Controlled Release Systems
Advances in Nanobottles and Active Nanoparticles

edited by
Alexander van Herk
Jacqueline Forcada
Giorgia Pastorin
Controlled Release Systems
Controlled Release Systems

Advances in Nanobottles and Active Nanoparticles

edited by
Alexander van Herk
Jacqueline Forcada
Giorgia Pastorin
# Contents

*Preface*  

**Part I  Fundamentals**

1. **General Introduction and Definitions**  
   *Alexander van Herk*  
   1.1 Introduction to Controlled Release Systems: Advances in Nanobottles and Active Nanoparticles  
   1  
   1.2 Concept of the Book  
   2  
   1.3 Relevant Definitions  
   3  
   1.3.1 Particle-Related Definitions  
   3  
   1.3.2 Polymerization Processes Related to Nanoparticle Formation  
   6  
   1.4 Conclusions  
   8

2. **Responsive Polymers: Types and Properties**  
   *Alexander van Herk*  
   2.1 General Principles of Polymerization Reactions  
   9  
   2.1.1 Radical Formation in Free-Radical Polymerization  
   11  
   2.1.2 Initiation  
   12  
   2.1.3 Propagation  
   12  
   2.1.4 Termination  
   12  
   2.2 Temperature-Responsive Polymers  
   16  
   2.3 pH-Responsive Polymers  
   17  
   2.4 Salt-Responsive Polymers  
   18  
   2.5 Electromagnetic Radiation-Responsive Polymers  
   19  
   2.6 Multiresponsive Systems  
   19

3. **Responsive Polymeric Nanoparticles**  
   *Jacqueline Forcada*  
   3.1 Introduction  
   21  
   3.2 Design and Production of RPNPs  
   23  
   3.3 Conclusions  
   35
4. Preparation of Micelles, Vesicles, and Liposomes  37
   Joan Estelrich
   4.1 Preparation of Micelles  38
   4.2 Preparation of Vesicles and Liposomes  38
      4.2.1 Thin-Film Hydration  39
      4.2.2 Ultrasonic Irradiation  39
      4.2.3 Homogenization Techniques  40
      4.2.4 Replacement of Organic Solvents by Aqueous Media  41
      4.2.5 Supercritical Fluid Methods  42
      4.2.6 Microfluidic Methods  43

5. Synthetic Strategies for Synthesis of Polymer Nanoparticles  45
   Alexander van Herk
   5.1 Solution Polymerization  46
   5.2 Precipitation Polymerization  47
   5.3 Dispersion Polymerization  48
   5.4 Emulsion Polymerization  50
   5.5 Miniemulsion Polymerization  53
   5.6 Microemulsion Polymerization  56
   5.7 Vesicle Polymerization and Vesicle-Templating Polymerization  58
   5.8 Polymerization-Induced Self-Assembly  59

6. Synthesis of Nanobottles  63
   Alexander van Herk
   6.1 Diffusion of Water and Active Ingredients through a Polymeric Wall  64
   6.2 The Concept of the Nanobottle  65
   6.3 Nanobottles  66
   6.4 Conclusion  67

7. General Criteria for the Selection of Nanoparticles for Certain Applications  69
   Dai Thien Nhan Tram and Giorgia Pastorin
   7.1 Introduction  69
   7.2 Is Passive Targeting indeed “Passive”?  70
   7.3 Nanoparticles as Delivery Vehicles  76
7.3.1 The Raid on Chemoresistance: Combination Therapy and siRNA 76
7.3.2 Charismatic Mediators: What It Takes 80
7.3.3 Cargo Release on Demand 81
7.3.3.1 Thermal trigger 82
7.3.3.2 pH trigger 83
7.3.3.3 Enzymatic trigger 84
7.3.3.4 Ultrasonic trigger 84
7.4 Without the Cargo, NPs Are Still Useful! 90
7.4.1 Organic NPs 90
7.4.2 Inorganic NPs 91
7.5 Conclusion 94

Part II State of the Art

8. Microgels and Nanogels for Drug Delivery 97

Niels M. B. Smeets and Todd Hoare

8.1 Introduction 97
8.2 Design Aspects 100
8.2.1 Microgel Size 101
8.2.2 Microgel Morphology 101
8.2.3 Degradability 102
8.2.4 Drug–Microgel Interactions 102
8.2.5 Protein Adsorption 103
8.2.6 Biocompatibility and Toxicity 103
8.2.7 Targeting 104
8.2.8 Stimulus Response 104
8.3 Stimuli-Responsive Drug Delivery Vehicles 105
8.3.1 Thermoresponsive Microgels 105
8.3.1.1 Preparation methods 105
8.3.1.2 Poly(N-isopropylacrylamide) 106
8.3.1.3 Poly(oligoethylene glycol (meth)acrylate) 113
8.3.1.4 Poly(N-vinyl caprolactam) 115
8.3.2 pH-Responsive Microgels 116
8.3.2.1 Preparation methods 116
8.3.2.2 Cationic (basic) microgels 118
8.3.2.3 Anionic (acidic) microgels 123
8.3.3 Chemoresponsive Microgels 125
8.3.3.1 Glucose-responsive microgels 125
8.3.3.2 Redox-responsive microgels 128
8.3.3.3 CO$_2$-responsive microgels 130
8.3.3.4 Enzyme-responsive microgels 131
8.3.3.5 Antigen-responsive microgels 132
8.3.4 Light-Responsive Microgels 134
8.3.5 Microgel-Based Nanocomposites 136
  8.3.5.1 Magnetic microgels 137
  8.3.5.2 Near-infrared-responsive microgels 139
  8.3.5.3 Microgel pore-filled membranes 140
  8.3.5.4 Hydrogel–microgel composites 141
8.4 Future Outlook 142

9. Magnetic Particles for Cancer Diagnosis and Drug Delivery 145

Naveed Ahmed, Ahmad Bitar, Michele Karoline Lima, Nasir Mahmood Ahmad, Hatem Fessi, and Abdelhamid Elaissari

9.1 Introduction 146
9.2 Nanoparticles in Drug Delivery 150
  9.2.1 Magnetic Particles 153
  9.2.2 Magnetic Silica Particle Preparation and Drug Delivery 155
    9.2.2.1 Controlled release from silica magnetic particles 155
9.3 Cancer Diagnosis 159
  9.3.1 In vivo Tumor Diagnosis with Special Focus on Magnetic Resonance Imaging 160
  9.3.2 In vitro Diagnostics 164
  9.3.3 Treatment of Cancer and Classification of Cancer Therapeutic Agents 168
    9.3.3.1 Conventional therapies 169
9.3.3.2 Nanoparticle-based therapies 173
9.4 Theranostics Application of Nanoparticles 174
9.5 Toxicities of Nanomaterials 176
9.6 Conclusion and Future Perspectives 178

10. Micelles, Liposomes, Bubble Liposomes, the Layer-by-Layer Approach, and Nanocapsules 179
Joan Estelrich and Alexander van Herk

10.1 Micelles 179
10.1.1 Small-Molecule Micelles 180
10.1.2 Block-Copolymer Micelles 180
10.1.3 Preparation of Micelles 181

10.2 Liposomes 181
10.2.1 Classification of Liposomes 182
10.2.2 Materials Used in the Preparation of Liposomes 184
10.2.3 Characterization of Liposomes 187

10.3 Bubble Liposomes 189

10.4 Layer-by-Layer Approach 191

10.5 Nanocapsules 192
10.5.1 Size of the Capsules and Composition and Thickness of the Wall 194

11. Inorganic Nanoparticles in New Upcoming Biomedical Applications 197
Manuel António Martins, Sónia Oliveira Pereira, and Tito Trindade

11.1 Introduction 198

11.2 Gold and Silver Nanoparticles 199
11.2.1 Gold Nanoparticles 199
11.2.1.1 Au NPs as sensors 200
11.2.1.2 Au NPs as biolabels 202
11.2.1.3 Au NPs in drug delivery 203

11.2.2 Silver Nanoparticles 203
11.2.2.1 Ag NPs for antimicrobial applications 204

11.3 Quantum Dots 205
11.3.1 Cadmium and Zinc Chalcogenides 205
Contents

11.3.1.1 QDs as biolabels 210
11.3.1.2 QDs in PDT 213
11.3.2 Carbon-Based Nanomaterials 213
11.4 Metal Oxides 214
11.4.1 Zinc Oxide 214
11.4.2 Iron Oxides 216
   11.4.2.1 Iron oxide NPs in bioseparation 217
   11.4.2.2 Iron oxide NPs in bioimaging 218
   11.4.2.3 Iron oxide NPs in drug delivery 219
   11.4.2.4 Iron oxide NPs in hyperthermia 219
11.5 Biofunctionalization Strategies of Inorganic Nanoparticles 219
   11.5.1 Conjugation via Covalent Binding 220
      11.5.1.1 Coupling using carbodiimides 220
      11.5.1.2 Coupling using maleimides 221
      11.5.1.3 Coupling by “click chemistry” 222
      11.5.1.4 Coupling via disulfide 223
   11.5.2 Specific Interaction between Biological Intermediates 224
      11.5.2.1 Coupling mediated by avidin–biotin binding 224
      11.5.2.2 Coupling using histidine residues 224
   11.5.3 Nonspecific Binding of Proteins 225
   11.5.4 Electrostatic Interaction 225
11.6 Conclusions 226

12. Carbon Nanotubes as Nanocarriers for Controlled Drug Delivery 229

Cécilia Ménard-Moyon and Tatiana Da Ros

12.1 Introduction 229
12.2 Endohedral Functionalization of Carbon Nanotubes for Controlled Release of Drugs 232
   12.2.1 Sustained Release of Encapsulated Drugs 233
12.2.2 Nanobottle Systems 235
12.2.3 Magnetically Induced Release of Encapsulated Drugs 238
12.2.4 NIR-Induced Release of Encapsulated Drugs 240
12.2.5 Electrically Controlled Release of Encapsulated Drugs 242
12.3 Stimulus-Induced Release of Drugs Adsorbed on Carbon Nanotubes 243
12.3.1 pH-Induced Release of Drugs 243
12.3.2 NIR-Induced Release 248
12.3.3 Thermosensitive Release 250
12.4 Functionalization of Carbon Nanotubes with Drugs via Enzyme-Cleavable Linkers 251
12.4.1 Disulfide Bonds 252
12.4.2 Peptide Linkers 254
12.4.3 Ester Bonds 255
12.4.4 Carbamate Bonds 256
12.5 Conclusion 257

13. Dendrimers 259
Karnaker R. Tupally, Ganesh R. Kokil, Sachin S. Thakur, Prachi Singh, and Harendra S. Parekh

13.1 Introduction 260
13.1.1 The Origin of Dendrimers 260
13.1.2 Dendrimer Architecture 261
13.1.3 Dendrimer Synthesis 261
13.2 Dendrimers: Fundamentally Interacting Architecture 263
13.2.1 Dendrimer–Lipid Membrane Interactions 263
13.2.2 Dendrimer–Protein Interactions 264
13.2.3 Dendrimer–Gene Interactions 265
13.3 Applications of Dendrimers: A Bird’s-Eye View 267
13.3.1 Delivery Vectors for Therapeutics: Drugs and Genes 267
13.3.1.1 Encapsulation and complexation 267
13.3.1.2 Chemical conjugation 269
13.3.2 Target Specificity 271
  13.3.2.1 PEGylation 271
  13.3.2.2 Folic acid conjugation 273
  13.3.2.3 Monoclonal antibody conjugation 273
  13.3.2.4 RGD–peptide conjugation 274
  13.3.2.5 Glycosylation 275
13.3.3 Theranostics 275
  13.3.3.1 Boron neutron capture therapy 276
  13.3.3.2 Photodynamic therapy 277
  13.3.3.3 Molecular probes 278
  13.3.3.4 Contrast agents 279
  13.3.3.5 Dendrimers as drug molecules 282
13.4 Concluding Remarks 284

14. Stimuli- Reactive Nanoparticles for Drug Targeting 287
  Aditi Jhaveri, Tao Wang, and Vladimir Torchilin
  14.1 Introduction 287
  14.2 Tumor Microenvironment and Nanoparticles 288
  14.3 Tumor-Targeting Strategies 291
    14.3.1 Passive Targeting 291
    14.3.2 Active Targeting 294
    14.3.3 Organelle-Specific Targeting 298
  14.4 Stimuli-Responsive Drug Release in Tumors 305
    14.4.1 Internal Stimuli 306
      14.4.1.1 pH 306
      14.4.1.2 Redox potential 313
      14.4.1.3 Tumor-expressed or overexpressed enzymes 318
      14.4.1.4 Temperature (hyperthermia) 324
    14.4.2 External Stimuli 328
      14.4.2.1 Light 328
      14.4.2.2 Ultrasound 336
      14.4.2.3 Magnetic field 340
  14.5 Multifunctional Nanocarriers 346
  14.6 Conclusions and Future Outlook 348
15. Potential Applications of Nanotechnologies to Neurodegenerative Diseases (Alzheimer’s and Parkinson’s Diseases) 351

Joan Estelrich and Gurutz Linazasoro

15.1 Introduction 351

15.2 Alzheimer’s Disease 356

15.2.1 Inhibition of Aβ Assembly by Association Colloids (Micelles and Liposomes) 359

15.2.2 Nanotechnologies for Alzheimer’s Disease 362

15.2.2.1 Nanotechnologies for AD diagnosis 362

15.2.2.2 Nanotechnologies for detection of AD biomarkers in biological fluids 364

15.2.2.3 Nanotechnologies for AD treatment 366

15.3 Parkinson’s Disease 371

15.3.1 Nanotechnology and the Diagnosis of PD 372

15.3.2 Therapeutic Applications of Nanotechnology 373

15.3.2.1 New routes of administration of drugs and other molecules 373

16. Nanotherapeutics for Cardiovascular, Pulmonary, and Hematologic Diseases 385

Denis B. Buxton

16.1 Introduction 385

16.2 Cardiovascular Disease 386

16.2.1 Atherosclerosis and Vascular Injury 386

16.2.2 Myocardial Infarction and Heart Failure 391

16.2.3 Peripheral Arterial Disease 398

16.2.4 Stroke 401

16.2.5 Vascular Grafts 401

16.3 Lung Disease 404
16.3.1 Asthma and Chronic Obstructive Pulmonary Disease 404
16.3.2 Cystic Fibrosis 406
16.3.3 Tuberculosis 409
16.3.4 Other Pulmonary Infections 412
16.4 Hematologic Diseases 413
16.4.1 Thrombosis and Thrombolysis 413
  16.4.1.1 Thrombolysis 413
  16.4.1.2 Hemostasis 416
  16.4.1.3 Inherited coagulation disorders 419
16.4.2 Sepsis 420
16.4.3 Hematologic Malignancies 422
16.5 Conclusions 423

17. Immunotherapy and Vaccines 425
Johanna Poecheim and Gerrit Borchard

17.1 Introduction 425
17.2 The Immune System 426
  17.2.1 The Innate Immune System 427
  17.2.2 The Adaptive Immune System 428
  17.2.3 Immunological Memory 429
17.3 Nanotechnology in Vaccines 429
  17.3.1 Particle Characteristics Interacting with the Immune System 429
    17.3.1.1 Particle size 430
    17.3.1.2 Charge 434
    17.3.1.3 Immunogenicity of nanoparticle materials 437
  17.3.2 Immune Receptor Targeting and Antigen Delivery 441
  17.3.3 Current Nanoparticle Vaccines on the Market and in Clinical Studies 443
17.4 Conclusions 446

Bibliography 449

Index 549
This book focuses on active nanoparticles, bringing together two interesting areas, nanoparticles and responsive polymers. This is due to the fact that nanoparticles are increasingly popular as carriers of therapeutic agents and as diagnostic tools.

The book consists of two parts: an introductory text targeting the fundamentals of the synthesis and characterization of active nanoparticles for controlled release of drugs and other molecules as well as nanoparticles containing inorganic moieties for therapeutic purposes. This part also includes a chapter on how to select particles for certain applications. The second part of the book contains contributions from experts in the field giving a state-of-the-art overview on the most intriguing biomedical applications of functionalized nanoparticles, with both contributions focusing on a class of particles as well as nanoparticulate formulations targeting certain diseases.

The book defines the new field of nanobottles along with the first scarce examples of such structures. It would be useful for students and researchers in the field of nanoparticle preparation and controlled release systems and bio-pharmaceutical scientists with an interest in the development of new therapeutic strategies.

Alexander van Herk
Jacqueline Forcada
Giorgia Pastorin
Autumn 2015