Dennis A. Smith, Han van de Waterbeemd, and Don K. Walker

Pharmacokinetics and Metabolism in Drug Design

Second Revised Edition
Dennis A. Smith,
Han van de Waterbeemd,
and Don K. Walker

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Metabolism in Drug Design
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Pharmacokinetics and Metabolism in Drug Design

Second Revised Edition
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A Personal Foreword to the First Edition

The concept of this book is simple. It represents the distillation of my experiences over 25 years within drug discovery and drug development, and in particular how the science of drug metabolism and pharmacokinetics impacts medicinal chemistry. Hopefully it will be a source of some knowledge, but more importantly, a stimulus for medicinal chemists wanting to understand as much as possible about the chemicals they make. As the work grew I realised it was impossible to fulfil the concept of this book without involving others. I am extremely grateful to my co-authors Don Walker and Han van de Waterbeemd for helping turn a skeleton into a fully clothed body, and in the process, contributing a large number of new ideas and directions. Upon completion of the book I realise how little we know and how much there is to do. Medicinal chemists often refer to the magic methyl. This term covers the small synthetic addition, which almost magically solves a discovery problem of transforming a mere ligand into a potential drug, beyond the scope of existing structure–activity relationships. A single methyl can disrupt crystal lattices, break hydration spheres, modulate metabolism, enhance chemical stability, displace water in a binding site and turns the sometimes weary predictable plod of methyl, ethyl, propyl, futile into methyl, ethyl, another methyl magic! This book has no magical secrets unfortunately, but time and time again the logical search for solutions is eventually rewarded by unexpected gains.

January 2001,

Sandwich

Dennis A. Smith
A Personal Foreword to the Second Edition

I took great personal satisfaction in seeing our thoughts turned into a book, and sat back to relax. Very soon as I glanced at the book I saw gaps, missing links, things I wish we had said better or included. Pride turned gradually to frustration and provided the catalysis for a second edition. The experience spans 29 years, but my wonder and admiration for the magic of medicinal chemistry and those that practice it remain undimmed.

July 2005

Dennis A. Smith
Abbreviations and Symbols

Chapter 1

Abbreviations

CPC  Centrifugal partition chromatography
CoMFA  Comparative field analysis
3D-QSAR  Three-dimensional quantitative structure–activity relationships
HDM  Hexadecane membrane
IUPAC  International Union of Pure and Applied Chemistry
MLP  Molecular lipophilicity potential
RP-HPLC  Reversed-phase high-performance liquid chromatography
PAMPA  Parallel artificial membrane permeability assay
PGDP  Propylene glycol dipelargonate
PSA  Polar surface area
SF  Shake flask, referring to traditional method to measure log $P$ or log $D$
TPSA  Topological polar surface area

Symbols

$AP_{SUV}$  Absorption potential measured in small unilamellar vesicles (SUV)
$\Delta \log D$  Difference between log $D$ in octanol/water and log $D$ in alkane/water
$\Delta \log P$  Difference between log $P$ in octanol/water and log $P$ in alkane/water
$f$  Rekker or Leo/Hansch fragmental constant for log $P$ contribution
$K_a$  Ionisation constant
$A$  Polarity term, mainly related to hydrogen bonding capability of a solute
$log P$  Logarithm of the partition coefficient ($P$) of neutral species
$log D$  Logarithm of the distribution coefficient ($D$) at a selected pH, usually assumed to be measured in octanol/water
Abbreviations and Symbols

$\log D_{\text{oct}}$  Logarithm of the distribution coefficient ($D$) at a selected pH, measured in octanol/water
$\log D_{\text{chex}}$  Logarithm of the distribution coefficient ($D$) at a selected pH, measured in cyclohexane/water
$\log D_{7.4}$  Logarithm of the distribution coefficient ($D$) at pH 7.4
$MW$  Molecular weight
$\pi$  Hansch constant; contribution of a substituent to log $P$
$pK_a$  Negative logarithm of the ionisation constant $K_a$

Chapter 2

Abbreviations

ADME  Absorption, distribution, metabolism and excretion
AUC  Area under plasma concentration time curve
CNS  Central nervous system
CYP2D6  Cytochrome P450 2D6 enzyme
GIT  Gastrointestinal tract
IV  Intravenous
PET  Positive emission tomography

Symbols

$A_{\text{av}}$  Average amount of drug in the body over a dosing interval
$A_{\text{max}}$  Maximum amount of drug in the body over a dosing interval
$A_{\text{min}}$  Minimum amount of drug in the body over a dosing interval
$C_o$  Initial concentration after IV dose
$C_{\text{avss}}$  Average plasma concentration at steady state
$C_{\text{p(f)}}$  Free (unbound) plasma concentration
$C_{\text{p(fo)}}$  Initial free (unbound) plasma concentration
$C_{\text{ss}}$  Steady state concentration
$Cl$  Clearance
$Cl_u$  Unbound clearance
$Cl_H$  Hepatic clearance
$Cl_i$  Intrinsic clearance
$Cl_{iu}$  Intrinsic clearance of unbound drug
$Cl_o$  Oral clearance
$Cl_p$  Plasma clearance
$Cl_R$  Renal clearance
$Cl_S$  Systemic clearance
$D$  Dose
$E$  Extraction
$E_{\text{F}}$  Fractional response
$E_{\text{M}}$  Maximum response
$F$  Fraction of dose reaching systemic circulation (bioavailability)
$F_{\text{da}}$  Fraction dose absorbed
Abbreviations

AUC Area under plasma concentration time curve
Caco-2 Human colon adenocarcinoma cell line used as absorption model
GI Gastrointestinal
MDCK Madin–Darby canine kidney cell line used as absorption model
PSA Polar surface area

Symbols

A% Percentage of dose absorbed as measured in portal vein
CLOGP MedChem/Biobyte log \( P \) estimation program
F% Percentage of dose bioavailable
\( F_a \) Fraction absorbed
\( F_{\text{non}} \) Fraction non-ionised at pH of 6.5
IFV Intestinal fluid volume (250 mL)
\( k_a \) Absorption rate constant in rats (min\(^{-1}\))
\( \log D \) Logarithm of distribution coefficient
Abbreviations and Symbols

\( \log P \) Logarithm of partition coefficient
\( \log S \) Logarithm of solubility in water
\( RT \) Average residence time in the small intestine (270 min)
\( S_{6.5} \) Solubility in phosphate buffer at pH of 6.5
\( S_0 \) Intrinsic solubility of the neutral species at 37 °C
\( V_L \) Volume of the luminal contents
\( X_0 \) Dose administered

Chapter 4

Abbreviations

CNS Central nervous system
CSF Cerebrospinal fluid

Symbols

\( Cl_p \) Plasma clearance
\( Cl_u \) Unbound clearance of free drug
\( \Delta \log P \) Difference in \( \log P \) values in octanol and cyclohexane
\( H\text{-bond} \) Hydrogen bond
\( k_e \) Elimination rate constant
\( \log D_{7.4} \) Distribution coefficient at pH 7.4 (usually octanol/water)
\( \log P \) Partition coefficient (usually octanol)
\( pK_a \) Ionisation constant
\( T_{\text{max}} \) Time to maximum observed plasma concentration
\( V_{d(f)} \) Unbound volume of distribution of the free drug

Chapter 5

Abbreviations

ATP Adenosine triphosphate
BTL Bilitranslocase
CYP450 Cytochrome P450
MOAT Multiple organic acid transporter
MRP Multi-drug resistance protein
Natp Sodium dependent acid transporter protein
OATP Organic acid transport protein
OCT1 Organic cation transporter 1
OCT2 Organic cation transporter 2
P-gp P-glycoprotein
TxRA Thromboxane receptor antagonist
TxSI Thromboxane synthase inhibitor
Chapter 8

Symbols

$Cl$  
Clearance

$log \, D_{7.4}$  
Distribution coefficient (octanol-buffer) at pH 7.4

$t_{1/2}$  
Elimination half-life

$V_d$  
Volume of distribution

Chapter 6

Abbreviations

GFR  
Glomerular filtration rate

Symbols

$C_{p(f)}$  
Free (unbound) plasma concentration

$log \, D_{7.4}$  
Logarithm of distribution coefficient (octanol-buffer) at pH 7.4

Chapter 7

Abbreviations

COMT  
Catechol-O-methyl transferase

CYP  
Cytochrome P450

CYP2D6  
2D6 isoenzyme of the cytochrome P450 enzyme family

CYP2C9  
2C9 isoenzyme of the cytochrome P450 enzyme family

CYP3A4  
3A4 isoenzyme of the cytochrome P450 enzyme family

FMO  
Flavin mono-oxygenase

GST  
Glutathione S-transferase

MAO  
Monoamine oxidase

NEP  
Neutral endopeptidase

P450  
Cytochrome P450

PAPS  
3’-Phosphoadenosine-5-phosphosulfate

UGT  
UDP-glucuronosyltransferases

Symbols

$log \, D_{7.4}$  
Logarithm of the octanol/water distribution coefficient at pH 7.4

$K_m$  
Affinity constant (concentration at 50% $V_{max}$)

Chapter 8

Abbreviations

ANF  
Atrial natriuretic factor (also ANP: atrial natriuretic peptide)

COX  
Cyclooxygenase

ENCC  
Electroneutral Na-Cl cotransporter

hFGF  
Human fibroblast growth factor
Abbreviations and Symbols

- **GSH**: Glutathione
- **HMG-CoA**: 3-Hydroxy-3-methylglutaryl coenzyme A
- **LH**: Luteinizing hormone
- **5-LPO**: 5-Lipoxygenase
- **NK**: Neurokinin
- **NKCC**: Old name for ENCC
- **PBPK/PD**: Physiologically-based pharmacokinetic/pharmacodynamic (modelling)
- **PCNA**: Proliferating cell nuclear antigen
- **PPAR-γ**: Peroxisome proliferator-activated receptor γ
- **TA2**: Thromboxane
- **VEGF**: Vascular endothelial growth factor

Chapter 9

**Abbreviations**

- **BW**: Body weight
- **CYP2C9**: Cytochrome P450 2C9 enzyme
- **GFR**: Glomerular filtration rate
- **IV**: Intravenous
- **MLP**: Maximum life span potential
- **P450**: Cytochrome P450
- **TxRAs**: Thromboxane receptor antagonists

**Symbols**

- $C_{\text{max}}$: Maximum plasma concentration observed
- $Cl$: Clearance
- $Cl_i$: Intrinsic clearance
- $Cl_{iu}$: Intrinsic clearance of unbound (free) drug
- $Cl_{ou}$: Oral unbound clearance (i.e. oral clearance correct for free fraction)
- $Cl_s$: Systemic clearance
- $f_b$: Fraction of plasma bound drug
- $f_u$: Fraction of drug unbound (to plasma proteins)
- $f_{ut}$: Fraction of unbound drug in tissues
- $ln$: Natural logarithm
- $Q$: Organ blood flow
- $R$: Ratio of binding proteins in extracellular fluid (except plasma) to binding proteins in plasma
- $r^2$: Correlation coefficient
- $t_{1/2}$: Elimination half-life
- $V_d$: Volume of distribution
- $V_e$: Volume of extracellular fluid
- $V_p$: Volume of plasma
- $V_r$: Volume of remaining fluid
## Abbreviations

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<td>Cytochrome P450 3A4</td>
</tr>
<tr>
<td>DMPK</td>
<td>Drug metabolism and pharmacokinetics</td>
</tr>
<tr>
<td>HTS</td>
<td>High-throughput screening</td>
</tr>
<tr>
<td>IAM</td>
<td>Immobilised artificial membrane</td>
</tr>
<tr>
<td>LC/MS</td>
<td>Liquid chromatography/mass spectrometry</td>
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<td>MDR1</td>
<td>Gene coding for P-glycoprotein (P-gp); newer coding as ABCB1</td>
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<tr>
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<td>Medium throughput screening</td>
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<td>NADPH</td>
<td>Nicotinamide adenine dinucleotide phosphate</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance</td>
</tr>
<tr>
<td>PAMPA</td>
<td>Parallel artificial membrane permeability assay</td>
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<tr>
<td>PBPK</td>
<td>Physiologically-based pharmacokinetics</td>
</tr>
<tr>
<td>P-gp</td>
<td>P-glycoprotein</td>
</tr>
<tr>
<td>PK</td>
<td>Pharmacokinetics</td>
</tr>
<tr>
<td>PK/PD</td>
<td>Pharmacokinetics/pharmacodynamics</td>
</tr>
<tr>
<td>PSA</td>
<td>Polar surface area</td>
</tr>
<tr>
<td>QSAR</td>
<td>Quantitative structure–activity relationships</td>
</tr>
<tr>
<td>SAR</td>
<td>Structure–activity relationship</td>
</tr>
<tr>
<td>7TMs</td>
<td>Seven transmembrane loop receptors</td>
</tr>
<tr>
<td>UHTS</td>
<td>Ultra-high-throughput screening</td>
</tr>
</tbody>
</table>

## Symbols

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Delta \log P$</td>
<td>Difference between octanol/water and alkane/water log $P$ as a measure for hydrogen bonding capacity</td>
</tr>
<tr>
<td>$K_i$</td>
<td>Binding constant (to receptor or metabolising enzyme)</td>
</tr>
<tr>
<td>$\log D_{7.4}$</td>
<td>Logarithm of the octanol/water distribution coefficient at pH 7.4</td>
</tr>
<tr>
<td>$\log P$</td>
<td>Logarithm of the octanol/water partition coefficient for the neutral species</td>
</tr>
<tr>
<td>$\log S_w$</td>
<td>Logarithm of the aqueous solubility</td>
</tr>
<tr>
<td>$MW$</td>
<td>Molecular weight</td>
</tr>
</tbody>
</table>