## Contents

*Preface* ix  
*Companion Website Directions* xii  

1. **Introduction: Basic Concepts**  
   1.1 Introduction 1  
   1.2 Drugs and drug nomenclature 3  
   1.3 Law of mass action 4  
   1.4 Ionization 9  
   1.5 Partition coefficients 12  
   1.6 Further reading 14  

2. **Drug Administration and Distribution** 15  
   2.1 Introduction 15  
   2.2 Drug transfer across biological membranes 16  
   2.3 Drug administration 22  
   2.4 Drug distribution 31  
   2.5 Plasma protein binding 38  
   2.6 Further reading 43  
   2.7 References 43  

3. **Drug Metabolism and Excretion** 45  
   3.1 Introduction 45  
   3.2 Metabolism 46  
   3.3 Excretion 58  
   3.4 Further reading 69  
   3.5 References 69  

4. **Single-compartment Pharmacokinetic Models** 71  
   4.1 Introduction 72  
   4.2 Systemic clearance 74  
   4.3 Intravenous administration 76  
   4.4 Absorption 79  
   4.5 Infusions 87  
   4.6 Multiple doses 90  
   4.7 Non-linear kinetics 94  
   4.8 Relationship between dose, and onset and duration of effect 98  
   4.9 Limitations of single-compartment models 99
4.10 Further reading 100
4.11 References 100

5. Multiple-compartment and Non-compartment Pharmacokinetic Models 102
5.1 Multiple-compartment models 102
5.2 Non-compartmental models 117
5.3 Population pharmacokinetics 121
5.4 Curve fitting and the choice of most appropriate model 122
5.5 Further reading 124
5.6 References 124

6. Kinetics of Metabolism and Excretion 126
6.1 Introduction 126
6.2 Metabolite kinetics 127
6.3 Renal excretion 137
6.4 Excretion in faeces 142
6.5 Further reading 143
6.6 References 144

7. Clearance, Protein Binding and Physiological Modelling 145
7.1 Introduction 145
7.2 Clearance 146
7.3 Physiological modelling 158
7.4 Further reading 161
7.5 References 161

8. Quantitative Pharmacological Relationships 162
8.1 Pharmacokinetics and pharmacodynamics 162
8.2 Concentration–effect relationships (dose–response curves) 163
8.3 Time-dependent models 169
8.4 PK-PD modelling 173
8.5 Further reading 177
8.6 References 177

9. Pharmacokinetics of Large Molecules 178
9.1 Introduction 178
9.2 Pharmacokinetics 179
9.3 Plasma kinetics and pharmacodynamics 184
9.4 Examples of particular interest 185
9.5 Further reading 191
9.6 References 191

10. Pharmacogenetics and Pharmacogenomics 192
10.1 Introduction 192
10.2 Methods for the study of pharmacogenetics 193
10.3 N-Acetyltransferase 194
10.4 Plasma cholinesterase 197
10.5 Cytochrome P450 polymorphisms 199
10.6 Alcohol dehydrogenase and acetaldehyde dehydrogenase 202
10.7 Thiopurine methyltransferase 202
10.8 Phase 2 enzymes 202
10.9 Transporters 204
10.10 Ethnicity 206
10.11 Pharmacodynamic differences 206
10.12 Personalized medicine 208
10.13 Further reading 209
10.14 References 209

11. Additional Factors Affecting Plasma Concentrations 211
11.1 Introduction 211
11.2 Pharmaceutical factors 213
11.3 Sex 214
11.4 Pregnancy 218
11.5 Weight and obesity 220
11.6 Food, diet and nutrition 225
11.7 Time of day 226
11.8 Posture and exercise 228
11.9 Further reading 231
11.10 References 231

12. Effects of Age and Disease on Drug Disposition 233
12.1 Introduction 233
12.2 Age and development 234
12.3 Effects of disease on drug disposition 242
12.4 Assessing pharmacokinetics in special populations 256
12.5 Further reading 257
12.6 References 258

13. Drug Interactions and Toxicity 260
13.1 Introduction 260
13.2 Drug interactions 261
13.3 Toxicity 273
13.4 Further reading 282
13.5 References 282

14.1 Drug disposition and fate 284
14.2 Pharmacodynamics 286
14.3 Quantification of drugs and pharmacokinetics 286
14.4 The future 289
14.5 Postscript 291
14.6 Further reading 292
14.7 References 292
Appendices
1 Mathematical Concepts and the Trapezoidal Method 293
2 Dye Models to Teach Pharmacokinetics 300
3 Curve Fitting 303
4 Pharmacokinetic Simulations 307
Index 312