a prolonged period and extremely high costs.

When all of the above-mentioned challenges are taken into consideration in the product development of drugs or chemopreventive agents, it is obvious that developing an appropriate oral dosage form for drug candidate or candidate of chemopreventive agent is not a trivial or straight forward task. Although pharmaceutical scientists have great difficulty in predicting and enhancing bioavailability, the reward is also immense as the vast majority of top revenue and prescription leaders are orally administered drugs. Therefore, we devote this chapter to briefly introduce each of the factors that influence bioavailability and guide the readers to the appropriate chapters in this book where they can obtain in-depth contents of each related topic.

As an oral dosage form enters the oral cavity and then the gastrointestinal (GI) tract, several barriers must be overcome before it can reach the systemic circulation and the therapeutic target. On its way to the therapeutic target, a drug in a given dosage form will need to first overcome the preabsorption barrier formed by the hostile acidic and enzymatic environment in the stomach and intestine. Then the drug would encounter the primary barrier formed by the biological membrane, that is, the wall of the GI tract. Once a drug successfully passes the intestinal epithelium barrier, the drug will need to overcome another barrier consisting of transporters and enzymes, which utilize the efflux mechanism to pump the drug back to the intestine and degrade the drug via the first-pass effect. There are