

Contents

About the Editors	ix
Preface	xi
Acknowledgments	xiii

Section I Novel Drug Modalities: Advancements and Their Pharmacokinetic Strategies 1

1	Proteolysis-Targeting Chimeras (PROTACs)	3
1.1	An Overview of PROTAC Technology and Drug Metabolism and Pharmacokinetic (DMPK) Research Strategies	3
1.2	Strategies to Improve the Oral Bioavailability of PROTACs	9
1.3	Research on PROTAC Metabolism: Strategies and Main Approaches	17
1.4	Metabolic Characteristics and Research Strategies for Metabolite Identification of PROTACs	23
1.5	Evaluation of Drug-Drug Interactions of PROTACs with Efflux Transporters	40
1.6	PROTAC Bioanalysis: Challenges and Strategies	44
2	Antibody–Drug Conjugates (ADCs)	49
2.1	General Considerations for Pharmacokinetic Studies of ADCs	49
2.2	Application of Integrated Bioanalysis in ADC DMPK Studies	53
2.3	Study Models and Bioanalysis Methods for the Payload-Related Metabolite Identification Studies of ADCs	62
2.4	Strategies and Challenges in the Determination of Drug-to-Antibody Ratio (DAR) Values for ADCs	67
2.5	<i>In Vitro</i> Stability of ADCs in Blood Matrices	78
2.6	Application of Radiolabeling Techniques in ADC Pharmacokinetic Studies	86
3	Peptide–Drug Conjugates (PDCs)	95
3.1	Introduction to PDCs and DMPK Research Strategies	95
3.2	Targeted Release Principle and Metabolite Identification Studies of PDCs	102
4	Peptide Drugs	115
4.1	Development, Characteristics, and Pharmacokinetic Research Strategies of Peptide Drugs	115
4.2	Metabolic Characteristics and Optimization Strategies of Peptide Drugs	123

4.3	Insights into ADME Studies of 37 Approved Therapeutic Peptides: Strategies and Radiolabeling Considerations	132
4.4	Challenges and Strategies in the Bioanalysis of Peptide Drugs	138
5	Oligonucleotide (OLIGO) Drugs	147
5.1	Oligonucleotide Drugs: An Introduction and Overview of Pharmacokinetic Strategies	147
5.2	Delivery Systems of siRNA Drugs and Their Effects on the Pharmacokinetic Profile	152
5.3	Bioanalytical Strategies for Oligonucleotide Drugs	157
5.4	Oligonucleotide Drugs: Strategies for Metabolism and Metabolite Profiling and Identification	183
5.5	ADME Characteristics of Approved siRNA and ASO Drugs	193
6	mRNA-Based Vaccines and Therapeutics	213
6.1	What Are mRNA Vaccines and Their Future	213
6.2	Strategies for Preclinical PK Evaluation of mRNA-Based Therapeutics: mRNA Vaccines, mRNA Therapeutic Drugs, and Novel Excipients	221
6.3	FDA-Approved mRNA Vaccines: Interpretation of Preclinical Pharmacokinetic (PK) Data	230
6.4	Application of Integrative Bioanalysis in mRNA Drugs DMPK Research	235
 Section II Pharmacokinetic and Metabolism Studies of Therapeutics for Disease Areas 243		
7	Ophthalmic Drugs	245
7.1	Ophthalmic Drugs: Preclinical Pharmacokinetic (PK) Profiles and Research Strategies	245
7.2	<i>In Vitro</i> Methods and Significance of Drug–Melanin Binding	253
7.3	Preclinical Pharmacokinetic Research of Ophthalmic Drugs: <i>In Vitro</i> and <i>In Vivo</i> Research Methods	259
7.4	<i>In Vivo</i> Bioanalysis in Ophthalmology: Challenges and Strategies	269
8	Respiratory Drugs	275
8.1	Inhaled Medications: Challenges and Strategies for Preclinical <i>In Vivo</i> Pharmacokinetic Studies	275
8.2	Chronic Obstructive Pulmonary Disease (COPD): Analysis of PK Profiles of Approved Inhaled Medications	285
9	Transdermal and Topical Drugs	291
9.1	Preclinical Pharmacokinetic Strategies for Topical and Transdermal Drug Products	291
9.2	Application of <i>In Vitro</i> Permeation Test (IVPT) for the Development of Transdermal and Topical Drugs	300
9.3	Evaluation of Transdermal Drugs in <i>In Vivo</i> Pharmacokinetic Studies	308
9.4	Challenges and Bioanalytical Strategies for Quantitative Detection of <i>In Vivo</i> Biological Samples from Skin Administration	313
10	Central Nervous System Drugs	317
10.1	Overview of Pharmacokinetic Research Strategies for Central Nervous System Drugs	317
10.2	Application of Microdialysis in Pharmacokinetic Research	329
10.3	Central Nervous System Drug Development Techniques: Exploration and Application in Large Animal Pharmacokinetics	337

Section III Research Strategies, Methods, and Applications in Pharmacokinetics and Metabolism 343

11 *In Vitro* ADME 345

- 11.1 Rapid Determination of Lipophilicity: Establishment and Application of Reversed-Phase High-Performance Liquid Chromatography (RP-HPLC) 345
- 11.2 Plasma Protein Binding Measurement of High Protein-Binding Drugs: Principles and Advantages of the Flux Dialysis Method 351
- 11.3 How to Measure the Metabolic Clearance of Slowly Metabolized Compounds 358
- 11.4 Non-P450 Enzyme-Mediated Metabolism and *In Vitro* Assessment Method 365
- 11.5 *In Vitro* Evaluation of CYP450 Time-Dependent Inhibition (TDI): A Novel Area Under the Curve Shift (AUC Shift) Approach 377
- 11.6 Cytochrome P450 Reaction Phenotyping for Four Additional CYPs: Why and How 383
- 11.7 Overview of the Application of the Na⁺-Taurocholate Cotransporting Polypeptide (NTCP) in Drug Development 388
- 11.8 The Significance and *In Vitro* Methods of Lysosomal Trapping in Drug Development 397

12 *In Vivo* Pharmacokinetics 407

- 12.1 Enhancing the Bioavailability of Poorly Soluble Compounds: Strategies for Formulation Optimization in Preclinical Studies 407
- 12.2 Self-Emulsifying Drug Delivery System (SEDDS): Enhancing the Oral Absorption of Lipophilic Compounds 414
- 12.3 Application of Anesthetics in Rodent Pharmacokinetic Studies 420
- 12.4 Application of *In Situ* Single-Pass Intestinal Perfusion (SPIP) Model in the Study of Intestinal Absorption of Oral Drugs 428
- 12.5 Application of Liver Biopsy in Preclinical Pharmacokinetic Studies 436

13 Metabolite Profiling and Identification 441

- 13.1 High-Throughput Identification of Drug Metabolic Soft Spots for Lead Optimization 441
- 13.2 Application of Metabolite Biosynthesis Technology in the Precise Identification of Drug Metabolite Structures 449
- 13.3 Detection of Reactive Metabolites and Its Application in Drug Research and Development 456
- 13.4 UGT Enzymes: Metabolite Identification and Toxicity Assessment Strategies 466
- 13.5 Insights into the R&D Strategies of Deuterated Drugs from the Drug Metabolism Perspective 472

14 Radiolabeled *In Vivo* ADME Studies 479

- 14.1 Placental Transfer and Milk Excretion Studies Based on Radioactive Tracer Technique 479
- 14.2 Visualization of Tissue Distribution: Quantitative Whole-Body Autoradiography (QWBA) 486
- 14.3 Preclinical and Clinical Research Strategy for Human Radiolabeled Mass Balance Studies 490
- 14.4 Key Considerations for Conducting Radiolabeled Human Mass Balance Studies 496

15 Bioanalysis 503

- 15.1 Application of High-Throughput Mass Spectrometry in *In Vitro* ADME 503
- 15.2 Application and Detection Techniques of Biomarkers in Drug Development 510
- 15.3 Analysis and Detection Strategies of Liposome Drugs in Biological Samples 516
- 15.4 DMPK Research Strategies of Chiral Drugs Based on UPCC-MS/MS and UPLC-MS/MS Dual Analytical Platforms 523
- 15.5 Integrated Qualitative and Quantitative Bioanalysis of Intact Protein with High-Resolution Mass Spectrometry 530
- 15.6 Nanobodies: Kinetics and Bioanalytical Strategies 540

Index 549