

Pulmonary Drug Delivery

Advances and Challenges

Edited by

ALI NOKHODCHI AND GARY P. MARTIN

WILEY

Contents

<i>List of Contributors</i>	xiii
<i>Series Preface</i>	xvii
<i>Preface</i>	xix
1. Lung Anatomy and Physiology and Their Implications for Pulmonary Drug Delivery	1
<i>Rahul K. Verma, Mariam Ibrahim, and Lucila Garcia-Contreras</i>	
1.1 Introduction	2
1.2 Anatomy and Physiology of Lungs	2
1.2.1 Macro- and Microstructure of the Airways and Alveoli as It Pertains to Drug Delivery	2
1.2.2 Lung Surfactant	4
1.2.3 Pulmonary Blood Circulation	5
1.3 Mechanisms of Aerosol Deposition	5
1.3.1 Impaction	6
1.3.2 Sedimentation	6
1.3.3 Interception	6
1.3.4 Diffusion	7
1.4 Drug Absorption	7
1.4.1 Mechanisms of Drug Absorption from the Lungs	7
1.5 Physiological Factors Affecting the Therapeutic Effectiveness of Drugs Delivered by the Pulmonary Route	8
1.5.1 Airway Geometry	8
1.5.2 Inhalation Mode	8
1.5.3 Airflow Rate	9
1.5.4 Mechanism of Particle Clearance	9
1.5.5 Lung Receptors	10
1.5.6 Disease States	11
1.5.7 Effect of Age and Gender Difference	11
1.6 Computer Simulations to Describe Aerosol Deposition in Health and Disease	11
1.6.1 Semiempirical Models	12
1.6.2 Deterministic Models	12
1.6.3 Trumpet Models (One-Dimensional)	12
1.6.4 Stochastic, Asymmetric Generation Models	13
1.6.5 Computation Fluid Dynamics (CFD)-Based Model	13

1.7	Conclusions	13
	References	14
2.	The Role of Functional Lung Imaging in the Improvement of Pulmonary Drug Delivery	19
	<i>Andreas Fouras and Stephen Dubsky</i>	
2.1	Introduction	19
2.1.1	Particle Deposition	20
2.1.2	Regional Action of Delivered Drug	22
2.1.3	The Role of Functional Lung Imaging in Pulmonary Drug Delivery	22
2.2	Established Functional Lung Imaging Technologies	23
2.2.1	Computed Tomography	23
2.2.2	Ventilation Measurement using 4DCT Registration-based Methods	24
2.2.3	Hyperpolarized Magnetic Resonance Imaging	24
2.2.4	Electrical Impedance Tomography	25
2.2.5	Nuclear Medical Imaging (PET/SPECT)	25
2.3	Emerging Technologies	26
2.3.1	Phase-contrast Imaging	26
2.3.2	Grating Interferometry	27
2.3.3	Propagation-based Phase-contrast Imaging	28
2.3.4	Functional Lung Imaging using Phase Contrast	28
2.3.5	Laboratory Propagation-based Phase-contrast Imaging	29
2.4	Conclusion	30
	References	31
3.	Dry Powder Inhalation for Pulmonary Delivery: Recent Advances and Continuing Challenges	35
	<i>Simone R. Carvalho, Alan B. Watts, Jay I. Peters, and Robert O. Williams III</i>	
3.1	Introduction	36
3.2	Dry Powder Inhaler Devices	37
3.2.1	Overview	37
3.2.2	Recent Innovations in Dry Powder Inhaler Technology	39
3.3	New Developments in DPI Formulations and Delivery	43
3.3.1	Particle Surface Modification	43
3.3.2	Particle Engineering Technology for Pulmonary Delivery	44
3.4	Characterization Methods of Dry Powder Inhaler Formulations	50
3.5	Conclusion	52
	References	53
4.	Pulmonary Drug Delivery to the Pediatric Population – A State-of-the-Art Review	63
	<i>Marie-Pierre Flament</i>	
4.1	Introduction	63
4.2	Patient Consideration	64
4.2.1	Anatomy and Physiology of Children’s Lungs	64

4.2.2	Nasal Versus Oral Inhalation	65
4.2.3	Patient-related Factors Influencing Aerosol Deposition	66
4.2.4	Age and Dosage Forms of Choice	67
4.3	Delivery Systems for the Pediatric Population	69
4.3.1	Nebulizers	69
4.3.2	Pressurized Metered Dose Inhalers	72
4.3.3	Dry Powder Inhalers	73
4.3.4	Interfaces	74
4.4	Recommendations	80
4.5	Conclusion	82
	References	82
5.	Formulation Strategies for Pulmonary Delivery of Poorly Soluble Drugs	87
	<i>Nathalie Wauthoz and Karim Amighi</i>	
5.1	Introduction	88
5.1.1	<i>In vivo</i> Fate of Inhaled Poorly Water-soluble Drugs	89
5.1.2	The Pharmacokinetics of Inhaled Poorly Water-soluble Drugs Administered for Local and Systemic Action	92
5.1.3	Formulation Strategies for Pulmonary Delivery of Poorly Water-soluble Drugs	93
5.2	Co-solvents	93
5.3	Cyclodextrins	97
5.4	PEGylation	99
5.5	Reduction of Size to Micro-/Nanoparticles	100
5.5.1	Nanocrystal Suspension	101
5.5.2	Nanocrystals in a Hydrophilic Matrix System	102
5.5.3	Nanoclusters	103
5.6	Solid Dispersion/Amorphization	103
5.7	Micelles	106
5.8	Liposomes	108
5.9	Solid Lipid Nanoparticles and Nanostructured Lipid Carriers	110
5.10	Conclusion	111
	References	114
6.	Lipidic Micro- and Nano-Carriers for Pulmonary Drug Delivery – A State-of-the-Art Review	123
	<i>Yahya Rahimpour, Hamed Hamishehkar, and Ali Nokhodchi</i>	
6.1	Introduction	124
6.2	Pulmonary Drug Delivery	125
6.3	Liposomal Pulmonary Delivery	126
6.4	Nebulization of Liposomes	126
6.5	Liposomal Dry-powder Inhalers	128
6.6	Solid Lipid Microparticles in Pulmonary Drug Delivery	129
6.7	Solid Lipid Nanoparticles in Pulmonary Drug Delivery	131
6.8	Nanostructured Lipid Carrier (NLC) in Pulmonary Drug Delivery	133

6.9	Nanoemulsions in Pulmonary Drug Delivery	134
6.10	Conclusion and Perspectives	135
	References	136
7.	Chemical and Compositional Characterisation of Lactose as a Carrier in Dry Powder Inhalers	143
	<i>Rim Jawad, Gary P. Martin and Paul G. Royall</i>	
7.1	Introduction	144
7.2	Production of Lactose	145
7.3	Lactose: Chemical Forms, Solid-State Composition, Physicochemical Properties	147
7.4	Epimerisation of Lactose	150
7.5	Analysis of Lactose	151
	7.5.1 Powder X-ray Diffraction	152
	7.5.2 Nuclear Magnetic Resonance	153
	7.5.3 Infrared Spectroscopy	156
	7.5.4 Differential Scanning Calorimetry	157
	7.5.5 Polarimetry	158
7.6	The Influence of the Chemical and Solid-State Composition of Lactose Carriers on the Aerosolisation of DPI Formulations	159
7.7	Conclusions	163
	References	163
8.	Particle Engineering for Improved Pulmonary Drug Delivery Through Dry Powder Inhalers	171
	<i>Waseem Kaialy and Ali Nokhodchi</i>	
8.1	Introduction	172
8.2	Dry Powder Inhalers	172
8.3	Particle Engineering to Improve the Performance of DPIs	172
	8.3.1 Crystallization	173
	8.3.2 Spray-drying	174
	8.3.3 Spray-freeze-drying	177
	8.3.4 Supercritical Fluid Technology	177
	8.3.5 Pressure Swing Granulation (PSG) Technique	178
8.4	Engineered Carrier Particles for Improved Pulmonary Drug Delivery from Dry Powder Inhalers	178
8.5	Relationships between Physical Properties of Engineered Particles and Dry Powder Inhaler Performance	182
	8.5.1 Particle Size	182
	8.5.2 Flow Properties	184
	8.5.3 Particle Shape	185
	8.5.4 Particle Surface Texture	187
	8.5.5 Fine Particle Additives	188
	8.5.6 Surface Area	188
8.6	Conclusions	189
	References	189

9. Particle Surface Roughness – Its Characterisation and Impact on Dry Powder Inhaler Performance	199
<i>Bernice Mei Jin Tan, Celine Valeria Liew, Lai Wah Chan, and Paul Wan Sia Heng</i>	
9.1 Introduction	200
9.2 What is Surface Roughness?	200
9.3 Measurement of Particle Surface Roughness	202
9.3.1 General Factors to Consider During a Measurement	202
9.3.2 Direct Methods to Profile or Visualise Surface Roughness	204
9.3.3 Indirect Measurement of Surface Roughness	206
9.4 Impact of Surface Roughness on Carrier Performance – Theoretical Considerations	206
9.4.1 Mixing and Blend Stability	206
9.4.2 Drug-carrying Capacity	207
9.4.3 Drug Adhesion	207
9.4.4 Drug Detachment	208
9.4.5 Particle Arrangement in Ordered Mixtures After the Addition of Fine Excipient	209
9.5 Particle Surface Modification	210
9.5.1 Spray Drying	210
9.5.2 Solution Phase Processing	211
9.5.3 Crystallisation	213
9.5.4 Sieving	213
9.5.5 Fluid-bed Coating	213
9.5.6 Dry Powder Coating	213
9.6 Conclusion	215
References	215
10. Dissolution: A Critical Performance Characteristic of Inhaled Products?	223
<i>Ben Forbes, Nathalie Hauet Richer, and Francesca Buttini</i>	
10.1 Introduction	223
10.2 Dissolution of Inhaled Products	224
10.2.1 Dissolution Rate	224
10.2.2 Dissolution in the Lungs	224
10.2.3 Case for Dissolution Testing	225
10.2.4 Design of Dissolution Test Systems	226
10.3 Particle Testing and Dissolution Media	226
10.3.1 Particle Collection	226
10.3.2 Dissolution Media	229
10.4 Dissolution Test Apparatus	230
10.4.1 USP Apparatus 1 (Basket)	231
10.4.2 USP Apparatus 2 (Paddle) and USP Apparatus 5 (Paddle Over Disc)	232
10.4.3 USP Apparatus 4 (Flow-Through Cell)	232
10.4.4 Diffusion-Controlled Cell Systems (Franz Cell, Transwell, Dialysis)	233
10.4.5 Methodological Considerations	234

10.5	Data Analysis and Interpretation	235
10.5.1	Modelling	236
10.5.2	Comparing Dissolution Profiles (Model-independent Method for Comparison)	237
10.6	Conclusions	237
	References	238
11.	Drug Delivery Strategies for Pulmonary Administration of Antibiotics	241
	<i>Anna Giulia Balducci, Ruggero Bettini, Paolo Colombo, and Francesca Buttini</i>	
11.1	Introduction	242
11.2	Antibiotics Used for the Treatment of Pneumoniae	243
11.3	Antibiotic Products for Inhalation Approved on the Market	244
11.4	Nebulisation	246
11.5	Antibiotic Dry Powders for Inhalation	250
11.5.1	Tobramycin	251
11.5.2	Capreomycin	252
11.5.3	Gentamicin	253
11.5.4	Ciprofloxacin	254
11.5.5	Levofloxacin	255
11.5.6	Colistimethate Sodium	256
11.6	Device and Payload of Dose	256
11.7	Conclusions	258
	References	258
12.	Molecular Targeted Therapy of Lung Cancer: Challenges and Promises	263
	<i>Jaleh Barar, Yadollah Omid, and Mark Gumbleton</i>	
12.1	Introduction	265
12.2	An Overview on Lung Cancer	266
12.3	Molecular Features of Lung Cancer	268
12.3.1	Tumor Microenvironment (TME)	269
12.3.2	Tumor Angiogenesis	269
12.3.3	Tumor Stromal Components	270
12.3.4	Pharmacogenetic Markers: Cytochrome P450	270
12.4	Targeted Therapy of Solid Tumors: How and What to Target?	271
12.4.1	EPR Effect: A Rational Approach for Passive Targeting	272
12.4.2	Toward Long Circulating Anticancer Nanomedicines	273
12.4.3	Active/Direct Targeting	273
12.4.4	Overcoming Multidrug Resistance (MDR)	273
12.4.5	Antibody-Mediated Targeting	274
12.4.6	Aptamer-Mediated Targeted Therapy	276
12.4.7	Folate Receptor-Mediated Targeted Therapy	276
12.4.8	Transferrin-Mediated Targeted Therapy	276
12.4.9	Targeted Photodynamic Therapy	277
12.4.10	Multimodal Theranostics and Nanomedicines	278

12.5	Final Remarks	278
	References	279
13.	Defining and Controlling Blend Evolution in Inhalation Powder Formulations using a Novel Colourimetric Method	285
	<i>David Barling, David Morton, and Karen Hapgood</i>	
13.1	Introduction	286
13.1.1	Introduction to Blend Pigmentation	287
13.1.2	Previous Work in the Use of Coloured Tracers to Assess Powder Blending	288
13.1.3	Colour Tracer Properties and Approach to Blend Analysis	288
13.2	Uses and Validation	290
13.2.1	Assessment of Mixer Characteristics and Mixer Behaviour	290
13.2.2	Quantification of Content Uniformity and Energy Input	293
13.2.3	Detection and Quantification of Unintentional Milling during Mixing	295
13.2.4	Robustness of Method with Tracer Concentration	295
13.3	Comments on the Applied Suitability and Robustness in of the Tracer Method	296
13.4	Conclusions	297
	Acknowledgements	297
	References	297
14.	Polymer-based Delivery Systems for the Pulmonary Delivery of Biopharmaceuticals	301
	<i>Nitesh K. Kunda, Iman M. Alfagih, Imran Y. Saleem, and Gillian A. Hutcheon</i>	
14.1	Introduction	302
14.2	Pulmonary Delivery of Macromolecules	302
14.3	Polymeric Delivery Systems	303
14.3.1	Micelles	304
14.3.2	Dendrimers	305
14.3.3	Particles	305
14.4	Preparation of Polymeric Nano/microparticles	305
14.4.1	Emulsification Solvent Evaporation	306
14.4.2	Emulsification Solvent Diffusion	307
14.4.3	Salting Out	307
14.5	Formulation of Nanoparticles as Dry Powders	308
14.5.1	Freeze-drying	308
14.5.2	Spray-drying	309
14.5.3	Spray-freeze-drying	309
14.5.4	Supercritical Fluid Drying	310
14.6	Carrier Properties	310
14.6.1	Size	310
14.6.2	Morphology	311
14.6.3	Surface Properties	311
14.7	Toxicity of Polymeric Delivery Systems	311
14.8	Pulmonary Delivery of Polymeric Particles	312

14.9	Conclusions	313
	References	313
15.	Quality by Design: Concept for Product Development of Dry-powder Inhalers	321
	<i>Al Sayyed Sallam, Sami Nazzal, Hatim S. AlKhatib, and Nabil Darwazeh</i>	
15.1	Introduction	322
15.2	Quality Target Product Profile (QTPP)	324
15.3	Critical Quality Attributes (CQA)	324
15.4	Quality Risk Management	325
15.5	Design of Experiments	326
15.6	Design Space	328
15.7	Control Strategies	328
15.8	Continual Improvement	329
15.9	Process Analytical Technology/Application in DPI	329
15.10	Particle Size	329
15.11	Crystallinity and Polymorphism	330
15.12	Scale-up and Blend Homogeneity	331
15.13	Applying of QbD Principles to Analytical Methods	331
15.14	Conclusion	332
	References	332
16.	Future Patient Requirements on Inhalation Devices: The Balance between Patient, Commercial, Regulatory and Technical Requirements	339
	<i>Orest Lastow</i>	
16.1	Introduction	340
	16.1.1 Inhaled Drug Delivery	340
	16.1.2 Patients	340
16.2	Requirements	341
	16.2.1 Patient Requirements	341
	16.2.2 Technical Requirements	343
	16.2.3 Performance Requirements	345
16.3	Requirement Specifications	346
	16.3.1 Requirement Hierarchy	346
	16.3.2 Developing the Requirements	347
16.4	Product Development	350
16.5	Conclusions	351
	References	352
	Index	353