Drug Bioavailability

Estimation of Solubility, Permeability, Absorption and Bioavailability

Edited by Han van de Waterbeemd, Hans Lennernäs and Per Artursson

WILEY-VCH

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Methods and Principles in Medicinal Chemistry

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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 Die Deutsche Bibliothek
Die Deutsche Bibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data is available in the Internet at http://dnb.ddb.de

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

Composition Asco Typesetters, Hong Kong
Printing betz-druck gmbh, Darmstadt
Bookbinding Litges & Dopf Buchbinderei GmbH, Heppenheim

ISBN 3-527-30438-X

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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 combinatorial 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 elimination (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 combinatorial 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 optimise 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 gastrointestinal wall, and its first pass gut wall and liver metabolism. Excluding liver metabolism, all other factors are characterized by the term oral absorption. Per-

meability 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.

This volume gives an overview of the current status and an outlook to future more reliable predictive approaches. It is subdivided in five sections dealing with studies of membrane permeability and oral absorption, drug dissolution and solubility, the role of transporters and metabolism in oral absorption, computational approaches to drug absorption and bioavailability, and finally with certain drug development issues.

The series editors would like to thank Han van de Waterbeemd, Hans Lennernäs, and Per Artursson for their enthusiasm to put together this book and to work with such a fine selection of authors. We also express our gratitude to Frank Weinreich and Gudrun Walter of Wiley-VCH for their valuable contributions to this project.

March 2003

Raimund Mannhold, Düsseldorf
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Foreword

This book aims at bringing together the strategies and tools currently available to investigate and make predictions about oral absorption and bioavailability of drugs in humans. Ideally, such predictive models can be used in drug discovery from the design of compounds and libraries throughout lead optimisation to clinical candidate selection. This book also aims to discuss more complex *in vivo* aspects of oral drug delivery.

The volume is divided into five sections. Part one looks at the experimental study of membrane permeability and oral absorption. In Part two, problems of measuring and prediction solubility, as one of the key determinants in the absorption process, will be discussed in detail. In the next part, progress in the science around transporter proteins and gut wall metabolism and their effect on the overall absorption process is presented. Part four looks at the *in silico* approaches and models to predict permeability, absorption and bioavailability. In the last part of the book, a number of drug development issues will be highlighted, which could have an important impact of the overall delivery strategies for oral pharmaceutical products.

In summary, progress in predicting oral absorption is based on a much better understanding of the transport processes across the intestinal epithelium along the gastrointestinal tract. The identification of the key physicochemical properties, and in addition the identification of key transporter proteins and metabolising enzymes in the gut wall has led to the development of new *in vitro* and *in vivo* screens that allow reasonably accurate estimates of oral absorption in man to be made. Predicting bioavailability is more challenging, but very promising progress has been made in recent years, both via the combination of several *in vitro* measures, as well as the development of predictive *in silico* tools. In many cases, the validity and the accuracy of the applied methods have been investigated to some extent, but more mechanistic research is needed in order to improve the performance of the various methods used in this field of drug development.

We are very grateful to the many contributors to this book. Their insightful chapters are the body of this book. Some were prepared to stand in at the last minute, and still delivered within the deadline, which is always a relief to the editors. Finally we thank Frank Weinreich for his continuous encouragement and light pressure to get the chapters in press on time.

December 2002,

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I
Studies of Membrane Permeability and Oral Absorption

1
Physico-chemical Approaches to Drug Absorption

Han van de Waterbeemd

Abbreviations

ADME	Absorption, distribution, metabolism, elimination (excretion)
BBB	Blood–brain barrier
BMC	Biopartitioning micellar chromatography
Caco-2	Adenocarcinoma cell line derived from human colon
CNS	Central nervous system
DMSO	Dimethyl sulfoxide
EVA	Ethylenevinyl acetate copolymer
IAM	Immobilized artificial membrane
ILC	Immobilized liposome chromatography
MAD	Maximum absorbable dose
MEKC	Micellar electrokinetic chromatography
MLR	Multiple linear regression
NMR	Nuclear magnetic resonance
PAMPA	Parallel artificial membrane permeation assay
PASS	Prediction of activity spectra for substances
PK	Pharmacokinetics
QSAR	Quantitative structure–activity relationship
QSPR	Quantitative structure–property relationship
SPR	Surface plasmon resonance
WDI	World Drug Index

Symbols

AP_{SUV}	Absorption potential measured in small unilamellar vesicles (SUV)
Brij35	Polyoxyethylene(23)lauryl ether
CLOGP	Logarithm of the calculated octanol/water partition coefficient (for neutral species)
diff(log P^{N-I})	Difference between log P^N and log P^I
Δ log P	Difference between log P in octanol/water and alkane/water

log D	Logarithm of the distribution coefficient, usually in octanol/water at pH 7.4
log P	Logarithm of the partition coefficient, usually in octanol/water (for neutral species)
log P^I	Logarithm of the partition coefficient of a given compound in its fully ionized form, usually in octanol/water
log P^N	Logarithm of the partition coefficient of a given compound in its neutral form, usually in octanol/water
MW	Molecular weight
pK_a	Ionization constant in water
S	Solubility
SITT	Small intestinal transit time (4.5 h = 270 min)
SIWV	Small intestinal water volume (250 mL)
V	Volume

1.1 Introduction

An important part of the optimization process of potential leads to candidates suitable for clinical trials is the detailed study of the absorption, distribution, metabolism and excretion (ADME) characteristics of the most promising compounds. Experience has learned that physico-chemical properties play a key role in drug metabolism and pharmacokinetics (DMPK) [1–3]. As an example, physico-chemical properties relevant to oral absorption are described in Fig. 1.1. It is important to note that these properties are not independent, but closely related to each other.

The change in work practice towards higher-throughput screening (HTS) in

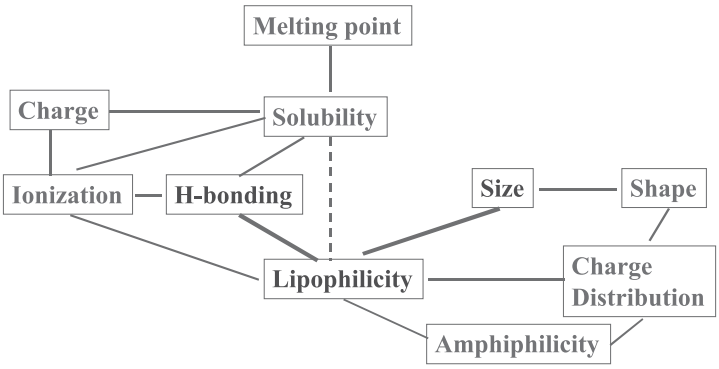

Fig. 1.1. Relationships between various physico-chemical properties believed to influence oral drug absorption.