Contents

Preface xiii
Glossary xv

1. Introduction to Biopharmaceutics and Pharmacokinetics 1
   - Drug Product Performance 1
   - Biopharmaceutics 1
   - Pharmacokinetics 3
   - Clinical Pharmacokinetics 4
   - Practical Focus 4
   - Pharmacodynamics 5
   - Drug Exposure and Drug Response 5
   - Toxicokinetics and Clinical Toxicology 5
   - Measurement of Drug Concentrations 6
   - Basic Pharmacokinetics and
     Pharmacokinetic Models 10
   - Chapter Summary 15
   - Learning Questions 17
   - References 17
   - Bibliography 18

2. Mathematical Fundamentals in Pharmacokinetics 19
   - Math Self-Exam 19
   - Estimation and the Use of Calculators and
     Computers 20
   - Practice Problems 22
   - Calculus 24
   - Graphs 26
   - Units in Pharmacokinetics 31
   - Measurement and Use of Significant Figures 32
   - Units for Expressing Blood Concentrations 33
   - Statistics 33
   - Practical Focus 34
   - Rates and Orders of Reactions 35
   - Chapter Summary 40
   - Learning Questions 40
   - References 42
   - Bibliography 42

3. One-Compartment Open Model:
   Intravenous Bolus Administration 43
   - Elimination Rate Constant 44
   - Apparent Volume of Distribution 45
   - Clearance 48
   - Practical Focus 50
   - Clinical Application 53
   - Calculation of k from Urinary Excretion Data 53
   - Practice Problem 54
   - Clinical Application 56
   - Chapter Summary 57
   - Learning Questions 57
   - Reference 59
   - Bibliography 59

4. Multicompartment Models:
   Intravenous Bolus Administration 61
   - Two-Compartment Open Model 63
   - Clinical Application 68
   - Practice Problem 68
   - Practical Focus 69
   - Three-Compartment Open Model 77
   - Determination of Compartment Models 79
   - Practical Application 84
   - Chapter Summary 86
   - Learning Questions 87
   - References 88
   - Bibliography 89

5. Intravenous Infusion 91
   - One-Compartment Model Drugs 91
   - Infusion Method for Calculating Patient
     Elimination Half-Life 95

References 88
Bibliography 89
6. Drug Elimination and Clearance 107

Drug Elimination 107
The Kidney 108
Renal Drug Excretion 111
Clinical Application 114
Practice Problems 114
Drug Clearance 114
Clearance Models 116
Renal Clearance 118
Determination of Renal Clearance 121
Relationship of Clearance to Elimination
Half-Life and Volume of Distribution 125
Chapter Summary 127
Learning Questions 127
References 129
Bibliography 129

7. Pharmacokinetics of Oral Absorption 131

Pharmacokinetics of Drug Absorption 131
Significance of Absorption Rate Constants 133
Zero-Order Absorption Model 133
Clinical Application—Transdermal
Drug Delivery 134
First-Order Absorption Model 134
Practice Problem 142
Chapter Summary 149
Learning Questions 149
References 150
Bibliography 151

8. Multiple-Dosage Regimens 153

Drug Accumulation 153
Clinical Example 157
Repetitive Intravenous Injections 158
Intermittent Intravenous Infusion 163
Estimation of $k$ and $V_p$ of Aminoglycosides
in Clinical Situations 165
Multiple-Oral-Dose Regimen 166
Loading Dose 168

9. Nonlinear Pharmacokinetics 177

Saturable Enzymatic Elimination Processes 179
Practice Problem 180
Drug Elimination by Capacity-Limited
Pharmacokinetics: One-Compartment
Model, IV Bolus Injection 181
Clinical Focus 191
Drugs Distributed as One-Compartment
Model and Eliminated by Nonlinear
Pharmacokinetics 191
Chronopharmacokinetics and Time-Dependent
Pharmacokinetics 193
Bioavailability of Drugs that Follow Nonlinear
Pharmacokinetics 196
Nonlinear Pharmacokinetics Due to
Drug-Protein Binding 196
Potential Reasons for Unsuspected
Nonlinearity 200
Chapter Summary 200
Learning Questions 200
References 202
Bibliography 203

10. Physiologic Drug Distribution and Protein Binding 205

Physiologic Factors of Distribution 205
Clinical Focus 213
Apparent Volume Distribution 213
Practice Problem 216
Protein Binding of Drugs 219
Clinical Examples 221
Effect of Protein Binding on the Apparent
Volume of Distribution 222
Relationship of Plasma Drug-Protein Binding
to Distribution and Elimination 227
Determinants of Protein Binding 231
Kinetics of Protein Binding 232
Practical Focus 233
Determination of Binding Constants and
Binding Sites by Graphic Methods 233
Clinical Significance of Drug-Protein
Binding 236
Modeling Drug Distribution 247
Chapter Summary 248
Learning Questions 249
References 250
Bibliography 251
11. Drug Elimination and Hepatic Clearance 253

Route of Drug Administration and Extrahepatic Drug Metabolism 253
Practical Focus 255
Hepatic Clearance 255
Enzyme Kinetics 257
Clinical Example 261
Practice Problem 263
Anatomy and Physiology of the Liver 265
Hepatic Enzymes Involved in the Biotransformation of Drugs 267
Drug Biotransformation Reactions 269
Pathways of Drug Biotransformation 270
First-Pass Effects 282
Hepatic Clearance of a Protein-Bound Drug: Restrictive and Nonrestrictive Clearance from Binding 287
Effect of Changing Intrinsic Clearance and/or Blood Flow on Hepatic Extraction and Elimination Half-Life after IV and Oral Dosing 288
Biliary Excretion of Drugs 289
Role of Transporters in Hepatic Clearance and Bioavailability 292
Chapter Summary 293
Learning Questions 294
References 296
Bibliography 298

12. Pharmacogenetics 301

Polymorphism 303
Pharmacogenomics 306
Adverse Drug Reactions Attributed to Genetic Differences 308
Genetic Polymorphism in Drug Metabolism: Cytochrome P-450 Isozymes 310
Genetic Polymorphism in Drug Transport: MDR1 (P-Glycoprotein) and Multidrug Resistance 311
Genetic Polymorphism in Drug Targets 312
Relationship of Pharmacokinetics/Pharmacodynamics and Pharmacogenetics/Pharmacogenomics 313
Clinical Example 315
Summary 316
Glossary 316
Abbreviations 317
References 317
Bibliography 318

13. Physiologic Factors Related to Drug Absorption 321

Drug Absorption and Design of a Drug Product 321
Route of Drug Administration 321
Nature of Cell Membranes 324
Passage of Drugs Across Cell Membranes 326
Oral Drug Absorption During Drug Product Development 333
Drug Interactions in the Gastrointestinal Tract 334
Oral Drug Absorption 336
Methods for Studying Factors that Affect Drug Absorption 348
Clinical Examples 351
Effect of Disease States on Drug Absorption 351
Miscellaneous Routes of Drug Administration 353
Chapter Summary 355
Learning Questions 356
References 357
Bibliography 359

14. Biopharmaceutic Considerations in Drug Product Design and In Vitro Drug Product Performance 361

Biopharmaceutic Factors Affecting Drug Bioavailability 361
Rate-Limiting Steps in Drug Absorption 363
Physicochemical Nature of the Drug 366
Formulation Factors Affecting Drug Product Performance 368
Drug Product Performance, In Vitro: Dissolution and Drug Release Testing 370
Compendial Methods of Dissolution 374
Alternative Methods of Dissolution Testing 376
Meeting Dissolution Requirements 378
Problems of Variable Control in Dissolution Testing 379
Performance of Drug Products: In Vitro–In Vivo Correlation 380
Dissolution Profile Comparisons 386
Drug Product Stability 386
Considerations in the Design of a Drug Product 387
Drug Product Considerations 389
Clinical Example 394
Chapter Summary 398
Learning Questions 399
References 399
Bibliography 401