Models for Assessing Drug Absorption and Metabolism
Pharmaceutical Biotechnology

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Volume 8 MODELS FOR ASSESSING DRUG ABSORPTION AND METABOLISM
Edited by Ronald T. Borchardt, Philip L. Smith, and Glynn Wilson
Models for Assessing Drug Absorption and Metabolism

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Preface

A major challenge confronting pharmaceutical chemists is the rational design of drug molecules to optimize pharmacological interactions with their therapeutic targets and to enable them to circumvent biological barriers (e.g., intestinal mucosa, liver, blood–brain barrier) that separate the site of drug action from the site of drug administration. The inability to circumvent such barriers often prevents leading drug candidates from being clinically developed (see Volume 4 in this series, *Biological Barriers to Protein Delivery*, edited by K. L. Audis and T. J. Raub).

Therefore, in the 1980s, scientists in the pharmaceutical industry began to employ *in situ* (e.g., perfused organ) and *in vitro* (e.g., tissue and cell culture) systems in the drug discovery process in order to optimize the pharmaceutical properties of drug candidates. These systems also started to play an important role in the evaluation of individual components of novel drug delivery formulations that had the potential to facilitate drug transport.

While the applications of these *in situ* and *in vitro* models are now being widely described in the scientific literature, the experimental details necessary to set up these systems in a research laboratory are not always provided in the primary publications. Furthermore, as these methodologies stem from a number of biological disciplines, the primary scientific literature will not be the normal purview of many pharmaceutical scientists.

Therefore, the editors of this book decided to provide pharmaceutical scientists ready access to these experimental methodologies. The first chapter, which is written by Ronald T. Borchardt, Philip L. Smith, and Glynn Wilson, provides an overview of the general principles for characterizing and using *in situ* and *in vitro* model systems for biopharmaceutical studies. Chapters 2 through 6 describe methodologies for studying drug absorption and metabolism after oral administration. These chapters describe the use of intestinal mucosal tissue (Chapter 2, Philip L. Smith), cultured intestinal epithelial cells (Chapter 3, Ismael J. Hidalgo), intestinal rings and isolated intestinal mucosal cells (Chapter 4, Joseph A. Fix), and *in situ* and conscious animals (Chapter 5, Robin Griffiths, Ann Lewis, and Phillip Jeffrey) for evaluating a drug
candidate’s ability to permeate the intestinal epithelium. In addition, Chapter 6 (Christopher J. H. Porter and William N. Charman) describes models for studying the intestinal lymphatic transport of drugs.

Methodologies are also described for studying other epithelial barriers, including the buccal epithelium (Chapter 7, Elizabeth Quadros, James P. Cassidy, and Harry Leipold), nasal epithelium (Chapter 16, Patricia M. Reardon), respiratory epithelium (Chapter 17, Kwang-Jin Kim and Edward D. Crandall), alveolar epithelium (Chapter 18, Doris Wall and Doreen Pierdomenico), pulmonary epithelium (Chapter 19, Mohammed Eljamal, Sudha Nagarajan, and John S. Patton), skin epithelium (Chapter 20, Robert L. Bronaugh; Chapter 21, Jim E. Riviere), vaginal epithelium (Chapter 22, Sy-Juen Wu and Joseph R. Robinson), and the ocular epithelium (Chapter 23, Vincent H. L. Lee).

This volume also describes methodologies for studying elimination barriers, such as the liver, by using isolated hepatocytes (Chapter 8, M. Vore, Y. Liu, and T. C. Ganguly), cultured hepatocytes (Chapter 9, Edward L. LeCluyse, Peter L. Bullock, Andrew Parkinson, and Jerome H. Hochman), and isolated perfused liver (Chapter 10, Kim L. R. Brouwer and Ronald G. Thurman). Methodologies are also provided for studying drug elimination in the kidney using isolated renal brush border and basolateral membrane vesicles and cultured renal cells (Chapter 11, Marcelo M. Gutierrez, Claire M. Brett, and Kathleen M. Giacomini) and isolated perfused kidney (Chapter 12, Noriko Okudaira and Yuichi Sugiyama).

Finally, included in this book are chapters describing the methodologies used to study drug transport and metabolism at the level of the blood–brain barrier (Chapter 13, Kenneth L. Audus, Lawrence Ng, Wen Wang, and Ronald T. Borchardt; Chapter 15, Quentin R. Smith) and the blood–cerebrospinal fluid barrier (Chapter 14, Carla B. Washington, Kathleen M. Giacomini, and Claire M. Brett).

Lastly, we thank all the authors, who are experienced practitioners in the development and use of the various model systems, for their valuable and timely contributions. We hope that the methodologies described in this book will facilitate the in situ and in vitro evaluation of drug candidates by scientists in the pharmaceutical/biotechnology industry and ultimately will lead to the expedited discovery of novel drugs together with formulations for improving their delivery.
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