Christine Vauthier · Gilles Ponchel
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A Guide for their Design, Preparation and Development

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Foreword

Polymers are macromolecules composed of many repeated subunits of different nature, leading to a broad range of compositions and properties. Both synthetic and natural polymers play a major role in the life sciences. Whereas *natural polymers* (nucleic acids, proteins, peptides) are the building blocks of biological structures and functions and are the support of genetic and epigenetic events, the polymerization of monomers through various modern synthetic routes (e.g., controlled anionic or radical polymerization, ring-opening polymerization, etc.) enables the design of *synthetic polymers* with unique physicochemical properties, including robustness, viscoelasticity, and a tendency to form glasses and semicrystalline structures rather than crystals. They may be combined to form tailor-made supramolecular architectures. The versatility of these polymer structures and the resulting properties offer many applications in the medical and pharmaceutical fields. «Smart» polymers, designed to undergo reversible physical or chemical changes in response to environmental stimuli (such as temperature, light, magnetic or electric field, pH, ionic strength or enzymes) also hold great promise as drug delivery systems, tissue engineering scaffolds, cell culture supports, bioseparation devices, sensors, and even actuators systems. Because of their extraordinary versatility, there is an increased interest to use polymers, either natural or synthetic, as transporter material for the design of nanomedicines. The encapsulation of a drug into polymer-based nanoparticles allows it, indeed, to protect the drug from degradation/metabolization; to defend healthy cells and tissues from drug's eventual toxicity; to improve drug bioavailability at the site of action (i.e., diseased cells); and to allow better intracellular penetration and trafficking for drugs that cannot cross the cell membrane. The ultimate goal is to increase the drug therapeutic index by improving the pharmacological efficacy while also reducing its toxicity. Of course, the design of polymers for the construction of nanodevices is key to making safe and efficient nanomedicines. When intravenous administration is considered, the use of biodegradable polymers is mandatory to avoid intracellular polymer overloading and thesaurismosis. The possibility to control the degradation kinetics of a drug subsequently allows tailoring the drug release according to its

therapeutic aim. The surface properties of the polymer when formulated as nanoparticles is another important issue to monitor and avoid excessive complement activation, protein aggregation or thromboembolic event after intravenous infusion. Therefore, surface functionalization of nanoparticles should help to hinder such events or, to better address the nanomedicine in a very specific way toward the targeted cells by decoration with specific ligands. Surface functionalization of polymer-based nanoparticles may also permit the bioadhesion along epitheliums or endotheliums or even the translocation through biological barriers, including the blood–brain barrier. Other approaches, albeit less advanced, include the development of polymer nanoparticles combining both therapeutic and imaging functionalities and even nanodevices containing two or more drugs for synergistic pharmacological efficacy.

The book edited by Drs. Vauthier and Ponchel, **Polymer Nanoparticles for Nanomedicines: A Guide for their Design, Preparation and Development**, represents a crucial and comprehensive work of information with highly advanced research about the construction of polymer nanoparticles. The logical succession of the different chapters runs in the following way.

Part I is devoted to the different methods for manufacturing nanoparticles with clear explanations about the physicochemical principles allowing their formation. Nanoparticles may be built using various preparation methodologies. For instance, the so-called nanoprecipitation technique based on the "Ouzo" effect, the flash nanoprecipitation process, and the solvent evaporation methods with their numerous adaptations, are well explained. Apart from being prepared by pre-formed polymers, nanoparticles may be constructed through the in situ polymerization of monomers which sometimes allows better drug loading. Thanks to the versatility of these different preparation processes, the size and the shape of the nanoparticles may be controlled, which may further influence in vivo pharmacokinetic and biodistribution after administration.

Therefore, the characterization of the nanoparticles is logically addressed in Part II of the book. Physicochemical characterization includes polymer characterization, nanoparticle size, nanoparticle surface properties, drug loading and release, nanoparticle stability, and batch-to-batch reproducibility. Electron microscopy, both transmission and scanning, are also important methodologies for the direct visualization of nanoparticles. The interactions with the immune system, the activation of the complement at the surface of the nanoparticles, as well as the interaction with cells and intracellular trafficking are dramatically influenced by the characteristics of the nanoparticles. These processes are discussed in great detail.

Part III of the book discusses how to adjust the characteristics of polymer nanoparticles with functionalities needed for specific pharmacological applications. In this view, the choice of the best polymer, the encapsulation process and the drug loading, as well as, the control of the drug release are at disposal of the formulation scientists to construct the more efficient nanomedicines. Of course, the toxicological aspects have to be taken into great consideration, especially the biodegradation of the nanoparticle polymer core, the safety of the metabolites, the excretion pathways, and the interaction with blood proteins which may also dramatically

influence the nanoparticle biodistribution. A special chapter describes the conception of theranostic nanoparticles combining therapeutic and imaging properties for personalized medicine.

The last part of the book discusses why polymer-based nanoparticles have attracted so much interest, whereas only a few of them have been approved and have reached the market or even the third phase of clinical trials. Regulatory developments are also considered in a separate chapter.

I recommend reading this book, which assembles a profuse array of knowledge on the conception and the development of polymer nanoparticles. It represents an essential reference for a broad scientific community, including academic researchers and industrial deciders. It should also attract students pursuing a master's degree or doctorate in the field of nanomedicine, whether their background is in education, pharmaceuticals, chemistry, physico-chemistry, or even physics.

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About the Editors

Christine Vauthier received her Ph.D. in polymer chemistry from the University Louis Pasteur at Strasbourg, France. She then joined the University of Paris-South, Faculty of Pharmacy as a research assistant. Presently, she is Director of Research at the CNRS (Centre National de la Recherche Scientifique) at the Institut Galien Paris Sud, Université Paris-Sud, Châtenay-Malabry, France. She also serves as an editor for *Pharmaceutical Research*, an AAPS journal. During her early career, she was visiting scientist at the Center for Chemical Controlled Delivery, University of Utah, USA and at the Federal University of Pernambuco, Recife, Brazil where she had been teaching every year since then. The focus of her research is about understanding the influence of the physicochemical characteristics of nanomedicines and their interactions with biological systems when the nanomedicines are intended to improve drug delivery after mucosal or intravenous administration. Based on a multidisciplinary approach, her work includes the synthesis and characterization of polymer nanoparticles from a physicochemical standpoint, the development of methods to study their interactions with proteins, the immune system, cells and the study of the influence of the various physicochemical characteristics of the nanoparticles on their in vivo fate. She is author and co-author of more than 120 research papers as well as over 20 review papers and book chapters on nanoparticle preparation, characterization methods, and on the application of nanoparticles as drug delivery systems. She has spoken at many conferences and has presented over 100 communications.

Gilles Ponchel is full Professor at the University of Paris-South where he teaches Pharmaceutical Technology and Biopharmacy. He leads a multidisciplinary research team that belongs to the Institut Galien Paris Sud, Université Paris-Sud and specializes in the field of drug delivery. The aim of the team is to conceive and to develop innovative drug delivery systems that can improve the crossing of active drugs through physico-chemical and biological barriers. His main research interests are: (i) the development and the evaluation of bioadhesive delivery systems and (ii) the conception of pharmaceutically acceptable nanomedecines, mainly multifunctionalized nanoparticles prepared from tailored polymers, polypeptides, cyclodextrins, etc., for optimizing their biodistribution in the context of drug targeting applications. Some of Prof. Ponchel's specific interests are: (i) the impact of their morphologic and structural characteristics and their capacity to overcome the barriers between the site of delivery and the site of activity. (ii) the relationships existing at the molecular level between surface properties of nanoparticles and their capacities of interacting in the body, such as by bioadhesion and specific recognition. Prof. Ponchel is the author of over 130 research papers, more than 170 communications, more than 50 invited lectures. He has been co-author and contributor to books and many book chapters.

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Abbreviations

γ-CDC6	γ-cyclodextrine modified with carbon chain in C6
γ-PGA-NPs	poly(γ-glutamic acid)
η	Intrinsic Viscosity
ρ	Density
τ_{mix}	Time scale of mixing
$\tau_{NP\ Assembly}$	Time scale of nanoparticle assembly
$\tau_{nucleation\ and\ growth}$	Time scale of nucleation and growth of the precipitating core material
$\tau_{self\text{-}assembly}$	Time scale of block copolymer self-assembly
2CTA	GFLGKGFG peptide
3D HFF	3D hydrodynamic flow focusing
A	Aggregation ratio
A	Adsorption
ABC	Accelerated blood clearance
ABCPA	4-4′-azobis(4-cyanopentanoic acid)
ACA	Alkylcyanoacrylate(s)
AEP	Anionic emulsion polymerization
aFFFF	Asymmetric flow field-flow fractionation
AFM	Atomic force microscopy
ag	Antigen
Ag	Silver
AH50 test	Hemolytic assay to measure the alternative pathway of complement activation
AIBN	Azobis(isobutyronitrile)
AIDS	Aquired immune deficiency syndrome
Alum	Aluminium salts used as adjuvant
AmB	Amphothericin B
ANDA	Abbreviated new drug application
APC	Antigen-presenting cells
API	Active pharmaceutical ingredient

APS	Ammonium persulfate
AS03	Oil-in-water emulsion
AS04	Oil-in-water emulsion (composed of monophosphoryl lipid A adsorbed to Alum)
AUC	Area under the curve
AuNPs	Gold nanoparticles
AuNRs	Gold nanorods
AZT	AZidoThymidine
BBB	Blood–brain barrier
BCA	Bicinchronic acid
BCO	Block co-oligomers
BCR	B cell receptor
BCS	Biopharmaceutical classification system
BHEM	*N*,*N*-bis(2-hydroxyethyl)-*N*-methyl
BLA	Biological license application
BMPO	5,6-benzo-2-methylene-1,3-dioxepane
BSA	Bovine serum albumin
c	Concentration
C3	Complement factor 3
CAD	Charged aerosol detector
CAP	Cellulose Acetate Phthalate
CARPA	Complement Activation Related Pseudoallergy
CCD	Charge-coupled device
CD	Cluster of differentiation
CDAN	N1-cholesteryloxycarbonyl-3,7-diazanonane-1,9-diamine
CDER	Center of drug evaluation and research
cDNA	Complementary deoxiribonucleic acid
CF	Chloroform
CFEG-HRSEM	Cold field-emission gun high-resolution scanning electron microscope
CFF	Cross-Flow Filtration
CFR	Code of federal regulations
cGMP	Current good manufacturing practices
CH50 test	Hemolytic assay to measure the classical pathway of complement activation
CIJ	Confined impinging jet mixer
CL	ε-caprolactone
clogP	Calculated octanol-water partition coefficient
CMC	Chemistry, Manufacturing, and Controls
CM-CS	O-carboxymethyl chitosan
CME	Clathrin-mediated endocytosis
CNS	Central nervous system
CPI	Catastrophic Phase Inversion
CPT	Camptothecin
CQA	Critical quality attribute

CR	Complement receptor
CS-αβ-GP	chitosan-αβ-glycerophosphate
CS	Chitosan
Core-shell-NPs	Core–shell nanoparticles
CT	X-ray computed tomography
CTAB	Cetyl trimethylammonium bromide
CTL	Cytotoxic T lymphocytes
Cu(I)	Copper I
CuAAc	Cu(I) catalyzed azide-alkyne cycloaddition
CUR	Curcumin
CvME	Caveolae-mediated endocytosis
CyA	Cyclosporine A
Da	Dalton
DC	Dendritic cells
DCC	dicyclohexylcarbodiimide
DC-FCCS	Dual-Color Fluorescence Cross-Correlation Spectroscopy
DCM	Dicyanomethylene-4*H*-pyran
DCs	Dendritic cells
DCU	Dicyclohexyl urea
D_{Drop}	Average diameter of the nanodroplets
DEAE	Diethylaminoethyl
DL	Drug loading
DLS	Dynamic light scattering
DMAEMA	*N*,*N*-dimethylaminoethyl methacrylate
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
d*n*/d*c*	Change in refractive index with change in concentration
DNA	Deoxyribonucleic acid
D_{NP}	Average diameter of the nanoparticles
DOPC	1,2-distearoyl-sn-glycero-3-phosphocholine
Dot blot	Semiqualitative method for rapid screening without electrophoresis
DOTA	Tertraazacyclododecane tetraacetic acid
Dox	Doxorubicin
DOX	Doxorubicin
DPI	Dual polarization interferometry
DPPC	Dipalmitoylphosphatidylcholine
DSC	Differential scanning calorimetry
DTT-SH	Dithiothréitol
DTX	Docetaxel
e.g.	"For example"
E	Entrapment
EA	Ethyl Acetate
EC	Ethylcellulose
EE	Encapsulation efficiency

EEM	Emulsification–Evaporation Method
EFSA	European Food Safety Authority
EGF	Epidermal growth factor
EGFR	Epithelial growth factor receptor
EL 14	Copolymer of lactic acid and ethylene glycol
ELISA	Enzyme-linked immunosorbent assay
ELISPOT	Enzyme-linked immunosorbent spot
ELSD	Evaporative light scattering detector
EM	Electron microscopy
EMA	European Medicines Agency
EPA	Environmental Protection Agency
EPR	Enhanced permeability and retention
EPS	Extrapyramidal side effects
et al.	"And others"
EU	European Union
F127	Pluronic® F-127
FA	Folic acid
FCS	Fluorescence Correlation Spectroscopy
FDA	Food and Drug Administration in the United States of America (FDA)
FFF	Field flow fractionation
FNP	Flash nanoprecipitation
FOXP3+CD4+T	T regulatory cell expressing the transcription factor FOXP3
FTIR	Fourier transform infrared spectroscopy
g7	Simil-opioid peptide
GAPDH	Glyceraldehyde 3-phosphate dehydrogenase
GEM	Gemcitabine
GI	Gastrointestinal Tract
GIT	Gastro-intestinal tract
GMP	Good manufacturing practice
GPC	Gel permeation chromatography
GRAS	Generally Recognized as Safe
HA	Hyaluronic acid
HA-SLN	Hyaluronic acid targeted solid lipid nanoparticles
HBSS	Hank's buffered salt solution
HCC	Hepatocellular carcinoma
HCE	Human corneal epithelial
HDL	High density lipoprotein
HEMA	2-hydroxyethyl methacrylate
HER2	Human epidermal growth factor receptor 2
HFIP	Hexafluoroisopropanol
HIFU	High intensity focused ultrasound
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HLA-DR	Human leukocyte antigen, class II molecule DR

HLB	Hydrophilic-lipophilic balance
HPH	High pressure homogenization
HPIMM	High pressure interdigital multilamination micromixer
HPLC	High Performance Liquid Chromatography
HPMA	Hydroxypropyl methacrylate
HPMAm	*N*-(2-hydroxypropyl) methacrylamide
HPβCD	Hydropropylbetacyclodextrin
HRP	Horse rabbit peroxidase
HSA	Human serum albumin
HTCC	*N*-((2-hydroxy-3-trimethylammonium) propyl) chitosan chloride
Hy-PEI	Hyper-branched poly(ethylene imine),
i.e.	"That is"
IBCA	isobutylcyanoacrylate
iC3b	Inactive complement factor C3
ICAM-1	Intracellular cell adhesion molecule 1
ICG	Indocyanine green
ICH	International Conference on Harmonization
ICP-MS	Inductively-coupled plasma mass spectrometry
IFN	Interferon
Ig	Immunoglobulin
IHCA	Isohexylcyanoacrylate
IL	Interleukin
IND	Investigational new drug
INF	Interferon
iNOS	Inducible nitric oxide synthase
INPs	Inorganic nanoparticles
IOBA-NHC	Human conjunctival epithelial cells
IONPs	Iron oxide nanoparticles
IOP	Intraocular pressure
Ip	Polymolecularity index
IPA	IsopropylAcrylamide
ITC	Isothermal titration calorimetry
KLH	Keyhole limpet hemocyanin
kV	Kilovolts
LAL	Limulus amebocyte lysate
LbL	Layer-by-layer
LC	Drug loading content
LC-MS	Liquid chromatography–mass spectrometry
LCST	Lower critical solution temperature
LD	Laser diffraction
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LE	Drug loading efficiency
Leu	L-leucine ethyl ester

LLC	Lewis lung carcinoma
LNs	Lipid nanoparticles
logP	Octanol–water partition coefficient used as a measure of hydrophobicity
LOP	Loperamide
LOP-PLGA-g7	Nanoparticles coated with simil-opioid peptide and containing loperamide
LOP-PLGA-SA-g7	Nanoparticles coated with sialic acid and simil-opioid peptide
LPS	Lipopolysaccharide
LSC	Lauryl succinyl
LSPR	Localized surface plasmon resonance
LTZ	Letrozole
MAA	Methacrylate Acid
Mab	Monoclonal antibody
MAC	Membrane attack complex
MA-GFLG-Dox	*N*-methacryloyl-glycylphenylalanylleucylglycyl-doxorubicin
Mag-NPs	Magnetic nanoparticles
MAL	Maleimide
MALLS	Multi-angle laser light scattering
MAPK	Mitogen-activated protein kinase
MC	Methylene Chloride
MCP-1	Monocyte chemoattractant protein-1
MDA	Malondialdehyde
MDR	multiple-drug resistance
MF59	Oil-in-water emulsion
MHC	Major histocompatibility complex
MIVM	Multi-inlet vortex mixer
MNPs	Mesoporous nanoparticles
$m_{\mathrm{p/Drop}}$	Mass of the polymer in the droplets
$m_{\mathrm{p/NP}}$	Mass of the polymer in the particles
MPE	Maximal possible effect
MPEG–PTMC	Poly(ethylene glycol)–poly(trimethylene carbonate)
MPS	Mononuclear phagocytic system
MRI	Magnetic resonance imaging
MS	Mass spectrometry
MTX	Mitoxantrone
MUA	11-mercaptoundecanoic acid
MW	Molecular weight
MWCO	Molecular weight cut-off
NAC1	*N*-acetyltransferase 1
nBCA	n-butylcyaoacrylate
NC	Nanocapsules
NCAM	Neural cell adhesion molecule
NCE	New chemical entity

NCS	Neocarzinostatin
NCs	Nanocapsules
NDA	New drug application
NF-kB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NG	Nanogel
NIR	Near-infrared
NK	Natural killer cells
nm	Nanometer
NMR	Nuclear magnetic resonance
NO	Nitric Oxide
NPs	Nanoparticles
ns	Not specified
NTs	nanotubes
O/W	Oil-in-water emulsion
ODN	Oligonucleotide
OEt	Ethyl ester
OI	Optical imaging
OLZ	Olanzapine
OSHA	Occupational safety and health administration
P4VP	Poly(4-vinylpyridine)
PAA	Poly(acrylic acid)
PACA	Poly(alkylcyanoacrylate)
PAGE	Polyacrylamide gel electrophoresis
PAH	Poly(allylamine hydrochloride)
PALM	Photo-activated localization microscopy
PAMAM	Poly(amido amine)
PAMPs	Pathogen-Associated Molecular Patterns
PBCA	Poly(ButylCyanoAcrylate)
PBDL	Poly(butylene succinate-co-butylene dilinoleate)
PBLG	poly(γ-benzyl-L-glutamate)
PBMC	Peripheral blood mononuclear cells
PBS	Phosphate buffered saline
PCC	Physicochemical characterization
PCDA	10,12-pentacosydonic acid
PCEP	Poly[(cholesteryl oxocarbonylamido ethyl) methyl bis(ethylene) ammonium iodide] ethyl phosphate
PCL	Poly (ε-Caprolactone)
PCL-*b*-PEG	Poly(ε-caprolactone)-block-poly(ethylene glycol)
PCR	Polymerase chain reaction
PCS	Photon Correlation Spectroscopy
PD	Pharmacodynamics
PDI	Polydispersity index
PDM	2-(dimethylamino)ethyl methacrylate
PDMAEMA	Poly(dimethylamino ethyl methacrylate)

PECs	Peritoneal exudate cell macrophages
PEC	Polyelectrolyte complexes
PEDOT	Poly(3,4-ethylenedioxythiophene)
PEG	poly(ethylene glycol)
PEG-PCL	Poly(ε-caprolactone)-poly(ethylene glycol)
PEG-PHDCA	Poly(methoxypolyethyleneglycol cyanoacrylate-co-hexadecyl cyanoacrylate)
PEG-PLA	poly(ethylene glycol)–poly(lactide)
PEG-PLL	poly(ethylene oxide)-poly(lysine)
PEI	poly(ethylene imine)
PEO	poly(ethylene oxide)
PES	Poly(ethyl sebacate)
PES-DOX	Poly(ethylene sebacate) nanoparticles loaded with doxorubicin
PET	Positron emission tomography
PEVA	Poly(ethylene-co-vinylacetate)
PFC	PolyFluoroCarbone
PFPE	Perfluoropolyether
PGA	Poly(glycolide)
PGGA	Poly(γ-glutamic acid)
PHB	Poly(β-Hydroxybutyrate)
Phe	L-phenyl alanine methyl ester
PHPMA	poly(2-hydroxypropyl methacrylate)
PHPMAm	*Poly* N-(2-Hydroxypropyl methacrylamide)
PIBCA	Poly(isobutylcyanoacrylate)
PIHCA	Poly(isohexylcyanoacrylate)
PIPAAN	Poly(isopropylacrylamide)
PIT	Phase-inversion temperature
PK	Pharmacokinetic
PLA	Poly(lactide)
PLA-*b*-PEG	Poly(lactide acid)-block-poly(ethylene glycol)
PLA-PEG	Poly(lactide)-poly(ethyleneglycol)
PLA-TPGS	Poly(lactide)–tocopheryl poly(ethylene glycol succinate)
PLGA	Poly(lactide-co-glycolide)
PLGA-*b*-PEG	Poly(lactide-co-glycolide)-block-poly(ethylene glycol)
PLGA-PEO	poly(lactide-co-glycolide)-poly(ethylene oxide)
PLG-NCA	γ-propargyl-L-glutamate N-carboxyanhydride
PLL	Poly-L-lysine
PLLA	Poly(L-lactide)
PLT	Platelet
PMA	Poly(methyl acrylate)
PMLA	Poly(malic acid)
PMLABe	Poly(benzyl malate)
$PMLABe_{80}H_{20}$	Poly(benzyl malate-co-malic acid)
PMLAHe	Poly(hexyl malate)

$PMLAHe_{90}H_{10}$	Poly(hexyl malate-co-malic acid)
PMLAMe	Poly(methyl malate)
$PMLAMe_xH_y$	Poly(methyl malate-co-malic acid)
PMM	Poly(methyl methacrylate)
P-NPs	Polymer nanospheres
PPG	Poly(propylene glycol)
PPIX	Protoporphyrin IX
PPO	Poly(propylene oxide)
PRINT™	Particle Replication IN non-wetting Template
PRP	Platelet-rich plasma
PRRs	Pattern Recognition Receptors
PhotoS	Photosensitizer
PS	Poly(styrene)
PS-*b*-P4VP	Poly(styrene)-block-poly(4-vinylpyridine)
PS-*b*-PEG	Poly(styrene)-block-poly(ethylene glycol)
PSD	Particle size distribution
PSMA	Poly(styrene-*co*-maleic acid/anhydride)
PSS	Poly(4-styrene-sulfonate)
PTMC	Poly(trimethylene carbonate)
PTX	Paclitaxel
PUL	Pullulan
PUL-PES-DOX	Poly(ethylene sebacate) nanoparticles loaded with doxorubicin
PVA	Poly(vinyl alcohol)
PVP	Poly(N-vinyl-2-pyrrolidone)
QCM-D	Quartz crystal microbalance with dissipation monitoring
QDs	Quantum dots
QELS	Quasi-elastic light scattering
qPCR	Quantitative Polymerase chain reaction
R&D	Research and Development Department
RA	Rheumatoid arthritis
RAFT	Reversible Addition Fragmentation Chain Transfer
RBCs	Red blood cells
real time-PCR	Real time polymerase chain reaction
RES	Reticuloendothelial system
Rg	radius of gyration
RGD	Tripeptide arginine-glycine-aspartic acid
RGDp	Tripeptide arginine-glycine-aspartic acid peptidomimetic
RI	Refractive index
RIA	Radio-immuno-analysis
RIS	Risperidone
RIV	Rivastigmine tartrate
RME	Receptor-mediated endocytosis
rms	Root mean square
RNA	Ribonucleic acid

ROS	Reactive Oxygen Species
RP-HPLC	Reversed phase high performance liquid chromatography
RREP	Redox radical emulsion polymerization
SA	Sialic acid
SAB	Sodium acetate buffer
SBF	Simulated body fluid
SBR	Signal-to-background ratio
sCD14	Soluble CD14
SDS	Sodium dodecyl sulfate
SEC	Size exclusion chromatography
SEM	Scanning electron microscopy
SGF	Simulated gastric fluid
SIF	Simulated intestinal fluid
siRNA	small interfering RNA
SLF	Simulated lachrymal fluid
SLNs	Solid lipid nanoparticles
SLS	Sodium lauryl sulfate
$SnOct_2$	Stannous octanoate
SPECT	Single photon emission computed tomography
SPION	Super paramagnetic iron oxide nanoparticles
SPR	Surface plasmon resonance
SQ	Squaraine
SR	Scavenger receptor
SRBC	Sheep red blood cell
ssDNA	Single stranded deoxyribonucleic acid
SSF	Simulated saliva fluid
STED	Stimulated emission depletion
STORM	Stochastic optical reconstruction microscopy
TAT	Trans-activating transcriptional activator peptide
Tc	T cytotoxic cell
TCR	T cell receptor
T-CS	Chitosan-glutathione conjugate
TDAR	T cell Antibody Response
TDCN	Thermo-responsive di-block copolymer nanoparticles
TEA	Triethanolamine
TEM	Transmission electron microscopy
Tf	Transferrin
TfR	Transferrin receptor
TGA	Thermogravimetric analysis
Th	T helper cell
THF	Tetrahydrofuran
Thr	N^{α}-(methacryloyl)-threonine
TLR	Toll-like receptor
TMC	TriMethylChitosan
TMT-Cys	Trimethyl chitosan-cysteine conjugate

TNF	Tumor necrosis factor
TPGS	d-α-tocopheryl poly(ethylene glycol) 1000 succinate
TPI	Transitional Phase Inversion
TPP	TriPhenylPhosphate
T-PS	Photosensitizer prodrug
TRA	All trans retinoic acid
Treg	T regulatory cell
TRPS	Tunable resistive pulse sensing
TSLs	Thermosensitive liposomes
U.S.	United States
UCNP	Up-converting nanophosphors
uPA	Urokinase plasminogen activator
uPAR	Urokinase plasminogen activator receptor
UPS	United state pharmacopoeia
US	Ultrasound
USA	United States of America
UV	Ultraviolet
UVA	Ultraviolet A
UVB	Ultraviolet B
v/v	Volume/volume proportion
VPTT	Volume phase transition temperature
W/O/W	Water-in-oil-in-water emulsion, double or multiple emulsion
W/O	Water-in-oil emulsion
w/v	Weight/volume proportion
WGA	Wheat germ agglutinin
WPM	Wet pearl milling
XRPD	X-ray powder diffraction
Z-Avg.	Z-average
ZnO	Zinc oxide

Part I
Methods for the Manufacturing of Nanoparticles: Principles

Chapter 1
Polymer Nanoparticles for In Vivo Applications: Progress on Preparation Methods and Future Challenges

Christine Vauthier

Abstract Polymer nanoparticles are one type of the arsenal of nanomedicines that are developed to improve efficacy and specificity of drug delivery and to design new contrast agents enhancing the performance of diagnostic methods based on imaging techniques. To answer the various challenges, it has lead the way to development of suitable nanoparticles. Many types of methods of preparation were proposed designing nanoparticles taking different structures and integrating various functions. The purpose of the introduction to the part I of the book devoted to the methods of preparation of polymer nanoparticles to be used as nanomedicines is to present the different types of polymer nanoparticles that were designed so far and to give an overview on their methods of preparation. It is also important to place these methodologies in a prospective view raising future challenges and bottlenecks.

Keywords Methods · Micelles · Polymer nanoparticles · Nanocapsules · Nanospheres · Nanogel · Polyelectrolyte complex · Self-assembling · Precipitation · Polymerization · Emulsion · Polymer solution · Layer-by-layer · Print · Microfluidic · Self-assembling · Complex · Spherical particles · Nonspherical nanoparticles · Multifunctional nanoparticles

1 Introduction

In the 1970s, polymer nanoparticles were found to be suitable materials thanks to their small size to serve the purpose of the "magic bullet" born behind the concept of drug targeting that was inspired by Paul Ehrlich, an imminent bacteriologist and immunologist who received the Nobel Prize in Physiology and Medicine in 1908. However, to be used as drug carriers, polymer nanoparticles need to comply with

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regulatory registration and fulfill stringent specifications. Besides, they must integrate all functionalities that are needed to complete a specific medical application. Among others, this includes a composition made of suitable materials for in vivo use and preparation conditions that are compatible with the production of pharmaceutical grade compounds.

2 Development of Methods of Preparation of Nanoparticles Made of Polymers: Progresses

By the time polymer nanoparticles were first introduced to be used as drug carriers, they were produced by polymerization methods (Birrenbach and Speiser 1976; See the historical perspective by Kreuter 2007; Couvreur 2013). In addition to regulatory constraints that are an important limitation for the choice of the polymer composing the nanoparticles, nanoparticles designed to become nanomedicines need to fulfill various types of functions. Drugs should be associated efficiently with nanoparticles while protection against degradation should be insured in storage conditions and in vivo during transportation of the nanomedicine toward the target site of delivery of the drug. This implies that the drug remains associated with the nanoparticles during transportation. However, the association needs to become unstable once the nanoparticle has reached the target site, where the drug should be available to express its biological activity. Behind mechanisms controlling the stability of the association of the drug with the nanoparticles, other functionalities are needed to help the nanoparticles to reach the delivery site. The requested properties, which are contradictory for some of them, can be associated customizing the design of new polymers. The number of suitable polymers that can compose nanoparticles developed to be used as nanomedicine produced by polymerization methods is extremely low being a bottleneck for an extensive development of the polymerization methods to prepare polymer-based nanomedicines. Other limitations of these methods include the use of organic solvents and sometimes of large amounts of surfactants, while the majority of polymer nanoparticles synthesized by polymerization methods are nonbiodegradable. Nevertheless, the first rapidly biodegradable nanoparticles were synthesized by emulsion polymerization using alkylcyanoacrylate monomers (Couvreur et al. 1979). A broad range of nanoparticles composed of poly(alkylcyanoacrylate) were synthesized since then and are used to develop innovative therapeutic strategies with many types of drugs with interests for developing treatments of serious diseases (Vauthier et al. 2003a, b, 2007; Andrieux and Couvreur 2009; Nicolas and Couvreur 2009). Today, poly (alkylcyanoacrylate) nanoparticles prepared by polymerization methods continue to generate interest on the international scene (Murthy and Harivardhan Reddy 2006; Vauthier et al. 2007; Graf et al. 2009; Nicolas and Couvreur 2009; Yordanov 2012; Sulheim et al. 2016). Polymerization methods were successful to provide with nanoparticles of interest that were translating to clinics being evaluated in clinical

trial phase II/III for the treatment of hepatocellular carcinoma (primary liver cancer) (Zhou et al. 2009; Soma et al. 2012; Onxeo 2016). However, all nanoparticles developed as nanomedicines and prepared by polymerization methods were synthesized with monomers of the alkylcyanoacrylate family limiting the choice of intrinsic properties that can be given to the particles although some flexibilities are allowed tuning conditions of polymerization (Chap. 5 from Vauthier).

To enlarge the choice of polymers composing nanoparticles to be used as nanomedicines, a series of methods were developed based on the use of polymers that were synthesized independently of the nanoparticles. Obtaining polymer nanoparticles from already prepared polymers was a challenge. The first series of attempts was based on the use of matrices formed by thin emulsions in which the polymer was dissolved in the tiny droplets composing the dispersed phase of the emulsion. The polymer was then forced to precipitate using various artifacts in order to obtain nanoparticles. Evaporation of the solvent contained in the droplets was the approach proposed in the pioneer work in the early 1980s (Gurny et al. 1981). The development of this emulsification-solvent evaporation method was applied first to the production of nanoparticles made of poly(lactide) (PLA), the most used polymer composing medical devices for parenteral administration. Since then, the method has been applied to a large choice of polymers. This method brought a real breakthrough. It was the first time nanoparticles were obtained directly from polymers while they were all obtained before by polymerization methods. It was an important milestone for the development of methods for the preparation of nanomedicines occurring as polymer nanoparticles. In a derived method also based on the precipitation of a polymer dissolved in the emulsion droplets, the polymer solvent is extracted from the droplets diluting the emulsion with a third solvent in which both the continuous and the dispersed phases of the parent emulsion are miscible. This operation causes the immediate precipitation of the polymer contained in the emulsion droplets that compose the dispersed phase of the emulsion. In general, both the emulsification-solvent evaporation method and the emulsification-solvent extraction method can be applied with polymers that are soluble in organic solvents (Chap. 4 from Mendoza-Muñoz et al.). Instead of precipitation, the polymer contained in the droplets of the emulsion can be gelified. This method was addressed to produce nanoparticles composed of hydrogels to associate hydrosoluble drugs with nanoparticles that was challenging with previous methods. The main difficulty with methods based on the use of emulsions is to prepare emulsion with a small size of the emulsion droplets. While the majority of works were based on the use of mechanical techniques to produce the thin emulsion required, several authors have suggested the formulation of miniemulsions and microemulsions as matrices to produce the nanoparticles. More recently, microfluidic techniques have been introduced. Droplets hence nanoparticles are formed one by one in a very well controlled manner (Karnik et al. 2008; Valencia et al. 2012; Pedro et al. 2013; Lim et al. 2014). To avoid the use of organic solvents, supercritical fluid technologies were envisaged (Sun et al. 2005; Meziani et al. 2006; Elizondo et al. 2012; Sheth et al. 2012; Girotra et al. 2013).

In another series of methods, nanoparticles are prepared directly from polymer solutions. Nanoparticles form by causing a rapid change of the physicochemical conditions that induces the nucleation of particles of small size. In general, they form by mixing the initial polymer solution with a second medium with which it is fully miscible. Mechanisms behind nucleation of nanoparticles include precipitation of the polymer, self-assembling of macromolecules providing that they were selected with the required architecture or specific properties, formation of complexes and gelation. Figure 1 illustrates the formation of nanoparticles based on the induction of nucleation from two examples of methods: the formation of polymer micelles resulting from self-assembling of amphiphilic polymers assisted by solvent diffusion (Fig. 1a) (Chap. 2 from Miladi et al. and Chap. 3 from Tang and Prud'homme), and the formation of nanogels triggered by self-assembling of two polymers having complemental groups to form inclusion complexes between alkyl chains grafted on one polymer and cyclodextrins grafted on a second polymer (Fig. 1b) (Gref et al. 2006; Hassani et al. 2012).

In some cases, the nucleated nanoparticles are stabilized in a second step that can be performed in the same vessels. For instance, after nucleation of polymer particles by precipitation, it is generally necessary to remove the solvent of the polymer from the dispersing medium. The so-called nanoprecipitation method in which nanoparticle nucleation is induced by a solvent shift belongs to this category of method (Fessi et al. 1989; Ganachaud and Katz 2005; Minost et al. 2012; Chap. 2 from Miladi et al. and Chap. 3 from Tang and Prud'homme). Nanoparticles obtained by gelation are sometimes stabilized by complexation with another polymer that sticks on the surface to stabilize the particle (Oh et al. 2008; Kabanov and Vinogradov 2009; Maya et al. 2013; Wu and Delair 2015). Interesting features with these methods are their rapidity and scalability because production can be performed with a continuous-based process as demonstrated with the nanoprecipitation method. These methods of preparation can be achieved with a large panel of polymers. Although precipitation methods and methods based on self-assembling of amphiphilic polymers generally require the use of organic solvents (Fig. 1a) (Chap. 2 from Miladi et al. Chap. 3 from Tang and Prud'homme, Weber 1998; Torchilin 2007; Kabanov and Vinogradov 2009; Rowan 2009; Guan et al. 2015; Fuks et al. 2011; Pearson et al. 2013; Robertson et al. 2013), self-assembling methods based on the formation of polymer complexes and those based on a gelation process can be performed in aqueous media avoiding totally the use of organic solvent (Fig. 1b) (Vauthier and Couvreur 2000; Janes et al. 2001; Gref et al. 2006; Kabanov and Vinogradov 2009; Daoud-Mahammed et al. 2009; Delair 2011; Hassani et al. 2012; Maya et al. 2013; Eckmann et al. 2014). Another marked advantage of the last category of method is given by the fact that nanoparticles form in gentle conditions that are suitable to associate very fragile hydrosoluble molecules with the nanoparticles. For instance, the methods based on the formation of complexes and nanogels can be used to associate biologically active peptides, proteins, and nucleic acids with nanoparticles. With methods based on the complexation of polyelectrolytes of opposite charges, peptides, and nucleic acids may compose one of the polyelectrolyte involved in the formation of the complex

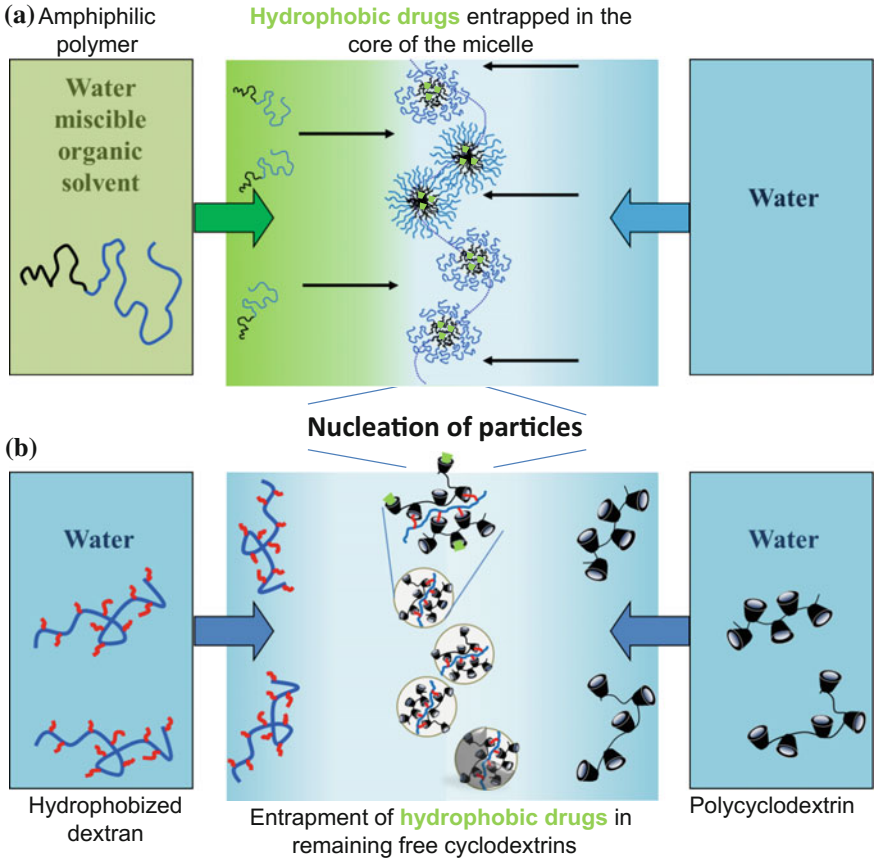

Fig. 1 Preparation of nanoparticles by nucleation of particles thanks to self-assembling of soluble polymers. Nucleation of polymer particles occurs while mixing two miscible solutions. **a** Formation of polymer micelles assisted by solvent diffusion. This can be applied with amphiphilic polymers. **b** Formation of nanogels by self-assembling of neutral hydrosoluble polymers including a polycyclodextrin and a hydrophobized dextran. The nanogels form, thanks to the formation of inclusion complexes between the cyclodextrins grafted on one of the polymers and alkyl chains grafted on the second polymer (hydrophobised dextran shown on the figure)

included in the final nanoparticles (Kabanov and Vinogradov 2009; Delair 2011; Kataoka et al. 2001; Mukhopadhyaya et al. 2012; Osada 2014; Bekale et al. 2015; Shiraki et al. 2016). All these techniques of preparation of polymer nanoparticles allow production of nanoparticles with a wide range of properties thanks to the nature of polymers that can be used to produce them.

3 Producing Polymer Nanoparticles with Different Structures and Characteristics

A broad range of methods of preparation of polymer nanoparticles was requested to permit association of drugs having various biological activities and physicochemical properties. In general, molecules are associated with the nanoparticles while they are solubilized in an appropriate solvent. Solubility properties of drug molecules are important factors to consider and that contribute for the success of drug to nanoparticle association. Although soluble molecules are the majority of compounds that were associated with nanoparticles so far, metal nanoparticles were interesting ingredients to associate with polymer nanoparticles designing a new generation of contrast agents for application in diagnostic based on imaging techniques (Khemtong et al. 2009; Maya et al. 2013; Cormode et al. 2014; See Chap. 17 from Herceg et al.). The solvent in which the drug molecule is soluble or metal nanoparticles occur as a stable dispersion is a key for the choice of the method of preparation. However, in general, methods of preparation need to be customized on a case-by-case basis to design each new nanomedicine. Existing methods can be used to inspire the development of new methods. They were applied to make nanoparticles with polymers of various nature and to produce nanoparticles having different structures to resolve many different challenges found to achieve efficient drug association and releasing issues (Fig. 2) (Chap. 13 from Zandanel and Charrueau, Chap. 14 from Charrueau and Zandanel).

Methods based on general principles that were described above are all suitable to prepare matrix-like-type nanoparticles. Reservoir-type nanoparticles, i.e., nanocapsules could be obtained modifying and adapting protocols of most of the previous methods (Couvreur et al. 2002; Mora-Huertas et al. 2010). Figure 3 summarizes the different methods of production of polymer nanoparticles and gives the type of nanoparticle produced.

Size and shape of nanoparticles are important characteristics to consider as they both influence the pharmacokinetic and cell uptake; hence, they can dramatically affect the efficacy of the nanomedicine (Truong et al. 2015). In general, size can be well controlled by experimental conditions used preparing the nanoparticles. Nanoparticles with a spherical shape are generally prepared by the above-mentioned methods. The obtaining of nanoparticles with a shape that differed from a sphere was reported only in a few cases producing nanoparticles by self-assembling of polymers and amphiphilic materials (Lee et al. 2010; Cauchois et al. 2013; Chap. 6 from Ponchel and Cauchois). New methods were specifically introduced to design nanoparticles with well-controlled nonspherical shapes (Chap. 6 from Ponchel and Cauchois). For instance, rod-like nanoparticles can be produced stretching spherical particles embedded in a stretchable matrix (Mitragotri 2009; Wang et al. 2011a). Print methods were introduced to design polymer nanoparticles with a wide range of shapes (Oh et al. 2008; Wang et al. 2011b; Perry et al. 2011; Sultana et al. 2013) (Fig. 4).

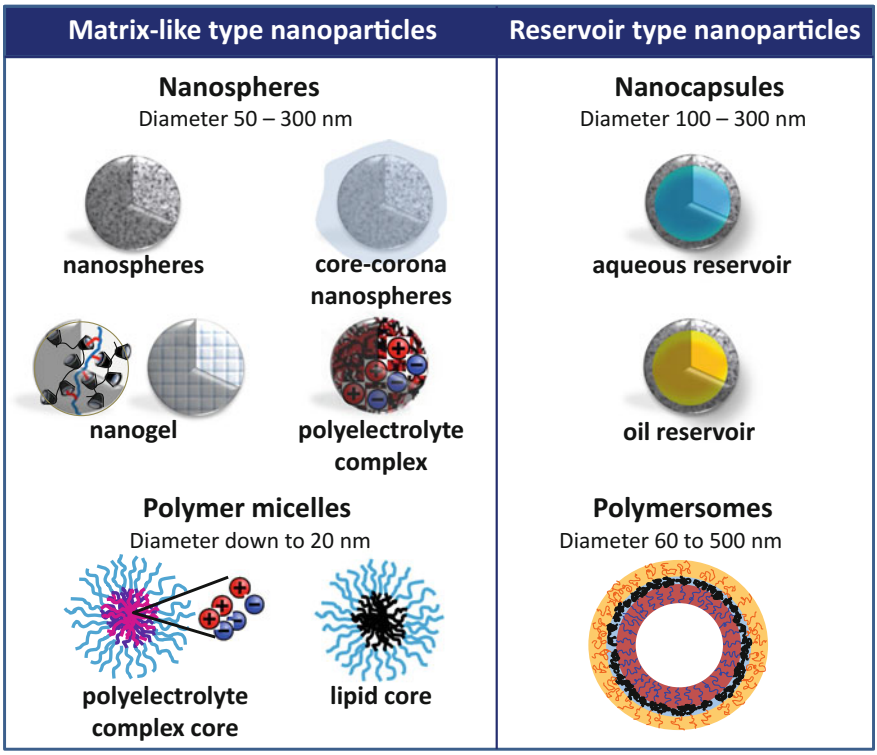

Fig. 2 Different types of polymer nanoparticles showing the structures

4 Future Challenges

In the infant age of their development, polymer nanoparticles were designed as very simple particles based on the association of a drug with a nanosized-scale particle made of biodegradable polymer. The evolution is to design multifunctional nanoparticles that may include diagnostic and therapeutic elements together with equipment's controlling the pharmacokinetic and biodistribution hence improving targeting efficiency of the carrier and its drug releasing properties. Table 1 summarizes the different functionalities that are desired to associate with nanoparticles and gives examples of items found in the corresponding toolbox to achieve each function.

The possibility to design very precise nanoparticles with polymers by tuning nanoparticle properties to optimize the benefit of the treatment for each patient taking into account the individual variability while the safety profile will be high is

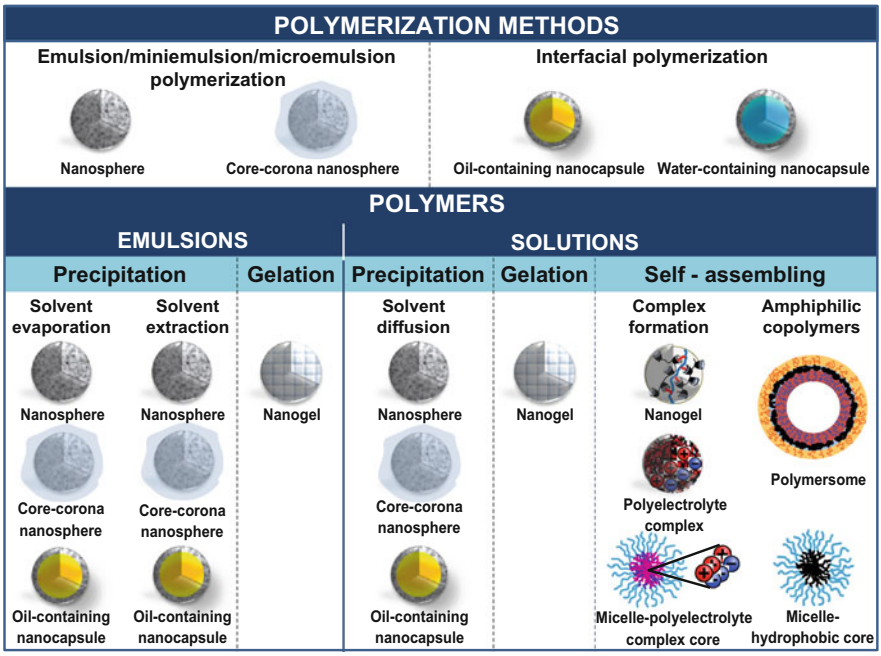

Fig. 3 Summary of general principles of methods of preparation of nanoparticles from polymerization procedure and protocols based on the use of polymers either included in the dispersed phase of an emulsion/miniemulsion/microemulsion or occurring as a polymer solution. This summary indicates the type of nanoparticles that are produced from these methods illustrating the spherical species

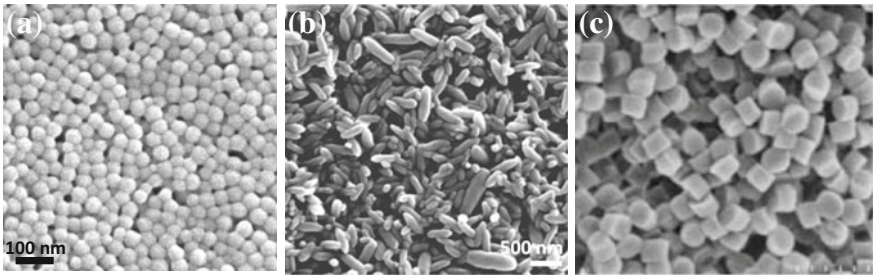

Fig. 4 Example of polymer nanoparticles obtained with different shapes as shown by scanning electron micrograph. **a** spherical nanoparticles obtained from anionic emulsion polymerization of isobutylcyanoacrylate (C. Vauthier, personal collection), **b** rod-like nanoparticles obtained by nanoprecipitation of poly(γ-benzyl-l-glutamate) (Mw:70 kDa) (Adapted from Cauchois et al. 2013, reproduced with permission), and **c** 200 × 200 nm cylindrical nanoparticles made of poly (lactide-co-glycolide) prepared by a print method (Adapted from Wang et al. 2011b, reproduced with permission)