

Drug-like Properties: Concepts, Structure Design and Methods

from ADME to Toxicity Optimization



metabolism • solubility • pharmacokinetics
permeability • CYP inhibition
toxicity • prodrugs

Edward H. Kerns and Li Di



Contents

Preface	xviii
Dedication	xx
Part 1 Introductory Concepts	1
1 Introduction	3
Problems	5
References	5
2 Advantages of Good Drug-like Properties	6
2.1 Drug-like Properties Are an Integral Part of Drug Discovery	6
2.1.1 Many Properties Are of Interest in Discovery	7
2.1.2 Introduction to the Drug Discovery and Development Process	8
2.1.3 Development Attrition is Reduced by Improving Drug Properties	9
2.1.4 Poor Drug Properties Also Cause Discovery Inefficiencies	9
2.1.5 Marginal Drug Properties Cause Inefficiencies During Development	10
2.1.6 Poor Properties Can Cause Poor Discovery Research	11
2.2 Changing Emphasis on Properties in Discovery	12
2.3 Property Profiling in Discovery	14
2.4 Drug-like Property Optimization in Discovery	15
Problems	15
References	16
3 Barriers to Drug Exposure in Living Systems	17
3.1 Introduction to Barriers	17
3.2 Drug Dosing	18
3.3 Barriers in the Mouth and Stomach	19
3.4 Gastrointestinal Tract Barriers	20
3.4.1 Permeation of the Gastrointestinal Cellular Membrane	22
3.4.2 Passive Diffusion at the Molecular Level	23
3.4.3 Metabolism in the Intestine	24
3.4.4 Enzymatic Hydrolysis in the Intestine	24
3.4.5 Absorption Enhancement in the Intestine	26
3.5 Barriers in the Bloodstream	27
3.5.1 Plasma Enzyme Hydrolysis	27
3.5.2 Plasma Protein Binding	27
3.5.3 Red Blood Cell Binding	28

3.6	Barriers in the Liver	28
3.6.1	Metabolism	29
3.6.2	Biliary Excretion	29
3.7	Barriers in the Kidney	29
3.8	Blood–Tissue Barriers	30
3.9	Tissue Distribution	30
3.10	Consequences of Chirality on Barriers and Properties	31
3.11	Overview of In Vivo Barriers	31
	Problems	32
	References	33
Part 2	Physicochemical Properties	35
4	Rules for Rapid Property Profiling from Structure	37
4.1	Lipinski Rules	37
4.2	Veber Rules	39
4.3	Other Rules	39
4.4	Application of Rules for Compound Assessment	39
	Problems	41
	References	42
5	Lipophilicity	43
5.1	Lipophilicity Fundamentals	43
5.2	Lipophilicity Effects	45
5.3	Lipophilicity Case Studies and Structure Modification	46
	Problems	47
	References	47
6	p<i>K</i>_a	48
6.1	p <i>K</i> _a Fundamentals	48
6.2	p <i>K</i> _a Effects	50
6.3	p <i>K</i> _a Case Studies	50
6.4	Structure Modification Strategies for p <i>K</i> _a	54
	Problems	54
	References	55
7	Solubility	56
7.1	Solubility Fundamentals	57
7.1.1	Solubility Varies with Structure and Physical Conditions	57
7.1.2	Dissolution Rate	57
7.1.3	Structural Properties Affect Solubility	57
7.1.4	Kinetic and Thermodynamic Solubility	60
7.2	Effects of Solubility	62
7.2.1	Low Solubility Limits Absorption and Causes Low Oral Bioavailability	62
7.2.2	Good Solubility is Essential for IV Formulation	63
7.2.3	Acceptance Criteria and Classifications for Solubility	63
7.2.4	Molecular Properties for Solubility and Permeability Often are Opposed	67

Contents	vii
7.3 Effects of Physiology on Solubility and Absorption	68
7.3.1 Physiology of the Gastrointestinal Tract	68
7.3.2 Species Differences in Gastrointestinal Tract	68
7.3.3 Food Effect	69
7.4 Structure Modification Strategies to Improve Solubility	70
7.4.1 Add Ionizable Groups	71
7.4.2 Reduce Log P	73
7.4.3 Add Hydrogen Bonding	73
7.4.4 Add Polar Group	74
7.4.5 Reduce Molecular Weight	74
7.4.6 Out-of-Plane Substitution	75
7.4.7 Construct a Prodrug	76
7.5 Strategies for Improving Dissolution Rate	77
7.5.1 Reduce Particle Size	77
7.5.2 Prepare an Oral Solution	78
7.5.3 Formulate with Surfactants	78
7.5.4 Prepare a Salt Form	78
7.6 Salt Form	78
7.6.1 Solubility of Salts	78
7.6.2 Effect of Salt Form on Absorption and Oral Bioavailability	80
7.6.3 Salt Selection	81
7.6.4 Precautions for Using Salt Forms	82
Problems	82
References	84
8 Permeability	86
8.1 Permeability Fundamentals	86
8.1.1 Passive Diffusion Permeability	87
8.1.2 Endocytosis Permeability	89
8.1.3 Active Uptake Permeability	89
8.1.4 Paracellular Permeability	89
8.1.5 Efflux Permeability	89
8.1.6 Combined Permeability	89
8.2 Permeability Effects	90
8.2.1 Effect of Permeability on Bioavailability	90
8.2.2 Effect of Permeability on Cell-Based Activity Assays	91
8.3 Permeability Structure Modification Strategies	92
8.3.1 Ionizable Group to Non-ionizable Group	92
8.3.2 Add Lipophilicity	92
8.3.3 Isosteric Replacement of Polar Groups	93
8.3.4 Esterify Carboxylic Acid	93
8.3.5 Reduce Hydrogen Bonding and Polarity	94
8.3.6 Reduce Size	94
8.3.7 Add Nonpolar Side Chain	96
8.3.8 Prodrug	96
Problems	97
References	98

Part 3 Disposition, Metabolism, and Safety	101
9 Transporters	103
9.1 Transporter Fundamentals	103
9.2 Transporter Effects	104
9.2.1 Transporters in Intestinal Epithelial Cells	108
9.2.2 Transporters in Liver Hepatocytes	108
9.2.3 Transporters in Kidney Epithelial Cells	110
9.2.4 Transporters in Blood–Brain Barrier Endothelial Cells	110
9.2.5 Consequences of Chirality on Transporters	110
9.3 Efflux Transporters	111
9.3.1 P-glycoprotein (MDR1, ABCB1) [Efflux]	111
9.3.2 Breast Cancer Resistance Protein (BCRP, ABCG2) [Efflux]	116
9.3.3 Multidrug Resistance Protein 2 (MRP2, ABCC2) [Efflux]	116
9.3.4 Efflux Transporters in the BBB	116
9.4 Uptake Transporters	117
9.4.1 Organic Anion Transporting Polypeptides (OATPs, SLCOs) [Uptake]	117
9.4.2 Di/Tri Peptide Transporters (PEPT1, PEPT2) [Uptake]	117
9.4.3 Organic Anion Transporters (OATs) [Uptake]	118
9.4.4 Organic Cation Transporter (OCT) [Uptake]	118
9.4.5 Large Neutral Amino Acid Transporter (LAT1) [Uptake]	118
9.4.6 Monocarboxylic Acid Transporter (MCT1) [Uptake]	118
9.4.7 Other Uptake Transporters	118
9.4.8 Structure Modification Strategies for Uptake Transporters	119
Problems	119
References	120
10 Blood–Brain Barrier	122
10.1 BBB Fundamentals	123
10.1.1 BBB Permeation Mechanisms	124
10.1.2 Brain Distribution Mechanisms	125
10.1.3 Brain–CSF Barrier	127
10.1.4 Interpreting Data for Brain Penetration	128
10.2 Effects of Brain Penetration	129
10.3 Structure–BBB Penetration Relationships	130
10.4 Structure Modification Strategies to Improve Brain Penetration	131
10.4.1 Reduce Pgp Efflux	132
10.4.2 Reduce Hydrogen Bonds	132
10.4.3 Increase Lipophilicity	133
10.4.4 Reduce MW	133
10.4.5 Replace Carboxylic Acid Groups	133
10.4.6 Add an Intramolecular Hydrogen Bond	133
10.4.7 Modify or Select Structures for Affinity to Uptake Transporters	133
Problems	134
References	135

11 Metabolic Stability	137
11.1 Metabolic Stability Fundamentals	138
11.1.1 Phase I Metabolism	139
11.1.2 Phase II Metabolism	143
11.2 Metabolic Stability Effects	145
11.3 Structure Modification Strategies for Phase I Metabolic Stability	146
11.3.1 Block Metabolic Site By Adding Fluorine	147
11.3.2 Block Metabolic Site By Adding Other Blocking Groups	149
11.3.3 Remove Labile Functional Group	150
11.3.4 Cyclization	151
11.3.5 Change Ring Size	151
11.3.6 Change Chirality	152
11.3.7 Reduce Lipophilicity	152
11.3.8 Replace Unstable Groups	153
11.4 Structure Modification Strategies for Phase II Metabolic Stability	154
11.4.1 Introduce Electron-Withdrawing Groups and Steric Hindrance	154
11.4.2 Change Phenolic Hydroxyl to Cyclic Urea or Thiourea	155
11.4.3 Change Phenolic Hydroxyl to Prodrug	155
11.5 Applications of Metabolic Stability Data	156
11.6 Consequences of Chirality on Metabolic Stability	160
11.7 Substrate Specificity of CYP Isozymes	162
11.7.1 CYP1A2 Substrates	162
11.7.2 CYP2D6 Substrates	163
11.7.3 CYP2C9 Substrates	164
Problems	165
References	167
12 Plasma Stability	169
12.1 Plasma Stability Fundamentals	169
12.1.1 Consequences of Chirality on Plasma Stability	170
12.2 Effects of Plasma Stability	170
12.3 Structure Modification Strategies to Improve Plasma Stability	172
12.3.1 Substitute an Amide for an Ester	172
12.3.2 Increase Steric Hindrance	173
12.3.3 Electron-Withdrawing Groups Decrease Plasma Stability for Antedrug	173
12.4 Applications of Plasma Stability Data	174
12.4.1 Diagnose Poor In Vivo Performance	174
12.4.2 Alert Teams to a Liability	174
12.4.3 Prioritize Compounds for In Vivo Animal Studies	174
12.4.4 Prioritize Synthetic Efforts	175
12.4.5 Screening of Prodrugs	175
12.4.6 Guide Structural Modification	176
Problems	176
References	177
13 Solution Stability	178
13.1 Solution Stability Fundamentals	178
13.2 Effects of Solution Instability	180

13.3	Structure Modification Strategies to Improve Solution Stability	180
13.3.1	Eliminate or Modify the Unstable Group	180
13.3.2	Add an Electron-Withdrawing Group	181
13.3.3	Isosteric Replacement of Labile Functional Group	182
13.3.4	Increase Steric Hindrance	182
13.4	Applications of Solution Stability Data	183
	Problems	185
	References	185
14	Plasma Protein Binding	187
14.1	Plasma Protein Binding Fundamentals	187
14.1.1	Consequences of Chirality on PPB	189
14.2	PPB Effects	190
14.2.1	Impact of PPB on Distribution	191
14.2.2	Effect of PPB on Clearance	192
14.2.3	Effect of PPB on Pharmacology	192
14.3	PPB Case Studies	193
14.4	Structure Modification Strategies for PPB	193
14.5	Strategy for PPB in Discovery	194
14.6	Red Blood Cell Binding	194
	Problems	194
	References	195
15	Cytochrome P450 Inhibition	197
15.1	CYP Inhibition Fundamentals	197
15.2	Effects of CYP Inhibition	199
15.3	CYP Inhibition Case Studies	201
15.3.1	Consequences of Chirality on CYP Inhibition	202
15.4	Structure Modification Strategies to Reduce CYP Inhibition	203
15.5	Reversible and Irreversible CYP Inhibition	204
15.6	Other DDI Issues	205
15.6.1	Candidate as Victim to a Metabolism Inhibition Perpetrator	205
15.6.2	Candidate as a Victim or Perpetrator at a Transporter	206
15.6.3	Candidate as a Victim or Perpetrator of Metabolic Enzyme Induction	206
	Problems	206
	References	207
16	hERG Blocking	209
16.1	hERG Fundamentals	209
16.2	hERG Blocking Effects	211
16.3	hERG Blocking Structure–Activity Relationship	212
16.4	Structure Modification Strategies for hERG	213
	Problems	213
	References	214
	Additional Reading	214

17 Toxicity	215
17.1 Toxicity Fundamentals	216
17.1.1 Toxicity Terms and Mechanisms	217
17.1.2 Toxicity Mechanisms	217
17.2 Toxicity Case Studies	221
17.3 Structure Modification Strategies to Improve Safety	222
Problems	222
References	223
18 Integrity and Purity	224
18.1 Fundamentals of Integrity and Purity	224
18.2 Integrity and Purity Effects	224
18.3 Applications of Integrity and Purity	226
18.3.1 Case Study	226
Problems	227
References	227
19 Pharmacokinetics	228
19.1 Introduction to Pharmacokinetics	228
19.2 PK Parameters	229
19.2.1 Volume of Distribution	229
19.2.2 Area Under the Curve	231
19.2.3 Clearance	231
19.2.4 Half-life	233
19.2.5 Bioavailability	234
19.3 Effects of Plasma Protein Binding on PK Parameters	234
19.4 Tissue Uptake	234
19.5 Using PK Data in Drug Discovery	235
Problems	240
References	241
20 Lead-like Compounds	242
20.1 Lead-likeness	242
20.2 Template Conservation	244
20.3 Triage	245
20.4 Fragment-Based Screening	245
20.5 Lead-like Compounds Conclusions	247
Problems	247
References	248
21 Strategies for Integrating Drug-like Properties into Drug Discovery	249
21.1 Assess Drug-like Properties Early	249
21.2 Rapidly Assess Drug-like Properties for All New Compounds	250
21.3 Develop Structure–Property Relationships	250
21.4 Iterative Parallel Optimization	251
21.5 Obtain Property Data that Relates Directly to Structure	251
21.6 Apply Property Data to Improve Biological Experiments	252
21.7 Utilize Customized Assays to Answer Specific Project Questions	252
21.8 Diagnose Inadequate Performance in Complex Systems Using Individual Properties	252

Problems	253
References	253
Part 4 Methods	255
22 Methods for Profiling Drug-like Properties: General Concepts	257
22.1 Property Data Should be Rapidly Available	257
22.2 Use Relevant Assay Conditions	257
22.3 Evaluate the Cost-to-Benefit Ratio for Assays	257
22.4 Choose an Ensemble of Key Properties to Evaluate	258
22.5 Use Well-Developed Assays	259
Problems	259
References	259
23 Lipophilicity Methods	260
23.1 <i>In Silico</i> Lipophilicity Methods	260
23.2 Experimental Lipophilicity Methods	264
23.2.1 Scaled-Down Shake Flask Method for Lipophilicity	265
23.2.2 Reversed-Phase HPLC Method for Lipophilicity	266
23.2.3 Capillary Electrophoresis Method for Lipophilicity	267
23.3 In-Depth Lipophilicity Methods	267
23.3.1 Shake Flask Method for Lipophilicity	267
23.3.2 pH-Metric Method for Lipophilicity	268
Problems	268
References	269
24 pK_a Methods	271
24.1 <i>In Silico</i> pK_a Methods	271
24.2 Experimental pK_a Methods	273
24.2.1 Spectral Gradient Analysis Method for pK_a	273
24.2.2 Capillary Electrophoresis Method for pK_a	273
24.3 In-Depth pK_a Method: pH-Metric	274
Problems	275
References	275
25 Solubility Methods	276
25.1 Literature Solubility Calculation Methods	276
25.2 Commercial Software for Solubility	277
25.3 Kinetic Solubility Methods	278
25.3.1 Direct UV Kinetic Solubility Method	278
25.3.2 Nephelometric Kinetic Solubility Method	280
25.3.3 Turbidimetric <i>In Vitro</i> Solubility Method	281
25.3.4 Customized Kinetic Solubility Method	282
25.4 Thermodynamic Solubility Methods	283
25.4.1 Equilibrium Shake Flask Thermodynamic Solubility Method	283
25.4.2 Potentiometric <i>In Vitro</i> Thermodynamic Solubility Method	283
25.4.3 Thermodynamic Solubility in Various Solvents	284
Problems	285
References	285

26	Permeability Methods	287
26.1	In Silico Permeability Methods	287
26.2	In Vitro Permeability Methods	288
26.2.1	IAM HPLC	288
26.2.2	Cell Layer Method for Permeability	288
26.2.3	Artificial Membrane Permeability Assay	292
26.2.4	Comparison of Caco-2 and PAMPA Methods	293
26.3	In Depth Permeability Methods	294
	Problems	295
	References	296
27	Transporter Methods	299
27.1	In Silico Transporter Methods	299
27.2	In Vitro Transporter Methods	300
27.2.1	Cell Layer Permeability Methods for Transporters	300
27.2.2	Uptake Method for Transporters	304
27.2.3	Oocyte Uptake Method for Transporters	304
27.2.4	Inverted Vesicle Assay for Transporters	305
27.2.5	ATPase Assay for ATP Binding Cassette Transporters	305
27.2.6	Calcein AM Assay for Pgp Inhibitor	306
27.3	In Vivo Methods for Transporters	307
27.3.1	Genetic Knockout Animal Experiments for Transporters	307
27.3.2	Chemical Knockout Experiments for Transporters	307
	Problems	308
	References	308
28	Blood–Brain Barrier Methods	311
28.1	In Silico Methods for BBB	312
28.1.1	Classification Models	312
28.1.2	Quantitative Structure–Activity Relationship Methods	312
28.1.3	Commercial Software	313
28.2	In Vitro Methods for BBB	314
28.2.1	Physicochemical Methods for BBB	314
28.2.2	Cell-based In Vitro Methods [BBB Permeability]	317
28.3	In Vivo Methods for BBB	319
28.3.1	B/P Ratio or Log BB [Brain Distribution]	319
28.3.2	Brain Uptake Index [BBB Permeability]	320
28.3.3	In Situ Perfusion [BBB Permeability, Log PS, $\mu\text{L}/\text{min}/\text{g}$]	321
28.3.4	Mouse Brain Uptake Assay [BBB Permeability and Brain Distribution]	322
28.3.5	Microdialysis Method for BBB	323
28.3.6	Cerebrospinal Fluid Method for BBB	324
28.4	Assessment Strategy for Brain Penetration	324
	Problems	325
	References	325
29	Metabolic Stability Methods	329
29.1	In Silico Metabolic Stability Methods	331
29.2	In Vitro Metabolic Stability Methods	331
29.2.1	General Aspects of Metabolic Stability Methods	331

29.2.2	In Vitro Microsomal Assay for Metabolic Stability	335
29.2.3	In Vitro S9 Assay for Metabolic Stability	338
29.2.4	In Vitro Hepatocytes Assay for Metabolic Stability	340
29.2.5	In Vitro Phase II Assay for Metabolic Stability	340
29.2.6	Metabolic Phenotyping	341
29.2.7	In Vitro Metabolite Structure Identification	342
	Problems	345
	References	346
30	Plasma Stability Methods	348
	Problems	351
	References	351
31	Solution Stability Methods	353
31.1	General Method for Solution Stability Assays	353
31.2	Method for Solution Stability in Biological Assay Media	355
31.3	Methods for pH Solution Stability	356
31.4	Methods for Solution Stability in Simulated Gastrointestinal Fluids	356
31.5	Identification of Degradation Products from Solution Stability Assays	357
31.6	In-Depth Solution Stability Methods for Late Stages of Drug Discovery	357
	Problems	358
	References	358
32	CYP Inhibition Methods	360
32.1	In Silico CYP Inhibition Methods	360
32.2	In Vitro CYP Inhibition Methods	361
32.2.1	Fluorescent Assay for CYP Inhibition	364
32.2.2	Single Substrate HLM Assay for CYP Inhibition	365
32.2.3	Cocktail Substrate HLM Assay for CYP Inhibition	365
32.2.4	Double Cocktail Assay for CYP Inhibition	367
32.3	CYP Inhibition Assessment Strategy	367
	Problems	368
	References	368
33	Plasma Protein Binding Methods	372
33.1	In Silico PPB Methods	372
33.1.1	Literature In Silico PPB Methods	372
33.1.2	Commercial In Silico PPB Methods	372
33.2	In Vitro PPB Methods	373
33.2.1	Equilibrium Dialysis Method	373
33.2.2	Ultrafiltration Method	374
33.2.3	Ultracentrifugation Method	375
33.2.4	Immobilized Protein High-Performance Liquid Chromatography Column Method	375
33.2.5	Microdialysis Method	375
33.2.6	Other PPB Methods	376
33.3	Red Blood Cell Binding	376

Problems	376
References	377
34 hERG Methods	378
34.1 In Silico hERG Methods	379
34.2 In Vitro hERG Methods	379
34.2.1 Membrane Potential–Sensitive Dye Method for hERG	379
34.2.2 Ligand Binding Method for hERG	381
34.2.3 Rubidium Efflux Method for hERG	381
34.2.4 Patch-Clamp Method for hERG	381
34.2.5 High-Throughput Patch-Clamp Method for hERG	383
34.3 In Vivo hERG Methods	384
Problems	384
References	385
35 Toxicity Methods	386
35.1 In Silico Toxicity Methods	387
35.1.1 Knowledge-Based Expert System In Silico Toxicity Methods	387
35.1.2 Statistically Based In Silico Toxicity Methods	388
35.2 In Vitro Toxicity Assays	388
35.2.1 Drug–Drug Interaction	388
35.2.2 hERG Block Assays	389
35.2.3 Mutagenicity/Genotoxicity	389
35.2.4 Cytotoxicity	391
35.2.5 Teratogenicity: Zebrafish Model	392
35.2.6 Selectivity Screens	392
35.2.7 Reactivity Screens	393
35.3 In Vivo Toxicity	393
35.3.1 Discovery In Vivo Toxicity	393
35.3.2 Preclinical and Clinical In Vivo Toxicity	393
35.3.3 Biomarkers of In Vivo Toxic Responses	395
Problems	396
References	396
36 Integrity and Purity Methods	399
36.1 Criteria for Integrity and Purity Assays	399
36.2 Samples for Integrity and Purity Profiling	400
36.3 Requirements of Integrity and Purity Profiling Methods	401
36.4 Integrity and Purity Method Advice	401
36.4.1 Sample Preparation	402
36.4.2 Component Separation	402
36.4.3 Quantitation	403
36.4.4 Identity Characterization	404
36.5 Follow-up on Negative Identity Results	405
36.6 Example Method	405
36.7 Method Case Studies	406
Problems	407
References	407

37 Pharmacokinetic Methods	409
37.1 PK Dosing	409
37.1.1 Single-Compound Dosing	409
37.1.2 Cassette Dosing	409
37.2 PK Sampling and Sample Preparation	410
37.3 Instrumental Analysis	411
37.4 Example Pharmacokinetic Data	412
37.5 Tissue Uptake	413
Problems	414
References	414
Part 5 Specific Topics	417
38 Diagnosing and Improving Pharmacokinetic Performance	419
38.1 Diagnosing Underlying Property Limitations from PK Performance	420
38.1.1 High Clearance After IV Injection	420
38.1.2 Low Oral Bioavailability	421
38.2 Case Studies on Interpreting Unusual PK Performance	421
38.2.1 PK of CCR5 Antagonist UK-427,857	421
38.2.2 PK of Triazole Antifungal Voriconazole	422
Problems	424
References	424
39 Prodrugs	426
39.1 Using Prodrugs to Improve Solubility	428
39.2 Prodrugs to Increase Passive Permeability	430
39.2.1 Ester Prodrugs for Carboxylic Acids	431
39.2.2 Ester Prodrugs for Alcohols and Phenols	432
39.2.3 Prodrugs Derived from Nitrogen-Containing Functional Group	433
39.3 Transporter-Mediated Prodrugs to Enhance Intestinal Absorption	434
39.4 Prodrugs to Reduce Metabolism	435
39.5 Prodrugs to Target Specific Tissues	436
39.6 Soft Drugs	437
Problems	437
References	438
40 Effects of Properties on Biological Assays	439
40.1 Effects of Insolubility in DMSO	441
40.2 Dealing with Insolubility in DMSO	443
40.3 Effects of Insolubility in Aqueous Buffers	443
40.4 Dealing with Insolubility in Aqueous Buffers	445
40.4.1 Modify the Dilution Protocol to Keep Compounds in Solution	445
40.4.2 Assess Compound Solubility and Concentrations	446
40.4.3 Optimize Assays for Low Solubility Compounds	447
40.4.4 Effects of Permeability in Cell-Based Assays	448
40.4.5 Dealing with Permeability in Cell-Based Assays	448
40.4.6 Effects of Chemical Instability in Bioassays	448
40.4.7 Dealing with Chemical Instability in Bioassays	449

Contents	xvii
Problems	449
References	450
41 Formulation	453
41.1 Routes of Administration	454
41.2 Potency Drives Delivery Opportunities	455
41.3 Formulation Strategies	456
41.4 Practical Guide for Formulation in Drug Discovery	462
41.4.1 Formulation for PK Studies	463
41.4.2 Formulation for Toxicity Studies	464
41.4.3 Formulation for Pharmacological Activity Studies	464
Problems	465
References	465
Appendix I Answers to Chapter Problems	468
Appendix II General References	492
Appendix III Glossary	493
Index	514