

Contents

Preface	xix
Health and Safety	xxi
Nomenclature, Symbols and Conventions	xxiii
Amount Concentration and Mass Concentration	xxv
Acknowledgements	xxvii
List of Abbreviations	xxix
1 Analytical Toxicology: Overview	1
1.1 Introduction	1
1.1.1 Historical development	1
1.2 Modern analytical toxicology	2
1.2.1 Drugs and pesticides	4
1.2.2 Ethanol and other volatile substances	6
1.2.3 Trace elements and toxic metals	7
1.3 Provision of analytical toxicology services	8
1.3.1 Samples and sampling	8
1.3.2 Choice of analytical method	8
1.3.3 Method implementation and validation	9
1.3.4 Quality control and quality assurance	11
1.4 Applications of analytical toxicology	13
1.4.1 Clinical toxicology	13
1.4.2 Forensic toxicology	14
1.4.3 Drug abuse screening	15
1.4.4 Therapeutic drug monitoring (TDM)	16
1.4.5 Occupational and environmental toxicology	17
1.5 Summary	18
2 Sample Collection, Transport, and Storage	21
2.1 Introduction	21
2.2 Clinical samples and sampling	21
2.2.1 Health and safety	21
2.2.2 Clinical sample types	23
2.2.2.1 Arterial blood	23
2.2.2.2 Venous blood	23
2.2.2.3 Serum	26
2.2.2.4 Plasma	26
2.2.2.5 Blood cells	27
2.2.2.6 Urine	28

2.2.2.7 Stomach contents	28
2.2.2.8 Faeces	28
2.2.2.9 Tissues	29
2.3 Guidelines for sample collection for analytical toxicology	29
2.3.1 Sample collection and preservation	32
2.3.2 Blood (for quantitative work)	32
2.3.3 Blood (for qualitative analysis)	33
2.3.4 Urine	33
2.3.5 Stomach contents	35
2.3.6 Saliva/oral fluids	36
2.3.6.1 Collection devices for saliva/oral fluids	37
2.3.7 Sweat	38
2.3.8 Exhaled air	38
2.3.9 Cerebrospinal fluid	38
2.3.10 Vitreous humour	38
2.3.11 Synovial fluid	39
2.3.12 Liver	39
2.3.13 Other tissues	39
2.3.14 Insect larvae	39
2.3.15 Keratinaceous tissues (hair and nail)	40
2.3.16 Bone and bone marrow	41
2.3.17 Injection sites	41
2.3.18 'Scene residues'	41
2.4 Sample transport and storage	42
2.5 Common interferences	44
2.6 Summary	45
3 Sample Preparation	49
3.1 Introduction	49
3.2 Modes of sample preparation	51
3.2.1 Direct analysis/on-line sample preparation	51
3.2.2 Protein precipitation	52
3.2.3 Microdiffusion	54
3.2.4 Headspace and 'purge-and-trap' analysis	55
3.2.5 Liquid–liquid extraction	57
3.2.5.1 Theory of pH-controlled liquid–liquid extraction	63
3.2.5.2 Ion-pair extraction	66
3.2.5.3 Liquid–liquid extraction columns	67
3.2.6 Solid-phase extraction	67
3.2.7 Solid-phase microextraction	73
3.2.8 Liquid-phase microextraction	76
3.2.9 Supercritical fluid extraction	77
3.2.10 Accelerated solvent extraction	78
3.3 Measurement of nonbound plasma concentrations	79
3.3.1 Ultrafiltration	80
3.3.2 Equilibrium dialysis	81

3.4 Hydrolysis of conjugated metabolites	82
3.5 Extraction of drugs from tissues	84
3.5.1 Hair analysis for drugs and organic poisons	85
3.6 Derivatization	87
3.7 Summary	88
4 Colour Tests, and Spectrophotometric and Luminescence Techniques	95
4.1 Introduction	95
4.1.1 Historical development	95
4.2 Colour tests	96
4.3 UV-visible spectrophotometry	97
4.3.1 The Beer-Lambert law	98
4.3.2 Instrumentation	100
4.3.2.1 Derivative spectrophotometry	102
4.3.3 Spectrophotometric assays	104
4.3.3.1 Salicylates in plasma or urine	106
4.3.3.2 Carboxyhaemoglobin (COHb) in whole blood	106
4.3.3.3 Cyanide in whole blood by microdiffusion	107
4.3.3.4 Colorimetric measurement of sulfonamides	108
4.4 Luminescence	108
4.4.1 Fluorescence and phosphorescence	108
4.4.1.1 Intensity of fluorescence and quantum yield	109
4.4.1.2 Instrumentation	110
4.4.1.3 Fluorescence assays	111
4.4.2 Chemiluminescence	112
4.4.2.1 Instrumentation	114
4.4.2.2 Chemiluminescence assays	114
4.5 Summary	115
5 Introduction to Chromatography and Capillary Electrophoresis	117
5.1 General introduction	117
5.1.1 Historical development	117
5.2 Theoretical aspects of chromatography	119
5.2.1 Analyte phase distribution	119
5.2.2 Column efficiency	121
5.2.3 Zone broadening	122
5.2.3.1 Multiple path and eddy diffusion	122
5.2.3.2 Longitudinal diffusion	123
5.2.3.3 Resistance to mass transfer	123
5.2.4 Extra-column contributions to zone broadening	125
5.2.5 Temperature programming and gradient elution	125
5.2.6 Selectivity	126
5.2.7 Peak asymmetry	127
5.3 Measurement of analyte retention	128
5.4 Summary	129

6 Thin-Layer Chromatography	131
6.1 Introduction	131
6.2 Preparation of thin-layer plates	132
6.3 Sample application	133
6.4 Developing the chromatogram	133
6.5 Visualizing the chromatogram	135
6.6 Retention factor (R_f)	137
6.7 Toxi-Lab	140
6.8 High-performance thin-layer chromatography	140
6.8.1 Forced-flow planar chromatography	141
6.9 Quantitative thin-layer chromatography	141
6.10 Summary	142
7 Gas Chromatography	145
7.1 Introduction	145
7.2 Instrumentation	146
7.2.1 Injectors and injection technique	147
7.2.1.1 Cryofocusing/thermal desorption	148
7.2.2 Detectors for GC	149
7.2.2.1 Thermal-conductivity detection	150
7.2.2.2 Flame-ionization detection	150
7.2.2.3 Nitrogen-phosphorus detection	151
7.2.2.4 Electron capture detection	152
7.2.2.5 Pulsed-discharge detection	154
7.2.2.6 Flame-photometric detection	155
7.2.2.7 Atomic-emission detection	155
7.2.2.8 Fourier-transform infrared detection	156
7.3 Columns and column packings	156
7.3.1 Packed columns	157
7.3.2 Capillary columns	160
7.3.3 Multidimensional GC	163
7.4 Derivatization for GC	164
7.4.1 Electron-capturing derivatives	165
7.5 Chiral separations	166
7.6 Applications of gas chromatography in analytical toxicology	167
7.6.1 Systematic toxicological analysis	167
7.6.2 Quantitative analysis of drugs and other poisons	179
7.6.2.1 Measurement of carbon monoxide and cyanide	170
7.6.2.2 Measurement of ethanol and other volatiles	170
7.7 Summary	173
8 High-Performance Liquid Chromatography	177
8.1 Introduction	177

8.2 HPLC: general considerations	178
8.2.1 The column	179
8.2.1.1 Column oven	180
8.2.2 The eluent	181
8.2.3 The pump	182
8.2.4 Sample introduction	184
8.2.5 System operation	185
8.3 Detection in HPLC	186
8.3.1 UV/visible absorption detection	188
8.3.2 Fluorescence detection	189
8.3.3 Chemiluminescence detection	189
8.3.4 Electrochemical detection	190
8.3.5 Chemiluminescent nitrogen detection	192
8.3.6 Evaporative light scattering detection	193
8.3.7 Charged aerosol detection	193
8.3.8 Radioactivity detection	194
8.3.9 Chiral detection	195
8.3.10 Post-column modification	195
8.3.11 Immunoassay detection	196
8.4 Columns and column packings	196
8.4.1 Column configuration	197
8.4.2 Column packings	197
8.4.2.1 Chemical modification of silica	198
8.4.2.2 Bonded-phase selection	199
8.4.2.3 Stability of silica packings	200
8.4.2.4 Monolithic columns	200
8.4.2.5 Hybrid particle columns	201
8.5 Modes of HPLC	202
8.5.1 Normal-phase chromatography	202
8.5.2 Reversed-phase chromatography	202
8.5.3 Ion-exchange chromatography	203
8.5.4 Ion-pair chromatography	204
8.5.5 Size-exclusion chromatography	204
8.5.6 Affinity chromatography	205
8.5.7 Semipreparative and preparative chromatography	206
8.6 Chiral separations	207
8.6.1 Chiral stationary phases	208
8.6.1.1 Amylose and cellulose polymers	208
8.6.1.2 Crown ethers	208
8.6.1.3 Cyclodextrins	209
8.6.1.4 Ligand-exchange chromatography	210
8.6.1.5 Macrocyclic glycopeptides	210
8.6.1.6 Pirkle brush-type phases	211
8.6.1.7 Protein-based phases	213
8.6.2 Chiral eluent additives	213

8.7 Derivatives for HPLC	214
8.7.1 Fluorescent derivatives	214
8.7.2 Electroactive derivatives	215
8.7.3 Chiral derivatives	215
8.8 Use of HPLC in analytical toxicology	216
8.8.1 Acidic and neutral compounds	216
8.8.2 Basic drugs and quaternary ammonium compounds	217
8.8.2.1 Nonaqueous ionic eluent systems	219
8.8.3 Systematic toxicological analysis	222
8.8.4 Chiral analyses	224
8.9 Summary	224
9 Capillary Electrophoretic Techniques	231
9.1 Introduction	231
9.2 Electrophoretic mobility	232
9.3 Efficiency and zone broadening	234
9.3.1 Joule heating	235
9.3.2 Electrodispersion	235
9.3.3 Adsorption of analyte onto the capillary wall	236
9.4 Sample injection	236
9.4.1 Hydrodynamic injection	236
9.4.2 Electrokinetic injection	237
9.4.3 Sample ‘stacking’	237
9.5 Detection	237
9.6 Reproducibility of migration time	239
9.7 Applications of capillary electrophoresis	240
9.8 Micellar electrokinetic capillary chromatography	240
9.9 Other capillary electrokinetic modes	242
9.9.1 Capillary electrochromatography	242
9.9.2 Capillary gel electrophoresis	244
9.9.3 Capillary isoelectric focusing	244
9.10 CE techniques in analytical toxicology	244
9.11 Chiral separations	244
9.12 Summary	246
10 Mass Spectrometry	249
10.1 Introduction	249
10.1.1 Historical development	250
10.2 Instrumentation	251
10.2.1 Sector instruments	252
10.2.2 Quadrupole instruments	253
10.2.3 Quadrupole ion-trap instruments	253
10.2.4 Ion cyclotron resonance	254

10.2.5 Controlled fragmentation (MS-MS)	254
10.3 Presentation of mass spectral data	255
10.4 Gas chromatography-mass spectrometry	256
10.4.1 Electron ionization	258
10.4.2 Chemical ionization	259
10.4.3 Application in analytical toxicology	260
10.5 Liquid chromatography-mass spectrometry	266
10.5.1 Atmospheric-pressure chemical ionization	268
10.5.2 Atmospheric-pressure photoionization	269
10.5.3 Electrospray or ionspray ionization	269
10.5.4 Flow fast-atom bombardment ionization	271
10.5.5 Particle-beam ionization	271
10.5.6 Thermospray	271
10.5.7 Application in analytical toxicology	272
10.6 Interpretation of mass spectra	274
10.7 Quantitative mass spectrometry	277
10.8 Summary	278
11 Trace Elements and Toxic Metals	281
11.1 Introduction	281
11.1.1 Historical development	281
11.2 Sample collection and storage	282
11.3 Sample preparation	284
11.3.1 Analysis of tissues	285
11.3.2 Analyte enrichment	285
11.4 Atomic spectrometry	286
11.4.1 General principles of AES, AAS and AFS	286
11.4.2 Atomic absorption spectrometry	287
11.4.2.1 Flame atomization	288
11.4.2.2 Electrothermal atomization	289
11.4.2.3 Sources of error	290
11.4.3 Atomic emission and atomic fluorescence spectrometry	292
11.4.3.1 Atomic emission spectrometry	292
11.4.3.2 Atomic fluorescence spectrometry	293
11.4.4 Inductively coupled plasma-mass spectrometry	293
11.4.4.1 Ion sources	294
11.4.4.2 Mass analyzers	294
11.4.4.3 Interferences	294
11.4.5 Vapour generation approaches	295
11.4.5.1 Hydride generation	295
11.4.5.2 Mercury vapour generation	296
11.4.6 X-ray fluorescence	297
11.5 Colorimetry and fluorimetry	298

11.6 Electrochemical methods	299
11.6.1 Anodic stripping voltammetry	299
11.6.2 Ion-selective electrodes	300
11.7 Catalytic methods	301
11.8 Neutron activation analysis	302
11.9 Chromatographic methods	302
11.9.1 Chromatography	302
11.9.2 Speciation	303
11.10 Quality assurance	303
11.11 Summary	304
12 Immunoassays and Enzyme-Based Assays	309
12.1 Introduction	309
12.1.1 Historical development	309
12.2 Basic principles of competitive binding assays	310
12.2.1 Antibody formation	310
12.2.2 Specificity	311
12.2.3 Performing the assay	313
12.2.3.1 Classical radioimmunoassay	313
12.2.3.2 Modern radioimmunoassay (RIA)	315
12.2.4 Non-isotopic immunoassay	315
12.2.5 Assay sensitivity and selectivity	316
12.2.6 Immunoassay development	317
12.2.7 Radioreceptor assays	318
12.3 Heterogeneous immunoassays	318
12.3.1 Tetramethylbenzidine reporter system	318
12.3.2 Antigen-labelled competitive ELISA	319
12.3.3 Antibody-labelled competitive ELISA	320
12.3.4 Sandwich ELISA	320
12.3.5 Lateral flow competitive ELISA	321
12.3.6 Chemiluminescent immunoassays (CLIA)	321
12.4 Homogenous immunoassays	321
12.4.1 Enzyme-multiplied immunoassay technique (EMIT)	321
12.4.2 Fluorescence polarization immunoassay (FPIA)	323
12.4.3 Cloned enzyme donor immunoassay (CEDIA)	324
12.5 Microparticulate and turbidimetric immunoassays	326
12.5.1 Microparticle enzyme immunoassay (MEIA)	326
12.5.2 Chemiluminescent magnetic immunoassay (CMIA)	327
12.6 Assay calibration, quality control and quality assurance	327
12.6.1 Immunoassay calibration	327
12.6.2 Drug screening	329
12.7 Interferences and assay failures	329
12.7.1 Digoxin	330
12.7.1.1 Digoxin-like immunoreactive substances (DLIS)	330
12.7.1.2 Other digoxin-like immunoreactive substances	331

12.7.1.3 Measurement of plasma digoxin after F _{ab} antibody fragment administration	331
12.7.2 Insulin and C-peptide	331
12.8 Enzyme-based assays	332
12.8.1 Paracetamol	332
12.8.2 Ethanol	333
12.8.3 Anticholinesterases	334
12.9 Summary	334
13 Toxicology Testing at the Point of Care	339
13.1 Introduction	339
13.1.1 Historical development	340
13.2 Use of POCT	340
13.2.1 Samples and sample collection	341
13.3 Analytes	343
13.3.1 Ethanol	343
13.3.1.1 Breath ethanol	343
13.3.1.2 Saliva ethanol	343
13.3.2 Drugs of abuse	344
13.3.2.1 Urine testing	345
13.3.2.2 Oral fluid testing	346
13.3.2.3 Sweat testing	346
13.3.3 Paracetamol and salicylates	346
13.3.4 Snake envenomation	347
13.3.5 Therapeutic drug monitoring	347
13.3.5.1 Lithium	348
13.3.5.2 Theophylline	348
13.3.5.3 Anticonvulsants	348
13.4 Interferences and adulterants	348
13.5 Quality assurance	349
13.6 Summary	350
14 Basic Laboratory Operations	353
14.1 Introduction	353
14.1.1 Reagents and standard solutions	354
14.1.2 Reference compounds	354
14.1.3 Preparation and storage of calibration solutions	356
14.2 Aspects of quantitative analysis	358
14.2.1 Analytical error	358
14.2.1.1 Confidence intervals	360
14.2.2 Minimizing random errors	361
14.2.2.1 Preparation of a solution of known concentration	362
14.2.3 Accuracy and Precision	362
14.2.3.1 Assessing precision and accuracy	363

14.2.3.2 Detecting systematic error (fixed bias)	363
14.2.3.3 Identifying sources of variation: analysis of variance	364
14.2.4 Calibration graphs	365
14.2.4.1 Linear regression	366
14.2.4.2 Testing for linearity	368
14.2.4.3 Weighted linear regression	370
14.2.4.4 Nonlinear calibration curves	370
14.2.4.5 Residuals and standardized residuals	372
14.2.4.6 Blank samples and the intercept	372
14.2.4.7 Method of standard additions	373
14.2.4.8 Limits of detection and quantitation	373
14.2.4.9 Curve fitting and choice of equation	374
14.2.4.10 Single point calibration	375
14.2.5 Batch analyses	375
14.3 Use of internal standards	376
14.3.1 Advantages of internal standardization	378
14.3.1.1 Reproducibility of injection volume	378
14.3.1.2 Instability of the detection system	379
14.3.1.3 Pipetting errors and evaporation of extraction solvent	379
14.3.1.4 Extraction efficiency	380
14.3.1.5 Derivatization and nonstoichiometric reactions	381
14.3.2 Internal standard availability	381
14.3.3 Potential disadvantages of internal standardization	382
14.4 Method comparison	382
14.4.1 Bland–Altman plots	383
14.5 Nonparametric statistics	384
14.5.1 Sign Tests	385
14.5.1.1 Wilcoxon signed rank test	386
14.5.2 Runs test	387
14.5.3 Mann–Whitney <i>U</i> -test	387
14.5.4 Spearman rank correlation	387
14.5.5 Nonparametric regression	388
14.6 Quality control and proficiency testing	389
14.6.1 Quality control charts	390
14.6.1.1 Shewhart charts	390
14.6.1.2 Cusum charts	390
14.6.1.3 J-chart	391
14.6.1.4 Westgard rules	392
14.6.2 External quality assurance	392
14.7 Operational considerations	393
14.7.1 Staff training	393
14.7.2 Recording and reporting results	394
14.7.3 Toxicology EQA schemes	395
14.8 Summary	397

15 Absorption, Distribution, Metabolism and Excretion of Xenobiotic Compounds	399
15.1 Introduction	339
15.1.1 Historical development	399
15.2 Routes of administration	400
15.2.1 Oral dosage	400
15.2.1.1 P-Glycoprotein	402
15.2.1.2 Presystemic metabolism	403
15.2.2 Intravenous injection	403
15.2.3 Intramuscular and subcutaneous injection	404
15.2.4 Sublingual and rectal administration	404
15.2.5 Intransal administration	405
15.2.6 Transdermal administration	405
15.2.7 Inhalation	405
15.2.8 Other routes of administration	405
15.3 Absorption	406
15.3.1 Passive diffusion	406
15.3.1.1 Partition coefficient	407
15.3.1.2 Ionization	407
15.3.2 Carrier-mediated absorption	408
15.3.3 Absorption from muscle and subcutaneous tissue	409
15.4 Distribution	409
15.4.1 Ion trapping	410
15.4.2 Binding to macromolecules	411
15.4.2.1 Plasma protein binding	411
15.4.3 Distribution in lipid	412
15.4.4 Active transport	412
15.5 Metabolism	412
15.5.1 Phase 1 metabolism	413
15.5.1.1 The cytochrome P450 family	413
15.5.1.2 Other phase 1 oxidases	414
15.5.1.3 Microsomal reductions	416
15.5.1.4 Hydrolysis	416
15.5.2 Phase 2 reactions	417
15.5.2.1 <i>O</i> -Glucuronidation	417
15.5.2.2 <i>O</i> -sulfation and <i>N</i> -acetylation	418
15.5.2.3 <i>O</i> -, <i>N</i> - and <i>S</i> -methylation	419
15.5.2.4 Conjugation with glutathione	419
15.5.2.5 Amino acid conjugation	419
15.5.3 Metabolic reactions of analytical or toxicological importance	420
15.5.3.1 Oxidative dealkylation	420
15.5.3.2 Hydroxylation	421
15.5.3.3 <i>S</i> - and <i>N</i> -oxidation	422
15.5.3.4 Oxidative dehalogenation	423

15.5.3.5 Desulfuration	425
15.5.3.6 Trans-sulfuration and trans-esterification	425
15.6 Excretion	425
15.6.1 The kidney	426
15.6.1.1 Tubular secretion	427
15.6.1.2 Excretion of metabolites	427
15.6.2 Biliary excretion	427
15.6.2.1 Enterohepatic recirculation	427
15.7 Summary	428
16 Pharmacokinetics	431
16.1 Introduction	431
16.1.1 Historical development	431
16.1.2 Symbols and conventions	432
16.2 Fundamental concepts	432
16.2.1 Rates, rate constants and reaction order	432
16.2.1.1 First-order elimination	433
16.2.1.2 Zero-order elimination	434
16.2.2 Dependence of half-life on volume of distribution and clearance	434
16.2.2.1 Apparent volume of distribution	435
16.2.2.2 Organ clearance	435
16.2.2.3 Whole body clearance	436
16.3 Absorption and elimination	437
16.3.1 First-order absorption	437
16.3.2 Bioavailability	438
16.3.3 Maximum concentration (C_{\max})	439
16.4 Drug accumulation	439
16.4.1 Intravenous infusion	439
16.4.1.1 Loading doses	440
16.4.2 Multiple dosage	440
16.5 Sustained-release preparations	441
16.5.1 Intramuscular depot injection	442
16.5.2 Other sustained-release preparations	443
16.6 Non-linear pharmacokinetics	443
16.6.1 Ethanol	445
16.7 Multicompartment models	447
16.7.1 Calculation of rate constants	449
16.7.2 Volumes of distribution in a two-compartment model	450
16.8 Model-independent pharmacokinetic parameters	451
16.8.1 Apparent volume of distribution	452
16.8.2 Clearance	453
16.8.3 Model-independent approach	453
16.9 Pharmacokinetics and the interpretation of results	454
16.9.1 Back-calculation of dose or time of dose	454

16.9.1.1 How much substance was administered?	455
16.9.1.2 When was the substance administered?	455
16.9.1.3 Practical examples	456
16.9.1.4 Calculation of time of cannabis exposure	456
16.9.2 Toxicokinetics	458
16.10 Summary	461
17 Clinical Interpretation of Analytical Results	463
17.1 Introduction	463
17.2 Pharmacogenetics	463
17.2.1 Acetylator status	465
17.2.1.1 Isoniazid	465
17.2.1.2 Sulfonamides	465
17.2.2 Cytochrome P450 polymorphisms	466
17.2.2.1 CYP2D6 polymorphism	466
17.2.2.2 CYP2C9 and CYP2C19 polymorphisms	467
17.2.2.3 Other CYP polymorphisms	467
17.2.3 Atypical cholinesterase	467
17.2.4 Glucose-6-phosphate dehydrogenase (G6PD)	468
17.2.5 Alcohol dehydrogenase and aldehyde dehydrogenase	468
17.3 Effects of age, sex and disease on drug disposition	468
17.3.1 Age	468
17.3.1.1 Effect of age on renal function	469
17.3.2 Disease	469
17.3.3 Sex	470
17.4 Enzyme induction and inhibition	471
17.4.1 Enzyme induction	471
17.4.2 Enzyme inhibition	472
17.5 Investigation of acute poisoning	472
17.5.1 Selectivity and reliability of analytical methods	474
17.5.2 Route and duration of exposure and mechanism of toxicity	474
17.5.3 Hair analysis	476
17.5.4 Sources of further information	477
17.6 Postmortem toxicology	478
17.6.1 Choice of sample and sample collection site	479
17.6.2 Assay calibration	480
17.6.3 Interpretation of analytical results	481
17.7 Gazetteer	483
17.7.1 Antidepressants	483
17.7.2 Anti-epileptics and antipsychotics	483
17.7.3 Carbon monoxide and cyanide	483
17.7.4 Cannabis	484
17.7.5 Cardioactive drugs	485
17.7.6 Cocaine	485
17.7.7 Drug-facilitated sexual assault	486

17.7.8 Ethanol (ethyl alcohol, 'alcohol')	487
17.7.9 Heroin/morphine	488
17.7.10 Hypoglycaemic agents	489
17.7.11 Methadone	489
17.7.12 Methylenedioxymetamphetamine and related compounds	490
17.7.13 Volatile substance abuse (VSA)	490
17.8 Summary	490

Index

Index	495
I. Pharmacokinetics	
16.1 Introduction	
16.1.1 Historical development	431
16.1.2 Seminal contributions	431
16.2 Fundamental concepts	
16.2.1 Rates, rate constants and compartmental analysis	432
16.2.2 First-order elimination	432
16.2.3 Zero-order elimination	433
16.2.4 Deceleration of first-order elimination	433
16.2.5 Half-lives of metabolites	434
16.2.6 Apparent volume of distribution	434
16.2.7 Drug clearance	435
16.2.8 Whole-body clearance	435
16.2.9 Absorption and elimination	436
16.3.1 First-order absorption	437
16.3.2 Bioavailability	438
16.3.3 Maximum concentration (C_{max})	439
16.3.4 Time to maximum concentration (t_{max})	439
16.3.5 Bioavailability coefficients in different bioavailability studies	440
16.4.2 Metabolism to excretion (bioconversion)	440
16.5.1 Bioavailability and release	441
16.5.2 Other sustained-release preparations	442
16.6 Non-linear pharmacokinetics	443
16.7 Examples	443
16.8 State-space model	444
16.7.1 Classification of rate constants	445
16.7.2 Veterans of discussion in a compartmental approach	446
16.8.1 Model-based pharmacokinetics	446
16.8.2 Compartmental pharmacokinetics	447
16.8.3 Non-linear pharmacokinetics	448
16.8.4 Covariance	449
16.8.5 Sustained-release products	449
16.9 Pharmacokinetics and the interpretation of results	450
16.9.1 Bioavailability of drugs in humans: biological and clinical	451