Methods and Principles in Medicinal Chemistry

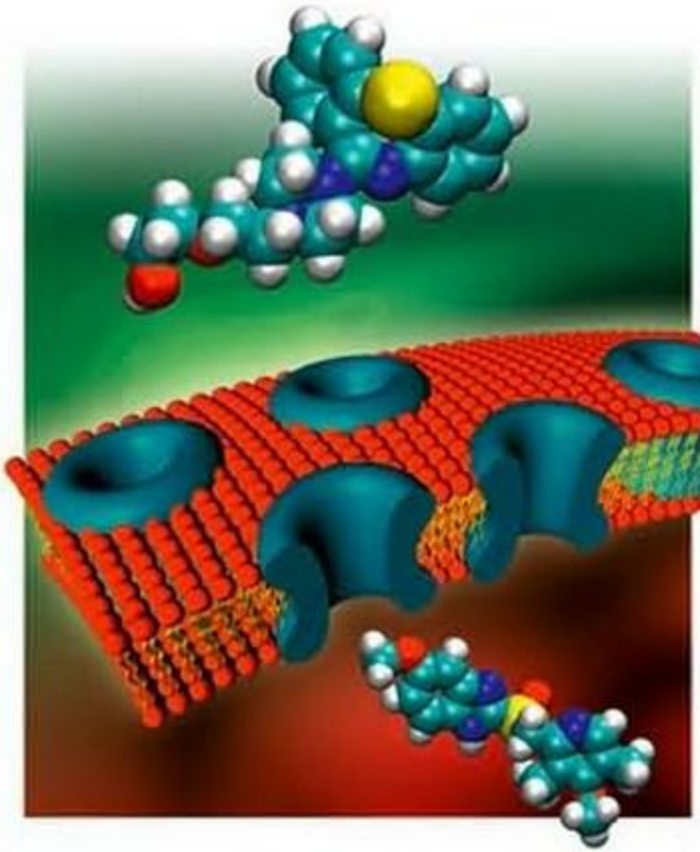
Edited by
Han van de Waterbeemd and Bernard Testa

WILEY-VCH

Drug Bioavailability

Estimation of Solubility, Permeability, Absorption and Bioavailability

Second, Completely Revised Edition



Volume 40

Series Editors:
R. Mannhold,
H. Kubinyi,
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WILEY-VCH Verlag GmbH & Co. KGaA

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Cover Description
Bioavailability involves the transfer of gut wall membranes in which a drug may encounter metabolising enzymes and transporters limiting or enhancing systemic drug levels.

Library of Congress Card No.:
applied for

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library.

Bibliographic information published by the Deutsche Nationalbibliothek
Die Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data are available on the Internet at http://dnb.d-nb.de.

Composition Thomson Digital, Noida, India
Printing Strauss GmbH, Mörlenbach
Bookbinding Litges & Dopf GmbH, Heppenheim
Cover Grafik-Design Schulz, Fußgönheim

Printed in the Federal Republic of Germany
Printed on acid-free paper

ISBN: 978-3-527-32051-6

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Preface

The processes involved in drug discovery have changed considerably in the past decade. Today we have access to the full human as well as several bacterial genomes offering a rich source of molecular targets to treat diseases. Methods in biology have moved to ultra-high-throughput screening (uHTS) of such precedented and unprecedented targets. Chemistry adapted to this progress by developing methods such as combinational and parallel synthesis allowing the rapid synthesis of hundreds to hundreds of thousands molecules in reasonable quantities, purities and timelines.

Historical data on the fate of potential drugs in development indicate that major reasons for attrition include toxicity, efficacy and pharmacokinetics/drug metabolism. Therefore, in today's drug discovery the evaluation of absorption, distribution, metabolism and excretion (ADME) of drug candidates is performed early in the process. In the last 10 years drug metabolism and physicochemical *in vitro* screening methods have increasingly been introduced. In recent years these methods more and more became medium to high throughput in order to cope with increasing numbers of compounds to evaluate after HTS.

Although HTS seems to be a very efficient approach, it must be stressed that there is also a high cost associated with it. Interest is thus shifting to prediction and simulation of molecular properties, which might hopefully lead to overall more efficient processes.

The next vague of tools will be around computational or *in silico* ADME approaches. These will allow to include ADME into the design of combinational libraries, the evaluation of virtual libraries, as well as in selecting the most promising compounds to go through a battery of *in vitro* screens, possibly even replacing some of these experimental screens. Several of these computational tools are currently under development as will be discussed in this volume.

For reasons of convenience for the patient and compliance to the therapy, most drugs are administered orally. To keep the dose at the lowest possible level, high oral absorption and high bioavailability are prime properties to optimize in a new drug. Drug bioavailability is the outcome of a complex chain of events, and is among others influenced by the drug's solubility, permeability through the gastrointenstinal wall, and its first pass gut wall and liver metabolism. Excluding liver metabolism, all

other factors are characterized by the term oral absorption. Permeability through the gut wall can be favoured or hindered through the effect of various transporter proteins such as P-glycoprotein. Our increased knowledge and understanding of all of these processes involved in permeability, oral absorption and bioavailability will make predictive tools more robust.

A previous volume in our series, edited in 2003 by Han van de Waterbeemd, Hans Lennernäs, and Per Artursson, was dedicated to summarize the current status in the estimation of relevant ADME parameters. This volume emerged as a top-seller in our series indicating the high impact of this topic in modern drug research.

Now, five years later, we are proud to present a complete revision, edited by Han van de Waterbeemd and Bernard Testa, which reflects the enormous developments in this research area. Few chapters were omitted and a new one on "Nanotechnology in Drug Discovery" was added. Some chapters were condensed and merged into others; some other chapters had to be split into two. The majority of chapters remained of high currency and were all comprehensively updated, some by the same and some by new authors such as the chapter on "Prodrugs" by Bernard Testa.

The series editors would like to thank Han van de Waterbeemd and Bernard Testa for their enthusiasm to put together this book and to work with such a fine selection of authors.

September 2008

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A Personal Foreword

"*Drug Bioavailability – Estimation of Solubility, Permeability, Absorption and Bioavailability*" was published in 2003 under the editorship of H. van de Waterbeemd, H. Lennernäs and P. Artursson. The book met with such success that it had to be reprinted 4 times. But given the many and fast advances in the field, even this solution was no longer satisfactory. A second, fully revised edition was thus envisaged. Professors Lennernäs and Artursson having too many other commitments, Han van de Waterbeemd found himself alone for the task and approached his colleague and friend Bernard Testa. Having just completed the joint editorship of the 1100-page ADMET volume in "*Comprehensive Medicinal Chemistry II*", we were happy to team up again in an exciting book project. Having decided on an updated content and a logical structure, it was clear that some chapters had to be split into two and rewritten to take latest advances into account. A few chapters could be condensed and merged into others, while yet other chapters remained of high currency and simply needed an in-depth updating. These changes in book structure and chapter contents implied a number of changes in authorship; we are grateful to contributors of the first edition and to our new authors for their enthusiastic cooperation. The final product is thus vastly different from the previous one and, we hope, will be found valuable by afficionados of the first edition as well as by new readers.

May 2008 *Han van de Waterbeemd,* Market Harborough, United Kingdom
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