

Contents

Preface to the Second Edition

vii

Preface to the First Edition

ix

1. Introduction to Biopharmaceutics and Pharmacokinetics (1–24)

- 1.1. Introduction 1
- 1.2. Historical Perspective of Biopharmaceutics 2
- 1.3. Extravascular Administration of a Drug 5
- 1.4. Scope of Biopharmaceutics 6
- 1.5. Variants in Biopharmaceutics 7
- 1.6. Pharmacokinetics 8
 - 1.6.1. Modus Operandi 8
 - 1.6.2. Salient Features of Pharmacokinetics 9
 - 1.6.3. Experimental Aspects of Pharmacokinetics 10
- 1.7. Clinical Pharmacokinetics 11
 - 1.7.1. Therapeutic Drug Monitoring (TDM) and Pharmacokinetics 12
- 1.8. Pharmacodynamics 13
- 1.9. Toxicokinetics and Clinical Toxicology 14
- 1.10. Bioavailability 15
 - 1.10.1. Absolute Bioavailability 16
 - 1.10.2. Relative Bioavailability 16
 - 1.10.3. Qualifying Absolute Availability 16
 - 1.10.4. Quantifying Relative Availability 18
- 1.11. Bioequivalence 18
 - 1.11.1. Bioequivalence: The Canadian Regularly Perspective 19
 - 1.11.2. Uncomplicated Drugs 20
 - 1.11.3. Guidelines for Equivalence Studies 21
 - 1.11.4. Plasma-Drug Concentration Versus Time Curve 21
 - 1.11.5. Modus Operandi 21

2. Biopharmaceutics

(25–125)

- 2.1. Introduction 25
 - 2.1.1. Alternative Distinctness of Biopharmaceutics 27
 - 2.1.2. Important Modalities Encountered by a Drug 27
 - 2.1.3. Pharmacokinetics 28
 - 2.1.4. Clinical Pharmacokinetics 28
- 2.2. Biopharmaceutics Classification System (BCS) 30
- 2.3. In Vitro-In Vivo Correlation (IVIVC): An Introspection 31
 - 2.3.1. Genesis of IVIVC 32
 - 2.3.2. FDA Definition for IVIVC 32
 - 2.3.3. Important Factors for Development of IVIVC 32
 - 2.3.4. IVIVC Utilization in Novel Dosage Forms 33
 - 2.3.5. Applications of IVIVC 33
- 2.4. Passage of Drugs Across Biological Barrier 34
 - 2.4.1. Simple Capillary Endothelial Barrier (CEB) 34
 - 2.4.2. Cell Membrane Barrier (CMB) 35
 - 2.4.3. Blood-Brain Barrier (BBB) 37
 - 2.4.3.1. Permeability of Cell and Capillary Membranes 38
 - 2.4.3.2. Highlights of BBB as a Lipoidal Barrier 39
 - 2.4.4. Blood-Cerebrospinal Fluid Barrier (BCSFB) 41
 - 2.4.5. Placental Barrier (PB) 42
 - 2.4.6. Blood-Testis Barrier (BTB) 44
- 2.5. Factors Influencing Drug Absorption 44
 - 2.5.1. Rate-Limited Stages in Oral Drug Absorption 45
 - 2.5.2. Drug Absorption via Gastrointestinal Tract (GIT) 46
 - 2.5.2.1. Cell Membrane Structure 47
 - 2.5.2.2. Pathways of Drug Absorption 48
 - 2.5.2.3. Gastrointestinal (GI) Physiology 49
 - 2.5.3. Fluid-Mosaic Model for Transcellular Diffusion of Polar Molecules 52
 - 2.5.4. Gastrointestinal Physiology 53
 - 2.5.4.1. Gastrointestinal Blood Flow 53
 - 2.5.4.2. Gastrointestinal pH 54
 - 2.5.5. Gastric Emptying 56
 - 2.5.5.1. Mechanism of Gastric Emptying 57
 - 2.5.6. Gastrointestinal GI Motility 59
- 2.6. Mechanism of Drug Absorption 60
 - 2.6.1. Passive Diffusion 61
 - 2.6.1.1. Fick's Law of Diffusion 62
 - 2.6.1.2. Characteristic Features of Passive Diffusion 63

2.6.1.3. Fate of Lipophilic and Hydrophilic Substituted Drugs	64
2.6.1.4. Implication of Henderson and Hasselbalch Equation	64
2.6.2. Pore Transport (Convective Transport)	65
2.6.2.1. Highlights of Pore Transport	65
2.6.3. Carrier-Mediated Transport	66
2.6.3.1. Important Characteristic Features of Carrier-Mediated Transport System	66
2.6.4. Active Transport	68
2.6.5. Facilitated Diffusion	70
2.6.6. Carrier-Mediated Intestinal Transport	71
2.6.7. Ionic Diffusion (or Electrochemical Diffusion)	71
2.6.7.1. Permeation Profile of Cationic Drug Molecules	72
2.6.8. Ion-Pair Transport	72
2.6.9. Endocytosis	72
2.6.10. Summary of Important Transport Processes <i>vis-à-vis</i> Critical Absorption of Drugs by Different Mechanism	74
2.7. Drug Absorption <i>vs</i> Bioavailability	74
2.7.1. Preamble	74
2.7.2. Pharmaceutical Factors (or Biopharmaceutic Considerations) Affecting Drug Bioavailability	75
2.7.2.1. Rate-Determining Step (RDS)	76
2.7.2.2. Noyes-Whitney Dissolution Rate Law	80
2.7.3. Factor Influencing GI Absorption of a Drug from Its Respective Dosage Forms	82
2.7.3.1. Pharmaceutical Factors	82
2.7.3.2. Patient-Related Factors	83
2.7.4. Physiochemical Nature of the Drug <i>vis-à-vis</i> Absorption	83
2.7.4.1. Drug Solubility and Dissolution Rate	84
2.7.4.2. Theories of Drug Dissolution	86
2.7.4.3. Particle Size and Drug Absorption	88
2.7.4.4. Polymorphic Crystals, Solvates and Drug Absorption	91
2.7.4.5. Drug pK_o Lipophilicity and GI pH (or pH-Partition Hypothesis)	93
2.7.4.6. Limitations of pH-Partition Hypothesis	101
2.7.4.7. Deviations from the pH-Partition Hypothesis	104
2.7.5. Product Form (Dosage Form) Characteristics <i>vis-à-vis</i> Pharmaceutic Ingredients Affecting Drug Absorption	106
2.7.5.1. Product Form Characteristics	107
2.7.5.1.1. Formulation Factors	107
2.7.5.1.2. Disintegration Time	111
2.7.5.1.3. Processing Variants	112
2.7.5.1.4. Granulation Variables	112

- 2.7.5.1.5. Applied Compression Force 114
- 2.7.5.1.6. Packing of Capsule Contents 115
- 2.7.5.2. Pharmaceutical Ingredients 116
- 2.7.6. Drug Absorption *vis-à-vis* Patient-Related Factors 122

3. Pharmacokinetics

(128–225)

- 3.1. Introduction 126
 - 3.1.1. Effects of Pharmacokinetics 127
 - 3.1.1.1. Preformulation 127
 - 3.1.1.2. Dissolution Testing 128
 - 3.1.1.3. Bioavailability and Bioequivalence 129
- 3.2. Clinical Significance of Plasma Protein Drug Concentration Measurement 130
 - 3.2.1. Significance of Drug-Protein Binding Complex 131
 - 3.2.1.1. Serum Albumin 133
 - 3.2.1.2. α_1 -Acid Glycoprotein (or α_1 -AGP or AAG) 135
 - 3.2.1.3. Lipoproteins 136
 - 3.2.1.4. Globulins (α -, β -, γ -Globulins) 138
 - 3.2.1.5. Erythrocytes [or Red Blood Cells (RBCs)] 138
- 3.3. Pharmacokinetic Models 140
 - 3.3.1. Pharmacokinetic Models *vis-à-vis* Mathematical Models 142
 - 3.3.2. Classification of Pharmacokinetic Models 143
 - 3.3.2.1. Compartment Models 143
 - 3.3.2.2. Flow Models (or Physiologic-Pharmacokinetic Models) 155
 - 3.3.2.3. Non-Compartmental Pharmacokinetics 159
 - 3.3.2.4. Non-Linear Pharmacokinetics 161
- 3.4. Pharmacokinetics of Drug Absorption 162
 - 3.4.1. Zero-Order Absorption Rate Constant 162
 - 3.4.1.1. Plasma Drug Level-Time Curve for a Drug Administered in Single Oral Dose 163
 - 3.4.2. First-Order Absorption Rate Constant 165
 - 3.4.3. The Loo-Riegelman and Wagner-Nelson Equations 167
 - 3.4.3.1. Loo-Riegelman Equation 168
 - 3.4.3.2. Wagner-Nelson Equation 171
 - 3.4.3.3. Estimation of $C_{\max}$ and $t_{\max}$ 175
 - 3.4.3.4. Influence of K_a and K_E upon $C_{\max}$, $t_{\max}$ and AUC 177
- 3.5. Volume of Distribution and Distribution Coefficient 178
 - 3.5.1. Volume of Distribution (VD) 178
 - 3.5.2. Presence of a Fraction of Drug Both Inside and Outside Plasma 179

3.5.3. Determination of Plasma Volume	179
3.5.4. Volume of Total Body Water (or Fluid)	180
3.5.5. Volume of Distribution (VD) vs Protein/Tissue Binding of Drugs	180
3.6. Organ-Specific Clearance	181
3.6.1. Concept of Organ-Specific Clearance	182
3.6.2. Renal Clearance	183
3.6.2.1. Two Substance Used to Determine GFR	184
3.6.2.2. Active Tubular Secretion (ATS)	184
3.6.2.3. Kinetics of Urinary Excretion	185
3.6.3. Hepatic Clearance	196
3.6.3.1. Venous Equilibrium Model of Hepatic Clearance	197
3.6.4. Extra Hepatic/Non-Renal Elimination	199
3.6.4.1. Biliary Excretion	200
3.6.4.2. Exhalation	203
3.6.4.3. Foecal Excretion	203
3.6.4.4. Intestinal Excretion	204
3.6.4.5. Excretion <i>via</i> Saliva/Skin	204
3.6.4.6. Excretion <i>via</i> Milk	205
3.7. Non-Linear Pharmacokinetics	205
3.7. 1. Preamble	205
3.7.2. Michaelis-Menten Equation	206
3.7.2.1. Accounting for Deviation of Michaelis-Menten Equation	206
3.7.2.2. Graphical Representation of Michaelis-Menten Equation	209
3.7.3. Drug Elimination by Capacity-Limited Process	211
3.7.4. Important Recognized Plot Variants in Non-Linear Pharmacokinetics	212
3.7.4.1. Lineweaver-Burk Plot (or Doubled-Reciprocal Plot)	212
3.7.4.2. Hanes-Woolf Plot	215
3.7.4.3. Woolf-Augustinsson – Hofstee Plot	215
3.7.4.4. Direct Linear Plot	216
3.8. Pharmacokinetic Profiles of Some Specific Examples from Various Classes of Drugs	216
3.8.1. Antihypertensives	217
3.8.2. Antiarrhythmics	218
3.8.3. Antianginal Drugs	220
3.8.4. Pharmacokinetics of Nitroglycerin after Intravenous Infusion in Normal Subjects	220
3.8.4.1. Experimental Procedure	220
3.8.5. Antineoplastic Agents	221
3.8.6. Pharmacokinetics of Oral and Intravenous Fluorouracil in Humans	222
3.8.6.1. Experimental Procedure	222

- 3.8.7. Antibiotics 223
- 3.8.8. Pharmacokinetics of Piperacillin and Gentamicin Following Intravenous Administration to Dogs 224
 - 3.8.8.1. Experimental Procedure 224

4. Clinical Pharmacokinetics

(226–297)

- 4.1. Introduction 226
 - 4.1.1. Scope of Pharmacokinetics 228
 - 4.1.2. Therapeutic Objective(s) 230
 - 4.1.2.1. Nonlinear Kinetics 232
 - 4.1.2.2. Bioavailability 232
 - 4.1.2.3. Drug Interactions 232
 - 4.1.2.4. Compliance 233
- 4.2. Dosage Regimens: Design-modalities and Implementation 233
 - 4.2.1. Design of Dosage Regimens 234
 - 4.2.1.1. Optimal Single Dosage Regimen 234
 - 4.2.1.2. Optimal Multiple Dosage Regimen 234
 - 4.2.2. Average Drug Concentration vs Body Content from Multiple Dosing to Steady State 241
 - 4.2.2.1. Preamble 241
 - 4.2.2.2. Loading and Maintenance Doses 242
 - 4.2.2.3. Maintenance of Drug Level Within the Therapeutic Range 244
 - 4.2.2.4. Perfect Design of Dosage Regimen Based Upon the Plasma-Drug Concentrations 245
 - 4.2.3. Individualization 247
 - 4.2.3.1. Objectives of Individualization 248
 - 4.2.3.2. Important Steps for Individualization 248
 - 4.2.3.3. Individualization Clinical Experience and Optimization Based upon Plasma-Drug Concentration (C) 256
 - 4.2.4. Drug Monitoring and Drug Therapy 259
 - 4.2.4.1. Preamble 259
 - 4.2.4.2. Therapeutic Endpoint 259
 - 4.2.4.3. Toxic Endpoint 259
 - 4.2.4.4. Importance of Monitoring Drug Therapy 259
 - 4.2.4.5. Variants in Drug Monitoring and Drug Therapy 260
- 4.3. Single Dose Bioequivalence Study: Design and Relevant Statistics 261
 - 4.3.1. Preamble 261
 - 4.3.2. Bioequivalence Study Parameters 265
 - 4.3.3. Bioequivalence Study Protocol 272
 - 4.3.4. Bioequivalence Study Design 273

- 4.3.4.1. Parallel Design 273
 - 4.3.4.2. Cross-Over Design 273
 - 4.3.5. Statistical Methods in Bioequivalence Study 275
 - 4.3.5.1. Statistical Method Variants 275
 - 4.3.6. Bioequivalence Data: Statistical Interpretation 278
 - 4.3.7. US-FDA/EMA Regulatory Requirements for Bioequivalence Studies 279
 - 4.3.8. Good Clinical Practices (GCPs) in Bioequivalence 280
 - 4.3.8.1. Commonly Observed Non-Compliance in Bioequivalence Study 281
 - 4.3.9. Exemptions in Bioequivalence Study 282
 - 4.3.10. Bioequivalence Studies: Not Necessary 282
 - 4.3.11. Absolute Bioavailable Dosage 283
 - 4.3.12. Practice Problems 288
- 4.4. Pharmacokinetics Drug Interaction: Significance in Combination Therapy 290
 - 4.4.1. Pharmacokinetic Interactions 290
 - 4.4.1.1. Drug Absorption 290
 - 4.4.1.2. Interactions Changing Drug Distribution 292
 - 4.4.1.3. Interactions Affecting Metabolism 293
 - 4.4.1.4. Interactions Affecting Renal Excretion 295
 - 4.4.2. Pharmacodynamic Interactions 296
 - 4.4.2.1. Pharmacological Synergism 297
 - 4.4.2.2. Pharmacological Antagonism 297

5. Bioavailability and Bioequivalence

(298–361)

- 5.1. Introduction 298
 - 5.1.1. Definitions 299
- 5.2. Bioavailability 305
 - 5.2.1. Preamble 305
 - 5.2.2. Absolute Bioavailability 306
 - 5.2.3. Relative Bioavailability 307
 - 5.2.4. Bioequivalence Assessment and Data Evaluation (or Importance of Bioequivalence) 307
 - 5.2.4.1. Bioequivalence Assessment 308
 - 5.2.4.2. Urinary Drug Amount-Time Profiles 308
 - 5.2.4.3. Peak-Height Concentration 309
 - 5.2.5. Bioavailability Studies in Human: Pharmacokinetic Profiles 311
 - 5.2.5.1. Comparison with a Reference Drug/Formulation 311
 - 5.2.5.2. Bioavailability Studies as per the Helsinki Declaration 312
 - 5.2.5.3. Drug Dissolution Rate and Bioavailability 313
 - 5.2.6. Statistical Methods for Bioavailability Studies 321

5.2.6.1. Methods of Data Analysis	322
5.2.6.2. Statistical Analysis	323
5.2.6.3. Statistical Interpretation of Bioequivalence Data	323
5.2.7. Factors that Decrease Bioavailability	323
5.2.7.1. Presystemic Metabolism	323
5.2.7.2. Instability	326
5.2.8. Factors that Increase Bioavailability	330
5.2.8.1. Overcoming Acute Bioavailability Issues	331
5.2.8.2. Physiochemical Characteristics of a Drug	332
5.3. Bioequivalence	342
5.3.1. Preamble	342
5.3.2. Design and Conduct of Bioequivalence Studies	343
5.3.2.1. Criteria for the Design of Bioequivalence Study	344
5.3.2.2. Design	345
5.3.2.3. Subjects (or Volunteers)	346
5.3.2.4. Reference and Test Product	347
5.3.2.5. Analytical Methods	347
5.3.2.6. Investigation of Characteristic Features	349
5.3.2.7. Generalized Approach: Single-Dose Pharmacokinetic Bioequivalence Studies	350
5.3.4. Bioanalytical Method Development and Validation for Bioavailability and Bioequivalence Studies	351
5.3.4.1. Preamble	351
5.3.4.1.1. Bioanalytical Instruments	352
5.3.4.2. Factors Governing Retention Time-Sensitivity-Selectivity	353
5.3.4.2.1. Instrument to Be Used	354
5.3.4.3. Selection of GC/HPLC Column	355
5.3.4.3.1. pH of Mobile-Phase Buffer	355
5.3.4.3.2. Specific Composition of 'Mobile-Phase'	356
5.3.4.3.3. Column-Oven Temperature	357
5.3.4.3.4. Sample Injection Volume	359
5.3.4.3.5. Extra Column Volume	359
5.3.4.4. Method Validation	360

Appendixes

(363–424)

Index

(425–450)