

Contents

Preface *xvii*

1	Impact of the Polymorphic Form of Drugs/NCEs on Preformulation and Formulation Development	1
	<i>MHD Bashir Alsirawan and Anant Paradkar</i>	
1.1	Introduction	1
1.1.1	Background	1
1.1.2	Types of Polymorphism	2
1.1.2.1	Conformational Polymorphism	2
1.1.2.2	Packing Polymorphism	4
1.1.3	Thermodynamic-Based Classification of Polymorphism	4
1.1.3.1	Enantiotropic Polymorphism	4
1.1.3.2	Monotropic Polymorphism	5
1.1.4	Concomitant Polymorphism	6
1.1.5	Debatable Polymorphism Cases	7
1.1.5.1	Tautomeric Polymorphism or Tautomerism	7
1.1.5.2	Enantiomerism/Stereoisomerism	7
1.1.5.3	Pseudopolymorphism	8
1.2	Polymorphism Impact on Drug/Excipient Properties	9
1.2.1	Physicochemical Properties	10
1.2.2	Mechanical Properties	11
1.2.3	Impact of Polymorphism on <i>In Vivo</i> Performance	13
1.2.3.1	Effect of Polymorphism on Solubility	14
1.2.3.2	Effect of Polymorphism on Dissolution Rate/Solubility Kinetics	17
1.2.3.3	Effect of Polymorphism on Bioavailability	20
1.3	Critical Impact of Polymorphic Form of API on Processing and Formulation	22
1.3.1	Process-induced Transformation Types	23
1.3.1.1	Grinding-induced Transitions	23
1.3.1.2	Granulation-induced Transitions	25
1.3.1.3	Tableting-induced Transition	30
1.3.1.4	Freeze-drying-induced Transition	32
1.3.1.5	Spray-drying-induced Transitions	33
1.3.1.6	Supercritical-fluid-induced Transitions	35
1.4	Conclusion	37
	References	38

2	Strategies for the Formulation Development of Poorly Soluble Drugs via Oral Route	49
	<i>Sanket Shah, Abhijit Date, and René Holm</i>	
2.1	Introduction	50
2.2	Quality by Testing (QbT) and Quality by Design (QbD)	50
2.3	Linking the Formulation to the Clinical Phase	52
2.4	Defining the Formulation Strategy	55
2.5	Nanosuspensions	58
2.5.1	Description	58
2.5.2	Method of Manufacturing	59
2.5.2.1	Top-Down Methods	59
2.5.2.2	Wet Media Milling Technology	60
2.5.2.3	High-pressure Homogenization	61
2.5.2.4	Bottom-Up Methods	62
2.5.2.5	Methods Utilizing a Hybrid Approach	63
2.5.3	Characterization of Nanosuspensions	63
2.5.3.1	Particle Size, Polydispersity Index, and Particle Morphology	63
2.5.3.2	Surface Charge	63
2.5.3.3	Particle Morphology	64
2.5.3.4	Solid-state Properties	64
2.5.3.5	Saturation Solubility and Dissolution Velocity	64
2.6	Solid Dispersion	64
2.6.1	Description	65
2.6.2	Method of Manufacturing	66
2.6.2.1	Melting/Fusion	66
2.6.2.2	Solvent Evaporation	67
2.6.2.3	Coprecipitation	67
2.6.3	Characterization	68
2.6.3.1	Investigation of Crystallinity	68
2.6.3.2	Investigation of Molecular Arrangement	69
2.7	Lipid-Based Drug Delivery Systems	69
2.7.1	Description	70
2.7.2	Method of Manufacture	71
2.7.3	Characterization	75
2.7.4	Role of API Property on Lipid-Based DDS	76
2.8	Micellar System	76
2.8.1	Description	76
2.8.2	Formulation Development and Optimization	80
2.8.3	Characterization	81
2.9	Mesoporous Silica Particles	81
2.9.1	Description	82
2.9.2	Method of Manufacturing and Characterization	83
2.9.3	Case Study on the <i>in Vivo</i> Efficacy of Mesoporous Silica Particles	84
2.10	Conclusion	84
	References	85

3	Effect of Residual Reactive Impurities in Excipients on the Stability of Pharmaceutical Products	91
	<i>Ankit Sharma</i>	
3.1	Introduction	91
3.2	Reactive Impurities in the Excipients and Their Impact on Drug Stability	92
3.3	Impact of Reactive Impurities on Drug–Excipient Compatibility	93
3.3.1	Physical Interactions	93
3.3.2	Chemical Interactions	94
3.3.3	Oxidative Degradation	94
3.3.4	Peroxides	95
3.3.5	Transition Metal Impurities	96
3.3.6	Condensation Reactions	99
3.3.7	Aldehyde Impurities	99
3.3.8	Reducing Sugars	102
3.3.9	Organic Acids	103
3.3.10	Hydrolytic Degradation	105
3.4	Risk Assessment for API Incompatibilities and Mitigation Strategies	107
3.5	Assessment of Incompatibilities of API with Excipients	108
3.6	Design and Selection of Drug Substance	109
3.7	Formulation Strategies to Circumvent API Degradation	110
3.8	Inhibition of Oxidative Degradation	110
3.8.1	Initiation Inhibitors	111
3.8.2	Propagation Inhibitors	111
3.8.3	Selection of Antioxidant	112
3.9	Super-Refined Excipients	113
3.9.1	Polyethylene Glycols (PEG)	114
3.9.2	Polysorbates	114
3.9.3	Fatty Acids	115
3.10	Packaging and Storage	115
3.11	Concluding Remarks	116
	References	116
4	Preclinical Formulation Assessment of NCEs	119
	<i>Raju Saka, Priyadarshini Sathe, Wahid Khan, and Sachin Dubey</i>	
4.1	Introduction	120
4.2	Significance of Various Properties of NCEs in Early Drug Discovery	122
4.2.1	Solubility	123
4.2.2	Permeability	124
4.2.3	Stability	125
4.3	Formulation Strategies to Improve Properties of NCEs	125
4.3.1	pH Modification	127
4.3.2	Cosolvents	127

4.3.3	Cyclodextrins	128
4.3.4	Surfactants	128
4.3.5	Suspensions and Nanosuspensions	129
4.3.6	Emulsions and Microemulsions	130
4.3.7	Solid Dispersions	130
4.3.8	Liposomes	131
4.4	Preclinical Formulation Assessment of Oral, Parenteral, and Topical Dosage Forms	131
4.4.1	Oral Formulations	131
4.4.1.1	Formulation Development	132
4.4.2	Parenteral Formulations	134
4.4.3	Topical Formulations	135
4.4.3.1	Structure of Skin and Effect on Permeation	136
4.4.3.2	Formulation Effect	136
4.4.3.3	Skin Metabolism	136
4.4.3.4	Formulation Development	136
4.4.3.5	Formulation Approaches	137
4.4.4	Excipients	138
4.4.5	Characterization and Stability of Preclinical Formulations	140
4.4.6	Formulation Selection for Pharmacokinetic Studies	141
4.4.7	Formulation Selection for Pharmacodynamic Studies	142
4.4.8	Formulation Development for Toxicity Studies	142
4.5	Case Studies	143
4.5.1	Case 1: Use of Surfactant to Prevent Precipitation of API in Cosolvent-Based Formulations	143
4.5.2	Case 2: Topical Gel Microemulsion Formulation of Lipophilic Drug WHI-07	144
4.5.3	Case 3: Salt Approach to Improve the Bioavailability of the Poorly Soluble Drug	144
4.5.4	Case 4: Use of SMEDDS Dosage Form to Improve Bioavailability	145
4.5.5	Case 5: Micronized Suspension of Poorly Soluble Lead Compounds Using Wet Milling Technique	145
4.5.6	Case 6: Polymer Addition in Cyclodextrin-Based Formulations and pH Adjustment	146
4.5.7	Case 7: Cyclodextrin Complexation to Improve Topical Delivery of a Poorly Soluble Compound	146
4.5.8	Case 8: Use of Solubilizers and Their Effect on PK of Preclinical Lead Candidates	147
4.5.9	Case 9: Self-nanoemulsifying Drug Delivery Systems (SNEDDS) to Improve Solubility and Bioavailability	147
4.6	Conclusion and Future Perspectives	148
	References	148
5	Regulatory Aspects for Formulation Design – with Focus on the Solid State	155
	<i>Michael Gruss</i>	
5.1	The Understanding of “Regulatory”	156
5.2	Formulation Design	157

5.3	An Extended Timescale	158
5.4	Solubility Data	158
5.5	Impact of Solubility and Dissolution Rate on Formulation Design	162
5.6	Single and Multicomponent Systems	163
5.6.1	Introduction	163
5.6.2	Scientific Point of View	164
5.6.2.1	Polymorphism	164
5.6.2.2	Polyamorphism	165
5.6.2.3	Multicomponent Compounds – Salt, Co-crystal, Solvate, and Hydrate	165
5.6.3	Fate and Pathway of a Compound During Development	166
5.6.4	Regulatory Point of View	167
5.6.4.1	Patents	167
5.6.4.2	Pharmacopeias	168
5.7	Analytical Techniques for the Characterization of the Solid State	168
5.7.1	Scientific Literature	168
5.7.2	Pharmacopeias	169
5.8	Control of Solid-state Constitution	171
5.8.1	The Process – from Synthesis to Patient	171
5.8.2	Change of Properties and Constitution	173
5.8.3	Need for Control of Solid-State Properties During the Process and Supply Chain	173
5.9	Regulatory Consideration of Solid Compounds	174
5.9.1	Definitions for Solid Compounds	174
5.9.1.1	Co-crystals and Solvates	174
5.9.1.2	Salts and Co-crystals	174
5.9.1.3	Polymorphism	175
5.9.2	Common Technical Document (CTD) – M4Q	175
5.9.2.1	CTD – Section 3.2.S – Drug Substance	175
5.9.2.2	CTD – Section 3.2.P – Drug Product	177
5.9.3	Guideline on the Chemistry of Active Substances	178
5.9.4	Guideline on Quality of Transdermal Patches	180
5.9.5	Quality Guidelines	181
5.9.5.1	ICH Q1A (R2) Stability Testing of New Drug Substances and Products	182
5.9.5.2	ICH Q1B Photostability Testing	182
5.9.5.3	ICH Q1C Stability Testing: Requirements for New Dosage Forms	183
5.9.5.4	ICH Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances	183
5.9.6	EMA – Consideration and Perspective	188
5.9.6.1	Abridged Applications	188
5.9.6.2	New Active Substance (NAS) Status	188
5.9.6.3	Marketing Authorization Application (MAA)	189
5.9.6.4	Co-crystals and GMP Manufacturing	189
5.9.6.5	Active Substance Master File (ASMF)	190
5.9.6.6	Pharmaceutical Acceptance	190
5.9.6.7	Compounds Containing More than One Therapeutic Moiety	190

5.9.7	FDA – Consideration and Perspective	190
5.9.7.1	Sources for Information	190
5.9.7.2	Naming of Drug Substances and Drug Products	191
5.9.7.3	Investigational New Drug Application (IND)	192
5.9.7.4	Marketing Authorization Application – New Drug Application (NDA)	194
5.9.7.5	ANDA – Abbreviated New Drug Applications	194
5.9.7.6	Regulatory Classification of Pharmaceutical Co-crystals and Salts	196
5.9.8	Similarities and Differences Between the Regulative Systems in the EU and United States	197
5.10	Conclusions and Recommendations	198
	Disclaimer	198
	References	198
6	Insight into Innovative Applications of Parenteral Formulations	209
	<i>Clara Fernandes</i>	
6.1	Introduction	209
6.2	Factors Affecting Development of Sustained-/Controlled-Release Formulations	209
6.3	Overview of Sustained and Controlled Release Parenteral Formulations	213
6.3.1	Suspension Based Formulations	213
6.3.1.1	Nanosuspension Based Formulations	213
6.3.1.2	Microsuspension Based Formulations	214
6.3.2	Particulate System Based Formulations	215
6.3.2.1	Polymer Nanoparticles Based Formulations	215
6.3.2.2	Lipid Nanoparticles Based Formulations	217
6.3.2.3	Inorganic Nanoparticles Based Nanoparticles	217
6.4	Case Studies	219
6.4.1	Nanosuspension Formulation of Paclitaxel – Abraxane®	219
6.4.2	PLGA Depot Based Formulation of Triptorelin – Trelstar®	219
6.4.3	Microemulsion Formulation of Propofol	220
6.4.4	Inorganic Metal Nanoparticle Based Formulation for Parenteral Applications	220
6.4.5	Polymeric Formulation of Glatiramer	221
6.5	Conclusion	222
6.6	Future Prospects	222
	References	222
7	Assessing Pharmacokinetics of Various Dosage Forms at Early Stage	227
	<i>Susanne Bonsmann and Joachim Ossig</i>	
7.1	Introduction	227
7.2	Definition of Pharmacokinetics	229

7.2.1	ADME Parameters	229
7.2.1.1	Absorption	229
7.2.1.2	Distribution	230
7.2.1.3	Metabolism and Excretion	231
7.2.2	Pharmacokinetic Parameters	231
7.2.2.1	Plasma Concentration Time Profile	231
7.2.2.2	Area Under the Curve (AUC)	232
7.2.2.3	Bioavailability (BA)	233
7.2.2.4	Volume of Distribution (V_d)	234
7.2.2.5	Clearance (Cl)	234
7.2.2.6	Half-life ($T_{1/2}$)	235
7.2.3	PK Studies During Drug Development	236
7.2.3.1	ADME <i>in Vitro</i> Studies	236
7.2.3.2	<i>In Vitro</i> Models	237
7.2.3.3	<i>In Vivo</i> Studies	238
7.3	Case Studies	241
7.3.1	Case Study 1	241
7.3.2	Case Study 2	241
7.3.3	Case Study 3	242
7.3.4	Case Study 4	243
7.4	Summary	243
	References	243
8	Transdermal Medical Devices: Formulation Aspects	245
	<i>Mayank Singhal, César E. S. Jimenez, Maria Lapteva, and Yogeshvar N. Kalia</i>	
8.1	Introduction	246
8.2	Microneedles	247
8.2.1	Delivery Using Solid Microneedles: Skin Pretreatment	248
8.2.1.1	Delivery of Low-Molecular-Weight Compounds	248
8.2.1.2	Delivery of High-Molecular-Weight Compounds	251
8.2.2	Delivery Using Coated Microneedles	252
8.2.2.1	Delivery of Low-Molecular-Weight Compounds	252
8.2.2.2	Delivery of High-Molecular-Weight Compounds: Formulation Challenges Related to the Formulation of Coated Microneedles – A Case Study	252
8.2.3	Delivery Using Dissolvable Microneedles	254
8.2.3.1	Delivery of Low-Molecular-Weight Compounds	254
8.2.3.2	Delivery of High-Molecular-Weight Compounds: Formulation Challenges Related to the Formulation of Dissolvable Microneedles – A Case Study	255
8.2.4	Delivery Using Hollow Microneedles	255
8.2.4.1	Delivery of Low-Molecular-Weight Compounds	255
8.2.4.2	Delivery of High-Molecular-Weight Compounds	256
8.2.5	Delivery of Vaccines	257
8.2.6	Modalities of Microneedle Use	259
8.2.7	Perspectives in Microneedle-Mediated Transdermal Delivery	259
8.3	Laser-Assisted Ablation: Skin Pretreatment	260

8.3.1	Laser–Skin Interaction	261
8.3.2	Formulation Aspects	262
8.3.3	Perspective	263
8.4	Iontophoresis	263
8.4.1	Clinical Benefits of Iontophoresis in Transdermal/Topical Delivery	264
8.4.2	Selection of Drug Candidates	265
8.4.3	Iontophoretic Device Formulation Characteristics: Compositions and Challenges	265
8.4.4	Earlier Approved Commercial Devices	266
8.4.5	Smart Ionto System Features	268
8.4.6	Perspectives	269
	References	269
9	Physical Characterization Techniques to Access Amorphous Nature	<i>Aniket Sabnis, Nitin Jadav, Tim Gough, Adrian Kelly, and Anant Paradkar</i>
9.1	Introduction	282
9.1.1	Limitations of the Amorphous Form	285
9.1.2	Stabilization of the Amorphous Form	285
9.1.3	Solid Dispersion	285
9.1.4	Factors Affecting Solubility of API in the Form of Solid Dispersions	287
9.1.5	Limitations	289
9.1.6	Co-Amorphous	289
9.2	Screening Techniques for Amorphization	290
9.2.1	Amorphization: Solution-Based Techniques	291
9.2.1.1	Melting and Quench Cooling	291
9.2.1.2	Spray-Drying	292
9.2.1.3	Freeze-Drying	293
9.2.1.4	Flash Evaporation/Rotary Evaporation	294
9.2.1.5	Supercritical Fluid Processing	294
9.2.2	Amorphization: Solid-State Techniques	294
9.2.2.1	Dehydration of Crystalline Hydrates	294
9.2.2.2	Milling	294
9.2.2.3	Vacuum Compression Molding	296
9.2.2.4	Hot Melt Extrusion	296
9.3	Characterization of Amorphous Materials	298
9.3.1	X-Ray Powder Diffraction (XRPD)	299
9.3.2	Thermal Methods	302
9.3.2.1	Differential Scanning Calorimetry	302
9.3.2.2	Dynamic Mechanical Thermal Analysis	305
9.3.3	Perfusion/Solution Calorimetry	307
9.3.4	Density Measurements	310
9.3.5	Sorption Technique: Dynamic Vapor Sorption (DVS)	310
9.3.6	Vibrational Spectroscopy	312
9.3.6.1	Mid-Infrared Spectroscopy	313

9.3.6.2	Raman Spectroscopy	316
9.3.6.3	Near-Infrared Spectroscopy	318
9.3.6.4	Terahertz Spectroscopy	319
9.4	Summary	321
9.5	Future Prospects	322
	References	323
10	Design and Development of Ocular Formulations for Preclinical and Clinical Trials	331
	<i>Mathieu Schmitt</i>	
10.1	Introduction	331
10.2	Ocular Anatomy and Physiology	332
10.3	Ocular Routes of Administration	336
10.4	Drug Discovery in Ophthalmology	337
10.4.1	Repositioning of Existing Drugs from Other Disease Area	337
10.4.2	Optimization of Compound Class to Enhance Selectivity, Tolerance Profile, and Efficacy	338
10.4.3	Specific Development	339
10.5	Topical Drug Administration	340
10.5.1	Ocular Bioavailability	340
10.5.2	Drug Design	340
10.5.3	Prodrugs	342
10.5.4	Physiological Factors	343
10.5.5	Formulation and Drug Delivery Systems	344
10.5.5.1	<i>In Situ</i> Gelling Systems	344
10.5.5.2	Emulsion	346
10.5.5.3	Nonaqueous Solutions	347
10.5.5.4	Polymeric Micelles and Dendrimers	348
10.5.5.5	Cyclodextrins	349
10.5.5.6	Multiparticulate Drug Delivery Systems	351
10.5.5.7	Sustained-release Strategies for Anterior Segment	352
10.5.6	Patient Compliance Through Packaging	354
10.6	Posterior Segment Delivery	356
10.6.1	<i>In Situ</i> Depot	357
10.6.2	Prodrugs	357
10.6.3	Intraocular Implants/Microparticles	358
10.7	Conclusion	360
	References	361
11	Preclinical Safety Aspects for Excipients: Oral, IV, and Topical Routes	367
	<i>Florian Engel</i>	
11.1	Introduction	368
11.2	General Considerations	369
11.3	Undesired Side Effects of Excipients	370
11.4	Novel Excipients	371
11.4.1	Regulatory Requirements	372

11.5	Rationale in Selecting an Excipient	375
11.5.1	Data Sources	376
11.5.1.1	Inactive Ingredient Database (IID)	376
11.5.1.2	Pharmacopoeias	376
11.5.1.3	Generally Recognized as Safe (GRAS)	376
11.5.1.4	Handbook of Pharmaceutical Excipients	377
11.5.1.5	STEP Database	377
11.5.1.6	Other Databases	377
11.5.1.7	<i>In Silico</i>	378
11.5.2	Strategies to Determine “Estimated Safe Excipient Doses”	378
11.5.3	Special Considerations for Oral Use	381
11.5.4	Special Considerations for Intravenous Use	381
11.5.5	Special Considerations for Topical Use	385
11.6	Conclusions	386
	References	387
12	Formulation of Therapeutic Proteins: Strategies for Developing Oral Protein Formulations	391
	<i>Saurabh Patil, Aditya Narvekar, Amita Puranik, Ratnesh Jain, and Prajakta Dandekar</i>	
12.1	Introduction	392
12.1.1	Use of Proteins for Different Therapeutic Indications	392
12.1.2	Importance of Physicochemical Properties on Preformulation and Formulation Development of Protein Therapeutics	394
12.1.3	Stability Constraints and Formulation Challenges	395
12.1.4	Current Market Status and Opportunities of Therapeutic Proteins	396
12.1.5	Current Technologies for Protein Formulation Development	398
12.1.6	Current Approaches in Oral Delivery of Proteins for Enhanced GIT Absorption	400
12.2	Types of Proteins Used in Therapeutic Indications	400
12.3	Important Physicochemical Properties of Proteins for Formulation Development	402
12.4	Existing Route of Administrations of Protein Formulations	404
12.5	Developmental Aspects of Oral Protein Formulations	405
12.5.1	Resource Requirements for Manufacturing of Protein-Based Formulations	406
12.5.2	Stability Concerns of Proteins in the Gastrointestinal Tract (GIT)	407
12.5.3	Physical Barriers to Delivering Proteins and Peptides	407
12.5.3.1	Unstirred Layer of Intestinal Fluid	407
12.5.3.2	Epithelial Cell Membrane	407
12.5.3.3	Biochemical Barriers to Proteins and Peptides	409
12.5.4	Formulation Strategies for the Oral Delivery of Proteins and Peptides	409
12.5.4.1	Peptidase/Enzyme Inhibition Approaches	409
12.5.4.2	Use of Permeation Enhancers	410
12.5.5	Modification of the Physicochemical Properties	411

- 12.5.5.1 PEGylation 411
- 12.5.5.2 Alteration of Amino Acids 412
- 12.5.5.3 Hydrophobization 412
- 12.5.6 Use of Particulate Formulations 412
 - 12.5.6.1 Microemulsions 413
 - 12.5.6.2 Solid Lipid Core Particles 414
 - 12.5.6.3 Liposomes 414
 - 12.5.6.4 Nanoparticles 415
 - 12.5.6.5 Microspheres/Microparticles 416
- 12.5.7 Colon-Targeted Delivery Systems for Proteins and Peptides 416
- 12.5.8 Mucoadhesive Polymeric Systems and Stimuli-Responsive Hydrogels 417
- 12.5.9 Cell-Penetrating Peptides 417
- 12.5.10 Prodrug Approach 417
- 12.6 Clinical Application of Oral Protein Formulations 418
- 12.7 Case Studies of Oral Protein Formulations 418
 - 12.7.1 Case Study I: Cyclosporine A 418
 - 12.7.2 Case Study II: Oral Insulin 421
 - 12.7.3 Case Study III: Prodrug Approach – Desmopressin 422
- 12.8 Conclusion 422
- References 423

Index 433

