BIOTECHNOLOGY: PHARMACEUTICAL ASPECTS

Pharmaceutical Profiling in Drug Discovery for Lead Selection

Edited by
Ronald T. Borchardt,
Edward H. Kerns,
Christopher A. Lipinski,
Dhiren R. Thakker, and
Binghe Wang

AAPS PRESS

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Ronald T. Borchardt
University of Kansas

Edward H. Kerns
Wyeth Research

Christopher A. Lipinski
Pfizer Global R&D (retired)

Dhiren R. Thakker
University of North Carolina

Binghe Wang
Georgia State University

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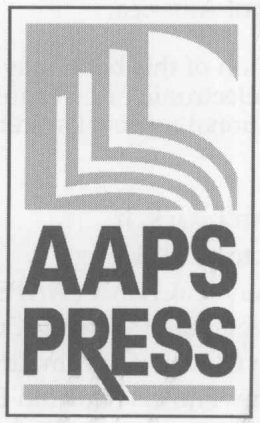

American Association of Pharmaceutical Scientists
Arlington, VA

Ronald T. Borchardt
University of Kansas
Dept. of Pharmaceutical Chemistry
2095 Constant Avenue
Lawrence, KS 66047

Christopher A. Lipinski
Pfizer Global R&D (retired)
Eastern Point Road, MS 8200-36
Groton, CT 06340

Binghe Wang
Georgia State University
Department of Chemistry
33 Gilmer Street, SE
Atlanta, GA 30303

Edward H. Kerns
Wyeth Research
CN 8000
Princeton, NJ 08453

Dhiren R. Thakker
University of North Carolina, Chapel Hill
2309 Kerr Hall, CB #7360
Chapel Hill, NC 27599

Series Editors:

Ronald T. Borchardt
University of Kansas
Dept. of Pharmaceutical Chemistry
2095 Constant Avenue
Lawrence, KS 66047

C. Russell Middaugh
University of Kansas
Dept. of Pharmaceutical Chemistry
2095 Constant Avenue
Lawrence, KS 66047

ISBN: 0-9711767-9-5

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Biotechnology: Pharmaceutical Aspects

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Ronald T. Borchardt and C. Russell Middaugh, Series Editors

Volume I: *Pharmaceutical Profiling in Drug Discovery for Lead Selection*

R.T. Borchardt, E.H. Kerns, C.A. Lipinski, D.R. Thakker, B.Wang

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PREFACE

Driven by the goal of improving the quality and length of human lives, the pharmaceutical sciences strive to discover and develop novel drugs that solve unmet medical needs. These needs include the treatment of diseases for which limited pharmaceutical treatments exist. Moreover, the enhancement of efficacy and selectivity, as well as the reduction of side effects, are priorities. Unfortunately, meeting these goals is increasingly difficult. The resources needed for drug discovery and development have steadily increased. The research and development investment for each new chemical entity (NCE) approved by the FDA is estimated at $800 million.

Because of this situation, pharmaceutical companies continually evaluate the effectiveness and efficiency of their research and development processes. This analysis has resulted in the introduction of new capabilities for high-throughput screening, to rapidly identify structures with affinity for targets; genomics, to effectively identify and validate biomolecular targets; and combinatorial chemistry, to rapidly synthesize chemical libraries. In a similar manner, analysis indicated that drug candidates have a high rate of failure during discovery and development, often due to their lack of "drug-like properties." Drug-like properties are the physicochemical (e.g., solubility, stability) and biological (e.g., absorption, metabolism, toxicity) characteristics that are consistent with good clinical performance.

Inadequate drug-like properties can result in increased development time, escalating costs, and project cancellation. The reasons are many and varied, including situations such as the following: an elaborate formulation may be needed for poorly soluble compounds, an expensive delivery vehicle may be needed for poorly permeable compounds, cost of goods or process steps can increase if a compound is chemically unstable, low bioavailability may cause concerns about patient variability, rapid clearance may necessitate multiple-dosing-per-day regimens, and clinical drug–drug interactions and toxicity can cause an immediate hold on further clinical development. Pharmaceutical companies would prefer to avoid these potential problems and have, in recent years, implemented profiling programs to examine pharmaceutical properties earlier in the drug discovery process.

There is also a growing recognition that drug-like properties cause inefficiencies and reduced effectiveness of research during drug discovery. In discovery experiments, poor properties result in inadequate and/or improper

evaluation of the biological activity of compounds. For example, the activity of a compound with low solubility may be underestimated in an enzyme or receptor assay; the activity of a compound with low permeability may be underestimated in a cell-based assay. As a consequence, potentially useful drug candidates may be discarded prematurely. On the other hand, if adequate solubility is not valued by the discovery project team, too much time may be spent on optimizing the biological activity of drug candidates that are not likely to result in efficacious therapeutic agents.

A strategy that was often repeated in the early days of property profiling was "fail early and cheaply." In reality, active pharmacophores are rare and precious. They cannot be discarded lightly. Thus, the medicinal chemist's imperative to discover active pharmacophores and improve structure–activity relationships (SARs) remains the highest priority in drug discovery. When faced with poor properties, there is a tendency to drive for increased activity to counteract poor properties or to assume that structural changes made during the optimization phase will improve the properties. The responsibility for improving inadequate properties is sometimes passed along to development so as to be corrected through formulation. Unfortunately, the drug candidates that result from many man-years of discovery work are often denied from reaching development by in-depth studies during late-discovery or because adequate solutions to poor properties are not found during development. It is becoming increasingly obvious that one month saved from the development of a special formulation or pharmacokinetic study allows a one-month longer clinical product lifetime and associated benefits to the company.

Many have argued that it is best to fix pharmaceutical properties during discovery through structural modifications and more informed project team decisions. Both of these require the measurement of property data. In recent years, concern about property inadequacies has indicated two phases of intervention during which property information can have an impact: lead selection and lead optimization. Property data can be considered as part of the entire portfolio of information available to discovery project teams by which a comprehensive assessment can be made on how to proceed with a compound or series. During lead selection, property data are gathered on "hits" from high-throughput screening, compounds from similarity searching, and structures from rational design. During lead optimization, this involves the property evaluation of synthesized compounds from lead series expansion. To meet these needs, capabilities for pharmaceutical property profiling during drug discovery and strategies for use of the data are emerging within pharmaceutical companies, conferences, and the scientific literature.

Recognizing the value of supporting this area, the American Association of Pharmaceutical Scientists (AAPS) has planned two focused workshops in the areas of pharmaceutical properties, first in lead selection and then in lead optimization during drug discovery. The first workshop, *"Pharmaceutical Profiling in Drug Discovery for Lead Selection,"* occurred in Whippany, NJ, on May 19–21, 2003, with co-sponsorship of the American Chemical Society,

Medicinal Chemistry Division, and Society for Biomolecular Screening. Its purpose was to contribute to the field by focusing on procedures for prediction, measurement, and application of compound properties to select and improve candidates. The workshop provided high-quality presentations, excellent discussions, and insightful posters which together provided a body of concepts, case studies, and informed ideas that strongly contribute to the goal of improving candidate drug-like properties to increase the efficiency of drug discovery and development. *In silico, in vitro,* and *in vivo* tools were discussed for the prediction and measurement of drug-like properties and application of this information in the selection of drug discovery leads. Sponsorship by the AAPS attracted a sophisticated faculty and audience, reduced barriers for attendance, and addressed goals of the association. It brought together experienced discovery scientists from diverse disciplines, including chemistry, drug metabolism, and development sciences, who often attend different scientific society meetings. The organizing committee (Ronald Borchardt, Edward H. Kerns, Christopher A. Lipinski, Dhiren R. Thakker, Binghe Wang, Thomas D.Y. Chung, and Sitta G. Sittampalam) gratefully acknowledges the contributions of AAPS staff, speakers, poster authors, and audience for an excellent exchange. Thanks are also extended to the organizations that co-sponsored the workshop: The Society for Biomolecular Screening and The American Chemical Society-Medicinal Chemistry Division. This volume provides valuable chapters from the speakers at this workshop, plus provides insights and strategies that will serve this developing area for years to come.

A second workshop titled *"Optimizing Drug-Like Properties During Discovery Lead Optimization"* is planned for September 19–22, 2004, in Parsippany, NJ.

It is clear that the integration of drug-like properties as a fundamental pillar of drug discovery is both necessary and advantageous in efficient and effective drug development. However, it requires support by discovery leaders through actions such as the following: continuing education to expand the depth and breadth of discovery scientists, an open drug discovery process that invites multidisciplinary discussions and input, criteria for advancement in the discovery and development process that include appropriate pharmaceutical properties, and a reward system that emphasizes teamwork and success in the approval of cost-effective NCEs. Toward these goals, the workshop speakers and organizers present the following chapters as a contribution to the pharmaceutical sciences and the enhanced patient therapy.

Edward H. Kerns, Wyeth Research
Ronald T. Borchardt, PhD, The University of Kansas
Christopher A. Lipinski, PhD, Pfizer
Dhiren R. Thakker, PhD, The University of North Carolina at Chapel Hill
Binghe Wang, PhD, Georgia State University

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Part I
In Silico *Tools*

I

Absorption Prediction

PER ARTURSSON and PÄR MATSSON

Department of Pharmacy, Uppsala University
Uppsala Biomedical Center
P.O. Box 580, SE-751 23 Uppsala, Sweden
Center for Pharmaceutical Informatics, Uppsala University
E-mail: Per.Artursson@farmaci.uu.se
E-mail: Par.Matsson@farmaci.uu.se

Introduction

Orally administered drugs account for 75% of the drug market, yet the inability to predict absorption, disposition, metabolism, excretion, and toxicity (ADMET) properties was not long ago reported to be the main reason (>50%) for termination of the clinical testing of drug candidates (Kennedy, 1997). Studies on drug absorption from the gastrointestinal tract are therefore of profound importance in the discovery and development of new drugs (Stenberg et al., 2002; van de Waterbeemd and Gifford, 2003). A drug that cannot be administered orally due to low absorption will generally not be considered for further development, simply because alternative administration routes are too complicated. The continued limited use of biotechnology drugs, such as peptides, proteins, and oligonucleotides, illustrates this fact. Unfortunately, modern drugs derived from combinatorial chemistry and pharmacological high-throughput screening (HTS) programs also have absorption problems since they are larger, more lipophilic, and have more hydrogen-forming groups than traditional drugs (Lipinski et al., 1997; Wenlock et al., 2003). Basic research aimed at predicting human drug absorption and, eventually, oral bioavailability has therefore been given increased attention in drug discovery in recent years.

Several different approaches are used to predict oral drug absorption *in silico*. In the most direct approach, the absorption of orally administered drugs is modeled directly from the molecular properties of the drug molecules (Palm et al., 1997; Raevsky and Schaper, 1998; Wessel et al., 1998; Egan et al., 2000; Zhao et al., 2001). This approach is

limited by the fact that the extent of oral drug absorption has only been characterized in sufficient detail for a small set of already approved drugs. Attempts to increase the size of this data set require the inclusion of approved drugs with more complex pharmacokinetics. This increases the uncertainty in the estimate of the absorbed fraction (F_{abs}) of such drugs (Zhao et al., 2001). Another approach is to model the discrete rate-limiting steps of oral drug absorption, such as drug solubility in the intestinal lumen, and passive drug permeability across the intestinal wall (Figure 1), and initial attempts to combine these two discrete rate-limiting steps in models that better predict intestinal drug absorption have been proposed (Amidon et al., 1995; Bergström et al., 2003).

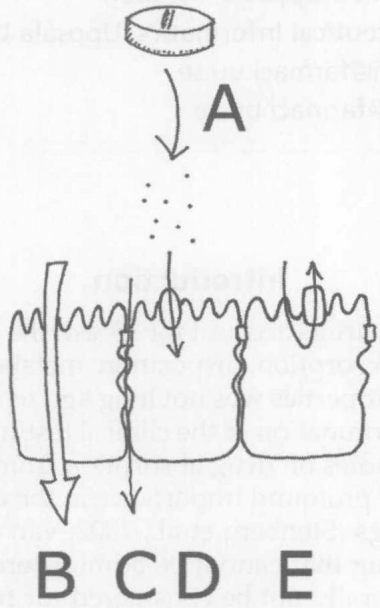

Figure 1 Schematic illustration of the intestinal drug absorption process. The rate-limiting step for intestinal drug absorption is generally either drug dissolution from the solid formulation (A) or drug transport through the epithelial cell layer. The different pathways that may participate in the epithelial transport of drug-like molecules are passive transcellular diffusion (B), passive paracellular diffusion (C), carrier-mediated active uptake (D), active efflux (E).

In a different approach, physiological pharmacokinetic models have been constructed to allow modeling of multiple factors that influence the absorption process. This more demanding approach, which requires experimental data or educated guesses (e.g., with regard to the role of active transport and drug metabolism in the intestine), has resulted in several commercial software packages for prediction of oral drug absorption (Table 1, on page 6). In general, the first two ap-

proaches have generated rapid and more qualitative methods suitable for drug discovery settings and pharmaceutical profiling, while the more demanding physiological models, which aim to present more quantitative results, have also found application in drug development. In our work we have focused on the first two approaches, and in this chapter, we will review some of our experiences from this work. Since the *in silico* prediction of drug solubility as well as active drug efflux is reviewed by other authors in this volume, our emphasis will be on prediction of drug permeability. However, we will also discuss how *in silico* models of drug solubility and permeability can be combined to predict human intestinal drug absorption. Although most of our examples are used in prediction of human intestinal drug permeability or absorption, our discussion is often of a generic nature, and many of the presented models of intestinal drug permeation are, after modifications, also applicable to predictions of drug permeation in other organs and species.

Rate-Limiting Steps to Oral Drug Absorption

There is some confusion with regard to the factors that influence oral drug absorption. We have probably contributed to this confusion in our early publication more than a decade ago on the prediction of oral drug absorption from permeability data in Caco-2 cells (Artursson and Karlsson, 1991). In that publication, we showed a strong correlation between the fraction absorbed after oral administration of approved drugs to humans and drug permeability in Caco-2 cell monolayers. The strong relationship could be established since approved oral drug products have been selected for properties that are favorable for oral drug absorption. Approved, orally administered drugs are generally transported across the intestinal wall mainly via passive mechanisms (i.e., without a significant contribution from active transport processes), and solubility is not a problem since this aspect has been dealt with during the drug development process. Moreover, the metabolic patterns of these drugs are often known and can be accounted for. Consequently, the rate-limiting step in the absorption of these drugs is the passive permeability of the intestinal wall. A strong relationship can be obtained between intestinal epithelial permeability *in vitro* and oral absorption. However, as has been frequently pointed out, drug discovery compounds selected by combinatorial chemistry and HTS are often poorly water-soluble (Lipinski, 2000). For this reason, it is primarily drug solubility, not permeability, that needs to be considered in initial predictions of the oral drug absorption of such drug discovery compounds. By contrast, in drug discovery programs focused on more polar, peptidomimetic drugs, drug permeability rather than solubility may remain the rate-limiting step (Lipinski, 2000).

Product	Company	URL	Solubility	Passive Permeability	Active Transport	Fraction Absorbed	Other PK Parameters
Absolv	Sirius Analytical Systems, pION	www.sirius-analytical.com www.pion-inc.com	X	X			
ADME Boxes, ADME/Tox Screens	Pharma Algorithms, pION	www.ap-alforithms.com www.pion-inc.com	X		X	X	
Cerius2-ADME	Accelrys	www.accelrys.com	X	X			
Cloe PK	Cyprotex	www.cyprotex.com				X	X
GastroPlus, QMPRplus	SimulationsPlus	www.simulations-plus.com	X	X		X	X
IDEA	Lion Bioscience	www.lionbioscience.com		X		X	X
OraSpotter	ZyxBio	www.zyxbio.com	X		X	X	
PK-Sim	Bayer Technology Services	www.bayertechnology.com		X		X	X
Qik-Prop	Schrödinger	www.schrodinger.com	X	X			
SLIPPER	O.A. Raevsky*	www.ibmh.msk.su/molpro www.timtec.net	X			X	

* Dept. of Computer-Aided Molecular Design, Russian Academy of Sciences, Moscow, Russia

Table 1 Examples of commercial software for prediction of molecular properties relating to intestinal absorption. Adapted from van de Waterbeemd and Gifford (2003). Functionalities listed are according to the information on the respective company's Web page.

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