

Contents

Preface XV

List of Contributors XIX

Part One Nanogels, Interfaces, Carriers, and Polymersomes 1

1 Towards Self-Healing Organic Nanogels: A Computational Approach 3 *German V. Kolmakov, Solomon F. Duki, Victor V. Yashin and Anna C. Balazs*

- 1.1 Introduction 3
- 1.2 Methodology 5
- 1.3 Towards Self-Healing Organic Nanogels 8
 - 1.3.1 Response of Samples to Tensile Deformation 8
 - 1.3.2 Stress–Strain Curve 10
 - 1.3.3 Tensile Strength of Nanogel Samples 14
 - 1.3.4 Modeling Viscoelastic Nanogel Particles 15
- 1.4 Conclusions 24
- Acknowledgments 24
- References 25

2 Synthesis and Characterization of Polymeric Nanogels 27 *Yoshifumi Amamoto, Hideyuki Otsuka and Atsushi Takahara*

- 2.1 Introduction 27
- 2.2 Synthesis of Polymeric Nanogels 28
 - 2.2.1 Chemical Nanogels 29
 - 2.2.1.1 Polymerization in Templates 29
 - 2.2.1.2 Crosslinked Micelles and Star Polymers 36
 - 2.2.1.3 Polymer Reaction of Linear Chain, Nanoparticles, and Nanocomplexes 40
 - 2.2.2 Physical Nanogels 42
 - 2.2.2.1 Hydrogen Bonding 42
 - 2.2.2.2 Ionic Bonding and Coordination Bonding 43
 - 2.2.2.3 Hydrophobic Interaction 44
 - 2.2.2.4 Protein Denaturation 46

2.2.3	Degradable Chemical Nanogels	47
2.3	Characterization of Polymeric Nanogels	48
	References	50
3	Stimulus-Responsive Polymers at Nanointerfaces	59
	<i>Roshan Vasani, Martin Cole, Amanda V. Ellis and Nicolas H. Voelcker</i>	
3.1	Introduction	59
3.2	Types of Stimulus-Responsive Polymer	60
3.2.1	Thermoresponsive Polymers	60
3.2.1.1	LCST Polymers	61
3.2.1.2	UCST Polymers	62
3.2.2	pH-Responsive Polymers	62
3.2.2.1	Polycations	62
3.2.2.2	Polyanions	64
3.2.2.3	Polyzwitterions	65
3.2.3	Photoresponsive Polymers	66
3.2.4	Dual and Multi-Stimulus-Responsive Polymers	67
3.3	Generating Stimulus-Responsive Interfaces	69
3.3.1	Covalent Routes	69
3.3.1.1	“Grafting-From” Techniques	69
3.3.1.2	“Grafting-To” Techniques	69
3.3.2	Noncovalent Routes	70
3.3.3	Interfacing SRPs with Flat and Porous Substrates	71
3.3.4	Nanoparticles and Nanotubes	72
3.3.4.1	Silica, Metal, and Metal Oxide Nanoparticles	72
3.3.4.2	Quantum Dots	73
3.3.4.3	Micelles	74
3.3.4.4	Liposomes	75
3.3.4.5	Nanotubes	76
3.4	Applications of Stimulus-Responsive Polymers at Interfaces	77
3.4.1	Controlled Drug Delivery	77
3.4.2	Control of Biointerfacial Interactions	79
3.4.3	Microfluidic Valves	82
3.4.4	Molecular Separation	85
3.5	Summary and Future Perspectives	86
	List of Abbreviations	88
	References	90
4	Self-Assembled Peptide Nanostructures and Their Controlled Positioning on Surfaces	105
	<i>Maria Farsari and Anna Mitraki</i>	
4.1	Introduction	105
4.2	Vertical and Horizontal Alignment on Surfaces	106
4.3	Printing Using Inkjet Technology	107
4.4	Vapor Deposition Methods	107

4.5	Positioning Using Dielectrophoresis	110
4.6	Laser Patterning	111
4.6.1	Laser-Induced Forward Transfer	111
4.6.1.1	Direct Transfer	112
4.6.1.2	Self-Assembly of Peptides on LIFT-Patterned Biotin	113
4.6.2	Nonlinear Lithography	114
4.7	Summary and Perspectives	117
	Acknowledgments	117
	References	117
5	Multifunctional Pharmaceutical Nanocarriers: Promises and Problems	121
	<i>Vladimir P. Torchilin</i>	
5.1	Introduction	121
5.2	Established Paradigms: Longevity and Targetability	122
5.2.1	Polymers for Longevity	123
5.2.2	Long-Circulating Liposomes	124
5.2.3	Nonliposomal Long-Circulating DDSs	126
5.2.4	Combination of Longevity and Targeting	127
5.3	Stimuli-Sensitivity and Intracellular Targeting	130
5.3.1	pH-Sensitive Systems	130
5.3.2	Temperature-Sensitive Systems	133
5.3.3	Magnetically Sensitive Systems	133
5.3.4	Ultrasound-Sensitive Systems	134
5.3.5	Redox-Sensitive Systems	135
5.3.6	Intracellular Delivery of Pharmaceutical Nanocarriers	135
5.4	A New Challenge: Theranostics	138
	References	141
6	Polymersomes and Their Biomedical Applications	157
	<i>Giuseppe Battaglia</i>	
6.1	Introduction	157
6.2	The Chemistry of Polymersomes	158
6.3	Polymersomes: Physico-Chemical Properties	160
6.3.1	Membrane Conformations	160
6.3.2	Responsive Polymersomes	163
6.3.3	Surface Chemistry of the Polymersomes	164
6.4	Polymersomes Formation and Preparation	167
6.5	Biomedical Applications	169
6.5.1	Medical Imaging	169
6.5.2	Cancer Therapy	172
6.5.3	Polymersomes as Delivery Vectors	172
6.5.4	Nanoreactors	172
6.5.5	Artificial Cells and Organelles	173
6.5.6	Gene Therapy	174

6.6	Conclusions	175
	References	175

Part Two Nanoparticles 185

7	Synthetic Approaches to Organic Nanoparticles	187
	<i>Stefan Köstler and Volker Ribitsch</i>	
7.1	Introduction	187
7.1.1	Types of Organic Particle and Scope of This Chapter	188
7.1.2	Characteristics of Organic Nanoparticles	189
7.2	Methods of Organic Nanoparticle Preparation	190
7.2.1	Top-Down Approaches to Organic Nanoparticles	190
7.2.1.1	Reduction of Particle Size by Mechanical Forces	190
7.2.1.2	Lithographic Methods	193
7.2.2	Bottom-Up Approaches to Organic Nanoparticles	194
7.2.2.1	Solution-Based Bottom-Up Methods	194
7.2.3	Vapor Condensation-Based Methods	206
7.3	Application of Organic Nanoparticles	207
7.4	Summary and Future Perspectives	208
	References	210
8	Organic Nanoparticles Using Microfluidic Technology for Drug-Delivery Applications	221
	<i>Wei Cheng, Lorenzo Capretto, Martyn Hill and Xunli Zhang</i>	
8.1	Introduction	221
8.1.1	Batch Synthesis of Organic Nanoparticles	222
8.1.2	Specifications of Reactors: Macroscale versus Microscale Syntheses	223
8.1.3	Properties and Application of Organic Nanoparticles for Drug Delivery	226
8.2	Microfluidic Synthesis of Organic Nanoparticles	227
8.2.1	Overview: Unique Features of Microfluidic Reactors for the Controlled Synthesis of Organic Nanoparticles	227
8.2.2	Microfluidic Reactors for Organic Nanoparticles	228
8.2.2.1	Emulsions	228
8.2.2.2	Nanoprecipitation	230
8.2.2.3	Liposomes	233
8.2.3	Controlled Operating Parameters of Microfluidic Reactors	234
8.2.3.1	Flow Velocity, Microfluidic Dimension, and Mixing Time	235
8.2.3.2	Mixing Time, Aggression Time, and the Damkohler Number	236
8.2.4	Synthetic Operations	238
8.2.4.1	Micromixing	238
8.2.4.2	Online Process of Various Reactants	239
8.2.4.3	Thermal Control and Heat Transfer	240
8.2.4.4	Spatial and Temporal Kinetic Control	242

8.2.4.5	Self-Assembly Mechanism and Competitive Reaction	243
8.3	Microfluidic-Related Organic Nanoparticles for Drug Delivery	244
8.3.1	Drug Encapsulation and Release	245
8.3.2	Stimuli-Responsive Release	246
8.3.3	Nanomedicine Delivery to Target Cells	248
8.4	Conclusions and Prospective Study	250
8.4.1	Materials, Design, and Fabrication	250
8.4.2	High-Throughput Microfluidic Processes	251
8.4.3	Controlled Synthesis of Organic Nanoparticles	252
8.4.4	Spatial and Temporal Kinetics Investigation of Nanoparticles	253
	References	253
9	Lipid–Polymer Nanomaterials	259
	<i>Corbin Clawson, Sadik Esener and Liangfang Zhang</i>	
9.1	Introduction	259
9.2	Lipopolymers	260
9.2.1	Synthesis and Fabrication of Lipopolymers	261
9.2.2	Properties and Characterization of Lipopolymers	263
9.2.3	Applications of Lipopolymers in the Life Sciences	263
9.3	Lipid–Polymer Hybrid Nanoparticles	264
9.3.1	Synthesis and Fabrication of Lipid–Polymer Hybrid Nanoparticles	266
9.3.1.1	Synthesis of Polymer-Protected Lipidic Nanoparticles	266
9.3.1.2	Synthesis of Lipid-Coated Polymeric Nanoparticles	269
9.3.2	Characterization of Lipid–Polymer Hybrid Nanoparticles	271
9.3.3	Applications of Lipid–Polymer Hybrid Nanoparticles	275
9.4	Lipid–Polymer Films and Coatings	277
9.4.1	Synthesis of Lipid–Polymer Films and Coatings	277
9.4.2	Characterization of Lipid–Polymer Films and Coatings	278
9.4.3	Applications of Lipid–Polymer Films and Coatings	279
9.5	Summary and Future Perspective	280
	References	281
10	Core–Shell Polymeric Nanomaterials and Their Biomedical Applications	285
	<i>Ziyad S. Haidar and Maryam Tabrizian</i>	
10.1	Introduction	285
10.2	Core–Shell Nanomaterials of Biomedical Interest	286
10.3	Core–Shell Polymeric Nanoparticles	287
10.3.1	Biodegradable Core–Shell Polymeric Nanoparticles	288
10.3.2	Core–Shell Colloids	290
10.3.3	Surface Properties and Modification Techniques	292
10.4	Biomedical Applications of Core–Shell Polymeric Nanostructures	293
10.4.1	Bioimaging, Biological, and Cellular Labeling	293
10.4.1.1	Cytotoxicity of QDs	295
10.4.2	Glucose Monitoring and Biosensing in Diabetes Mellitus	295

10.4.3	Drug Delivery	296
10.4.3.1	Natural Polymer-Based Drug-Delivery Systems: Layer-by-Layer Self-Assembly	297
10.4.3.2	Synthetic and Composite Drug-Delivery Systems: Functionalized Nanoshells	298
10.4.4	Cancer	300
10.4.5	Miscellaneous Applications	302
10.5	Future Prospects	302
	Acknowledgments	303
	References	303
11	Polymer Nanoparticles and Their Cellular Interactions	311
	<i>Volker Mailänder and Katharina Landfester</i>	
11.1	Introduction	311
11.1.1	Nanoparticle Synthesis by Miniemulsion	313
11.2	Nanoparticles as Labeling Agents for Cellular Therapeutics	314
11.2.1	Experimental Polystyrene Nanoparticles with Iron Oxide (Magnetite) and a Fluorescent Dye as Reporter	314
11.2.2	Gadolinium as a Reporter in Nanoparticles	316
11.3	Uptake of Polymeric Nanoparticles into Cells	317
11.3.1	Influence of Polymer on Uptake	318
11.3.1.1	Polystyrene	318
11.3.1.2	Polyisoprene	318
11.3.1.3	Nanoparticles Composed of Different Proportions of Polystyrene and Polyisoprene	320
11.3.1.4	Poly (n-butylcyanoacrylate) (PBCA) Nanoparticles	320
11.3.1.5	Polyester Nanoparticles: Poly(ϵ -Caprolactone), Poly(D,L-Lactide), Poly(D,L-lactide-co-Glycolide)	321
11.3.2	Influence of Transfection Agents: Surface Modifications of Nanoparticles by Covalently Linked Groups	324
11.3.2.1	Functionalization of Nanoparticle Surfaces by Carboxylic and Amino Side Groups	324
11.3.3	Size Dependency of Cellular Uptake	328
11.4	Influence of Nanoparticles on (Stem) Cell Differentiation	329
11.5	Endocytosis	331
11.6	Summary	334
	References	335
12	Radiopaque Polymeric Nanoparticles for X-Ray Medical Imaging	343
	<i>Shlomo Margel, Anna Galperin, Hagit Aviv, Soenke Bartling and Fabian Kiessling</i>	
12.1	Introduction	343
12.2	Synthesis of the Monomer MAOETIB	345
12.3	Radiopaque Iodinated P(MAOETIB) Nanoparticles	346

12.3.1	Synthesis of the P(MAOETIB) Nanoparticles	346
12.3.2	Characterization of the P(MAOETIB) Nanoparticles	346
12.3.2.1	Effect of the MAOETIB Concentration	347
12.3.2.2	Effect of the Initiator Concentration	348
12.3.2.3	Effect of the Surfactant Concentration	349
12.3.3	<i>In Vitro</i> X-Ray Visibility of the P(MAOETIB) Nanoparticles	349
12.3.4	<i>In Vivo</i> X-Ray Visibility of the P(MAOETIB) Nanoparticles: Preliminary Studies	351
12.4	Radiopaque Iodinated P(MAOETIB–GMA) Copolymeric Nanoparticles	351
12.4.1	Synthesis of P(MAOETIB–GMA) Copolymeric Nanoparticles	353
12.4.2	Influence of the Weight Ratio [MAOETIB]/[GMA] on the Iodine Content and Size and Size Distribution of the Copolymeric Nanoparticles	353
12.4.3	Characterization of the P(MAOETIB-GMA) Nanoparticles Prepared at a Weight Ratio [MAOETIB]/[GMA] of 99/1	355
12.4.4	<i>In Vivo</i> X-Ray Visibility of the P(MAOETIB-GMA) Nanoparticles	358
12.5	Summary	361
	References	362

13 Solid Lipid Nanoparticles to Improve Brain Drug Delivery 365

Paolo Blasi, Aurélie Schoubben, Stefano Giovagnoli, Carlo Rossi and Maurizio Ricci

13.1	Introduction	365
13.2	The General Problem of Brain Drug Delivery	366
13.2.1	Basic Brain Physiology	366
13.2.2	Brain Drug-Delivery Strategies	368
13.3	Solid Lipid Nanoparticles for Brain Drug Delivery	369
13.3.1	General Information	369
13.3.2	Physico-Chemical Aspects of Lipid Packing and SLN Structure	371
13.3.3	Surfactants and SLNs for Brain Targeting	375
13.3.4	Evidence of Brain Drug Accumulation	376
13.3.5	SLN Potentiality in Brain Imaging	380
13.3.6	Toxicity Issues	382
13.4	Concluding Remarks	384
	References	384

Part Three Nanoscaffolds, Nanotubes, and Nanowires 395

14 Architectural and Surface Modification of Nanofibrous Scaffolds for Tissue Engineering 397

Jerani T.S. Pettikiriarachchi, Clare L. Parish, David R. Nisbet and John S. Forsythe

14.1	Introduction	397
------	--------------	-----

14.2	Tissue Engineering Scaffolds	397
14.3	Nanofibrous Scaffolds	399
14.4	Electrospinning	399
14.5	Cellular Interactions with Polymeric Nanofibers	401
14.6	Optimizing Fiber and Scaffold Architecture	403
14.6.1	Fiber Diameter	403
14.6.2	Fiber Orientation	404
14.6.3	Core–Shell Fibers	405
14.6.4	Pore Size	407
14.6.5	Layering Fibers	408
14.7	Optimizing the Fiber Surface	410
14.7.1	Polymer Blending	410
14.7.2	Coating Fibers	411
14.7.3	Chemical Modification of Fibers	412
14.7.4	Polymer Grafting onto Surfaces	413
14.7.5	Plasma Treatment of Fibers	414
14.7.6	Biomolecule Attachment	416
14.8	Challenges with Fibrous Scaffolds in Tissue Engineering	417
14.9	Summary	419
14.10	Future Perspectives	419
	References	420

15 Controlling the Shape of Organic Nanostructures: Fabrication and Properties 429

Rabih O. Al-Kaysi and Christopher J. Bardeen

15.1	Introduction	429
15.2	Milling, Soft-Templating, and Other Methods for Preparing Organic Nanostructures	431
15.2.1	Mechanical Milling	431
15.2.2	Vapor Growth	431
15.2.3	Supramolecular Self-Assembly	432
15.2.4	Reprecipitation	432
15.2.5	Electrospinning	434
15.2.6	Emulsification	434
15.3	Hard-Templating Methods for Preparing Organic Nanostructures	434
15.3.1	AAO Templates	435
15.3.2	Template-Assisted Synthesis of Polymer Nanowires, Nanotubes, and Nanorods	436
15.3.3	Template-Assisted Synthesis of Small-Molecule Nanowires, Nanotubes, and Nanorods	437
15.3.3.1	Solution-Based Template Wetting Method	437
15.3.3.2	Melting–Recrystallization Template Wetting Method	437
15.3.3.3	Sublimation Method	438
15.3.3.4	Electrophoretic Deposition Method	438
15.3.3.5	Solvent-annealing Method	439

15.4	Applications of Noncovalent Organic Nanostructures	444
15.4.1	Electronic and Optical Devices	444
15.4.2	Chemical Sensing	445
15.4.3	Photomechanical Actuation	446
15.5	Future Challenges and Outlook	448
	Acknowledgments	449
	References	449
16	Conducting Polymer Nanowires and Their Biomedical Applications	455
	<i>Robert Lee and Adam K. Wanekaya</i>	
16.1	Introduction	455
16.2	Fabrication of Conducting Polymer Nanowires	457
16.3	Surface Modification of Conducting Polymer Nanowires	458
16.4	Assembly/Alignment of Conducting Polymer Nanowires	461
16.5	Biomedical Applications of Conducting Polymer Nanowires	462
16.5.1	Sensing and Detection	462
16.5.1.1	Proteins and Disease Markers	462
16.5.1.2	Detection of Bacteria	464
16.5.1.3	Detection of Small Molecules	466
16.5.1.4	Detection of Heavy-Metal Ions and Pesticides	466
16.5.2	Drug Delivery and DNA Carriers	467
16.6	Summary and Future Perspectives	468
	References	468
17	Organic Nanowires and Nanotubes for Biomedical Applications	473
	<i>Keunsoo Jeong and Chong Rae Park</i>	
17.1	Introduction	473
17.2	Fabrication of Organic Nanowires and/or Nanotubes	474
17.2.1	Self-Assembly Processes	474
17.2.2	Template-Based Synthetic Processes	476
17.2.3	Nanotubes Based on Modified CNTs	478
17.3	Biomedical Applications of Nanowires and/or Nanotubes	480
17.3.1	Biosensors	480
17.3.2	Cancer Therapy	482
17.3.2.1	CNTs for Photothermal Therapy	482
17.3.2.2	CNTs for Radiofrequency Ablation	483
17.3.3	Optical Bioimaging	484
17.4	Summary	487
	References	487
18	Rosette Nanotubes for Targeted Drug Delivery	493
	<i>Sarabjeet Singh Suri, Hicham Fenniri and Baljit Singh</i>	
18.1	Introduction	493

18.2	Peptide-Based Nanotubes	494
18.3	Self-Assembling Rosette Nanotubes	495
18.3.1	Self-Assembly Peptides	495
18.3.2	G [^] C Motif Self-Assembly: Novel Helical Rosette Nanotubes	495
18.3.2.1	Novelty	495
18.3.2.2	G [^] C Motif Self-Assembly Process	496
18.3.2.3	Built-In Strategy for Manipulating the Properties of RNTs	496
18.3.3	Biological Functions of RNTs	498
18.4	Stability Issues	502
18.5	Nanomaterials for Receptor-Mediated Targeting	502
18.5.1	Human Epidermal Growth Factor Receptor (EGFR)	503
18.5.2	Vasoactive Pituitary Adenylate Cyclase (VPAC)-Activating Peptide Receptors	503
18.5.3	Transferrin Receptor (TfR)	503
18.5.4	Folate Receptor (FR)	504
18.6	Ethical Issues and Future Directions	504
18.7	Conclusions	505
	References	505

Index	509
--------------	-----