# Contents

A Personal Foreword IX

## **1** Physicochemistry 1

- 1.1 Physicochemistry and Pharmacokinetics 2
- 1.2 Partition and Distribution Coefficients as Measures of Lipophilicity *2*

v

- 1.3 Limitations on the Use of 1-Octanol 5
- 1.4 Further Understanding of log *P* 6
- 1.4.1 Unraveling the Principal Contributions to log *P* 6
- 1.4.2 Hydrogen Bonding 7
- 1.4.3 Polar Surface Area 8
- 1.4.4 Molecular Size and Shape 9
- 1.5 Alternative Lipophilicity Scales 10
- 1.6 Computational Systems to Determine Lipophilicity 10
- 1.7 Membrane Systems to Study Drug Behavior 10
- 1.8 Dissolution and Solubility 12
- 1.9 The BCS Classification and Central Role of Permeability 13 References 15

## 2 Pharmacokinetics 19

- 2.1 Setting the Scene 20
- 2.2 Intravenous Administration: Volume of Distribution 21
- 2.3 Intravenous Administration: Clearance 22
- 2.4 Intravenous Administration: Clearance and Half-life 23
- 2.5 Intravenous Administration: Infusion 24
- 2.6 Oral Administration 26
- 2.7 Repeated Doses 27
- 2.8 Development of the Unbound (Free) Drug Model 29
- 2.9 Unbound Drug and Drug Action 29
- 2.10 Unbound Drug Model and Barriers to Equilibrium 32
- 2.11 Pharmacodynamic Models 34

Contents

2.12	Slow Offset Compounds	35	
------	-----------------------	----	--

2.13 Factors Governing Unbound Drug Concentration - 38 References 40

#### 3 Absorption 41

- 3.1 The Absorption Process 42
- Dissolution 42 3.2
- Membrane Transfer 44 3.3
- 3.4 Barriers to Membrane Transfer 49
- 3.5 Prodrugs to Increase Oral Absorption 51
- 3.6 Active Transport 55
- 3.7 Models for Absorption Estimation 56
- Estimation of Absorption Potential and other Computational 3.8 Approaches 56 References 57

#### Distribution 61 4

- 4.1 Membrane Transfer Access to the Target 62
- 4.2 Brain Penetration 63
- 4.2.1 Accumulation of Lower Permeability Compounds into the Brain 67
- 4.2.2 Distribution into Tumors 68
- 4.2.3 Volume of Distribution and Duration 70
- 4.2.4 Distribution and  $T_{\text{max}}$  77 References 78

#### 5 Clearance 81

- 5.1 The Clearance Processes 82
- 5.2 Role of Transport Proteins in Drug Clearance 83
- 5.3 Interplay Between Metabolic and Renal Clearance 87
- 5.4 Role of Lipophilicity in Drug Clearance 87
- 5.5 Active Metabolites 88
- Balancing the Rate of Renal and Metabolic clearance 5.6 and Potency 91 References 101

#### 6 Renal Clearance 103

- 6.1 Kidney Anatomy and Function 103
- 6.2 Lipophilicity and Reabsorption by the Kidney 105
- 6.3 Effect of Charge on Renal Clearance 106
- Plasma Protein Binding and Renal Clearance 6.4 106
- Balancing Renal Clearance and Absorption 6.5 108
- Renal Clearance and Drug Design 109 6.6 References 110

- 7 Metabolic (Hepatic) Clearance 111
- 7.1 Symbols 111
- 7.2 Function of Metabolism (Biotransformation) 112
- 7.3 Cvtochrome P450 112
- 7.3.1 Catalytic Selectivity of CYP2D6 115
- Catalytic Selectivity of CYP2C9 7.3.2 117
- Catalytic Selectivity of CYP3A4 7.3.3 119
- 7.4 Other Oxidative Metabolism Processes 126
- 7.4.1 Aldehyde Oxidase 126
- 7.4.2 Flavin-Containing Monooxygenases 130
- 7.4.3 Monoamine Oxidases 133
- 7.5 Oxidative Metabolism and Drug Design 138
- 7.6 Nonspecific Esterases 138
- 7.6.1 Function of Esterases 138
- 7.6.2 Ester Drugs as Intravenous and Topical Agents 140
- 7.7 Prodrugs to Aid Membrane Transfer 142
- Enzymes Catalyzing Drug Conjugation 144 7.8
- Glucuronosyl- and Sulfotransferases 144 7.8.1
- 7.8.2 Methyl Transferases 147
- Glutathione-S-Transferases 148 7.8.3
- 7.9 Stability to Conjugation Processes 149
- 7.10 Pharmacodynamics and Conjugation 152 References 153
- 8 Toxicity 159
- 8.1 Toxicity Findings 160
- Pharmacologic Mechanism-Based Toxicity 8.1.1 160
- Chemotype-Dependent Toxicity 8.1.2 161
- 8.1.3 Metabolism-Induced Toxicity 164
- 8.2 Structure–Toxicity Analyses 167
- 8.3 Reactive Metabolite Screening in Drug Discovery 171
- 8.4 Structural Alerts/Toxicophores in Drug Design 173
- 8.5 Dealing with Reactive Metabolite Positives in Drug Discovery. Risk Assessment Strategies – Effect of Daily Dose 173
- Dealing with Reactive Metabolite Positives in Drug Discovery. 8.6 Risk Assessment Strategies - Competing Detoxication Pathways 182
- 8.7 Stratification of Toxicity 183
- Toxicity Prediction: Computational Toxicology 8.8 183
- 8.9 Toxicogenomics 184
- Pharmacogenomics 185 8.10
- Enzyme Induction and Drug Design 8.11 186
- 8.12 Enzyme Inhibition and Drug Design 191
- 8.12.1 Quasi-Irreversible Inhibition 191

II Contents

- 8.12.2 Irreversible CYP Inactivation via Apoprotein and/or Heme Covalent Modification *193*
- 8.12.3 CYP Inhibition by Nitrogen-Containing Heterocycles 195 References 202

## 9 Predicting Human Pharmacokinetics 209

- 9.1 Objectives of Predicting Human Pharmacokinetics 210
- 9.2 Allometric Scaling of Preclinical In Vivo PK Parameters 211
- 9.2.1 Volume of Distribution 211
- 9.2.2 Clearance 214
- 9.3 Prediction of Human PK Parameters Using *In Vitro* Data 220
- 9.3.1 Predicting Human Volume of Distribution from *In vitro* Data 220
- 9.3.2 Predicting Human Clearance from Human *In Vitro* Data 222
- 9.3.3 Species Scaling: Incorporating Differences in Metabolic Clearance 223
- 9.4 Elimination Half-Life 224
- 9.5 Moving Forward 224 References 225

## 10 ADME Screening 229

- 10.1 The High-Throughput Synthesis and Screening Trend 230
- 10.2 The Concept of ADME Space 231
- 10.3 Drug Metabolism and Discovery Screening Sequences 233
- 10.4 Physicochemistry 234
- 10.4.1 Solubility 235
- 10.4.2 Ionization 236
- 10.4.3 Lipophilicity 236
- 10.4.4 Polar Surface Area 237
- 10.5 Absorption/Permeability 238
- 10.6 Metabolism, Induction, and Inhibition 239
- 10.7 Transporters 240
- 10.8 Protein Binding 242
- 10.9 Pharmacokinetics 243
- 10.10 In silico Approaches to ADME 243
- 10.10.1 QSAR Approaches to ADME 244
- 10.10.2 Theoretical Models for Predicting Metabolism 244
- 10.10.3 Physiologically-Based Pharmacokinetic Modeling 245 References 246

## Index 251

VIII