

TABLE OF CONTENTS

PREFACE	V
1 INTRODUCTION	1
<i>J. GAJZIOK, K. KUBOVÁ, K. HICKEY AND J. MUSELÍK</i>	
1.1 Quality control of raw materials (APIs and excipients)	1
1.2 Quality control in formulation development and pharmaceutical manufacture	4
1.3 References	6
2 INFRARED SPECTROSCOPY	7
<i>J. MUSELÍK AND K. HICKEY</i>	
2.1 Theoretical background	8
2.2 Instruments and measuring techniques used in IR spectroscopy	12
2.2.1 Michelson's interferometer and fourier's transformation	14
2.2.2 Measuring techniques	15
2.3 Evaluation of IR spectra: chemometrics	18
2.3.1 Multi-component analysis	18
2.4 Application of IR spectroscopy in pharmaceutical analysis	22
2.4.1 Application of MIR spectroscopy	23
2.4.2 Application of NIR spectroscopy	27
2.5 References	33
3 RAMAN SPECTROSCOPY	34
<i>J. MUSELÍK AND J. VYSLOUŽIL</i>	
3.1 Theoretical basics of Raman's scattering	34
3.2 Instrumentation and data analysis techniques	37
3.2.1 Raman measuring techniques	37
3.2.2 Raman microscopy	39
3.2.3 Raman data analysis	40
3.3 Application of Raman spectroscopy in pharmaceutical analysis	40
3.3.1 Identification of raw materials	41
3.3.2 Content and content uniformity analysis	42
3.3.3 Drug solid phase identification	43
3.3.4 Investigations of drug-excipient interaction and dosage form stability	44
3.3.5 Enantiomeric compositions analysis	45
3.3.6 Counterfeit detection	47
3.3.7 Other pharmaceutical applications	47
3.4 References	48

4 THERMAL ANALYSIS 49

J. MUSELÍK AND J. VYSLOUŽIL

4.1	Thermogravimetry	49
4.2	Differential thermal analysis	50
4.3	Differential scanning calorimetry	52
4.3.1	Instrumentation	52
4.4	Application of thermal analysis methods in pharmaceutical technology	55
4.4.1	Glass transition temperature	56
4.4.2	Crystallisation	57
4.4.3	Polymorphism and pseudo-polymorphism	57
4.4.4	Melting temperature	58
4.4.5	Investigations of drug-exipient interaction and dosage form stability	59
4.5	References	60

5 X-RAY DIFFRACTION ANALYSIS 61

J. MUSELÍK, E. BARTONÍČKOVÁ AND K. HICKEY

5.1	Theoretical basics of X-ray diffraction	61
5.1.1	Sources of X-ray radiation	62
5.1.2	Principles of X-ray diffraction	63
5.1.3	Single crystal diffraction	67
5.1.4	X-ray powder diffraction	69
5.2	Data Processing	73
5.3	Application of XRPD in pharmaceutical technology	74
5.3.1	Identification of raw materials	74
5.3.2	Drug solid phase identification	75
5.3.3	Investigations of drug-exipient interaction and dosage form stability	76
5.3.4	Quantitative analysis	77
5.4	References	77

6 SOLID-STATE NMR SPECTROSCOPY 79

M. URBANOVÁ, J. BRUS AND I. ŠEDĚNKOVÁ

6.1	Theoretical basics of NMR spectroscopy	81
6.1.1	Nuclear interactions in ssNMR Spectroscopy	83
6.2	Instruments and measuring techniques used in ssNMR spectroscopy	86
6.2.1	Magic angle spinning	86
6.2.2	High-power heteronuclear decoupling	88
6.2.3	Cross polarization	88
6.2.4	Correlation spectroscopy	89
6.2.5	NMR instrument composition	90
6.2.6	The basic specific features of ssNMR spectra	91
6.3	Application of ssNMR spectroscopy in pharmaceutical technology	92
6.3.1	Representative cases	94
6.4	References	100

K. KUBOVÁ, D. VETCHÝ AND J. MUSELÍK

7.1	Dissolution test equipment and conditions	103
7.1.1	Instrumentation	103
7.1.2	Conditions and procedure of the dissolution testing	105
7.2	Application of dissolution tests in pharmaceutical technology	110
7.2.1	Formulation optimization	111
7.2.2	Drug release rate and mechanism	112
7.2.3	Prediction of <i>in vivo</i> performance of the dosage forms	114
7.2.4	Evaluation of bio-equivalence of generic drugs	114
7.2.5	Stability evaluation	116
7.2.6	Quality control	117
7.3	References	120

8 EVALUATION OF SIZE, SHAPE AND SURFACE OF PARTICLES

J. VYSLOUŽIL, M. KEJDUŠOVÁ, K. HICKEY, S. PAVLOKOVÁ AND J. MUSELÍK

8.1	Size and shape of particles	121
8.1.1	Sieving and sieve analysis	122
8.1.2	Laser diffraction	123
8.1.3	Dynamic light scattering	127
8.1.4	Image analysis	130
8.1.5	Sedimentation methods	134
8.1.6	Coulter particle counter	138
8.2	Particle surface structure	138
8.2.1	Specific surface area determination	139
8.2.2	Mercury porosimetry	140
8.2.3	Profilometry	140
8.2.4	Inverse gas chromatography	143
8.3	References	143

9 MODERN MICROSCOPIC METHODS

J. VYSLOUŽIL, S. PAVLOKOVÁ, M. KEJDUŠOVÁ, K. HICKEY AND J. MAŠEK

9.1	Optical (light) microscopy	145
9.1.1	Principle of display and magnification by microscope	146
9.1.2	Design of microscope	150
9.1.3	Bright field microscopy	154
9.1.4	Fluorescent microscopy	158
9.1.5	Laser confocal microscopy	159
9.2	Electron microscopy	160
9.2.1	Properties of electron flow and principles for image creation	161
9.2.2	Design of electron microscope	165
9.2.3	Transmission electron microscopy	168
9.2.4	Scanning electron microscopy	170
9.2.5	Cryo-electron microscopy imaging	174
9.3	Scanning probe microscopy	178
9.3.1	Design of scanning probe microscope	178

9.3.2	Scanning tunnelling microscopy	179
9.3.3	Atomic force microscopy	181
9.3.4	Other techniques	184
9.3.5	SPM application	185
9.4	References	186

10 VALIDATION AT A GLANCE 188

A. FRANC AND J. MUSELÍK

10.1	Analytical method validation	189
10.2	Process validation	192
10.2.1	Types of process validation	193
10.2.2	Representative cases	194
10.3	References	201

11 INTELLECTUAL PROPERTY AND PATENT PROTECTION OF PHARMACEUTICALS 203

A. FRANC, J. MUSELÍK AND J. GAJDZIOK

11.1	Reasons for intellectual property protection	203
11.2	Forms of intellectual property protection	204
11.3	Conditions of intellectual property protection	204
11.4	Structure of patent application	204
11.5	General patent filing procedure	205
11.6	Subject of intellectual property protection in the pharmaceutical technology	206
11.7	Representative cases	207
11.7.1	Polymorphism	208
11.7.2	Dissolution	209
11.7.3	Content uniformity	210
11.8	References	213

12 LIST OF ABBREVIATIONS 215