

Drug Bioavailability

Estimation of Solubility, Permeability, Absorption and Bioavailability

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

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*Edited by H. van de
Waterbeemd, H. Lennernäs
and P. Artursson*

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Contents

	Preface	<i>xvii</i>
	Foreword	<i>xix</i>
	List of Authors	<i>xxi</i>
I	Studies of Membrane Permeability and Oral Absorption	1
1	Physico-chemical Approaches to Drug Absorption	3
	<i>Han van de Waterbeemd</i>	
	Abbreviations	3
	Symbols	3
1.1	Introduction	4
1.2	Drug-like Properties	5
1.3	Dissolution and Solubility	6
1.3.1	Calculated Solubility	7
1.4	Ionization (pK _a)	7
1.5	Lipophilicity	8
1.5.1	Calculated log P	9
1.6	Molecular Size and Shape	9
1.6.1	Calculated Size Descriptors	9
1.7	Hydrogen Bonding	9
1.7.1	Calculated Hydrogen-Bonding Descriptors	10
1.8	Amphiphilicity	11
1.9	Permeability	11
1.9.1	Artificial Membranes	11
1.9.2	IAM, ILC, MEKC, and BMC	12
1.9.3	Liposome Partitioning	13
1.9.4	Biosensors	13
1.9.5	Ghost Erythrocytes and Diffusion Constants	13
	References	14
2	High-throughput Measurement of log D and pK_a	21
	<i>John E. A. Comer</i>	
	Abbreviations	21
	Symbols	21

2.1	Introduction	22
2.2	Relationship between Ionization and Lipophilicity	24
2.3	Measuring log D	26
2.3.1	Shake-flask Method	26
2.3.2	pH-metric Method	27
2.3.3	Direct Chromatographic Methods	28
2.3.3.1	Chromatographic Hydrophobicity Index (CHI)	28
2.3.3.2	Microemulsion Electrokinetic Chromatography (MEEKC)	29
2.3.3.3	Chromatography in the Presence of Octanol	29
2.3.3.4	Reversed-Phase Chromatography	30
2.3.3.5	Liquid–Liquid Partition Chromatography	30
2.4	Measuring pK _a	32
2.4.1	Review of Methods	32
2.4.2	The Effect of Co-solvents on pK _a	34
2.4.3	pH-Metric Titration	34
2.4.4	Hybrid pH-Metric/UV Method	35
2.4.5	Other Methods	35
2.4.6	pH Gradient Titration	36
2.5	Some Thoughts about High-throughput Analytical Chemistry	39
	Acknowledgments	41
	References	42
3	High-throughput Measurement of Permeability Profiles	46
	<i>Alex Avdeef</i>	
	Abbreviations	46
	Symbols	46
3.1	Introduction	47
3.2	Key Historical Developments in Artificial-Membrane Permeability Measurement	47
3.3	The Ideal <i>in vitro</i> Artificial Membrane Permeability Model	52
3.3.1	Lipid Compositions in Biological Membranes	52
3.3.2	Permeability–pH Considerations	53
3.3.3	Role of Serum Proteins	54
3.3.4	Effects of Cosolvents, Bile Acids, and other Surfactants	55
3.3.5	Components of the Ideal	56
3.4	New Directions in PAMPA	56
3.4.1	Concentrated and Charged Phospholipid Membranes	56
3.4.2	Gradient-pH Permeability Equation	57
3.4.3	Permeability Measurements: High-phospholipid in Surfactant-free Solutions	58
3.4.4	Membrane Retention Measurements: High-phospholipid in Surfactant-free Solutions	59
3.4.5	Egg Lecithin and the Degree of Negative Charge	60
3.4.6	Summary: Increasing Phospholipid Content in the Absence of Sink Conditions	60

3.4.7	Effects of Surfactant on High-phospholipid Membrane Permeability and Retention	61
3.4.8	Quality and Usefulness of the UV Spectra	63
3.4.9	Iso-pH and Gradient-pH Mapping in 2% DOPC-Dodecane	65
3.4.10	Iso-pH Mapping in 20% Soy Lecithin-Dodecane, with Surfactant	68
3.4.11	Predictions of <i>in vivo</i> Human Jejunal Permeabilities using the Improved 20% Soy Lecithin with Surfactant <i>in vitro</i> PAMPA Technique	68
	Acknowledgments	69
	References	69
4	Caco-2 and Emerging Alternatives for Prediction of Intestinal Drug Transport: A General Overview	72
	<i>Per Artursson and Staffan Tavelin</i>	
	Abbreviations	72
	Symbols	72
4.1	Introduction	72
4.2	Research Opportunities with the Caco-2 Cell Model	73
4.2.1	Transport Mechanisms	73
4.2.2	Prediction of Drug Permeability <i>In Vivo</i>	74
4.3	Limitations of Caco-2 Cells in Predicting Intestinal Drug Transport	76
4.3.1	Technical Issues	76
4.3.2	Limitations Related to Transport Studies and Their Solutions	77
4.3.2.1	Active Transport	77
4.3.2.2	Passive Transport	80
4.4	Conclusion	82
	Acknowledgements	82
	References	82
5	Cell Cultures in Drug Discovery: An Industrial Perspective	90
	<i>Anna-Lena Ungell and Johan Karlsson</i>	
	Abbreviations	90
	Symbols	91
5.1	Introduction	91
5.2	Permeability Screening in Different Phases of Discovery	93
5.3	Cell Cultures for Assessment of Intestinal Permeability	94
5.3.1	Caco-2	95
5.3.2	MDCK Cells	97
5.3.3	2/4/A1 Cells	97
5.3.4	HT29	98
5.3.5	Other Cell Lines	99
5.4	Screening for Intestinal Permeability	99
5.4.1	Caco-2 Culture and Transport Experiments	99
5.4.2	Automated Caco-2 Assay	101
5.4.3	Quality Control and Standardization of Caco-2 Assay	103
5.4.4	Correlation to Fraction of Oral Dose Absorbed	104

5.4.5	Optimization of Experimental Conditions: pH	108
5.4.6	Optimizing Experimental Conditions: Solubility and BSA	109
5.5	Mechanistic Use of Cell Models	111
5.5.1	Paracellular Pathway	111
5.5.2	Transcellular Pathway	113
5.5.3	Carrier-mediated Transport	113
5.5.4	Evaluation of Metabolism During Transport	116
5.5.5	Evaluation of Toxicity	117
5.5.6	Computational Models for Prediction of Intestinal Permeability	118
5.6	Concluding Remarks	120
	References	120
6	Use of Animals for the Determination of Absorption and Bioavailability	132
	<i>Chris Logan</i>	
	Abbreviations	132
	Symbols	132
6.1	Introduction	133
6.1.1	ADME/PK in Drug Discovery	133
6.1.2	The Need for Prediction	134
6.2	Consideration of Absorption and Bioavailability	136
6.3	Choice of Animal Species	138
6.4	Methods	139
6.4.1	Radiolabels	139
6.4.2	<i>Ex vivo</i> Methods for Absorption	140
6.4.2.1	Static Method	140
6.4.2.2	Perfusion Methods	140
6.4.3	<i>In vivo</i> Methods	141
6.5	<i>In vivo</i> Methods for Determining Bioavailability	141
6.5.1	Cassette Dosing	141
6.5.2	Semi-simultaneous Dosing	142
6.5.3	Hepatic Portal Vein Cannulation	143
6.6	Inhalation	144
6.7	Relevance of Animal Models	145
6.7.1	Models for Prediction of Absorption	145
6.7.2	Models for Prediction of Volume	145
6.8	Prediction of Dose in Man	146
6.8.1	Allometry	146
6.8.2	Physiologically Based Pharmacokinetics	147
6.8.3	Prediction of Human Dose	148
6.9	Conclusion	150
	References	150
7	<i>In vivo</i> Permeability Studies in the Gastrointestinal Tract of Humans	155
	<i>Niclas Petri and Hans Lennernäs</i>	
	Abbreviations	155
	Symbols	155

7.1	Introduction	156
7.2	Pharmacokinetic Definition of Intestinal Absorption (f_a), Presystemic Metabolism (E_G and E_H) and Absolute Bioavailability (F) of Drugs Administered Orally to Humans	160
7.3	Methodological Aspects on <i>in vivo</i> Intestinal Perfusion Techniques	160
7.4	Paracellular Passive Diffusion	165
7.5	Transcellular Passive Diffusion	166
7.6	Carrier-mediated Intestinal Absorption	169
7.7	Jejunal Transport and Metabolism	172
7.8	Regional Differences in Transport and Metabolism of Drugs	179
7.9	Conclusion	180
	References	180
II	Drug Dissolution and Solubility	189
8	Gastrointestinal Dissolution and Absorption of Drugs	191
	<i>Gladys E. Granero, Chandrasekharan Ramachandran, and Gordon L. Amidon</i>	
	Abbreviations	191
	Symbols	191
8.1	General Dissolution	192
8.2	Absorption Models	197
8.3	Gastrointestinal Variables	200
8.3.1	Bile Salts	201
8.3.2	Gastric Emptying	201
8.3.2.1	Effect of Volume	202
8.3.2.2	Effect of Size and Density of the Drug Particle	203
8.3.2.3	Effect of pH	203
8.3.3	Gastrointestinal Transit	203
8.3.4	Gastrointestinal pH	204
8.4	Solubilization and Dissolution	205
8.4.1	Surfactants	206
8.4.2	Effect of Surfactants and pH on Dissolution Rate	206
8.4.3	Effect of pH	207
8.4.4	Bio-relevant Dissolution Media	207
8.4.5	Particle Size	208
8.4.6	Biopharmaceutics Classification System: Redefining BSC Solubility Class Boundary	209
	References	210
9	Aqueous Solubility in Discovery, Chemistry, and Assay Changes	215
	<i>Chris Lipinski</i>	
	Abbreviations	215
	Symbols	215
9.1	Introduction	215
9.2	Compound Synthesis	216

9.3	Compound Physical Form	216
9.4	Compound Distribution	217
9.5	Compound Physical Form: Ostwald's Rule of Stages	218
9.6	Polymorph Form and Aqueous Solubility	218
9.6.1	Implications for <i>in vitro</i> Assays	219
9.6.2	Implications for <i>in vivo</i> Assays	221
9.7	Solubility, Potency and Permeability Inter-relationships	221
9.8	Acceptable Aqueous Solubility for Oral Activity	222
9.8.1	Traditional Definition	222
9.8.2	Current Era Definition	223
9.9	Solubility in Practice: Development versus Discovery	223
9.9.1	Development Thermodynamic Solubility as a Benchmark	223
9.9.2	Turbidimetric/Particle-based Solubility	224
9.9.3	UV Detector-based Solubility	226
9.9.4	Other Methods-based Solubility	227
9.10	Solids not Characterized in Early Discovery	228
9.11	Solids Solubilized in DMSO in Early Discovery	229
	References	230
10	Factors Influencing the Water Solubilities of Crystalline Drugs	232
	<i>James W. McFarland, Chau M. Du, and Alex Avdeef</i>	
	Abbreviations	232
	Symbols	232
10.1	Introduction	233
10.2	Crystallinity	233
10.3	Solubility Datasets	234
10.4	MLR Analyses	235
10.5	The Absolv Approach	236
10.6	The PLS Approach	238
10.7	Discussion	238
	Acknowledgments	240
	References	240
III	Role of Transporters and Metabolism in Oral Absorption	243
11	Transporters in the GI Tract	245
	<i>Ho-Chul Shin, Christopher P. Landowski, Duxin Sun, and Gordon L. Amidon</i>	
	Abbreviations	245
11.1	Introduction	246
11.2	Intestinal Transporters	249
11.2.1	Peptide Transporters	249
11.2.2	Nucleoside Transporters	253
11.2.3	Amino Acid Transporters	256
11.2.4	Organic Cation Transporters	257
11.2.5	Organic Anion Transporters	259

11.2.6	Glucose Transporters	261
11.2.7	Vitamin Transporters	263
11.2.8	Bile Acid Transporters	264
11.2.9	Fatty Acid Transporters	265
11.2.10	Phosphate Transporters	266
11.2.11	Monocarboxylic Acid Transporters	266
11.2.12	ATP-Binding Cassette Transporters	267
11.2.13	Other Transporters	268
11.3	Summary	268
	References	269
12	Hepatic Transport	288
	<i>Hiroshi Suzuki and Yuichi Sugiyama</i>	
	Abbreviations	288
12.1	Introduction	288
12.2	Hepatic Uptake	289
12.2.1	Hepatic Uptake of Organic Anions	289
12.2.1.1	Quantitative Prediction of <i>in vivo</i> Disposition from <i>in vitro</i> Data	289
12.2.1.2	Transporter Molecules Responsible for Hepatic Uptake of Organic Anions	289
12.2.2	Hepatic Uptake of Organic Cations	292
12.2.3	Utilization of Transporters as a Target for the Drug Delivery	293
12.3	Biliary Excretion	294
12.3.1	Biliary Excretion Mediated by P-Glycoprotein	294
12.3.2	Biliary Excretion Mediated by Multidrug Resistance-Associated Protein 2 (MRP2)	294
12.3.3	Biliary Excretion Mediated by Breast Cancer-Resistant Protein (BCRP)	297
12.3.4	Biliary Excretion of Monovalent Bile Salts	297
12.4	Inter-individual Differences in Transport Activity	297
12.5	Drug–Drug Interactions	299
12.5.1	Effect of Drugs on the Activity of Transporters Located on the Sinusoidal Membrane	299
12.5.2	Effect of Drugs on the Activity of Transporters Located on the Bile Canalicular Membrane	300
12.6	Concluding Remarks	301
	References	301
13	The Importance of Gut Wall Metabolism in Determining Drug Bioavailability	311
	<i>Kevin Beaumont</i>	
	Abbreviations	311
13.1	Introduction	311
13.2	The Human Gastrointestinal Tract	312
13.3	Enzymes Expressed at the Gut Wall	314

13.3.1	UDP-Glucuronyltransferases	314
13.3.2	Sulfotransferases	314
13.3.3	Esterases	315
13.3.4	Cytochromes P450	316
13.4	Non-metabolic Barriers to Oral Absorption	319
13.4.1	P-glycoprotein	319
13.4.2	A Combined Role for P-gp and CYP3A4 in the Gut Wall	321
13.4.3	CYP Interactions	322
13.4.4	P-gp Interactions	323
13.5	Summary and Conclusions	324
	References	325
14	Modified Cell Lines	329
	<i>Charles L. Crespi</i>	
	Abbreviations	329
14.1	Introduction	329
14.2	Cell/Vector Systems	330
14.3	Expression of Individual Metabolizing Enzymes	333
14.4	Expression of Transporters	334
14.4.1	Efflux Transporters	334
14.4.2	Uptake Transporters	336
	References	336
IV	Computational Approaches to Drug Absorption and Bioavailability	339
15	Intestinal Absorption: the Role of Polar Surface Area	341
	<i>Per Artursson and Christel A. S. Bergström</i>	
	Abbreviations	341
	Symbols	341
15.1	Introduction	341
15.2	Drug Transport Across the Intestinal Epithelium	344
15.3	Passive Membrane Permeability and the Polar Surface Area	345
15.4	Generation of Molecular Surface Area Descriptors	347
15.5	The Polar Surface Area and Its Application in Drug Discovery	347
15.6	The Partitioned Total Surface Areas and Their Potential Application in the Drug Discovery Process	349
15.7	Future Perspectives and Conclusions	351
	Acknowledgement	353
	References	353
16	Calculated Molecular Properties and Multivariate Statistical Analysis in Absorption Prediction	358
	<i>Ulf Norinder and Markus Haeberlein</i>	
	Abbreviations	358

	Symbols	358
16.1	Introduction	359
16.2	Descriptors Influencing Absorption	359
16.2.1	Solubility	360
16.2.2	Membrane Permeability	360
16.3	Datasets	361
16.3.1	The Palm Dataset	361
16.3.2	The Wessel Dataset	361
16.3.3	The Egan Dataset	363
16.3.4	Yoshida Dataset	363
16.4	Computational Models of Absorption	363
16.4.1	Rule-of-5	363
16.4.2	Polar Surface Area (PSA)	388
16.4.3	PSA and A log P	389
16.4.4	MolSurf Descriptors	390
16.4.5	Molecular Hash Key Descriptors	391
16.4.6	GRID-related Descriptors	392
16.4.7	ADAPT Descriptors	392
16.4.8	HYBOT Descriptors	393
16.4.9	2D Topological Descriptors	394
16.4.10	2D Electrotopological Descriptors	394
16.4.11	1D Descriptors	397
16.5	Statistical Methods	398
16.5.1	Multiple Linear Regression	398
16.5.2	Partial Least Squares	399
16.5.3	Neural Networks	400
16.5.4	Distance-to-model Considerations	400
	References	403
17	VOLSURF: A Tool for Drug ADME-properties Prediction	406
	<i>Gabriele Cruciani, Mirco Meniconi, Emanuele Carosati, Ismael Zamora, and Raimund Mannhold</i>	
	Abbreviations	406
	Symbols	406
17.1	Introduction	406
17.2	The Molecular Descriptors	407
17.3	Practical Examples: Structure–Disposition Relationships	410
17.3.1	Predicting Membrane Partitioning	410
17.3.2	Predicting Thermodynamic Water Solubility	414
17.3.3	Predicting Metabolic Stability	416
17.4	Conclusions	418
	Software	418
	Acknowledgements	418
	References	419

18	Simulation of Absorption, Metabolism, and Bioavailability	420
	<i>Michael B. Bolger, Balaji Agoram, Robert Fraczekiewicz, and Boyd Steere</i>	
	Abbreviations	420
	Symbols	420
18.1	Introduction: Simulation Studies Relevant to Oral Absorption	420
18.2	Background	421
18.3	Use of Rule-Based Computational Alerts in Early Discovery	422
18.4	Mechanistic Simulation (ACAT models) in Early Discovery	428
18.4.1	Automatic Scaling of k'_a as a Function of Peff, pH, and log D	432
18.4.2	Mechanistic Correction for Active Transport and Efflux	434
18.5	Mechanistic Simulation of Bioavailability (Drug Development)	436
18.6	Conclusions	439
	References	439
19	Prediction of Bioavailability	444
	<i>Arun K. Mandagere and Barry Jones</i>	
	Abbreviations	444
	Symbols	444
19.1	Introduction	444
19.2	Oral Bioavailability Definition	445
19.2.1	Cassette Dosing	446
19.2.2	Across-species Prediction of Bioavailability	447
19.3	<i>In silico</i> Models for Estimating Human Oral Bioavailability	450
19.3.1	Quantitative Structure–Activity Relationship (QSAR) Approaches	450
19.3.2	Molecular Properties Influencing Bioavailability	452
19.3.3	Estimation of Bioavailability from Calculated Absorption	453
19.3.3.1	ACE Inhibitors	453
19.3.3.2	β -Blockers	454
19.3.3.3	Calcium Antagonists	454
19.4	<i>In vitro</i> Model for Predicting Oral Bioavailability in Human and other Species	455
19.5	<i>In vivo</i> Method for Estimating Human Oral Bioavailability from Animal Pharmacokinetic Studies	458
19.6	Factors to Consider in Optimizing Oral Bioavailability	458
	References	459
20	Towards P-Glycoprotein Structure–Activity Relationships	461
	<i>Anna Seelig, Ewa Landwojtowicz, Holger Fischer, and Xiaochun Li Blatter</i>	
	Abbreviations	461
	Symbols	461
20.1	Introduction	461
20.1.1	P-glycoprotein	461
20.1.2	Conventional SAR Studies	463
20.1.3	Why Conventional SAR Studies may not be Adequate to Understand P-gp	463

20.2	The Role of Lipid Binding for SAR	464
20.2.1	Membrane Partitioning Determines Drug Concentration at Half-Maximum P-gp-ATPase Activation, K_m	464
20.2.2	The Membrane Concentration of Substrates Relevant for P-gp Activation	466
20.2.3	Molecular Size: Is it Relevant for P-gp Activation?	467
20.3	In Search of a Pharmacophore	468
20.3.1	The Local Environment Determines the Nature of Substrate–Transporter Interactions	468
20.3.2	H-bond Donors in Putative Transmembrane α -Helices of P-gp	469
20.3.3	H-Bond Acceptor Patterns in Compounds Interacting with P-gp	470
20.3.4	The Number and Strength of H-Bonds Determines the Drug-Transporter Affinity	472
20.3.5	The Effect of Charge for Interaction with P-gp	475
20.3.6	H-bond Acceptor Patterns in P-gp Inducers	475
20.4	SAR Applied to Experimental Results	477
20.4.1	P-gp-ATPase Activation Assays: H-Bonding Determines Activation Rate	477
20.4.2	Competition Assays: The Compound with the Higher Potential to Form H-Bonds Inhibits the Compound with the Lower Potential	480
20.4.3	Transport Assays: Two Type I Units are Required for Transport	481
20.5	P-gp Modulation or Inhibition	483
20.5.1	How to Design an Inhibitor	486
	References	487
V	Drug Development Issues	493
21	Application of the Biopharmaceutic Classification System Now and in the Future	495
	<i>Bertil Abrahamsson and Hans Lennernäs</i>	
	Abbreviations	495
	Symbols	495
21.1	Introduction	496
21.2	Definition of Absorption and Bioavailability of Drugs following Oral Administration	499
21.3	Dissolution and Solubility	501
21.4	The Effective Intestinal Permeability (P_{eff})	506
21.5	Luminal Degradation and Binding	512
21.6	The Biopharmaceutical Classification System	514
21.6.1	Regulatory Aspects	514
21.6.1.1	Present Situation	514
21.6.1.2	Potential Future Extensions	516
21.6.2	Drug Development Aspects	517
21.6.2.1	Selection of Candidate Drugs	517
21.6.2.2	Choice of Formulation Principle	518

21.6.2.3	IVIVC	520
21.6.2.4	Food–Drug Interactions	523
21.7	Conclusion	526
	Disclaimer	526
	References	526
22	Prodrugs	532
	<i>Bente Steffansen, Anne Engelbrecht Thomsen, and Sven Frokjaer</i>	
	Abbreviations	532
22.1	Introduction	532
22.2	Prodrug Design	533
22.3	Peptide-Prodrugs and the Cyclic Peptide-Prodrug Concept	535
22.4	Prodrug Designed for PepT1-Mediated Absorption	536
22.4.1	Stabilized Dipeptide Promoieties	537
22.4.2	Amino Acid Prodrugs	538
22.5	Site Activation	539
22.6	Conclusions	539
	References	541
23	Modern Delivery Strategies: Physiological Considerations for Orally Administered Medications	547
	<i>Clive G. Wilson</i>	
	Abbreviations and Symbols	547
23.1	Introduction	547
23.2	The Targets	548
23.3	Upper Gastrointestinal Tract: Mouth and Esophagus	548
23.3.1	Swallowing the Bitter Pill . . .	550
23.4	Mid-gastrointestinal Tract: Stomach and Intestine	551
23.4.1	Gastric Inhomogeneity	551
23.4.2	Modulation of Transit to Prolong the Absorption Phase	555
23.4.3	Ileocecal Movement	555
23.4.4	Fat and the Small Intestine	556
23.4.5	Absorption Enhancement	556
23.4.6	Alteration of Flux across the Small Intestine	557
23.5	Lower Gastrointestinal Tract: The Colon	558
23.5.1	Colonic Transit	558
23.5.2	Time of Dosing	559
23.5.3	Colonic Water	560
23.6	Pathophysiological Effects on Transit	561
23.7	Pathophysiological Effects on Permeability	563
23.8	pH	564
23.9	Conclusions	564
	References	565
	Index	569

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

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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.

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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)
$diff(\log P^{N-1})$	Difference between $\log P^N$ and $\log P^1$
$\Delta \log P$	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

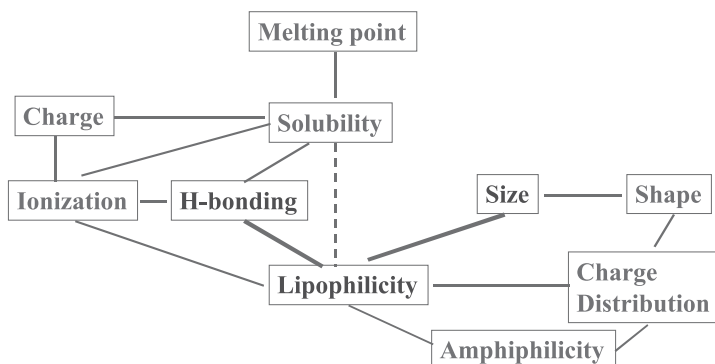


Fig. 1.1. Relationships between various physico-chemical properties believed to influence oral drug absorption.