Polymer Nanoparticles for Nanomedicines

Christine Vauthier · Gilles Ponchel
Editors

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A Guide for their Design, Preparation and Development

Springer

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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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Contents

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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