Pharmaceutical Nanotechnology

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Fundamentals and Practical Applications

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This World, The Small, The Great!
Odysseus Elytis
Axion esti – Worthy It Is
(Το Άξιον Εστί, 1959)

This book is dedicated with respect and love to the memory of my parents, Nikos and Maria.
This book is dedicated to those who stood beside me with a lot of love throughout my academic career. To my wife and colleague Voula Dimitriou and to my daughters Katerina and Maria.

Foreword

It was in the 1980s that the word nano, used as a prefix to a variety of important-sounding words, reached me from various directions. “What is this nano thing I’m hearing about daily?”, I asked a colleague at the university. “I’m worried I’m missing something. I feel as if I’m left behind, in the middle ages of science so to speak”. “Don’t you know?” he said, expelling streams of tobacco smoke through his nostrils (smoking was not a sin then). “It’s the technology of small, dwarfish things. Nano is Greek, it means dwarf”. “Thanks for telling me” I said, subtly reminding him I am Greek. I was working on liposomes at that time, small vesicular fatty particles, around 100 nm in diameter, dwarfish in other words. Does this mean I’m doing nanotechnology myself? I wondered. Hope was already enveloping me.

Actually, those of us working on liposomes in drug delivery were not the only ones doing nanotechnology and not being aware of it. Others were doing it as well, for instance those engaged in research with synthetic nanoparticles, dendrimers, viruses and gold particles. As nanotechnology, by convention, deals with systems of sizes in the range of about 1–100 nm, it would also include research on small and large molecules such as sugars, proteins, genetic material and polymers. In fact, work on small, dwarfish structures was so extensive prior to the emergence of the term “nanotechnology”, it encompassed a plethora of fields of science and technology. The only thing missing was a name for it. A name that would represent all nano-scale technological activities. And what would that name be? Nanotechnology, obviously! As fate would have it, the first to think of it was Norio Taniguchi, back in 1974.

Nanotechnology is now a huge, ever-growing, ever-expanding discipline. It seems that the name itself has galvanised a massive thrust of related activities. The term nanotechnology has attained such a heavy-weight status in science and technology, it is used by academics and others to name a lab, a department, a new journal, or even to bestow a certain respectability to an activity related to dwarfish things. Nano is king nowadays. Nanotechnology is now taken so seriously, it has predictably attracted the attention of those guarding our health and environment. I refer to research on the toxicology of nanomaterials, usually non-biodegradable ones which, in the form of airborne nanoparticles, were shown to promote fibrosis

of the lungs. However, tight regulation by licensing bodies should ensure avoidance of such problems.

Of particular importance to those of us engaged in drug delivery is the role of nanotechnology in advancing the science of therapeutics and their application in the clinic. It has been therefore a great personal pleasure to write the Foreword of the present book by Professor Costas Demetzos. His monograph, *Pharmaceutical Nanotechnology: Fundamentals and Practical Applications*, is a unique publication designed to serve as a scientific textbook for those involved in new technologies, especially nanotechnology of pharmaceutics, as well as to educate students on the nano aspects of the science and technology of pharmaceutics.

This book is divided into three main parts. It begins with an introduction to nanotechnology, the physical chemistry, thermodynamics and biophysics of nanosystems, offering an analysis of basic facts regarding the size and thermotropic behaviour of systems used in nanotechnology. We learn that nanotechnology deals with the application of technology in the grey area in between classical mechanics and quantum mechanics. It also refers to size-measuring devices that are so minute, they can only be observed under electron microscopy. Remarkably, an existing device of this kind is so sensitive, it is reputed to measure the weight of protons! This is of utmost importance because nanotechnology cannot progress without the means of measuring nano sizes. A section on the historical background discusses the development of modern nanotechnology and the personalities involved. It then deals with the biophysics of a variety of nanosystems, their stability and other properties as well as their physicochemical characterisation.

The author focuses on three different aspects of applied pharmaceutical nanotechnology: imaging, diagnostics and therapy. There is extensive discussion on a variety of drug carrier nanosystems, of drug incorporation into such systems, as well as their pharmacokinetics. An all-important consideration of pharmaceutical nanotechnology that enables its application clinically is the evaluation of toxicity and safety of nanosystems. To that end, this book deals with issues of safety, nanotoxicity of nanosystems and the regulatory framework. This includes the procedures that must be followed in order to achieve approval by agencies such as FDA in the USA and EMEA in Europe. Such issues, treated comprehensively in the third part of the book, serve as a reminder of the complexity of steps that must be followed prior to the approval and commercialization of clinically effective drugs.

Pharmaceutical Nanotechnology: Fundamentals and Practical Applications is certain to prove of considerable value to those committed to the science of pharmaceutics and related technologies. It will open new avenues of research and development in pharmaceutical academia and industry. The author is to be congratulated for this achievement.

London, UK Gregory Gregoriadis

Preface

The textbook entitled *Pharmaceutical Nanotechnology. Fundamentals and Practical Applications* is addressed to those in the fields of pharmaceutics, medicine, biology, and life sciences and to those who are interested in materials and new technologies. This textbook includes an introduction to the science of nanotechnology, the basic principles of physical pharmacy, and nanoparticle applications in the fields of diagnostics, imaging, and therapeutics. They are presented in the chapters, the principles of thermodynamics and biophysics as important milestones and as tools for developing and evaluating nanomaterials, nanodevices, and nanosystems. The relationship between the membrane biophysics of artificial nanostructures and the cell membranes' behavior could be studied using thermodynamic parameters' changes, and issues are discussed in terms of the development process of drug delivery nanosystems.

This textbook also presents the applications of innovative nanosystems that are considered as carriers of bioactive molecules, diagnostic and imaging nanotechnology, and relevant nanosystems like liposomes, dendrimers, polymers, polymeric nanocarriers, carbon nanotubes, nanoshells, etc. The toxicity of nanomaterials and nanostructures and the regulatory framework for the approval of the new nanotechnological products are presented at the very last chapters of this book.

Furthermore, I would like to underline in this monograph the usefulness of fundamental sciences such as biophysics and thermodynamics. It is worth mentioning that the investigation of the *mesoscopic* word and of the *metastable phases* of the liquid crystalline state of the matter could be emerged as the building blocks for designing better medicines and improving the health. The principles of basic science can help to rationally design and develop innovative medicinal formulations and to translate the basic scientific principles of manufacturing to improve medicine development process and to meet more efficiently the regulatory requirements. For these reasons, biophysics and thermodynamics could create the science-based platform for s*ystems therapeutics* and hopefully contribute efficiently to the *cycle of innovation* of nanotechnology-based products, which maps the regulation of new health technology demands.

In other words, my vision is for the scientist, in the field of the development and evaluation of nanosystems that is applied to therapeutics, diagnostics, and imaging, to understand the important position that he holds in the research and development of pharmaceutics, the *systems pharmaceutics.*

The monograph provides fundamental aspects of nanotechnology and fills the gap between nanotechnological systems and functionality of living organisms, providing new aspects on their physicochemical, biophysical, and thermodynamic behavior.

The monograph is addressed to all those involved in recent advances in pharmaceutics. The book is divided into three major parts, each of which is divided into subchapters. Part I refers to the physicochemical and thermodynamic aspects of nanosystems, while their biophysical behavior is correlated with that of the cells of the living organisms. Part II refers to the application of nanotechnology in imaging, diagnostics, and therapeutics. Part III is focused on issues regarding safety, nanotoxicity of nanosystems, and regulatory framework. The monograph promotes the concept that biophysics, thermodynamics, and nanotechnology are considered to be emerging tools that when following the regulatory guidelines provide new and integrated knowledge, for the production of new medicines.

As an academic professor, my vision is that young researchers will use this textbook as a springboard for new knowledge and research for the science of tomorrow. I would like this book to fulfill the verse of Odysseus Elytis, the person who intuitively and unmistakably touched nanotechnology: "*This you should only know: Whatever you save during the lightning, it will remain clean throughout the century*" [(Axion esti – Worthy It Is (*Το Άξιον Εστί*, 1959)].

Zografou, Athens, Greece Costas Demetzos

Acknowledgments

This monograph is the result of a hard and long-term academic effort in the continuously developing field of nanotechnology, in the area of medicines, treatment, diagnostics, and imaging. I have been fortuned enough to have as a mentor, not only a pioneer in the field of nanotechnology, but also a wonderful person, Professor Demetrios Papahadjopoulos, from the University of California, San Francisco (UCSF). He familiarized me with the science of nanotechnology and taught me that the scientific research is a determinant condition for the approach to the truth and the scientific dignity a researcher, a *homo universalis,* must have. I owe my scientific steps of the past 20 years to the acquaintance with the scientist and human, Demetrios Papahadjopoulos. His presence in my life gave me the necessary tools for the scientific being, a refreshing way out to the continuous search of a researcher with social references.

I owe credits to all those who, with their long-term research in our laboratory or with their collaboration, helped us progress in the field of pharmaceutical nanotechnology.

I would like to thank my colleagues Assist. Professor Sofia Hatziantoniou, Assist. Professor Kostas Dimas, and the chemist Aris Georgopoulos for their collaboration.

My special gratitude goes to my colleague Dr. Natassa Pippa for years of her outstanding efforts and fruitful discussions for a long time period to formalize the content of this book and to complete it as a textbook.

I also would like to thank Dr. Aggeliki Siamidi and Dr. Natassa Pippa for their fruitful discussions, the opposite remarks, the uninterrupted research activities, and the continuous research for knowledge, the mutual trust, and their teamwork in order to attribute complex scientific issues.

Finally, I appreciate the fruitful discussions with Mrs. Margarita Parisianou-Papailiou from PARISIANOU S.A., regarding the presentation of this textbook. I would also like to thank Prof. C. Papailiou for his kind consultation on procedural matters.

Contents

Abbreviations

ADC	Antibody drug conjugates
ADME	Absorption distribution metabolism excretion
AFM	Atomic force microscopy
APC	Antigen-presenting cells
ASTM	American Standards for Testing and Materials
ATMP	Advanced therapy medicinal products
ATP	Adenosine triphosphate
AUC	Area under the curve
BBB	Blood brain barrier
BNCT	Boron neuron capture therapy
CAT	Committee for Advanced Therapies
CBER	Center for Biological Evaluations and Research
CDER	Center for Drug Evaluation and Research
C-DOPE	N-citraconyl-dioleoyl-phosphatidylethanolamine
C-DOPS	N-citraconyl-dioleoyl-phosphatidylserine
CDRH	Center for Device and Radiological Health
CHMP	Committee for Medicinal Products for Human Use
CMV	Cytomegalovirus
CNT	Carbon nanotube
COMP	Committee for Orphan Medicinal Products
CPD	Continuing Professional Development
Cryo-AFM	Cryogenic atomic force microscopy
Cryo-TEM	Cryogenic TEM
CTA	Center for Technology Assessment
CV	Coefficient variation
CVM	Center for Veterinary Medicine
CVMP	Committee for Medicinal Products for Veterinary Use
DAPE	Diacetylenic phosphatidylethanolamine
DDS	Drug delivery system
DLS	Dynamic light scattering
DMA	Dynamic mechanical analysis

DOPC	Dioleoyl phosphatidylcholine
DOPE	Dioleoyl phosphatidylethanolamine
DPPC	Dipalmitoyl phosphatidylcholine
DPPG	Dipalmitoyl phosphatidylglycerol
DSC	Differential scanning calorimetry
DSPG	Distearoyl phosphatidylglycerol
DTA	Differential thermal analysis
DTG	Differential thermogravimetry
DTPA	Diethylene triamine pentaacetatic acid
EGA	Evolved gas analysis
ELISA	Enzyme-linked immunosorbent assay
EM	Electron microscopy
EMA	European Medicinal Agency
EPC	Egg phosphatidylcholine
EPR	Enhanced permeability and protection
FDA	Food and Drug Administration
FFEM	Freeze fracture electron microscopy
GMP	Good manufacturing practice
GTMPs	Gene therapy medicinal products
HAI	Health Association Infection
HMPC	Committee on Herbal Medicinal Products
HMV	Heating method vesicles
HPE	Handbook of Pharmaceutical Excipients
HSPC	Hydrogenated soy phosphatidylcholine
ICH	International Committee for Harmonization
ICTAC	International Confederation for Thermal Analysis and Calorimetry
IMI2	Innovative Medicines Initiative 2
LFM	Lateral force microscopy
LLD	Liposomal lock in dendrimers
LTD	Ligand-targeted liposome
LUV	Large unilamellar vesicles
MAAs	Marketing Authorization Applications
Mab	Monoclonal antibody
MEMS	Microelectromechanical system
MLCRS	Modulatory Liposomal Controlled Release System
MLV	Multilamellar vesicle
MPS	Mononuclear phagocyte system
MRAM	Magnetoresistive random access memory
MRFM	Magnetic resonance force microscopy
MRI	Magnetic resonance imaging
mtDNA	Mitochondrial DNA
MVV	Multivesicular vesicles
MWNT	Multi-wall nanotube
NAS	National Academy of Science
NASA	National Aeronautics and Space Administration

NASBA	Nucleic acid sequence-based amplification
NCI	National Cancer Institute
NCL	Nanostructured lipid carriers
NCST	National Strategy for Combating Terrorism
NFAS	Non-flame atomic spectroscopy
NIH	National Institute for Health
NMR	Nuclear magnetic resonance
NNI	National Nanotechnology Initiative
NSOM	Near-field scanning optical microscopy
O/W	Oil in water
OLV	Oligolamellar vesicles
ORA	Office of Regulatory Affairs
PCR	Polymerase chain reaction
PDCO	Pediatric Committee
PDI	Polydispersity index
PE	Phospahtidylethanolamine
POPE	Palmitoyl-oleoyl-phosphatidylethanolamine
QbD	Quality by design
QD	Quantum dots
RAM	Random access memory
RES	Reticuloendothelial system
REV	Reverse phase evaporation
RIA	Radioimmunoassay
RSV	Respiratory syncytial virus
RT-PCR	Real-time PCR
SARS	Severe acute respiratory syndrome
SEM	Scanning electron microscopy
SFM	Scanning force microscopy
SLN	Solid lipid nanoparticle
SPARC	Secreted protein acidic and rich in cysteine
SPM	Scanning probe microscopy
STM	Scanning tunneling microscope
SUV	Small unilamellar vesicle
TEM	Tunneling electron microscopy
TEPs	Tissue-engineered products
TG	Thermogravimetry
TMA	Thermomechanical analysis
W/O	Water in oil
W/O/W	Water in oil in water
XPS	X-ray photoelectron spectroscopy

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